PUBLICAÇÃO OFICIAL DO NÚCLEO HOSPITALAR DE EPIDEMIOLOGIA DO HOSPITAL SANTA CRUZ E PROGRAMA
DE PÓS GRADUAÇÃO EM PROMOÇÃO DA SAÚDE - DEPARTAMENTO DE BIOLOGIA E FARMÁCIA DA UNISC

Revista de Epidemiologia e Controle de Infecção

Hospital Santa Cruz

ORIGINAL ARTICLE

Historical geographic overlap of human rickettsiosis with animal reservoirs in Juiz de Fora, Minas Gerais, Brazil

Sobreposição geográfica histórica da riquetsiose humana com reservatórios animais em Juiz de Fora, Minas Gerais, Brasil

Historical geographic overlap of human rickettsiosis with animal reservoirs in Juiz de Fora, Minas Gerais, Brazil

https://doi.org/10.17058/reci.v12i3.17039

Received: *10/10/2021*
Accepted: *03/14/2022*
Available online: *09/26/2022*

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ABSTRACT

Background and objectives: we investigated the existence of a historical geographic overlap between the location of spotted fever group rickettsiosis human cases, a disease caused by the gram-negative bacterium *Rickettsia* sp., and that of mammalian reservoirs, specifically domestic horses and capybaras, in the urban perimeter of the city of Juiz de Fora, Minas Gerais, Brazil. **Methods:** cases of human rickettsiosis that occurred during a period of 17 years (2003-2020) were geolocated and the distribution of cases in time and geographic space was assessed using 1st and 2nd order geospatial association indicators. We also analyzed the overlap between the locations of human rickettsiosis cases and the area of occurrence of domestic horses and capybaras. **Results:** men were diagnosed more often than women, but a large proportion of affected women died. The results indicate an aggregation of human rickettsiosis cases in time (cases tend to occur close to each other at each epidemic event) and in geographic space (cases are concentrated in a specific geographic region of the urban perimeter). Human cases seem to be more associated with city regions with: i) higher local frequency of domestic horses and not capybaras; ii) lower rates of family development. **Conclusion:** it is suggested that, in the local epidemiological scenario, domestic horses appear to be the main sources of the rickettsia infecting humans, not capybaras.

Keywords: *Spatio Temporal Analysis. Geographical Localization of Risk. Rickettsia rickettsii. Spotted Fever Group Rickettsiosis.*

RESUMO

Justificativa e objetivos: foi investigada a existência de uma sobreposição geográfica histórica entre a localização dos casos de riquetsiose humana do grupo da febre maculosa, um grupo de doenças causadas pela bactéria

Gram-negativa *Rickettsia* sp., e dos reservatórios mamíferos, especificamente cavalos domésticos e capivaras, no perímetro urbano do município de Juiz de Fora, Minas Gerais, Brasil. **Métodos:** foram geolocalizados os casos de riquetsiose humana ocorridos durante um período de 17 anos (2003-2020), sendo avaliada a distribuição dos casos no tempo e espaço geográfico através de indicadores de associação geoespacial de 1ª e 2ª ordem. Também analisamos a superposição dos locais dos casos de riquetsiose humana com a área de ocorrência de cavalos domésticos e capivaras. **Resultados:** homens foram diagnosticados mais frequentemente que as mulheres, mas grande proporção das mulheres acometidas faleceu. Os resultados indicam uma agregação dos casos de riquetsiose humana no tempo (os casos tendem a ocorrer próximos entre si a cada evento epidêmico) e no espaço geográfico (os casos se concentram em uma região geográfica específica do perímetro urbano). Os casos humanos aparentam ser mais associados às regiões da cidade com: i) maior frequência local de cavalos domésticos e não das capivaras; ii) menores índices de desenvolvimento familiar. **Conclusão:** sugere-se que, no cenário epidemiológico local, são os cavalos domésticos que aparentam ser as principais fontes da riquétsia infectando os humanos, não as capivaras.

Descritores: *Análise Espaço-Temporal. Localização Geográfica de Risco. Rickettsia sp. Rickettsiose do Grupo da Febre Maculosa.*

RESUMEN

Justificación y objetivos: investigamos la existencia de una superposición geográfica histórica entre la localización de casos de rickettsiosis exantemáticas humana, enfermedad causada por la bacteria gramnegativa *Rickettsia* sp., y la de mamíferos reservorios, específicamente caballos domésticos y capibaras, en el perímetro urbano de la ciudad de Juiz de Fora, Minas Gerais, Brasil. **Métodos:** se geolocalizaron los casos de rickettsiosis humana ocurridos durante un período de 17 años (2003-2020), y se evaluó la distribución de casos en el tiempo y espacio geográfico utilizando indicadores de asociación geoespacial de 1er y 2do orden. También analizamos la superposición entre las ubicaciones de los casos de rickettsiosis humana y el área de ocurrencia de los caballos domésticos y capibaras. **Resultados:** los hombres fueron diagnosticados con más frecuencia que las mujeres, pero una gran proporción de mujeres afectadas fallecieron. Los resultados indican una agregación de casos de rickettsiosis humana en el tiempo (los casos tienden a ocurrir cerca uno del otro en cada evento epidémico) y en el espacio geográfico (los casos se concentran en una región geográfica específica del perímetro urbano). Los casos humanos parecen estar más asociados con regiones urbanas con: i) mayor frecuencia local de caballos domésticos y no de capibaras; ii) menores tasas de desarrollo familiar. **Conclusión:** se sugiere que, en el escenario epidemiológico local, los caballos domésticos parecen ser las principales fuentes de la rickettsia que infecta a los humanos, no los capibaras.

Palabras clave: *Análisis Espacio-Temporal. Localización Geográfica de Riesgo. Rickettsia rickettii. Rickettsiosis Exantemáticas.*

INTRODUCTION

Spotted fever group (SFG) rickettsiosis is an infectious, systemic disease caused mainly by the Gram-negative bacterium *Rickettsia rickettsii* (Wolbach 1919) Brumpt 1922, although other species of the same genus may cause a milder disease. These bacteria are mainly transmitted by ticks *Amblyomma sculptum* (Berlese, 1888) and *Amblyomma aureolatum* (Pallas, 1772), which acquire them from an infected host during hematophagy, especially during the rickettsia' bloodstream phase, amplifying transmission to new hosts in subsequent blood repast. In addition to the human species, a wide range of domestic and wild mammals, including carnivores, rodents and herbivores, can be infected, and each of these *taxa* participates with different competences in transmission cycle and in the local maintenance of rickettsiae. Regardless of hematophagy, transovarian and transstadial transmission allows the spread of rickettsia to its progeny, but in the case of *R. rickettsii* infecting *A. sculptum*, the levels of vertical transmission do not ensure bacterium maintenance without the participation of amplifying vertebrate hosts.[2,3] In endemic areas for such rickettsiae, where capybaras (*Hydrochoerus hydrochaeris*, Linneaus, 1766) occur, the tick population is predominantly *A. sculptum,* while in non-endemic areas, there is a population balance of this species with *Amblyomma dubitatum* (Neumann, 1899). These invertebrates tend to have larger populations in degraded areas covered by grasses.[1]

Domestic horses and free-ranging capybaras have been described as preponderant for the local persistence of rickettsia in urban and peri-urban environments. Horses appear to be less competent as reservoirs than capybaras, but both are capable of sustaining the local transmission cycle for tick vectors and, consequently, for humans. Regarding capybaras, an ecological phenomenon has added to their competence as a reservoir: the growing urbanization in Brazil since the end of the last century. The largest rodent in the world has become accustomed to human presence, gradually expanding its presence in urban centers with hydrology favorable to its presence, as it prefers riparian forest associated with freshwater courses and collections, where they find shelter and feed on riverine vegetation.[4,5,6]

These SFG have been sparsely diagnosed in Minas Gerais municipalities since 1945. In Juiz de Fora, speci-

fically, the first confirmed case was described in 1995. Since then, intermittent outbreaks of Brazilian spotted fever (BSF) in humans have been diagnosed by health agencies in the municipality, as well as horses, dogs and ticks infected with *R. rickettsii* in several regions.[7,8]

As the participation of horses, dogs and their ticks in transmission cycle was already well characterized at the time, after successive episodes of SFG in Juiz de Fora since 1995, the City Hall carried out a program to fumigate horses in the municipality from 2007 to 2011, notably in the so-called "carrier" horses. These are informal workers who use horses for animal traction, performing small cargo transport services where other forms of transport are unfeasible, costly or non-existent. Usually, these workers live in poor regions and, commonly, horses "live" together with people in a complex equine stall room, intensely facilitating horse-tick-human transmission, being such an interaction a risk factor for the disease occurrence in humans, as well as the proximity to capybaras.[8]

The hydrological situation of the city of Juiz de Fora favors the presence of capybaras in the urban environment. The city is cut in its lower part by the Paraibuna river valley, which receives several streams and streams tributaries of all the hills and mountains surrounding the city. Thus, capybaras perennially occupy the Paraibuna valley and can be seen in other water bodies in the city. Occupation by capybaras is considered a risk for rickettsia transmission to humans, due to its central ecological role in the bacterium transmission cycle. Government agencies are considering the culling of capybaras in the urban perimeter as a way of controlling SFG in humans (Rafael Veríssimo Monteiro, personal communication), following examples from other situations.[9]

In this way, the conditions that describe the favorable scenario for SFG transmission to humans can be summarized as: i) proximity to transitional vegetation areas, with greater presence of grasses and low shrubs; ii) proximity to capybaras and horses; iii) presence of transmitting ticks, *Amblyomma sculptum*. All these conditions are present in Juiz de Fora.[9,10]

Considering the conditions described above, this research aimed to investigate the possibility of a geospatial overlap between the location of human cases of spotted fever group rickettsiosis and mammalian reservoirs in the urban perimeter of Juiz de Fora. To achieve these objectives, we: i) georeferenced the human cases registered in the urban perimeter of Juiz de Fora, from 2003 to 2020; ii) we verified the geographic overlap of SFG cases with the areas of occurrence of horses and capybaras in the urban perimeter of the city, to estimate which of these hosts offers the greatest risk of transmission to humans; iii) we verified, through spatial analysis tools, the potential existence of aggregations of human cases in time and geographic space that could reveal areas in the city with greater risk of occurrence of SFG.

METHODS

Human cases

SFG human cases in the urban perimeter of Juiz de Fora were georeferenced, using public information and/or registered in the Information System of Notifiable Diseases (SINAN - *Sistema de Informação de Agravos de Notificação*) of the Ministry of Health, from 2003 to 2020. According to Resolution 510/2016 of the Brazilian National Health Council (CNS), this type of study is exempt from an ethical license. One of us (JGCJ) was primarily responsible for epidemiological surveillance and epidemiological screening of 80% of cases, in addition to collecting data from SINAN. From these sources, in addition to the geographical coordinate relating to the affected person's place of residence, information was collected on whether the probable infection site of the case was autochthonous or not in the municipality, gender, whether there was hospitalization, the type of diagnosis used and the final result (death/cure). For georeferencing, the WGS 84 datum, and the QGIS® 3.16 software and the Rstudio 1.1® platform running R® version 3.5.3 were used for map generation and statistical analysis. Fisher's exact test was used to compare the rates of death from SFG between the sexes, with a significance level at $p<0.05$.

Capybara location

To map the geographic occurrence of capybaras, observations from two different sources were included, obtained from September 2016 to December 2017:

Information on the collection of capybaras in the urban perimeter made by the fire department teams, IBAMA (Brazilian Institute for the Environment and Renewable Natural Resources) and IEF (State Institute of Forestry, Minas Gerais), georeferenced from the collection address (5 locations).

Information obtained from the Information System for Wild Health (SISS-GEO) application, managed by the Biodiversity and Wild Health Institutional Platform/Fiocruz, for monitoring wild animals and generating epizootic alerts. The application captures the geographic coordinates by GPS of the animal's photographic record in real time, in addition to other observations.[11]

Domestic horse location

The locations of sightings of domestic horses found in the city were mapped, georeferenced from Google Earth® satellite image. Cart horses, although they circulate throughout the city, occupy fixed points of waiting for work, often on the banks of the Paraibuna river. Four of the known points have been geolocated. The places defined as tick fumigation points for domestic horses were also mapped, chosen by the city hall precisely because they are places of concentration of cart horses for grazing, walking and/or waiting for requisition for work. Tick fumigation took place from 2007 to 2011, from June to November, with intervals of approximately 21 days between each tick fumigation, at nine different points, also including the horses eventually parked on the banks of the Paraibuna river.

Epidemiological and geospatial analyzes

Two epidemiological and geospatial analyzes were

performed concerning human cases. First, the density of observations in the study area was assessed, a 1st order property of the case distribution pattern, capable of revealing local clusters of cases. For this analysis, a heatmap or Kernel density map was generated, with a parabolic density probability function, based on geographic occurrence of human cases of BSF in the urban perimeter of Juiz de Fora, from 2003 to 2020 (Heatmap plugin QGIS 3.10). A distance of 2,000 m was used as the influence radius of each point in the model, based on the fact that the average daily walking distance of a normal person is around 4,000 m. This heatmap (Kernel) intends to reveal an eventual overlap of the area of daily displacement of human cases of SFG that occurred in the analyzed period. Areas of great overlap would be areas of greater risk of exposure to rickettsia contamination. The property of the 2nd order of distribution pattern of cases was also assessed, i.e., whether each case can interfere with the occurrence of others. To this end, we calculated the Average Nearest Neighbor (ANN) of observed cases and compared it with a Monte Carlo simulation (600 iterations), based on the random generation of cases in the geographic occurrence window delimited by the cases that have already occurred. We compare the observed ANN with the average obtained in the 600 iterations, generating the probability that the observed cases present a certain pattern of geographic aggregation (random, uniform or aggregated).[12-14]

RESULTS

A total of 34 cases of human SFG were identified in the urban perimeter of Juiz de Fora in the period from 2003 to 2020, i.e., an average frequency of two cases of SFG per year. The fatality rate was 47% among those infected (16 deaths), and there was a statistical difference in lethality between the sexes (Fisher's exact test, p=0.03), with women presenting a lethality rate of 85.7% (6 deaths in 7 cases). All cases underwent hospitalization. Thirty of the cases had laboratory confirmation by indirect fluorescent antibody test (IFAT), while the rest underwent clinical diagnosis; however, two of these cases occurred almost simultaneously with cases of relatives who had laboratory confirmation by IFAT.

Human case geospatial distribution (2003-2020)

The temporal distribution of BSF cases in Juiz de Fora can be seen in Figure 1. It is noted that there are annual gaps in disease occurrence, while some years bring together several cases. Apparently, there is a 6-year cycle between epidemic peaks. Although cases can happen in almost any month of the year, there is a concentration of cases in the period from August to November, months that concentrated 56% of cases in the analyzed period.

Geographic occurrence of human cases in the considered period can be seen in Figure 2. The concentration of disease cases can be observed in the northwest to east quadrants, mainly in peripheral places to the Krambeck Forest. Another cluster of cases to the south can also be characterized.

Host geospatial distribution

Figure 2 shows the distribution of capybaras and domestic horses that were located in the urban perimeter of the city. Capybaras are stably distributed along the course of the Paraibuna river, but can occasionally be seen in other watercourses that cross the entire municipality. They are mostly seen in family groups, but solitary individuals can be found. Cart horses occupy several points on the edge of the Paraibuna, usually individually. The nine tick fumigation points, marked on the map in Figure 2, are distributed throughout the urban perimeter. It was not possible to map carters' horses that are housed inside the families' homes.

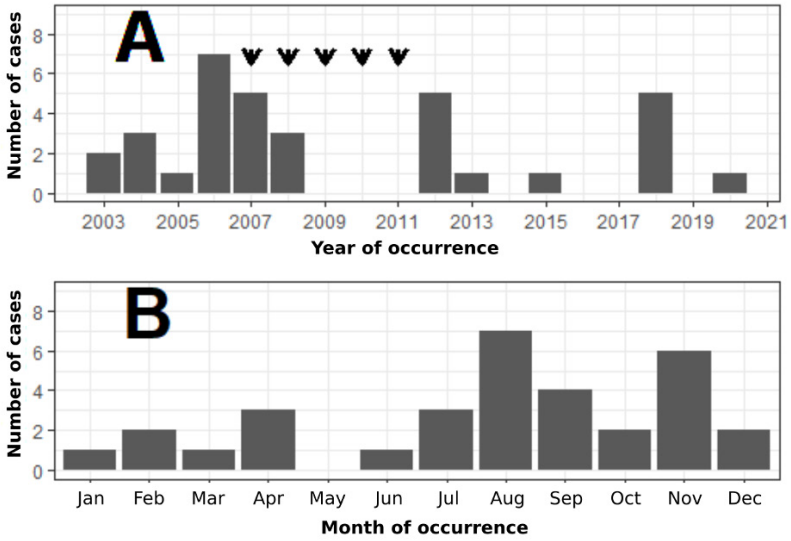

Figure 1. Distribution of frequency of human cases of Brazilian spotted fever in the urban perimeter of Juiz de Fora, Minas Gerais, from 2003 to 2020. **Caption:** A) clustered by year of occurrence. B) clustered by month of occurrence. The arrows on panel A indicate the years in which there was an equine tick fumigation program carried out by the city.

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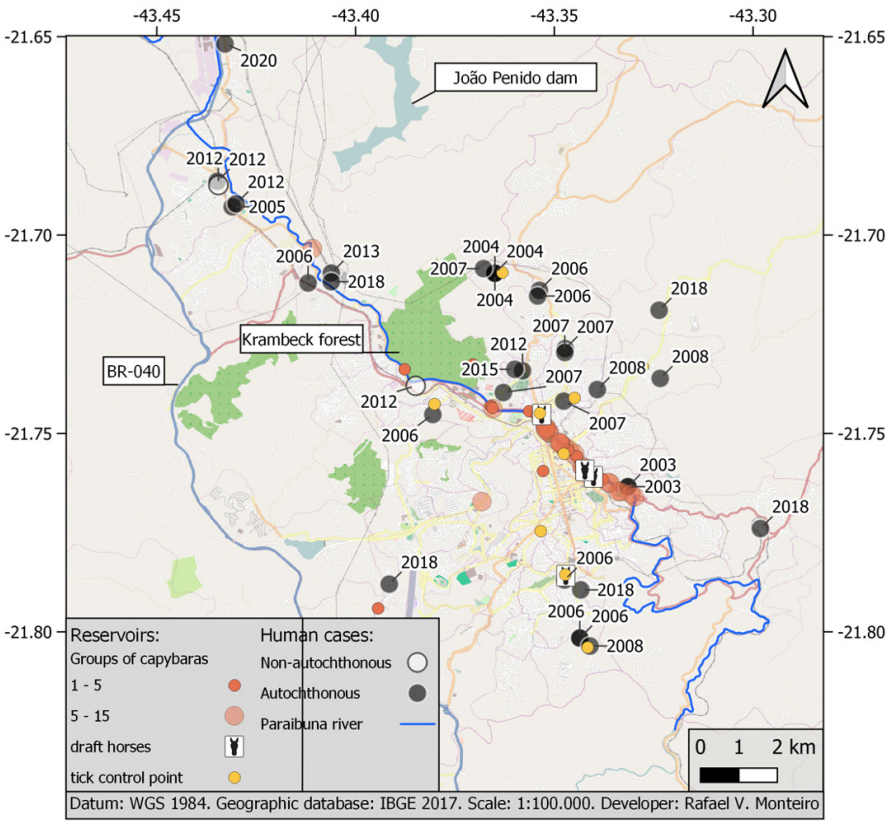

Figure 2. Geolocation of human cases of Brazilian spotted fever that occurred in the urban perimeter of Juiz de Fora, Minas Gerais, Brazil, from 2003 to 2020.
Note: geolocation of capybara sightings, the waiting points for carters and tick fumigation points used by the city hall from 2007 to 2011 is also indicated.

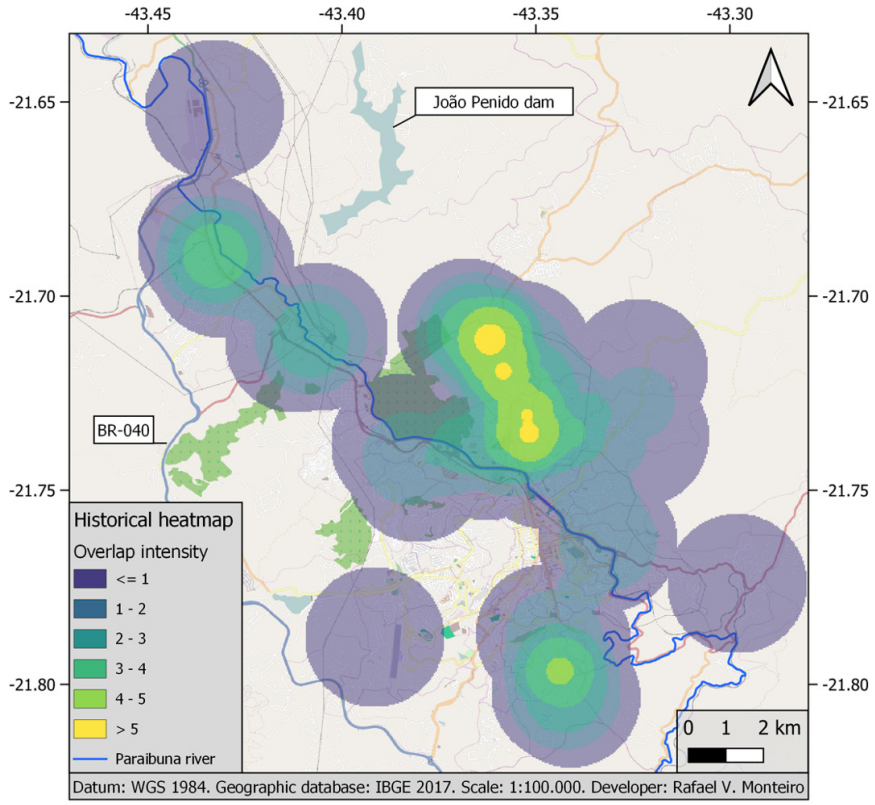

Figure 3. Heatmap, prepared with a parabolic function, on geolocation of human cases of Brazilian spotted fever in the urban perimeter of Juiz de Fora, Minas Gerais, Brazil
Note: higher overlap intensities would indicate overlap of daily circulation site of more cases. Used radius: 2,000 m.

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Epidemiological and geospatial analyzes

Figure 3 shows a heatmap of occurrence of human cases of BSF in the municipality of Juiz de Fora, resulting from the first-order geospatial analysis. It can be seen that, under the conditions of comparison established here, there seems to be an area that concentrates the probability of acquiring the infection in the municipality in the years analyzed. On the other hand, the second--order analysis indicated a geospatial pattern of distribution of cases of aggregate character, since the average distance to the nearest neighbor observed (712.1 m) was statistically smaller than the average obtained in the Monte Carlo simulation (1,422.7 m; p=0.002). This aggregate character indicates that, in each outbreak, the cases tend to happen close together. The neighborhoods in the urban perimeter of Juiz de Fora that are included in the hottest spot in Figure 3, relative to overlap intensities greater than 5 (Bairu, Bandeirantes, Granjas Bethânia, Manoel Honório, Progresso and Santa Terezinha), had an average Family Development Index (FDI) of 0.733 (ranging from 0.665 to 0.779), an index equivalent to category D3, low-income families.[15]

DISCUSSION

The occurrence of SFG in Juiz de Fora follows a pattern equivalent to an endemic area with disease outbreaks. In the historical sequence analyzed here, it can be noted that there are years with a higher occurrence (7 cases in the highest frequency), while in other years, there are no cases (up to 3 years without cases). It is noteworthy that the 3-year gap in occurrence of human cases coincided with the execution of the city hall's tick fumigation program from 2007 to 2011 (Graph 1, panel A). Regarding lethality, the local rate is within the disease historical rates, although the lethal involvement in women has been statistically pointed out.[16] The higher number of cases in men than in women is also in line with the traditional disease epidemiological characteristics, as men have greater exposure to transmitting ticks during their daily work. Another common aspect of SFG is the concentration of human cases from August to November of each year, when larvae and nymphs predominate in the local population of ticks. These immature forms are considered to be at greater risk for transmission, as they are of small size, which makes it difficult to identify the presence of a tick and does not alert the infected person to infestation, increasing the probability that the tick remains on individuals and the time required for rickettsiae transmission.[17]

The geographic distribution of cases seems to follow an aggregate pattern in time and geographic space. Over the years, the cases were concentrated in a preferred geographic region (Figures 2 and 3), and the cases tended to occur in regions close to each other or even within the same family/residential group (Average Nearest Neighbor). This could be due to: i) higher concentration of infected ticks in the region where such cases occur; ii) increased likelihood of adequate contact between ticks and people in such locations.

Two factors should be associated to justify the higher concentration of locally infected ticks: i) having vertebrate animals that support a large population of ticks; ii) that rickettsia is circulating in the region. Thus, these two factors would allow that, with proximity between people and the population of infected ticks, transmission cycle can be completed with human infection, that is, there is an increase in the probability of adequate contact between ticks and people. Other factors may be associated with this higher probability of contact between a tick and a human host, such as residents' occupation, whether they work with horses or frequent pastures for leisure or work, risk factors already characterized for SFG. The presence of this set of factors is complete in the common scene in the countryside cities of Brazil: people living in situations of vulnerability, living together or very close to their horses' stalls, often in peri-urban places.[9,10]

In the situation described above, the participation of capybaras in occurrence of local human cases can be considered small, with the exception of places where rickettsia is introduced from these rodents. This situation does not seem to be the case in Juiz de Fora, where rickettsia has already been identified in *A. sculptum* in a neighboring municipality and in *R. sanguineus* in the municipal kennel.[7,18] However, recent research on ticks collected on the banks of the Paraibuna river revealed the presence only of *Rickettsia amblyommii*, a bacterium whose pathogenicity is unknown.[19] This condition of lesser relevance of capybaras in the local epidemiological chain is strengthened by the decrease in human cases during the period in which the city carried out tick fumigation of cart horses, indicating that transmission from ticks parasitizing horses is the most common epidemiological situation (Figure 1, panel A). Additionally, the municipal legislation of Juiz de Fora started to prohibit the circulation of cart horses in the urban perimeter as of December 2019. Although it is premature to assess the effect of such legislation for the future, we hope that, if horses really are the main carriers of ticks transmitting BSF rickettsiae in Juiz de Fora, the annual average of cases drops to levels below the current 2 cases per year.

The spatial distribution of capybaras also does not show a spatial overlap in agreement with human cases (Figures 2 and 3). Capybaras are distributed throughout the city following the waterways, and reside permanently on the banks of the Paraibuna river. However, most human cases did not occur near this watercourse, weakening the possibility that ticks of the capybaras of this river are the main sources of transmission to humans, although these rodents possibly contribute to the maintenance and potential infection by *R. rickettsii* in local populations of *A. sculptum*, a tick species proven to be resident in endemic areas for the disease.[1,20] The presence of established immunity against rickettsia in these family groups of capybaras permanently residing in the riverbed of the Paraibuna cannot be ruled out, which would reduce rickettsia transmissibility to the tick population on the edge of the Paraibuna.[21] Thus, the presence of these fixed groups of capybaras occupying the Paraibuna river could

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be attenuating the infection of *R. rickettsii* on the local populations of *A. sculptum*. The finding of *R. amblyommii* adds another species of rickettsia to the local population of capybaras and ticks, and this may be involved in the local immunity of these hosts against *R. rickettsii*, a phenomenon already characterized.[19,22]

Culling of wild animals is often proposed as a way to control human and farm animal diseases, in which these animals are considered relevant in transmission cycle.[9] This approach may not always be the most appropriate, as ecological studies and mathematical simulations show that, in certain situations, the disturbance caused in the wild population subjected to such a procedure can increase disease prevalence in them, increasing the risk for human and animal populations for which disease control was desired.[23-25] Bearing this in mind, the culling of capybaras is not suggested as a strategy to control BSF in the urban perimeter of Juiz de Fora without a greater ecoepidemiological knowledge of the place, since such action may be inappropriate and/or counterproductive.

ACKNOWLEDGMENTS

The authors would like to thank the Municipality of Juiz de Fora for their authorization and assistance in data search and compilation.

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AUTHORS' CONTRIBUTIONS:

José Geraldo Castro Jr contributed with article field data collection, design and writing. **Ralph Maturano** contributed to article conception, experimental design and writing. **Rafael Veríssimo Monteiro and Márcia Chame** contributed to the planning, experimental design, data collection, data analysis, writing and final approval of the article.