Spatial Dynamics of Chikungunya Virus, Venezuela, 2014

Erley Lizarazo,1 Maria Vincenti-Gonzalez,1 Maria E. Grillet,2 Sarah Bethencourt, Oscar Diaz, Noheliz Ojeda, Haydee Ochoa, Maria Auxiliadora Rangel, Adriana Tami2

Since chikungunya virus emerged in the Caribbean region in late 2013, ≈45 countries have experienced chikungunya outbreaks. We described and quantified the spatial and temporal events after the introduction and propagation of chikungunya into an immunologically naive population from the urban north-central region of Venezuela during 2014. The epidemic curve (n = 810 cases) unraveled within 5 months with a basic reproductive number of 3.7 and a radial spread traveled distance of 9.4 km at a mean velocity of 82.9 m/day. The highest disease diffusion speed occurred during the first 90 days, and space and space–time modeling suggest the epidemic followed a particular geographic pathway with spatiotemporal aggregation. The directionality and heterogeneity of transmission during the first introduction of chikungunya indicated existence of areas of diffusion and elevated risk for disease and highlight the importance of epidemic preparedness. This information will help in managing future threats of new or reemerging arboviruses.

Chikungunya, a reemerging mosquito-borne viral infection, is responsible for one of the most explosive epidemics in the Western Hemisphere in recent years. Since its introduction in the Caribbean region at the end of 2013, chikungunya virus (CHIKV) rapidly expanded within a year to most countries of South, Central, and North America (1,2). CHIKV belongs to the genus Alphavirus (Togaviridae), first isolated in Tanzania during 1952 (3). Its sylvatic (enzootic) cycle in Africa involves nonhuman primates; the virus is transmitted by an ample range of forest-dwelling Aedes spp. mosquitoes (4). Within the urban (human) cycle across Asia, the Indian Ocean, and the Americas, CHIKV is transmitted by Aedes aegypti and Ae. albopictus mosquitoes (5–7). Most (72%–93%) infected persons develop symptomatic disease characterized by fever, rash, and incapacitating arthralgia, progressing in 42%–60% of patients to chronic, long-lasting relapsing or lingering rheumatic disease (8,9). The lack of population immunity to CHIKV in the Americas alongside the ubiquitous occurrence of competent Ae. aegypti mosquitoes and human mobility may explain the rapid expansion of CHIKV across the Americas; cases doubled each month during the epidemic exponential phase (10,11). At the end of 2014, >1 million suspected and confirmed cases, including severe cases and deaths, were reported in 45 countries and territories; this figure reached almost 3 million cases by mid-2016 (12). The real number of cases is most likely higher because of misdiagnosis with dengue virus (DENV) infection and underreporting.

In Venezuela, the first official imported chikungunya case was reported in June 2014, and local transmission followed soon thereafter. Chikungunya quickly spread, causing a large national epidemic affecting the most populated urban areas of northern Venezuela, where DENV transmission is high. Given the paucity of official national data, epidemiologic inference was used to estimate the number of cases. Although nationally the disease attack rate was estimated at 6.9%–13.8% (13), the observed attack rate in populated urban areas was ≈40%–50%, comparable to those reported in the Dominican Republic (14) and Asia and higher than those in La Reunion (15,16).

The rapid expansion and worldwide spread in the last decade make CHIKV one of the most public health–relevant arboviruses (17). With the reemergence of other arboviruses, new large-scale outbreaks in the near future seem likely (18). Clarifying and quantifying the introduction and propagation range in space and time of the initial epidemic wave of chikungunya within the complex urban settings of Latin America will shed light on arboviral transmission dynamics and help in managing future threats of new or emerging arboviruses operating under similar epidemiologic dynamics. We characterized the epidemic wave of chikungunya in a region highly affected by the 2014

1These authors contributed equally to this article.
2These authors contributed equally to this article.
outbreak in Venezuela. To this end, we described the spatial progression of the epidemic using geographic information systems (GIS), quantified the global geographic path that CHIKV most likely followed during the first 6 months of the epidemic by fitting a polynomial regression model (trend surface analysis), determined the general direction and speed of the propagation wave of the disease, and identified the local space–time disease clusters through spatial statistics.

Materials and Methods

Study Area
Carabobo State is situated in the north-central region of Venezuela (Figure 1). It is one of the most densely populated regions (19).

Study Design and Data Collection
To determine the spatiotemporal spread of the 2014 chikungunya epidemic at local and global scales, we conducted a retrospective study of patient and epidemiologic data collected through the national Notifiable Diseases Surveillance System (NDSS). Suspected chikungunya was diagnosed in 810 persons of all ages by their physicians; these patients were reported through the NDSS to the epidemiologic department of the Regional Ministry of Health of Carabobo State. Patients suspected of having chikungunya were those with fever of sudden onset, rash, and joint pain with or without other influenza-like symptoms. Patients who attended public or private healthcare centers across Carabobo State municipalities were included in this study.

Patient data were obtained for June 10–December 3, 2014 (epidemiologic weeks 22–49), coinciding with the Venezuela chikungunya outbreak. Data corresponding to the first visit of the patients to a healthcare center were included and comprised patient address, clinical manifestations, and epidemiologic risk factors. This information was entered in a database, checked for consistency, and analyzed anonymously. We defined the index case as the first chikungunya patient reported by the NDSS within this region.

Temporal Dynamics of CHIKV Spread
We described the growth rate of the disease by plotting the cumulative cases per epidemiologic week and fitted a
logistic curve after examining the shape of the epidemiologic curve (Appendix Figure 1, https://wwwnc.cdc.gov/EID/article/25/4/17-2121-App1.pdf). We estimated the average number of secondary cases resulting from a primary case in a completely susceptible population—the epidemic’s basic reproductive number ($R_0$)—from the initial phase of the epidemic using the exponential growth method (20) and then calculated a real-time estimate of $R_0$, called $R_1$ (21,22), to explore the time-varying transmissibility of chikungunya (Appendix).

**Spatiotemporal Trend of the Epidemic Wave of Chikungunya**

We georeferenced the address of every patient into a GIS so that the $X_i$ (east–west) and $Y_i$ (north–south) coordinates of each chikungunya case were derived. We drew the weekly spatial progression of the 810 reported cases with respect to the index case in a map. To assess the spreading pattern before the epidemic reached the steady (plateau) state (Figure 2), we selected cases that occurred 0–125 days (up to epidemiologic week 40) after the index case. Within this time range, the case notification rate maintained a sustained growth.

To explore the general spatial trend of chikungunya cases (or the movement of the epidemic wave of infection) across the study area, we developed a map of time of disease spread using trend surface analysis, a global surface fitting method (Appendix). We created the variable `time` (in days) using the symptom onset date from the index case as the baseline date across the 810 case localities; that is, `time` ($X_i$, $Y_i$). Thus, `time` is considered the number of days elapsed between the appearance of a case in a specific locality $Z_i$ and the index case. We used results of the trend surface analysis to generate a contour map or smooth surface; each contour line represented a specific predicted time period in this urban landscape setting since the initial invasion of the virus. The local rate and direction of the spread of infection was estimated as the directional derivative at each case using the trend surface analysis fitted model to obtain local vectors that depicted the direction and speed (inverse of the slope along the direction of the movement) of infection propagation from each locality in $X$ and $Y$ directions. In addition, we used kriging, a local geostatistical interpolation method, to generate an estimated continuous surface from the scattered set of points (i.e., `time`) with $z$ value to better capture the local spatial variation of chikungunya spread across the urban landscape (23). We used ordinary kriging to predict values of the time period since the initial invasion of the virus. We selected the model with the best fit out of 3 theoretical variogram models tested by cross-validation to predict the values at unmeasured locations and their associated errors (Appendix).

We also obtained an empirical basic baseline rate of disease spread to quantify the observed velocity for each case $z_i$ directly from the data by measuring the linear distance (meters) of case $Z_i$ to the index case and then dividing it by the time in days that elapsed since the index case was reported. We assessed differences between velocities by using the Kruskal-Wallis test, a nonparametric method to test differences between groups when these are nonnormally distributed (24).

Finally, to identify general space–time clusters of chikungunya transmission, we performed a Knox analysis (25), and to identify interactions at specific temporal intervals, we used the incremental Knox test (IKT) (26). For general space–time clusters we selected critical values of 100 m (`distance`) and 3 weeks (`time`) after multiple distance and time windows testing (Appendix Table 2). Our selection was based on the *Aedes* mosquito flight range and the maximum duration of the intrinsic and extrinsic incubation periods of the virus, respectively (27,28). Upon identification of the cluster, we calculated the distance between the first case of a cluster ($C_i$) and the cases within the cluster $Z_i$, considering this distance as a measure of virus disease spread. For interactions at specific temporal intervals, we used the IKT in an exploratory mode over the time intervals from 1 day to 31 days and space distances from 25 m to 500 m (Appendix). We conducted spatial analyses using R software (The R-Development Core Team, http://www.r-project.org) and ArcGIS version 10.3 (ESRI Corporation, https://www.esri.com) using the Spatial Analyst Toolbox and generated maps with Quantum GIS 2.14.3 Essen (QGIS Development Team GNU—General Public License, https://www.qgis.org) software. Space-time (K Knox) analysis was performed using ClusterSeer 2.0 (Terraseer, https://www.biomedware.com/software/clusterseer).

**Ethics Statement**

Data were analyzed anonymously, and individuals were coded along with the information of address with a unique numeric identifier. The epidemiologic department of the
Regional Ministry of Health of Carabobo State approved the study.

**Results**

**Temporal Dynamics of CHIKV Spread**

A total of 810 suspected chikungunya cases were reported in Carabobo State in 2014 during epidemiologic weeks 22–49 (28 weeks), representing the first introduction and propagation of the virus in the north-central region of Venezuela. The index case was an imported case (in a returning traveler from the Dominican Republic) in epidemiologic week 22 in the north-central zone of the capital city (Valencia) (Figure 1). The index case was followed by the other imported cases and soon after by locally transmitted cases.

The cumulative cases during epidemiologic weeks 22–49 followed a logistic growth (Appendix Figure 1; $R = 0.99, n = 810; p<0.05$). The reported cases displayed a characteristic epidemic curve with a single wave and peaked at epidemiologic week 33, eleven weeks after the index case (Figure 2). The epidemic takeoff occurred at epidemiologic week 31 (i.e., 9 weeks after the index case). The total duration of the outbreak was ≈28 weeks; however, the main epidemic curve lasted ≈3 months, from epidemiologic week 30 until epidemiologic weeks 43–44. The initial global growth rate of the epidemic was 0.53 cases per week, and $R_0 = 3.7$ (95% CI 2.78–4.99) secondary chikungunya cases per primary case (epidemiologic weeks 22–31). We obtained comparable results when we calculated the instantaneous reproductive number ($R_t = 4.5$, 95% CI 2.4–7.1) during the epidemic peak. Beginning with epidemiologic week 34, $R_t$ values fell below 1, and they gradually decreased from there onward (Appendix Figure 2).

**Spatiotemporal Distribution of the Chikungunya Epidemic**

The chikungunya outbreak progressed chronologically and spatially through Carabobo State (Figure 3; Video, https://wwwnc.cdc.gov/EID/article/25/4/17-2121-V1.htm). The cases reported in Valencia during the first 6 weeks were located in the central area of the city close to the index case, whereas a few cases were reported in the southwestern part of Valencia and in other small urban towns of Carabobo (Figure 3, panel A). The first autochthonous case occurred during this interval in the south-central area of Valencia, relatively close to the index case (Figure 3, panel A). During epidemiologic weeks 28–31, the number of reported cases increased in parishes around the autochthonous case (Figure 3, panel B). During epidemiologic weeks 32–35, the number of cases exploded exponentially, and the disease spread rapidly throughout the capital city and surrounding smaller urban centers (Figure 3, panel C). New cases were actively reported during 8 consecutive weeks (Figure 3, panels C, D) to later decrease from epidemiologic week 40 to epidemiologic week 49 (Figure 3, panels E, F). The epidemic progressed in 2 directions (movement axes) in the region: a north–south direction and a northeastern and southwestern direction. Both shifts consistently overlapped with the populated centers of the region and the main traffic routes (motorways and main roads).

![Figure 3. Spatial and temporal spread of chikungunya epidemic, Carabobo state, Venezuela, June–December 2014. Time is presented at epidemiologic week intervals as follows: A) weeks 22–27; B) weeks 28–31; C) weeks 32–35; D) weeks 36–39; E) weeks 40–45; F) weeks 46–49. Red circles indicate the appearance of new cases for the given interval; blue indicates the cumulative cases in prior intervals. Light yellow lines depict the road system of the area of study; light gray areas represent the populated areas (urban centers) within the parishes. Yellow star indicates index case; green diamond indicates first autochthonous case.](https://wwwnc.cdc.gov/EID/article/25/4/17-2121-V1.htm)
Figure 4, panel A, depicts the general direction and propagating wave of disease derived from the trend surface analysis. Contour lines that are far apart indicate that the epidemic diffused quickly through the area, whereas lines that are closer together show a slower progression. The direction of diffusion is also given by the edges of the contour lines. The model located the wave of disease dispersal in the central part of the region and included the index case and autochthonous case. The bulk of the outbreak unfolded within 90 days, spreading mainly to the southwestern and northern parts of the capital city. During this time, the maximum radial distance traveled was 9.4 km. A slower diffusion was predicted toward the northeast and southern part of the region. However, the limitation of the method resulting from edge effects determines that the best area for prediction is the central one.

To visualize the local diffusion of CHIKV at each location, we drew the vector field across the modeled surface (Figure 4, panel A). Overall, the model confirms the previous observation of a general trend or corridor of diffusion of chikungunya cases southwest and northeast of the capital city within the first 80 days. After 90 days, the epidemic wave varied its direction and magnitude by location. Although agreeing with the general pattern shown by the trend surface analysis, the resulting kriging Gaussian (selected) model interpolation surface (Figure 4, panel B;
Appendix Table 1) predicts a more heterogeneous spread pattern of chikungunya cases by matching the patchy (uneven population density) distribution of human neighborhoods and the road network. In addition, kriging identified a faster propagation of the epidemiologic wave at the southwestern and eastern areas where the model showed its best fit (Appendix Figure 3, panel A) and a slower movement to the northeastern and south-central areas than estimated by the trend surface analysis.

We calculated the virus diffusion velocities for each parish through the empirical method (Table). The mean velocity of disease spread across the state was 82.9 m ± 53.6 m/day, and overall, the pattern of diffusion of CHIKV was highest in the suburban and rural settlements near the capital city. However, the observed velocities varied significantly by location (n = 735; p<0.05). For instance, the parishes at the center of the capital (San Jose, Catedral, Candelaria, San Blas, Santa Rosa) showed velocities <60 m/day, whereas in the remaining localities, including both rural and suburban towns, the speed was >60 m/day. The maximum velocity of the outbreak was 483 m/day, measured south of the capital.

### Spatiotemporal Clusters of the Epidemic Wave

Results after multiple space and time parameters testing showed that core clusters remained similar through time (Appendix Figure 4), and the relative risk (RR) within the clusters remained important (RR >1.5) up to 3 weeks (Appendix Figure 5). Using selected critical values, we identified 75 general space–time clusters using Knox analysis (Appendix Table 3; Appendix Figure 6, panel A). These clusters included at least 2 space–time-linked cases and a total of 205 (27.9%) cases that showed a space–time relation. The major accumulation of clusters occurred in the southern and southwestern parts of the capital. The earliest cluster (cluster 7; Figure 5) was located in the west-central parts of the capital and comprised 3 cases, including the index case. From this cluster, the average distance from each case to the index case was 32 m, and the cases were reported within 25 days after the index case. In addition, the major cluster (cluster 57, 12 cases) was located in the west-central area of the capital 4 km from the index case (Figure 5). The cases belonging to this cluster occurred within 9 days (1.3 cases per day); these cases occurred an average of 70 days (range 69–77 days) after the index case (Appendix Table 3). The median time between the first notified case (symptom onset) and the last case within a cluster was 9 days (range 3–18 days). Furthermore, the average distance between cases within the clusters was 75.2 m ± 25.6 m (range 110.6–39.2 m) (Appendix Table 4). Furthermore, the baseline velocity in Carabobo State was similar to the average velocity within the clusters (69.9 ± 34.4 m/day). These results agree with IKT findings, where the temporal intervals with the strongest spatial clustering and RR occurred at 1–7 days and 25–150 m (Appendix Figures 7, 8).

### Discussion

We described and quantified the spatial and temporal events that followed the introduction and explosive propagation of CHIKV into an immunologically naive population living in the urban north-central region of Venezuela during 2014. The main epidemic curve developed within 5 months, with a maximum value of the estimate of $R_0 = 3.7$ by epidemiologic week 12. The speed of disease diffusion was greatest during the first 90 days, and the spatial spread was heterogeneous following mostly a southwest spatial corridor at a variable local rate of diffusion across the

### Table. Average velocities of chikungunya virus spread across Carabobo state, Venezuela, 2014

| Civil parish          | No. cases | Mean (95% CI) | SD  | Minimum | Maximum | Location* |
|-----------------------|-----------|---------------|-----|---------|---------|-----------|
| Candelaria            | 29        | 39.4 (33.5–45.2) | 15.3 | 17      | 96      | Central   |
| Catedral              | 11        | 28.8 (22.4–35.3) | 9.5  | 15      | 50      | Central   |
| Ciudad Alianza        | 1         | 146.7         | Not applicable | 147 | 147 | East-southeast |
| El Socorro            | 6         | 47.2 (13.5–80.9) | 32.1 | 25      | 98      | South-southwest |
| Guacara†              | 4         | 206.2 (135.1–447.6) | 151.7 | 98      | 430     | East-northeast |
| Guigue‡               | 5         | 256.7 (151.7–361.8) | 84.6 | 163     | 344     | Southeast |
| Independencia†        | 6         | 206.7 (138.8–274.5) | 64.7 | 138     | 310     | South-southwest |
| Los Guayos            | 42        | 115.1 (105.3–124.9) | 31.4 | 52      | 176     | East-southwest |
| Miguel Peña           | 228       | 80.6 (75.3–86.0) | 40.6 | 21      | 483     | South     |
| Naguanagua            | 41        | 85.9 (77.3–94.6) | 27.3 | 47      | 174     | North     |
| Rafael Urdaneta       | 84        | 87.2 (79.5–94.8) | 35.3 | 23      | 186     | Southeast |
| San Blas              | 27        | 43.6 (39.0–48.3) | 11.7 | 21      | 62      | Central   |
| San Diego             | 35        | 73.3 (63.5–83.1) | 28.5 | 41      | 150     | North-northeast |
| San Jose              | 68        | 27.6 (21.3–34.0) | 26.2 | 0       | 202     | North-central |
| Santa Rosa            | 70        | 58.4 (55.9–60.9) | 10.4 | 35      | 97      | Central   |
| Tacarigua‡            | 6         | 197.0 (147.7–246.3) | 47.0 | 149     | 259     | South-southwest |
| Tocuyito†             | 70        | 149.8 (137.2–162.4) | 52.8 | 61      | 365     | Southwest |
| Yagua‡                | 2         | 111.0 (3.9–225.4) | 12.7 | 102     | 120     | East-northeast |
| Total                 | 735       | 82.9 (79.0–86.7) | 53.6 | 0       | 483     | Entire state |

*Location refers to relative locations from the center of the capital city, Valencia.
†Suburban settlements.
‡Rural settlements.
The radial spread traveled distance was 9.4 km at a mean velocity of 82.9 m/day. The chikungunya epidemic showed spatiotemporal aggregation predominantly south of the capital city, where conditions for human–vector contact are favorable.

The temporal dynamics here described, $R_0$ and its time variable form $R_t$, suggest high transmissibility of CHIKV in this population. These results agree with previous CHIKV introductions into naive populations (29–31) and with the 2014 predicted values for the mid-latitude countries ($R_0 = 4–7$) of the Americas (31). High values of $R_0$ are also described during first introduction outbreaks of other Aedes mosquito–borne pathogens, such as DENV in Chile ($R_0 = 27.2$) (32) and Zika virus in Brazil ($R_0 = 1.5–6$) (33) and French Polynesia (34). Yet, overall $R_0$ estimates for dengue are ≈2–6 (35). The similarity between the $R_0$ of CHIKV, DENV, and Zika virus infections, all transmitted by the same main vector, the Ae. aegypti mosquito, strongly suggests that the major factor driving the exponential increase of the epidemic curve of arboviruses in naive populations is the transmission efficiency of the vector.

Spatially, trend surface and kriging analyses showed a primary wave of disease spread within the first 80 days in the most likely area of transmission (the southwestern center of Valencia), whereas a second wave at 90 days showed the spread of cases toward the southern, western, and northern areas. This sequential pattern is similar to that of dengue, where transmission within neighborhoods most likely is driven by mosquito presence or abundance and/or short-distance movement of viremic hosts (36–38), whereas long-distance dissemination is probably generated by human mobility patterns through main roads and motorways. Both movements powerfully affected disease transmission (39,40). Moreover, population density modulates the chance of vector–host contact, whereas long-distance dissemination is probably generated by human mobility patterns through main roads and motorways (39,40). Population density modulates the chance of vector–host contact (30,41), a fact reflected in the variation of calculated velocities across different spatial points and the increased diffusion speed of the epidemic toward the southernmost populated area.

Although CHIKV was introduced into a naive population in Venezuela, the distribution of cases was not random but aggregated into 75 significant space–time clusters, indicating an increased likelihood of vector–host contact. The area with most clusters, the southern part of Valencia city, is characterized by densely populated neighborhoods, lower socioeconomic status, and crowded living conditions. Similar factors increased the risk for dengue transmission and clustering (hot spots) in highly endemic urban areas of Venezuela (42). Poverty and human behavior fostering potential mosquito breeding sites (such as storing water at home) were linked with a greater risk for dengue (42,43). In Venezuela, long-lasting deficits in public services, such as frequent and prolonged interruptions in water supply and electricity, have become regular in recent years. These inadequacies have obliged residents to store water, maintaining adequate breeding conditions for Aedes vectors during the dry season and throughout the year (44). During the CHIKV epidemic, the proportion of houses infested with Aedes larvae/pupae (house index) in Venezuela was >20% (45). The World
Health Organization recommends a house index <5% for adequate vector control (46).

In our study, the average distance among cases within chikungunya clusters was 75 m, which coincided with the reported flying range of urban Aedes aegypti females during mark-release-recapture studies (37,47). Aedes aegypti females have been reported to visit a maximum of 3 houses in a lifetime while not traveling far from their breeding sites (48,49). Thus, the distance traveled by the vector and the number of possible host encounters with an infected vector cannot explain the entire disease epidemic spread. Other factors, such as movement of viremic hosts, a widely distributed vector, and the lack of herd immunity, may play a role, as for DENV, in long-range spread (37).

The lack of entomologic data and estimates of human movement limit our study. We expect that our estimates based on epidemiologic records are accurate because chikungunya is symptomatic in >80% of cases. Likewise, surveillance in Venezuela is based on symptomatic patient reporting by treating doctors.

Our analysis suggests that the epidemic of chikungunya in Venezuela followed a determined geographic course. This propagation was potentiated south and southwest of the study area. Chikungunya is now established in Venezuela, along with other Aedes mosquito–borne infections, such as dengue and Zika. However, further epidemics of these and other reemerging arboviruses (i.e., Mayaro virus [18,50]) are likely to arise. The insights gained in our study will help identify and predict future epidemic waves of upcoming vectorborne infections and quickly define intervention areas and improve outbreak preparedness response in Venezuela and countries with similar settings.

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About the Author
Mr. Lizarazo is a PhD candidate at the University Medical Center Groningen. His research interests are vectorborne diseases and molecular epidemiology. Dr. Vincenti-Gonzalez is a postdoctoral researcher at the University Medical Center Groningen. Her research interests are vectorborne diseases and spatial–temporal dynamics of infectious diseases.

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Address for correspondence: Adriana Tami, Department of Medical Microbiology, University Medical Center Groningen, Hanzeplein 1 (HPC EB80), 9713 GZ Groningen, the Netherlands; email: a.tami@umcg.nl
Spatial Dynamics of Chikungunya Virus, Venezuela, 2014

Appendix

1. Materials and Methods

1.1. Estimating the Reproductive Number (R₀)

For new emerging infectious diseases, the value of the reproductive number R₀ can be inferred indirectly from the initial epidemic phase by estimating the exponential epidemic growth rate (r) of new observed infections and relating these parameters to the generation time of infection (Tg) through the following equation (1).

\[ R = \frac{1}{M(-r)} \]

where M is the moment generating function of the disease generation time distribution. A generation time distribution for chikungunya (CHIK) was defined using a gamma distribution with a mean of 1.86 weeks and a standard deviation of 0.05 weeks. This includes both the human and vector infection cycle, by assuming a short mosquito infection lifespan case as reported before by Boëlle et al. (2). For this method we applied the ‘R₀’ package version 1.2–6 developed by Boëlle and Obadia (3) (The R-Development Core Team, http://www.r-project.org).

1.2. Estimating the Effective Reproductive Number (R_t)

Given that the behavior of the force of chikungunya virus (CHIKV) infection through time was unknown, we calculated a real-time estimate of the basic reproductive number of the disease, that is the effective reproductive number at time t (R_t) as originally proposed by Nishiura et al. (4). We then explored the time-varying transmissibility using the Rt series derived following the methodology of Coelho and Carvalho (5). Hence, R_t was estimated as

\[ R_t = \left( \frac{Y_{t+1}}{Y_t} \right)^{1/n} \]
where $Y_t$ and $Y_{t+1}$ are taken to be the number of reported disease cases for a particular time $t$ and $t+1$, respectively, while $n$ defines the ratio between the length of the reporting interval and the mean generation time of the disease. The reporting interval was defined as the duration of an epidemiologic week (7 days), while the generation time was assumed to be of 2 weeks as established above. To run the calculation, we applied the R code developed by Coelho and Carvalho (5) available on the GitHub repository at https://github.com/fccoelho/paperLM1 (The R-Development Core Team).

1.3. Trend Surface Analysis (TSA) and Local Vectors of Direction and Speed of Infection

TSA methodology consists in fitting, through the method of least squares, a function in a multiple-regression–like procedure where the response variable, in this case, *time*, is expressed as a polynomial function of geographic coordinates $(X_i, Y_i)$ of individual case-points i.e., *time* = $f(X, Y)$, a model known as a polynomial regression (6). The order of the polynomial chosen as the best fit-model or the best polynomial equation will determine the shape of the curve or surface. Here, we used a third-order polynomial. The variable *time* (in days) was created using the symptoms onset date from the index case (IC) as the baseline date across the 810 case localities, this is, *time* $(X_i, Y_i)$. Thus, *time* is considered as the number of days elapsed between the appearance of a case in a specific locality $Z_i$ and the IC. Results of the TSA were used to generate a contour map or smoothed surface, with each contour line representing a specific predicted time-period in this urban landscape setting since the initial invasion of the virus. Finally, we proceeded to estimate the local rate and direction of the spread of infection as the directional derivative at each case using the TSA fitted model to obtain local vectors that depicted the direction and speed (inverse of the slope along the direction of the movement) of infection propagation from each locality in $X$ and $Y$ directions. To this end, we calculated partial differential equations of *time* with respect to the $X$- and $Y$-coordinates ($\partial{\textit{TIME}}/\partial{X}$ and $\partial{\textit{TIME}}/\partial{Y}$) to obtain local vectors that depicted the direction and speed (inverse of the slope along the direction of the movement) of infection propagation from each locality in $X$ and $Y$ direction. The resultant vector for each case will represent, in turn, the overall velocity (in m/day) and direction of disease spread in each point. The set of vectors were assembled in a vector field and overlapped over the fitted surface to visualize the pattern of local spread of the virus along the urban landscape. TSA has been previously used to study pathogen dispersal processes in space and time (7). Further details of this methodology can be found in Moore (8)
and Adjemian et al. (9). All the analyses were carried out in R software (The R-Development Core Team). Maps of time contours and vectors were generated in the ArcGIS software (v.10.3, ESRI Corporation, Redlands, CA), while general maps were constructed using Quantum GIS 2.14.3 Essen (GNU—General Public License).

1.4. Kriging Interpolation

Kriging is a local interpolation method based on a set of linear regressions that determine the best combination of weights to interpolate the data points by minimizing the variance as derived from the spatial covariance in the data (10). The weights are based on the spatial parameters of a theoretical variogram model such that sampling locations within the spatial range (close distances) of influence has more weight on the predicted value than the distant locations. Although kriging and trend surface analysis share some features (i.e., to describe the general spatial trend), the local interpolation performed by kriging shows an enhanced picture of the local spatial pattern given that the kriged values are very close to the observed ones. Kriging analyses (and resulting surface maps) were carried out in the Geostatistics tool from the ArcGIS software (v.10.3, ESRI Corporation).

1.5. Spatiotemporal Analysis

Even though CHIKV was introduced into a naïve population, i.e., the individuals had a similar immunological likelihood of becoming infected, we wanted to assess the hypothesis of heterogeneity during disease transmission. In this sense we aimed to find whether aggregation of cases was present during the CHIK epidemic and if the likelihood of being infected could have varied depending on space and time distances. Thus, to identify general space-time aggregation (clusters) of CHIK transmission during the whole epidemic (28 weeks) we performed the Knox analysis (11) and the incremental Knox test (IKT) proposed by Aldstadt in 2007 (12) to identify linked transmission events.

1.5.1. Knox Test

This method measures potential space–time interactions by analyzing pairs of cases that belong to a particular space (distance) and time (days) window. This intuitive method provided simplicity and promptness (13). Yet, the Knox test requires prior selection of a “critical” time and distance to classify whether the pairs are close in space, or in time, or both. The test statistic, $X$, is the number of pairs of cases that are close in both space and time, and its calculated as
\[ X(s, t) = \sum_{i=1}^{N} \sum_{j=1}^{i} a_{ij}^s a_{ij}^t \]

where \( s \) and \( t \) being the selected spatial and temporal distances, \( N \) is the number of cases, and the pair of cases are represented by \( i \) and \( j \). The exact p value is obtained by the Monte Carlo procedure.

To select the “critical” value of space and time for our analysis, we performed a series of repetitions of the Knox method varying the time windows from 1 to 4 weeks (30 days in total) and the space window ranging from 25 to 200 m. Such analyses were made using the software ClusterSeer 2.0 (Terraseer, Ann Arbor, MI), which provides the graphical output of the space–time interactions (10,000 Monte Carlo iterations). The relative risk (RR) of each space and time window was calculated according to Tran et al. (14); where the RR is considered to be the ratio between the observed number of pairs of cases found at the space-distance \( s \) (in meters) and the time-distance \( t \) (in weeks) and the number of expected pairs of cases found at these same distances.

1.5.2. Incremental Knox Test

The incremental Knox test (IKT) is similar to other tests of the general hypothesis of space–time dependence (cases close to one another are much more likely to interact than cases far apart). However, this technique tests the interaction at specific time intervals rather than the more general space–time interaction hypothesis. The IKT examines consecutive links in the chain of transmission by identifying significant clusters in determined space and time intervals. The test assumes that cases that are nearer together than would be expected in the absence of an infectious process belong to one similar linked event of transmission (12).

Therefore, the IKT was used to understand in which time interval the clusters of cases of CHIK belonging to the same chain of transmission occurred helping to understand the linked transmission processes occurring in certain temporal span. The interval Knox statistic is formulated as

\[ IK(s, t) = \sum_{i=1}^{N} \sum_{j=1}^{i} a_{ij}^s b_{ij}^t \]
Were \( s \) and \( t \) are the selected spatial and temporal distances, \( N \) is the number of cases, and the pair of cases are represented by \( i \) and \( j \). When the cases \( i \) and \( j \) are time interval \( (t) \) apart \( b_{ij}^t = 1 \). The Monte Carlo procedure with 10,000 iterations was used to construct reference distribution for IK (Z values) and the test results are also reported as the epidemiologic notion of excess of risk (details of this methodology can be found in [12]). over the time intervals from 1 to 31 days, and space distances from 25 to 500 m (selected distances in meters: 25, 50, 75, 100, 125, 150, 175, 200, 300, 400, 500).

2. Results

From surveillance data collected during the months following the introduction of CHIKV, the dynamics and timing of the 810 chikungunya reported cases were studied. Appendix Figure 1 depicts the distribution of cases and cumulative cases along the 28 weeks of the chikungunya epidemic. Since the detection of the index case (IC) in June of 2014, the north-central region of Venezuela experienced a continuous reporting of chikungunya cases. During the first 9 weeks (epidemiologic week [EW] 21-EW 29), a low number of cases were reported. After EW 30 cases increased rapidly with the exponential growth of the epidemic being observed between EW 30 and EW 33. The cumulative cases during the EW 22–49 followed a logistic growth (Appendix Figure 1: \( R = 0.99, n = 810, p < 0.05 \)) reaching the plateau at EW 44 (787 cases). The total growth rate estimated from the logistic fitted curve was 0.53 cases per EW.

2.1. Reproductive Number (\( R_0 \)) and Effective Reproductive Number (\( R_t \))

To better understand the CHIK transmission dynamic, the basic reproductive number (\( R_0 \)) was calculated during the exponential growth of the epidemic, that is during (EW 21–EW 33). During these first 12 weeks, the maximum value of \( R_0 \) reached was equal to 3.7 secondary chikungunya cases per primary case. Furthermore, we estimated the effective reproductive number (\( R_t \)) with a reporting interval of 1 week, to assess changes of \( R_0 \) through time. The curve of \( R_t \) values fluctuates in time as shown in Appendix Figure 2, where the maximum value of \( R_t \) obtained was 4.7 (95% CI 2.4–7.1) occurring during the EW 31 (Appendix Figure 2). Both measures are similar in principle, and estimate the transmission dynamic of the disease whether is at the initial phase of the epidemic (\( R_0 \)) or as an estimate for the whole epidemic (\( R_t \)). The usefulness of \( R_t \) is the possibility to estimate its uncertainty (confidence interval) throughout the epidemic curve. This could be relevant and applicable to other diseases as well. Due to the
intrinsic variability of the Rt series, the examination of its credible intervals is essential to identify periods of sustained transmission (5).

2.2. Kriging Interpolation

We performed an ordinary kriging using 3 anisotropic variogram models. The models were compared by cross-validation and evaluated in terms of their overall robustness: optimality and validity of the model to fit the observed data (Appendix Table 1, Appendix Figure 3). Overall, all the models underestimated the variability in their predictions as is shown by: i) negative values of the mean standardized errors (MSE), ii) average standard error (ASE) values lower than the root-mean-squared prediction error (RMSE) values, and iii) standardized root-mean-squared prediction error (RMSSE) values >1 (Appendix Table 1). This can be due to too few sampled locations within the spatial range of the study area. However, our best selected model (Gaussian) was the one that had the MSE nearest to 0, the smallest RMSE, the ASE nearest to the RMSE, and a RMSSE nearest to 1 (15).

The model was adjusted for the directional spatial trend of our data (anisotropy) in the semivariogram (10). Maps showing the kriging standard errors of the Gaussian model and of the other 2 models (for comparison) are presented in Appendix Figure 3. Darker colors in the error map (Appendix Figure 3) show larger kriging standard errors. Overall, the model failed to predict in areas out of the main spatial range of the data (where there are fewer and scarcer case locations) and showed a better prediction toward the south-west and eastern zones of the study area where a larger number of locations are presented. Indeed, this analysis identified a faster propagation of the epidemiologic wave at the south-west and eastern areas where the model showed its better fit (Appendix Figure 3, panel a), and a slower movement to the north-east and south-center areas.

2.3. Knox Test

The results obtained after the analysis with different critical values of s and t showed that the core clusters (main clusters) found at week 1 (25–200 m) are the same than those (core clusters) found at week 2, 3, and 4 (25–200 m), therefore, we have selected to show on Appendix Figure 4 the graphical output of the critical values of t with a fixed space window of 100 m. However, the size of the core clusters is susceptible to the change of the space and time
windows, making the clusters bigger or smaller in terms of number of links (Appendix Table 1), i.e., from 164 space-time links (1W,100 m) to 220 space-time links (3W,100 m).

Regarding the RR at different space and time windows (Appendix Table 1), the highest RR were found at the space–time window of 1 week and 25–200 m (RR = between 3 and 2), but also showing RR >1.5 up to week 3 at the same space windows, while from week 4, values showed RR <1.5 (Appendix Figure 5). These results provided useful information that allowed to observe the extent of the interaction of s and t values that shows the highest RR. Hence, RR values that show an important strength of association are present up to week 3 (21 days) within a distance that varies between 25 and 150 m. This agrees with previous results obtained by Vincenti-Gonzalez et al. (16) for Venezuela, where the significant hot spots of high dengue seroprevalence values were found between 25–100 m, suggesting a focal transmission.

Even though the RR in week 3 decreased along the different distances (average 32 ± 7%) when compared to the RR of week 1, the RR remained higher than one (RR>1) in week 3. Given the fact that the Knox test results showed the same core clusters along the different t windows and the RR remained epidemiologically relevant after 3 weeks (general clustering of symptoms onset date, and RR>1), we used the window of 3 weeks with a distance window of 100 m to show the global clusters of transmission (Appendix Figure 6). We decided to choose these distance and time variables based on biologic and ecologic knowledge as explained in the manuscript and in agreement with other authors (17,18). Where 100 m is the distance referred by most as the average flight range radius of Aedes spp. and a time window of 3 weeks gives enough time span for most transmission events to occur (19–21).

### 2.3.1. General Clusters of Transmission Events During the Epidemic Wave of Chikungunya

Our results (Appendix Table 3) show that the average cluster duration since the symptoms onset of the first case to the symptoms onset of the last case within the clusters is 12.5 days ranging from 1–67 days. The choosing of 100 m does not preclude the finding of larger distances between cases within a cluster as the range of distances found was between 8–216 m. We expect that within clusters >1 chain of transmission will occur each with a duration of ~1 week or less.
2.4. Incremental Knox Test

The IKT was the second method used to assess the uncertainty of the cluster analysis. The previous was made employing an exploratory mode where the p-values (Appendix Figure 7) and the RR (Appendix Figure 8) were examined for a range of values of s and t. The results of the IKT analysis proved to be useful to identify linked transmission events, and showed that the temporal intervals with the strongest spatial clustering (belonging to the same chain of transmission) and RR occurs between 1–7 days suggesting multiple vector feeding within a gonotrophic cycle (22), with less strong clustering around 12–14 days. High RR results within 1 week are consistent for all tested distances, but values of RR >5 were found to be in distances between 25 and 150 m (Appendix Figures 7, 8), favoring our previous selection of a space-time window of 100 m.

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### Appendix Table 1. Model parameters of Kriging interpolation*

| Model    | Nugget (C₀) | Range (a) | Partial Sill (C₁) | MSE  | RMSE  | ASE  | RMSSE |
|----------|-------------|-----------|-------------------|------|-------|------|-------|
| Gaussian | 8.88        | 30.89     | 188.42            | -0.014 | 17.35 | 14.29 | 1.18  |
| Spherical| 0.05        | 48.84     | 117.51            | -0.015 | 17.45 | 11.04 | 1.53  |
| Exponential | 2.06  | 984.85    | 388.71            | -0.016 | 18.13 | 15.07 | 1.40  |

*ASE, average standard error; MSE, mean standardized error; RMSE, root-mean-square error; RMSSE, root-mean-square standardized error.
## Appendix Table 2. Knox test with alternative definitions of spatial and temporal proximity*  

| Time, wk | Distance, m | Expected | Observed | RR  |
|----------|-------------|----------|----------|-----|
| 1        | 25          | 22       | 72       | 3.27|
|          | 50          | 28       | 81       | 2.86|
|          | 75          | 45       | 117      | 2.57|
|          | 100         | 72       | 164      | 2.27|
|          | 125         | 97       | 213      | 2.20|
|          | 150         | 122      | 258      | 2.11|
|          | 175         | 159      | 316      | 1.99|
|          | 200         | 199      | 376      | 1.89|
| 2        | 25          | 34       | 77       | 2.28|
|          | 50          | 44       | 95       | 2.18|
|          | 75          | 70       | 138      | 1.98|
|          | 100         | 110      | 202      | 1.83|
|          | 125         | 148      | 264      | 1.78|
|          | 150         | 187      | 322      | 1.72|
|          | 175         | 243      | 404      | 1.66|
|          | 200         | 304      | 497      | 1.63|
| 3        | 25          | 43       | 79       | 1.85|
|          | 50          | 55       | 97       | 1.76|
|          | 75          | 88       | 144      | 1.63|
|          | 100         | 140      | 220      | 1.57|
|          | 125         | 168      | 293      | 1.56|
|          | 150         | 237      | 360      | 1.52|
|          | 175         | 308      | 457      | 1.48|
|          | 200         | 386      | 566      | 1.47|
| 4        | 25          | 50       | 80       | 1.59|
|          | 50          | 65       | 99       | 1.53|
|          | 75          | 104      | 150      | 1.45|
|          | 100         | 164      | 236      | 1.44|
|          | 125         | 221      | 313      | 1.42|
|          | 150         | 279      | 383      | 1.37|
|          | 175         | 362      | 493      | 1.36|
|          | 200         | 453      | 617      | 1.36|

*Monte Carlo simulations performed in each analysis:10,000.

## Appendix Table 3. Description of the space–time cluster identified for the chikungunya epidemic in the north-central region of Venezuela*  

| Cluster ID | No. cases | Day occurrence, first–last case | Cluster duration, d | Average distance from IC, m | Range of distance from IC, m | Velocity average, m/day | Velocity range, m/day |
|------------|-----------|----------------------------------|---------------------|-----------------------------|-------------------------------|------------------------|----------------------|
| 1          | 2         | 95–105                           | 11                  | 10132.0                     | 10128–10136                   | 102.0                  | 97–107               |
| 2          | 4         | 77–105                           | 29                  | 7659.8                      | 7636–7686                     | 86.8                   | 73–100               |
| 3          | 4         | 72–85                            | 14                  | 2556.0                      | 2518–2613                     | 32.3                   | 30–36                |
| 4          | 3         | 72–94                            | 23                  | 2872.0                      | 2857–2898                     | 33.7                   | 30–40                |
| 5          | 2         | 121–126                         | 6                   | 6685.6                      | 6661–6710                     | 54.0                   | 53–55                |
| 7          | 3         | 0–25                             | 26                  | 31.7                        | 0–95                          | 1.3                    | 0–4                  |
| 8          | 2         | 125–135                          | 11                  | 2598.5                      | 2598–2599                     | 20.0                   | 19–21                |
| 9          | 3         | 64–95                            | 78                  | 2553.7                      | 2515–2585                     | 33.3                   | 27–34                |
| 10         | 5         | 71–99                            | 29                  | 2344.0                      | 2299–2429                     | 29.6                   | 24–33                |
| 11         | 2         | 73–73                            | 1                  | 1857.0                      | 1856–1858                     | 25.0                   | 25.0                 |
| 12         | 2         | 61–61                            | 1                  | 3673.5                      | 3673–3674                     | 60.0                   | 60.0                 |
| 13         | 2         | 73–80                            | 8                  | 2505.0                      | 2506–2594                     | 33.4                   | 32–34                |
| 14         | 4         | 79–107                           | 29                  | 2680.3                      | 2647–2714                     | 29.0                   | 25–34                |
| 15         | 5         | 72–108                           | 37                  | 3463.0                      | 3418–3508                     | 43.4                   | 32–51                |
| 16         | 3         | 43–57                            | 15                  | 3687.0                      | 3680–3700                     | 75.3                   | 65–86                |
| 18         | 3         | 3–31                             | 33                  | 3015.3                      | 3011–3020                     | 45.3                   | 39–50                |
| 19         | 2         | 91–99                            | 9                  | 3354.5                      | 3315–3394                     | 35.0                   | 33–37                |
| 20         | 3         | 63–78                            | 16                 | 3198.3                      | 3192–3205                     | 46.0                   | 41–51                |
| 22         | 2         | 61–82                            | 22                 | 3531.5                      | 3491–3571                     | 50.5                   | 44–57                |
| 23         | 2         | 66–66                            | 1                  | 3573.0                      | 3571–3575                     | 54.0                   | 54.0                 |
| 24         | 2         | 65–65                            | 1                  | 3684.0                      | 3683–3685                     | 57.0                   | 57.0                 |
| 25         | 9         | 59–72                            | 14                 | 3786.2                      | 3734–3882                     | 57.8                   | 54–64                |
| 26         | 3         | 75–88                            | 14                 | 3967.0                      | 3957–3967                     | 53.0                   | 45–53                |
| 27         | 12        | 69–77                            | 9                  | 4092.8                      | 4008–4241                     | 57.8                   | 54–59                |
| 28         | 2         | 66–65                            | 3                  | 5688.5                      | 5643–5574                     | 83.5                   | 83–84                |
| 29         | 3         | 0–66                             | 67                 | 6799.0                      | 6194–6204                     | 97.0                   | 94–103               |
| 30         | 2         | 67–68                            | 2                  | 3617.0                      | 3616–3618                     | 53.5                   | 53–54                |
| Cluster ID | No. cases | Day occurrence, first–last case | Cluster duration, d | Average distance from IC, m | Range of distance from IC, m | Velocity average, m/day | Velocity range, m/day |
|-----------|-----------|--------------------------------|---------------------|----------------------------|----------------------------|------------------------|-----------------------|
| 31        | 2         | 74–70                           | 7                   | 3970.0                     | 3820–3997                  | 51.5                   | 39–44                 |
| 32        | 2         | 16–19                           | 4                   | 3822.0                     | 3820–3824                  | 220.0                  | 201–239              |
| 33        | 5         | 65–82                           | 18                  | 4311.7                     | 4528–4344                  | 59.8                   | 53–66                |
| 34        | 2         | 67–72                           | 6                   | 4483.0                     | 4471–4495                  | 64.5                   | 62–67                |
| 35        | 2         | 88–94                           | 7                   | 5555.0                     | 5554–5556                  | 61.0                   | 59–63                |
| 36        | 3         | 89–109                          | 21                  | 6709.7                     | 6694–6739                  | 67.7                   | 61–76                |
| 37        | 2         | 72–76                           | 5                   | 4601.0                     | 4571–4631                  | 62.0                   | 61–63                |
| 38        | 3         | 86–88                           | 3                   | 4760.3                     | 4752–4775                  | 54.3                   | 54–55                |
| 39        | 3         | 68–86                           | 19                  | 4940.3                     | 4894–4998                  | 62.3                   | 57–72                |
| 40        | 2         | 76–76                           | 1                   | 4645.5                     | 4623–4668                  | 61.0                   | 61.0                 |
| 41        | 2         | 61–64                           | 4                   | 4938.0                     | 4938–4964                  | 77.0                   | 77–81                |
| 42        | 2         | 50–63                           | 14                  | 5138.0                     | 5138.0                     | 103.0                  | 82–103               |
| 44        | 2         | 103–107                         | 5                   | 5561.5                     | 5518–5605                  | 53.0                   | 52–54                |
| 45        | 2         | 116–117                         | 2                   | 5564.5                     | 5562–5567                  | 48.0                   | 48.0                 |
| 46        | 2         | 119–121                         | 3                   | 5596.0                     | 5536–5556                  | 47.0                   | 47.0                 |
| 47        | 2         | 108–115                         | 8                   | 5750.5                     | 5727–5774                  | 51.5                   | 50–53                |
| 48        | 2         | 92–101                          | 10                  | 6126.5                     | 6126–6127                  | 64.0                   | 61–67                |
| 49        | 2         | 80–80                           | 1                   | 6368.5                     | 6368–6369                  | 84.0                   | 84.0                 |
| 50        | 2         | 76–76                           | 1                   | 6368.5                     | 6368–6369                  | 84.0                   | 84.0                 |
| 51        | 3         | 103–132                         | 30                  | 6501.6                     | 6512–6479                  | 56.0                   | 49–63                |
| 52        | 2         | 85–85                           | 1                   | 6796.5                     | 6796–6802                  | 73.0                   | 73.0                 |
| 53        | 3         | 75–111                          | 37                  | 6382.5                     | 6373–6392                  | 71.0                   | 64–57                |
| 54        | 2         | 99–103                          | 5                   | 7305.5                     | 7279–7332                  | 72.5                   | 71–74                |
| 55        | 2         | 92–103                          | 12                  | 7734.5                     | 7704–7765                  | 79.5                   | 84–75                |
| 56        | 2         | 60–74                           | 15                  | 7046.0                     | 7011–7081                  | 106.5                  | 96–117               |
| 57        | 6         | 60–77                           | 18                  | 7341.8                     | 7262–7428                  | 108.3                  | 96–122               |
| 58        | 2         | 81–83                           | 3                   | 7526.5                     | 7495–7558                  | 92.0                   | 91–93                |
| 59        | 3         | 63–72                           | 10                  | 7598.6                     | 7535–7661                  | 112.3                  | 106–120              |
| 60        | 2         | 76–76                           | 1                   | 8228.5                     | 8221–8626                  | 108.0                  | 88–97                |
| 61        | 2         | 72–86                           | 5                   | 8396.5                     | 8381–8414                  | 113.5                  | 115–116              |
| 62        | 2         | 89–100                          | 12                  | 8547.5                     | 8626–8669                  | 91.5                   | 86–97                |
| 63        | 2         | 86–86                           | 1                   | 8778.5                     | 8774–8783                  | 102.0                  | 102.0                |
| 64        | 2         | 102–115                         | 14                  | 9355.0                     | 9349–9361                  | 86.5                   | 81–92                |
| 65        | 2         | 76–76                           | 1                   | 8228.5                     | 8221–8236                  | 108.0                  | 108.0                |
| 66        | 2         | 75–80                           | 6                   | 8460.0                     | 8359–8453                  | 108.5                  | 106–111              |
| 67        | 2         | 80–86                           | 1                   | 8804.0                     | 8783–8825                  | 110.0                  | 110.0                |
| 68        | 2         | 79–79                           | 1                   | 10491.5                    | 10397–10442                | 132.0                  | 132.0                |
| 69        | 2         | 83–84                           | 2                   | 10822.0                    | 10819–10825                | 129.5                  | 129–130              |
| 70        | 3         | 70–85                           | 16                  | 10653.7                    | 10603–10679                | 135.7                  | 125–153              |
| 71        | 2         | 142–163                         | 22                  | 11749.5                    | 11726–11776                | 77.5                   | 72–83                |
| 72        | 5         | 69–99                           | 31                  | 7611.0                     | 7599–7622                  | 103.4                  | 77–110               |
| 73        | 2         | 59–81                           | 23                  | 7943.0                     | 7920–7966                  | 116.5                  | 98–135               |
| 74        | 3         | 70–92                           | 23                  | 12291.7                    | 12224–12341                | 153.7                  | 134–175              |
| 75        | 2         | 134–136                         | 3                   | 9903.5                     | 9803–9904                  | 73.5                   | 73–74                |
| 76        | 2         | 65–79                           | 15                  | 7636.5                     | 7630–7643                  | 107.5                  | 97–118               |
| 77        | 2         | 78–78                           | 1                   | 1651.5                     | 1644–1659                  | 21.0                   | 21.0                 |
| 78        | 3         | 129–133                         | 5                   | 5477.0                     | 5477.0                     | 41.7                   | 42.0                 |

*Appendix Table 4. Linear distance between cases within the major spatiotemporal clusters*
Appendix Figure 1. Logistic fitted model for reported chikungunya cases during the epidemic of 2014 in Carabobo State, Venezuela. Chikungunya cases are depicted by open black dots, red line depicts the fitted curve (logistic model).

Appendix Figure 2. Reproduction number of chikungunya fever in Carabobo State, Venezuela, during 2014. Blue bars show the epidemic curve; the cases are shown in a weekly interval. Solid black line corresponds to the estimated Rt for the epidemic, dashed red line depicts the 95% CI, whereas green dashed line depicts the threshold Rt = 1.
Appendix Figure 3. Spatial prediction map for the ordinary kriging interpolation of number of days elapsed between the appearance of a case in a specific locality and the IC obtained using the Gaussian (A), spherical (B), and exponential (C) models. Surface maps showing the kriging standard errors for each model in the right side of each map.
Appendix Figure 4. Space–time output varying the time window from 1 to 4 weeks. In red, the space-time clusters. Distance window was set at 100 m.

Appendix Figure 5. Relative risk from the Knox test with alternative definitions of spatial and temporal proximity.
Appendix Figure 6. A) Geographic distribution of chikungunya reported cases in Carabobo state, Venezuela. a) Red dots denote case location, black dashed lines (b, c, d) are the different panels division (arbitrary) within Carabobo state selected to show in detail (zoom in) the general clusters of transmission. B) Geographic distribution and significant space–time clustering of chikungunya reported cases. Zoom in of the different cluster of transmission detected (including the IC), red dots denote case location, black circles identify a significant space–time cluster and yellow lines shows the interaction between cases (time–space link). The analysis was performed using 100 m as clustering distance and 3 weeks as time window. Significance level for local clustering detection was of 0.05. C) Geographical distribution and significant space–time clustering of chikungunya reported cases. Zoom in of the different cluster of transmission detected (including IC and AC), red dots denote case location, black circles identify a significant space–time cluster and yellow lines shows the interaction between cases (time–space link). The analysis was performed using 100 m as clustering distance and 3 weeks as time window. Significance level for local clustering detection was of 0.05. D) Geographic distribution and significant space–time clustering of chikungunya reported cases. Zoom in of the different cluster of transmission detected (including IC and AC), red dots denote case location, black circles identify a significant space–time cluster and yellow lines shows the interaction between cases (time–space link). The analysis was performed using 100 m as clustering distance and 3 weeks as time window. Significance level for local clustering detection was of 0.05.
Appendix Figure 7. Significant values of the exploratory IKT analysis. In red the significant (p value < 0.05) of space–time interactions within the specific space–time intervals.

Appendix Figure 8. Values of relative risk for the exploratory IKT analysis. The colors in the heatmap depict the range of values of RR (refer to the legend) within the specific space–time intervals.