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One World, One Health Challenge: The Holistic Understanding of Rickettsiosis Integrating Multi-Criteria Analysis Techniques and Spatial Statistics

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Abstract

Among the human diseases caused by etiological agents transmitted by ticks in Brazil, the most prevalent and public health interest is that one caused by species of *Rickettsia*—Spotted Fever (SF). We applied the concept “One World, One Health” to achieve a proper understanding of SF and determine risk scenarios for human infection by pathogenic *Rickettsia* in the state of Rio de Janeiro (RJ). Multi-criteria decision analysis and spatial statistics were performed on data encompassing epidemiology, health care, biotic determinants, and socioeconomic and demographic variables. The construction of multi-criteria descriptors used 33 indicators ordered in 12 sub criteria of 5 major categories: public health, environmental health, acarology, veterinary health, and microbiology. SF happened nonrandomly in RJ and the risk was heterogeneous in the weight of indicators contribution mainly associated with the criteria acarology (35.11%), microbiology (33.25%), and veterinary medicine (23.96%). Spatially, and according to the PROMETHEE algorithm, ticks from *Amblyomma sculptum* class and dogs are determinants for the occurrence of human cases of SF in RJ. To define indicators of SF and plan health actions, the “One World, One Health” concept proved to be applicable at three levels: (i) the local or possible areas of infection, (ii) the population or municipality, and (iii) the ecosystem or state. The model of study is flexible according to the reality of the endemic areas and also demonstrates its applicability from a national to a local (home) scale.

Keywords: one world, one health, tick-borne diseases, risk, spotted fever, multi-criteria decision analyses

1. Introduction

A total of 1415 species of infectious agents have been associated with human diseases throughout the world. From these, about 60% (868) are considered zoonosis [1], representing 75% of emerging diseases and 80% of agents with bioterrorist potential [2]. These high prevalence have led to new considerations regarding understanding pathogens that have negative impacts on public and veterinary health [2].

“One World, One Health” is a holistic and interdisciplinary vision that integrates ecosystem or environmental health, animal health, public health and food safety at local, country and global scales [3–7].

The concept, which has many historical backgrounds, was presented in 2004 by the Wildlife Conservation Society [8]. It is now widely accepted, incorporated, and disseminated by the World Health Organization (WHO), the World Organization for Animal Health (OIE), and the Food and Agriculture Organization of the United Nations (FAO). The first joint efforts of this vision gave rise to the Global Early Warning System for Major Animal Diseases including Zoonosis – GLEWS [9].

Several interdisciplinary, cooperative, and holistic studies have been developed toward understanding and combating a wide variety of pathogenic diseases [3, 5–7, 10–17].

In the present work, we consider the concept “One World, One Health” *sensu lato*; that is, as synonymous with “One Medicine”, “One Health”, Universal Health and Risk, and Disease Ecology and Eco-epidemiology [3, 5, 6, 10, 16, 17] for the prevention, surveillance, and control of infectious diseases of zoonotic origin.

Among zoonosis, rickettsiosis are produced by Gram-negative proteobacteria of the genus *Rickettsia* that are transmitted mainly by ticks to mammalian hosts and, accidentally, to man [18–21].

In Brazil, among the diseases caused by etiological agents transmitted by ticks, the most prevalent and of most interest to public health are Brazilian spotted fever (FMB) produced by *Rickettsia rickettsii*, and caused by other species of *Rickettsia* that are considered as emerging (species of the spotted fever group of *Rickettsia*-SFGR) such as *Rickettsia* strain Atlantic rainforest [22–24]. However, for the purposes of the present study all these types of spotted fever will be treated collectively as spotted fever (SF).

In the transmission cycle of *Rickettsia*, different co-specific relationships between ticks and vertebrate hosts have been identified that involve geographical, ecological, and evolutionary processes [19, 25–27].

Recent studies [24, 27–29] indicate that the dynamics of SF in the endemic states of Brazil is of a seasonal nature, with the highest incidence rates in the second part of the year (June to October). This seasonality has been associated with the population dynamics of species of ticks of the genus *Amblyomma*, but particularly high densities of larvae and nymphs of *Amblyomma sculptum* [22, 30–34]. This tick is considered the main vector of *R. rickettsii* among the human population of Brazil [22, 23, 27].

However, there are a number of species of ticks that could be considered reservoirs and vectors of pathogenic *Rickettsia* and some mammalian species that could function as amplifiers and reservoirs of these bioagents. These elements are potentially responsible for the occurrence

and maintenance of epizootic cycles and the emergence and/or reemergence of epidemic outbreaks of SF in Brazil. Although they are main determinants of bacterial transmission cycles, they are not significant hazards due to the establishment of vulnerability and risk areas, and surveillance programs, as well as efforts to control human outbreaks, as demonstrated by the findings of a number of studies [25, 35–39].

An integrated approach is a promising strategy for understanding the dynamics of SF and determining risk scenarios for infection of humans by pathogenic *Rickettsia* because it would result in the establishment of SF surveillance and environmental control programs. This is precisely what we aim to achieve in the present work by employing the concept of “*One World, One Health*”. With the establishment of a clear risk scenario, clinically suspected cases in high risk areas may be treated early [40, 41].

2. Materials and methods

2.1. Study area

The state of Rio de Janeiro is located in the eastern portion of Brazil’s Southeast Region and occupies an area of 43,777.954 km² divided into 92 municipalities. It is the fourth smallest state (by area) in Brazil, yet has the highest population density (365.23 inhabitants/km²) with an estimated population of 16,640,00 inhabitants. It is also the most urbanized state in the country, with 97% of the population living in cities [42].

2.2. Epidemiological data and health care

The epidemiological data presented here was obtained from the Sistema de Informação de Agravos de Notificação—SINAN (Notifiable Diseases Information System) [43] and provided by the Secretaria de Estado de Saúde do Rio de Janeiro—SES/RJ (State Secretary Health of Rio de Janeiro). The data comprised cases confirmed by laboratory tests (PCR or serology) and/or clinical and epidemiological nexus of SF between 2007 and 2016.

These data were made available with the protection of the identity of the patients; therefore, information such as names or addresses cannot be displayed at any time to comply with national ethical regulations of Brazil [44].

To assess access to health care, the following municipal indicators were used: number of health professionals (HP) and number of hospital beds (HB) per 100 thousand inhabitants. For these indicators, we used the average of the information from the years 2010 and 2016 obtained from the Secretaria de Atenção em Saúde-SAS (Health Care Secretary) of the Ministério da Saúde do Brasil (Ministry of Health-MH) [45].

2.3. Biotic determinants

Information regarding potential vectors of SF and hosts of the tick was obtained from the database of the Laboratório de Referência Nacional em Vetores das Riquetsioses (LIRN—Laboratory of the National Reference of Rickettsial Vectors), built from samples received and analyzed within the workflow of the Rede Nacional de Vigilância de Ambiental para Febre Maculosa

e outras Rickettsioses (National Network for Environmental Monitoring for spotted fever and other rickettsial diseases) of MH from 2007 to 2016. The samples were collected in sampling units (specimens originating from the same host or environment), by cloth-dragging, visual searches on hosts and inspection of plant litter and abiotic surfaces by state and municipal health teams from Rio de Janeiro for environmental surveillance and investigation of cases of SF.

Ticks were identified using dichotomous keys, while species of *Rickettsia* infecting ticks were identified using PCR [see in detail in Montenegro et al. [27]].

To characterize conditions of climatic suitability throughout the study region, potential distribution models for *A. sculptum*, *Amblyomma autreolatum*, and *Amblyomma ovale*, the main vectors of SF in Brazil [22], were produced using the Maxent algorithm version 3.2.1 [46]. For this, we used seven climatic variables that we considered crucial to the biology of the species and which had already been evaluated for collinearity by principal component analysis (PCA) in Niche Software version 3.0: annual mean temperature, mean diurnal temperature range, maximum temperature in the warmest month, minimum temperature in the coldest month, annual precipitation, and precipitation in the wettest and driest months [37, 38, 47, 48].

To generate the final models, we selected the logistic values for the final output of the 25 bootstrap interactions. The mean number of repetitions was selected as the final model and converted into binary models to generate adequacy maps that were overlaid as a shape-file to subtract information about adequacy in relation to the municipality of occurrence of these vectors (**Figure 1**).

2.4. Socioeconomic and demographic data

Data for socioeconomic and demographic indicators are being used to understand the dynamics of spotted fever [49–51]. It was obtained from Brazilian census data acquired by the Instituto Brasileiro de Geografia e Estatística-IBGE [52]. The following indicators were used for the analysis: Municipal Human Development Index (MHDI), GINI Index (IG), Demographic Density (DD), Land Use Municipality (LUM), Percentage of Poverty in the Rural Area (PPRA), Degree of Urbanization (DU), and the Percentage of the Agricultural Contribution to the Municipal GDP (GDP-AM).

2.5. Analysis of data

The first phase of analysis evaluated whether human infections with SF-causing pathogens occur randomly with respect to time. Three statistical tests were used in statistical software [53], with at least two coincident tests with confidence levels of 95% determining randomness, or not, of human cases of SF.

In the second phase of analysis, two multi-criteria decision analyses (MDA) were performed, for the risk of human infection with pathogenic tick-borne *Rickettsia*. Multi-criteria decision analysis is a method that approaches a certain object from different characteristics that influence the occurrence of a given problem. The method has become increasingly used for understanding of events of interest in public health [54].

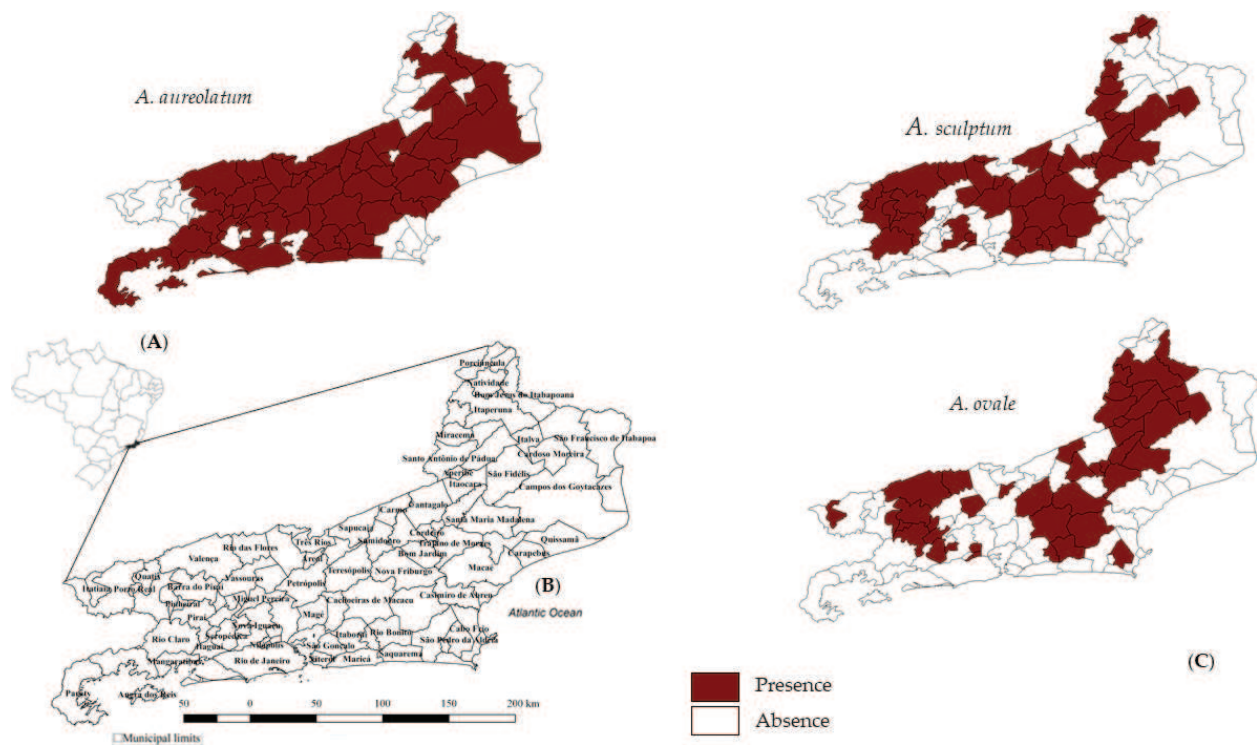


Figure 1. Location of the state of Rio de Janeiro, Brazil (A), its municipalities (B) and potential distribution models for *A. sculptum*, *A. aureolatum*, and *A. ovale* by Maxent algorithm (C).

The following phases of MDA were defined: Structuring Phase, Modelling Phase and Evaluation Phase. The objective of the Structuring Phase is to understand the decision tree formed by the determinant variables of SF. The Modelling Phase mathematically expresses human risk to SF and the Evaluation Phase presents the results of the model.

2.5.1. MDA structuring phase

To construct multi-criteria descriptors and decision-making processes, three criteria comprising 13 subcriteria, which in turn include 34 indicators of similar nature and that are considered determinants of SF, were used (**Box 1**).

2.5.2. MDA modelling phase

For modelling MDA, numerical values of criteria, subcriteria, and indicators were incorporated into the decision-making model by employing peer-to-peer comparison. This comparison method attributes a preferential value to two criteria, two sub-criteria or two indicators, which are graphically compared to one another using the D-sight program [55]. Theoretical weights, ranging from 1 to 100, for the components of the decision-making model were generated using the PROMETHHE method (preference ranking method for enrichment evaluation) through peer-to-peer comparison [56].

Criteria	Subcriteria	Indicators	Sources
Public Health	Health care	HP	SAS
		HB	
		Ratio HP/HB	
	Social	MHDI	IBGE
		GI	
		PPRA	
Environmental Health	Land use	LUM	IBGE
		DU	
		GDP-AM	
	Demographic	DD	
Acarology	Vector fitness (presence of vectors in the environment (not hosts))	Modeled presence	LIRN
		Real presence	LIRN
	Tick vector (proven <i>R. rickettsii</i> transmission)	<i>A. aureolatum</i>	LIRN
		<i>A. sculptum</i>	
		<i>A. ovale</i>	
		<i>R. sanguineus</i>	
	Tick carrier synanthropic (infected with <i>Rickettsia</i> but without proof of transmission to hosts and associated with anthropized environments)	<i>A. dubitatum</i>	
		<i>D. nitens</i>	
		<i>Rh. microplus</i>	
		<i>A. longirostre</i>	
	Tick wild (infected or not with <i>Rickettsia</i>)	<i>Ha. leporispalustris</i>	
		<i>Ornithodoros</i> sp.	
Veterinary health	Reservoir animals (proven infection of tick)	<i>C. familiares</i>	LIRN
		<i>H. hydrochaeris</i>	
	Host animals (has not been shown to function as a reservoir)	<i>E. caballus</i>	
		<i>B. taurus</i>	
		<i>F. catus</i>	
		<i>E. asinus</i>	
		Mula	
	Parasitism in humans	<i>H. sapiens</i>	
Microbiology	Etiological agent	<i>R. rickettsii</i>	LIRN and Montenegro et al. [27]
		Spotted fever group of <i>Rickettsia</i> – SFGR	
		<i>Rickettsia</i>	

Box 1. Criteria, sub-criteria, and indicators of multi-criteria decision analysis (MDA).

It should be noted that the PROMETHEE method was developed in order to help the individual or collective decision maker. These methods serve to solve problems by selecting, or making arrangements of, possible alternatives (municipality, options, and shares), subject to an assessment of various criteria (variables, qualitative and quantitative indices, indicators, attributes, and any criteria with numerical or nominal values), which may be in conflict with each other, and seek to simultaneously satisfy different solutions for decision making [56, 57].

The third phase of analysis involved using the scores resulting from the PROMETHEE model for spatial statistical analysis. Spatial dependence of risk for each area assessed was analyzed using the Moran Local Index—LISA (Anselin 2010), with 9999 permutations, no spatial autocorrelation and statistical significance (LISASig) considered to be greater than 0.05. All spatial statistical analyses were performed using the program TerraView [58].

Finally, using data points from data on probable infection sites for confirmed SF cases (using addresses reported in the epidemiological form with Google Maps), we sought to focus on areas with the highest probability of human SF infection within the biomes, and the greatest spatial association with hosts and ectoparasites in RJ, using the program QGIS [59].

2.5.3. MDA evaluation phase

This is the phase where the results of the modelling are presented

3. Results

Human infections with pathogenic *Rickettsia* in RJ occur mainly between the months of March–April and August–October, with it being more pronounced in the latter (**Figure 2**).

Two of the three tests employed showed that the temporal dynamics of SF cases is not a sequence of temporally random events. The first test counted the number of times the data sequence was above and below the median and determined that the sample size was too small to perform a valid test (it was inconclusive).

The second test counted the number of times a sequence went up or down (number of executions up and down = 46, expected number of runs = 77, and Z statistic = 6.77, $P_v = 1.3^{-11}$) and the third was based on the sum of squares of the autocorrelation coefficients—*Box Pierce test* (based on the first 24 autocorrelation coefficients, $Z = 37.3$, $P_v = 0.040$).

Multi-criteria modelling found the risk to tick-borne transmission of spotted fever group of *Rickettsia* in Rio de Janeiro to be heterogeneous with regard to the contribution of the weights of the two scenarios examined. The main sources of variation are in the contributions of the criteria acarology (35.11%), microbiology (33.25%), and veterinary medicine (23.96%) (**Table 1**). The five criteria are made up of 13 subcriteria, and 21 of the original 34 priority indicators and variables, contributed at least 2% to the two models of MDA.

With the exception of environmental health, all criteria contributed equally to the determination of risk scenarios for SF; the greatest influence was by acarology, with 27.3% of the total

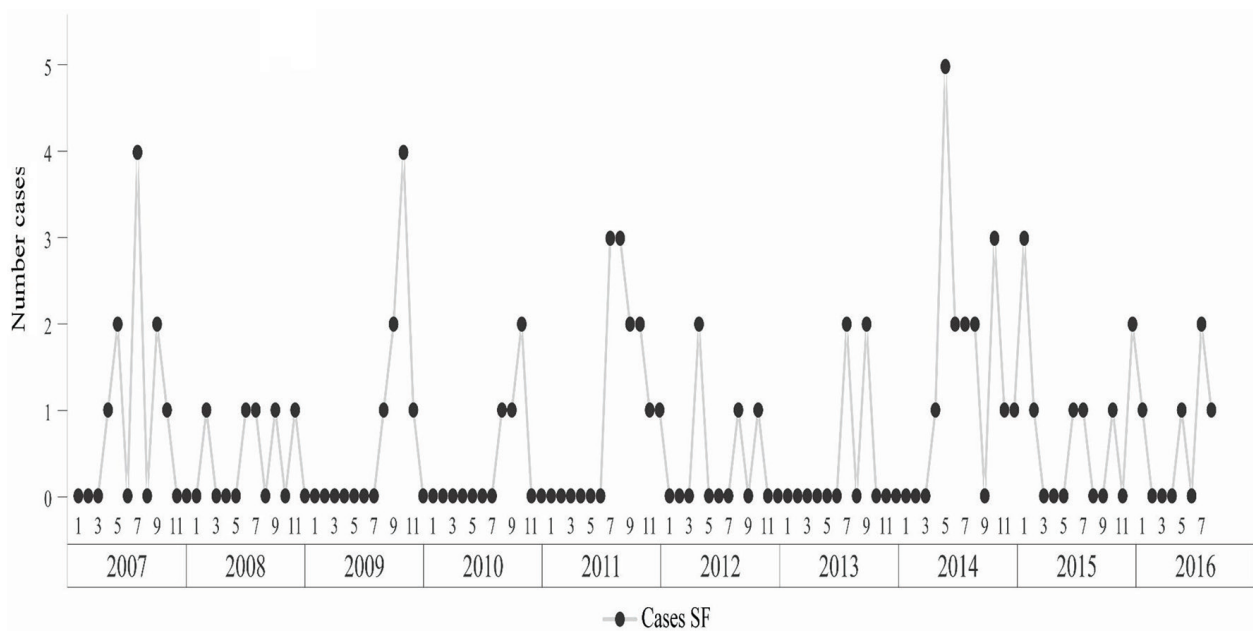


Figure 2. Temporal (monthly) dynamics of human infection with tick-borne pathogenic *Rickettsia* that causes spotted fever in the state of Rio de Janeiro.

weight of the model. On the other hand, the risk scenario was found to be more associated with acarology and microbiology (**Table 1**). The five criteria are made up of 13 subcriteria, and 21 of the original 34 priority indicators and variables; the indicators contributed at least 2% to the two models of MDA (**Table 1**).

According to the weight of each indicator, the largest (5%) absolute value generated by the PROMETHEE algorithm for the occurrence of infection with SFGR is the criteria associated with the subcriteria health care (rate HP/HB), reservoir animals (*C. familiares*), human parasitism, tick vector (*A. sculptum*), and etiological agent (*R. rickettsii* and SFGR) (**Table 1**).

The multi-criteria evaluation of the results of the PROMETHEE method found heterogeneous risk scores for the 92 municipalities of the state of RJ. Based on the scores, 25% (23/92) of the territories are located in the highest level (4th quartile) of risk for SF (**Figure 3a**).

The LISA technique identified 48.9% (45/92) of the municipalities as having high spatial dependence, with 19.6% (18/92) are in the category High (High-High) and 29.3% (27/92) in the category Low (Low-Low). For the same categories of spatial dependence mentioned for risk were found (**Figure 3b**). Statistically significant spatial correlation was found in 13.0% (12/92) of the municipalities (LISASig $\leq 5\%$) (**Figure 3c**).

The risk model was sensitive to identifying areas with human SF infection (**Figure 3d**).

Finally, it was possible to georeference 50% (39/78) of the confirmed cases of SF with probable areas of infection (PAIs) in RJ. The PAIs are located mainly in the areas where the Atlantic Forest biome and anthropic areas intersect (**Figure 4**). The ticks *A. sculptum* and *R. sanguineus* were the most frequent and abundant species in the PAIs, while dogs and the environment are the most significant host and site of infestation, respectively, with the most ticks occurring in places where humans acquire rickettsias.

Criterion	Subcriterion	Indicators	Theoretical weight (%)	Absolute weight (%)—PROMETHEE
Public Health			18.16	
	Health care		75	
		Rate HP/HB	50	6.81
		HP	25	3.4
		HB	25	3.4
	Social		25	
		PPRA	33.33	1.51
		GI	33.33	1.51
		MHDI	33.33	1.51
Environmental Health			11.98	
	Land use		29.7	
		GDP-AM	42.86	1.52
		DU	28.57	1.02
		LUM	28.57	1.02
	Demographic		16.34	
		DD	100	1.96
	Vector fitness		53.96	
		Real presence	66.67	4.31
		Modeled presence	33.33	2.16
Veterinary Health			23.96	
	Reservoir animals		31.89	
		<i>H. hydrochaeris</i>	33.33	2.55
		<i>C. familiares</i>	66.67	5.09
	Host animals		22.11	
		Mula	9.59	0.51
		<i>E. asinus</i>	9.59	0.51
		<i>F. catus</i>	14.53	0.77
		<i>B. taurus</i>	30.46	1.61
		<i>E. caballus</i>	35.83	1.9
	Parasitism in humans		46	
		<i>H. sapiens</i>	100	11.02
Acarology			35.11	
	Tick vector		52.78	
		<i>R. sanguineus</i>	13.16	2.44
		<i>A. aureolatum</i>	25.23	4.68
		<i>A. sculptum</i>	42.43	7.86

Criterion	Subcriterion	Indicators	Theoretical weight (%)	Absolute weight (%)—PROMETHEE
Microbiology	Tick carrier	<i>A. ovale</i>	19.17	3.55
		<i>Rh. microplus</i>	33.33	3.89
		<i>D. nitens</i>	33.33	3.89
		<i>A. dubitatum</i>	33.33	3.89
	Tick wild		13.96	
		<i>Ornithodoros</i> sp.	33.33	1.63
		<i>Ha. leporispalustris</i>	33.33	1.63
		<i>A. longirostre</i>	33.33	1.63
			33.25	
	Etiological agent		100	
<i>Rickettsia</i>		9.53	1.03	
SFGR		24.99	2.7	
<i>R-rickettsii</i>		65.48	7.07	

Table 1. Weights of the criteria used for determining vulnerability for tick-borne transmission of the spotted-fever group of *Rickettsia* to humans.

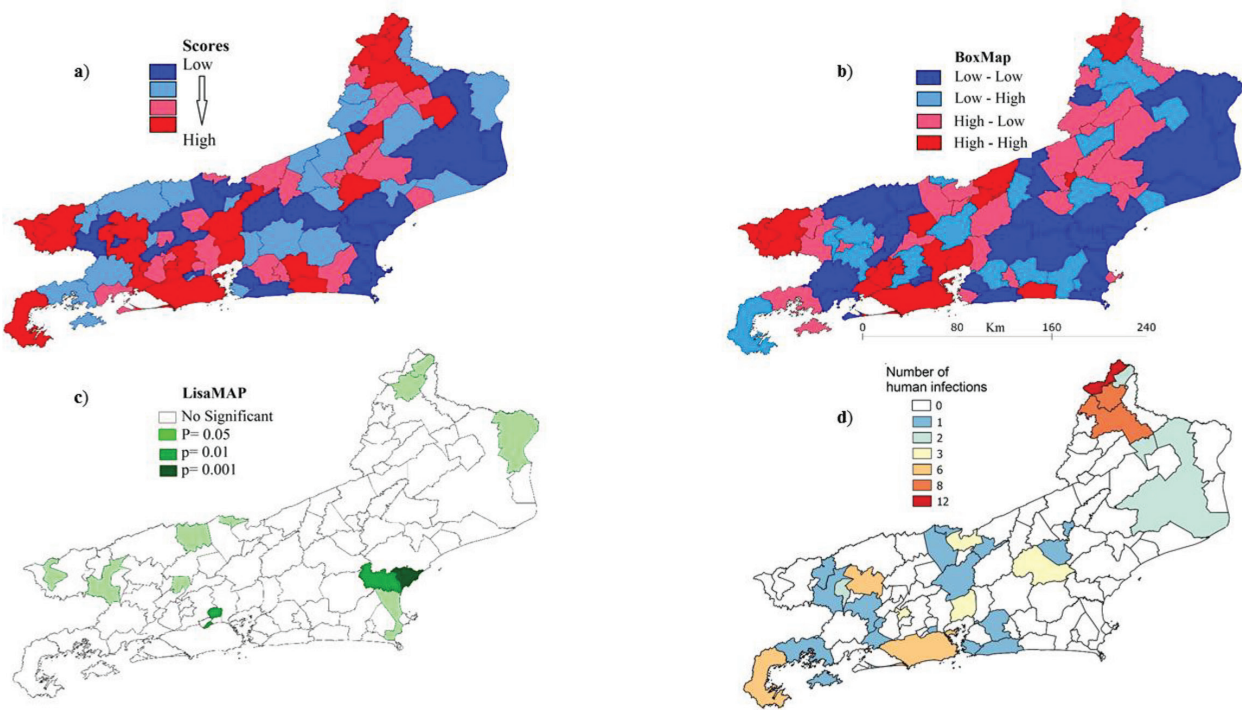


Figure 3. Spatial vulnerability for SF in the state of Rio de Janeiro. The letter **a** corresponds to the range of absolute values, **b** to spatial dependence, **c** to the statistical significance of spatial correlation and **d** to the number of cases with local infection.

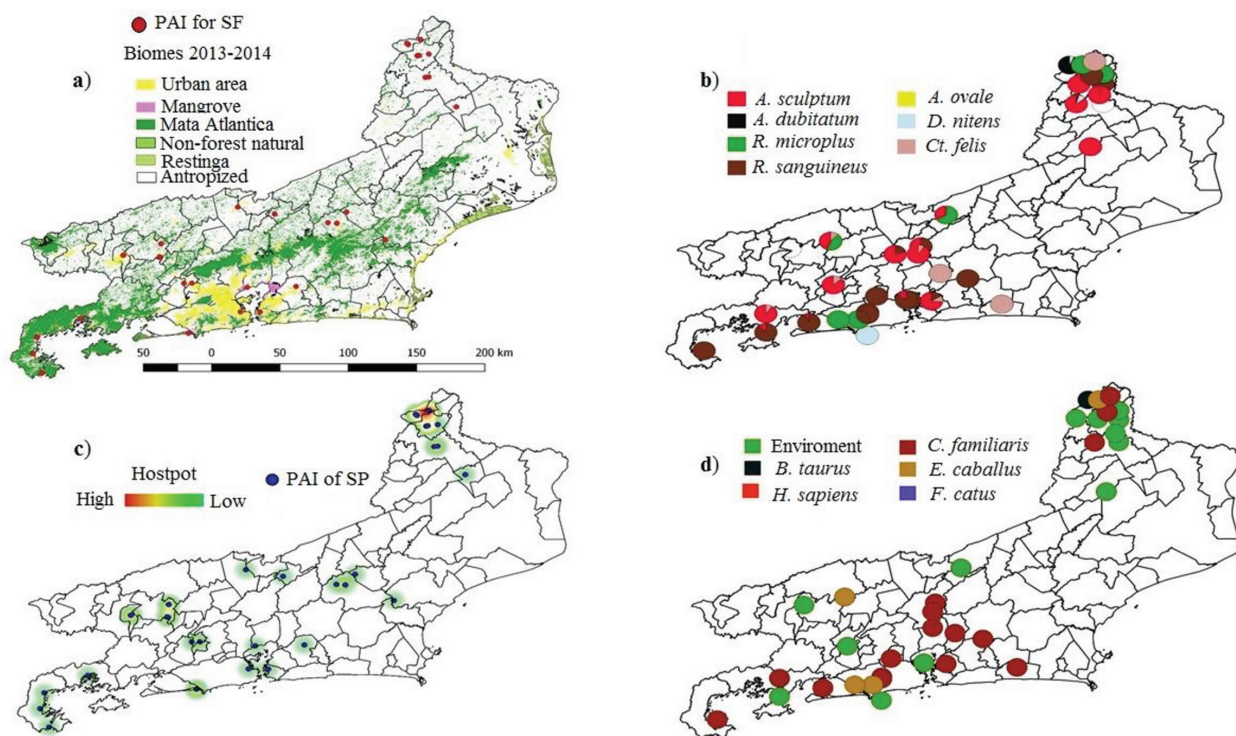


Figure 4. Distributions of biological and environmental determinants of probable areas of infection (PAIs) of pathogenic *Rickettsia* in the state of Rio de Janeiro, 2007–2016: (a) PAIs relative to the biomes of RJ, (b) tick species, (c) hostpots for SF with 5Km radius, and (d) host and environment infested with ticks.

The municipalities of Porciúncula, Natividade, and Itaperuna are located in a hostpot for human acquisition of bacteria (**Figure 4**).

4. Discussion

In the state of RJ, human infections with pathogenic *Rickettsia* are an event of significant public health interest that do not happen randomly; there is seasonality with occurrence between March and April and between August to October, as in all endemic states of Brazil [24, 28, 29, 60]. This understanding requires that collective health actions be deployed before, during, and after these periods, in order to combat the scenario of high mortality in RJ [27, 60].

There exists a spatial association between increased frequency and abundance of the tick species *A. sculptum* and *R. sanguineus*, the presence of dogs and the environment (grass and vegetation) infested. At least spatially, and according to the PROMETHEE algorithm, *A. sculptum* and dogs are essential determinants for the occurrence of human cases of SF in RJ. However, we emphasize the need for focused studies on the participation of *R. sanguineus* in outbreaks in RJ [27].

This tick (*R. sanguineus*) functions as reservoir and vector among hosts, keeping other *Rickettsia* wild strains brought to the peridomicile environment by other species of ticks that parasitize dogs (*A. aureolatum*), as happens in the state of São Paulo, Brazil [61].

Recent studies of SF epidemiology in RJ [60] have found that 69% (72/104) of SF cases confirmed in the last 10 years were in urban areas and the rate of lethality for people infected in

the peri-urban environment is greater (86.6%, 13/15). Thus, in addition to solving this problem, it is also necessary to determine the degree to which the dog tick participates in urban outbreaks and what strains of *Rickettsia* it amplifies.

The application of the concept of “*One World, One Health*” in the present study addresses three scales for defining indicators and health action plans: (i) the individual or PAIs; (ii) the population or municipality; and (iii) The ecosystem or state. The first level includes hotspots for human acquisition of the bacteria (**Figure 4c**). These same areas possess the greatest number of biological elements in the PAI and thus are the places where advertising posters should be placed announcing the risk of SF acquisition [41].

Note that health care represents a considerable weight in the categorization of risk (13.61%), indicating that intersectoral municipal policies (second level) could have an impact on this indicator. Ensuring that the number of health care sites, the number of health professionals and, above all, the actions of epidemiological surveillance and health care, including treatment of suspected patients are sufficient to reverse the lethality coefficients in the state, even without confirmatory evidence [40, 41].

The third level serves to define and prioritize indicators in public health and environmental health, as well as interdisciplinary, to intervene and monitor in the state of RJ. The adequacy of resources and the development of pilot eco-epidemiological studies at a sub-regional level, following the patterns of risk and spatial dependence (**Figure 3a and b**), are also recommended.

Despite the fact that climate data were used for modelling suitability for the presence of the principal vectors in Brazil, these variables (temperature, humidity, rainfall, elevation, etc.) did not permit a local evaluation, as recommended [26, 37, 38, 47, 48, 62–66]. This limitation is associated with the low number of georeferenced cases (50% of the cases confirmed with PAIs were in RJ) and the lack of a necessary control of georeferenced unconfirmed cases of SF.

We urgently recommend that all cases (suspected and confirmed) be georeferenced. For this purpose, we recommend using the free, Internet-based GPS application essentials, which also functions from satellites without the need of an internet connection (<http://www.gpsessentials.com/>).

Although this is not the first interdisciplinary effort to integrate different determinants for understanding SF [22, 61], it is the first in Brazil to use multi-criteria analysis with mathematical algorithms applied to that pathology.

The present work uses the PROMETHEE algorithm to transform qualitative perceptions to quantitative values of the different dangers and threats that comprise the socio-environmental risk of human infection and defines the spatial dependence for infection with SF. Therefore, in addition to being a model study for cases where weights of the contributions of each element of the transmission chain are flexible according to the realities of the endemic areas, this study also demonstrates applicability from a national to local (domicile) scale.

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Conflict of interest

The authors declare that we have prepared the manuscript in accordance with the standards of the journal, possess exclusive responsibility for the accuracy and correctness of the contents of the submitted article and declare that we have no conflicts of interest. The opinions expressed by authors contributing to this journal do not necessarily reflect the opinions of the journal or the institutions with which the authors are affiliated.

Author contributions

DM—contributed to the concept, design, and application of MDA techniques and spatial statistics; APC and MP—contributed to the design and application of MDA techniques; SVO made the climate suitability modelling for vector; IBM, LD, SVO, GSG and RPB—contributed to research project design and concept, data gathering and interpretation of results. All authors contributed to critically revising for important intellectual content, final approval of the version to be published, and all are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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