Climate drives spatial variation in Zika epidemics in Latin America

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Between 2015 and 2017, Zika virus spread rapidly through populations in the Americas with no prior exposure to the disease. Although climate is a known determinant of many Aedes-transmitted diseases, it is currently unclear whether climate was a major driver of the Zika epidemic and how climate might have differentially impacted outbreak intensity across locations within Latin America. Here, we estimated force of infection for Zika over time and across provinces in Latin America using a time-varying susceptible–infectious–recovered model. Climate factors explained less than 5% of the variation in weekly transmission intensity in a spatio-temporal model of force of infection by province over time, suggesting that week to week transmission within provinces may be too stochastic to predict. By contrast, climate and population factors were highly predictive of spatial variation in the presence and intensity of Zika transmission among provinces, with pseudo-$R^2$ values between 0.33 and 0.60. Temperature, temperature range, rainfall and population size were the most important predictors of where Zika transmission occurred, while rainfall, relative humidity and a nonlinear effect of temperature were the best predictors of Zika intensity and burden. Surprisingly, force of infection was greatest in locations with temperatures near 24°C, much lower than previous estimates from mechanistic models, potentially suggesting that existing vector control programmes and/or prior exposure to other mosquito-borne diseases may have limited transmission in locations most suitable for Aedes aegypti, the main vector of Zika, dengue and chikungunya viruses in Latin America.

1. Introduction

The emergence and re-emergence of mosquito-borne diseases presents a global public health concern, yet trends in mosquito-borne disease transmission are hard to predict because they are influenced by the underlying immunity in the population, which is usually unknown [1–3]. The emergence and spread of Zika virus through Latin America in a population with no prior exposure or immunity to the disease provides an opportunity to characterize relationships among the environment, populations and disease transmission without the confounding effects of pre-existing immunity (although cross-reactivity between dengue antibodies and Zika virus may provide some protection) [4]. Between 2015 and 2017, Zika rapidly spread to 51 countries and territories in the Americas, with over 800 000 cases reported [5]. Here, we quantified the force of infection for Zika and studied factors that contributed to variation in transmission across time and space as Zika emerged.

Force of infection, or the per capita rate at which susceptible individuals contract an infection, can be used to compare disease transmission over the course of an outbreak and across geographical regions [2,6]. Force of infection estimates can account for variation in the number of immune individuals and entomological factors that influence the time it takes for mosquito-borne diseases to be transmitted [2,6]. It can take several weeks for mosquitoes to
spread diseases because transmission requires a mosquito to bite an infectious person, the pathogen to replicate and disseminate in the mosquito (during the extrinsic incubation period), and the mosquito to bite and infect a susceptible person [2,7–9]. Force of infection can be calculated over time to study how transmission rate changes over the course of an outbreak and to compare outbreaks of the same disease in different places [2,6,10–12].

The progression of an epidemic can be characterized and compared through measures of burden, intensity and transmission rate [13,14]. We can quantitatively differentiate between epidemics with sharp peaks in case incidence that quickly burn through the susceptible population and more sustained, low-level transmission [6,15,16]. Instances when high case incidence coincides with a low force of infection may indicate the presence of imported cases [17]. Each of these epidemic metrics may be affected to a different extent by climate and population factors, in addition to country- and province-level features like existing transportation infrastructure and vector control resources [4,9,18,19]. Additionally, conditions that enable the establishment of a disease may differ from those that drive higher epidemic intensity following establishment [20].

Climate is a key determinant for whether mosquito-borne disease transmission can occur and the intensity of outbreaks because of its effects on vector dynamics. The primary vector of Zika in Latin America is Aedes aegypti, which also spreads chikungunya and dengue viruses [21]. Disease transmission can only occur if climate conditions are suitable for pathogen and vector survival and reproduction, while the intensity of transmission may be affected by how close humidity, temperature, and rainfall are to optimal climate conditions for vector and pathogen performance [2,9,22–27]. Humidity is positively associated with mosquito survival [23]. Temperature influences mosquito fecundity, development and survival, as well as factors contributing directly to transmission, including the extrinsic incubation period and mosquito biting rate [9,24,27–29]. These thermal responses are nonlinear, with optimal disease transmission expected at 29°C for viruses transmitted by A. aegypti based on mechanistic models parametrized from laboratory experiments [20,25]. Mosquitoes require water to complete their life cycle and breed, but the relationship between mosquito abundance and rainfall is variable [30–36]. The most notable reasons for this varying relationship are associated with extreme conditions, such as heavy rainfall that can kill and wash away larvae [37,38], and drought, which in certain regions promotes humans storing water in open containers that serve as breeding habitats [35,36]. Understanding how climate drives the emergence and intensity of Zika will be important for identifying regions where the disease is likely to become endemic, and, more generally, for predicting the potential trajectories of other mosquito-borne diseases that could emerge and re-emerge in the future, such as o’nyong nyong, Mayaro and yellow fever [1,19,39–41].

In this study, we estimate weekly force of infection for Zika from human case reports across Latin America to examine the role of climate in driving the emergence and intensity of the 2015–2017 outbreak. Specifically, we use the models to ask how climate and population variation affect (i) when and where epidemics occur, (ii) epidemic dynamics over time, and (iii) geographical variation in the intensity of epidemics. We use disease case reports and force of infection estimates in two modelling frameworks. First, we examine variation in force of infection over time within provinces to understand how strongly climate predicts the probability of weekly local transmission and the intensity of weekly force of infection. Then, we examine spatial variation in several epidemic metrics, including total human cases and mean force of infection, to understand how climate and population factors shape epidemics geographically.

2. Material and methods
(a) Epidemiological data
To investigate Zika transmission dynamics over time and space in Latin America, we downloaded and preprocessed publicly available human case data. We used weekly suspected and confirmed Zika cases between November 2015 and November 2017 for 156 provinces across six countries in Latin America (Colombia = 32 provinces, Dominican Republic = 32 provinces, Ecuador = 24 provinces, El Salvador = 14 provinces, Guatemala = 22 provinces and Mexico = 32 provinces) from the Centers for Disease Control and Prevention (CDC) Zika Data Repository, which includes epidemiological bulletins provided by each country’s ministry of health [42]. We excluded 14 provinces with fewer than ten weeks of case reporting or irregular reporting intervals, because those provinces provided insufficient data to observe meaningful trends in transmission (excluded provinces: Ecuador = eight provinces, Guatemala = two provinces and Mexico = four provinces). For the remaining provinces, we temporally interpolated case data for weeks with missing data and reporting errors by averaging cases from the weeks immediately preceding and following these intervals.

(b) Weather data
To investigate the effects of climate on Zika transmission, we downloaded weather data and calculated climate metrics with time lags relevant to diseases spread by the Aedes aegypti vector. We downloaded daily mean relative humidity, total rainfall, and mean, minimum and maximum temperatures from Weather Underground [43]. For each province, we used the weather station nearest to the province’s centroid that had the most complete climate record in the timespan corresponding to the case data. We excluded from our analyses an additional 15 provinces that had no nearby weather station reporting in the desired time period (excluded provinces: Colombia = six provinces, Dominican Republic = one province, Ecuador = two provinces, El Salvador = two provinces, Guatemala = two provinces and Mexico = two provinces), and further excluded 277 weeks with mean temperatures outside of the range of 0–40°C and rainfall values exceeding 250 mm, as these extreme values are likely to be weather station errors. Our analyses included the remaining 127 provinces with a total of 7109 weekly observations of epidemiological and weather data. We believe weather station data provides more accurate measurements of climate near populated areas (as weather stations are located at airports or operated for personal use) compared with modelled weather data such as the NOAA National Centers for Environmental Prediction Reanalysis data (NCEP; see electronic supplementary material, figure S1 for a comparison between data from Weather Underground and NCEP, a gridded global model based on satellite data), and therefore chose to conduct our analyses with weather station data with a reduced sample size due to missing weather stations in some provinces.

To investigate the spatio-temporal dynamics of transmission, we calculated lagged climate metrics (see electronic supplementary material, figure S2 for heatmaps showing variation in climate near populated areas (as weather stations are located at airports or operated for personal use) compared with modelled weather data such as the NOAA National Centers for Environmental Prediction Reanalysis data (NCEP; see electronic supplementary material, figure S1 for a comparison between data from Weather Underground and NCEP, a gridded global model based on satellite data), and therefore chose to conduct our analyses with weather station data with a reduced sample size due to missing weather stations in some provinces.
Table 1. Response variables for the spatio-temporal (ST) and spatial (S) models, with their corresponding thermal optima. $R^2$ values were calculated for the spatio-temporal models and pseudo-$R^2$ values were calculated for the spatial models using Nakagawa’s pseudo-$R^2$ for the mixed-effect local transmission model (which produces a marginal and conditional pseudo-$R^2$ and Nagelkerke’s pseudo-$R^2$ for the other spatial models.

| response variable | description | model type | thermal optimum (°C) | $R^2$/pseudo-$R^2$ | sample size |
|-------------------|-------------|------------|----------------------|--------------------|-------------|
| weekly local transmission | the likelihood that $\beta_t$ exceeded zero for a given week | ST | n.a. | 0.037 | 7109 |
| intensity of weekly force of infection | the magnitude of $\ln(\beta_t)$, given that it exceeded one | ST | n.a. | 0.011 | 2031 |
| local transmission | the likelihood that $\beta_t$ exceeded zero for any week | S | n.a. | marginal: 0.281 | 127 |
| | | | | conditional: 0.599 | |
| maximum force of infection | logged maximum value for $\beta_t$ in provinces with local transmission | S | 23.93 (95% CI: 22.02–26.90) | 0.534 | 114 |
| mean force of infection | logged mean value for $\beta_t$ in provinces with local transmission | S | 23.63 (95% CI: 22.20–25.49) | 0.596 | 114 |
| cumulative cases | total number of cases reported | S | 22.51 (95% CI: 20.57–30.68) | 0.330 | 127 |
| mean weekly cases | mean number of cases in weeks with any cases reported | S | 23.69 (95% CI: 19.57–26.12) | 0.348 | 127 |

climate by province over time), as humidity, temperature and rainfall influence transmission at a delay, which is commonly assumed to be between one and two months [30–32,34,35,44]. Specifically, we calculated humidity, mean temperature and temperature range (difference between the maximum and minimum temperatures observed) over a three-week period, lagged by six weeks from the week of case reporting (i.e. nine to seven weeks prior, following previous work) [20,45,46]. Similarly, we calculated the cumulative rainfall over a six-week period, lagged by three weeks from the week of case reporting (i.e. nine to four weeks prior), extending the window applied to lagged temperature period by three weeks in order to better capture the effects of water accumulation over time [47,48]. To compare differences in overall epidemic characteristics (e.g. total number of cases, mean force of infection, table 1; electronic supplementary material, figure S3) among provinces, we also calculated province-level mean humidity, mean temperature, temperature range and cumulative rainfall over the biologically relevant time lag described above.

(c) tSIR model

We estimated weekly force of infection by fitting time-varying susceptible–infectious–recovered (tSIR) models to the human case data [42]. We assumed a static population size because the human population did not change significantly over the course of the epidemic, and we assumed that Zika was introduced to a fully susceptible population since it had never been documented before in this region. Therefore, we set the initial susceptible population ($S_0$) as the most recent estimate of population (N) available from City Population as of June 2017, and modelled the susceptible population following Zika introduction as $S_t = S_{t-1} - I_t$ where $S$ indicates the susceptible population at time $t$ or $(t-1)$ and $I$ indicates the infected population at time $t$ [49]. We defined effective infectious individuals based on the modification of the tSIR model for vector-borne diseases developed by Perkins et al. [2] for chikungunya transmission because of similarities in the transmission ecology of their shared vector [2,34]. Using the infectious periods derived for chikungunya, we assumed that humans can transmit the parasite to mosquitoes for five days after reporting symptoms and that secondary human infections can arise from primary cases reported one to five weeks prior [50]. We calculated the effective number of infectious individuals ($I_t$) as a weighted sum of infectious individuals ($I_{t-k}$) within a five-week serial interval ($k = 5$). We used the same methods as the Perkins et al. [2] model for chikungunya transmission to solve for the weights ($\omega_k$) and substituted the appropriate serial interval distribution for Zika (a Gaussian distribution with mean 20 days and standard deviation 7.4 days) [2,51,52].

$$\tilde{I}_t = \sum_{n=1}^{k} \omega_n I_{t-n}.$$  \hspace{1cm} (2.1)

Individuals entered the recovered class after the five-week serial interval. We fitted tSIR models to case data for each province to calculate time-varying force of infection ($\beta_t$),

$$I_t = \beta_t \frac{R^\alpha_{1} S_{t-1}}{N}.$$  \hspace{1cm} (2.2)

Here, the mixing parameter $\alpha$ indicates homogeneous frequency-dependent contact rate between cases in each province. We fixed the mixing parameter due to the trade-off between capturing heterogeneity in transmission or mixing, a method commonly used in tSIR studies focused on transmission dynamics [10,53–56]. Given the similar transmission dynamics of chikungunya and Zika, we set the mixing parameter equal to 0.74, the value for chikungunya calculated in the Perkins et al. study [2,51]. By rearranging equation (2.2), we solved for $\ln(\beta_t)$ using the equation

$$\ln(\beta_t) = \ln(I_t) + \ln(N) - \ln(S_{t-1}) - \alpha \ln(I_t).$$  \hspace{1cm} (2.3)

(d) Spatio-temporal model

We investigated how strongly climate predicts the probability of weekly local transmission and the intensity of weekly force of infection by regressing force of infection against biologically relevant lagged and normalized climate factors. Since the transmission parameters ($\beta_t$) were zero-inflated, we fitted a two-step hurdle model that first predicts the probability that the force of
infection, $\beta_0$, will exceed zero in a given province ($i$) and week ($t$) (i.e. presence of local transmission), and then predicts the magnitude of logged force of infection, $\ln(\beta_0)$ (i.e. intensity), given that $\beta_0$ exceeds zero. To capture nonlinear relationships between transmission and temperature, we included a squared term for temperature [2,9,20].

We performed stepwise model selection using backward elimination, selecting the best-fit models for both steps of the hurdle model as those with the highest adjusted $R^2$, and further constrained the selection process to prohibit models that include a nonlinear temperature term without a linear temperature term. To account for autocorrelation between observations within each province over time, we fitted panel models with a two-way random effect:

step 1—presence/absence: $p(\beta_0 > 0) \sim c_{\beta_0} + \mu_i + \eta_t + \epsilon_{it}$

(2.4)

and

step 2—intensity given presence: $\ln(\beta_0) \sim c_{\beta_0} + \mu_i + \eta_t + \epsilon_{it}$.

(2.5)

The hurdle models include climate covariates ($\chi$), their corresponding coefficients ($c$), time-independent province random effect ($\mu$), province-independent random effect of week ($\eta$), and an observation-specific error term ($\epsilon$) accounting for time ($t$) and province ($i$). Regressions were conducted in R statistical software v. 3.4.3 using the glm function in the base package. We also fitted alternative fixed effect spatio-temporal models with month or month nested in province fixed effects.

(e) Spatial models
We examined the factors that drove broad-scale geographical differences in Zika transmission by using linear regressions to compare epidemic metrics with normalized climate and population factors. The response variables included epidemic metrics based on incidence and force of infection (presence of local transmission, logged maximum force of infection, logged average force of infection, cumulative cases, and mean weekly cases), where each response variable was aggregated to a single value per province (table 1; electronic supplementary material, figure S3). To account for additional variation among countries beyond climate and population factors, we included country as a fixed effect. Since some countries had local transmission in all provinces, we included country as a random effect in the spatial model for the probability of local transmission in a given province. For the population factor, we used the number of people living in the largest city in each province based on census results and official estimates as of June 2017 downloaded from City Population [49]. The mean value of each lagged climate covariate was taken for each province across the time that cases were reported. For each spatial model, we performed stepwise model selection using backwards elimination, selecting the best-fit models as those with the lowest AIC, and calculated pseudo-$R^2$ with Nakagawa and Shielzeth’s method for the model of the probability of local transmission and Cragg, Uhler and Nagelkerke’s method for remaining spatial models [58–61]. All regressions were conducted in R statistical software v. 3.4.3 using the glm function in the base package.

3. Results
(a) Epidemiological data and tSIR model
The duration and burden of Zika transmission and timing of epidemic peaks varied considerably both between and within countries (figure 1). Within the countries included in this study, Zika emerged earliest in El Salvador in November of 2015, and latest in Colombia, which first reported a Zika case almost one year later in January of 2016 (figure 1a). The weights for the serial interval were: $\omega_1 = 0.081, \omega_2 = 0.448; \omega_3 = 0.372; \omega_4 = 0.089; \omega_5 = 0.010$. Force of infection ranged from 0 to 15.409 cases per 100 000 people per week (model fit shown in electronic supplementary material, figure S4). In all countries there were weeks with no weekly local transmission ($\beta_0 = 0$), but high case incidence resulting from imported cases. All countries included in our analyses had at least one province with local transmission (figure 1b).

(b) Spatio-temporal model
The spatio-temporal hurdle model indicated that different climate factors were associated with the presence of weekly local transmission versus the intensity of weekly force of infection in a given province (electronic supplementary material, tables S1–S3). The best-fit model for the presence of weekly
local transmission included positive linear relationships with mean temperature and humidity and explained 3.7% of the variation in the likelihood of week to week transmission within provinces. The best-fit model for the intensity of weekly force of infection included negative linear effects of mean temperature and humidity, as well as a positive linear effect of rainfall. This model explained 1.1% of the variation in the intensity of weekly force of infection. Alternative fixed effects models with month or month nested in province fixed effects produced similar results (electronic supplementary material, tables S4–S6).

(c) Spatial models
The spatial models indicated that geographical variation in epidemics was driven by climate and human population sizes (figures 2 and 3; electronic supplementary material, tables S7–S11). There was considerable geographical variation in Zika presence and intensity within and among countries in Latin America (e.g. figure 2). We found a positive linear relationship between the presence of local transmission and humidity and mean temperature (figure 3). For all other epidemic metrics, we found a unimodal relationship with mean temperature (positive linear effect of mean temperature and negative quadratic effect of mean temperature; figures 3 and 4), although this relationship is not statistically significant in the models of cumulative cases and mean weekly cases. In provinces that had local transmission, mean force of infection peaked at 23.63°C (95% confidence interval: 22.20°C–25.49°C; figure 4b). The population of the largest city had a positive relationship with all epidemic characteristics aside from maximum force of infection (figure 3). Mean humidity had a slight positive linear relationship with cumulative cases, while rainfall had a slight positive relationship with average weekly cases (figure 3). All spatial models fitted well based on their pseudo-$R^2$ values (0.33–0.60) (table 1).

4. Discussion
Climate and population factors were strong drivers of geographical variation in Zika epidemics, with different factors influencing where local transmission occurred compared with the intensity of transmission. Relative humidity, temperature, temperature range and the population of the largest city were key determinants for whether local transmission occurred, and these factors could be used to determine regional likelihood for future Aedes aegypti transmitted diseases. Both the spatio-temporal and spatial models for the presence of local transmission included a positive linear
Figure 4. Nonlinear relationship between temperature and epidemic characteristics. Plots showing the relationship between mean temperature and (a) logged maximum force of infection and (b) logged mean force of infection. The model prediction is indicated by the blue lines, and the 95% confidence interval is indicated by the red dashed lines. The grey shaded region indicates the 95% confidence interval for the thermal optimum. The F-statistic for the nonlinear effect of temperature and its p-value are given in the inset. The response variables are scaled between zero and one. (Online version in colour.)

The 2015 to 2017 Zika outbreak provided an opportunity to investigate how population size and climate affect epidemic dynamics over time and space in a previously unexposed population. The results provide valuable insight into where Zika is likely to become endemic and how future outbreaks transmitted by *Aedes aegypti* could spread. Specifically, given that provinces with greater populations in their largest cities had longer and more intense outbreaks, regions with larger urban population sizes that also have suitable climate conditions for most of the year are most likely to sustain endemic Zika transmission. However, it is important to carefully consider these results could apply to other regions, especially in places where Zika may be transmitted by other mosquito species, such as *Aedes africanus*, which exhibit different responses to climate [66]. Zika epidemics in Latin America were characteristically different across countries: some regions experienced large epidemics that spread quickly while others experienced low levels of sustained transmission (figure 1). We would expect similar epidemic metrics to characterize other mosquito-transmitted diseases that could emerge and re-emerge in the future, such as o’nyong nyong, Mayaro and yellow fever [1,19,39–41]. Given this climate-driven geographical variation in
epidemics, we would expect climate change to alter patterns in transmission for emerging and re-emerging mosquito-borne diseases in the future.

Data accessibility. All data and code are accessible in GitHub repository: https://github.com/mjharris95/Climate-Drivers-of-Zika.

Authors’ contributions. E.A.M. and J.M.C. conceived of the project; M.H. acquired data and conducted analyses; M.H., J.M.C. and E.A.M. interpreted data and wrote the manuscript.

Competing interests. All authors declare that there are no competing interests.

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