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Geospatial modeling of microcephaly and Zika virus spread patterns in Brazil

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Resumo:

Brazil was considered the epicenter of the outbreak Microcephaly and Zika virus (ZIKV) infection. However, the occurrence of both ZIKV infection and microcephaly in Brazil were not evenly distributed across the country's regions. In this paper, we investigate the regional characteristics at the municipal level that can be associated with the incidence of microcephaly and the relation between the disease and ZIKV infection. Using exploratory spatial data analysis and spatial autoregressive Tobit models, our results show that microcephaly incidence in Brazil is significantly related not only to ZIKV, but also to access to primary care, population size, GNP, mobility and environmental attributes of the municipalities. These findings contribute to advance recent literature that shows that incidence of microcephaly in Brazil varies considerably across regions when correlated only with ZIKV, i.e. that ZIKV alone cannot explain the differences in microcephaly across regions. Our results indicate how regional cofactors or effect modifiers have an important role in explaining this variation in microcephaly risk.

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Abstract

Brazil was considered the epicenter of the outbreak Microcephaly and Zika virus (ZIKV) infection. However, the occurrence of both ZIKV infection and microcephaly in Brazil were not evenly distributed across the country's regions. In this paper, we investigate the regional characteristics at the municipal level that can be associated with the incidence of microcephaly and the relation between the disease and ZIKV infection. Using exploratory spatial data analysis and spatial autoregressive Tobit models, our results show that microcephaly incidence in Brazil is significantly related not only to ZIKV, but also to access to primary care, population size, GNP, mobility and environmental attributes of the municipalities. These findings contribute to advance recent literature that shows that incidence of microcephaly in Brazil varies considerably across regions when correlated only with ZIKV, i.e. that ZIKV alone cannot explain the differences in microcephaly across regions. Our results indicate how regional cofactors or effect modifiers have an important role in explaining this variation in microcephaly risk.

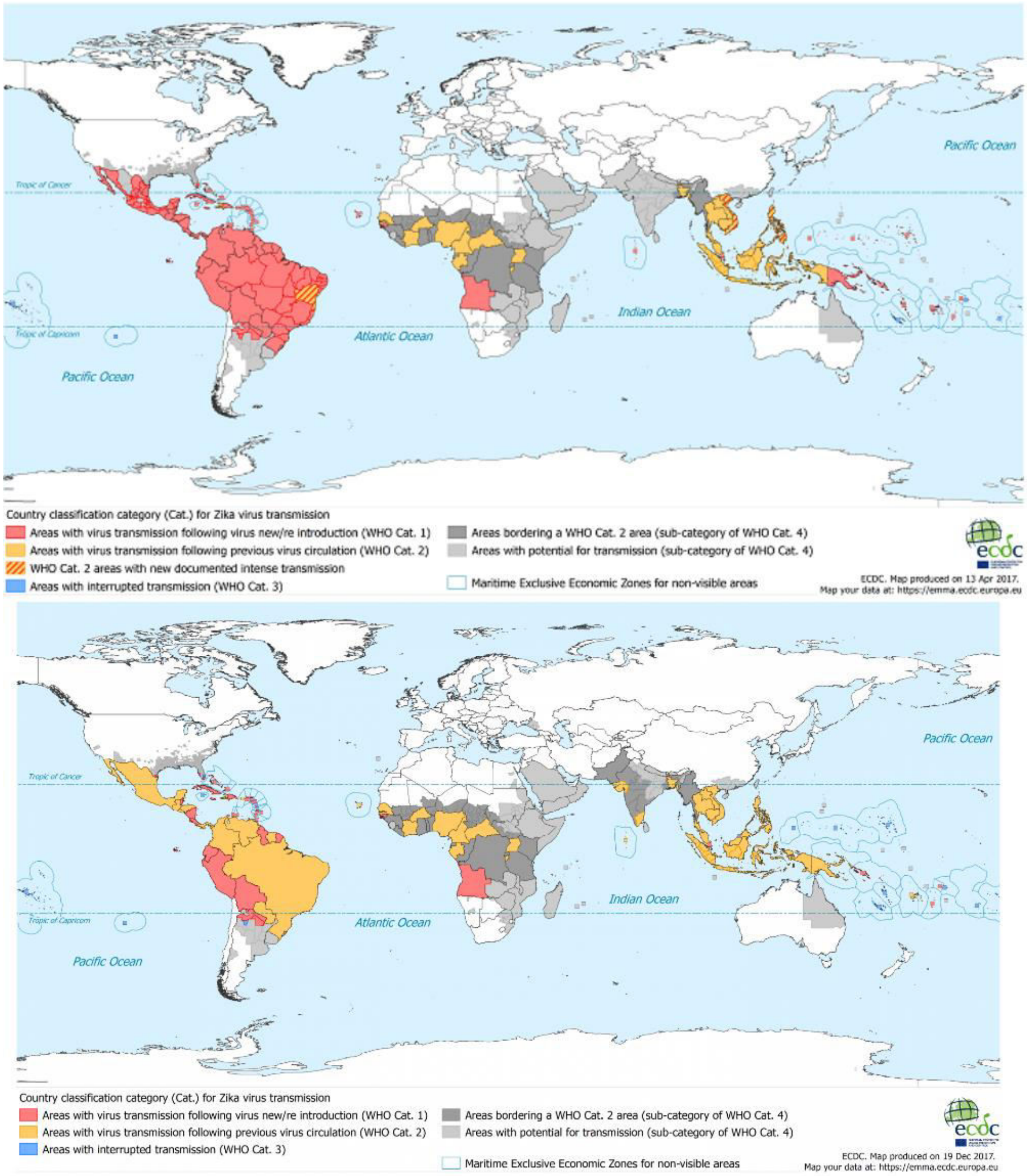
Keywords: Zika Virus Infection; Virus, Zika; Microcephaly; Distribution, spatial; Spatial Analysis.

Introduction

The Zika virus infection (ZIKV) has been defined as a priority in terms of a health emergency by the World Health Organization (World Health Organization 2016). During 2017, nearly all countries among the tropics were considered as autochthonous regions of ZIKV transmission and the number of new countries categorized in the same way keeps increasing – figure 1. Brazil was considered the epicenter of the epidemic, with reports of 130,000 ZIKV infections in 2016.

The fast increase in the number of reports prompted international attention and dedicated research increasingly suggested an association between ZIKV infection and neurological syndromes such as Guillain-Barré and microcephaly. In 2015 and 2016, 2,229 cases of microcephaly in infants were confirmed in Brazil, compared to a yearly average of only 157 cases between 2000 and 2014.

Figure 1 - Countries classification regarding the ZIKV status.



Source: European Centre for Disease Prevention and Control 2017.

Several studies of different backgrounds established the link between the ZIKV and microcephaly and other neurological disorders (Brasil et al. 2016; Calvet et al. 2017; França et al. 2016; Garcez et al. 2016). These findings highlight the importance of monitoring efforts of ZIKV incidence to forecast future levels of microcephaly cases, for example. Considering the importance to discuss approaches capable to handle the challenges regarding the congenital ZIKV syndrome it is important to define strategies capable to support public policies. Brazil plays a center role in this matter. The large availability of geolocated information leverage the analytical possibilities regarding epidemiological data. By using a framework of health geography, we can provide insights into disease spread patterns, high-risk areas, and correlated regional attributes that allow for inferences regarding the determinants of these outcomes (Macintyre et al. 2002).

The use of geospatial modeling techniques has proven its value for studying infections such as dengue fever (Xavier et al. 2017) and chikungunya (Nsoesie et al. 2015). Health geography studies have been used to identify high risk areas, considering the presence of elements capable to predict the levels associated to the incidence of arbovirus diseases. The geospatial approach is capable to create insights to support health policies and surveillance strategies dedicated to minimizing the negative consequences of ZIKV. Despite this potential few studies have examined the spatial patterns associated with ZIKV and the neurological conditions resulting from the infection (Vissoci et al. 2018).

All Brazilian states have been classified as areas with transmission of ZIKV. However, the occurrence of both ZIKV infection and microcephaly were not evenly distributed across the country's regions. The Brazilian Northeast concentrated the largest share of microcephaly reports, although the Zika virus infection was also very preeminent in other regions such as the Centre-West and part of the Southeast. This regional imbalance suggests that regional attributes have also played an important role in the spread of Zika virus and in mediating its association with microcephaly. Jaenisch et al. (2017) found the estimated risk that a baby born to a woman infected by the Zika virus during pregnancy would have microcephaly varied substantially across Brazil. According to the authors, the geographical area is one of the main factors affecting the risk. However, the investigation of geographical attributes related to this is not one of the objectives of their study.

Taking into consideration the lack of studies that evaluate the regional incidence of microcephaly and ZIKV, in this paper, we investigate the regional characteristics at the municipal level that can be associated with the incidence of microcephaly and the relation between the disease and ZIKV infection.

Methods

We designed an ex-post-facto ecological study based on secondary databases. Brazilian health system is composed by a public-private mix. The public portion of the system is responsible for the coverage of nearly 75% of the population. Besides this, all monitoring activities performed in the country were realized by the Ministry of Health (MoH). Among the responsibilities of the MoH is the monitoring of cases related to diseases of compulsory notification, as ZIKV and microcephaly, which must be notified by both public and private practitioners.

The Brazilian Universal Health System (SUS) is responsible for sharing all information collected regarding the epidemiological situation of the country. The availability of publicly accessible government databases at the national level, coupled with the socio-geographic landscape of the country and manifestations of the ZIKV epidemic, turn Brazil into an optimal setting in which to investigate the geospatial association between ZIKV infection and microcephaly pattern (Vissoci et al. 2018).

All epidemiological data used in this work was gathered from DATASUS, which is the department of the MoH responsible for publicizing health system databases. Data of confirmed ZIKV cases was obtained from the Compulsory disease notification system (SINAN). A case was considered as confirmed if one of the following circumstances were met: viral RNA track, positive viral detection or IgM serology. The microcephaly cases were obtained through the System for Specialized Management Support (Laguardia et al. 2004). To be considered as a microcephaly case the following criteria should be met: infant with 37 or more weeks of gestation with a head circumference equal to or less than 31.9 cm for male infants, or equal to or less than 31.5 cm for female infants, in concurrence with WHO standards (World Health Organization 2016). The confirmation of microcephaly was only performed after the delivery. The volume of cases related to ZIKV and microcephaly were weighted by the population at the municipality level. The municipality's population size was also obtained through Brazilian Institute of Geography and Statistics (IBGE) repository and refers to all inhabitants living in each municipality for 2016. Data related to primary care coverage was obtained at MoH. All data covering ZIKV and microcephaly was categorized by quarters related to January to December of 2016.

In addition to the data listed above, we used information on the urban structure of the Brazilian municipalities. This data was obtained from the Brazilian index of urban structure (IBEU) and refers to 2013. The IBEU index is based on several dimensions associated with with sanitation, urban structure and health conditions. Data from the IBEU was gathered at Observatory of the Metropoles of the National Institute of Science and Technology (Ribeiro and Ribeiro 2013).

The IBEU index covers five different urban dimensions: mobility, environmental conditions, housing conditions, sanitation and infrastructure. The mobility dimension assesses the ratio of inhabitants that take at least one hour in commuting between home and work. The environmental aspect evaluates the lack of rubbish around residences, the existence of open sky sewage and afforestation index. The housing conditions is a composed score related to five indicators: proportion of people living in shanty towns, number of bedrooms with a maximum of two people, number of households with a maximum ratio of 4 people by restroom, proportion of households which walls were made of bricks or appropriate wood, rate of inadequate households. The sanitation dimension covers aspects related to four indicators: households with adequate sewage, homes with appropriate water and sewage services, coverage by garbage collection service and availability of energy services. The last dimension regarding the urban structure comprises the infrastructure index with the following metrics: the proportion of people living in households covered by public illumination, streets made of asphalt or concrete paving and household identification. The IBEU index was calculated considering all indicators with the same weight and computing an average score covering all five dimensions. The final IBEU index varied from 0 to 1. Finally, to better characterize the socioeconomic status of each municipality, we consider information on the Gross Domestic Product (GDP) per capita in 2013, provided by IBGE.

Data Analysis

The variable of interest in this study is the incidence of microcephaly in each municipality in Brazil. However, of the 5,560 municipalities in the sample, 4,831 (86.9%) did not register any incidence of microcephaly in the fourth quarter of 2016. Given this pattern of the data, to estimate the correlation between regional attributes and incidence of microcephaly we used a Tobit model approach.

Censored regression models or Tobit models can be applied when the variable of interest is truncated. The Tobit model, developed by James Tobin (1958), estimates the relationship between a non-negative variable and independent variables. The generic specification of a Tobit model is described as follows:

$$y_i^\star = x_i\beta + \varepsilon_i$$

$$y_i = 0 \; if \; y_i^\star \leq 0$$

$$y_i = y_i^\star \; if \; y_i^\star > 0$$

where y* indicates a latent variable that depends on the matrix of explanatory variables (x) and a vector of parameters β and a normally distributed error term ε.

The estimation consists of two steps. The first step corresponds to a simple regression for the non-truncated portion of the data, whereas the second step proceeds with the estimation including the truncated portion of the data.

However, this type of estimation does not account for spatial correlation, which may render the Tobit model estimation inefficient or even inconsistent (Amaral and Anselin 2014). Given the spatial pattern of the spread of both microcephaly and ZIKV, this is a hypothesis that we must investigate. Hence, to incorporate spatial correlation, a SAR Tobit (spatial autoregressive Tobit) was estimated as presented in the following equation:

$$y_i^\star = S^{-1}x_i\beta + S^{-1}\varepsilon_i$$

$$y_i = 0 \; if \; y_i^\star \leq 0$$

$$y_i = y_i^\star \; if \; y_i^\star > 0$$

$$S = I_n - \rho W$$

where I_n indicates an identity matrix of order n, ρ is a spatial autoregressive parameter and W is a spatial weights matrix, assumed here as first order Queen contiguity type.

Although these models have been implemented through the maximum-likelihood (MLE), their estimation demands high computational costs, especially in cases where the dependent variable is discrete or truncated, as is the case for the SAR Tobit model. For this reason, the Bayesian approach provides a less demanding computational alternative. In particular, a Monte Carlo Bayesian approach will be used via the Markov Chain (MCMC) employing Gibbs algorithm. The implementation used for the SAR Tobit model was proposed by LeSage and Pace (2009) and implemented in R by the *spatialprobit* package (Wilhelm and de Matos 2013).

Because they are spatial models, we consider the possibility of spatial spillovers, i.e. the effects of a change in any municipality affecting other municipalities. Hence, the total effect of an explanatory variable x on the dependent variable y can be decomposed into direct effects and indirect effects. The direct effects refer to the predicted direct impact of variations in x on the variable of interest y in the same municipality. The indirect effects are the impacts due to spatial spillovers of the variations of x within the neighborhood. Total effects, therefore are the sum of both direct and indirect effects.

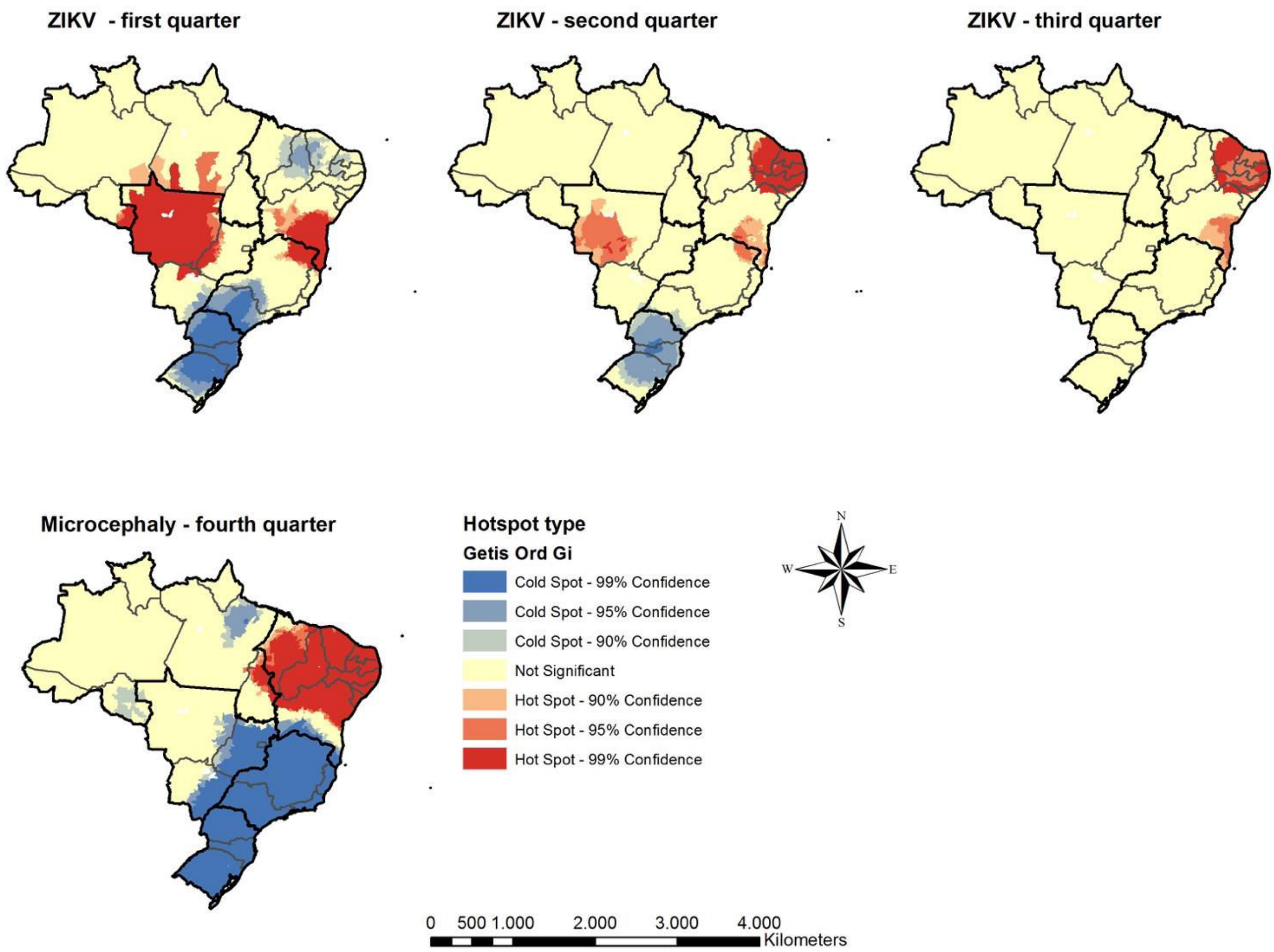
Results

Figure 2 shows the spatial autocorrelation of the main variables in this study, i.e. microcephaly incidence in the fourth quarter of 2016 and ZIKV in the first three quarters. The spatial structure of the spread of these infections is shown in detail in Vissoci et al. (2018). In this study, the most important aspect of the spatial distribution of microcephaly and ZIKV is their spatial concentration, which indicates a possible spillover effect. The coincidence of areas, specially between the second quarter of ZIKV and microcephaly is also an important aspect to highlight which will be further explored in this study.

The results of the estimation of the spatial Tobit models are shown in Tables 1 and 3. Since the coefficients are estimated from a spatial Tobit model, they cannot be directly interpreted as representing how changes in the explanatory variables affect microcephaly incidence. Tables 2 and 4 show the direct, indirect and total effects on the dependent variable of marginal changes in the explanatory variables.

Tables 1 and 2 regress microcephaly incidence on ZIKV incidence variables only. This result is shown only to compare with Tables 3 and 4, which add regional attributes as explanatory variables. This way, we can evaluate how regional attributes mediate the relationship between ZIKV and microcephaly. Given that our model is based on Bayesian MCMC estimates, the significance inference was based on p-levels instead of standard t-statistics. For more information on inference based on Bayesian MCMC estimates, see Gelman et al. (1995).

Figure 2 – Spatial autocorrelation measured by Getis-Ord Gi of ZIKV and microcephaly



Source: Own elaboration.

Table 1 - Results of SAR Tobit – Dependent variable: microcephaly incidence (4th quarter)

Variable	Posterior mean	Standard deviation	p-level	
Constant	-20.4983	1.2941	0.0000	†
Zikv incidence (3rd quarter)	-0.0650	0.0393	0.0440	†
Zikv incidence (2nd quarter)	0.0845	0.0475	0.0370	†
Zikv incidence (1st quarter)	-0.0197	0.0113	0.0400	†
Sig_e	562.01	59.82	0.0000	†
Rho	0.3345	0.0381	0.0000	†

†Significant at the 95% level.

Table 2 - Results of SAR Tobit – Direct and Indirect effects - Dependent variable: microcephaly incidence (4th quarter)

Variable	**Lower 0.05**	**Posterior mean**		**Upper 0.95**
(a) Direct effects				
Zikv incidence (3rd quarter)	-0.0648	-0.0317	†	-0.0010
Zikv incidence (2nd quarter)	0.0035	0.0413	†	0.0710
Zikv incidence (1st quarter)	-0.0187	-0.0097	†	0.0020
(b) Indirect effects				
Zikv incidence (3rd quarter)	-0.1836	-0.0826	†	-0.0040
Zikv incidence (2nd quarter)	0.0039	0.0979	†	0.2350
Zikv incidence (1st quarter)	-0.0363	-0.0151	†	-0.0020
(c) Total effects				
Zikv incidence (3rd quarter)	-0.2545	-0.1242	†	-0.0050
Zikv incidence (2nd quarter)	0.0137	0.1616	†	0.3150
Zikv incidence (1st quarter)	-0.0735	-0.0378	†	-0.0030

†Significant at the 95% level.

Table 3 - Results of SAR Tobit – Dependent variable: microcephaly incidence (4th quarter)

Variable	**Posterior mean**	**Standard deviation**	**p-level**	
Constant	-91.9230	9.9291	0.0000	†
Zikv incidence (3rd quarter)	-0.0612	0.0431	0.0430	†
Zikv incidence (2nd quarter)	0.0716	0.0476	0.0400	†
Zikv incidence (1st quarter)	-0.0100	0.0084	0.1140	
Primary care	0.1218	0.0270	0.0000	†
Ln municipal GDP	-20.0970	1.8606	0.0000	†
Ln population	39.2147	2.6992	0.0000	†
Mobility	18.4701	6.8232	0.0040	†
Environmental	-11.5750	3.6015	0.0000	†
Housing	-7.0651	8.1223	0.1860	
Sanitation	-4.6374	3.4631	0.0900	
Infrastructure	6.9194	4.7694	0.0820	
Sig_e	336.9353	27.5831	0.0000	†
Rho	0.2401	0.0378	0.0000	†

†Significant at the 95% level.

Table 4 - Results of SAR Tobit – Direct and Indirect effects - Dependent variable: microcephaly incidence (4th quarter)

Variable	Lower 0.05	Posterior mean		Upper 0.95
(a) Direct effects				
Zikv incidence (3rd quarter)	-0.0532	-0.0254	†	0.0000
Zikv incidence (2nd quarter)	0.0006	0.0308	†	0.0620
Zikv incidence (1st quarter)	-0.0125	-0.0056		0.0020
Primary care	0.0394	0.0580	†	0.0770
Ln municipal GDP	-10.9581	-9.4500	†	-7.9490
Ln population	16.2770	18.4727	†	20.6540
Mobility	3.6007	8.9145	†	14.1640
Environmental	-8.3755	-5.5626	†	-2.6920
Housing	-10.0473	-3.6000		2.5940
Sanitation	-5.2690	-2.3451		0.5640
Infrastructure	0.0107	3.5152		6.8470
(b) Indirect effects				
Zikv incidence (3rd quarter)	-0.1565	-0.0750	†	0.0000
Zikv incidence (2nd quarter)	0.0018	0.0912	†	0.1840
Zikv incidence (1st quarter)	-0.0370	-0.0166		0.0050
Primary care	0.1164	0.1715	†	0.2270
Ln municipal GDP	-32.3536	-27.9277	†	-23.5740
Ln population	48.2199	54.5917	†	60.8530
Mobility	10.5738	26.3474	†	41.8960
Environmental	-24.6091	-16.4406	†	-7.9400
Housing	-29.5589	-10.6396		7.6620
Sanitation	-15.5699	-6.9310		1.6560
Infrastructure	0.0313	10.3907		20.2350
(c) Total effects				
Zikv incidence (3rd quarter)	-0.2099	-0.1003	†	0.0000
Zikv incidence (2nd quarter)	0.0024	0.1220	†	0.2460
Zikv incidence (1st quarter)	-0.0495	-0.0222		0.0060
Primary care	0.1558	0.2295	†	0.3040

Ln municipal GDP	-43.2407	-37.3777	†	-31.5110
Ln population	64.5281	73.0644	†	81.4700
Mobility	14.1721	35.2618	†	56.0620
Environmental	-32.9348	-22.0033	†	-10.6250
Housing	-39.6063	-14.2396		10.2550
Sanitation	-20.8298	-9.2761		2.2200
Infrastructure	0.0420	13.9060		27.0660

†Significant at the 95% level.

The results presented in Tables 3 and 4 show that microcephaly incidence in Brazil is significantly and positively related to access to primary care, population size, and mobility index of the municipalities. On the other hand, microcephaly incidence shows a negative significant association with GDP and environmental index of the municipalities.

There is also a significant spatial autocorrelation of the dependent variable, of which coefficient ρ is more than 6 standard deviations away from zero, indicating that municipalities that have a high incidence of microcephaly tend to be spatially clustered, even after controlling for their attributes and ZIKV incidence. To evaluate the evolution of the relation between microcephaly and ZIKV across different time lapses between notifications, incidence of ZIKV is considered separately for the first three quarters of 2016, whilst microcephaly incidence was considered for the fourth quarter only. The results show a significant positive relationship between ZIKV incidence in the second quarter of the year and microcephaly, a significant negative relationship between ZIKV incidence in the third quarter of the year and microcephaly and a non-significant relationship between microcephaly and ZIKV in the first quarter.

The effect of each of the significant explanatory variables on the incidence of microcephaly can be seen in Table 4. Municipal GDP (logged) exerts a total effect of -37.4. In other words, for every 1% increase in the GDP, the incidence of microcephaly decreases by 0.37 points, being -0.095 points in direct effects and -0.279 in indirect effects. Primary care coverage exerts a compound (total) effect of 0.229, i.e. for each additional percentage point of coverage, microcephaly incidence is raised in 0.23 points, being 0.06 originated in direct effects and the remaining 0.17 in indirect effects. Large municipalities tend to present higher microcephaly rates, so that a 1% increase in population size is related to a 0.73 increase in microcephaly, being 0.18 direct and 0.55 indirect effects. For the IBEU indices, mobility has a total impact of 35 points and environment of -22. Since these indices vary between 0 and 1, we have that an increase of 0.01 point in the indices is related to 0.35 increase in microcephaly for the mobility index and 0.22 decrease in microcephaly for the environmental index.

The total effect of ZIKV on microcephaly is of -0.10 for the third quarter and 0.12 for the second quarter. These mean results are different from those shown for the model considering only ZIKV as an explanatory variable and no measure of regional attributes. When no regional variable was considered, the results were -0.12 and 0.16, respectively. Hence, not controlling the relationship between ZIKV and microcephaly for different regional attributes may overestimate the effects of ZIKV on microcephaly.

Discussion

Our results show that regional attributes can significantly contribute to explaining microcephaly incidence rates across Brazilian municipalities and that disregarding these attributes may lead to overestimation of the magnitude of the relationship between ZIKV and microcephaly. Municipalities with greater GDP per capita and with better environmental urban structures show a lower incidence of microcephaly. The effect of greater GDP per capita may be related to a smaller malnutrition rate and better knowledge of the effects of drug abuse during gestation, which are potential causes of microcephaly. On its turn, a better environmental structure may lead to lower reproductive rates of mosquitoes, specially *aedes aegypti*, potentially affecting the probability of infection of other viruses such as dengue or chikungunya, which may also cause microcephaly.

On the other hand, municipalities with larger population size and better mobility index show a greater incidence of microcephaly. This may be due to easier spread of other infections which can also result in microcephaly, such as rubella, cytomegalovirus and toxoplasmosis or other diseases such as meningitis, HIV, etc. Primary care coverage was also found to be positively correlated with microcephaly incidence. This correlation may be linked to better diagnosis and information on microcephaly.

Regarding the relationship between ZIKV and microcephaly, the positive association between the notification of ZIKV in the second quarter of 2016 and confirmation of microcephaly in the fourth quarter is expected from previous literature given the higher risk of microcephaly when ZIKV infection occurs in the first trimester of pregnancy. However, the negative relationship between ZIKV in the third quarter of the year and microcephaly in the fourth quarter is intriguing. One possible explanation is a fast reduction of ZIKV in municipalities who had high levels in the previous term. Given the time lapse between ZIKV and microcephaly notifications, municipalities with a significant drop of ZIKV in the third quarter should show a lower incidence of microcephaly only in the first quarter of the following year. As shown on Figure 2, the incidence rate of ZIKV changed very fast in Brazil, especially in the Western region of the country, which may be a conjoint result of public policies to reduce the population of *aedes aegypti* and decrease in average temperatures on the third quarter.

In sum, ZIKV incidence is very important to predict microcephaly incidence. However, regional attributes also play a significant role in explaining the differences in microcephaly incidence and may be, at least partially, cofactors that explain the varied risk ratio of microcephaly in pregnant women infected with ZIKV found by Jaenisch et al. (2017).

Final Remarks

The emergence regarding ZIKV and microcephaly was considered of global interest. The quick increase in the number of countries facing an active circulation of ZIKV and the evidence linking this disease with microcephaly is the main source of concerns. The adequate monitoring of the spread patterns of ZIKV and incidence of microcephaly are essential to support actions aiming at an adequate response to this epidemiological crisis. Taking into consideration this challenge, the main objective of this work was to evaluate how precedent ZIKV incidence and regional cofactors can help to understand the spatial spread pattern of microcephaly.

The capability to anticipate future regions that might face a high volume of microcephaly cases resulting from a previous peak in ZIKV incidence can support the ability to provide appropriate emergency response interventions. Aiming at the minimization of the negative consequences of ZIKV and microcephaly, public policies can be better implemented once the right locations can be prioritized based on risk levels. Previous research using health econometrics approach identified a spatial shift of spatial clusters of high levels of microcephaly from Northeast to Mid-west region of Brazil (Vissoci et al. 2018). The model developed in the present work can act as a tool to support the formulation of responses to ZIKV and microcephaly health crisis in this new frontier.

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