

## Major Article

# Emergence of chikungunya and Zika in a municipality endemic to dengue, Santa Luzia, MG, Brazil, 2015-2017

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### Abstract

**Introduction:** The recent circulation of arboviruses transmitted by vectors, such as dengue, chikungunya, and Zika, is concerning due to the high morbidity rates, clinical complications, and increased demand on health services. The objective of this study was to analyze the clinical and epidemiological aspects of an epidemic caused by arboviruses in the municipality of Santa Luzia, Minas Gerais, Brazil. **Methods:** Longitudinal study of patients with acute febrile disease and suspected arbovirus infection reported to Brazilian Notifiable Disease Information System (Sistema de Informação de Agravos de Notificação) from the epidemiological week 44 of 2015 to epidemiological week 52 of 2016. Patients with confirmed chikungunya were followed-up for 18 months and those with Zika for 15 months. Additionally, we analyzed and described the temporal distribution of confirmed cases of these arboviruses in this municipality. **Results:** Overall 3,531 arboviruses cases, including 3,481 (98.7%) cases of dengue, 38 (1.0%) cases of chikungunya, and 12 (0.3%) cases of Zika were confirmed. The highest incidence of arbovirus infection occurred in the first quarter of 2016 (epidemiological week 7 to 14). The most frequent symptoms were for dengue, which included fever, headache, retro-orbital pain, and exanthema. Chikungunya infection was associated with fever, myalgia, arthralgia, and rash while Zika infection with pruritus and rash. **Conclusions:** Given the similarities in the initial clinical profiles of these arboviruses, it is important to perform a detailed clinical analysis, laboratory diagnosis, and patient follow-up.

**Keywords:** Dengue. Diagnosis. Chikungunya. Outbreak. Symptoms. Zika.

### INTRODUCTION

Vector-borne infectious diseases account for more than 700,000 deaths per year worldwide and have become a concern for public health systems due to their increasing incidence in recent decades<sup>1</sup>. Dengue, chikungunya, and Zika show high morbidity rates, severe clinical forms, and lead to increased

demand for health and other support services. Moreover, the increasing number of epidemic regions showing co-circulation of the respective viruses DENV, CHIKV, and ZIKV is alarming<sup>1,2</sup>.

The high transmissibility and the changes in ecosystems associated with human occupation<sup>3,4</sup> have made these diseases a challenge to public health. The entry of the arboviruses, CHIKV and ZIKV, into countries endemic to dengue, such as Brazil, considerably impacts the health services, thus leading to negative economic, political, and social consequences<sup>1,5</sup>.

It is estimated that 390 million cases of dengue infections occur each year, worldwide<sup>6</sup>. Despite the low mortality rate of

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the disease, 60.9% of the deaths reported in the Americas in 2017 occurred in Brazil<sup>7</sup>. Moreover, dengue is responsible for considerable loss of healthy years of life in the country, as it affects people from all age groups<sup>8</sup>.

Regarding chikungunya, most of the patients do not show complete recovery after the acute phase of the disease, with symptoms taking weeks or months to start regressing, and functional limitations interfering with the patient's occupational activities<sup>9,10</sup>. In 2017, Brazil was associated with 81.8% of the cases and 92.4% of the deaths due to chikungunya in the Americas<sup>11</sup>.

Zika infection, on the other hand, can lead to the development of Guillain-Barre syndrome with autoimmune and neurological alterations<sup>12</sup>. In the Americas, 45.1% of the cases and 50% of the deaths due to Zika were concentrated in Brazil in 2016<sup>11-13</sup>.

Given the similar initial symptomatology, the clinical diagnoses of DENV, CHIKV, and ZIKV may be hindered by the co-circulation of these pathogens<sup>13-15</sup>. Laboratory diagnosis, which is still unavailable for most patients, has the drawback of long processing time; the resultant effect of the delay is helpful for epidemiological control but of little use for the treatment<sup>11</sup>. Therefore, a better characterization of these arboviruses is required for differential diagnoses, especially in regions endemic to dengue, with co-circulation of CHIKV and ZIKV viruses. Moreover, a clinical and epidemiological follow-up of chikungunya and Zika infections would help to better understand the morbidity patterns of these diseases according to their severity, thus leading to a more comprehensive evaluation of the magnitude of the problem.

The highest incidence of cases of dengue in Brazil in 2017 was observed in the state of Minas Gerais<sup>16</sup>, and, in this state, the municipality of Santa Luzia was the first to report cases of chikungunya (November 2015), being a region endemic to dengue, with co-circulation of CHIKV and ZIKV viruses.

To better understand the clinical patterns and the consequences of the co-occurrence of these diseases, we characterized the temporal distribution of dengue, chikungunya, and Zika infections and analyzed the clinical and epidemiological characteristics of these three arboviruses in this endemic region. Understanding these patterns may help to guide and evaluate the interventions carried out by the public health system, thus improving the management of these arboviruses in endemic regions.

## METHODS

**Study Area** - The municipality of Santa Luzia, MG (Brazil) is located in the metropolitan mesoregion of Belo Horizonte and had an estimated population of 218,897 inhabitants in 2017. Santa Luzia had a demographic density of 862.38 inhabitants/km<sup>2</sup> and a territorial area of 235,076 km<sup>2</sup> in 2015. Its climate is tropical with monthly average temperatures ranging from 18.4 to 29.2°C and mean temperatures oscillating around 5.4°C throughout the year<sup>17</sup>.

Geographically it is subdivided into 82 neighborhoods, which are distributed into five regions: Parte Alta (28 neighborhoods), Parte Baixa, (23 neighborhoods), the São Benedito district (20

neighborhoods), expansion zone (eight neighborhoods), and the rural zone (three neighborhoods)<sup>17</sup>. The Unified Health System (Sistema Único de Saúde – SUS) of the municipality has 26 public basic health units (Unidades Básicas de Saúde – UBS), one early care unit (Unidade de Pronto Atendimento - UPA), and one hospital<sup>18</sup>.

**Participants and inclusion criteria** - We conducted a longitudinal case series study. Data were obtained from the Brazilian Notifiable Disease Information System (Sistema de Informação de Agravos de Notificação - SINAN). We collected information from patients with acute febrile illness that consulted public health system with suspicion of arboviruses infection from the epidemiological week (EW) 44 of 2015 to EW 52 of 2016. Cases classified as 'discarded' or 'blank' by the SINAN and those in which the diagnosis was not compatible with dengue, chikungunya, or Zika were excluded. Only patients with clinical, epidemiological, and laboratory confirmation of arboviruses infection were included.

Clinical confirmation was based on the Pan American Health Organization (PAHO)/World Health Organization (WHO) clinical inclusion criteria for dengue, chikungunya, and Zika<sup>19</sup>, which were established for patients presenting with acute febrile illness and two or more of the following signs and symptoms:

- Dengue: headache, retro-ocular pain, myalgia, arthralgia or rash; persistent vomiting, drowsiness and/or irritability, postural hypotension, painful hepatomegaly >2 cm, decreased diuresis, temperature drop, mucosal bleeding, abrupt platelet collapse (<100,000) associated with hemoconcentration<sup>19</sup>.
- Chikungunya: severe joint pain, headache, diffuse back pain, myalgia, nausea, vomiting, polyarthrititis, rash, and conjunctivitis<sup>20</sup>.
- Zika: exanthema, conjunctivitis, muscle and joint pains, malaise or a headache, which is usually mild<sup>13</sup>.

Collected blood samples were submitted for viral RNA extraction, and then a reverse transcription followed by real-time polymerase chain reaction (qRT-PCR) was performed using the following kits:

- Dengue: Biogene Dengue PCR Kit - Bioclin Quibasa. Registration with Anvisa: 10269360302;
- Chikungunya: Biogene Kit Chikungunya PCR - Bioclin Quibasa. Registration at Anvisa: 10269360301;
- Zika: Biogene Kit Zika PCR Virus - Bioclin Quibasa. Anvisa Registration: 10269360300.

**Characterization of patients** - Subsequently, we evaluated the clinical evolution of chikungunya once confirmed in a patient, for up to 18 months. Patients were monitored through three stages of their clinical evolution as follows: The first monitoring occurred between one and six months after the initial diagnosis. The second and the third monitoring occurred between 7 and 12 months, as well as between 13, and 18 months after the initial diagnoses, respectively.

For Zika cases, two medical evaluations were carried out between 1 and 6 months after the initial diagnosis (first

monitoring), and between 12 and 15 months after diagnosis (second monitoring).

Patients with dengue were not followed-up in the present study.

**Analyses** - We analyzed and described the temporal distribution of confirmed cases of dengue, chikungunya, and Zika in the municipality of Santa Luzia throughout the duration of the study.

The sociodemographic characteristics (age, gender, race, pregnancy, and region of origin) of the study population were described. The clinical signs and symptoms were characterized according to the PAHO/WHO<sup>19</sup> case definitions during the initial phases for these three arboviruses infections. Results were expressed as percentages and confidence intervals of 95% (95% CI).

Paired observations were evaluated to determine the occurrence of signs and symptoms in the same chikungunya patients during the acute and chronic phases of the disease.

**Ethical considerations** - This study was approved by the Research Ethics Committee of Hospital Foundation of Minas Gerais State (FHEMIG), Protocol number 63286116.0.0000.5119.

## RESULTS

### Temporal distribution of confirmed cases

During the study period, from EW 44 of 2015 to EW 52 of 2016, 7,063 cases with International Classification of Diseases, Tenth Revision (ICD-10) diagnoses compatible with arboviruses were notified to SINAN in the municipality of Santa Luzia including 6,757 (95.7%) cases of dengue, 253 (3.5%) cases of

Zika, and 58 (0.8%) cases of chikungunya. Among those, 3,532 (3,276 of dengue, 236 of Zika, and 20 of chikungunya) were excluded as they did not meet the clinical, epidemiological, and/or laboratory criteria. Therefore, the remaining 3,531 confirmed cases were included in the present study. These included 3,481 (98.7%) cases of dengue (with 954 (27.4%) confirmed by laboratory criteria and 2,527 (72.6%) by clinical-epidemiological criteria); 38 (1.0%) of chikungunya (confirmed by laboratory criteria); and 12 (0.3%) of Zika (confirmed by laboratory criteria).

In general, the highest incidence of arboviruses in the municipality occurred between February (EW 7) and April (EW 14) 2016. The three diseases were observed occurring concomitantly. However, while cases of dengue fever were diagnosed during most of the period (November 2015 to November 2016); chikungunya cases occurred mainly between December (EW 51) 2015 and June (EW 23) 2016, with three new cases reported in December (EW 51) 2016. Confirmed cases of Zika were restricted to the period between February (EW 6) and May (EW 21) 2016 (**Figure 1**).

### Demographic profile of patients with arboviruses

The mean age of patients with dengue was 29.4 (median, 25) years with 21.2% of patients aged between 21 to 30 years. The mean age of patients with chikungunya was 44.3 (median, 46) years, and 23.7% of patients were aged between 51 and 60 years. The mean age of patients with Zika was 29.2 (median, 26) years, with 41.7% of patients aged between 21 and 30 years.

For the three diseases, most of the notifications occurred up to three days following the onset of symptoms and the majority of the patients were females, Pardos, and urban region residents (**Table 1**).

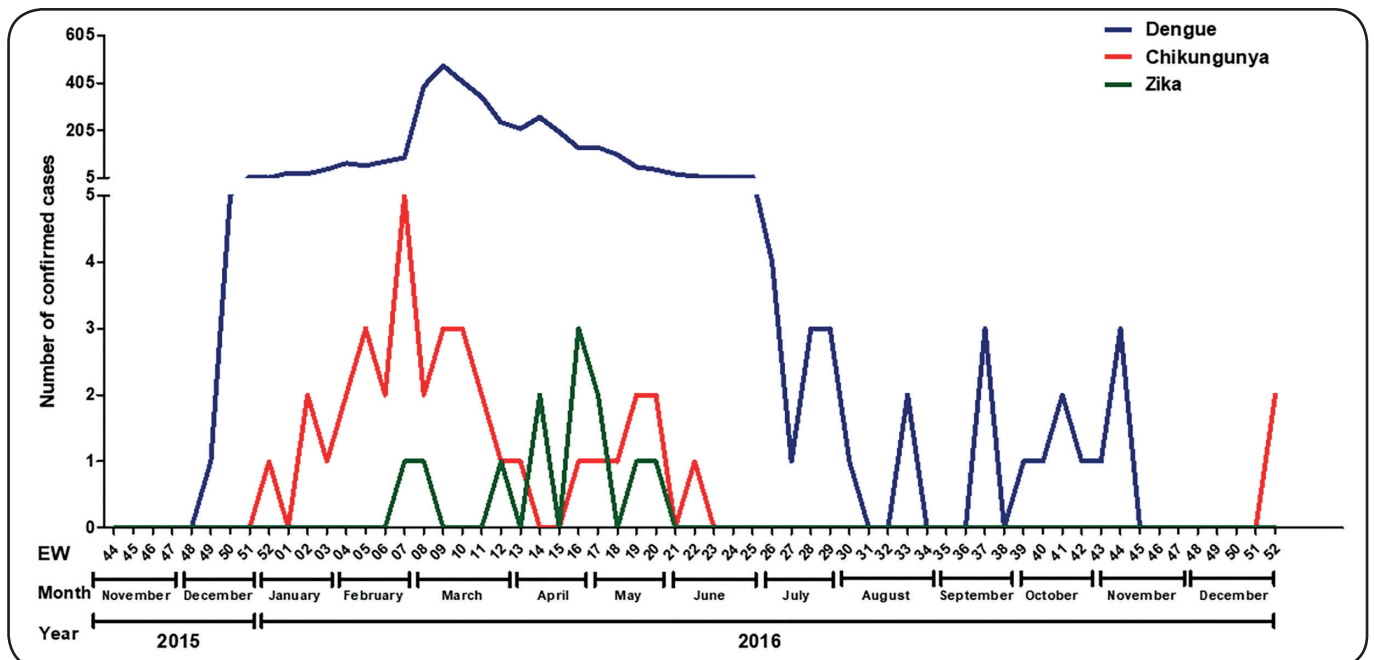


FIGURE 1: Temporal distribution of confirmed cases of arboviruses in Santa Luzia, Minas Gerais, Brazil, 2015-2016. EW: epidemiological week.

**TABLE 1:** Surveillance and epidemiological characteristics of patients with arboviruses in Santa Luzia, Minas Gerais, Brazil, 2015-2016.

Variable	Dengue EW44 of 2015 to EW52 of 2016		Chikungunya EW51 of 2015 to EW52 of 2016		Zika EW01 to EW52 of 2016	
	(n = 3,481)	%	(n = 38)	%	(n = 12)	%
<b>Time between onset of symptoms and notification (days)</b>						
0-3	1,978	56.8	22	57.9	10	83.4
4-6	963	27.7	7	18.4	1	8.3
7+		15.5	9	23.7	1	8.3
<b>Age (years)</b>						
0-4	174	5.0	0	0.0	0	0.0
5-14	524	15.1	0	0.0	0	0.0
15-29	1,117	32.1	7	18.4	10	83.4
30-49	1,137	32.7	13	34.2	1	8.3
50-64	422	12.1	13	34.2	1	8.3
65 +	107	3.1	5	13.2	0	0.0
<b>Gender</b>						
Female	1,962	56.4	35	92.1	12	100.0
Male	1,519	43.6	3	7.9	0	0.0
<b>Pregnancy</b>						
Yes	24	0.7	4	10.5	10	83.3
No	3,457	99.3	34	89.5	2	16.7
<b>Race</b>						
White	457	13.1	9	23.7	4	33.4
Black	202	5.8	9	23.7	1	8.3
Pardo	1,733	49.8	16	42.1	6	50.0
Others*	35	1.0	0	0.0	1	8.3
Ignored**	1,054	30.3	4	10.5	0	0.0
<b>Zone</b>						
Urban	3,454	99.2	29	76.3	12	100
Rural	27	0.8	9	23.7	0	0.0

\*Yellow and indigenous; \*\*Ignored: Not reported; **EW**: epidemiological week.

### Clinical characterization

Among dengue patients, symptoms observed in the acute phase were fever (61.2%, 95% CI 59.5-62.7), headache (60.5%, 95% CI 58.8-62.0), retro-ocular pain (55.4%, 95% CI 53.7-57.1), and exanthema (56.8% 95% CI 55.2-58.5). Regarding chikungunya, the most frequent symptoms were fever and myalgia (84.2%, 95% CI 69.6-92.6), arthralgia (78.9%, 95% CI 63.6-89.0), and exanthema (84.2% 95% CI 69.6-92.6). The main symptoms observed among Zika patients were pruritus (91.7%, 95% CI 64.6-98.0) and exanthema (100.0%, 95% CI 75.7-100.0) (**Table 2**).

The proportions of signs and symptoms observed during the clinical follow-up of chikungunya patients are presented in **Figure 2**. Eight (21.1%) patients showed no symptoms during the first monitoring; 12 (31.6%) patients lacked symptoms

during the second; and 27 (73.3%) presented no symptoms during the third evaluation.

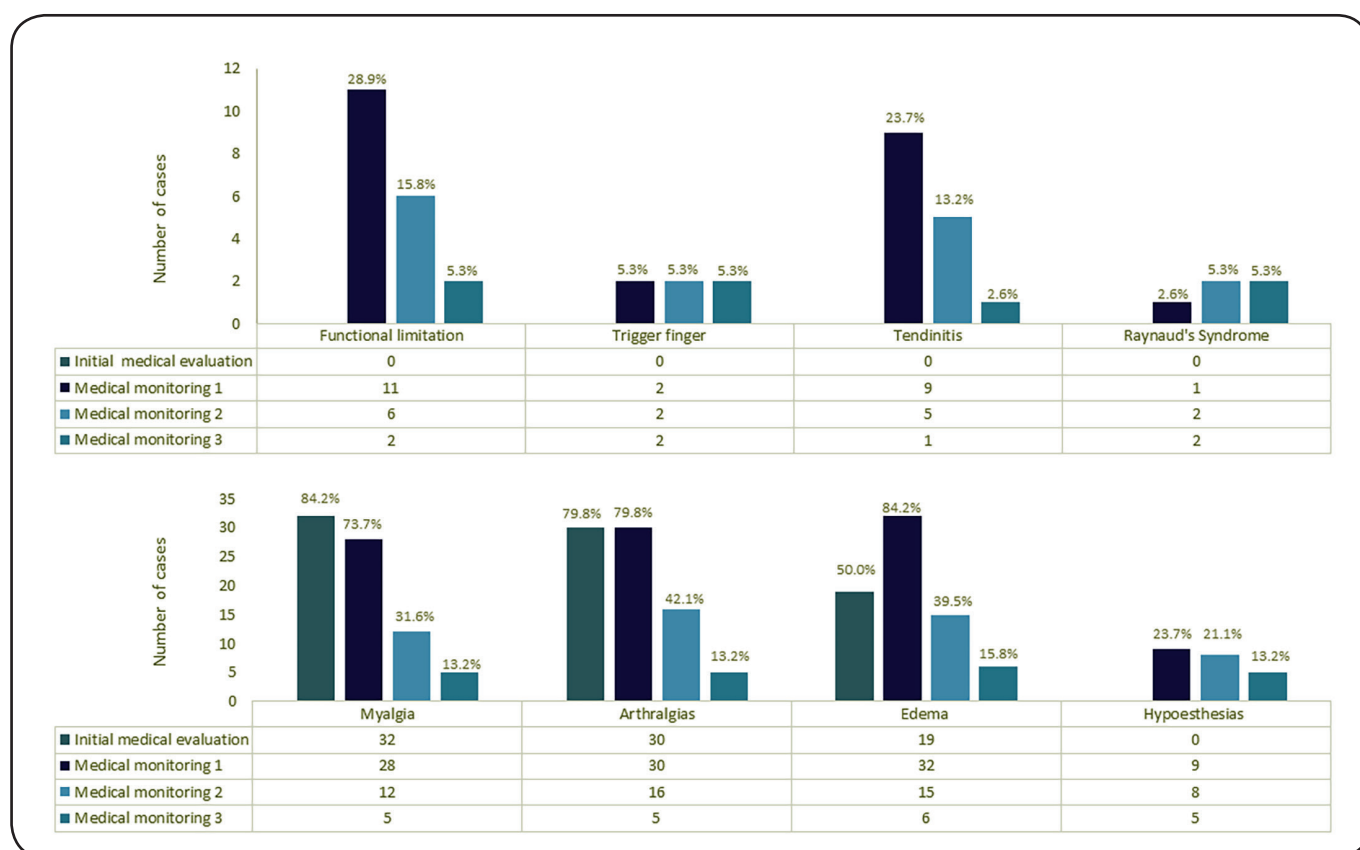
Among the 38 cases of chikungunya confirmed by the laboratory and clinical criteria, 16 (42.1%) showed complicated clinical evolution, presenting with myalgia, arthralgia, edema, or hypoesthesia (**Figure 2**). Some additionally presented with clinical alterations involving the upper extremities, such as functional limitation, trigger finger, tendinitis, and Raynaud's syndrome. Eleven of these patients were being treated for inflammatory arthropathy (comorbidity), while the other five had no history of comorbidity (**Figure 2**).

Among the signs and symptoms evaluated in the study (myalgia, arthralgia, prostration and edema), four were verified in patients during the acute and chronic phases. In the acute phase, 32 patients (84.2%) presented with myalgia, 30 (78.9%)

**TABLE 2:** Clinical signs and symptoms of patients with arboviruses. Santa Luzia, Minas Gerais, Brazil, 2015-2016.

Signs and symptoms	Dengue 2015-2016*		Chikungunya 2016		Zika 2016	
	EW44 of 2015 to EW52 of 2016		EW51 of 2015 to EW52 of 2016		EW01 to EW52 of 2016	
	(n = 3,481)	% (95% CI)	(n = 38)	% (95% CI)	(n = 12)	% (95% CI)
Fever	2,132	61.2 (59.6-62.8)	32	84.2 (69.6-92.6)	1	8.3 (1.5-35.4)
Headache	2,105	60.5 (58.8-62.0)	23	60.5 (44.7-74.4)	3	25 (8.9-53.2)
Retro-ocular pain	1,930	55.4 (53.7- 57.1)	20	52.6 (37.3-67.5)	4	33.3 (14-61)
Myalgia	**	**	32	84.2 (69.6-92.6)	2	16.7 (4.7-45)
Malaise	**	**	11	28.9 (17-44.8)	1	8.3 (1.5-35.4)
Arthralgia	**	**	30	78.9 (63.6-89)	1	8.3 (1.5-35.4)
Nausea	725	20.8 (19.5- 22.2)	7	18.4 (9.2-33.5)	2	16.7 (4.7-45)
Vomiting	697	20.0 (18.7-21.4)	10	26.3 (15-43.4)	**	**
Abdominal pain	345	9.9 (8.9-10.8)	3	7.9 (2.8-21.0)	**	**
Chills	114	3.3 (2.7-3.9)	4	10.5 (4.2-24.2)	**	**
Pruritus	**	**	13	34.2 (21.2-50.1)	11	91.7 (64.6-98)
Exanthema	1,979	56.8 (55.2-58.5)	32	84.2 (69.6-92.6)	12	100 (75.7-100)
Lymphadenopathy	**	**	12	31.6 (19-47.5)	2	16.7 (4.7-45)
Edema	**	**	19	50.0 (34-66.4)	2	16.7 (4.7-45)
Joint effusion	**	**	2	5.3 (1.5-17.3)	**	**

\*SINAN; \*\* Uninformed; **EW:** epidemiological week; 95% CI: 95% Confidence Interval.



**FIGURE 2:** Signs and symptoms observed during the clinical follow-up of chikungunya patients, Santa Luzia, Minas Gerais, Brazil, 2015-2016. Initial medical evaluation corresponded with the time of diagnosis. In the medical monitoring 1, 33 (86.8%) patients were in the sub-acute phase, while 5 (13.2%) were in the chronic phase. In the medical monitoring 2 and 3, all patients were in the chronic phases.



with arthralgia, 19 (50.0%) with edema, and 8 (21.1%) with prostration. In the chronic phase, 21 (55.3%) patients had arthralgia, 17 (44.7%) had myalgia, 15 (39.5%) had edema, and 6 (15.8%) had prostration (**Figure 3A**). The following symptoms presented in the same patient in both phases: arthralgia (21, [55.2%] patients), myalgia (16, [42.1%]), edema (10, [26.3%]), and prostration (3, [7.8%]), (**Figure 3B**).

Regarding the Zika cases, only 12 (4.8%) were confirmed by laboratory tests, 10 (83.3%) of which were pregnant women. From the pregnant women, two, one, and seven were in the first, second, and third trimesters of gestation, respectively. These patients presented with exanthema maculopapular cases at consultation, which declined progressively (12 cases), and pruritus (11 cases). The lesions affected the face (nine cases), upper extremities (11 cases), trunk (11 cases), abdomen (12 cases), and lower extremities (10 cases). The palms and the soles of the feet showed fewer lesions (five and three cases, respectively).

During the two medical follow-ups (first and second monitoring), these Zika patients were asymptomatic. The infants of these women were born at full term, and the initial neonatal assessments did not reveal any neurological changes until the first year of life.

## DISCUSSION

In the present study, we characterized the temporal distribution and the clinical and epidemiological characteristics of arboviruses in a Brazilian municipality, endemic to dengue with co-occurrence of chikungunya and Zika. The municipality studied was the first to register the simultaneous occurrence of these diseases in the state of Minas Gerais. A descriptive analysis of the CHIKV and ZIKV transmission scenario revealed that, in the years 2015 and 2016, cases of chikungunya were observed in 2,933 Brazilian municipalities, while Zika was reported in 2,759 municipalities<sup>16</sup>. In the same period, dengue was reported in all federated units<sup>7</sup>.

Santa Luzia is endemic for dengue and first reported cases of chikungunya occurred in November 2015. Zika cases emerged

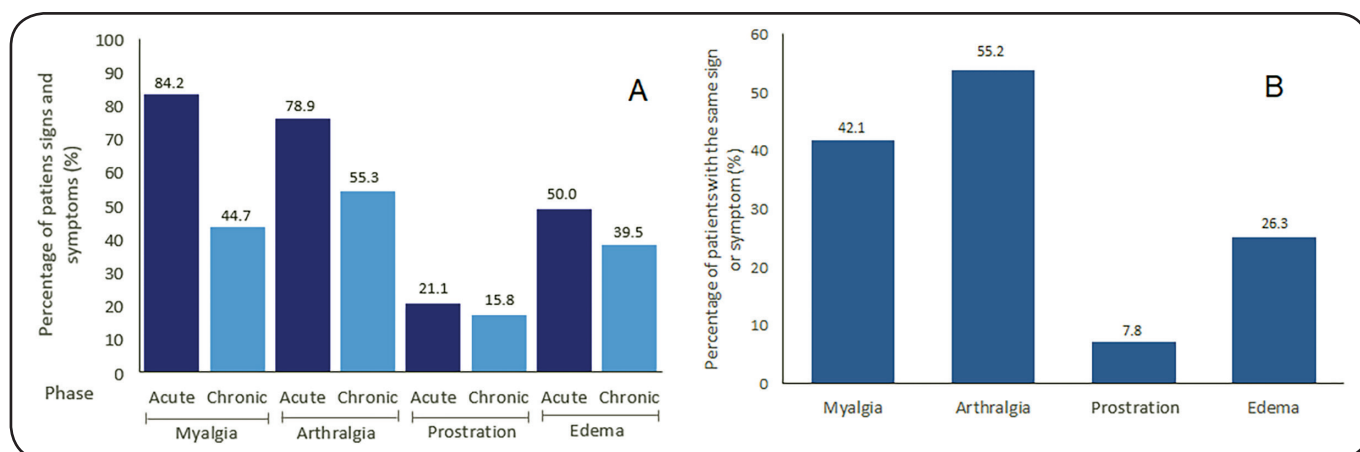
in the municipality in February of the following year. Between December 2015 and June 2016, the three diseases were observed occurring concomitantly. While dengue cases were reported throughout the study period, cases of chikungunya were observed only from December (EW 51) 2015 to June (EW 23) 2016, and confirmed cases of Zika were restricted to the period from February (EW 6) to May (EW 21) 2016.

The patterns of co-circulation of these three arboviruses in Santa Luzia differed compared to that observed in another Brazilian municipality (Recife) in the Northeast state of Pernambuco. While the three arboviruses occurred concomitantly in Santa Luzia, in Recife they occurred at different periods, with chikungunya cases being observed from October 2015 to February 2016, and Zika occurring in March and May 2016 only<sup>21</sup>. On the other hand, co-circulation of DENV, ZIKV, and CHIKV was recorded in the municipality of Tuparetama (also located in the state of Pernambuco), with laboratory confirmation of two patients co-infected with DENV and ZIKV, in April 2015<sup>22</sup>.

The emergence of CHIKV and ZIKV in a region endemic for dengue creates new challenges for public health authorities, since the initial clinical profiles of these arboviruses are very similar<sup>1,12,23</sup>, and laboratory tests are not always available for rapid confirmation, which makes accurate diagnosis difficult. Some authors emphasize the importance of detailed clinical analyses on the first three days of acute symptoms, which should be followed by laboratory diagnosis and follow-up of the patients' progression<sup>24,25</sup>.

In Santa Luzia, the highest proportion of patients with dengue (1,394 cases, 40%) and Zika (nine cases, 75%) were between the second and fourth decades of life. For chikungunya, the majority of the patients were aged between 40 and 60 years (14 cases, 36.8%). Similar patterns in age distribution have been reported in clinical follow-up surveys on the epidemiological dynamics of these three arboviruses in Brazil and other countries<sup>26,27</sup>.

Regarding the gender distribution, predominantly, the incidence was higher in women with chikungunya, as has been



**FIGURE 3:** Signs and symptoms present (A) in the acute and chronic phase of all patients; (B) in acute and chronic phase of the same patient in Santa Luzia, Minas Gerais, Brazil, 2015-2016.

documented in other studies, which reported the history of musculoskeletal system disorders<sup>28,29</sup>.

Ecological, climatological, and epidemiological conditions facilitate the propagation of mosquitoes transmitting pathogens<sup>30</sup>. In this sense, Zika and chikungunya outbreaks in Brazil have been most commonly reported in urban areas, thus confirming that the characteristics of the landscape play a significant role in the distribution of the diseases, especially with regards to the life cycle of the vector *Aedes aegypti*<sup>31</sup>. The increased population concentration, precarious basic sanitation, and poor health education of the population in Santa Luzia may explain the high density of the vector in this region.

The temporal distribution of arboviruses provides a useful tool that may help the public health system in making more informed decisions to reduce the occurrence and consequent burden of these diseases in the population<sup>32,33</sup>. Investments in preparation for rapid response for dengue, chikungunya, and Zika, including surveillance and diagnosis, behavioral and social interventions, and communication, are essential not only for early detection but also for the management of acute events<sup>14</sup>.

The most frequent symptoms observed among dengue patients were fever, headache, retro orbital pain, and exanthema. Similar symptoms including myalgia, retro orbital pain, nausea, and arthralgia have been described in the literature as being consistently associated with adults, while vomiting and rash are the most common symptoms in children<sup>34</sup>. Other authors have shown that the most frequent manifestations in dengue patients in the acute phase were fever, myalgia, headache, and arthralgia<sup>35</sup>.

The predominance of pregnant women among Zika patients is explained by the protocol adopted by the government, which establishes that laboratorial confirmatory tests should be performed only for this group of patients<sup>7</sup>. Among these patients, exanthema and pruritus were the most frequent clinical manifestations in Santa Luzia. Given the similarity of these initial symptoms to those of other arboviruses, we highlight the importance of correlating the epidemiological context and the evolution of individual symptoms. Similarly, in Guadeloupe, France, the dermatological characteristics at the time of appearance of Zika in 60 confirmed cases were exanthema associated with pruritus<sup>36,37</sup>. Moreover, certain clinical characteristics of the exanthematous lesions strongly point towards the viral etiology. This happens because the rash associated with the Zika virus infection is generally morbilliform, separates the palms and the plants, and begins on the face and extends cephalocaudally<sup>38</sup>.

In Brazil, especially in the North, Northeast, and Southeast regions, ZIKV outbreaks have been a cause of concern for pregnant women as the intrauterine infection is associated with multiple cerebral malformations and microcephaly<sup>39</sup>. A study on newborns, from the Brazilian states of Pernambuco and Ceará, whose mothers had Zika infection during pregnancy revealed that, despite the absence of microcephaly at birth, 11 out of 13 babies presented with brain abnormalities associated with congenital Zika syndrome at the age of five months<sup>40</sup>. In our study, children delivered by the ten pregnant patients who had

a positive diagnosis for ZIKV infection did not present with neurological sequelae when evaluated at birth. Although it was not in the scope of our study, we highlight that it is important to ensure the clinical follow-up of these newborns, according to the recommendations of the Ministry of Health<sup>7</sup>.

For chikungunya, the most frequent symptoms were fever (84.2%), myalgia (84.2%), and arthralgia (78.9%). This is in agreement with a previous prospective cohort study showing fever (89.7%) and arthralgia (87.6%) to be the most common symptoms among the 97 chikungunya patients; arthralgia persisted for up to six weeks, especially among women<sup>41</sup>.

Our chikungunya patients were clinically evaluated over a period of up to 18 months from the date of confirmation of infection. Sixteen patients presented with complicated clinical evolution, including clinical manifestations such as arthropathy, arthralgia, myalgia, edema, or hypoesthesia, as well as functional limitation, trigger finger, tendinitis, and Raynaud's syndrome. These findings are consistent with an evaluation in 50 patients with chronic musculoskeletal symptoms secondary to chikungunya fever during the 2016 outbreak that occurred in Rio de Janeiro, (Brazil), which revealed joint synovitis and tenosynovitis symptoms<sup>42</sup>.

Among the signs and symptoms that were present in the three clinical phases of evolution of chikungunya (acute, subacute, and chronic), we observed that prostration and edema improved over time, in contrast to the accentuation of myalgia and arthralgia. Similarly, a randomly sampled survey of 1,094 patients with IgG positive for chikungunya 18 months after the outbreak that occurred in Isla Reunion revealed that 45% of them still presented with musculoskeletal pain<sup>43</sup>.

Likewise, a prospective cohort study with 500 patients who were clinically diagnosed and serologically confirmed with chikungunya during the 2014-2015 epidemic in Colombia estimated that, after 20 months, a quarter of the participants presented with persistent joint pain, and 16% of them reported interference with their daily activities, documenting that they were missing school or work<sup>44</sup>. Therefore, it is noteworthy that the clinical follow-up assessments should focus on these signs and symptoms to optimize the treatment according to the individuals' comorbidities.

One could argue that the main limitation of this study is the quality of the data obtained retrospectively from the SINAN database. In addition, the completion of clinical data during epidemics is only mandatory for patients with severe dengue, as it is assumed that dengue without warning signs usually presents with the classical symptomatology. Moreover, the Zika cases included only pregnant women who were laboratory-tested for the disease. Nevertheless, our study provides a long-term clinical evaluation of patients during an important outbreak of chikungunya and Zika in a region with high incidence of dengue, thus representing a relevant contribution to the understanding of the co-occurrence of these arboviruses.

In summary, the data provided herein are important and useful for countries endemic to dengue with co-occurrence of Zika and chikungunya epidemics and may help direct the strengthening of the health surveillance system for the

monitoring of the geographical distribution and temporal trend of the infection, to characterize the presentation of the disease, and to identify serious complications<sup>13,14</sup>.

The public health system of countries endemic to these arboviruses should be aware of the clinical and laboratory indicators verified at the time of diagnosis, as well as being vigilant for the *Ae. aegypti* vector, responsible for the transmission of these and other viral diseases, such as yellow fever. The entomological research, together with the knowledge of the temporal distribution of these arboviruses, must also be taken into account to better prevent the spread of these diseases.

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