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ORIGINAL ARTICLE

A threshold analysis of dengue transmission in terms of weather variables and imported dengue cases in Australia

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Dengue virus (DENV) transmission in Australia is driven by weather factors and imported dengue fever (DF) cases. However, uncertainty remains regarding the threshold effects of high-order interactions among weather factors and imported DF cases and the impact of these factors on autochthonous DF. A time-series regression tree model was used to assess the threshold effects of natural temporal variations of weekly weather factors and weekly imported DF cases in relation to incidence of weekly autochthonous DF from 1 January 2000 to 31 December 2009 in Townsville and Cairns, Australia. In Cairns, mean weekly autochthonous DF incidence increased 16.3-fold when the 3-week lagged moving average maximum temperature was <32 °C, the 4-week lagged moving average minimum temperature was ≥24 °C and the sum of imported DF cases in the previous 2 weeks was >0. When the 3-week lagged moving average maximum temperature was ≥32 °C and the other two conditions mentioned above remained the same, mean weekly autochthonous DF incidence only increased 4.6-fold. In Townsville, the mean weekly incidence of autochthonous DF increased 10-fold when 3-week lagged moving average rainfall was ≥27 mm, but it only increased 1.8-fold when rainfall was <27 mm during January to June. Thus, we found different responses of autochthonous DF incidence to weather factors and imported DF cases in Townsville and Cairns. Imported DF cases may also trigger and enhance local outbreaks under favorable climate conditions.

INTRODUCTION

Dengue fever (DF) is the most common mosquito-borne viral disease in Australia. The global distribution and incidence of DF has increased markedly over the last two decades.[1] In particular, the frequency and intensity of DF outbreaks have been increasing in most tropical and subtropical regions.[2] Currently, no vaccine for dengue exists. Prevention and control rely upon the disruption of transmission through vector management, environmental modification and modification of human behavior to minimize exposure. In addition, there are no effective strategies for limiting the spread of *Aedes* mosquitoes to prevent the geographical expansion of DF.[3,4] Therefore, it is important to improve our understanding of the complexities of Dengue virus (DENV) transmission to facilitate the development of more effective DF prevention strategies.

The epidemiological dynamics of DF has been linked to temporal variations of mosquito vectors, DENV and weather conditions.[5] It is well known that DF is strongly associated with multiple weather variables, particularly temperature, rainfall and relative humidity.[6,7] However, weather variables have been shown to play diverse roles in different tropical and subtropical regions.[8,9] Threshold effects of weather factors on DF have also been documented in previous research.[10] Potentially important thresholds in high-order interactive relationships of weather variables to DF are, however, poorly understood.

To date, Australia has managed to remain a non-endemic country for DF, but there is significant risk that DF may become endemic in the country.[11,12] Infected international travelers are a major driver of the expanding global distribution of DF,[13] and local DF outbreaks in northern Australia are triggered annually by the arrival of infected international travelers. Most imported DF cases arrive from the Pacific and Southeast Asia regions.[14] So far, locally acquired DF cases have been restricted to northern Queensland, with the highest number of locally acquired DF cases occurring in the cities of Cairns and Townsville. Although the geographic distribution of *Aedes aegypti* is widespread throughout urban settings of northern Queensland, there are distinct differences in transmission levels and temporal patterns of outbreaks between geographic locations, as highlighted by Townsville and Cairns.[15] It is not known whether there are threshold effects of weather factors and imported DF cases on autochthonous DF cases in the two tropical areas. Thus, acquiring a comprehensive understanding of factors that modulate DENV transmission will facilitate the development of effective strategies to detect and respond to emerging dengue events.

In this study, our aim is to examine and compare the nonlinear relationships in Townsville and Cairns among local weather variables, imported DF cases and autochthonous DF incidence and to assess the thresholds in the hierarchical relationships of the predictors to autochthonous DF incidence using a time-series regression tree.

MATERIALS AND METHODS

Study site and data collection

Our study sites, Townsville (latitude: −19.15°, longitude: 146.49°) and Cairns (latitude: −16.55°, longitude: 145.46°), are located 281 km apart on the northeastern coast of Queensland (Figure 1). Townsville and

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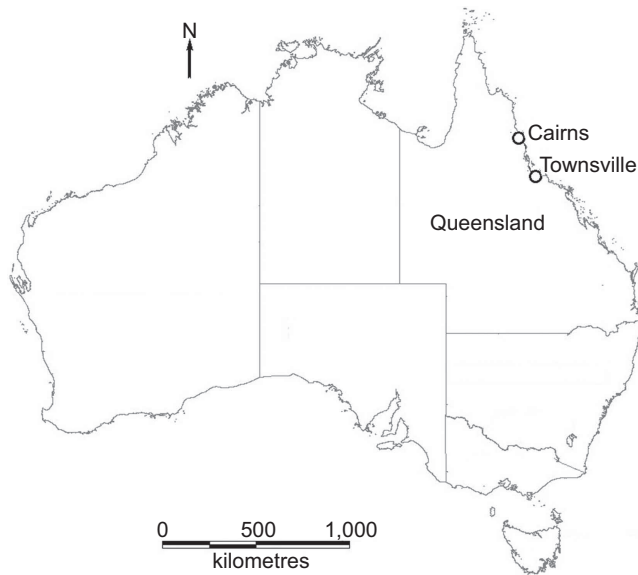
Figure 1 Location of Townsville and Cairns, Queensland, Australia.

Cairns are the two largest cities in North Queensland, with populations of 189 931 and 170 586, respectively, in 2011.[16,17] Rainfall in Townsville is substantially lower than in Cairns;[18] the annual mean total rainfall is 1152.4 mm in Townsville and 2017.8 mm in Cairns.[19] However, the annual mean, maximum and minimum temperatures in Townsville and Cairns are similar. In the Cairns area, there are many national parks, state forests and agricultural areas. In Townsville, landscapes typically comprise wetlands, rivers and tropical savannah hills.

DF is a notifiable disease in Queensland, and notification of possible cases is mandated under the provisions of the Public Health Act 2005. We obtained data from Queensland Health on the numbers of notified DF cases (acquired locally and overseas) in Townsville and Cairns (the areas based on Cairns and Townsville Public Health Units) for the period 1 January 2000 to 31 December 2009. Data provided for each notified DF case include a unique record reference number, date of onset and the confirmation status of the report. All notified DF cases had been confirmed with positive test results by diagnostic laboratory testing. Imported DF cases were defined as confirmed DF cases with a recent travel history from a known DF endemic region.[14] Climatic data for Townsville and Cairns, including temperature (minimum and maximum, ℃), relative humidity (%) and rainfall (mm), were obtained from the Australian Bureau of Meteorology. Population statistics for both regions was obtained from the Australian Bureau of Statistics.

Statistical analysis and modeling
Classification and regression tree is a statistical method for exploring and constructing a nonlinear model, by a decision tree, which can be expressed as a regression tree for a continuous response variable or a classification tree for a categorical variable.[20,21] Classification and regression tree has the ability to handle data with large numbers of independent variables, outliers, missing values and high-order interactions.[21,22] The most important advantage of a classification and regression tree model is that it can determine threshold effects of an ordered relationship between explanatory factors conditional on other factors on response, via a visualized decision tree.

A decision tree was built by repeating best splits of observations of weather variables (e.g., rainfall, relative humidity, minimum temperature

and maximum temperature), where a single splitting weather variable was selected at each split using the principle of impurity reduction.[22] In the separated data, the splitting process was applied separately to each partition with the same response variable (e.g., incidence of autochthonous dengue). Splits were repeated until the subgroups reached a minimum size or there was no improvement in results. The resulting tree can be highly complex and may need to be trimmed to a more manageable size. The trimming methods employed assumed that the best tree minimizes the value for a risk of a tree $R_c(N) = R(N) + c|N|$, where $R(N)$ is the residual sum of squares, N is the number of terminal nodes and c is a complexity parameter. Cross-validation was used to select a value of c that minimized $R_c(N)$. The main procedure for cross-validation was as follows: (i) data were divided into m subgroups $G_1, \ldots, G_i, \ldots, G_m$, and a tree was fitted to each subgroup separately, except the test subgroup G_i; (ii) each tree was used to predict for each observation in G_i, and calculate $R_c(N_j)$, $1 < j < m$; (iii) an estimate was obtained of risk $R_c(N)$ for each complexity parameter by summing over G_i; and (iv) a value for c was determined with the smallest estimated error of a tree, and then N was calculated for the best-trimmed tree on the full data.[20,22]

As a result of biological plausibility and seasonal variability of DF outbreaks,[5] 20 independent variables were applied to the time-series regression tree model, including weekly weather data (minimum, maximum temperature, relative humidity and rainfall) at a lag of 1 week; weekly imported DF cases at a lag of 1 week; 2- to 4-week lagged moving average weather data; seasonality (harmonic factors: $\sin(2\pi t/52)$ and $\cos(2\pi t/52)$); and the sum of imported DF cases in the previous 2 weeks. Student's t-test was used to examine the differences between weather data in Townsville and Cairns. The differences between mean values in the two cities were considered significant if P values were less than 0.05.

RESULTS
Autochthonous and imported DF cases in Townsville and Cairns
Table 1 shows that the mean weekly number of autochthonous DF cases was much higher in Cairns than Townsville ($t = 15.0$, $P < 0.000$),

Table 1 Summary statistics of weekly data for all variables between 1 January 2000 and 31 December 2009 in Townsville and Cairns

Variable	Mean	SEM[f]	Minimum	Maximum	1st quartile	3rd quartile
Townsville						
ADF[a]	0.07	0.006	0	6	0	0
IMDF[b]	0.01	0.002	0	2	0	0
MinT[c] (℃)	20.0	0.08	5.0	28.9	16.6	23.9
MaxT[d] (℃)	29.4	0.05	13.9	41.0	27.5	31.5
RH[e] (%)	89.6	0.19	23.6	100.9	83.1	100
Rainfall (mm)	3.1	0.25	0.0	271.6	0.0	0.0
Cairns						
ADF	0.5	0.03	0	20	0	0
IMDF	0.02	0.003	0	2	0	0
MinT (℃)	20.9	0.06	7.9	28.0	19.1	23.5
MaxT (℃)	29.3	0.04	21.0	37.4	27.5	31.2
RH (%)	90.0	0.16	26.3	100.0	84.5	98.8
Rainfall (mm)	5.4	0.30	0.0	278.4	0.0	2.2

[a] ADF: autochthonous DF cases.
[b] IMDF: imported DF cases.
[c] MinT: minimum temperature.
[d] MaxT: maximum temperature.
[e] RH: relative humidity at minimum temperature.
[f] SEM : standard error of mean.

as was the mean weekly number of imported DF cases ($t=3.9$, $P<0.000$).

Error bar plots show the temporal patterns of mean weekly autochthonous and imported DF cases during the study period (Figure 2). Strong seasonal patterns in autochthonous DF cases were evident in both regions, and the mean weekly autochthonous DF cases in Townsville were less than observed for Cairns, except between June and September. In Cairns, the mean weekly number of autochthonous DF cases was the highest in March and lower between July and September. There was more variation in mean weekly autochthonous DF cases in Cairns. In Townsville, higher mean weekly autochthonous DF cases occurred in January through May. The highest mean weekly imported DF cases were notified in March in both regions. The trend of mean weekly imported DF cases was negative from January to December in Townsville. No clear pattern for mean weekly imported DF cases was observed throughout the study period in Cairns. Although mean weekly imported DF cases in Cairns were greater than those of Townsville in most weeks (Figure 2), the difference in mean weekly imported dengue cases between Townsville and Cairns was smaller than the difference

in mean weekly autochthonous DF cases. Furthermore, no annual trends for mean weekly autochthonous DF cases and mean imported DF cases were observed during the 10-year period in either region.

Weather variables

Weekly minimum temperature in Cairns was greater than Townsville ($t=9.62$, $P<0.000$), and weekly rainfall in Townsville was less than Cairns ($t=5.81$, $P<0.000$). The weekly mean for relative humidity was also slightly higher in Cairns than Townsville ($t=1.45$, $P=0.073$). However, weekly averages for maximum temperature were similar in both study regions. Figure 3 shows the temporal patterns and changes in weekly weather variables during the study period. The weekly mean minimum temperature and weekly mean relative humidity in Townsville had more variation than those of Cairns. There were also seasonal variations in weekly mean maximum and minimum temperature and weekly mean rainfall in both regions. Higher monthly maximum temperatures occurred in January, February and December, and lower monthly minimum temperatures occurred between June and August in Townsville and Cairns. Higher monthly rainfall was observed in January and February in both regions.
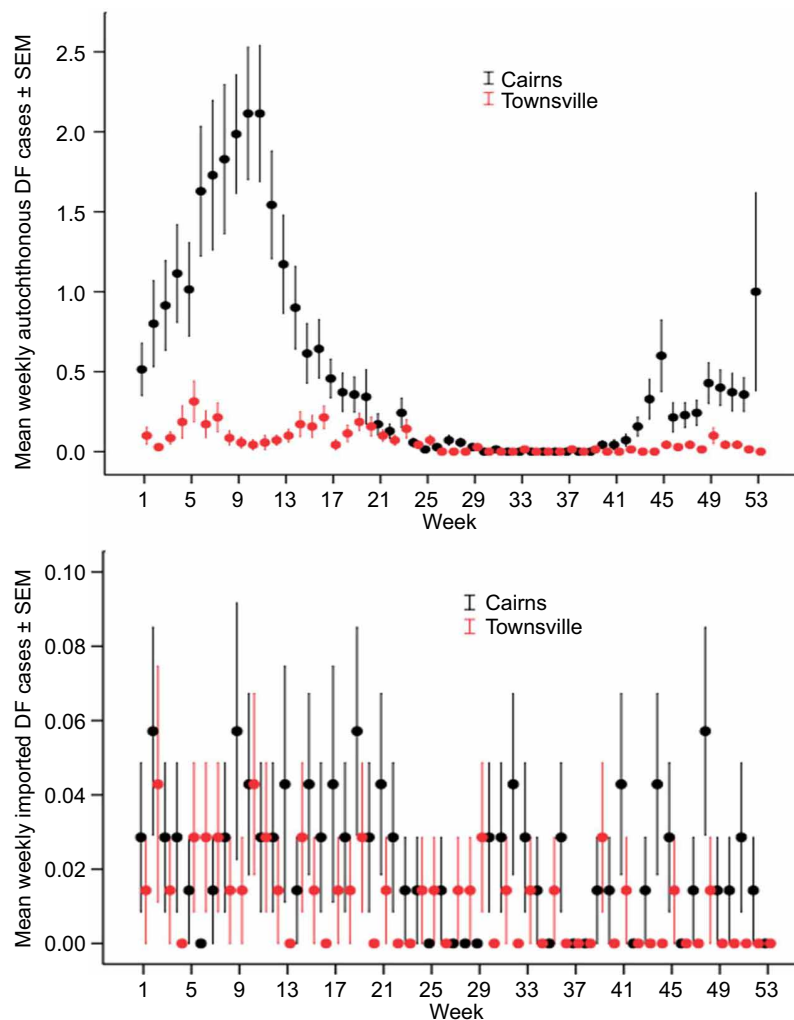
Figure 2 Error bar plots for weekly autochthonous and imported DF cases in Townsville and Cairns, from 1 January 2000 to 31 December 2009. Dots represent observed mean weekly autochthonous and imported DF cases. Bars represent standard error of mean.
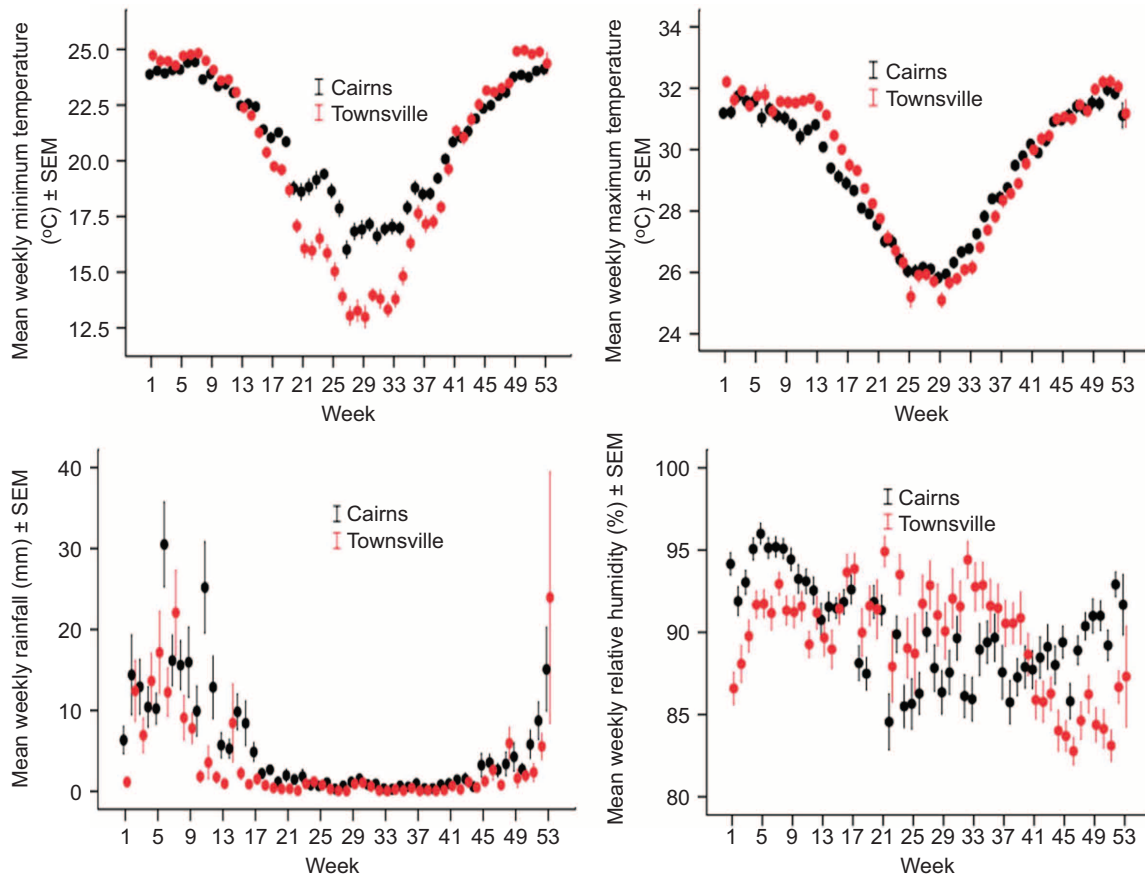
Figure 3 Error bar plots for weekly weather variables in Townsville and Cairns, from 1 January 2000 to 31 December 2009. Dots represent observed weekly mean of weather variables. Bars represent standard error of mean.
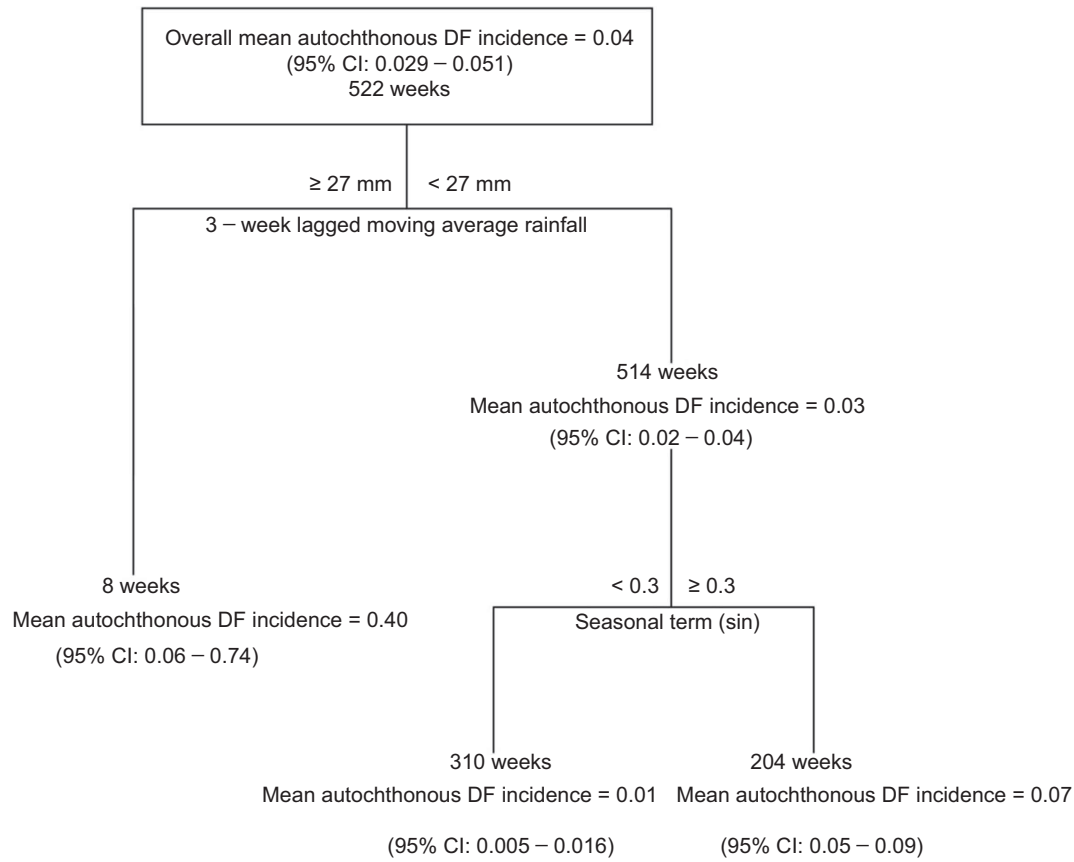
Regression tree

The optimal trees had three terminal nodes for Townsville and four terminal nodes for Cairns, respectively (Figures 4 and 5). Figures 4 and 5 indicate that the optimal regression trees for Townsville and Cairns are very different. In Townsville, only two factors were found to be determinants of weekly autochthonous DF incidence: the 3-week lagged moving average rainfall and seasonality. The overall mean weekly incidence of autochthonous DF was 0.04. The most important splitting factor was the 3-week lagged moving average rainfall, with a threshold value of 27 mm. Mean weekly autochthonous DF incidence increased 10-fold (to mean autochthonous DF incidence of 0.4 relative to an overall mean autochthonous DF incidence of 0.04) when the 3-week lagged moving average rainfall was greater or equal to 27 mm. Seasonality was included as a second split in the right branch of the tree, with a threshold value of sin=0.3. According to the threshold value, the time interval was divided into two periods: January–June (sin≥0.3) and July–December (sin<0.3). Thus, the right branch showed that mean weekly autochthonous DF incidence increased 1.8-fold (to mean autochthonous DF incidence of 0.07 relative to an overall mean autochthonous DF incidence of 0.04) when 3-week lagged moving average rainfall was <27 mm during January to June. However, there was only a weak association (increased 0.25-fold) for the other months.

For Cairns, the 4-week lagged moving average minimum temperature, the 3-week lagged moving average maximum temperature and the sum of imported dengue cases in the previous 2 weeks were found

to be associated with weekly incidence of autochthonous DF. The overall mean weekly incidence of autochthonous DF was 2.42. The most important factor (as indicated by the first split) was the 4-week lagged moving average minimum temperature, with a threshold of 24 ℃ (Figure 5). Mean weekly autochthonous DF incidence, on the right branch, increased 16.3-fold (to mean autochthonous DF incidence of 39.48 compared to an overall mean autochthonous DF incidence of 2.42) when the 4-week lagged moving average minimum temperature of ≥24 ℃, when the 3-week lagged moving average maximum temperature of <32 ℃, and when the sum of imported DF cases in the previous 2 weeks was >0. The mean weekly autochthonous DF incidence only increased 4.6-fold (to a mean autochthonous DF incidence of 11.09 relative to an overall mean autochthonous DF incidence of 2.42) at a 3-week lagged moving average maximum temperature of ≥32 ℃ if the 4-week lagged moving average minimum temperature was ≥24 ℃ and the sum of imported DF cases in the previous 2 weeks was >0. Moreover, mean weekly autochthonous DF incidence increased 1.7-fold (to a mean autochthonous DF incidence of 4.09 relative to an overall mean autochthonous DF incidence of 2.42) when the 4-week lagged moving average minimum temperature of ≥24 ℃ and there were no imported DF cases in the previous 2 weeks (Figure 5). The left branch had a mean autochthonous DF incidence of 1.08 (95% confidence interval: 0.71–1.45) when the 4-week lagged moving average minimum temperature of <24 ℃.

The mean 4-week lagged moving average minimum temperature in Cairns was greater than that of Townsville (t=4.29, P<0.000). There

Figure 4 Regression tree modeling the ordered relationship between weekly autochthonous DF incidence and weather variables and imported dengue cases between 1 January 2000 and 31 December 2009 in Townsville. The regression tree showed the threshold values, mean weekly autochthonous DF incidence and 95% confidence intervals (CI).

was no significant difference between the mean values of the 3-week lagged moving average maximum temperature between the two regions ($t=0.95$, $P=0.343$). The mean 3-week lagged moving average rainfall in Cairns was greater than that of Townsville ($t=5.13$, $P<0.000$).

DISCUSSION

This study compared the importance of weather variables and imported DF cases as factors associated with weekly autochthonous DF incidence in Townsville and Cairns. The regression trees, built on data from the two study regions, provided a temporally sensitive estimation of complex hierarchical interactions between the predictors. Our main findings indicate that the effects of previous weather conditions on weekly autochthonous DF incidence are different and complex in both regions.
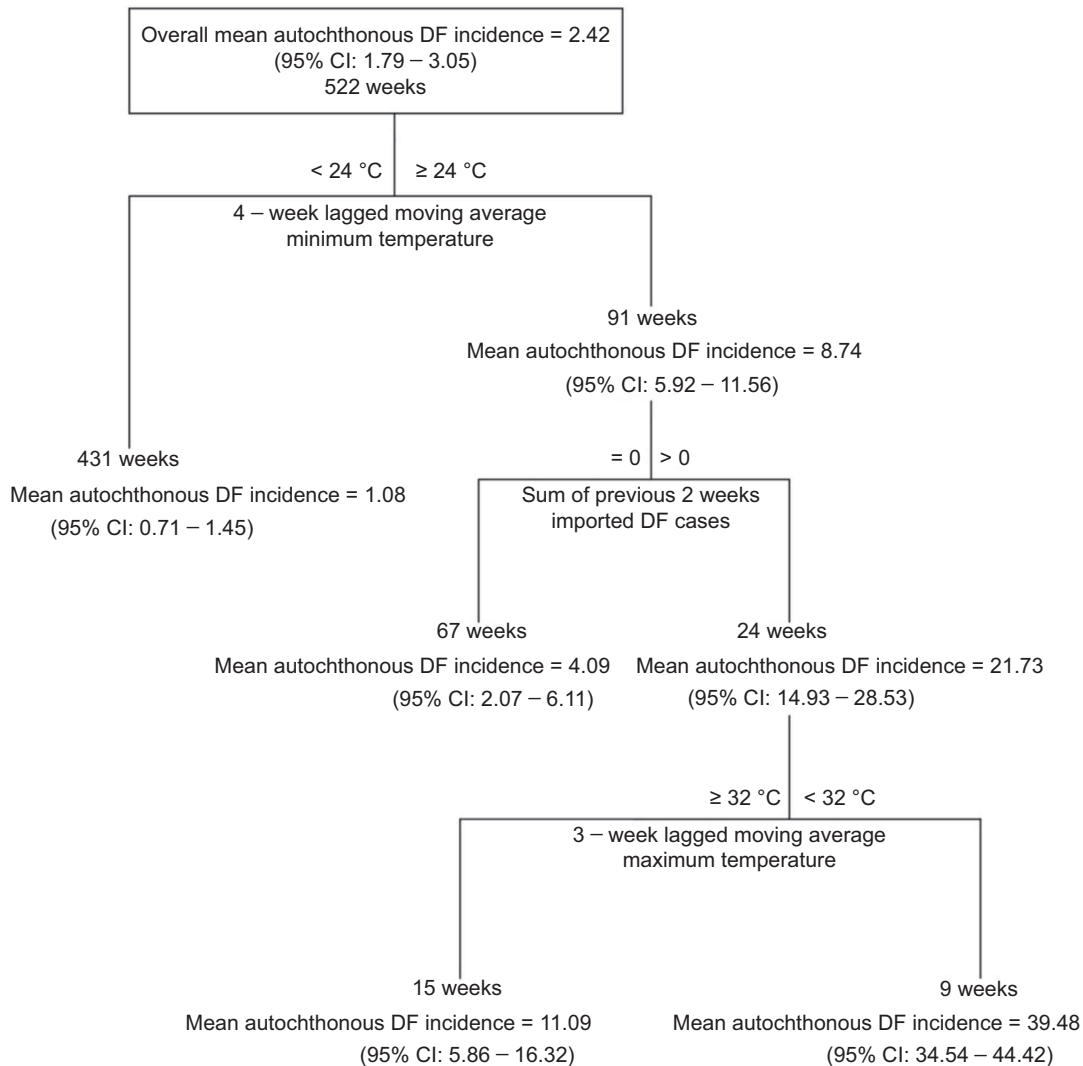
Although local DF outbreaks are often ascribed to imported DF cases in the two study sites,[14] our results show that the sum of imported DF cases in the previous 2 weeks is a determinant of incidence of weekly autochthonous DF in Cairns, but not in Townsville. Imported DF cases did not feature a primary splitting factor in the two regression trees (Figures 4 and 5). During the study period, imported DF cases were reported randomly throughout the years, particularly in Cairns (Figure 2). It was likely that the mean weekly number of imported DF cases in Cairns was greater than Townsville because Cairns has an international airport and is a popular tourist destination. Although imported DF cases were notified during July to September, there were almost no autochthonous DF cases during this period in either region (Figure 2). This evidence supports the hypothesis that imported DF cases trigger and enhance local DF outbreaks in Cairns, but only under specific, favorable weather conditions. Furthermore, our study suggests that initiation of local DENV transmission in Townsville requires both imported DF and specific weather conditions.

The results of this study suggest that the magnitude of effects of imported cases on autochthonous DF cases can be modulated by local surrounding circumstances in different non-endemic areas. Both regions are tropical, support similar-sized populations and are separated by a distance of only 281 km. However, the difference in the total number of autochthonous DF cases was much larger than the difference in the total number of imported DF cases between Townsville and Cairns during the study period (Figure 2). Temperature and rainfall were factors that strongly influenced incidence of DENV transmission. We found thresholds of 24 ℃ (with a 4-week lag) for minimum temperature and 32 ℃ (with a 3-week lag) for maximum temperature to be important thresholds in determining incidence of autochthonous DF in Cairns. We also found 27 mm (with a 3-week lag) to be an important threshold for rainfall in determining the incidence of autochthonous DF in Townsville.

Rainfall has been found to impact the amount of larval breeding places and, by extension, the population size of Ae. aegypti mosquitoes.[13,23] Rainfall intensity typically affects relative humidity and ambient temperature. Annual total rainfall and weekly rainfall in

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        Overall mean autochthonous DF incidence = 2.42
                 (95% CI: 1.79 − 3.05)
                      522 weeks

              < 24 °C  |  ≥ 24 °C

          4 − week lagged moving average
               minimum temperature

                              91 weeks
                    Mean autochthonous DF incidence = 8.74
                         (95% CI: 5.92 − 11.56)

                              = 0  |  > 0

 431 weeks                  Sum of previous 2 weeks
 Mean autochthonous              imported DF cases
 DF incidence = 1.08
 (95% CI: 0.71 − 1.45)
                      67 weeks                24 weeks
             Mean autochthonous        Mean autochthonous
             DF incidence = 4.09       DF incidence = 21.73
             (95% CI: 2.07 − 6.11)     (95% CI: 14.93 − 28.53)

                                ≥ 32 °C  |  < 32 °C

                            3 − week lagged moving average
                                 maximum temperature

                   15 weeks                        9 weeks
          Mean autochthonous DF incidence = 11.09   Mean autochthonous DF incidence = 39.48
               (95% CI: 5.86 − 16.32)                   (95% CI: 34.54 − 44.42)
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Figure 5 Regression tree modeling the ordered relationship between weekly autochthonous DF incidence and weather variables and imported dengue cases between 1 January 2000 and 31 December 2009 in Cairns. The regression tree showed the threshold values, mean weekly autochthonous DF incidence and 95% confidence intervals.

Townsville are less than in Cairns, and it is possible that rainfall is a more important limiting factor for DENV transmission in Townsville than in Cairns. Our results suggest that autochthonous DF cases are restricted when rainfall is below a required amount in tropical regions.

In Cairns, a 4-week lagged moving average minimum temperature of ⩾24 °C and a 3-week lagged moving average maximum temperature of <32 °C were found to be the most favorable weather conditions for DENV transmission. Increasing temperature improves mean time intervals of the maturation period (i.e., from egg to adult), feeding frequency, viral replication rate and extrinsic incubation period for *Ae. aegypti* mosquitoes.[2,24,25] In general, *Ae. aegypti* mosquitoes have lower mortality rates at temperatures between 15 °C and 30 °C in comparison to temperatures of <15 °C and > 30 °C.[26] The most favorable temperature for survival in North Queensland is between 20 °C and 30 °C.[27] A minimum temperature threshold of 24 °C is consistent with the known optimum temperature range for survival in North Queensland. However, the incidence of autochthonous DF has a small increase of 4.6-fold at a maximum temperature ⩾32 °C compared with an increase of 16.3-fold at a maximum temperature

<32 °C in Cairns (Figure 5). This increase related to temperature might be due to changes in human behavior, such as reducing outdoor activities, as well as increasing mortality rates of *Ae. aegypti* mosquitoes at a higher ambient temperatures. Nonetheless, feeding frequency increases due to a shorter *Ae. aegypti* gonotrophic cycle at temperatures above 32 °C.[25] Overall, we conclude that there is a difference in the effects of weather between Townsville and Cairns as a consequence of different local environmental conditions. Additionally, transmission of dengue may require a minimum amount of rainfall and a favorable ambient temperature range in the tropics.

This study provides novel insights into the hierarchical interactions between predictors of DF at the two study sites. These thresholds, developed by the regression tree, can be used in the assessment of risk of DENV transmission and guide DF management decisions at a local level. For example, local health departments may promote DF education, control potential breeding sites and provide a close surveillance of DF vectors when weather conditions are favorable for DENV transmission. Known threshold values could enhance intervention planning because they are easy for local health officials to understand. The

method applied in this study also can be used to assess the threshold effects of weather variables in other endemic/non-endemic regions. A limitation of this study is that solely incorporating weather variables and imported DF cases in the two regression trees may not be adequate to explain the complex interaction between ecological and social factors. How a small difference in the number of imported DF cases can yield a large difference in the number of autochthonous DF cases between Townsville and Cairns still remains unclear, although our study showed that there was a significant difference in weekly rainfall in the two regions. We suggest that incorporating additional factors into future regression-tree models, such as entomological variables, socioeconomic variables and other weather variables, can help better understand DENV transmission.

This study emphasizes the high-order interactive relationships among autochthonous DF incidence, weather variables and imported dengue cases. Our research highlights differences in weather conditions that are favorable for DENV transmission in Townsville and Cairns. Imported DF was not the most important first split factor in the two regression trees as we might have expected. The results suggest that imported DF cases trigger and enhance local outbreaks only under favorable weather conditions, particularly in Cairns. We conclude that a primary rainfall amount might be an essential condition for DENV transmission in the tropics. Weather thresholds can provide clues to develop DF management strategies and public health interventions based on routinely collected weather data.

ACKNOWLEDGMENTS

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