








Epidemiological and Clinical Factors Associated with the Prevalence of Dengue and Zika in Febrile Patients in the Lambayeque Region of Peru

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Abstract

Dengue and Zika are arboviruses transmitted by the *Aedes aegypti* mosquito and cause high morbidity and mortality rates. This study aimed to identify epidemiological and clinical factors related to dengue and Zika in febrile patients in the Lambayeque region of Peru from July 2022 to June 2023. This was a prospective observational cross-sectional study of 403 patients. Arboviruses were diagnosed serologically by enzyme immunoassay using NS1 antigen markers and IgM antibodies against dengue and Zika viruses. Clinical and epidemiological data were collected using clinical-epidemiologic research forms. The sample was characterized by a mean age of 31 years and 46.4% male. Headache (71.7%), myalgia (57.1%), and hand arthralgia (54.1%) were the most common symptoms. The prevalence of dengue and Zika was estimated at 19.9% and 3.4%, respectively. Patients from the province of Ferreñafe (RPa = 2.15, P = 0.011), those who reported no history of the disease (RPa = 2.99, P = 0.002) and those who reported low back pain (RPa = 1.75, P = 0.015) were more likely to present dengue. Comorbidities were associated with Zika (ORa = 13.57, P = 0.012). Dengue and Zika are prevalent arboviruses in febrile patients in the Lambayeque region of Peru, where the origin, lack of history, comorbidities, and some clinical manifestations are associated with a greater likelihood of these diseases.

Keywords: Dengue Fever, Zika, Epidemiological Factors, Prevalence, Febrile Illnesses (DeCS-BIREME)

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INTRODUCTION

Dengue, an arbovirus with a global impact, is responsible for serious conditions such as hemorrhagic fever and shock, with approximately 390 million infections per year worldwide.¹ Zika is associated with complications such as microcephaly and orofacial anomalies in newborns² and Guillain-Barré syndrome in adults.³ Both viruses are transmitted mainly by *Aedes aegypti* and *Aedes albopictus*, vectors that represent critical public health challenges in tropical and subtropical areas, whose geographic distribution has expanded due to climate change, globalization of trade, and population movements.⁴

In vector-borne diseases, the basic reproductive number is a measure of the epidemic potential of a disease that is mainly temperature-dependent.⁵ Recent studies have shown that an increase in the environmental temperature significantly increases the efficiency of infection, dissemination, and viral transmission in mosquitoes, exacerbating the problem in tropical and subtropical areas.⁶ Associated risk factors, such as advanced age, secondary infections, and chronic comorbidities also contribute to this increase.⁷ Consequently, a 20% increase in cases of dengue, Zika, and chikungunya is expected over the next 30 years due to climate change.⁵

In December 2023, the World Health Organization (WHO) declared the current global dengue outbreak a grade 3 emergency, the highest level of alert, with the objective of strengthening surveillance and response capacities in affected countries.⁸ In Peru, a particularly alarming event was recorded in 2023, where, in the first 30 weeks of the year, 222,620 cases of dengue and 381 associated deaths were reported, figures that exceeded ten times the average of the previous five years.⁹ The Lambayeque region of northwestern Peru has been one of the most affected areas with recurrent dengue outbreaks since its reintroduction between 2016 and 2017.¹⁰ In addition, recent studies suggest a possible association between the simultaneous circulation of dengue and Zika in this region and an increase in cases of Guillain-Barré syndrome, which reinforces the need for integrated surveillance of these two arboviruses.¹¹

Febrile patients in endemic areas represent a priority population for epidemiological surveillance, since the initial symptoms of dengue and other arboviruses often overlap with other prevalent infections, complicating differential diagnosis.¹² In the Lambayeque region, local studies have identified key risk factors such as inadequate water storage, high vector mosquito density, unfavorable socioeconomic conditions, and limited community participation in prevention strategies.¹³ Despite this knowledge, there are still critical gaps in our understanding of the clinical and epidemiological determinants that explain the high prevalence of these viruses in this region, limiting the design of effective interventions.

Therefore, this study aimed to identify the epidemiological and clinical factors related to dengue and Zika in febrile patients in the Lambayeque region of Peru. These findings could help optimize prevention and control strategies in line with the WHO recommendations for the integrated management of arboviruses.

MATERIALS AND METHODS

Type and design of research

This was a prospective observational, cross-sectional, analytical study.

Population and sample

The study population consisted of febrile patients assisted by an institution of the Health Services Network of the Department of Lambayeque, Peru, between July 2022 and June 2023.

The sample included 403 patients, statistically calculated to estimate the proportion, considering an unknown population, a confidence level of 95%, an error of 5%, and a theoretical expected proportion of 50%. Patients were selected probabilistically using systematic sampling by recruiting every second patient according to the correlative code assigned by the Laboratorio de Referencia Regional de Salud Pública (LARESA/L), from which a copy of the clinical epidemiological form and an aliquot of blood serum were obtained for subsequent serological analyses.

Patients older than one year were included; similarly, asymptomatic patients with

incomplete data and those with more than 15 days of illness were excluded according to the epidemiological clinical form. In addition, participants whose samples were hemolyzed, lipemic, in obvious microbial contamination, or in insufficient quantity (less than 500 μ L) were excluded.

Data collection techniques and instruments

The outcome variables studied were prevalence of dengue and Zika. The independent variables were the epidemiological and clinical characteristics of the patients. The epidemiological variables included sex, age, pregnancy status, travel in the previous 15 days, type of IPRESS (healthcare provider institution), and occupation. The clinical variables were the time of illness, frequent signs and symptoms (headache, myalgia, arthralgia of the hands, arthralgia of the feet, lumbar pain, nausea/vomiting, rash/exanthema, and conjunctivitis), alarm signs (severe abdominal pain, chest pain or dyspnea, serous effusion, and persistent vomiting), signs of severity (weak and undetectable pulse, differential BP <20 mmHg, and severe organ involvement), and dengue classification (no alarm signs, with alarm signs, and severe).

Arboviruses were measured by serological diagnosis using the following enzyme immunoassays: NS1 antigen (Bio-Rad Laboratories, USA) and IgM antibodies (Vircell Microbiologist, Spain) against dengue and Zika. The tests were performed at the Viral Immunology Laboratory of the Lambayeque Regional Hospital, following the procedures described by a commercial company. Serum samples with indeterminate results were repeated; if the result persisted, it was considered negative.

The clinical and epidemiological data were collected using the documentation technique of the "Clinical-epidemiological research form for the surveillance of dengue, chikungunya, Zika, yellow fever and other arboviruses", official document of the Peruvian Ministry of Health for the surveillance of these diseases. They were then recorded on an ad hoc data collection sheet.

Statistical analysis

The data were recorded on a Microsoft Excel 2019 spreadsheet, considering the variables

in the columns and cases in the rows. Statistical analyses were performed using Stata.¹⁴ Descriptive analyses were performed on the outcomes and independent variables according to their nature. Relative and absolute frequencies were calculated for categorical variables, and means and deviations (parametric) or medians with interquartile ranges (non-parametric) were calculated for numerical variables.

To relate the independent variables to the prevalence of dengue and Zika, bivariate analysis was performed according to the nature of the independent variables. Categorical variables were analyzed using the chi-square (polytomous) and Fisher's exact (dichotomous) tests, and numerical variables were analyzed using Student's t-tests. Likewise, crude and adjusted prevalence ratios and 95% confidence intervals were calculated as measures of strength of association between the independent variables and dengue, whereas odds ratios were calculated for Zika. Confounding variables were controlled using Poisson and logit multiple regression models for adjusted prevalence ratios and adjusted odds ratios, respectively. In addition, a variance inflation factor of less than 8 was assessed for correct model fit. Statistical significance was set at P-value of less than 0.05.

Ethical considerations

This study was approved by the Ethics Committee of the hospital in charge of the serum and epidemiological forms of the study patients (0914-016-22 CEI). All collected data were securely stored by the study authors, and access was restricted to the research team only.

RESULTS

In total, 403 febrile patients from the Lambayeque region were studied (Figure). The sample showed prevalences of 19.9% and 3.4% of dengue and Zika, respectively (Table 1). It was also epidemiologically characterized by a mean age of 31 years and by 46.4% of the participants being men (Table 2). Table 3 shows the clinical characteristics, with a median of three days of illness and headache (71.7%), myalgia (57.1%), and arthralgia of hands (54.1%) as the most frequent manifestations. Table 4 shows the

bivariate analysis of epidemiological and clinical characteristics and the prevalence of dengue and Zika.

Table 5 shows the measures of the strength of association between the factors and dengue, where the origin, history of dengue, and manifestation of low back pain were associated with a greater likelihood of suffering from the disease ($P < 0.050$). Indeed, patients from the province of Ferrenafe had a 115% higher likelihood of dengue than those from Chiclayo ($RP_a = 2.15$, $P = 0.011$). Also, those patients who stated that they were unaware of a history of dengue fever were 199% more likely to present it, compared to those who stated that they had no history ($RP_a = 2.99$, $P = 0.002$). Similarly, patients who reported low back pain as a clinical manifestation were 75% more likely to have the disease ($RP_a = 1.75$, $P = 0.015$).

Table 6 shows the measures of the strength of association between the factors and Zika, showing that patients with some comorbidities were more than 13 times more likely to present Zika, compared to those who did not report comorbidities ($OR_a = 13.57$, $P = 0.012$).

Model adjusted for age, sex, origin, history, comorbidities and clinical manifestations (hand arthralgia, foot arthralgia, myalgia, headache, eye pain, low back pain, nausea/vomiting, rash/exanthema and conjunctivitis).

Table 1. Prevalence of dengue and zika in febrile patients in the Lambayeque region, Peru, during July 2022 to June 2023

Arbovirosis	N	95% CI
Dengue (n = 403)	80	19.9 (16.0-23.8)
Zika (n = 291)	10	3.4 (1.3-5.5)
Dengue + zika (n = 291)	3	1.0 (0.0-2.2)

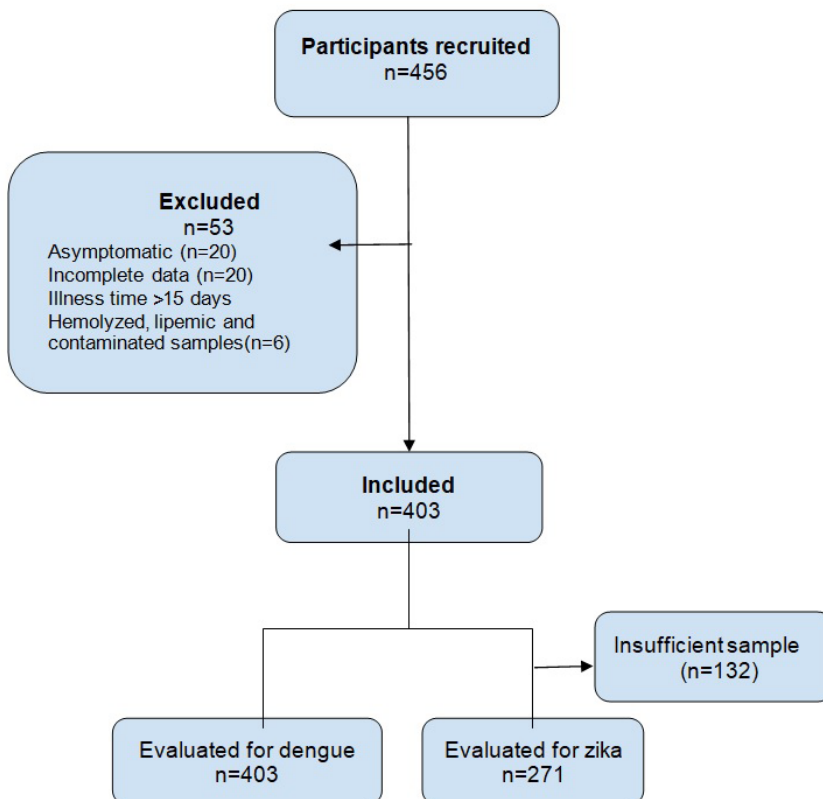


Figure. Flowchart describing the participant selection process

Table 2. Epidemiological characteristics of febrile patients in the Lambayeque region, Peru, during July 2022 to June 2023 (n = 403)

Epidemiological characteristics	N	%
Age (years)*	31.7	18.3
Sex		
Male	187	46.4
Female	216	53.6
Pregnant	19	4.7
Trips 15 days prior	52	12.9
Type of IPRESS		
Minsa	334	82.88
EsSalud	58	14.39
Police	8	1.99
Private	3	0.74
Occupation		
Student	108	26.8
Homemaker	77	19.1
Farmer/Worker	45	11.2
Healthcare Professional	20	5.0
Commerce/Transportation	15	3.7
Teacher	15	3.7
Police Officer	11	2.7
Office Worker	10	2.5
Other	102	25.3
Province of origin		
Chiclayo	252	62.5
Lambayeque	101	25.1
Ferreñafe	39	9.7
Other	11	2.7
Case Type		
Autochthonous	351	87.1
Imported	52	12.9
History of dengue		
Not	302	74.9
Yes	49	12.2
Unknown	52	12.9
Comorbidity		
Unknown	83	20.6
Not	269	66.7
Yes	51	12.7
Type of comorbidity		
Hypertension (n = 51)	16	31.4
Diabetes mellitus (n = 51)	6	11.8
Autoimmune disease (n = 51)	5	9.8
Other comorbidities (n = 51)	16	31.4

*Mean and standard deviation; IPRESS = institution that provides health care services

DISCUSSION

The most frequent epidemiological and clinical characteristics of the febrile patients studied were an average age of 31 years, female sex, IPRESS of MINSA and origin from the province of Chiclayo, autochthonous cases, no history of dengue and no comorbidities, clinical illness between 2 and 5 days, headache, myalgia, and arthralgia. These characteristics are consistent with a local study in 2017, which reported similar characteristics.¹⁴ Therefore, it is likely that the characteristics of this population are mainly defined by the climatic (El Niño Costero),

Table 3. Clinical characteristics of febrile patients in the Lambayeque region, Peru, from July 2022 to June 2023 (n = 403)

Clinical features	N	%
Sick time (days)*	3	(2-5)
Common signs and symptoms		
Headache	289	71.7
Myalgia	230	57.1
Arthralgia in hands	218	54.1
Arthralgia in feet	176	43.7
Eye pain	183	45.4
Lower back pain	154	38.2
Nausea/vomiting	144	35.7
Rash/exanthema	42	10.4
Conjunctivitis	21	5.2
Other	58	14.4
Warning signs		
Severe abdominal pain	31	7.7
Chest pain or dyspnea	29	7.2
Serous effusion	3	0.7
Persistent vomiting	16	4.0
Other	13	3.2
Signs of severity		
Weak, undetectable pulse	1	0.2
Differential BP <20 mmHg	2	0.5
Severe organ involvement	1	0.2
Dengue classification		
Dengue SSA	309	76.7
Dengue CSA	92	22.8
Dengue grave	2	0.5

*Median and interquartile range; BP = blood pressure; SSA = no alarm signs; CSA = with alarm signs

geographic, and cultural conditions that cause arbovirolosis.

The prevalence of dengue observed in febrile patients in this study was 19.9%. These results, although relevant, were lower than those reported for other regions with high endemicity. Thus, a study of febrile patients in a Colombian hospital revealed that 51% presented dengue, 44% of whom corresponded to secondary infections.¹⁵ Brazil has also historically documented a high burden of disease, accounting for up to 60% of all cases reported worldwide.¹⁶ These differences can be explained by the geographical, climatic, and vector density characteristics. However, in Peru, areas such as Madre de Dios had a prevalence similar to that reported in Colombia and Brazil, given its status as an Amazonian

region with active transmission.¹⁷ Furthermore, in the Lambayeque region, where this study was conducted, a prevalence of 28.1% has been previously documented in 2017,¹⁰ a figure that supports the prevalence of the virus in a range close to that currently detected.

Regarding Zika virus infection (3.4%), the prevalence was lower compared to that reported for other countries in the region. In Nicaragua, during the 2016 outbreak, seropositivity of 36% was observed in children, 46% in households, and 56% in adults.¹⁸ Similarly, in the general population, a review estimates that the average seroprevalence of Zika in the Americas was approximately 40%.¹⁹ These findings reflect considerable exposure to the virus in urban and rural contexts of high transmission, much higher

Table 4. Association of epidemiological and clinical factors with dengue and Zika in febrile patients in the Lambayeque region, Peru, from July 2022 to June 2023

Variables	Dengue/Total (%)	P-value	Zika/Total (%)	P-value
Age (years)*	30.8-35.1	0.031	23.3-31.5	0.087
Sick time (days)	4.0-3.7	0.134	3.8-3.9	0.445
Male sex	38/187 (20.3)	0.900	7/135 (5.19)	0.196
Pregnant	5/19 (26.3)	0.553	0/14 (0.0)	0.999
Province of Origin				
Chiclayo	43/252 (17.1)	0.006	8/186 (4.3)	0.676
Ferrenafe	14/39 (35.9)		1/28 (3.6)	
Lambayeque	18/101 (17.8)		1/69 (1.5)	
Other	5/11 (45.5)		0/8 (0.0)	
Trips 15 days prior	12/52 (23.1)	0.576	1/41 (2.4)	0.999
History of dengue				
Not	53/302 (17.6)	0.078	8/221 (3.6)	0.403
Yes	11/49 (22.5)		0/35 (0)	
Unknown	16/52 (30.8)		2/35 (5.7)	
Comorbidity				
Not	47/269 (17.5)	0.073	5/203 (2.5)	0.218
Yes	16/51 (31.4)		3/37 (8.1)	
Unknown	17/83 (20.5)		2/51 (3.9)	
Arthralgia in hands	50/218 (22.9)	0.104	4/162 (2.5)	0.347
Arthralgia in feet	45/176 (25.6)	0.012	4/127 (3.2)	0.999
Myalgias	54/230 (23.5)	0.043	4/170 (2.4)	0.328
Headache	64/289 (22.2)	0.072	8/215 (3.7)	0.738
Eye pain	45/183 (24.6)	0.033	4/135(3.0)	0.756
Lower back pain	45/154 (29.2)	<0.001	3/111(2.7)	0.746
Nausea/vomiting	31/144 (21.5)	0.602	3/105 (2.9)	0.753
Rash/exanthema	13/42 (31.0)	0.066	2/31 (6.5)	0.607
Conjunctivitis	5/21 (23.8)	0.778	1/15 (6.7)	0.999

*Mean infected-uninfected patients; Student's P-value. **Fisher Exact for dichotomous variables and Chi-square for polytomous variables

Table 5. Strength of association between epidemiological and clinical factors with dengue in febrile patients in the Lambayeque region, Peru, from July 2022 to June 2023

Variables	Simple regression		Multiple regression	
	PRc (95% IC)	P-value	PRa (95% IC)	P-value
Age (years)	1.01 (1.00-1.02)	0.039	1.00 (0.99-1.02)	0.393
Province of Origin				
Chiclayo	Ref.		Ref.	
Ferreñafe	2.10 (1.28-3.47)	0.004	2.15 (1.19-3.89)	0.011
Lambayeque	1.04 (0.63-1.72)	0.865	0.92 (0.55-1.54)	0.747
Other	2.66 (1.32-5.38)	0.006	1.52 (0.77-3.03)	0.231
History of dengue				
Not	Ref.			
Yes	1.28 (0.72-2.27)	0.402	1.15 (0.65-2.03)	0.632
Unknown	1.75 (1.09-2.82)	0.021	2.99 (1.48-6.05)	0.002
Comorbidity				
Not	Ref.			
Yes	1.80 (1.11-2.91)	0.017	1.59 (0.93-2.71)	0.092
Unknown	1.17 (0.71-1.93)	0.531	0.50 (0.24-1.05)	0.066
Arthralgia in hands	1.41 (0.94-2.13)	0.096	0.79 (0.46-1.35)	0.379
Arthralgia in feet	1.66 (1.11-2.46)	0.012	1.49 (0.88-2.55)	0.140
Myalgias	1.56 (1.02-2.39)	0.040	1.08 (0.66-1.78)	0.753
Headache	1.58 (0.95-2.61)	0.076	1.21 (0.69-2.12)	0.509
Eye pain	1.55 (1.04-2.30)	0.031	1.16 (0.71-1.89)	0.551
Lower back pain	2.08 (1.40-3.08)	<0.001	1.75 (1.12-2.75)	0.015
Rash/exanthema	1.67 (1.01-2.75)	0.046	1.42 (0.83-2.40)	0.198

Table 6. Strength of association between epidemiological and clinical factors with Zika in febrile patients in the Lambayeque region, Peru, from July 2022 to June 2023

Variable	Simple regression		Multiple regression	
	ORc (95% IC)	P-value	ORa (95% IC)	P-value
Age (years)	0.97 (0.93-1.01)	0.166	0.96 (0.92-1.02)	0.169
Sex				
Female	0.36 (0.09-1.41)	0.143	0.27 (0.05-1.43)	0.123
Male	Ref.		Ref.	
Comorbidity				
Not	Ref.		Ref.	
Yes	3.5 (0.80-15.30)	0.097	13.57 (1.79-102.65)	0.012
Unknown	1.62 (0.30-8.58)	0.573	0.76 (0.04-16.55)	0.860
Arthralgia in hands	0.52 (0.14-1.88)	0.318	0.96 (0.75-1.23)	0.754
Arthralgia in feet	0.86 (0.24-3.10)	0.813	4.8 (0.46-50.15)	0.190
Rash/exanthema	2.17 (0.44-10.72)	0.341	4.53 (0.60-34.37)	0.144

Model adjusted for age, sex, origin, history, comorbidities and clinical manifestations (hand arthralgia, foot arthralgia, myalgia, headache, eye pain, low back pain, nausea/vomiting, rash/exanthema and conjunctivitis). Average variance inflation factor = 2.4

than that observed in the Lambayeque region, mainly because in this study, active infection was sought through IgM detection, unlike previous studies that focused on seroprevalence (IgG). However, the low prevalence of Zika in Lambayeque should be actively monitored because of its epidemic potential in the context of co-circulation with other arboviruses.

In terms of age, most patients with positive serological markers for dengue were between 30.8 and 35.1 years old ($P = 0.031$), whereas for Zika they were between 23.3 and 31.5 years old ($P = 0.087$, marginally not significant). These age groups belong to a young economically active population, in which intense physical activity may be related to the growth of bacteria that generate metabolites attractive to mosquitoes.²⁰ CO₂ emission is a factor that influences the attraction of mosquitoes, and children have lower emissions of CO₂, which explains why more cases are observed in adults in the intradomestic environment.²¹ In addition, active metabolism in adults generates greater body heat and promotes the growth of metabolite-producing bacteria that are attractive to mosquitoes.²¹ However, a systematic review that evaluated the epidemiological impact of dengue in Colombia found that 50% of the cases occurred in children under 20 years of age, with the highest incidence in the age group of 5-14.²²

Low back pain was the only clinical manifestation that showed an association with dengue. Although other classic symptoms, such as myalgia, eye pain, and exanthema, showed a possible association in the bivariate analysis, they lost statistical significance in the multivariate analysis, suggesting less diagnostic utility when other clinical or epidemiological variables were considered. The prevalence of low back pain as a clinical manifestation of dengue has also been previously reported in Peru: 65.9% in Amazonas,²³ 73% in La Libertad,²⁴ and 74.8% in Lambayeque.¹⁴ These findings highlight the high frequency of this symptom in patients with dengue, reinforcing its value as a potentially relevant clinical marker in the context of epidemics.

This study identified a significant association between certain epidemiological

factors and dengue infection, in particular, origin from Ferreñafe. Indeed, a high frequency of cases in this province has been reported previously²⁵ and could be explained by environmental factors, urbanization conditions, variations in vector density, and sociocultural factors. In this regard, in Pueblo Nuevo, one of the most affected districts in the province, a marked community resistance to fumigation campaigns was reported, with only 47.4% of families allowing health personnel to enter their homes,²⁶ which limits vector control actions and favors transmission.

Finally, this study revealed active circulation of dengue and Zika viruses in the Lambayeque region, in addition to a co-infection rate of 1.0%. These values are lower than those reported in highly endemic regions of Latin America, but confirm the persistence of epidemiological risks in this area of northern Peru.¹⁹ Cases of dengue and Zika together account for 23.4% of the febrile cases, accounting for only a quarter of the febrile cases, which can be explained by other prevalent febrile diseases such as leptospirosis, which has been reported to account for more than 26% of the febrile population in Lambayeque.²⁷

As for Zika, only comorbidities were found to be associated with the highest prevalence, probably due to the increased susceptibility of the person to these conditions. In this regard, other Latin American studies have reported that comorbidities such as diabetes, hypertension, and sickle cell anemia were associated with severe disease and a fatal outcome due to this virus.²⁸

The study had some limitations: probable information bias in the completion of the clinical-epidemiological forms and probable measurement bias in the detection of Zika by serological methodology, since the commercial ELISA kit used has not been standardized for use in the Peruvian population. However, the observed results are plausible in the existing theory and can be generalized to the febrile population of the Lambayeque region because of the representative sample size. Potential confounding factors were controlled in the association analyses.

CONCLUSION

It was concluded that dengue and Zika are prevalent arboviruses in febrile patients in the Lambayeque region of Peru, where the province of origin, unawareness of history, and low back pain were associated with a greater possibility of having dengue, whereas comorbidities were associated with Zika. This finding suggests the influence of environmental, urban and sociocultural variables, such as low acceptance of vector control measures, on local transmission dynamics. Overall, these results reinforce the need to strengthen epidemiological surveillance, promote sustained community interventions, and improve prevention and differential diagnostic strategies, especially in the context of arbovirus co-circulation.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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DATA AVAILABILITY

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

This study was approved by the Ethics Committee, Lambayeque Regional Hospital (0914-016-22 CEI).

INFORMED CONSENT

Written informed consent was obtained from the participants before enrolling in the study.

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