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ARBOVIRUSES EPIDEMIC ASSOCIATES WITH GUILLAIN-BARRÉ SYNDROME: TEMPORAL SERIES IN NORTHEAST BRAZIL

Johnnatas Mikael Lopes[a]
https://orcid.org/0000-0002-9679-5287
Maylon Wellik dos Santos Carvalho[b]
https://orcid.org/0000-0003-3659-4894
Gustavo Roberto Santana Souza[c]
https://orcid.org/0000-0001-8688-9194
Romero Henrique de Almeida Barbosa[d]
https://orcid.org/0000-0001-6386-8550
Poliana Kalinne Simões de Melo Barbosa[e]
https://orcid.org/0000-0002-6160-5383
Rodrigo Pegado de Abreu Freitas[f]
http://orcid.org/0000-0002-7227-1075
Clécio Gabriel de Souza[g]
https://orcid.org/0000-0001-9005-7956

Abstract

Arboviruses cause public health problems in several countries, and records show that they can generate central and peripheral neurological complications with permanent sequelae.

[a] *Physiotherapist. PhD in Collective Health. Professor at Universidade Federal do Vale do São Francisco. Paulo Afonso, Bahia, Brasil. E-mail: johnnatas.lopes@univasf.edu.br*
[b] *Physician. Undergraduate in Medicine. Universidade Federal do Vale do São Francisco. Paulo Afonso, Bahia, Brasil. E-mail: mwscmedicina@outlook.com*
[c] *Physician. Undergraduate in Medicine. Universidade Federal do Vale do São Francisco. Paulo Afonso, Bahia, Brasil. E-mail: g.r.s.souzaaa@gmail.com*
[d] *Physician. PhD candidate in Biology Applied to Health. Professor at Universidade Federal do Vale do São Francisco. Paulo Afonso, Bahia, Brasil. E-mail: romero.henrique@univasf.edu.br*
[e] *Physician. Neurologist at Instituto São Francisco. Paulo Afonso, Bahia, Brasil. E-mail: polianasimoes@gmail.com*
[f] *Physiotherapist. PhD in Physiotherapy. Professor at Universidade Federal do Rio Grande do Norte. Natal, Rio Grande do Norte, Brasil. E-mail: rodrigopegado@gmail.com*
[g] *Physiotherapist. PhD in Collective Health. Professor at Universidade Federal do Rio Grande do Norte. Santa Cruz, Rio Grande do Norte, Brasil. E-mail: cleciogabriel1@hotmail.com*
Correspondence: *Universidade Federal do Vale do São Francisco. Avenida da Amizade, n. 1.900, Sal Torrado. Paulo Afonso, Bahia, Brasil. CEP: 48605-250. E-mail: Johnnatas.lopes@univasf.edu.br*

However, it is not certain which arbovirus is responsible for outbreaks of the Guillain-Barré Syndrome (GBS), especially in Brazil. Thus, the objective of this study is to verify if there is a coincidence between the GBS outbreak and the most common arboviruses in Northeastern Brazil, as well as their relationship. An ecological time series study was designed with the federative units of Northeastern Brazil, using hospitalizations for Guillain-Barré syndrome and notifications of arbovirus infections between 2014 and 2019 as a data source. Distribution incidence curves were constructed for the conditions studied, and generalized estimating equations (GEE) models were applied to estimate the relationship between arboviruses and Guillain-Barré. The results showed a similar distribution for the incidences of Chikungunya virus ($z=7.82$; $p=0.001$), Zika virus ($z=3.69$; $p=0.03$), and Guillain-Barré syndrome ($z=2.98$; $p=0.05$) from 2014 to 2019. The GEE model revealed that the distribution of Chikungunya incidence is associated with the distribution of GBS incidence in each year (x^2Wald=3,969; $p=0.046$). This pattern was repeated in seven of the nine states, while the Zika virus had a significant relationship with GBS in only two states. The outbreak of GBS in Northeastern Brazil appears to be probabilistically related to outbreaks of the Chikungunya virus.
Keywords: Guillain-Barre Syndrome. Zika Virus. Chikungunya virus. Dengue Virus. Brazil.

EPIDEMIA DE ARBOVIROSES ASSOCIADA À SÍNDROME DE GUILLAIN-BARRÉ: SÉRIE TEMPORAL NO NORDESTE BRASILEIRO

Resumo

As arboviroses são problemas de saúde pública em vários países e há registros de que podem produzir complicações neurológicas centrais e periféricas com sequelas permanentes. Entretanto, não se sabe ao certo qual delas é realmente responsável pelos surtos da Síndrome de Guillain-Barré (SGB), principalmente no Brasil. Assim, o objetivo é verificar se há coincidência entre o surto de SGB e as arboviroses mais comuns no Nordeste do Brasil e suas relações. Foi desenhado um estudo ecológico de série temporal com as unidades federativas do Nordeste do Brasil, adotando como fonte de dados as internações Guillain-Barré e as notificações de infecções por arbovírus entre 2014 e 2019. Curvas de distribuição de incidência foram construídas para as condições estudadas, e foram aplicados modelos de equações generalizadas estimadas (GEE) para estimar a relação entre arbovírus e Guillain-Barré. Evidencia-se que há

distribuição semelhante para as incidências do vírus Chikungunya (z=7,82; p=0,001), vírus Zika (z=3,69; p=0,03) e síndrome de Guillain-Barré (z=2,98; p=0,05) entre 2014 e 2019. O modelo GEE revelou que a distribuição da incidência de Chikungunya está associada à distribuição da incidência de SGB em cada ano (x^2Wald=3,969; p=0,046). Esse padrão se repetiu em sete dos nove estados, enquanto o zika vírus teve uma relação significativa com o GBS em apenas dois estados. Conclui-se, então, que o surto de SGB no Nordeste do Brasil parece estar probabilisticamente relacionado aos surtos do vírus Chikungunya.

Palavras-chave: Síndrome de Guillain-Barré. Zika vírus. Vírus chikungunya. Vírus da dengue. Brasil.

EPIDEMIA DE ARBOVIROSIS ASOCIADA AL SÍNDROME DE GUILLAIN-BARRÉ: SERIE TEMPORAL EN EL NORESTE DE BRASIL

Resumen

Los arbovirus causan problemas de salud pública en varios países y, según indican los reportes, pueden producir complicaciones neurológicas centrales y periféricas con secuelas permanentes. Sin embargo, no se sabe cuál de ellos es realmente el responsable de los brotes del síndrome de Guillain-Barré (SGB), especialmente en Brasil. Así, el objetivo de este estudio es verificar si existen coincidencias entre el brote del SGB y los arbovirus más comunes en el Noreste de Brasil y sus asociaciones. Se diseñó un estudio de series temporales ecológico en las unidades federativas del Noreste de Brasil, adoptando como fuente de datos las hospitalizaciones y las notificaciones de arbovirosis de Guillain-Barré entre 2014 y 2019. Se construyeron curvas de distribución de incidencia para las condiciones científicas, y se aplicó una ecuación estimada generalizada (GEE) para estimar la relación entre arbovirus y Guillain-Barré. Se encontró que existe una distribución similar en las incidencias de virus del chikunguña (z=7,82; p=0,001), virus del Zika (z=3,69; p=0,03) y síndrome de Guillain-Barré (z =2,98; p=0,05) entre 2014 y 2019. El modelo GEE reveló que la distribución de la incidencia de chikunguña está asociada con la distribución de la incidencia de SGB en cada año (x^2Wald=3,969; p=0,046). Este patrón se repitió en siete de los nueve estados, mientras que el virus del Zika presentó una relación significativa con el SGB en solo dos estados. El brote del SGB en el Noreste de Brasil parece estar relacionado probabilísticamente con los brotes del virus del chikunguña.

Palabras clave: Síndrome de Guillain-Barré. Virus Zika. Virus Chikunguña. Virus del Dengue. Brasil.

INTRODUCTION

Arboviruses are transmitted by arthropods, and part of their replicative cycle occurs inside these insects[1]. The arboviruses that are most studied, due to their geographical dispersion and impacts on human populations, are the Dengue, Chikungunya, Zika, and yellow fever viruses, which cause high rates of deaths and disabilities[2]. The Dengue (DENV), Zika (ZIKV), and Chikungunya (CHIKV) viruses are transmitted by the Aedes aegypti mosquito[3,4], which is commonly found in many Brazilian cities[1].

In the absence of wild animals, especially non-human primates, humans become hosts for these viruses[5]. CHIKV, ZIKV, and DENV remain in the urban human-mosquito-human transmission cycle, which involves *Ae. aegypti* and *Ae. Albopictus*[6]. In this urban context, humans are not only hosts, but also amplifiers[7].

There is evidence that the DENV, ZIKV, and CHIKV can predispose the body to the development of peripheral or central neurological conditions via virus-mediated or immune-mediated mechanisms[8]. Research carried out in French Polynesia in 2013[8], in Venezuela, and in the Caribbean American countries[9] revealed that high incidences of Guillain-Barré syndrome (GBS) occur concomitantly with Zika outbreaks. A recent Brazilian study focusing on Rio de Janeiro revealed that CHIKV was responsible for GBS[10]. However, the findings of Mehta et al. do not indicate which arboviruses caused GBS[11] in a sample from Rio de Janeiro.

GBS is a polyradiculopathy that includes characteristics such as post-infection onset, which is often severe; and it is a demyelinating disease with an autoimmune basis[8]. However, the inconsistency between Brazilian studies regarding the possible etiological agent(s) involved in the development of GBS shows the uncertainty surrounding arbovirus outbreaks, from the perspective of post-infection.

In addition, the highest incidence of arboviruses occurred during the outbreak that took place from 2015 to 2017 in Northeastern Brazil, with a new increase in 2019. Therefore, there is a need for large-scale studies to identify which virus(es) contributes to increase the GBS load in the Brazilian population and control the interaction effect with the incidence, since there was a concomitant outbreak of these arboviruses in Brazil.

Thus, this study aims to verify whether there was a change in the incidence of GBS at the beginning of the DENV, ZIKV, and CHIKV arbovirus epidemics in Northeastern Brazil, on a macroregional scale. Furthermore, the study aims to estimate which arbovirus(es) explains the magnitude and distribution trend of GBS, associating it with the incidence of this syndrome from 2014 to 2019.

MATERIAL AND METHODS

This ecological study is an analysis of a time series going from 2014 to 2019[12]. This type of design allows for the verification of outbreaks and epidemics, as well as the identification of public policy impacts[13].

The events of interest were the CHIKV, DENV, and ZIKV epidemics included in the epidemiological reports of the Notifiable Diseases Information System, as well as hospital admissions due to GBS registered in the Hospital Information System of the Unified Health System.

The number of cases notified in the Notifiable Diseases Information System (SINAN) and Hospital Information System (SIH) was transformed into a measure of frequency of the type of accumulated incidence, and the total number of occurrences was divided by the general population size of the investigated period (2014-2019) for each federative unit (FU), multiplied by a constant of 100,000 inhabitants. This generated the resulting values for CHIKV incidence (CHIKVI), DENV incidence (DENVI), ZIKV incidence (ZIKVI), and Guillain-Barré Syndrome incidence (GBSI).

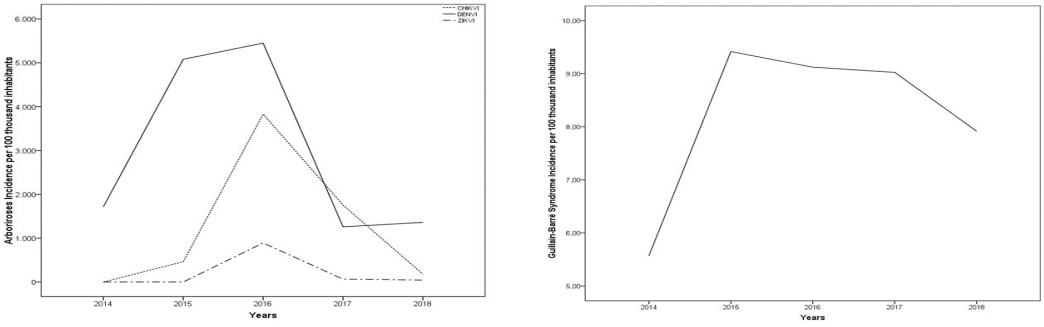
To verify the trend of the incidences, using the FUs as the units of observations, the curve of adherence was estimated using the polynomial regression methods[14]. The removal of the autocorrelation of the predicted data series was also applied based on Prais-Winsten regression[12,13]. The standardized β was obtained to compare the magnitude of CHIKVI, DENVI, and ZIKVI.

The GBSI curve explanation was tested with a Generalized Estimating Equation (GEE)[14] and an order-1 autoregression correlation matrix. CHIKVI, DENVI, and ZIKVI can be considered independent variables in the model with data combined and stratified by FU. The different years and their interactions with the arbovirus incidence variables were also considered independent variables. A gamma distribution with a log ligand function was used in this analysis. In the adjusted model, a significance level of 5% was used.

RESULTS

The incidence of hospitalizations due to GBS revealed a distribution peak in 2015 and 2019 in the FUs of Northeastern Brazil (**Figure 1**). GBSI was 5.56 cases per 100 thousand inhabitants in 2014, but grew to 9.41 cases per 100 thousand inhabitants in 2015 and 10.08 cases per 100 thousand inhabitants in 2019. This means that, considering 2014 as the starting point, GBSI increased by approximately 69% in 2015 and 81.10% in 2019. **Table 1** shows the gross incidence in each period.

Figure 1 – The gross incidence in each period.



Source: authors' own.

Table 1 – Distribution of incidences of arboviruses and GBS in Northeastern Brazil from 2014 to 2019 at end of epidemiologic week 52

Year	CHIKVI	DENVI	ZIKVI	GBSI
2014	178.94	160.50	0	5.56
2015	649.75	578.50	134.40	9.41
2016	420.30	554.90	132.10	9.12
2017	250.10	145.50	9.00	9.02
2018	19.90	118.50	4.30	7.91
2019	59.40	376.70	9.50	10.0

Source: Notifiable Diseases Information System.
CHIKVI = Chikungunya virus incidence
DENVI = Dengue virus incidence
ZIKVI = Zika virus incidence
GBSI = Guillain-Barré Syndrome incidence

Similar to GBS, the CHIKV and DENVI case records peaked in 2015 in the time series, with 649.75 and 578.50 cases per 100 thousand inhabitants, respectively, with a further increase in 2019. **Figure 1** evidences that DENVI presented a plateau from 2017 to 2018, while CHIKVI and GBSI were on a downward trend during the same period, the latter being less pronounced. ZIKV infections showed the same distribution as the other arboviruses, but to a lesser extent. They peaked in 2015, with 134.40 cases per 100 thousand inhabitants, and sharply declined in the following years, without showing a significant growing trend like GBSI, CHIKVI, and DENVI in 2019 (**Table 1**).

To estimate the magnitude of the effect of arboviruses on the evolution of GBSI, a model was built with CHIKVI, DENVI, and ZIKVI and their interactions with the years of the time series. **Table 2** shows that only the CHIKVI-Year interaction showed a direct and positive relationship with the evolution of GBSI ($B=9.59.10^{-3}$, x^2 Wald=3.96; p=0.04). The main effect of CHIKVI also showed a significant relationship with this variable (B=-1.93; x^2 Wald=3.96; p=0.04), but this association was controlled by the previously presented CHIKVI-Year interaction. The relationship between GBSI and the other arboviruses did not show a significant statistical effect.

Table 2 – General adjusted model of the relationship between arboviruses and Guillain-Barré syndrome in Northeastern Brazil, in the 2014-2019 time series

	B	Standard Error	95%CI Wald		Hypothesis Test		
			Lower	Upper	Wald X^2	df	Sig.
Main Effect							
ZIKVI	49.02	28.110	-6.077	104.116	3.041	1	0.081
DENVI	-0.59	0.5874	-1.744	0.558	1.019	1	0.313
CHIKVI	-1.93	0.9712	-3.838	-0.031	3.968	1	0.046
Years	0.06	0.0430	-0.017	0.151	2.439	1	0.118
Interactions							
DENVI* Years	$2.94.10^{-4}$	0.0003	$2.77.10^{-4}$	0.001	1.020	1	0.312
CHIKVI* Years	0.001	0.0005	1.554E-5	0.002	3.969	1	0.046
ZIKVI* Years	-0.024	0.0139	-0.052	0.003	3.041	1	0.081
ZIKVI* CHIKVI* DENVI* Years	-7.508E-13	8.8599E-13	-2.487E-12	9.857E-13	0.718	1	0.397

Source: authors' own.
CHIKVI = Chikungunya virus incidence
DENVI = Dengue virus incidence
ZIKVI = Zika virus incidence
GBSI = Guillain-Barré Syndrome incidence
B = model coefficient
Sig. = significance
CI = Confidence Interval
df = degree of freedom

When the analysis was stratified by FU, a heterogeneous distribution of cases was detected, which meant that a more in-depth analysis of the general model was needed. Thus, adjusted and stratified models were constructed for each FU (**Table 3**). In these models, only the main effects of arboviruses on GBSI were estimated, due to the lower variability of data for the construction of parsimonious equations. Therefore, we can verify that CHIKVI was directly associated (B positive) with the evolution of GBSI in seven of the nine FUs (AL, BA, MA, PB, PE, RN, and SE), whereas ZIKVI was only associated in two (PE and PI), and DENVI in five (BA, CE, MA, PB, and RN).

Table 3 – Adjusted model of the relationship between arboviruses and Guillain-Barré Syndrome in Northeastern Brazil, in the 2014-2019 time series, stratified for each federation unit

Parameter	B	Standard Error	95%CI Wald		Sig.
			Lower	Upper	
AL					
ZIKVI	-0.164	6.4943E-10	-0.16	-0.17	<0.001
DENVI	-0.004	3.2662E-12	-0.003	-0.005	<0.001
CHIKVI	0.069	2.5778E-10	0.068	0.070	<0.001
Years	0.192	1.6934E-9	0.191	0.193	<0.001
BA					
ZIKVI	-0.004	6.0337E-11	-0.003	-0.005	<0.001
DENVI	0.001	6.9806E-12	0.0009	0.0012	<0.001
CHIKVI	0.004	7.4347E-11	0.0039	0.0045	<0.001
Years	0.035	1.1996E-9	0.034	0.0359	<0.001
CE					
ZIKVI	-0.003	2.1997E-9	-0.002	-0.0038	<0.001
DENVI	$3.84.10^{-4}$	2.1201E-10	$3.82.10^{-4}$	$3.87.10^{-4}$	<0.001
CHIKVI	-8.6909E-5	2.5989E-11	-8.64E-5	-8.72E-5	<0.001
Years	-0.013	2.0539E-8	-0.011	-0.014	<0.001
MA					
ZIKVI	-0.033	7.6456E-9	-0.032	-0.034	<0.001
DENVI	0.006	1.3391E-9	0.0059	0.0063	<0.001
CHIKVI	0.001	3.5745E-10	0.0008	0.0011	<0.001
Years	0.011	1.2906E-8	0.010	0.013	<0.001
PB					
ZIKVI	-0.021	1.3136E-9	-0.021	-0.021	<0.001
DENVI	0.001	1.5121E-11	0.0009	0.0011	<0.001
CHIKVI	0.004	2.1424E-10	0.004	0.004	<0.001
Years	0.023	1.6986E-9	0.023	0.023	<0.001
PE					
ZIKVI	0.068	2.8431E-9	0.066	0.069	<0.001
DENVI	-6.979E-6	2.3875E-11	-6.94E-6	-6.99E-6	<0.001
CHIKVI	$3.82.\ 10^{-4}$	1.1813E-11	$3.80.\ 10^{-4}$	$3.85.\ 10^{-4}$	<0.001
Years	0.109	5.6847E-9	0.109	0.109	<0.001
PI					
ZIKVI	0.098	1.6311E-8	0.098	0.098	<0.001
DENVI	-0.003	2.4068E-9	-0.003	-0.003	<0.001
CHIKVI	-0.002	1.2461E-9	-0.002	-0.002	<0.001
Years	0.160	8.0047E-8	0.160	0.160	<0.001
RN					
ZIKVI	-0.020	3.3030E-10	-0.019	-0.024	<0.001
DENVI	0.001	2.0796E-11	0.0009	0.0013	<0.001
CHIKVI	0.002	8.9162E-11	0.0018	0.0023	<0.001
Years	-0.095	7.9255E-10	-0.094	-0.096	<0.001
SE					
ZIKVI	-0.083	7.4263E-9	-0.082	-0.084	<0.001
DENVI	-0.002	1.0568E-10	-0.002	-0.0023	<0.001
CHIKVI	0.003	1.3900E-10	0.0028	0.0032	<0.001
Years	-0.070	1.1048E-8	-0.068	-0.071	<0.001

Source: authors' own.
AL = Alagoas
BA = Bahia
CE = Ceará
MA = Maranhão
PB = Paraíba
PE = Pernambuco
PI = Piauí
RN = Rio Grande do Norte
SE = Sergipe
B = model coefficient
Sig. = significance
CI = Confidence Interval

DISCUSSION

Surveillance systems and clinical staff need epidemiological information to assist in their decision making and prepare for adverse situations, such as epidemiological outbreaks[9]. This is relevant because epidemic outbreaks of different arboviruses often occur simultaneously in Brazil, generating chronic complications that harm individual health, possibly increasing social care costs[15,16].

The increase in DENVI is not one of the triggers of GBS: this theory was refuted by the general and stratified analysis of cases in the Northeast, even though DENV is the most prevalent infection among arboviruses. This corroborates the fact that there is no new viral strain of this arbovirus in scientific records, which prevents the construction of a factual etiological thesis. There have also been other outbreaks of DENV in Northeastern Brazil with no concomitant change in the epidemiological pattern of GBS[17].

A study carried out in 2013 with a one-year clinical follow-up found that the reports of GBS increased up to nine times after an outbreak of ZIKV in French Polynesia[8]. In a sample of 396 confirmed cases, it was found that 72 patients had severe neurological symptoms, including 40 GBS cases diagnosed in just three months[18]. Beys-da-Silva et al.[19] identified that ZIKV infection generates other neurodegenerative complications in addition to microcephaly. Studies conducted in Brazil by Vieira et al.[20], from 2015 to 2016, included 21 GBS cases, and positive serology for ZIKV or CHIKV was more common for encephalopathies. However, this study lacks adequate data analysis, which prevents better inferences.

A cross-sectional study from Pakistan included 997 patients who were showing clinical signs and symptoms of arboviruses, and neurological symptoms were found in 49% of patients with suspected CHIKV and in 46.6% of those with confirmed infections[21]. Anand et al.[22] also found patients with neurological complications following CHIKV infections in Delhi, with no reports of GBS cases; whereas Mehta et al.[11] reported that GBS is one of the most common neurological conditions following CHIKV infection[23].

CHIKV is prone to infecting fibroblasts in the joints, dermis, and muscles. The virus itself does not directly damage the nervous system. Astrocytes and oligodendrocytes have been shown to be susceptible to CHIKV infection[24]. The onset seems to occur in the choroid plexus, as has been evaluated in mice, although in humans, further pathological evaluations are still needed to determine the degree of involvement of the cerebral parenchyma[25].

The findings of Batista et al.[10] and Mehta et al.[11] are conflicting and need further analysis to be properly judged. Batista et al.[10] carried out a descriptive study and reported that 52.4% of patients with GBS also had CHIKV infection, 4.8% had concomitant ZIKV and

DENV infections, and none had concomitant CHIKV and ZIKV infections. They also found that GBS affected adults in almost 60% of cases. However, the lack of inferential statistics prevents us from extrapolating these data beyond chance.

Mehta et al.[11], on the other hand, identified 35 patients who developed neurological diseases and found that 12 of them had a laboratory diagnosis of ZIKV, while only five had a diagnosis of CHIKV. However, no data distribution analysis was performed to reveal the association of GBS with ZIKV or CHIKV, specifically. This study also lacks a chronologically adequate data analysis to find out whether there was a considerable increase in neurological cases or whether arbovirus infections coincidentally affected patients who were already immunologically sensitized, generating a causal relationship bias.

In 2017, Oliveira et al.[24] showed that an increase of GBS cases coincided with the increase of ZIKV cases from 2015 to 2016, in Brazil, based on ecological data. However, the authors did not control the possibility that the effect of other arboviruses could impact the occurrence of GBS, despite being mentioned in their study.

It is possible that both ZIKV and CHIKV predispose the body to developing GBS, as supported by several international reports. In Brazil, there was a concomitant outbreak of these arboviruses, which makes it difficult to know whether one of them was the main cause of the GBS outbreak or whether there was an interaction between them both and other factors that conditioned the emergence of this neurological syndrome and other conditions, as verified for ZIKV and microcephaly[9].

It is also possible that a minimal infection load by these arboviruses already produces GBS outbreaks when it reaches a susceptible population. This is supported by our data since the GBS outbreak pattern peaked in 2015, concurrently with the outbreak peak of these arboviruses, and, from 2019, a new arbovirus outbreak scenario also contributed to the increase in GBSI. The delayed decline in GBSI related to the speed of arboviruses should also be taken into account, and may be a summative effect of other post-infections or a sensitizing effect of the immune system at a later time.

CONCLUSION

We showed that CHIKVI, DENVI, and GBSI has a similar distribution pattern in the federative units of Northeastern Brazil. Our results showed that CHIKVI is associated with GBSI beyond chance in the studied sample, as well as DENVI. ZIKVI may be associated with an increase in GBSI; however, a new outbreak of this neurological condition occurred in 2019 and was not shown to have been influenced by the epidemiological pattern of this arbovirus across Northeastern Brazil.

PARTICIPATION

1. Project design, analysis and data interpretation: Johnnatas Lopes, Maylon Wellik dos Santos Carvalho.

2. Writing and critical review of intellectual content: Gustavo Roberto Santana Souza, Johnnatas Lopes, Maylon Wellik dos Santos Carvalho, Romero Henrique de Almeida Barbosa, Poliana Kalinne Simões de Melo Barbosa, Rodrigo Pegado de Abreu Freitas, Clécio Gabriel de Souza.

3. Review and/or approval of the final version: Johnnatas Lopes.

4. Responsible for all aspects of the study, ensuring accuracy and integrity in all of its sections: Johnnatas Lopes and Maylon Wellik dos Santos Carvalho.

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