EPIDEMIOLOGY OF ROCKY MOUNTAIN SPOTTED FEVER IN BRAZIL, 2010-2020

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ABSTRACT: Rocky Mountain spotted fever is a tick-borne rickettsiosis. The main clinical signs and symptoms are fever, severe headache, rashes and myalgia. It is considered difficult to diagnose and underreported. The study aims to descriptively analyze the epidemiology of cases of Rocky Mountain spotted fever in Brazil from 2010 to 2021. This is a retrospective cohort study that statisticall analyzes the cases of spotted fever in Brazil between 2010 and 2020 through data obtained by the Information System of Notifiable Diseases. The proportions of spotted fever cases were calculated according to: sex, age, race/color, infection environment and evolution. There are 1967 cases were confirmed. The regions with the most cases were the Southeast (n%=72.24) and the South (n%=24). However, there are 4 deaths in the south while the lethality coefficient from the southeast is 47.78%. The most affected age group was 40-59 years old (n%=34.87), and 20-39 years old (n%=28.98). 71.17% of the cases are male. As for color/race, 60% of the cases are in whites. As for the infection environment, 35.23% are at home, 15.3% are at work, 26.13% are leisure places. The prevalence in males and the predominant age group 20-59 years can be linked to work activity, which leaves hem more exposed to ticks. The high numbers in adulthood can also be related to ecotourism. The lethality of the disease differs between the South and Southeast regions. One explanation for this phenomenon would be the different etiological agents, R. rickettsi, predominant in the Southeast, generating more severe clinical conditions.
KEYWORDS: Rocky Mountain Spotted Fever; Severe Headache; Epidemiology.

EPIDEMIOLOGIA DA FEBRE DAS MONTANHAS ROCHOSAS NO BRASIL, 2010-2020

RESUMO: A febre maculosa é uma riquetsiose transmitida por carrapatos. Os principais sinais e sintomas clínicos são febre, cefaleia intensa, erupções cutâneas e mialgia. É considerada de difícil diagnóstico e subnotificada. O estudo visa analisar descritivamente

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a epidemiologia dos casos de febre maculosa do Brasil no período de 2010 até 2021. Trata-se de um estudo de coorte retrospectivo que analisa estatisticamente os casos de febre maculosa no Brasil entre 2010 e 2020 por meio de dados obtidos pelo Sistema de Informação de Agravos de Notificação. As proporções de casos de febre maculosa foram calculadas segundo: sexo, idade, raça/cor, ambiente de infecção e evolução. Foram confirmados 1967 casos. As regiões com mais casos foram Sudeste (n%= 72,24) e Sul (n%= 24). No entanto, há 4 óbitos no Sul enquanto o coeficiente de letalidade do Sudeste é de 47,78%. A faixa etária mais acometida foi de 40 a 59 anos (n%= 34,87) e de 20 a 39 anos (n%= 28,98). 71,17% dos casos são do sexo masculino. Quanto à cor/raça, 60% dos casos são de brancos. Quanto ao ambiente de contágio, 35,23% são em casa, 15,3% são no trabalho, 26,13% são locais de lazer. A prevalência no sexo masculino e a faixa etária predominante de 20 a 59 anos pode estar ligada à atividade laboral, que os deixa mais expostos aos carrapatos. Os altos números na idade adulta também podem estar relacionados ao ecoturismo. A letalidade da doença difere entre as regiões Sul e Sudeste, sendo que uma explicação para esse fenômeno seriam os diferentes agentes etiológicos, *R. rickettsi*, predominante na região Sudeste, gerando quadros clínicos mais graves.
PALAVRAS-CHAVE: Febre Maculosa; Cefaleia Severa; Epidemiologia.

EPIDEMIOLOGÍA DE LA FIEBRE DE LAS MONTAÑAS ROCOSAS EN BRASIL, 2010-2020

RESUMEN: La fiebre maculosa es una rickettsiosis transmitida por garrapatas. Los principales signos y síntomas clínicos son fiebre, cefalea intensa, erupciones cutáneas y mialgias. Se considera difícil de diagnosticar y poco notificada. El estudio tiene como objetivo analizar descriptivamente la epidemiología de los casos de fiebre manchada en Brasil en el período de 2010 a 2021. Se trata de un estudio de cohortes retrospectivo que analiza estadísticamente los casos de fiebre manchada en Brasil entre 2010 y 2020 a través de datos obtenidos del Sistema de Información de Agraves de Notificación. Se calcularon las proporciones de casos de fiebre manchada según: sexo, edad, raza/color, ambiente de infección y evolución. Se confirmaron 1967 casos. Las regiones con más casos fueron el Sudeste (n%= 72,24) y el Sur (n%= 24). Sin embargo, hubo 4 muertes en el Sur, mientras que el coeficiente de letalidad en el Sureste fue del 47,78%. El grupo de edad más afectado fue el de 40 a 59 años (n%= 34,87) y el de 20 a 39 años (n%= 28,98). El 71,17% de los casos eran varones. En cuanto al color/raza, el 60% de los casos son de raza blanca. En cuanto al entorno de la infección, el 35,23% se produce en el domicilio, el 15,3% en el trabajo y el 26,13% en lugares de ocio. La prevalencia en los hombres y el grupo de edad predominante de 20 a 59 años pueden estar relacionados con la actividad laboral, que los deja más expuestos a las garrapatas. El elevado número en la edad adulta también puede estar relacionado con el ecoturismo. La letalidad de la enfermedad difiere entre las regiones Sur y Sudeste, y una explicación para este fenómeno serían los diferentes agentes etiológicos, R. rickettsi, predominante en la región Sudeste, generando cuadros clínicos más severos.
PALABRAS CLAVE: Fiebre Manchada; Cefalea Severa; Epidemiología.

1. INTRODUCTION

Brazilian spotted fever (BSF) is a fatal zoonosis because of the difficulties in its early diagnosis and treatment (OTOMURA *et al.*, 2016). Brazil, two pathogenic Rickettsia species have been identified causing tick-borne spotted fever. Rickettsia are small, obligately intracellular, gram-negative bacilli. They are distributed among a variety of hematophagous arthropod vectors and cause illness throughout the world (BLANTON *et al.*, 2019).

The aetiological agent Rickettsia rickettsii causes serious illness, particularly in the south-eastern region of the country (OLIVEIRA *et al*., 2017). Brazilian Spotted Fever is an endemic disease at the country's southeast, with Amblyomma sculptum as its major vetor contributor, followed by A. aureolatum and potentially Rhipicephalus sanguineus (CAMPOS *et al*., 2016). Moreover, the Rickettsia sp. strain Atlantic Rainforest cause milder clinical manifestationsin south-eastern, south and north-east region. (OLIVEIRA *et al*., 2017).

Capybaras and horses are important in the epidemiological chain of the disease, because are the main reservoirs of trans- spotted fever transmitters. the animals in dirty pastures, with high vegetation, or in riparian forests, find a very favorable environment for infestation by Amblyomma cajennense (DEL FIORI *et al*., 2010) The BSF-endemic areas were characterized by much higher tick burdens on both capybaras and in the environment, when compared to the BSF-nonendemic areas (LUZ *et al*., 2019). Dogs have been considered sentinels, and in some areas the disease in dogs can precede human disease (CAMPOS *et al.*, 2016). The transmission process occurs with when the tick injects reactivated R rickettsii intothe host during the process of taking a blood meal. RMSF infection can also occur because of exposure to hemolymph when ticks are accidentally crushed during removal (CHEN *et al*., 2008).

The pathogenetic sequence includes rickettsial entry into the dermis, hematogenous dissemination to vascular endothelial cells (most critically in brain and lungs), increased vascular permeability, edema, and immunity mediated by NK cells, IFN-gamma, TNF-alpha, RANTES, antibodies, and cytotoxic T lymphocytes (WALKER *et al.*; 2003). Cultured human endothelial cells (EC) are highly susceptible to infection and respond by altering the expression of adhesion molecules, regulatory cytokines, and the antioxidant enzyme heme oxygenase (RYDKINA *et al*., 2006).

Rickettsioses present as an acute undifferentiated febrile illness, cutaneous manifestations include rash and eschar and inespecific common symptoms are malaise,

myalgias and headache (BLANTON *et al*., 2019). The headache is severe (patients often describe the headache as the worst they have ever had) (DANTAS-TORRES, 2007).

Initially, the rash consists of lesions 1 to 5 mm in diameter where dilation of the small blood vessels imparts apink color to the skin in and surrounding the foci of rickettsial vascular infection. At this stage of illness, pressure applied to the pink spot results in temporary blanching of therash by removal of blood from the dilated vessels. Later in the course, particularly in severely ill patients, a pinpointhemorrhage occurs in the center of the pink spot (WALKER; VALBUENA; OLANO, 2003). Various neurological manifestations have been reported. Some 40% of patients may develop lethargy, photophobia, meningismus, amnesia, bizarre behaviour suggestive of psychiatric illness, or transient deafness (WALKER, 1989).

Doxycycline is the drug of choice due to their best efficacy, safety and dosage. The best method of prevention is to avoid areas potentially infested with infected ticks and perform frequent physical examination of people who were in these areas, for proper removal of arthropods (WALKER, 1989).

The diagnosis can be difficult, especially during the first days of illness, when the clinical manifestations can suggest leptospirosis, dengue, viral hepatitis, salmonellosis or encephalitis. With development of rash, meningococcemia, measles, rubella, enteroviral infection, infectious mononucleosis, staphylococcal septicemia, gram-negative sepsis, may be confused with BSF (LEMOS *et al*., 2002). As this disease is rare and has high mortality rates in Brazil, the clinical aspects and epidemiological data may help the diagnosis (COUTO *et al*., 2015).

2. METHODOLOGY

This is a retrospective cohort study, which aims at epidemiological analysis based on secondary data of notified cases of Brazilian spotted fever registered in the Information System of Notifiable Diseases (SINAN) during the period from 2010 to 2020 in Brazil, as available at the Information Technology Department of the Unified Health System (DATASUS).

To calculate the incidence of new cases in the country, the total number of confirmed cases obtained divided by the population estimated by IBGE was used. The calculation of lethality was performed by the ratio between the number of deaths and confirmed cases. The mean, median and mode of cases during this period were also estimated.

In addition, the distribution of cases in the country and each region will be analyzed according to the variables available in SINAN: age group, schooling, sex, skin color, environment of infection, confirmation criteria, month of first symptoms and occurrence in pregnant women. These variables will also be used in the descriptive analysis of the evolution of the cases (cure, death from the disease or death not related to the disease).

3. RESULTS

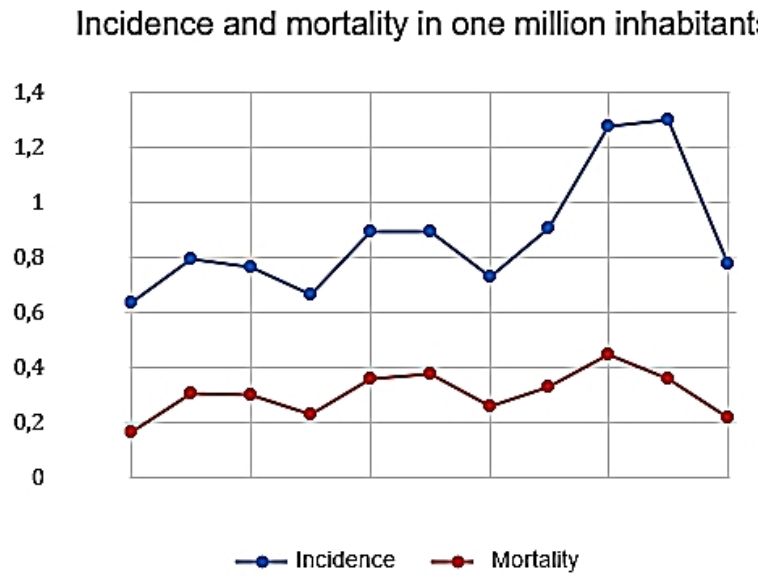
In total, there were 1967 reported cases, with an average of 178.8 cases per year (Table 1). Of this cases, 685 evolved to death (n%= 34.82), 25 died from another cause and 97 cases had unknown outcome.

Table 1: Cases of Rocky Mountain spotted fever in Brazil by year from 2010 to 2020

Year	Cases
2010	122
2011	153
2012	148
2013	134
2014	182
2015	183
2016	151
2017	189
2018	266
2019	274
2020	165

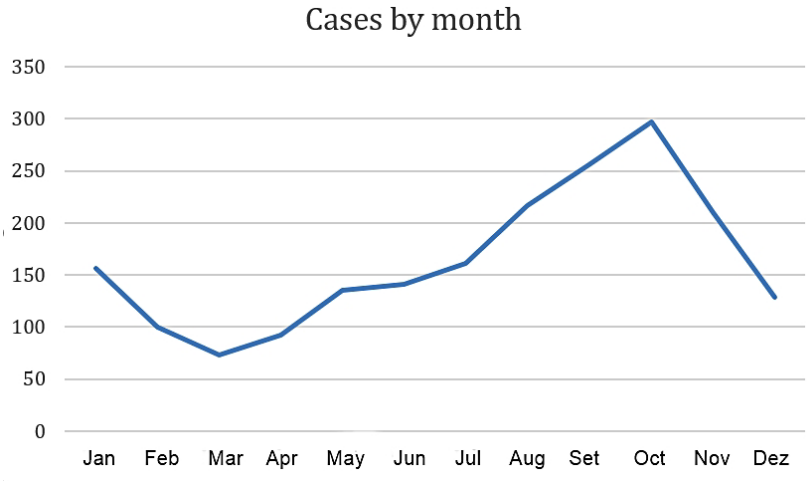
The lowest incidence observed was 0.639 cases per million inhabitants in 2010 and the highest incidence was 1.3 in 2019. Mortality follows a pattern symmetric to incidence and Pearson's correlation coefficient between them is 0.82 (Graphic 1).

Graphic 1: Incidence and Mortality of Rocky Mountain spotted fever in Brazil from 2010 to 2020



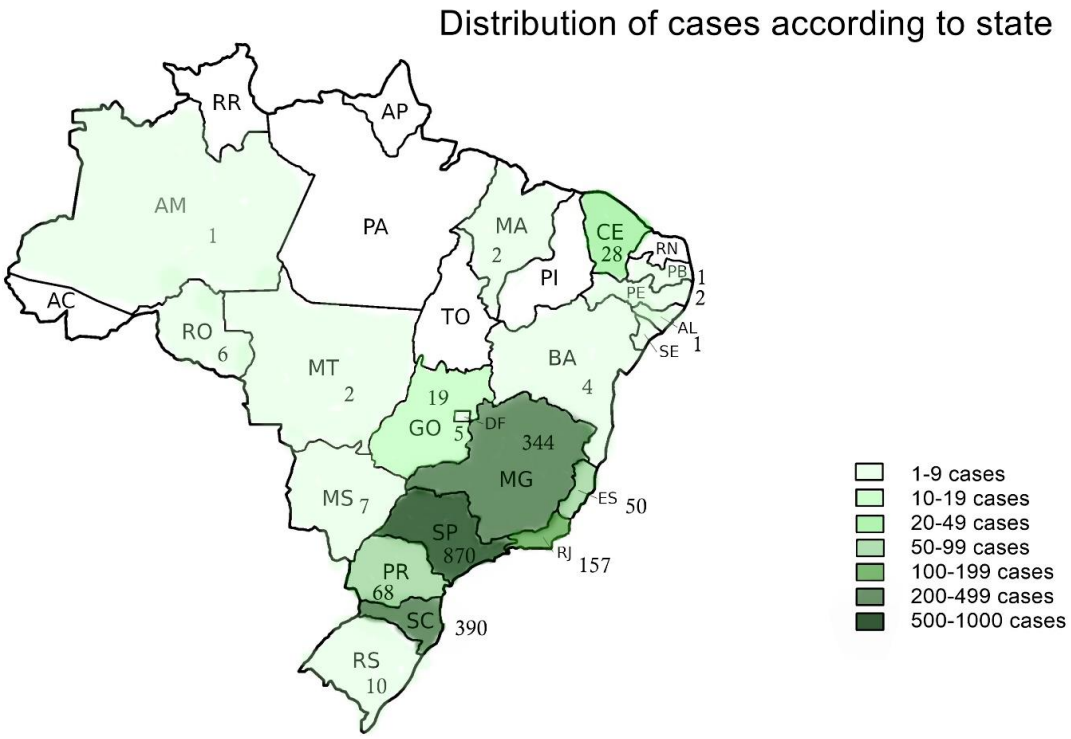
The average of the lethality coefficients is 34.93%. The highest lethality rate was 42% in 2015 (Graphic 2). The incidence of notified cases rises from August to November and a drop from February to April, showing a seasonality profile.

Graphic 2: Cases by month of Rocky Mountain spotted fever in Brazil from 2010 to 2020



There were 9 cases reported in the North region, 36 in the Northeast, 33 in the Midwest. The regions with the most cases were the Southeast (n=1421, n%=72.24) and the South (n=471, n%=24). The state with the most cases was São Paulo (n=870) followed by Santa Catarina (n=393). About 1,439 cases were contracted in the state while 319 were not and 209 are in undetermined status (Graphic 3).

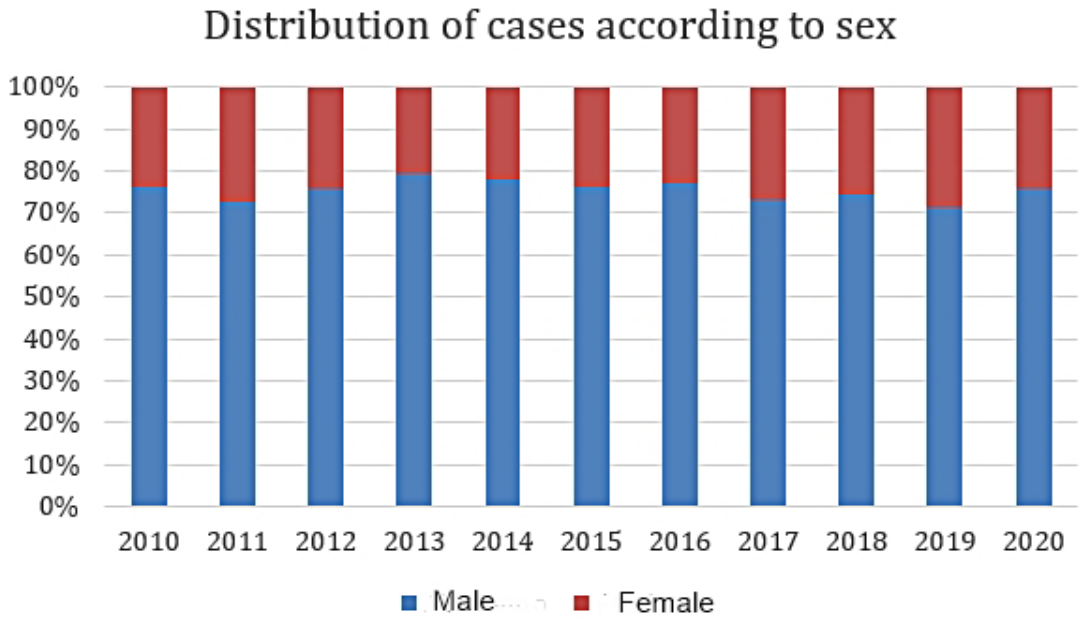
Graphic 3: Distribuition of cases of Rocky Mountain spotted fever according to state in Brazil from 2010 to 2020



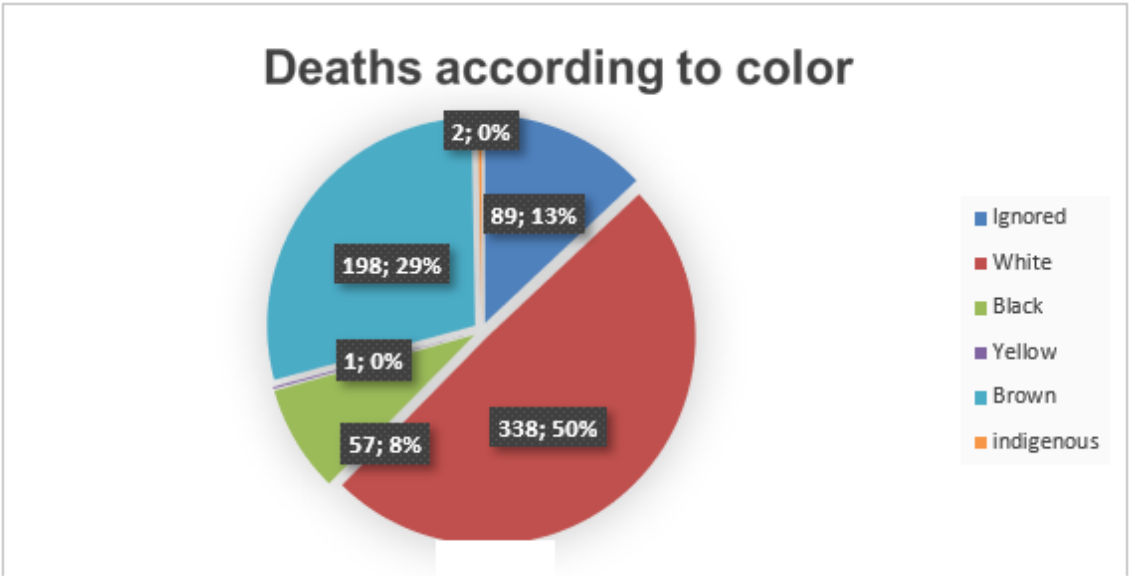
The epidemiological analysis indicated that the highest percentage of patients who contracted Rocky Mountain spotted fever were male (n%= 71.17; n=1400) (Graphic 4). There were 1194 (n%=60) cases in whites, 473 (n%=24) in browns, 100 (n%=5) in blacks, 6 in indigenous peoples and 8 in yellows (Graphic 5). Of the total, 178 (n%=12.52) cases were classified according to unknown skin color or white, 738 (n%=51.93) occurred in whites, 93 (n%=6.54) in blacks, 402 (n%=28.29) in brown and 6 in yellow.

The most affected age group was 40-59 years old (n=686, n%=34.87), followed by 20-39 years old (n=570, n%=28.98). Elderly over 60 years old corresponded to 285 cases (n%=14.49). There were 205 (n%=5) cases in children aged 1 to 9 years, 208 in the 10-19 years age group, and 14 cases in children aged less than one year.

Graphic 4: Distribuition of cases of Rocky Mountain spotted fever according to sex in Southeast from 2010 to 2020



Graphic 5: Distribuition of deaths according to color of cases of Rocky Mountain spotted fever in Brazil from 2010 to 2020



About the infection environment, 693 (n%=35.23) are registered as at home, 299 at work, 514 (n%= 26.13) at leisure, highlighting the impacts of ecotourism on the infection, and 239 (n%= 12,15) occurred in another environment or the information was ignored in the notification form. There were only 8 cases in pregnant women, 3 in the first trimester, 2 in the second trimester and 3 in the third trimester.

As for the mortality profile, 38% of the men and 27.1% of the women died due to the reported condition. The most affected age groups were 40-59 years old that had 251 deaths and 20-39 years old that had 187 deaths.

4. REGIONS

North: In total, there were 7 cases, 1 in Amazonas and 6 in Rondônia. Of the total, only 4 were considered autochthonous in the state. The only reported case of death happend in the state of Amazonas, not determined whether it was adquired in state.

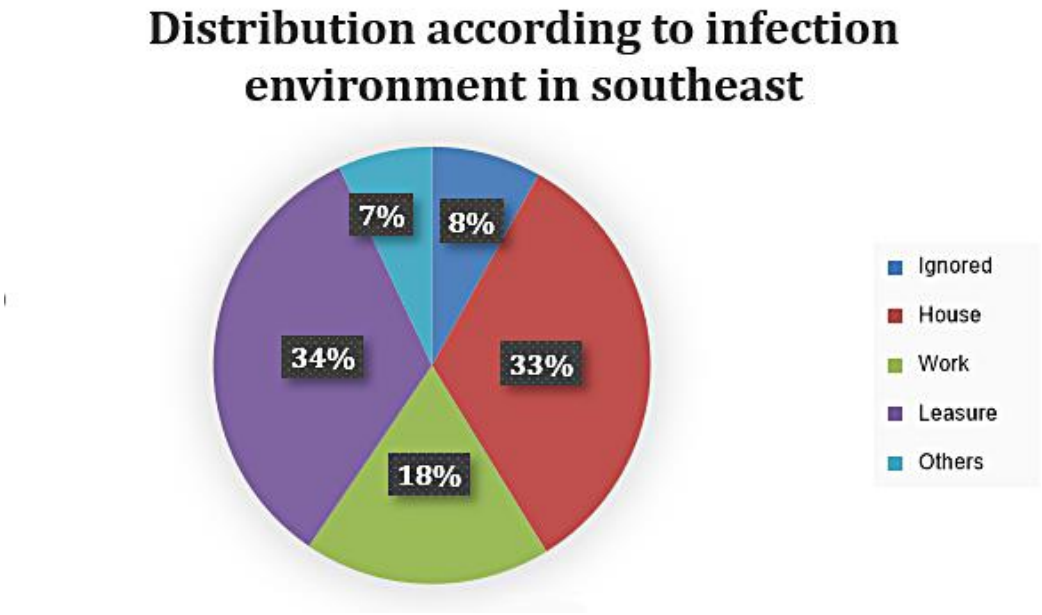
Northeast: There were 38 reported cases, 28 of which were from Ceará. In total, 21 were considered autochthonous, 5 were not considered and 12 were undetermined. There was a report of one death.

Midwest: There were 33 cases, 19 of them in Goiás. In total, 16 were autochthonous, 8 were not and 9 were undetermined. There were no deaths recorded.

Southeast: There were 1421 registered cases, of which 870 (n%= 61.22) were in São Paulo, 344 (n%=24.20) in Minas Gerais, 50 (n%=3.51) in Espírito Santo and 157 in Rio de Janeiro (n%=11.04). Of the total, 1,003 of the cases were autochthonous in the state, 254 were not and 170 were undetermined. Over the years, the pattern of infected people has always been predominantly male, as can be seen in the graph below:

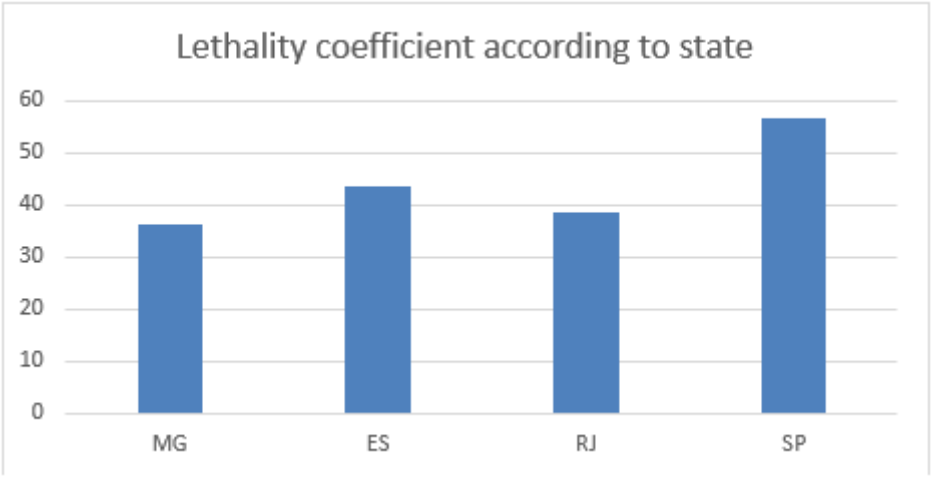
As for age group, 10 cases occurred in children under 1 year old, 181 (n%=12.74) in the age group from 1 to 9 years old, 162 in age group (n%=11.4) from 10 to 19 years old, 397 (n %=26.67) in age group from 20-39 years old, 466(n%=32.79) cases in age group 40-59 and 205 (n%=14.42) cases in patients over 60 years old, showing a predominant pattern of infection in adults (Graphic 6). Concerning the environment of infection, the conformation was as follows:

Graphic 6: Distribuition of cases of Rocky Mountain spotted fever according to infection environment in Southeast from 2010 to 2020



About deaths, the total for the region was 679, generating a lethality coefficient of 47.78%. The state with the highest mortality rate was São Paulo, with 56.20% (Graphic 7).

Graphic 7: Distribuition of cases of Rocky Mountain spotted fever according to state in Southeast from 2010 to 2020



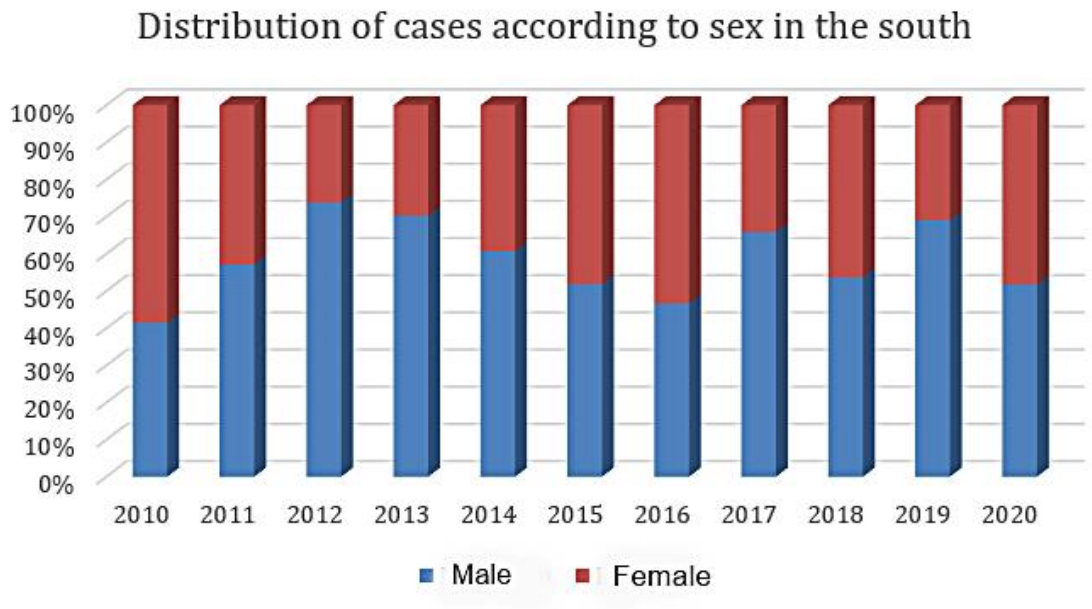
As for their profile, 528 of the deaths were men, generating a male letality rate of 49.53% while the female letality rate was 42.53%. The age group with the highest number of deaths was 40-59 years(n=250, n%=36.82), the second age group with the most cases was 20-39 (n=182, n%=26.80) cases. As for skin color, the highest lethality rate found

was 60% in the black population and the second highest lethality rate was 49% in brown people.

5. SOUTH

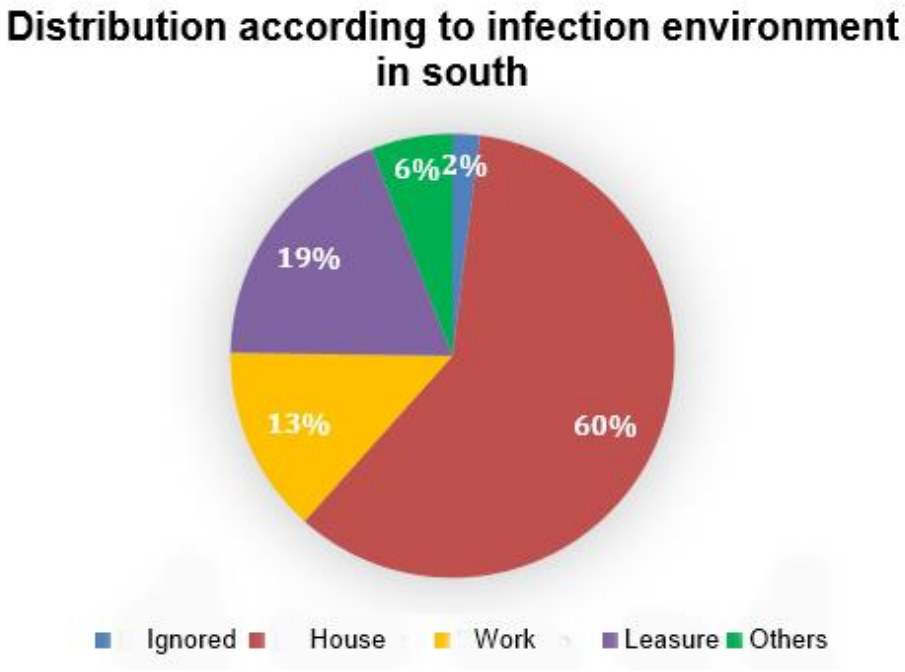
In the South, there were 468 cases distributed as follows: 68 (n%=14.53) in Paraná, 390 (n%=83.33) in Santa Catarina and 10 (n%=2.14) in Rio Grande do Sul. Of the total, 399 (n%=85.26) are native to the reporting municipality, 52 (n%=11.11) are not and 17 (n%=3.63) are classified as undetermined. The distribution of cases according to gender varies over the years, unlike the Southeast, where the infection predominates in men. However, in total, 279 (n%=59.61) occurred in men and 189 (n%=40.38) in women (Graphic 8).

Graphic 8: Distribuition of cases of Rocky Mountain spotted fever according to sex in South from 2010 to 2020



As for skin color, 440 (n%=94.02) cases were whites, 19 browns, 4 blacks and 4 were classified as unknown or white. Regarding age group, there were 4 cases in patients under one year of age, 15 in patients aged 1 to 9 years, 38 (n%=8.12) from 10-19 years, 145 (n%=30.98) from 20-39, 196 (n%=41.88) from 40-59 and 70 (n%=14.96) cases in people over 60 years old, again, the disease is more common in adults (Graphic 9). The infection pattern according to environment can be seen below:

Graphic 9: Distribuition of cases of Rocky Mountain spotted fever according to infection environment in South from 2010 to 2020



In the South, there are more cases linked to household infection and fewer cases linked to leisure than the Southeast. About the deaths, there were only 4. Of the total, 447 patients were cured and 17 had the information ignored or not completed. Regarding deaths, 1 was male, aged 65-69 years and 3 were female, one in the age group 10-14 years and two in the age group 20-39 years. Of this total, only 1 case was confirmed as autochthonous in the municipality of residence, which in this case was Paraná.

6. DISCUSSION

Brazilian spotted fever (BSF) is a zoonosis with a seasonal profile, with an increase in cases from August to November. One explanation for the high incidence in this period is the vector's life cycle. From July to December, *A. cajennense*, the main vector of spotted fever, is in its nymph stage, its most common parasitic form in humans (LABRUNA *et al.*, 2022). More than 96% of the cases occurred in the South and Southeast, demonstrating the predominance of the disease in this region. The distribution of cases is similar to the previous studies, as described by the Ministry of Health (BRASÍLIA, 2010).

On the subject of the epidemiological profille, the notification in male adults, represents a doubled incidence compared to females, as it is related to occupational

activities in rural areas, ecotourism, exploration of forests, areas inhabited by capybaras and other intermediate hosts of the disease (FERREIRA *et al*., 2021).

Besides, adult age is a risk fator. This predominance is explained in the literature. Adult age is related to activities in areas at risk of infections (ARAÚJO *et al.*, 2016). Previously, it has been described that age over 40 years is a risk factor for disease worsening (DÍAZ & CATAÑO, 2010).

As for skin color, the results for the South and Southeast differ. The southeast has a heterogeneous distribution of infection and proportional to the state's population division according to skin color, according to IBGE data and the high prevalence of infection in whites in South can be explained by the population distribution in the southern region, in which the IBGE records that 75.1% are white[20].

In Southest, the lethality coefficient is 47.78%, elevated due to the difficulties in make the diagnosis and establish the adapted therapy, related to little knowledge about the disease and the not very specific symptomatology[5]. Furthermore, the most common etiological agent in the Southeast, *Rickettsia rickettsii*, is associated with high lethality (OLIVEIRA *et al*., 2016).

In South, the low lethality in comparison with the Southeast can be explained by the etiological agent most prevalent, *Rickettsia parkeri* strain Mata Atlântica, whose clinical manifestations, with the presence of fever, inoculation eschar, skin rash and lymphadenopathy, tend to be less severe that the clinical course triggered by *R. rickettsi (*FACCINI-MARTÍNEZ *et al*., 2018).

7. CONCLUSION

Rocky Mountain spotted fever is a rickettsiosis that concentrates most of its percentage of cases in the Southeast and South regions. The disease has a seasonal pattern as cases increase from August to November, a period that coincides with the nymph stage of the vector. In general, it tends to affect more adults and men, which can be explained by exposure to the vector in activities such as rural work, ecotourism and exploration of forests.

The lethality of the disease differs between the South and Southeast regions. The South has 24% of cases, but only 4 registered deaths, while the Southeast has 679 more registered deaths, resulting in a fatality rate of 47.78%. One explanation for this phenomenon would be the different etiological agents, with R. rickettsi, predominant in

the Southeast, generating more severe clinical conditions, while R. parkeri, more common in the south, generating milder clinical conditions.

8. STUDY LIMITATIONS

There is a high number of cases classified as ignored/not recorded in relation to a characteristic. For example, there is no record of the skin color of 12.52% of the cases in the Southeast. In addition, it is an underdiagnosed disease due to its clinical characteristics which can be nonspecific. Therefore, it is possible that there are more cases than reported. These lack of information can reduce the accuracy of the epidemiological analysis

RECOMMENDATIONS FOR FUTURE STUDIES

In future studies, it would be interesting to use descriptive data to perform a logistic regression and see which characteristics are a risk factor for death. In addition, to minimize the lack of data, the ideal would be to carry out prospective studies in partnership with the Sanitary Surveillance of the studied region.

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