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Event history analysis of dengue fever epidemic and inter-epidemic spells in Barbados, Brazil, and Thailand

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SUMMARY

Objective: This study investigated meteorological and demographic factors affecting the length of dengue fever epidemics and the length of time between epidemics in Barbados, Brazil, and Thailand.
Methods: Region-specific meteorological and demographic data were collected for 104 sites from public sources. Fixed effects piecewise logistic event history analysis was used to quantify the effects of time-varying covariates on the duration of inter-epidemic spells and for the duration of epidemics.
Results: Mean monthly temperature was the most important factor affecting the duration of both inter-epidemic spells ($\beta = 0.543$; confidence interval (CI) 0.4954, 0.5906) and epidemic spells ($\beta = -0.648$; CI −0.7553, −0.5405). Drought conditions increased the time between epidemics. Increased temperature hastened the onset of an epidemic, and during an epidemic, higher mean temperature increased the duration of the epidemic.
Conclusions: By using a duration analysis, this study offers a novel approach for investigating the dynamics of dengue fever epidemiology. Furthermore, these results offer new insights into prior findings of a correlation between temperature and the geographic range and vector efficiency of dengue fever.

1. Introduction

Dengue fever (DF) is the result of infection by a dengue virus (DENV), a small group of mosquito-transmitted, infectious arboviruses of the genus *Flavivirus*, family *Flaviridae*.[1] Infected individuals can become febrile and may experience retro-orbital pain, myalgia, arthralgia, and severe abdominal and back pain.[2] Infection results in immunity to the specific serotype; however individuals infected by one serotype remain susceptible to infection by other serotypes.[2] This re-infection is associated with the much more severe dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).[3] Currently there is no vaccine for DENV, in part because a vaccine would need to account for the four different serotypes and until recently there had been no non-human animal model for the virus.[4–6] Although dengue has been present in the environment for at least 200 years, there has been an increase in both the severity and frequency of outbreaks, and a more widespread global distribution in the last 60 years.[1] With an estimated 50 to 100 million people infected each year, DENV is the most prevalent arbovirus in the world (http://www.cdc.gov/dengue/).

The complex pathogen cycle of DF involves and is affected by numerous environmental, socio-cultural, economic, demographic, and biological factors. The disease is found primarily in cities of the tropical and subtropical world. The ecological and biological requirements of the vector, Aedes mosquitoes, largely affect both the transmission and geographic spread of DF. *Aedes aegypti*, the main vector, prefers humid regions with temperatures near 28 °C and is well adapted to urban settings, often undergoing immature life stages in small containers or tires.[7] The virus is capable of vertical transmission, from infected mother to offspring.[8] These biological characteristics have allowed the spread of *A. aegypti* and *Aedes albopictus*, both dengue vectors, and subsequently DENV, in cargo ships throughout much of the world.

Several investigations have sought to uncover and model important factors in the transmission of DF and its geographic spread.[9–14] Hopp and Foley devised a climate-based model for explaining mosquito population dynamics and compared this model to dengue incidence data for much of the world. They found significant associations between predicted mosquito population sizes and dengue infection numbers in Southeast Asia and Central America.[15] Hales et al. investigated the potential role of

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meteorological covariates on the geographical distribution of dengue fever. They found that vapor pressure was the most significant predictor of the distribution of DF.[12]

There have also been several environmental models focusing on specific endemic regions.[11,16–19] Cummings et al. used an empirical mode decomposition model in order to investigate the spatio-temporal dynamics of DHF in Thailand. They found waves of DHF incidence that emanated from Bangkok – the largest metropolitan region in Thailand.[16] Cazelles et al. used a wavelet approach to modeling dengue epidemiology with regards to El Niño in Thailand.[20] Like Cummings et al., they found that outbreaks sometimes originated in Bangkok and flowed outwards to other provinces. However, strong El Niño events appear to cause non-synchronous dengue outbreaks that do not follow the Bangkok centered wave-like patterns.

Models for describing universal outbreak patterns through the simultaneous examination of region-specific patterns have been rare. One example is an investigation in which Johansson et al., used wavelet analysis to examine the effects of El Niño on dengue epidemiology in Mexico, Thailand, and Puerto Rico.[21] However, this study found little-to-no correlation between El Niño-driven weather patterns and DF epidemiology, perhaps because of unique dynamics within each region.

Finally, some investigations into the influence of climate on dengue epidemiology have been concerned with the potential of increasing DENV ranges in the event of increased global warming.[12] Building off of their DF geographic range model, Hales et al. used global simulations to predict the potential future spread of dengue fever under the Intergovernmental Panel on Climate Change climate change scenario.[12]

Ultimately, these models have found that there are strong temporal and spatial dynamics with regards to DF epidemiology, and these dynamics are at least sometimes driven by meteorological factors such as precipitation, temperature, and vapor pressure. While these relatively seasonal factors appear to be strongly influential in DF dynamics, individual regions exhibit heterogeneity in the drivers of dengue epidemiology. Therefore while several studies have shown that environmental, demographic, and biological factors are important in DF transmission, few studies have shown consistency in the most important factors across geographically different regions.

Given previous investigations, we hypothesized that the timing of dengue fever outbreaks is influenced by meteorological, physical, and demographic covariates. Specifically, we predicted that higher temperature, more precipitation, and greater population densities would be associated with shorter periods between outbreaks, because these factors can increase vector populations and vector feeding habits. Furthermore, we expected that these same factors may increase the actual length of outbreaks. Finally, we predicted that natural disasters would exacerbate the situation, leading to outbreaks regardless of the meteorological situation. Natural disasters have been associated with disease outbreaks.[22] We used the World Health Organization (WHO) Collaborating Centre for Research on the Epidemiology of Disasters (CRED) definition of disaster as a "situation or event, which overwhelms local capacity, necessitating a request to national or international level for external assistance." While not all such events are 'natural' we only considered droughts, floods, and storms in our analysis (all events that are considered by CRED to be natural disasters).

This research used another approach to examine the effects of environmental and physical covariates on DF. We used event history methods to analyze the effects of covariates (Tables 1 and 2) on the duration of both DF outbreaks and inter-epidemic spells within endemic regions.

The covariates we included were chosen for theoretical, empirical, and practical reasons. Previous research has shown that meteorological factors such as average ambient temperature and precipitation affect the distribution and dynamics of dengue epidemics.[12,15,20] Natural disasters such as earthquakes, landslides, and tropical storms can disrupt daily routines for communities and may leave individuals more susceptible to infection through greater exposure and poorer health.[22] Disasters may also affect vector habitat, leading to an increase in vector population size and ultimately to increased dengue transmission. Finally, dengue has largely been considered a disease of dense urban centers. Therefore we included population density (people per square kilometer) as a covariate.

Our analytical model is novel in that it specifically investigates the duration of both inter-epidemic and epidemic spells in different regions: Barbados, Brazil, and Thailand. Dengue outbreaks are processes that occur over time, therefore a model that explicitly incorporates time as a factor is warranted. We expected

Table 1
Inter-epidemic spell ($N = 9170$ monthly observations)

Covariates	Unit of measure	Mean	SD	Min	Max
Mean monthly temperature	Celsius	26.85	2.34	8.80	33.40
Total monthly precipitation	Millimeter	250.7	376.2	0.0	4385.5
Humidity	Percent of maximum humidity	73.30	8.14	39.74	97.21
Duration	Month	6.04	7.13	0.00	68.00
Drought	Absence/presence	0.0001	NA	0.00	1.00
Flood	Absence/presence	0.0057	NA	0.00	1.00
Storm	Absence/presence	0.0040	NA	0.00	1.00

SD, standard deviation; NA, not applicable.

Table 2
Epidemic spell ($N = 2706$ monthly observations)

Covariates	Unit of measure	Mean	SD	Min	Max
Mean monthly temperature	Celsius	27.76	1.38	8.80	35.33
Total monthly precipitation	Millimeter	415.7	415.0	0.0	3201.8
Humidity	Percent of maximum humidity	77.39	6.47	29.67	97.11
Duration	Month	1.48	2.08	0.00	24.00
Drought	Absence/presence	0.0037	NA	0.00	1.00
Flood	Absence/presence	0.0048	NA	0.00	1.00
Storm	Absence/presence	0.0092	NA	0.00	1.00

SD, standard deviation; NA, not applicable.

that meteorological, physical, and demographic processes would affect both the length of epidemics and the length of inter-epidemic spells, but the effects would differ for each process. For example, we expected that temperature may hasten the onset of dengue outbreaks but we did not expect it to also hasten the end of an outbreak. Therefore we analyzed epidemic and inter-epidemic spells separately. Rather than using infection counts directly, each epidemic within a region was treated as a single observation in one analysis. Each inter-epidemic spell within a region was a single observation in the second analysis. Because infection counts are only used within a region to determine the start and stopping months of each epidemic, this method is relatively insensitive to regional differences in ascertainment of infected individuals. This is a robust alternative to explicitly modeling individual counts of infections since there may be systematic reporting differences among regions.

Barbados, Brazil, and Thailand were chosen for several reasons. Each has regions of high population density, and Thailand and Brazil also contain sparsely populated regions. Dengue is one of the most important public health threats to each of these regions.

Our analyses suggest that mean monthly temperature exhibits strong influence on the duration of DF epidemics and that the duration of inter-epidemic spells is affected by temperature and drought conditions in endemic regions.

2. Materials and methods

2.1. Data

Monthly infection numbers were gathered from the WHO DengueNet database and from a previous investigation[16] into dengue epidemic behavior (http://apps.who.int/globalatlas/default.asp). Infection numbers were recorded at the state or provincial level, and our analyses covered all provinces of Thailand, all states of Brazil, and all of Barbados (we did not find sub-national data for Barbados). Climate data for each island, state, or province were collected from the National Oceanic and Atmospheric Administration (NOAA) National Data Center (NNDC) weather station database (http://www7.ncdc.noaa.gov/CDO/country). We used station data from each region rather than grid data. The gridded data sets use station data to interpolate meteorological conditions across entire grids, a method that makes its use for monthly disease incidence studies questionable.[14,23] Since we are interested in the sensitivity of epidemic and inter-epidemic spells to meteorological conditions at sites typically smaller than grids, weather station data were more appropriate for this analysis. Population data were taken from the United Nations Department of Economic and Social Affairs Population Division (http://www.un.org/esa/population/), the Brazilian Geography and Statistics Institute (http://www.ibge.gov.br/home/), and from a previous investigation.[16] Population estimates are available in 5-year increments. Month and year estimates within the intervals were interpolated from these estimates. Data concerning natural disasters came from EM-DAT, the OFDA/CRED International Disaster Database, Université Catholique de Louvain, Brussels, Belgium (http://www.emdat.be/). A total of 1730 epidemic spells, 1731 inter-epidemic spells, and 12 378 monthly observations were included in this analysis, corresponding to over 1000 combined years of observation.

Since the regions are dengue endemic, there is always an underlying (baseline) level of infection present, with epidemics manifesting as sharp peaks above these baseline levels (Figure 1). We developed an algorithm to mark the beginning and ending of the epidemics. We calculated the standard deviation of a moving 3-month period of time, σ by:

$$\sigma = \sqrt{\frac{\sum_1^3 (x_i - \theta)}{3}}$$

where x_i is the number of infections in month i, and θ is the mean number of infections for the 3-month sequence. Then we calculated the difference between the third and first month normalized by σ. A difference greater than two was coded as an event: either the beginning or end of an epidemic:

$$\frac{x_3 - x_1}{\sigma} = \begin{cases} z = 1, \text{ if} > 2 \\ z = -1, \text{ if} < -2 \\ z = 0, \text{ otherwise} \end{cases}$$

An epidemic increase in infections occurs when $z = 1$, and a decrease in infections denoting the end of an epidemic occurs when $z = -1$. This algorithm also recognized epidemic surges after the initial beginning of an epidemic; therefore we considered the first positive ($z = 1$) and subsequent first negative ($z = -1$) changes in infection numbers to represent the beginning and ending of an epidemic. While the choice of two standard deviations is relatively arbitrary, this algorithm is efficient at capturing the large surges in infection numbers that are commonly associated with epidemic situations. Furthermore, this coding scheme allowed us to control for the likely biases in infection reporting. While variations in absolute numbers of infections may be prone to error we believe that the large spikes in reporting (which we code as the beginning of an epidemic) are in fact indicative of a real, qualitative change and are therefore more believable than monthly counts.

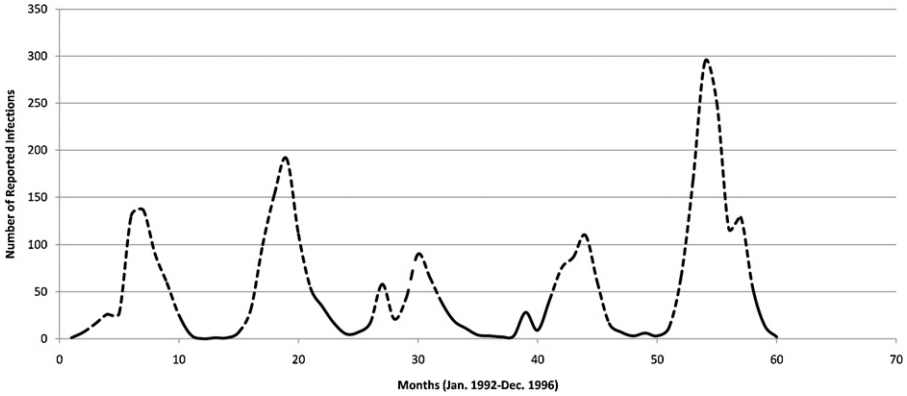

Figure 1. Example of infection data and epidemic coding. The solid lines represent inter-epidemic periods whereas the dotted lines represent epidemic periods. Data are from Yasothon Province, Thailand from January 1992 through December 1996.

2.2. Analysis

Event history analysis was used to model the monthly probability of an event (a change of state to either an epidemic or inter-epidemic spell) occurring in the study sites, controlling for each site's exposure to the risk of such an event occurring. The data were combined into a single data set with location-specific identifiers and with each row constituting an observation for each month. Two separate analyses were completed: one for epidemic spells and one for inter-epidemic spells. Since infection numbers were reported in monthly counts we assumed risk of infection was equal across the month and we used a discrete, piecewise fixed effects logistic regression model to find maximum likelihood estimates of parameters for covariates that affect the duration of both epidemic and inter-epidemic spells. The logistic model is:

$$\log\left[\frac{p_{it}}{1-p_{it}}\right] = \alpha_i + \beta_1 x_{it1} + \ldots + \beta_k x_{itk}$$

where p_{it} is the conditional probability that an event will occur given that it has not already occurred (within a specific spell); i indicates the specific site; t indicates the month for an observation; α is the constant; and the βs are the estimated coefficients for the k covariates (x). This model estimates the log odds of an event occurring, controlling for the accumulated risk associated with time. The result of taking the antilog of an estimated parameter (e^{β}) is the estimated odds ratio. A commonly used transformation of the parameter estimates is $100(e^{\beta} - 1)$, which in our case gives the percent change in monthly odds of an event occurring for every one unit increase in the given parameter.

Event history analysis accommodates right censoring that arises at the last (incomplete) observation for a region and also allows for modeling the effect of time-varying covariates.[24] In order to account for potential unexplained heterogeneity, we included a fixed effect term for each of the regions within our study. We tested for interactions between climatological factors (mean monthly and total monthly precipitation, mean monthly temperature and humidity, and total monthly precipitation and humidity) and found that humidity was a function of both precipitation and temperature, therefore subsequent models excluded humidity. (Models that included humidity exhibited no difference in significant covariates or effect sizes, therefore exclusion of humidity in the model is warranted.) In all models, covariate effects were considered significant at $\alpha = 0.05$. The Akaike information criterion (AIC) was used to test alternative specifications of the model. Lower AIC values are conventionally associated with better model fit, while accounting for an increase or decrease in the number of parameters.[25] We tested three specifications for the effect of time: a linear effect, a quadratic effect, and a cubic effect of time. AIC suggested that a model including a linear and quadratic effect of time provided the best fit.

A third analysis used a generalized linear model with a negative binomial distribution to evaluate the relationship between length of outbreaks and the counts of infections. This was done to ascertain whether the length of an outbreak is associated with a more severe or less severe epidemic. All models were run using SAS 9.3.

3. Results

3.1. Inter-epidemic spell analysis

Mean monthly temperature and drought conditions were the strongest covariates affecting the duration of an inter-epidemic spell (Table 3). Mean monthly temperature had the largest positive coefficient ($\beta = 0.543$; confidence interval (CI) 0.4954, 0.5906) indicating that temperature hastened the onset of a dengue outbreak during an inter-epidemic spell. An increased monthly temperature of 1 °C results in a 72% increase in the monthly odds of an outbreak occurring. Total precipitation also had a significant ($\beta = 0.0014$; CI 0.0012, 0.0015) positive effect, however the effect size was extremely small, with a 0.14% increase in the monthly odds of an outbreak occurring. The presence of a drought conferred a strong, significant ($\beta = -1.0717$; CI −1.9496, −0.1938) negative effect on the odds of an outbreak occurring. The model suggests that, under drought conditions, the monthly odds of a DF outbreak occurring are decreased by 66%. Population density also had a significant ($\beta = -0.0012$; CI −0.0020, −0.0005) but small (0.12% decrease in the monthly odds) effect.

3.2. Epidemic spell analysis

Mean monthly temperature and time both significantly affected the duration of epidemics (Table 4). The negative coefficient for mean temperature ($\beta = -0.648$; CI −0.7553, −0.5405) indicates that during an epidemic spell an increase of 1 °C in average monthly temperature is associated with a 48% decrease in the odds of the epidemic ending. In other words, increased temperature appears to prolong epidemics. The duration of an outbreak (in months) also influences its odds of ending. Duration (time) is incorporated in this model as a polynomial. The positive linear covariate ($\beta = 0.93$) and negative quadratic covariate ($\beta = -0.0819$) indicate that the risk of an epidemic occurring increases as a function of time, but the rate of increase is decreasing.

A recent investigation found that daily temperature fluctuations may be more important than monthly averages for dengue virus transmission.[26] For example, relatively drastic fluctuations in daily temperature may result in decreased vector population size and/or decreased vector feeding behavior. Our data are monthly counts and therefore we cannot directly look at the effect of daily fluctuations on daily infections. However, in another model

Table 3
Inter-epidemic spells

Covariate	Coefficient	SE	CI
Mean temperature	0.543	0.0243	(0.4954, 0.5906)
Total precipitation	0.0014	0.0001	(0.0012, 0.0015)
Density	−0.0012	0.0004	(−0.0020, −0.0005)
Time	−0.0491	0.0117	(−0.0720, −0.0262)
Time^2	0.0013	0.0003	(0.0007, 0.0019)
Drought	−1.0717	0.4479	(−1.9496, −0.1938)
Flood	0.1606	0.2458	(−0.3212, 0.6424)
Storm	0.3841	0.2897	(−0.1837, 0.9519)

SE, standard error; CI, confidence interval.
'Time' is the linear term for time whereas 'Time^2' is the quadratic term. Inclusion of the quadratic term allows the effect of time to vary non-linearly.

Table 4
Epidemic spells

Covariate	Coefficient	SE	CI
Mean temperature	−0.6479	0.0548	(−0.7553, −0.5405)
Total precipitation	0.0002	0.0001	(0.0000, 0.0005)
Density	0	0.0009	(−0.0017, 0.0017)
Time	0.9269	0.0839	(0.7625, 1.0913)
Time^2	−0.0819	0.011	(−0.1035, −0.0603)
Drought	6.002	172.4	(−331.9020, 343.9060)
Flood	−0.1424	0.3854	(−0.8978, 0.6130)
Storm	−0.3812	0.2279	(−0.8279, 0.0655)

SE, standard error; CI, confidence interval.
'Time' is the linear term for time whereas 'Time^2' is the quadratic term. Inclusion of the quadratic term allows the effect of time to vary non-linearly.

(summarized here) we included a covariate that took the difference between the average daily maximum and average daily minimum temperature for each month. While the effects were significant, the effect sizes were very small ($\beta = -0.0399$ for epidemic spells and $\beta = -0.1027$ for inter-epidemic spells), the AIC values were smaller for the models without the temperature difference covariate, and since there is likely interaction between this covariate and mean monthly temperature, the temperature spread variable was excluded from final models.

3.3. Epidemic duration and severity

The negative binomial analysis yielded a small positive association between duration of an outbreak and counts of infections ($\beta = 0.0584$; CI 0.0417, 0.0751). We interpret this finding to mean that a longer duration of an outbreak is associated with increased numbers of infections. Even so, since this analysis used individual count data (and since there is probably a lack of independence between monthly counts) it should be interpreted with some caution.

4. Discussion

This investigation has shown that both meteorological factors and natural disaster conditions can influence the epidemiology of DF outbreaks. Mean monthly temperature significantly affected the length of both epidemic and inter-epidemic spells across large, diverse landscapes. This finding is consistent with previous studies that have shown temperature to affect mosquito behavior, mosquito–virus interaction, and dengue transmission.[7,11,14,27–31] While the influence of climate on dengue epidemiology appears to be well established, some authors suggest the influence of climate is overplayed and that other factors are more important in dengue management and control.[32] Our investigation shows that, even across geographically distant regions, climate is still relevant and important.

Our findings are also supported by previous research into biological and socio-economic factors in dengue epidemiology. For example, a field study by Yasuno and Tonn in 1967–1968 showed a significant association between temperature and the biting rate of Aedes mosquitoes.[31] Biting rates in Bangkok increased during warmer months.[31] Additionally, temperature is known to affect the extrinsic incubation period for several arboviruses.[30] While those effects tend to vary depending on both the mosquito and serotype, a laboratory study showed that extrinsic incubation times for the dengue 2 serotype reduced from 12 days at $\leq$30 °C to 7 days at temperatures between 32 °C and 35 °C.[30] Warmer temperatures appear to increase the blood feeding habits of Aedes mosquitoes while simultaneously shortening the period of time necessary for them to become infectious to humans, resulting in a more efficient pathogen vector.

Social and economic factors may also play a role in the climate–epidemic relationship. Humans may spend more time outdoors in warmer temperatures; they may additionally wear less protective clothing. An increase of temperature might also lead people to leave windows and/or doors to their houses open, allowing an entry way for the vector. If households do not have screens covering potential entry ways, the risk is increased. An investigation in the USA–Mexico border town known as Los Dos Laredos (Laredo in the USA and Nuevo Laredo in Mexico) showed unequal infection rates between the USA residents and those in Mexico.[33] Despite finding higher populations of *A. aegypti* in Laredo, infection rates (determined by immunoglobulin M antibody serosurvey) were higher in Nuevo Laredo. The survey showed that structures in the USA were more likely to have and use air conditioning than their counterparts in Mexico. Additionally, window screen use was more prevalent on the USA side of the border.[33]

The effect of drought conditions on dengue epidemiology is also intuitive. Water is necessary for mosquito reproduction and propagation. What is surprising, however, is the stronger impact of drought conditions when compared to total monthly precipitation – a meteorological variable that influences drought. Drought conditions, as represented in our model, probably represent a threshold level of precipitation. Crossing this threshold is more explanatory with regards to dengue epidemiology than is the continuous precipitation covariate.

Previous models, mostly looking at El Niño events with regards to dengue outbreaks, have also shown correlation between droughts and dengue epidemiology. In some cases, water storage containers during droughts can serve as a reservoir for the mosquito vector, leading to a positive correlation and complicating the drought–DF relationship.[34,35] However, studies that have found positive relationships between drought and DF outbreaks have generally shown that rainy periods following droughts are correlated with outbreaks.[27,36]

Our results suggest that rising temperature exacerbates dengue epidemiology in endemic regions by both reducing the time between outbreaks and increasing the length of outbreaks. During an inter-epidemic spell an increase of 1 °C almost doubles the odds of an outbreak occurring, while an increase of 1 °C during an epidemic spell reduces (by almost half) the monthly odds of the outbreak ending. This finding is important in consideration of recent models that predict a global average temperature increase of 1.1 to 6.4 °C within the 21st century.[37] The increased burden on already stressed health care systems could result in severe health consequences for tropical and sub-tropical regions. Increased DF or DHF cases could divert limited resources in regions that may also be endemic for one or several other infectious diseases. In the absence of adequate medical attention, mortality from DHF can exceed 20% (http://apps.who.int/globalatlas/default.asp). The emerging evidence is that an increase in mean temperature can have profound effects on DF, resulting in increased morbidity and mortality.

A methodological contribution of this work is the use of event history analysis to assess the effects of covariates on the dynamics of DF epidemics. An advantage of this approach is it reduces potential problems with infection count data. Infection surveillance methods that differ among regions, resulting in systematic undercounting of infections in some regions, will not affect the analysis. So long as the pattern of infections is unchanged, the rise and fall in infection numbers will still identify the start and end of epidemics. The tradeoff in doing this is that the unit of analysis is the start and end of epidemics, giving a relatively small 'sample size' of 1730 epidemic spells and 1731 inter-epidemic spells. An extension of this method may prove useful for predicting epidemic lengths or inter-epidemic spell lengths by making use of the pattern of infections, rather than direct counts to denote the start of each type of spell.

Conflict of interest: The authors have no conflict of interest to report.

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