Spatiotemporal patterns of dengue and Zika incidence during the 2015-2018 outbreak of Zika in Mexico

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Abstract

Objective. Evaluate spatially and temporally simultaneous presence of clusters of dengue and Zika clinical cases and their relationship with expected dengue transmission risk. **Materials and methods.** A classification of dengue risk transmission was carried out for whole country, and spatial autocorrelation analyses to identify clusters of confirmed clinical cases of dengue and Zika from 2015 to 2018 was conducted using Moran's Index statistics. **Results.** Clusters of both diseases were identified in dengue-high risk municipalities at the beginning of the outbreak, but, at the end of the outbreak, Zika clusters occurred in dengue low-risk municipalities. **Conclusion.** This study identified Zika clusters in low-risk dengue areas suggesting participation of several factors that favor virus introduction and dissemination, such as differences in entomological and control interventions, and the possibility of cross-immunity in the population.

Keywords: Dengue; Zika; spatiotemporal transmission; spatial autocorrelation

Cortes-Escamilla A, Roche B, Rodríguez-López MH, López Gatell-Ramírez H, Alpuche-Aranda CM. Patrones espaciotemporales de la incidencia de dengue y Zika durante el brote de Zika 2015-2018 en México. Salud Publica Mex. 2022;64:478-487.
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Resumen

Objetivo. Evaluar espacial y temporalmente la presencia simultánea de conglomerados de casos clínicos de dengue y Zika y su relación con el riesgo esperado de transmisión del dengue. **Material y métodos.** Se realizó una clasificación de la transmisión del riesgo de dengue para todo el país y un análisis de autocorrelación espacial para identificar conglomerados de casos clínicos confirmados de dengue y Zika entre 2015 a 2018, utilizando el Índice de Moran. **Resultados.** Al inicio del brote se identificaron conglomerados de ambas enfermedades en municipios de alto riesgo de transmisión de dengue, sin embargo, al final del brote, los grupos de Zika se produjeron en municipios de bajo riesgo de transmisión de dengue. **Conclusión.** En este estudio se identificaron conglomerados de Zika en áreas de bajo riesgo de dengue, lo que sugiere la participación de múltiples factores que favorecen la introducción y diseminación del virus, como las diferencias en la entomología y el control y la posibilidad de inmunidad cruzada en la población.

Palabras clave: Dengue; Zika; transmisión espaciotemporal; autocorrelación espacial

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Climate change, urbanization, human mobility, and environmental disturbances facilitate the territorial expansion of mosquitos, increasing the spread of vector-borne diseases to new geographical municipalities.[1,2] Dengue (DENV), and Zika viruses (ZIKV) are pathogens transmitted by *Aedes* mosquitoes.[3]

The four DENV serotypes have been reported in Mexico for the past 40 years.[4,5] Currently, 30 out of the 32 Mexican states have sustained dengue (DEN) transmission with a predominance of DENV-1 and DENV-2 serotypes.[6] The wide distribution of the vector and the co-circulation of different serotypes favor the maintenance of endemic and hyperendemic regions.

The first official reports of Zika (ZIK) from Southern Mexico were published in November 2015, although it is possible that the virus was circulating in other states (Veracruz and Yucatán).[7] The peak of the ZIK outbreak occurred in 2016 (with 8 859 confirmed cases) and since then, its circulation decreased, with 860, 86, 20, and 28 confirmed cases in 2018, 2019, 2020 and 2021, respectively.[8]

The effect of continuous DENV circulation in the spread of ZIKV is controversial; on one hand some studies reported a strong correlation between endemic DEN and ZIK incidence,[9,10] and on the other, no geospatial correlation in the distribution of the incidence of both viruses was reported by others.[11]

DENV and ZIKV are flaviviruses with high similarities in their structural envelope proteins,[1] which results in frequent induction of cross-reactivity antibody responses.[12] Thus, is likely that the incidence of DEN and ZIK outbreaks may interfere in the susceptibility of the human population to infection with both viruses.[13,14] In the case of Mexico, the continuous circulation of DENV may affect the incidence and dissemination of ZIK,[15] and vice versa. In order to evaluate the spatial patterns and potential temporal and geographical simultaneous presence of clusters of DEN and ZIK clinical cases, and their relationship with expected risk for DEN transmission, spatial autocorrelation models were performed using data of nominal DEN and ZIK cases by municipality from the Mexican National System of Epidemiology for the years 2015 to 2018.

Materials and methods

Data from confirmed cases of DEN and ZIK during the 2015-2018 period were acquired from the Mexican National System of Epidemiological Surveillance of the General Office for Epidemiological Intelligence (*Sistema Nacional de Vigilancia Epidemiológica*, Sinave), which forms part of Mexican Ministry of Health. Information was anonymous and nominally separated. These included registration dates and geographical data allowing identification of spatiotemporal parameters in the information. In this system, confirmed cases are registered when they are positive to viral RNA by real-time PCR.[16]

Risk index

The annual incidence rates of DEN and ZIK were calculated using incidence data provided by Sinave[17] and divided into five categories, ranging from 1 case to more than 200 cases per 100 000 inhabitants. 1) 1 case; 2) 2 to 10 cases; 3) 11 to 50 cases; 4) 51 to 200 cases; 5) 201 to > 400 cases per 100 000 inhabitants).

The average annual temperature and average annual precipitation per municipality were calculated using data from digital climatic surface layers that are representative of Mexican municipalities and which were developed by Cuervo-Robayo and colleagues based on the monthly climatic averages for the years 1910 to 2009.[18] Temperature data were divided into two categories (< 16°c and > 16°C), and the annual precipitation, into two categories (< 250 mm and > 250 mm) (supplementary information).[19]

The categories created under the two environmental variables (temperature and precipitation), combined within the five categories for DEN incidence rates, resulted in a five-level risk index. Each level was assigned a value ranging from zero to four, where zero represented no risk (temperatures below 16°C and low humidity, indicating no mosquito breeding conditions and extremely low or zero incidence rates), and 4 represented optimal conditions for high mosquito populations (temperature above 16°C and rainfall above 250 mm) and high DEN incidence rates.[20-22] Two possible criteria were considered for each risk level, corresponding to environmental conditions and DEN incidence rates (*e.g.*, for the medium risk, the first criterion considered temperatures below 16°C, precipitation above 250 mm, and incidence rates of 1.1 to 10 cases per 100 000 habitants; for the second criterion, higher temperatures above 16°C, precipitation above 250 mm, and incidence rates of 10.9 to 50 cases per 100 000 habitants were considered) (figure 1).

All municipalities in the country were ranked according to five risk levels for DEN; zero-risk municipalities were not included in the spatial autocorrelation model estimations. Risk classifications were created with the ArcMap tool of the ArcGIS software, version 10.3. Redlands, CA: Environmental Systems Research Institute, Inc., 2010.[23] The risk classification was used as the base cartographic layer for subsequent spatial autocorrelation analyses, which were performed with the software

GeoDa1.14 software (2016 Center for Spatial Data Science of the University of Chicago). This exercise was carried out for each year of the study period (2015-2018).

Spatial autocorrelation analysis

Spatial coherence describes the possibility of DEN and ZIK case clusters, occurring in the same space for all times evaluated, *i.e.*, the degree of spatial correlation for DEN and ZIK clusters.[24] The occurrence of clusters of DEN and ZIK incidences among municipalities was evaluated using Univariate Local Moran's statistics. These models represent local clusters of DEN and ZIK cases across the geographic space, identifying the presence of spatial patterns and the degree to which the local incidences affect neighboring incidences,[25] being defined as:

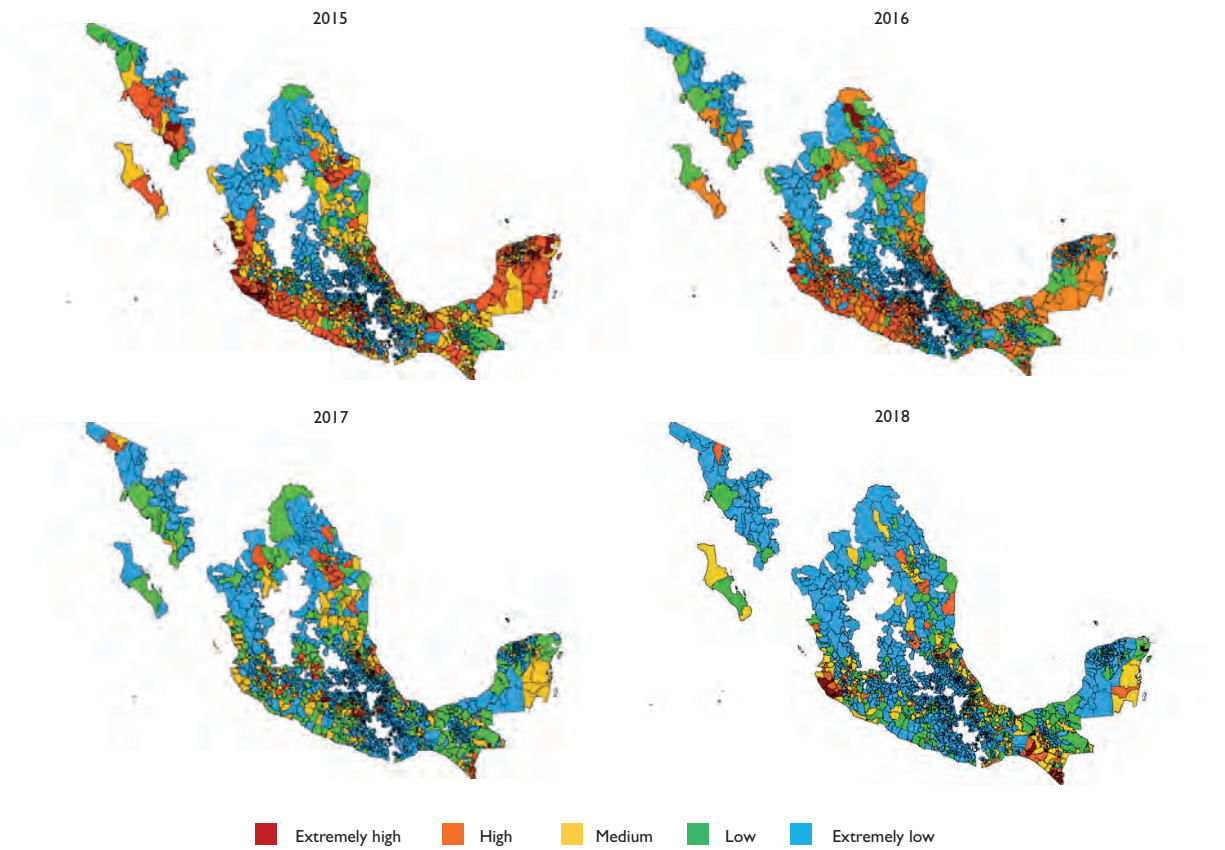
$$I = \frac{\sum i \sum j w_{ij} z_i z_j}{\sum j z_t^2}$$

Where w is a n by n matrix in which n is the number attributes (variables) in the dataset, z is the deviation from the mean, zi and zj are variable values in municipalities i and j, and wij represents spatial weights for each observation.[26,27]

Moran index values range from +1.0 to - 1.0; a positive value (+1) denotes a perfect spatial autocorrelation or hot spot; a negative value (-1) expresses a perfect negative spatial autocorrelation or cold spot, and a zero value indicates absence of spatial autocorrelation and presence of random patterns.[26]

The degree of spatial autocorrelation of DEN and ZIK clusters was determined using bivariate Moran's I statistics.[28] Moran's I measures the correlation coefficient between a variable and its surrounding values —in this case, a municipality with reported cases of DEN or ZIK (positive municipality) and its neighbors,[29]— and is defined as:[30]

$$(1) \quad I = \frac{N}{\sum_t^N \sum_J^N W_{tj}} \frac{\sum_t^N \sum_j^N W_{tj} (Xi-X) (Xj-\bar{X})}{\sum_t^N (Xi-\bar{X})^2}$$



The maps represent the distribution of dengue risk transmission; risk levels are color-coded, where lighter colors represent municipalities with lower risk and darker colors represent a higher risk of transmission.

Figure 1. Dengue transmission risk classification by municipalities. Mexico, 2015-2018

Bivariate local Moran's I Analysis tests the relationship between the value for a variable located at *Xj* or *Xi* and of the mean values for the neighboring variables. In (1), where *N* represents total number of spatial units, ∑ is the summation of the attributes, *Xi* and *Xj* are the values of attributes in areas *i* and *j*, *x* is the mean value of the observations in *n* municipalities, and *wij* is the matrix for the spatial weights.[27,30-32]

The analysis of the simultaneous presence (coexistence) of DEN and spatial simultaneous ZIK clusters was compared with the DEN Risk of Transmission Classification for 2016 and 2017 only, because ZIK incidence was extremely low in 2015 and 2018.

The ethics, research and biosafety committees of the National Institute of Public Health (*Instituto Nacional de Salud Pública*, INSP) approved the study protocol. The project involves secondary data analysis and, therefore, does not pose a risk to humans.

Results

Based on the mapping of the risk classification by municipality, we estimated the spatial autocorrelation of the DEN and ZIK. A univariate spatial autocorrelation analysis identified the presence of municipalities with high spatial clustering or hot spots for DEN and ZIK, representing regions of high infection, and cold spots or regions of low infection.

A total of 83 (0.169 MI), 71 (0.213MI), 58 (0.89 MI) and 75 (0.203 MI) high correlation (HC) clusters were identified in 2015, 2016, 2017, and 2018, respectively (univariate analysis). The 50% of DEN cluster located in high and medium risk municipalities (figures 2 and 3), the coefficient of variation (CV) in high-risk municipalities for DEN was 0.7. Unexpectedly, in 2016 an outbreak of ZIK occurred in one area of low DEN an ZIK risk.

Only two ZIK clusters were identified in 2015 in the states of Chiapas and Oaxaca; these were located in DEN high-risk municipalities (0.198 Moran's I correlation coefficient). In 2016, 85 clusters (0.130 Moran's I correlation coefficient) were identified; 79 clusters (0.143 Moran's I) were registered in 2017; and 33 clusters (0.350 Moran's I correlation coefficient) occurred during 2018. ZIK clusters were distributed in medium risk (58%) and low-risk municipalities for DEN transmission (22%) during 2016. During 2017 clusters occurred in extremely low risk (23.5%), low risk (37%) and medium-risk municipalities (33%); in 2018, ZIK clusters were registered in municipalities that range from high to extremely low risk of DEN transmission (figures 2 and 3).

The states with the highest number of DEN clusters were Veracruz (46), Chiapas (40), Nuevo León (40), Jalisco (25) and Guerrero (16); ZIK clusters occurred in Veracruz (30), Jalisco (19), Nayarit (19), Morelos (16), Tamaulipas (14) and Yucatán (12); the disaggregation by cluster numbers per municipality can be reviewed in tables of the supplementary information.[19]

Correlation of DEN and ZIK clusters and DEN risk municipalities

Bivariate spatial autocorrelation analyses were carried out to explore the spatial presence of DEN clusters with neighboring municipalities with ZIK clusters and municipalities at risk of DEN transmission (bivariate local Moran statistics). The greatest spatial-correlation of the DEN and ZIK clusters were observed between 2016 and 2017. During 2016 and 2017, 61 (0.095 Moran's I) and 25 (0.001 Moran's I) clusters respectively with neighboring municipalities with ZIK presence were identified, these municipalities did not occur in specific country regions, the value of Moran's index for 2017 is nearly zero, indicating a random behavior in the appearance of the clusters.

In 2016, 57% of the clusters were present in medium risk municipalities for DEN transmission in 35 municipalities of 19 states (Chiapas, Colima, Guerrero, Hidalgo, Jalisco, Morelos, Nuevo León, Quintana Roo, Tabasco, Veracruz, and Yucatán). Thirty-four percent of the DEN and ZIK clusters occurred in high-risk DEN municipalities, and these were located in the states of Guerrero, Hidalgo, Michoacán, Morelos, Nuevo León, Puebla, and Veracruz, and only 8% of these clusters occurred in municipalities with low risk of DEN transmission; these were located in Chiapas, Nuevo León, and Yucatán (figures 4 and 5).

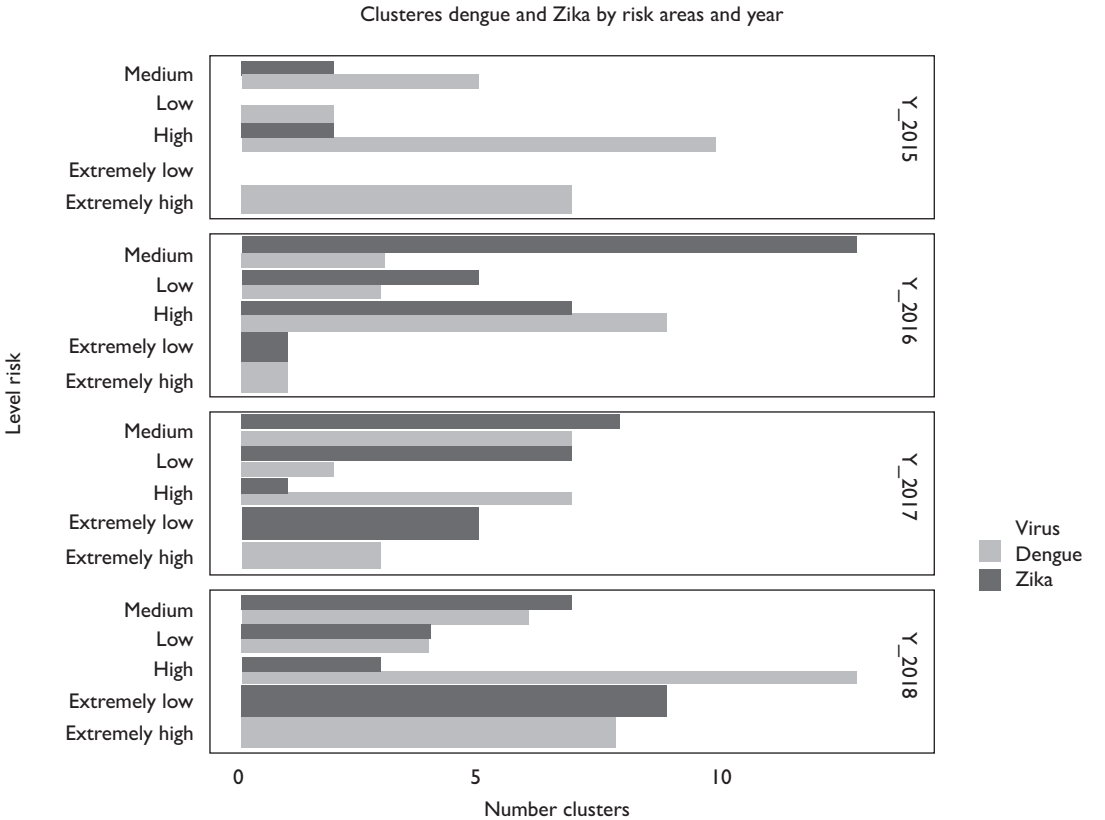
In 2017, 25 DEN clusters neighboring municipalities with ZIK transmission were identified in the central and northern regions of Mexico. Of these, 0.08% occurred in one municipality with extremely high risk of DEN transmission (Veracruz), 28% in high risk DEN transmission municipalities (Guerrero, Morelos, Nuevo León, Puebla, and Morelos), 35% in medium-risk DEN transmission areas (Morelos, Veracruz, Nayarit, San Luis Potosi, Tamaulipas, and Veracruz), and 28% in low-risk municipalities (Coahuila, Morelos, Nayarit, and Tamaulipas) (figure 4 and supplementary information).[19]

Discussion

This work examined spatial patterns and potential temporal and geographical simultaneous occurrence of DEN and ZIK clusters and their relationship with DEN transmission risk in Mexico. The analysis expanded from early 2015, at the introduction of the ZIKV, when

Cluster maps of spatial autocorrelation for DENV and ZIKV were created with Univariate Moran's I statistic. The red color (high-high) shows the significative clusters with positive autocorrelation. The blue color shows clusteres with no time-space coincidence, and the light red and light blue colors represent the atypical space values with negative autocorrelation; the grey areas represent non-significant locations.
DENV: Dengue virus
ZIKV: Zika virus

Figure 2. Spatial distribution of DENV and ZIKV clusters, univariate analyses by using Moran Local Index. Mexico, 2015-2018



Dengue and Zika clusters were compared with areas defined as extremely high, high, medium, and low risk and extremely low risk for dengue transmission; each graph represents one year of the study period (2015 to 2018). The Y-axis shows the classification by transmission risk zone (extremely high to extremely low). The number of clusters found by risk zone and year is shown on the Y-axis.
DENV: Dengue virus
ZIVK: Zika virus

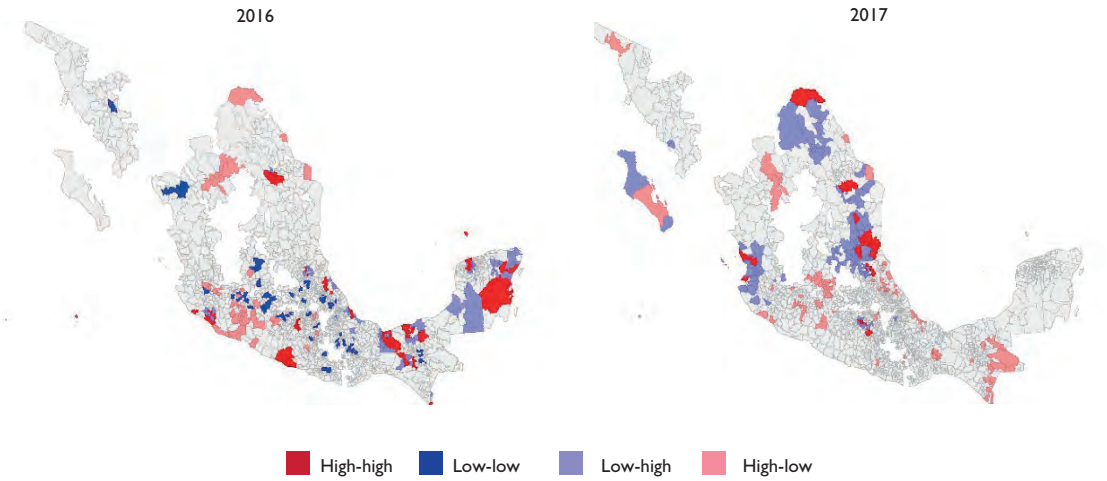
Figure 3. Independent clusters for DENV and ZIKV by risk classification. Mexico, 2015-2018

the population was fully susceptible, until the end of 2018, when the incidence was waning out,[17] making it possible to observe the spatial progress after the introduction of a new arbovirus in a geographic area with endemic and pre-existing immunity to DEN.[11]

Previous findings on the simultaneous presence of both arboviruses are discordant, a significant spatial correlation between DEN, Chikungunya and ZIK clusters was documented in Yucatán[9] and in nine cities of Mexico;[33] however, a different spatial pattern of distribution for the three arboviruses has been documented in Rio de Janeiro.[9-11] Our results describe the occurrence for both scenarios. At the beginning of the outbreak and spatial correlation between DEN and ZIK, clusters were observed in municipalities of medium DEN risk in the southern areas of the country; but at the end of the epidemic, a higher number of ZIK clusters occurred in low DEN risk municipalities of the north.

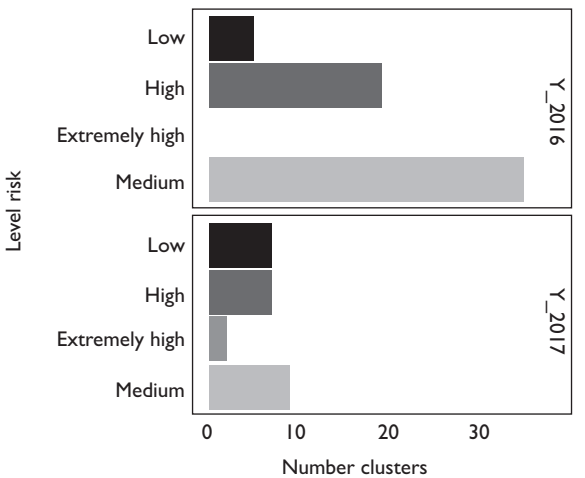
DEN and ZIK incidence rates for each year could vary due to the abundance and survival of the vectors;[34] we used temperature and precipitation parameters as a proxy for these entomological parameters in the calculations of risk of DEN transmission; however, we recognized these as a limitation of our study.

Clusters of DEN and ZIK (bivariate analysis) were fewer compared to the number of clusters identified as independent (univariate analysis). This may be the result of the spread of ZIK virus transmission. In the early days of the outbreak, cases appeared in the southern and central regions of Mexico,[7] we reanalyzed the stored samples from the states of Veracruz and Yucatán, which were originally collected to test for DEN (DENV where a greater number of high-risk municipalities for DEN transmission are located) (figure 1) . In 2017, the outbreak spread to the northern regions, in which the historical DEN incidence has been lowest.[17]



Cluster maps of spatial autocorrelation coherence between DENV and ZIKV were created with Bivariate Moran's I statistic. The red color (high-high) shows the significative clusters with positive autocorrelation. The blue color shows clusteres with no time-space coincidence, and the light red and light blue colors represent the atypical space values with negative autocorrelation; the grey areas represent non-significant locations.
DENV: Dengue virus
ZIVK: Zika virus

Figure 4. Spatial distribution of DENV and ZIKV clusters, bivariate analyses by using Moran Local Index. Mexico, 2016-2017



Each graph presents the clusters with spatial correlation reported for the years 2016 and 2017. The Y-axis shows the classification by transmission risk zone (extremely high to extremely low). The number of clusters found by risk zone and year is shown on the Y-axis. The colors in this graphic are for visual purposes only.
DENV: Dengue virus
ZIVK: Zika virus

Figure 5. Clusters of DENV and ZIKV with spatial correlation by risk classification. Mexico, 2016-2017

During 2016, an apparent decrease in DEN incidence was observed compared to that of 2015, which continued in the following two years, in parallel with a decrease in ZIK incidence.[17] The abatement of infections by both viruses could be the result of increased vector control interventions,[35,36] usually dedicated to focus vector control activities in DEN risk areas.[37]

In Mexico, the Chikungunya virus emerged at end of 2014,[38] less than six months after[39] the Zika outbreak emerged,[40] and this induced an intensification of vector control interventions,[41] particularly in municipalities with a history of DENV circulation, but with possibly heterogeneous efforts among municipalities.[42] However, the information of vector control is not routinely organized or analyzed, which limits the assessment of the effect of vector control on the ZIK outbreak intensity and its geographic dissemination.

On the other hand, populations in historical DENV circulation areas experience high exposure to the vector *Ae. aegypti* at an early age and consequently get infected and accumulate more than one infection throughout their life.[43-45] Both viruses share common antigenic epitopes and induce potential cross-protection between them.[46,47] Although there is no evidence for specific DENV serotype cross-reactivity with ZIKV, it

is plausible that populations living in municipalities with a very high risk of DEN exhibit higher immunity levels to historically circulating DEN serotypes and eventually to ZIK due to cross reactivity.[46,47] Thus, a low population immunity in municipalities with low risk of DEN transmission could explain a greater incidence of individual ZIK clusters.

This potential combination of entomological and control interventions,[48] the depletion of the susceptible population, human population cross-immunity,[11,49] and the adoption of personal protection against the vectors[50] could have caused the shifting of ZIK incidence to the central and northern regions of the country, with a significant proportion in non-endemic DEN municipalities. Displacement between two arboviruses which share a common host and vector has previously been reported.[49] For DEN, displacement of one serotype by another has been observed in high endemic countries including Mexico;[51,52] the displacement of Zika after an outbreak of Chikungunya was reported in Brazil.[11,49] Our findings on the temporal spread of ZIK transmission, depending on the evolution of the outbreak and the endemicity status of DEN, could provide insights for the interpretation of previous inconsistencies in the observed presence of ZIK transmission in high and low DEN transmission areas.[9-11]

Up to now, infection with ZIKV has not exhibited an endemic behavior similar to that of the DENV. Nevertheless, considering the widespread distribution of *Ae. aegypti* and *Ae. albopictus*, a latent risk of the recurrence of outbreaks of Chikungunya and ZIK may exist, and it is possible that novel arboviruses will be introduced, as there is a continuous mobility of human populations between high and low-risk municipalities.[53,54] In Mexico, entomological and virology surveillance involves the monitoring of DEN clusters and other arboviruses that may be circulating. Nevertheless, a methodology for risk classification of ZIK and DEN is a potential tool for identifying vulnerable zones to the spread of new arboviruses. Our findings provide a useful baseline to characterize the spatial-temporal dynamics of DEN and ZIK transmission in various Mexican geographic regions.

The main limitation of this work is the use of secondary data, since errors can appear in their collection, classification, notifications, and capture timing, affecting information reliability and, therefore, impacting the robustness of our models. In addition, the surveillance of DEN in Mexico is passive and depends on the reporting of cases. It would have been important to include DEN serotype information in the spatial analysis; however, the serotype surveillance information available cannot be disaggregated at the municipal level and restricts the possibility of comparing between municipalities.

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Declaration of conflict of interests. The authors declare that they have no conflict of interests.

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