











Original Articles

## Association between hantavirus cardiopulmonary syndrome in humans and landscape configuration in the Cerrado region of Minas Gerais, Brazil

Associação entre síndrome cardiopulmonar do hantavírus em humanos e configuração da paisagem na região do Cerrado de Minas Gerais, Brasil

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### ABSTRACT

The objective of this study was to analyze the spatiotemporal distribution of 193 autochthonous cases that were confirmed as hantavirus cardiopulmonary syndrome (HCPS) from 1998 to 2007 and its association with landscape configuration in the Cerrado region of Minas Gerais, Brazil. Among the 193 autochthonous cases, the probable sites of infection (PSI) of 129 cases (66.8%) were geoprocesed. We then evaluated the association between the HCPS cases and landscape variables through a multivariate analysis of the main components. Particularly, the mesoregion of Triângulo Mineiro/Alto Paranaíba had 130 autochthonous cases (67.3%). In addition, the chance of conglomeration of cases in municipalities located in this mesoregion was greater than that in other mesoregions. HCPS cases were positively associated with the increase in the area of planted pastures and natural forests in the Cerrado region. Rice, beans, maize, and sugar cane cultivations were less associated with HCPS. We concluded that the changes in the Cerrado ecosystem due to agricultural activities propitiate the maintenance of rodent populations and HCPS virus reservoirs. Additional training for health professionals for early diagnosis and reduction of the causes of the disease must be carried out in the endemic areas of Minas Gerais.

### RESUMO

O objetivo deste estudo foi analisar a distribuição espaço-temporal de 193 casos autóctones confirmados com Síndrome Cardiopulmonar por Hantavírus (SCPH) de 1998 a 2007 e sua associação com a modificação da paisagem na região do Cerrado de Minas Gerais, Brasil. Entre os 193 casos autóctones, os locais prováveis de infecção (LPI) de 129 casos (66,8%) foram geoprocessados. Em seguida, avaliamos a associação entre os casos de SCPH e as variáveis da paisagem por meio de uma análise multivariada dos principais componentes. Particularmente, a mesorregião do Triângulo Mineiro / Alto Paranaíba teve 130 casos autóctones (67,3%). Além disso, a chance de conglomeração de casos nos municípios localizados nessa mesorregião foi maior do que em outras mesorregiões. Os casos de SCPH foram associados positivamente ao aumento da área de pastagens plantadas e florestas naturais na região do Cerrado. Cultivos de arroz, feijão, milho e cana-de-açúcar foram menos associados ao SCPH. Concluímos que as mudanças no ecossistema do Cerrado devido às atividades agrícolas propiciam a manutenção de populações de roedores e reservatórios do vírus SCPH. Treinamento adicional para profissionais de saúde para diagnóstico precoce e redução das causas da doença deve ser realizado nas áreas

*Palavras-chave:*

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## INTRODUCTION

Hantaviruses (genus *Hantavirus*, family *Bunyaviridae*) causes zoonoses that are associated with hemorrhagic fever (BENNETT et al., 2014). In Brazil, the wild reservoirs responsible for transmitting this virus to the human population include rodents of the *Muridae* family, *Sigmodontinae* sub-family (BUSCH et al., 2004; BENNETT et al., 2014). Hantavirus Pulmonary Syndrome is lethal to 60% of patients at present (TORO et al., 1997; SCHMALJOHN; HJELLE, 1997) and is strongly associated with the presence of wild reservoirs (SCHMALJOHN; HJELLE, 1997; TORO et al., 1997; BUSCH et al., 2004; BENNETT et al., 2014).

Currently, there have been continuous changes in the environments globally. The environment can be modified by climate changes and landscape interventions including agricultural activities. These changes, along with the increase in wild reservoir populations predispose the emergence of diseases (FANG et al., 2010; BAGAMIN et al., 2012; MONTGOMERY et al., 2012).

Hantavirus cardiopulmonary syndrome (HCPS), identified in the US in 1993 (PINI et al., 2003; PALMA et al., 2012), is transmitted to humans through the inhalation of viral particles from the aerosols present in the excreta of rodents, mainly in closed and covered places (MIR, 2010; KUENZLI et al., 2018), and is influenced by changes in the environment. Recent studies have also demonstrated the role of bats as reservoirs and potential transmitters to humans (BENNETT et al., 2014; SABINO-SANTOS et al., 2018).

The expansion of agricultural activities has replaced some preserved areas by plantations and pasture lands and changed the dynamics of the wild reservoir populations (MORENS; FOLKERS; FAUCI, 2004; MORENS; FOLKERS; FAUCI, 2008; LUONG et al., 2011; BAGAMIN et al., 2012), forcing them to leave their natural habitat (SLINGENBERGH et al., 2004; MILLS, GAGE, KHAN, 2010). This expansion causes changes in the feeding pattern, shelter, and reproduction rate of these wild reservoirs and consequently increases the risk of spreading the disease (VALCOUR et al., 2002; DASZAK et al., 2007; WOODFORD, 2009).

Climate changes, particularly due to the alteration in the landscape configuration prevalent throughout the world, cause many alterations in the ecosystems, and lead to the emergence of several diseases in the human population (EBI; SEMENZA, 2008; SEMENZA; MENNE, 2009; LUIS et al., 2010; BAGAMIN et al., 2012). The increase in the populations of wild rodents due to greater availability of food and decrease in the number of natural predators is responsible for the prevalence of the hantavirus and increase of infections in the human

population. (EBI; SEMENZA, 2008; SEMENZA; MENNE, 2009; LUIS et al., 2010).

The modifications in the Cerrado ecosystem, imposed by the use of land for agricultural activities, can aid in the resurgence of HCPS in this region. The initial cases described in Brazil correspond to this region and suggest that the region is responsible for the prevalence of the disease (SUZUKI et al., 2004; ROSA et al., 2005; LIMONGI et al., 2009).

HCPS has been described in different parts of the world, with localized characteristics and epidemiological understanding in each region; thus, there are specific forms of prevention and control in each studied habitat (TORO et al., 1997; EISEN et al., 2007; ARMIÉN et al., 2009; HJELLE; TORRES-PÉREZ, 2010; PALMA et al., 2012; BENNETT et al., 2014; TIAN et al., 2018). Therefore, the objective of this study was to assess the spatiotemporal distribution of the HCPS cases and determine its correlation with landscape alterations due to agricultural activities in Minas Gerais during the first ten years of its notification (1998 to 2007).

## MATERIAL AND METHODS

### *Study area*

The state of Minas Gerais is located in the southeastern Brazil, has 853 cities, subdivided into 12 mesoregions, with an estimated population of 21,040,662 in 2018 (IBGE, 2019a; IBGE, 2019b). The vegetation of the state is composed of 54% savanna, 40% Atlantic forest, and 6% caatinga, with 32.9% of the territory of Minas Gerais being remnants of native forest (IEF, 2019). This state is known to produce milk, meat, pigs, poultry, grains, and pastures. The state's agricultural and livestock produce majorly contribute to Brazil's economy (FJP, 2019).

### *Study design and data sources*

We conducted an observational, ecological, and retrospective study using the secondary databases of confirmed cases HCPS in Minas Gerais from 1998 to 2007. The data were obtained from the Sistema de Informação de Agravos de Notificação (SINAN). The year 1998, when the first autochthonous case of HCPS was detected in Minas Gerais, was considered as the initial period of the study. The definitions for suspected, confirmed, and discarded cases were according to the recommendations given in the Epidemiological Surveillance Guide (BRASIL, 2010).

### *Georeferencing*

Forty-one municipalities with confirmed cases from the following mesoregions of the state of Minas Gerais were selected: Triângulo / Alto Paranaíba, Central Mineira,

South / Southwest, and West of Minas. Additionally, spatial analysis of each case of HCPS was carried out, with the aid of the Satscan version 7.0 program to identify and define the probable site of infection (PSI) through notification forms and epidemiological field investigations. It was possible to obtain the geographic coordinates (latitude and longitude) of the PSI, in the form of signals using the Global Positioning System (GPS) model GARMIN 76S. However, only 3 period clusters were observed: from 1998 to 2002, 2003, and 2007. The georeferencing maps of HCPS cases were produced using the QGIS 2.18.14 program.

*Landscape modifications for agricultural activities*

To assess the association between HCPS cases and landscape configuration, data from the Agricultural Census in the years 1996 and 2006, performed by the Instituto Brasileiro de Geografia e Estatística (IBGE), were used. (IBGE, 2014c; IBGE, 2014d).

During each census, major land uses were listed by the municipality and defined by the following variables: permanent tillage, temporary tillage, planted pasture, natural pasture, natural forest, planted forest, and unusable land. In addition, the production of rice,

sugarcane, beans, and corn were included due to the importance of these variables in the epidemiology of HCPS in Brazil. These variables correspond to the total area planted in hectares.

*Statistical analysis of the data*

A multivariate analysis of principal components (PCA) was performed (HOTELLING, 1993) using the STATA program version 12.0. The analysis of odds ratios in the case study between mesoregions with and without conglomerates for the same period was carried out with the aid of the Epi info program version 3.5.3.

**RESULTS**

During the study period, 193 cases of autochthonous HCPS were confirmed. Among the mesoregions, Triângulo Mineiro / Alto Paranaíba in the Cerrado Mineiro had 67.3% of the confirmed cases. Cases were also recorded in South / Southwest of Minas (22.8%), West of Minas (5.2%), and Central Mineira (1.6%) mesoregions. However, it was not possible to identify the municipality associated with the infection in 3.1% of the cases (Table 1).

Table 1. Number of confirmed cases of Hantavirus Cardiopulmonary Syndrome in the mesoregions of the state of Minas Gerais.

CASES OF HCPS												
Mesoregion	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	Total	
											Nº	%
Central Mineira	0	0	0	0	0	1	1	1	0	0	3	1.5
West of Minas	0	0	0	0	0	1	1	4	3	1	10	5.1
South /Southwest of Minas	0	0	0	0	5	9	15	6	5	4	44	22.8
Triângulo/Alto Paranaíba	1	3	9	5	9	9	20	27	23	24	130	67.3
Ignored	1	0	0	0	0	1	2	1	1	0	6	3.1
Total	2	3	9	5	14	21	39	39	32	29	193	100.0

The data related to the spatial analysis of the PSI for the confirmed human cases of HCPS are shown in Figure 1. In total, 129 PSIs were geoprocessed, each referring to a confirmed case, corresponding to 66.8% of the total cases. A total of 98.5% of the geoprocessed PSIs were related to rural areas with agricultural activity (n = 127), 1.5% (n = 2) in peri-urban areas with agricultural activities. It was not possible to identify the PSI of 58 cases due to inconsistent data and difficulties in determining the likely sites of infection.

A conglomeration of PSI was observed in the Triângulo / Alto Paranaíba mesoregion with 130 confirmed cases of HCPS (67.3%) (Figure 2). This mesoregion presented an Odds Ratio five times greater than that of the mesoregion of the South / Southwest of Minas (OR = 5.73; CI = 1.53 to 23.18 p = 0.0019) from 1998 to 2002. In 2003, the Triângulo / Alto Paranaíba mesoregion was twice as likely to have municipalities with confirmed

cases, than the mesoregions of South / Southwest of Minas, West of Minas, and Central de Minas. In 2007, this mesoregion had a 12.73 times greater chance of having municipalities with confirmed cases than the mesoregions of West of Minas and South / Southwest of Minas (Table 2).

In the PCA, a greater correlation was observed between HCPS cases and landscape variables such as pasture planted areas and natural forests. From the data analyzed by the PCA, the crops of corn, rice, beans, and sugar cane, corresponded with lower prevalence of HCPS cases (Figure 3). The efficiency of the observed results can be assessed by the high percentage of inertia of the system (79%) represented in the first three axes. Our results demonstrate that HCPS in the Cerrado region of Minas Gerais is associated with the increase in the area of pasture cultivation and decrease in natural forests. Among the crops considered, increase in the area of

cultivation of rice is associated most with the increase in the number of HCPS cases, followed by that of beans, corn, and sugarcane. Thus, showing a greater adaptation

of the wild reservoirs to rice cultivations, when compared to that of other crops.

Figure 1. Probable Sites of Infection (PSI) confirmed cases of Hantavirus Cardiopulmonary Syndrome in the state of Minas Gerais, 1998 to 2007.

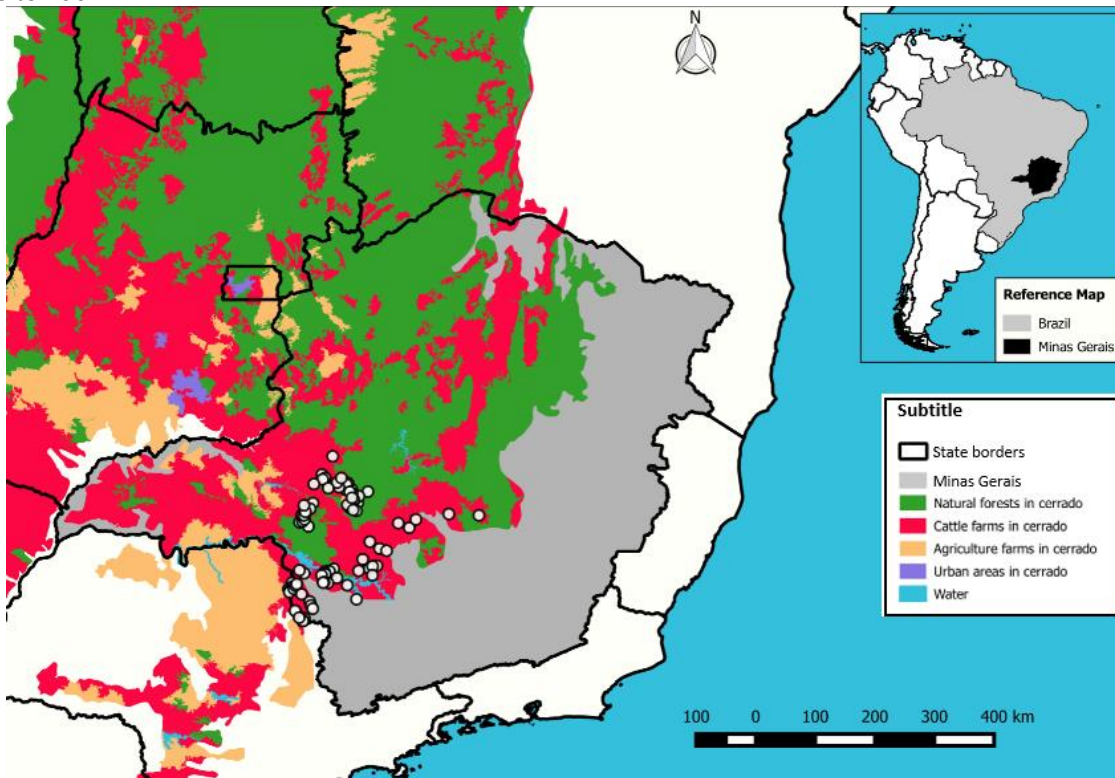
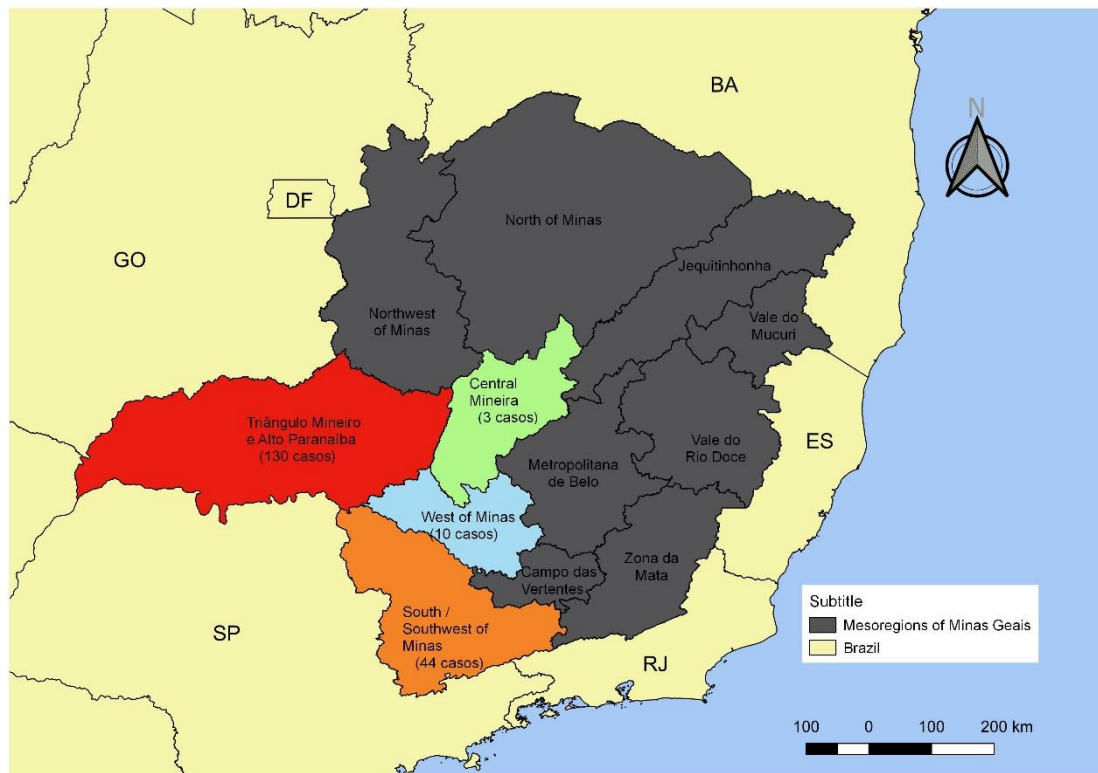


Figure 2. Mesoregion of Minas Gerais with confirmed cases of Hantavirus Cardiopulmonary Syndrome in the state of Minas Gerais, 1998 to 2007.

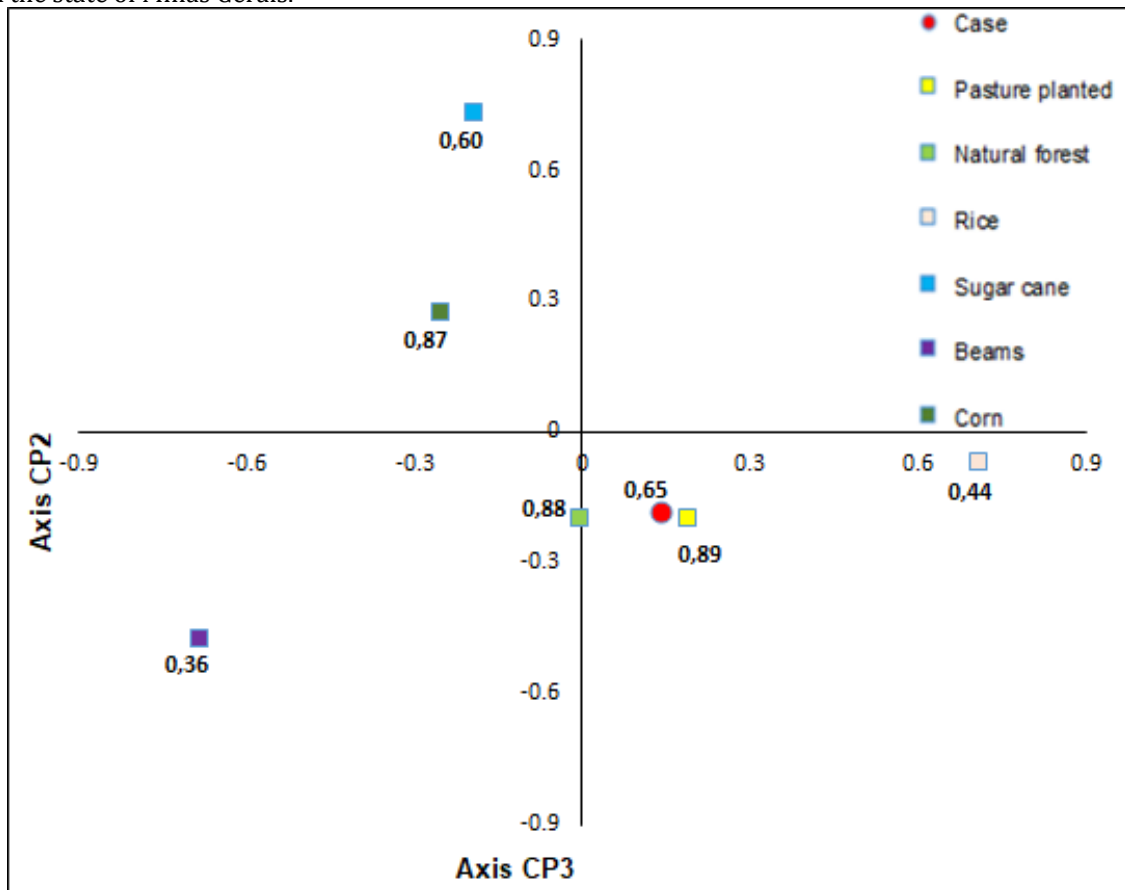


\* 6 cases without location.

Table 2. Odds Ratio of cities in the mesoregions of Minas Gerais that presented PSI conglomerates of confirmed cases of Hantavirus Cardiopulmonary Syndrome.

Year	Mesoregion	Number of Cities		OR	Confidence Interval 95%	p Value
		Case	Control			
1998 a 2002	Triângulo/Alto Paranaíba	9	55	5,73	1,53 a 23,18	0,001915
	South/Southwest of Minas	4	140	0,17	0,04 a 0,66	0,001915
2003	Triângulo/Alto Paranaíba	4	60	2,00	0,47 a 7,95	0,272975
	South/Southwest of Minas	5	139	0,79	0,20 a 2,99	0,695058
	Central of Minas	1	29	0,83	0,48 a 3,90	0,862110
	West of Minas	1	42	0,54	0,03 a 4,30	0,559365
2007	Triângulo/Alto Paranaíba	11	53	12,73	3,13 a 59,90	0,000003
	South/Southwest of Minas	2	142	0,11	0,02 a 0,54	0,000795
	West of Minas	1	42	0,36	0,02 a 2,74	0,307350

Figure 3. Principal component analysis of the relationship between Hantavirus Cardiopulmonary Syndrome and land use variables in the state of Minas Gerais.



**DISCUSSION**

A progressive increase in the number of confirmed cases was observed from the data of the first ten years of HCPS in Minas Gerais. Nunes et al. (2011), when describing the clinical / epidemiological aspects of cases of hantavirus in Cerrado areas, found a progressive increase in the number of cases mainly in the states of Minas Gerais, São Paulo, Distrito Federal, Goiás, and Mato Grosso. The

increase in the diagnostic capacity and greater sensitivity of the healthcare system, particularly in areas where hantavirus cases have been recorded, justify the increase in notifications (DONALISIO et al., 2008).

The results revealed that the Triângulo / Alto Paranaíba mesoregion had the highest occurrence of cases. This mesoregion, in the Cerrado, has intense agricultural activity. Therefore, has higher presence of rodents that

transmit the hantavirus. The presence of HCPS in Cerrado Mineiro is also linked to the distribution of the virus reservoir, in a native rodent species. These findings

peridomestic rodents in endemic areas (Figueiredo et al., 2009). In addition, other studies (ROSA et al., 2005; PEREIRA et al., 2007) have shown that the Cerrado biome also harbors rodents of the *Necromys lasiurus* and *Bolomys lasiurus* species, which are the reservoirs of a variant of the Araraquara virus. Donalisio et al. (2008) stated that it is necessary to investigate the epidemiological conditions, such as contact with rodents, types of cultures, grain storage, work process, and housing conditions, which may interfere with the risk of transmission of hantavirus.

Environmental changes can cause greater contact between humans and wild rodents, leading to an increased chance of occurrence of HCPS (SUZUKI et al. 2004; EBI, SEMENZA, 2008; SEMENZA; MENNE, 2009; JONSSON, FIGUEIREDO, VAPALAHTI, 2010).

This study suggests that HCPS is positively associated with deforestation. The Cerrado region is the natural habitat of the rodent *Necromys lasiurus*, the main transmitter of the Araraquara virus, which causes hantavirus in Minas Gerais (SUZUKI et al., 2004; DOS SANTOS et al., 2016). Human activities associated with deforestation for planting or urbanization, agricultural technological development, expansion for grain planting, and cattle breeding can intensify environmental changes (MYERS, 2013). These factors can contribute to the increase in human contact with wild rodents and reservoirs of the virus.

The increase in the area of environmental degradation caused by agricultural activities and the consequent decrease in the area of natural forests can predispose the prevalence of HCPS (BUSCH et al., 2004; DONALISIO, PETERSON, 2011). Beuchle et al. (2010) stated that the Cerrado and Caatinga biomes suffered continuous losses of natural vegetation between the years 1990 and 2010. Hence, it can be inferred that the environmental changes in the Cerrado region may affect the population dynamics of rodents responsible for the transmission of HCPS.

In our study, a conglomeration of PSIs was mainly observed in the rural and peri-urban environments of the Triângulo / Alto Paranaíba mesoregion. In addition, the Cerrado biome is located in an area of intense agricultural activity, with medium-sized and large rural properties with storage and processing infrastructure for grains, favoring the presence of wild rodents.

Despite the low association between the occurrence of HCPS cases and the planted area of rice, beans, corn and sugarcane, it is important to consider these factors in the epidemiology of the disease. The stored grains serve as food, in times of food scarcity, for the wild reservoirs. The excretory products of the rodents found in the

were corroborated and it was demonstrated that the epidemiology of hantavirus infections was largely related to the incidence of human exposure to

storage units facilitate the inhalation of the aerosols contaminated by the virus by humans (TORO et al., 1997; DONALISIO et al., 2008). Sugarcane cultivation can shelter the *Necromys lasiurus* rodent species, similar to the planted pastures, especially *Brachiaria decumbens* (VERDADE et al., 2012). The practice of grain housing and storage is common in Cerrado farms. It is beneficial for prolonged subsistence consumption and as an economic tool to provide better sale prices during off-season periods.

The association between pasture planted areas and HCPS can be observed because the rodent *Necromys lasiurus* prefers the brachiaria grass (*Brachiaria decumbens*) to hide and feed on the roots. This grass is associated with the advanced livestock in Brazil. The importance of landscape alteration for pasture planting and its association with HCPS should be emphasized, especially in the Brazilian municipalities that have a strong aptitude for agricultural activities (DONALISIO et al., 2008; VERDADE et al., 2012).

## CONCLUSIONS

The increase in the detection of HCPS cases is due to an improvement in the implementation of health surveillance and knowledge about the epidemiology of the disease. However, it is necessary to adopt proactive measures in the surveillance and clinical research of HCPS to consolidate the knowledge of the natural history of this disease in Minas Gerais. Additional training for health professionals in endemic areas must be carried out continuously, for early diagnosis and reduction of lethality.

Georeferencing revealed four mesoregions of Minas had cases of HCPS: Triângulo / Alto Paranaíba, South / Southwest of Minas, Central Mineira, and West of Minas. In addition, it was found that the mesoregion of Triângulo / Alto Paranaíba presented a higher risk for the incidence of HCPS cases, when compared to others that presented cases in the same period.

There is a greater association between the occurrence of HCPS, in Minas Gerais, with natural forests and pastures planted. The association of the occurrence of HCPS cases with the planted areas of rice, beans, sugar cane, and corn was not very significant, although among the cultivated crops, rice was most associated with HCPS.

Issues related to the environment should be considered in exposure to HCPS. The detrimental interference that humans have caused in the Cerrado region due to increase in agricultural productivity has augmented the appearance of diseases in these places. Our results suggest that an increase in the population of rodents is positively associated with the number of confirmed



HCPS cases in Minas Gerais, particularly pasture plantations and natural forests.

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