scientific reports

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Factors associated with infection and hospitalization of Zika cases during the 2016–2018 outbreak in Mexico

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The Mexican Social Security Institute registered a significant number of suspected Zika virus (ZIKV) cases during the 2016–2018 outbreak. This study aims to describe the distribution of confirmed ZIKV cases, their correlation with rainfall and temperature, and associated factors with infection or hospitalization, considering pregnancy. A retrospective analysis was performed on 13,259 suspected ZIKV cases. Binary logistic regression was performed to determine potentially associated factors with infection or hospitalization. Correlations between positive cases and environmental factors were analyzed using the Pearson correlation and an autoregressive integrated moving average (ARIMA) test. Female sex and age > 30 were associated with ZIKV infection when excluding pregnant women. In pregnant women, a higher infection rate in the first and second trimesters compared to third trimester was observed. In Veracruz, rainfall correlated with positive cases in 2016 ($n = 5$; $r = 0.9977$, $p < 0.001$) and 2017 ($n = 12$; $r = 0.7467$, $p = 0.005$) correlated with rainfall only in 2017 ($r = 0.7975$, $p = 0.002$); this was not significant with the ARIMA analysis. Further research is suggested to elucidate factors involved in the transmission, pathogenicity and epidemiology of this and other vector-borne disease viruse.

Keywords Flavivirus, Vector-borne diseases, Epidemiology

Vector-borne diseases were recognized at the beginning of the last century, but they have gained greater importance in the last decade due to significant outbreaks[1]. One vector-borne disease that had a great impact in Latin America is the Zika virus disease (ZVD), which is caused by the *Orthoflavivirus zikaense* species and is transmitted to humans by mosquitoes of the genus *Aedes*[2,3]. From the 1960s to the 1980s, local Zika outbreaks occurred in Africa and Asia. Favorable weather and the flow of travelers caused the spread of the virus in India, China, Indonesia, the Philippines, and Thailand[3,4], but it was not until 2007 that the first global Zika virus (ZIKV) outbreak occurred in Yap Island, Micronesia[5]. Later, in 2015, the transmission of ZIKV was confirmed in Latin American countries including Brazil, Colombia, and Mexico[6]. In 2016, due to multiple outbreaks and

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aspects such as the association between ZIKV with Guillain-Barre syndrome, microcephaly in newborns[7], and the confirmation of sexual, blood transfusion–related, and maternal–fetal transmission of ZIKV[8], the World Health Organization declared ZVD to be a global emergency[7]. ZIKV was initially detected through RNA determination and neutralizing antibodies in the patient's serum[5,9]; nonetheless, the gold standard is the reverse transcription and quantitative polymerase chain reaction (RT-qPCR) assay[10], performed on blood, saliva, milk, semen, and conjunctival and vaginal secretions[11,12].

Many studies have been conducted to elucidate an algorithm that allows for predicting ZIKV outbreaks; however, the intervention of a vector for transmission makes this a complex task[13–15]. Among the most studied variables for ZIKV outbreak prediction, some socio-demographic and environmental conditions have been associated with the vector distribution[16–18]. Moreover, climate change has increased the prevalence of vector-borne diseases, including ZIKV[19]. Environmental factors such as rainfall and temperature, which contribute to the reproduction of the respective vectors, must be analyzed in the context of every specific population to determine their impact.

Since the 2016 outbreak, ZVD remains under epidemiological surveillance in most countries[20–23]. In Mexico, there is an epidemiological surveillance system for ZIKV and other mosquito-transmitted diseases[6]. The Mexican Social Security Institute (IMSS, its acronym in Spanish) is the largest health system in Mexico, covering more than 50% of the national population[24]. It offers healthcare and social security services to private sector workers and individual contributors and their dependents; it is financed by the federal government, employer contributions, and employee tax payrolls. Since 2009, the IMSS has established a network of epidemiological surveillance laboratories carrying out the molecular diagnosis of viral diseases including influenza, chikungunya, dengue, Zika and, more recently, COVID-19. The collected information is integrated into the National Epidemiological Surveillances System (SINAVE), which belongs to the General Directorate of Epidemiology.

To the best of our knowledge, the distribution of Zika cases, the potential associated factors with infection and hospitalization in a Mexican population including pregnant women have not been described, even when it is known that pregnancy implies variability and alterations of the immune response[25]. This work aims to describe the confirmed RT-qPCR ZIKV cases reported by the epidemiological surveillance laboratory network from the IMSS from August 2016 to January 2018, the potential factors associated with infection and hospitalization, and the relationship of ZIKV positive cases with average rainfall scores and temperature. This study thus contributes to the knowledge of ZIKV transmission in Mexico and explores their relationship with factors previously described in the literature.

Methods

Study design and selection criteria

A retrospective study was conducted based on the IMSS ZIKV surveillance data system of four regional molecular diagnostic laboratories authorized by the Institute of Epidemiological Diagnosis and Reference (InDRE), the National Reference Laboratory of the country; they are located in Nuevo Leon, Jalisco, Yucatan, and Mexico City[6]. Data were analyzed from symptomatic suspected cases of ZIKV whose patient samples were sent for molecular diagnosis by RT-qPCR test from August 2016 to January 2018. The information collected corresponds to those symptomatic patients who came seeking medical attention, including pregnant women, treated in first- and second-level medical units throughout the national territory, who met the operational definition of a suspected case of ZVD. Records with missing data for age, residence state, sampling date, pregnancy status, weeks of pregnancy, sample type, patient type (outpatient or hospitalized), or ZIKV RT-qPCR result, as well as rejected samples that could not be processed due to low quality, were excluded. Samples with negative or positive results were analyzed.

This study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of the Mexican Social Security Institute (Registration No. R-2023-1912-065). Due to the retrospective nature, the Clinical Research Ethics Committee waived the need to obtain informed consent for this study.

Case definitions

The operational definition of a suspected case followed the national guidelines for ZIKV epidemiological surveillance[6]: Any individual with a rash and at least 2 of the following symptoms: fever, headache, conjunctivitis (non-purulent/hyperemia), arthralgia, myalgia, periarticular edema, pruritus or retroocular pain, as well as an epidemiological association such as a history of residence or travel to an area with local ZIKV transmission two weeks prior to the onset of symptoms and/or a history of unprotected sexual contact in the 2 weeks prior to the onset of symptoms with a person who, in the 8 weeks prior to sexual contact, had a history of residence or traveled to an area with local ZIKV transmission. The operational definition of a suspected case for pregnant women is as previously described without the rash as a constant symptom. All suspected cases must undergo an RT-qPCR diagnostic test within the first 5 days of clinical onset and must be registered in the vector-transmitted diseases database.

RT-qPCR for ZIKV diagnosis

RT-qPCR was performed as previously described[26]. Briefly, after the sample processing, a 76-bp fragment was amplified using the following primers: Forward 1086–1102, 5'-CCGCTGCCCAACACAAG-3', Reverse 1162 – 1139, 5'-CCACTAACGTTCTTTTGCAGACAT-3', probe 1107–1137; and dCAL Fluor Red 610-AGCC TACCTTGACAAGCAGTCAGACACTCAA-BHQ-2, which align with the coding region of the viral E protein gene. Results were visualized and analyzed using 7500 Real-Time PCR System software v.2.3 (Applied Biosystems by Life Technologies).

Variable definitions

The database included independent categorical variables such as sex, age, state of residence, sampling date indicated by months and year, and pregnancy status including trimesters of pregnancy (first trimester < 14 weeks, second trimester 14–27 weeks, third trimester ≥ 28 weeks). The outcome variables (dependent) were PCR result (positive or negative) and patient type according to their status during sampling for qRT-PCR diagnosis, with the categories of hospitalized (patients who met the operational definition of a suspected Zika case and who were admitted to the unit and remained there for more than 24 h), outpatient, and death. All data were obtained from the clinical records. Information about weather conditions (average rainfall in millimeters and environmental temperature in degrees Celsius) was obtained from the Mexican National Meteorological System for each state by month and year[27].

Statistical analysis

All the information corresponding to the study variables was recorded in the Microsoft Excel program (Microsoft 365) and analyzed using the IBM SPSS for Windows, Version 26.0 (Armonk, NY: IBM Corp) statistical package in Spanish. Frequencies and percentages were obtained for the categorical variables. The relationship between the independent and outcome variables was analyzed using binary logistic regression models to calculate adjusted odds ratios (AOR) and 95% confidence intervals for each outcome of interest. Continuous variables such as average rainfall and temperature were analyzed using Pearson's correlation test for the number of cases by state and year. In addition to the correlation test, and given the potential for autocorrelation in time-series data and the complexity of vector-borne disease transmission, a time-series analysis was performed to explore these temporal dependencies and the potencial association between exogenous variables such as average rainfall and temperature and the number of positive cases by month and year. A widely used time series technique suitable for data characterised by autocorrelation, and seasonality - common features of vector-borne disease dynamics - is the autoregressive integrated moving average (ARIMA) test. The parameters of this ARIMA model were (1, 0, 0), which considers a 1 month lag to take into account the mosquito life cycle and the virus incubation times in humans and the vector. Average rainfall and temperature were included in the analysis as exogenous variables. Data analysis was performed using a 95% confidence level and statistical significance of $p < 0.05$.

Results

Sample characteristics

A total of 13,259 suspected ZIKV cases with a RT-qPCR result reported from August 2016 to January 2018 were included, of which 10.7% ($n = 1{,}419$) had a positive test for ZVD (Fig. 1). The sample size was sufficiently large for an estimated prevalence of 30.8% ZIKV-positive cases[28] at a 95% confidence level.

Timeline and demographic data

The national distribution of ZIKV suspected cases according to the RT-qPCR results is presented in Table 1 and Supplementary Fig. S1 online. From August 2016 to January 2018, the largest number of ZIKV-positive cases occurred in Veracruz (27.8%), followed by Nuevo León (16.4%) and Yucatan (15.4%). However, the highest positivity rate was observed in Nayarit, at 23.8%. Veracruz reported an 11.4% positivity rate, Nuevo Leon 8.5%, and Yucatan 19.1%.

Most positive cases were reported in 2016 (Supplementary Fig. S2 online). From August to December 2016, out of 7,673 suspected cases, a total of 1,105 (14.4%) were positive for ZVD. Towards the east coast, the states of

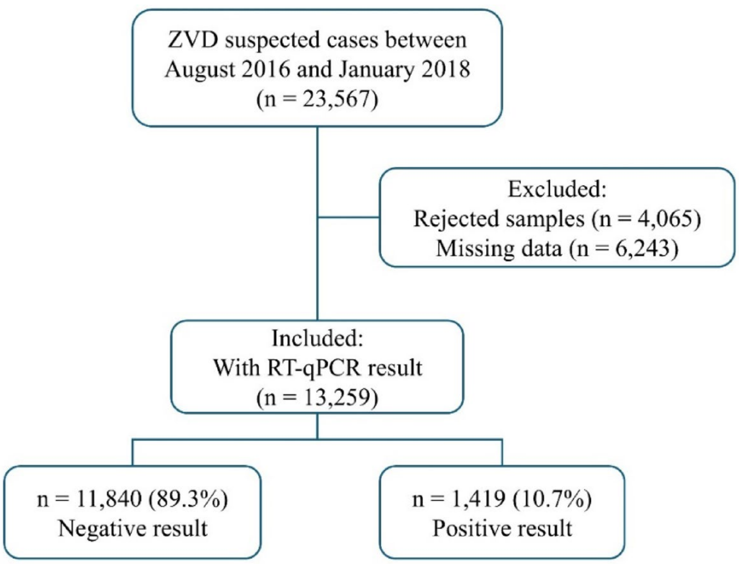

Fig. 1. Zika outbreak in Mexico. Case selection from the IMSS ZVD surveillance database, period August 2016 to January 2018.

State of residence	National distribution *n* (%)			Positivity
	Total	Negative	Positive	State rate (%)
Veracruz	3,460 (26.1)	3,065 (25.9)	395 (27.8)	11.4
Nuevo Leon	2,745 (20.7)	2,512 (21.2)	233 (16.4)	8.5
Yucatan	1,142 (8.6)	924 (7.8)	218 (15.4)	19.1
Guanajuato	1,042 (7.9)	1,039 (8.8)	3 (0.2)	0.0
Jalisco	733 (5.5)	650 (5.5)	83 (5.8)	11.3
Tamaulipas	540 (4.1)	495 (4.2)	45 (3.2)	8.3
Oaxaca	400 (3.2)	370 (3.2)	30 (2.1)	7.5
Quintana Roo	388 (2.9)	315 (2.7)	73 (5.1	18.8
Michoacan	354 (2.7)	319 (2.7)	35 (2.5)	9.9
Sinaloa	349 (2.6)	316 (2.7)	33 (2.3)	9.5
Colima	334 (2.5)	275 (2.3)	59 (4.2)	17.7
Baja California Sur	281 (0.2)	264 (0.2)	17 (0.0)	6.0
Tabasco	275 (2.1)	232 (2.0)	43 (3.0)	15.6
Morelos	217 (1.6)	203 (1.7)	14 (1.0)	6.5
Campeche	212 (1.6)	171 (1.4)	41 (2.9)	19.3
Nayarit	143 (1.1)	109 (0.9)	34 (2.4)	23.8
Mexico City	136 (1.0)	123 (1.0)	13 (0.9)	9.6
Guerrero	101 (0.8)	90 (0.8)	11 (0.8)	10.9
Chiapas	100 (0.8)	87 (0.7)	13 (0.9)	13.0
Coahuila	80 (0.6)	64 (0.5)	16 (1.1)	20.0
Queretaro	38 (0.3)	35 (0.3)	3 (0.2)	7.9
Mexico	37 (0.3)	33 (0.3)	4 (0.3)	10.8
Durango	32 (0.2)	31 (0.3)	1 (0.1)	3.1
Puebla	32 (0.2)	31 (0.3)	1 (0.1)	3.1
San Luis Potosi	32 (0.2)	31 (0.3)	1 (0.1)	3.1
Baja California	29 (0.2)	29 (0.2)	0 (0.0)	0.0
Chihuahua	12 (0.1)	12 (0.1)	0 (0.0)	0.0
Tlaxcala	6 (0.0)	6 (0.1)	0 (0.0)	0.0
Sonora	4 (0.0)	4 (0.0)	0 (0.0)	0.0
Zacatecas	3 (0.0)	3 (0.0)	0 (0.0)	0.0
Hidalgo	2 (0.0)	2 (0.0)	0 (0.0)	0.0
Aguascalientes	0 (0.0)	0 (0.0)	0 (0.0)	0.0
Total	13,259 (100)	11,840 (100)	1,419 (100)	–

Table 1. Data collected during the ZIKV outbreak in Mexico from August 2016 to January 2018 and the National distribution of confirmed RT-qPCR ZIKV cases with the positivity state rate.

Veracruz and Quintana Roo had the most positive cases during August. On the Pacific coast, cases began in the state of Michoacan. During this period, the states of Veracruz, Nuevo Leon, and Yucatan had the highest number of positive cases at 321 (29.0%), 219 (19.8%), and 217 (19.6%), respectively.

In 2017, out of 5,429 suspected cases, 313 (5.76%) positive ZIKV cases were reported; fewer than 20 confirmed cases were detected in the first 3 months of the year and, on July, the beginning of the rainy season, the first cases occurred in the states of Nayarit on the Pacific coast and Tamaulipas and Veracruz on the coast of the Gulf of Mexico. During the season, Jalisco, Veracruz, and Tamaulipas had the most cases, with 80 (25.6%), 74 (23.6%), and 43 (13.7%) cases, respectively. In January 2018, only 1 positive case was reported by the epidemiological surveillance laboratory network of the Mexican Social Security Institute.

Percentages were calculated by columns. The positive state rate was calculated as the ratio of positive cases and total cases by state, multiplied by 100. Data collected during the Zika outbreak in Mexico from August 2016 to January 2018. Total, negative, and positive cases confirmed with RT-qPCR assays at the epidemiological surveillance laboratory network of the Mexican Social Security Institute.

In the total sample, the mean age was 30 ± 15 years (median 29, IQR 18), and 68% were women; 36.7% were pregnant with a mean age of 27 ± 6 years. The age distribution shows that most suspected cases occurred in people between 20 and 29 years old (31.8%) (Table 2). Most patients received outpatient treatment (84.2%), and 15.6% were hospitalized. The total case fatality rate was 0.2%, with deaths occurring only in ZIKV-negative RT-qPCR cases (Supplementary Table S1 online). ZIKV was detected in different types of samples, of which 93.3% were serum; the other 6.7% corresponded to urinary sediment, saliva, placental, umbilical cord, and biopsies (Supplementary Table S1 online).

Variable	n (%)	Positive	Negative	Wald Chi-square	p value	AOR (95% CI)
		n (%)	n (%)			
Sex						
Female	9,022 (68.0)	1,223 (86.2)	7,799 (65.9)	151.47	< 0.001*	2.86 (2.44–3.34)
Male	4,237 (32.0)	196 (13.8)	4,041 (34.1)			Ref.
Age (years)						
0–9	1,146 (8.6)	37 (2.6)	1,109 (9.4)	19.11	< 0.001*	0.37 (0.24–0.58)
10–19	1,543 (11.6)	109 (7.7)	1,434 (12.1)	0.92	0.338	0.84 (0.58–1.20)
20–29	4,220 (31.8)	650 (45.8)	3,570 (30.2)	9.83	0.002*	1.66 (1.21–2.28)
30–39	3,199 (24.1)	384 (27.1)	2,815 (23.8)	2.47	0.116	1.30 (0.94–1.79)
40–49	1,643 (12.4)	118 (8.3)	1,525 (12.9)	2.15	0.143	0.77 (0.54–1.10)
50–59	975 (7.4)	75 (5.3)	900 (7.6)	0.96	0.327	0.82 (0.56–1.21)
≥ 60	533 (4.0)	46 (3.2)	487 (4.1)			Ref.

Table 2. Factors associated with ZIKV infection in the Mexican population ($n = 13{,}259$). *Indicates significant *p value < 0.05.* Binary logistic regression analysis adjusted for sex and age. CI, confidence interval; AOR, adjusted odd ratio; Ref., Reference group. Data collected during the Zika outbreak in Mexico from August 2016 to January 2018 confirmed with RT-qPCR assays at the epidemiological surveillance laboratory network of the Mexican Social Security Institute.

Variable	n (%)	Hospitalized	Outpatients	Wald Chi-square	p value	AOR(95% CI)
		n (%)	n (%)			
Sex						
Women	1,223 (86.2)	127 (78.9)	1,096 (87.1)	3.16	0.075	0.67 (0.43, 1.04)
Men	196 (13.8)	34 (21.1)	162 (12.9)			Ref.
Age (years)						
0–9	37 (2.6)	5 (3.1)	32 (2.5)	1.07	0.301	0.54 (0.17, 1.73)
10–19	109 (7.7)	18 (11.2)	91 (7.2)	0.58	0.446	0.72 (0.30, 1.69)
20–29	650 (45.8)	61 (37.9)	589 (46.8)	5.88	0.015*	0.39 (0.18, 0.84)
30–39	384 (27.1)	38 (23.6)	346 (27.5)	5.21	0.022*	0.41 (0.19. 0.88)
40–49	118 (8.3)	13 (8.1)	105 (8.3)	3.62	0.057	0.42 (0.17, 1.03)
50–59	75 (5.3)	15 (9.3)	60 (4.8)	0.13	0.715	0.85 (0.35, 2.06)
≥ 60	46 (3.2)	11 (6.8)	35 (2.8)			Ref.

Table 3. Factors associated with hospitalization among Zika virus-positive patients ($n = 1{,}419$). *Indicates significant *p value < 0.05.* Binary logistic regression analysis adjusted for sex and age. CI, confidence interval; AOR, adjusted odd ratio; Ref., reference group. Data collected during the Zika outbreak in Mexico from August 2016 to January 2018 confirmed with RT-qPCR assays at the epidemiological surveillance laboratory network of the Mexican Social Security Institute.

Factors associated with ZIKV infection and hospitalization

Of the 13,259 suspected cases, 1,419 (10.7%) were positive for ZIKV infection. A higher infection rate was observed in women (AOR 2.86, 95% CI 2.44–3.34; $p < 0.001$) and ages between 20 and 29 years (AOR 1.66, 95% CI 1.21–2.28; $p = 0.002$). A lower infection rate was observed in children between 0 and 9 years of age (AOR 0.37, 95% CI 0.24–0.58; $p < 0.001$) (Table 2).

Given the presentation of microcephaly in newborns, there was a special interest in recruiting pregnant women for ZIKV detection. An additional analysis excluding pregnant women was performed for comparative purposes, and the same results were obtained for sex (AOR 1.48, 95% CI 1.24–1.76; $p < 0.001$). For patients under 30 years of age, a significantly lower association (AOR 0.64, 95% CI 0.45–0.91, $p = 0.013$) was observed (Supplementary Table S2 online).

Another regression model was performed to determine factors associated with hospitalization. Groups between 20 and 29 years of age and 30 to 39 years had an AOR for hospitalization of 0.39 (95% CI 0.18–0.84, $p = 0.015$) and 0.41 (95% CI 0.19–0.88; $p = 0.022$), respectively (Table 3). This analysis was also performed excluding pregnant women (Supplementary Table S3 online), where no significant results were observed for any age group.

Given the higher association observed between infection and female sex, an analysis was performed on the female population. Ages < 10 years had a significantly lower association with infection (AOR 0.56, 95% CI 0.32–1.00; $p = 0.046$), whereas pregnancy was highly associated with ZIKV infection (AOR 4.11 95% CI 3.52–4.80; $p < 0.001$) (Table 4).

Variable	n (%)	Positive n (%)	Negative n (%)	Wald Chi-square	p value	AOR (95% CI)
Age (years)						
0–9	609 (7.0)	27 (2.3)	582 (7.7)	4.33	0.037*	0.55 (0.31–0.97)
10–19	804 (9.2)	85 (7.3)	719 (9.5)	0.60	0.440	0.83 (0.51–1.34)
20–29	3,087 (35.4)	581 (49.7)	2,506 (33.2)	0.001	0.971	1.01 (0.65–1.57)
30–39	2,188 (25.1)	324 (27.7)	1,864 (24.7)	0.084	0.772	0.94 (0.60, 1.46)
40–49	1,076 (12.3)	80 (6.8)	996 (13.2)	0.428	0.513	0.85 (0.53, 1.37)
50–59	642 (7.4)	49 (4.2)	593 (7.9)	0.006	0.938	0.98 (0.59, 1.63)
≥ 60	311 (3.6)	24 (2.1)	289 (3.8)			Ref.
Pregnancy						
Yes	3,008 (34.5)	774 (66.2)	2,234 (29.6)	328.65	< 0.001*	4.272 (3.65, 5.00)
No	5,709 (65.5)	396 (33.8)	5,313 (70.4)			Ref.

Table 4. Factors associated with Zika virus infection in women ($n = 8{,}717$). *Indicates significant *p value* < *0.05*. Binary logistic regression analysis adjusted for age and pregnancy status. CI, confidence interval; AOR, adjusted odd ratio; Ref., reference group. Data collected during the Zika outbreak in Mexico from August 2016 to January 2018 confirmed with RT-qPCR assays at the epidemiological surveillance laboratory network of the Mexican Social Security Institute.

Variable	Total n (%)	Positive n (%)	Negative n (%)	Wald Chi-square	p value	AOR (95% CI)
Age						
≥ 30	980 (32.6)	234 (30.2)	746 (33.4)	3.22	0.073	0.85 (0.71–1.02)
≤ 29.9	2,028 (67.4)	540 (69.8)	1,488 (66.6)		Ref.	
Stage of gestation						
First trimester	720 (23.9)	180 (23.3)	540 (24.2)	19.76	< 0.001*	1.71 (1.35–2.17)
Second trimester	1,281 (42.6)	428 (55.3)	853 (38.2)	81.82	< 0.001*	2.55 (2.08–3.13)
Third trimester	1,007 (33.5)	166 (21.4)	841 (37.6)		Ref.	

Table 5. Factors associated with infection in pregnant women ($n = 3{,}008$). *Indicates significant *p value* < *0.05*. Binary logistic regression analysis adjusted for age and stage of gestation. CI, confidence interval; AOR, adjusted odd ratio; Ref., reference group. Data collected during the Zika outbreak in Mexico from August 2016 to January 2018 confirmed with RT-qPCR assays at the epidemiological surveillance laboratory network of the Mexican Social Security Institute.

In pregnant women, a higher infection rate was observed with the first (AOR 1.71, 95% CI 1.35–2.17; $p < 0.001$) and second trimester of gestation (AOR 2.55, 95% CI 2.08–3.13; $p < 0.001$) (Table 5). There were no significant differences observed regarding the association of hospitalization with age nor with stage of gestation (Supplementary Table S4).

Environmental factors associated with the ZIKV positivity in Veracruz

During the entire study period (August 2016 to January 2018), positive cases were mainly found in the states of Veracruz, Nuevo Leon, and Yucatan. Correlations between positive cases, average rainfall scores and temperatures were performed only for Veracruz due to its high number of ZIKV-positive cases. In Veracruz, the average rainfall and temperature for the entire period were 158 ± 118 mm and 23.3 ± 2.1 °C, respectively. Also in this state, from August to December 2016 (5 months), a significant correlation was observed between the number of total ZIKV-positive cases and the rainfall scores ($r = 0.531$, $p = 0.027$) (Supplementary Fig. S3 online) and the average temperature (23.5 ± 1.87 °C) (0.9739, $p = 0.0017$) (Supplementary Fig. S4 online). In 2017, from January to December, also in Veracruz, a correlation was observed between hospitalized cases and rainfall scores ($r = 0.7975$, $p = 0.002$) (Supplementary Fig. S5 online). These interactions were analyzed with the ARIMA test (1, 0, 0 model) with a 1-month lag and average rainfall and temperature as exogenous variables; there was insufficient evidence to demonstrate an association between environmental factors and the number of positive ZIKV cases (Supplementary Fig. S6 online).

Discussion

This is an exploratory study investigating the association of age, sex, and stage of gestation in pregnant women, in addition to environmental variables, with infection and hospitalization of ZIKV positive-patients during the ZIKV 2016–2018 outbreak. ZIKV outbreaks peaked in 2016 and have declined significantly since 2018. However, as the WHO reported in the epidemiological update from 2019 to 2022, Mexico is on the list of countries with evidence of autochthonous transmission of ZIKV[29]; in 2024, there were 30 autochthonous confirmed cases of ZVD, as reported by the National Epidemiological Surveillance System of the Ministry of Health[30]. Furthermore, up to July 21, 2025, there are 2 cases already reported, one taking place in Michoacan and the other in Veracruz[31]. Therefore, ZIKV continues to be monitored in Mexico[32].

The Mexican Social Security Institute (IMSS) is the largest health institution, with a coverage of 51% of the Mexican population[33], and it has become a representative institution of the national epidemiology situation. A study carried out with IMSS ZIKV data for a total of 43,725 ZIKV suspected cases dating from January to December 2016 reported that 1,700 (3.8%) were positive for ZIKA[28]. Compared to our study, we observed a higher positivity (6.0%), which could be due to the period analyzed and the elegibility criteria used.

Factors associated with ZIKV infection and hospitalization

Regarding age, we observed that the group between 20 and 29 years old was significantly associated with ZIKV infection overall, which agrees with previous literature[28], except when pregnant women were excluded from the analysis. This could be due to less outdoor exposure and fewer work responsibilities compared with the older groups, as well as the fact that a significant number of pregnant women ($n = 3{,}008$) who by sex were already associated with infection, as shown here and elsewhere[17], were removed from the analysis.

Regarding sex, our results demonstrate that ZIKV infection was higher in women, even when pregnant women were not considered in the analysis; this agrees with previous reports[17,34–36]. Some of the theories proposed for a higher infection in female sex[37,38] is the skin microbiome, which has been shown to predispose women to *Aedes* mosquito bites[37] and other non-vectorial routes[38] like the sexual transmission of ZIKV[39]. Considering an 80% rate of asymptomatic ZIKV cases and since it has been reported that ZIKV RNA can be detected in semen after six months of symptom presentation[40], sexually active women are far more likely to get ZIKV than men (90% increase), and this makes direct sexual contact the most probable transmission route since the 2015 outbreak[17]. Another factor to consider is that in general, there are more women affiliated with the health system compared to men (75% vs. 72% in 2020)[41]. This is also reflected in the number of women that seek consultation at the IMSS, which in 2020 was 83.2% compared to 81.9% by men[41]. Furthermore, it has been shown that in Mexico, men consult less than women; in 2016, only 34% of 320 million consults were required by men[42].

Even when several studies have reported that there is no difference between pregnant and non-pregnant women regarding their probability to infection neither hospitalization[5,43], blood components such as iron have been investigated as potential factors involved in mosquito feeding preferences, and it has been shown that *Aedes aegypti* feeds more on iron-deficient mice and that iron supplementation reduces dengue virus prevalence and viral load[44]. Therefore, women with iron deficiency, a common situation in pregnancy, could be more susceptible to the *Aedes* mosquito bite[37].

The present study, observed 25% ($n = 3{,}313$) ZIKV positive cases in Mexican pregnant women, which agrees with previous studies[28]. Our analysis showed an association between infection and the first and second trimesters of pregnancy, which coincides with previous national reports[45]. These findings highlight the importance of surveillance in this particular population given that ZIKV infection during the first trimester of pregnancy is associated with a higher risk of microcephaly[46,47]; multiple reports have described their exposure and effects on their fetuses[48,49], and the incidence of microcephaly has increased with ZIKV circulation compared with periods when ZIKV was not present[47]. Therefore, prevention strategies and epidemiological surveillance expansion to pregnant women without symptoms during an epidemic outbreak is suggested, specially during the first two trimesters of pregnancy.

Regarding hospitalization, ZIKV-positive cases had a low rate (11.3%), with zero fatality cases, which is consistent with published literature[48,50]; in pregnant women, no significant differences in hospitalization by trimester were observed.

Environmental factors and ZIKV infection and hospitalization

ZIKV was introduced in Mexico at the end of 2015. The first cases were observed in areas already endemic to dengue and chikungunya virus since 2014[51].

The three states with the highest number of ZIKV-positive cases were Veracruz, Nuevo León, and Yucatán, the latter also reported by Grajales-Muñiz et al., (2019)[28]. A significant correlation was observed between hospitalized positive patients and rainfall scores in 2017 when this was analyzed for Veracruz, the state with most suspected cases.

The abundance of mosquitoes and rainfall has been previously investigated and controversial results have been published where some authors do observe a positive correlation[52], whereas others disagree[53]. Regarding environmental temperatures, it was previously shown that ZIKV spreads efficiently through the host population across a broad range of environmental temperatures, from 17 °C to 37 °C[54]. This is consistent with our findings where a distribution in climatologically diverse areas, such as Nuevo Leon (dry-warm) and Veracruz (warm-humid) was observed[55]. Several studies carried out in Ecuador and Vietnam have documented an association between temperature levels and the number of cases and hospitalization; in addition, the relationship of rainfall levels with epidemic outbreaks has been demonstrated in Brazil, Colombia, and Bangladesh[15,16,56–58]. In Mexico, an association between environmental factors and vector-borne diseases has been documented; an increase in environmental temperature, sea surface temperature, precipitation and the "El Niño" phenomenon have been associated with dengue fever[59], a disease with a seasonality similar to ZVD, and an increase in cases between the months of July and January[60]. This is the first exploratory study reporting the number of cases and hospitalizations of the 2016–2018 ZVD outbreak and their relationship with climatic factors in the country.

The influence of climate variability in vector-borne diseases has been evaluated using the index P, which measures the transmission potential of mosquito-borne pathogens. The mathematical model, which includes humidity, temperature, and precipitation variables, showed a high correlation with dengue incidence, chikungunya, and Zika[18]. Nonetheless, the potential use of mathematical predictor tools based in the epidemiology data of vector-borne diseases is only effective for endemic diseases like dengue because of the high number of cases; for Zika and chikungunya, other factors besides environmental climate conditions must also be considered[18].

Low rates of ZIKV in Mexico after the 2016–2018 outbreak

Some theories have been proposed to explain the reason for the low prevalence of ZIKV infections. For instance, a study reporting the vector distribution and transmission risk states that Mexico is one of the countries particularly affected according to their mathematical model. However, their model included habitat suitability and temperature, and underscored that there are very few areas where suitable habitat and optimal temperature conditions overlap for the two main vector species[13]. Furthermore, competition between vectors is possible—for instance, between *Ae. aegypti* and *Ae. albopictus*, it has been reported that vector competition varies among collections and geographic regions, with a lower rate in northeastern Mexico and the highest rate on the Pacific coast[61]. *Cx. quinquefasciatus* has been shown to be refractory to ZIKV infection, dissemination, and transmission using adult mosquitoes that were collected in the larva or egg stage from areas where no human confirmed cases were reported in Guadalajara, Jalisco, Mexico[62]. In addition, the presence of other mosquito species might impact the virus dissemination. It has been shown that at the beginning of the 2015 ZIKV outbreak in Mexico, both Zika and dengue were present in locations with high dengue risk; at the end of the outbreak, Zika was mainly present in areas with low dengue risk[14].

Another reason for the low incidence could be that cases are not being officially reported; a research group has investigated the prevalence of ZIKV on serum samples from suspected patients (with symptoms consistent with flavivirus infection) from Yucatan, Mexico, from 2021 to 2022 and a total of 25 cases were positive to ZIKV with an estimated incidence of 2.8 symptomatic cases per 1,000 persons per year[63]. This emphasized the need for continuous ZIKV surveillance and reporting in Mexico.

Limitations

Among the limitations of this study is the use of a secondary data source; there is a lack of information about the hospital setting and the confirmed cause for hospitalization. In addition, an undercount of cases is possible. During the first year of co-circulation of these arboviruses, there was a generalized underestimation because the diagnostic algorithm consisted of uniplex PCR reactions for each virus and was limited to only 1 reaction per sample; the physician's clinical suspicion was the only factor defining the laboratory diagnosis[64]. Furthermore, changes in the internal surveillance policies and diagnostic algorithms ocurred during the study period, which may have impacted the number of reported cases. The generalizability of our findings might be limited due to the combination of specific climatic and environmental conditions for ZIKV during the period of study in Mexico. It is necessary to integrate mosquito genetic, vector, and climatic factors to identify the dynamics of their interaction and temporality. In addition, the process for diagnosis also affects temporality, mainly due to the differences in the times for seeking medical attention and the presentation of the first symptom or the time until sampling. It is also important to consider the low circulation or disappearance of ZIKV in the American continent from 2018 onwards[49], which has limited the period of study. Because the database is constructed from passive surveillance, only symptomatic patients who required ZIKV testing were included in this study.

Conclusions

Recently, minimal circulation of ZIKV has been reported in Mexico, with only 30 cases in 2024 and 2 cases up to july 21, 2025[31]. However, the coexistence of three mosquito species of medical importance for vector-borne diseases, *Aedes aegypti*, *Aedes albopictus*, and *Culex quinquefasciatus*, have been reported in urban and semiurban areas[65]. Therefore, we should not ignore the potential reemergence of ZIKV in the coming years because of the similar seasonality and persistent appearance every 7 or 8 years have been reported for other arboviruses[66]. Entomological surveillance and appropriate implementation of strategies to control the three species are necessary to avoid the combination of factors such as weather, susceptible population, and vector-borne viruses with infectious potential. Epidemiologic surveillance of ZIKV and exploratory reports like ours must be maintained, emphasizing analysis that includes pregnant women.

Data availability

Data are available as supplementary files.

Received: 22 October 2024; Accepted: 13 August 2025
Published online: 28 October 2025

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Acknowledgements
We are grateful for the work of the epidemiologists of the Mexican Social Security Institute who were responsible for generating the databases supporting this project.

Author contributions
M.B.L. and F.G.S. performed the conceptualization. B.L.E.G. and M.B.L. performed investigation. J.E.M.M. provided resources. M.E.C.M., B.T.C. and B.L.E.G. performed data curation. M.E.C.M. and B.L.E.G. performed formal analysis. M.E.C.M., M.B.L. and B.L.E.G. proposed the methodology. M.E.C.M., F.G.S. and B.L.E.G. wrote original draft. M.B.L., B.T.C., A.M.S., K.P.U., J.G.I., C.R.G.B., C.S.T., Y.L.H, H.M.F. and A.M.P. wrote and edited the manuscript. All authors reviewed the manuscript.

Declarations

Competing interests
The authors declare no competing interests.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-16239-3.

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