UNIVERSIDADE DE BRASÍLIA
CAMPUS PLANALTINA
Programa de Pós-Graduação em Ciências Ambientais

Tais Barbosa

Análise espacial da hantavirose no Distrito Federal, Brasil

Brasília-DF, Brasil

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TAIS BARBOSA

Análise Espacial da Hantavirose no Distrito Federal, Brasil

Dissertação apresentada ao corpo docente da Universidade de Brasília em cumprimento parcial dos requisitos para o grau de Mestre em Ciências do Programa de Pós-Graduação em Ciências Ambientais.

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Resumo

As hantaviroses são zoonoses emergentes que provocam enfermidades humanas graves, como a Síndrome Cardiopulmonar por Hantavírus (SCPH), incidente no continente americano, e a Febre Hemorrágica com Síndrome Renal (FHSR), com ocorrência na Ásia e Europa. No Brasil, a SCPH é uma enfermidade de alta letalidade e tem notificação obrigatória aos serviços de saúde. O principal reservatório de SCPH são espécies de roedores generalistas, como o *Necromys lasiurus*, incidente no bioma do cerrado, que aumentam em abundância em paisagens nativas alteradas, podendo elevar o risco de transmissão da doença. No Distrito Federal (DF), têm surgido novos casos de SCPH em decorrência do contato dos seres humanos com o hábitat desses roedores. Nesse contexto, a pesquisa é composta por dois artigos. No primeiro, foi feita uma revisão sistêmica dos métodos utilizados para analisar a hantavirose e sua relação com o uso do solo pela metodologia *Preferred Reporting Items for Systematic Reviews and Meta Analyses* (PRISMA). O segundo trata da análise espacial dos locais prováveis de infecção no período de 2007 a 2017 no Sistema de Informações Geográficas (SIG) por meio do *Índice Moran Global e local*, *Getis-Ord Gi** e pela modelagem ambiental no *Dinâmica de EGO*, a fim de indicar as áreas de maior risco e as variáveis ambientais que mais favorecem a disseminação da doença na região do Distrito Federal. O estudo fornece informações sobre a ação de fatores paisagísticos e climáticos na incidência de hantavirose. Essas informações podem ser utilizadas para fornecer um melhor entendimento de como a SCPH se comporta no DF e trazer subsídios para a orientação de estratégias de monitoramento e de vigilância epidemiológica em saúde pública.

Palavras-chave: Hantavirus, zoonoses, roedores, uso do solo, paisagem, análises geoespacial, revisão sistemática, modelagem ambiental.

Abstract

Hantaviruses are emerging zoonoses that cause severe human illnesses, such as Hantavirus Cardiopulmonary Syndrome (HCPS), incident in the American continent, and Hemorrhagic Fever with Renal Syndrome (HFRS) in Asia and Europe. In Brazil, HCPS is a highly lethal disease and must be treated by health services. The main cause of HCPS are species of generalist rodents, such as *Necromys lasiurus*, incident in the cerrado biome and increase in abundance in altered native landscapes, which may increase the risk of disease transmission. In the Federal District, new cases of HCPS emerged due to the contact of humans with the habitats of these rodents. In this context, the research consists of two articles. In the first article, a systemic review of the methods used to analyze hantavirus disease and its relationship with land use was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology. The second article is the spatial analysis of the probable sites of infection for the period from 2007 to 2017 in the Geographic Information System (GIS) through the Global and local Moran Index, Getis-Ord Gi * and by the environmental modeling in the EGO Dynamics. These analyses indicate the areas of greatest risk and the environmental variables that most predispose the disease in the region of the Federal District. This study provides information on the action of landscape and climatic factors on the incidence of hantavirus. The information can be used to understand better how SCPH behaves in the Federal District and provide subsidies for the guidance of monitoring strategies and epidemiological surveillance of public health.

Keywords: Hantavirus, zoonoses, rodent, land use, landscape, geospatial analysis, systematic review, environmental modeling.

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CAPÍTULO 1 – CONTEXTO GERAL

A modificação humana das paisagens naturais, a invasão de hábitats selvagens e fatores ecológicos são essenciais no aumento de novas doenças (Kilpatrick e Randolph, 2012). Entre elas, incluem-se as zoonoses (Woolhouse e Gowtage-Sequeria, 2005), que se beneficiam da globalização e são impactadas por questões sociais, econômicas, políticas, climáticas, tecnológicas e ambientais. A compreensão dessas doenças depende da perspectiva do contexto do ecossistema e da sociedade (Santos, 2013). A Organização Mundial da Saúde (OMS) reporta desde 1976 o surgimento e reemergência de 40 doenças infecciosas, a maioria das quais é uma consequência direta da mudança no uso e na cobertura do solo (OMS, 1996), com um efeito significativo na distribuição e ecologia dos organismos (Dearing e Dizney, 2010). A composição da paisagem e sua configuração afetam a incidência da doença, alternando as interações entre a abundância e o movimento de hospedeiros, vetores e pessoas (Lambin *et al.*, 2010), por isso a importância de estudar a dinâmica da doença na paisagem.

A OMS considera o hantavírus uma doença de alta gravidade com alta taxa de letalidade (até 15% para HFRS e 50% para HPS) (Avšič-Županc *et al.*, 2019), por isso é necessário um diagnóstico rápido, tanto clínico quanto laboratorial, juntamente com tratamento clínico adequado (Jonsson et al. 2010). Hantavírus é uma zoonose causada pela família *Bunyaviridae* (Blasdell *et al.*, 2011) que causa duas síndromes clínicas distintas: Síndrome Cardiopulmonar por Hantavírus (SCPH) e Febre Hemorrágica com Síndrome Renal (FHSR) (Duchin *et al.*, 1994). Ambas as formas têm suas distribuições geográficas em continentes diferentes: HCPS ocorre nas Américas; e HFRS, na Ásia e Europa (Yates *et al.*, 2002). Durante a Guerra da Coreia (1950-1953), ocorreu o primeiro surto de hantavírus. Entre os soldados das Nações Unidas que contraíram a doença, dos 3.000 infectados, 400 morreram de Febre Hemorrágica com Síndrome Renal (FHSR) (Jonsson *et al.*, 2010). Em 1993, os primeiros casos de Síndrome Pulmonar por Hantavírus começaram a aparecer nos Estados Unidos, mais especificamente no quadrilátero formado pelos estados de Utah, Novo México, Colorado e Arizona, devido às mudanças ambientais e climáticas causadas pelo El Niño nos anos de 1991 e 1992 (Nichol *et al.*, 1993). No Brasil, os primeiros casos foram diagnosticados em 1993, no estado de São Paulo, em Juquitiba, e no Distrito Federal em 2004. O primeiro surto no Brasil, em São Paulo e no Distrito Federal, esteve relacionados a dois fatores; o desmatamento de áreas naturais e a ocorrência de populações de ratos (Ferreira, 2003).

O risco de contrair hantavírus está diretamente relacionado à densidade de roedores em uma região, pois aumenta a probabilidade de uma pessoa ter contato com um roedor infectado (Reusken e Heyman, 2013). No Brasil, existem oito espécies de roedores considerados generalistas de hábitat, comumente residindo em ambientes antropicamente alterados, principalmente em áreas agrícolas (Oliveira, 2013). Mudanças antropogênicas direcionam a redução das comunidades de mamíferos, que tendem a ser dominadas por espécies generalistas, que por sua vez são relatadas como hospedeiros importantes para o hantavírus (Suzan, 2009). As variantes e reservatórios encontrados no Brasil são respectivamente: Juquitiba (*Oligorizomys nigripis*), Araraquara (*Necromys lasiurus*), Castelo dos Sonhos (*Oligoryzomys* aff. *Moojeni*), Anajutuba (*Oligoryzomys fornesis*), Laguna negra (*Collomys* aff. *Collosus*), Rio Mearim (*Holochilus sciurus*), Rio Marmoré (*Oligoryzomys microtes*) e Jaburá (*Akondon montensis*) (Oliveira, 2013). No Distrito Federal, o vírus Araraquara está associado ao roedor *Necromys lasiurus*, que é o mais abundante em áreas de hábitat de caatinga e cerrado, onde há gramíneas para atividades agropastoris (Donalisio *et al*., 2008).

A paisagem epidemiológica proposta por Pavlovsky (1966) é baseada na compreensão de como a doença ocorre em padrões espaciais que derivam de mudanças subjacentes nas características das paisagens e nos fatores relevantes que influenciam a dinâmica e distribuição das populações de hospedeiros, patógenos e vetores. Além disso, esses padrões podem ser delimitados em mapas (Ostfeld *et al*., 2005). Para Pavlovsky, a doença natural ocorre quando há clima benéfico, vegetação, solos específicos e microclima nos locais onde são encontrados vetores, doadores e recipientes de infecção. Atualmente, a modelagem é uma área em desenvolvimento com possíveis trabalhos nas áreas de geografia e ecologia de transmissão de doenças. Os ciclos de transmissão de doenças apresentam complexidade e heterogeneidade que, quando combinadas, orientam a biologia e as paisagens com os componentes causais da distribuição da doença (Peterson, 2006).

Na literatura, os estudos são escassos e dispersos com informações associadas à distribuição regional do reservatório de hantavírus em relação a variáveis climáticas e ambientais. Assim, para o desenvolvimento da pesquisa, além das considerações gerais, estruturamos o estudo na forma de artigos independentes. No primeiro, optamos por uma revisão sistemática para compreender como a hantavirose se comporta em nível global e gerar informações úteis sobre as técnicas, métodos e variáveis preditivas mais utilizadas em pesquisas científicas no mundo que relacionam os hantavírus ao uso do solo e paisagem, bem como às espécies de roedores, variáveis respostas. Essa melhor compreensão nos auxiliou na escolha das metodologias e das variáveis preditivas mais adequadas para a análise da hantavirose em nível regional, no Distrito Federal, apresentada no segundo artigo.

Para a análise do primeiro artigo, utilizamos a revisão sistemática de acordo com a plataforma PRISMA, que indica procedimentos para revisões sistemáticas e meta-análises para torná-las passíveis de repetição e evitar um viés metodológico na busca das publicações revisadas (Moher *et al*., 2009). Realizamos a pesquisa no idioma inglês sem restrição de data de publicação, nas plataformas *Scopus*, *Pubmed* e *Web of Science* entre o período de 22 a 25 de agosto de 2019. As análises incluíram a combinação dos termos descritos no título, *abstract* e palavras-chaves por meio da combinação das palavras: (hantavirus ou hantaan ou sindrome pulmorar por hantavirus ou febre hemorragica por sindrome renal) e (uso de terra ou cobertura de terra ou paisagem). Selecionamos os artigos que abrangeram simultaneamente os seguintes critérios: somente pesquisa sobre hantavirose e o uso do solo e/ou paisagem; todos os trabalhos que tenham técnicas e métodos de análise da hantavirose com o uso do solo e/ou paisagem. Portanto, foram excluídos: artigos que não avaliaram diretamente a hantavirose e o uso do solo e/ou paisagem; os que apresentaram uma avaliação sem apresentar o método utilizado; e estudos teóricos e revisões sistemáticas. Para a seleção dos estudos, os artigos que apresentaram duplicidade entre as bases foram excluídos. Além disso, dois revisores independentes analisaram os artigos; quando houve divergência sobre a elegibilidade de um artigo, um terceiro revisor foi consultado. Após essa etapa, os artigos foram lidos na íntegra para avaliar se preenchiam os critérios de elegibilidade. Em relação aos que preenchiam, foram extraídas as seguintes informações: primeiro autor e ano de publicação; instituição do primeiro autor; objetivos; métodos e variáveis preditivas; variável resposta; efeito encontrado; local de estudo e período.

Incluímos 56 artigos científicos nas análises, publicados entre os anos de 2000 e 2019. No total, as pesquisas foram feitas em 23 países, principalmente China (15%), Bélgica (12%), Brasil (10%) e Argentina e França (9%). Verificamos que, de acordo com os primeiros autores, o Brasil, Bélgica, China e Estados Unidos são grandes polos de pesquisas no campo da hantavirose, paisagem e uso do solo, e que a variável resposta mais estudada foi o roedor. Foram estudadas 218 espécies de roedores, entre as quais estão o *Myodes glareolus* (21%), *Mus musculus* (14%), *Zygodontomys brevicauda* (11%) e, em especial, *Necromys laciurus* (5%), encontrado na região do cerrado brasileiro (Oliveira, 2013). Os roedores estão associados a um grupo de espécies de hantavírus e suas distribuições geográficas (Pereira, 2006), o que explica por que algumas regiões e roedores são mais estudados do que outras. Os métodos e as variáveis preditivas mais utilizadas nos estudos foram o Índice de Vegetação Normalizada (NDVI) (20%), Análises Bayesianas e Distribuição Espacial (14%). Percebemos que a aplicação do Sistema de Informações Geográficas (SIG), juntamente com técnicas de estatísticas espaciais, forneceram elementos para a compreensão da dinâmica do hantavírus e sua relação com os elementos da paisagem. No geral, os estudos analisaram a dinâmica da incidência de HPS e HFRS, bem como a dinâmica, abundância e soroprevalência dos roedores associados ao risco e aos padrões espaciais e sazonais de distribuição do hantavírus na paisagem das áreas estudadas. Portanto, a revisão sistemática permitiu compreender os métodos predominantes de determinação de risco para hantavírus e o comportamento dos principais roedores estudados em todo o mundo.

No segundo artigo, analisamos espacialmente os casos de hantavírus no Distrito Federal de 2004 a 2017, a fim de verificar a dependência e correlação espacial dessas ocorrências e avaliar estatisticamente a influência das variáveis de uso do solo na dinâmica da doença por meio do modelo de análise de pesos e evidências. O objetivo foi compreender os padrões espaciais de ocorrência dos casos de hantavírus no DF, a fim de preencher possíveis lacunas no conhecimento sobre como a doença se comporta na região. Para isso, utilizamos duas metodologias. A primeira, baseada na estatística espacial, levou à espacialização das 43 coordenadas das residências dos casos confirmados autóctones de hantavirose nos anos de 2007 a 2017 a partir das bases das regiões administrativas do DF do Instituto Brasileiro de Geografia e Estatística (IBGE) e do uso e ocupação do solo do DF do Ministério do Meio Ambiente. Utilizamos os endereços residenciais para verificar se estes poderiam ser os locais prováveis de infecção e se as pessoas infectadas residiam perto dos hábitats do *Necromys lasiurus*, uma das espécies reservatórias do hantavírus. As 43 coordenadas e os locais prováveis de hábitats dos roedores (ocupação de áreas campestres, vegetação campestre, pastagem com manejo, silvicultura, vegetação florestal, florestas públicas e unidades de conservação permanente) foram georreferenciados e, a partir dos dados de distância em metros entre esses dois pontos, foram feitas as estatísticas espaciais.

A primeira análise, com o Índice de Moran Global, foi realizada com o intuito de demostrar a autocorrelação espacial e observar a semelhança dos dados espaciais, além de investigar quantitativamente as características das distribuições espaciais dos casos nas regiões administrativas do DF. Em seguida, analisamos a covariância espacial entre os polígonos através do Índice de Moran Local (Anselin, 1995) e o algoritmo de Getis-Ord Gi*, que indicou os agrupamentos levando em conta a estatística prevista de um polígono e seus vizinhos em comparação com a média de todas as verificações (Getis, 1995). O georreferenciamento indicou que a maioria das residências dos casos de hantavírus confirmados no período estudado estão a menos de 1.000 metros dos prováveis hábitats dos roedores reservatórios e que os resultados obtidos por meio do Índice de Moran Global (0,27) e Índice de Moran Local (0,38), que indicaram autocorrelação positiva entre os valores de distância e as Regiões Administrativas. Foi percebida, através do Índice de Moran Local e do algoritmo de Getis-Ord Gi*, a formação de grupos homogêneos principalmente na Região Administrativa do Paranoá, que apresenta alta ocorrência da doença. O contágio pode ter sido influenciado por fatores ambientais e sociais das regiões vizinhas, a exemplo de Planaltina e São Sebastião, como é o caso de surgimento de novos condomínios, loteamento de fazendas, invasão de terras, produção agrícola em locais com trechos de vegetação silvestres que são hábitat do roedor, permitindo que haja contato ocasional com o homem e por consequência a transmissão da doença.

A segunda metodologia adotada foi a modelagem ambiental. Para isso, utilizamos o software Dinâmica EGO como plataforma de simulação do modelo para a análise de pesos e evidências que quantificou as mudanças na cobertura de terra, com base em cadeias markovianas convertendo em uma matriz de transição as taxas de mudanças a serem usadas na simulação. Calculamos a matriz de transição utilizando o intervalo de 14 anos, entre o início da doença (2004) e o final (2017). No processo de calibração foram realizados testes no sistema, buscando identificar, no intervalo de 14 anos, parâmetros que definiram melhor o ajuste do modelo e a realidade observada no mapa. Pautado nisso, o programa utilizou o teorema de probabilidade condicional de Bayes (Bonham-Carter, 1994) para empregar a correlação entre presença ou ausência da doença. O conjunto de banco de dados foi representado para a região do Distrito Federal. Empregamos 9 variáveis na modelagem, entre as quais estão: altimetria, rede de drenagem, rodovias, unidades de conservação, transição do uso de terra, precipitação média, temperatura média, geomorfologia e locais prováveis de infecção dos casos confirmados autóctones dos anos de 2004 a 2017.

Na análise de pesos e evidências, todas as categorias apresentaram classes de retração e atração para a doença, exceto a variável de distância de rodovias e estradas viciais, que indicou somente a refração. Em relação à hantavirose, é mais provável que ela ocorra em locais próximos aos hábitats naturais, cursos d’água e locais prováveis de infecção. A expansão natural urbana no Distrito Federal tem promovido a construção de moradias em direções às regiões rurais, agrícolas e silvestres que são hábitats do roedor, permitindo que haja contato ocasional com o homem e facilitando a transmissão da hantavirose ao humano. As áreas de transição de uso do solo indicaram mais atração para áreas de transição para a pastagem. Percebe-se que o roedor *Necromys lasiurus* é adaptado a viver no interior do pasto de *urochloa*, onde se alimenta das sementes e da água de suas raízes principalmente em período de estiagem, o que promove a manutenção da população de roedores com alta densidade nestes locais (Alvin e Xavier, 2002). A análise da variável geomorfológica mostrou retração para todas as categorias, exceto a área de Zona de Erosão Recuante, que apresentou atração para a doença, com uma vegetação arbórea alta e densificada. Em relação à análise de correlação entre as variáveis, o critério de Crammer demonstrou para a maioria das variáveis uma correspondência de dados com baixa correlação entre si, o que apontou elementos independentes, exceto as variáveis altitude e temperatura média, que indicaram uma correlação de 73% entre si, o que demostra uma relação significativa. O Distrito Federal apresenta clima predominantemente tropical de altitude, onde há duas estações bem definidas, quente e úmida e fria e seca (Cardoso *et al.*, 2014). Esta sazonalidade, no Distrito Federal, influencia a dinâmica da produção agrícola da região. Estas alterações podem disponibilizar alimentos em grande quantidade em períodos naturalmente escassos, interferindo na dinâmica e abundância da população de roedores (Klemba, 2009). Em vista disso, foi percebido que os casos de hantavirose no Distrito Federal se concentram na época de estiagem (Santos, 2011).

A análise espacial do hantavírus no Distrito Federal contribuiu para uma visão espacial da ocorrência da doença. Simultaneamente, a modelagem da cobertura do solo mostrou como as variáveis ambientais influenciam a distribuição das espécies de roedores. No período estudado, de 2004 a 2017, as ocorrências de hantavírus no Distrito Federal apresentaram distribuição sazonal e variaram de acordo com a região geográfica. Segundo o Dr. Roberto Dusi, pesquisador e servidor da Secretaria de Vigilância Epidemiologica do Distrito Federal, diz que no Distrito Federal, no ano de 2020 já ocorreram três confirmações sorológicas de hantavirose. Os exames realizados com as amostras guardadas no período de 2018 e 2019 levaram a uma confirmação em cada ano. Porém, essas confirmações são limitadas, pois já não se faz a pesquisa de IgM e IgG, sendo feito atualmente somente o IgM. No caso do tipo de teste laboratorial adotado pela Coordenação-Geral de Laboratórios de Saúde Pública da Secretária de Vigilância em Saúde do Ministério da Saúde (CGLAB-SVS-MS), com antígeno da variante *Araucaria*, pode ter especificidade menor com o IgM. Com o advento da pandemia do novo coronavírus, o número de casos de hantavirose poderá ser mais subnotificado, pois apresenta sintomas similares aos da Covid-19 (MS, 2020).

A revisão sistemática e o estudo da dinâmica da doença por hantavírus no Distrito Federal reafirmaram o impacto da perturbação de nichos ecológicos com atividades antrópicas de produção agrícola e assentamento para habitação humana. Essas atividades humanas favorecem a disseminação do hantavírus entre roedores e têm repercussão direta na saúde humana. Nesse sentido, é preciso observar o dinamismo que ocorre no Distrito Federal, cujo território apresenta mudanças cada vez mais agressivas, resultando na perda de áreas silvestres e, consequentemente, maior vulnerabilidade para o surgimento e reemergência de doenças como hantavírus. Técnicas como a modelagem no Dinâmica EGO poderiam ser aplicadas para analisar outras doenças, principalmente as de origem zoonótica, para apoiar a sociedade na gestão de programas de vigilância em saúde pública.

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CAPÍTULO 2 – RELATIONSHIP BETWEEN HANTAVIROSIS OCCURRENCE AND LANDSCAPE CHANGES CAUSED BY HUMAN ACTIVITIES: A SYSTEMATIC REVIEW[1]

Abstract: Changes in the landscape caused by human action is one of the main factors responsible for increases in the outbreak of infectious diseases. This study aims to analyze the main results found through analysis of the relationship between changes in the landscape and increased incidence of hantavirus in the scientific literature. The analysis included a combination of descriptive terms in the title, abstract, and keywords: (hantavirus* OR hantaan* OR hantavirus pulmonary syndrome*" OR hemorrhagic fever with renal syndrome*) AND (land use* OR land cover* OR landscape*). A systematic review of articles in English, with no restriction on publication date, was carried out in the following scientific literature databases *Scopus*, *PubMed*, and *Web of Science*. The search took place in August 22-25, 2019. Indexed articles that met the selection criteria were selected. From 2000 to August 2019, geospatial analysis technologies were applied in most of the studies analyzed, and their applicability is used in the analysis of diseases transmitted by related diseases. It is essential to emphasize the importance of developing methodologies that address the study of this association in order to contribute to the knowledge of the dynamics between land use, landscape, and hantavirus.

Keywords: Hantavirus; Land use; Landscape, Geospatial Analysis, Systematic Review.

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2.1 Introduction

The hantavirus (*Bunyaviridae* family) causes disease such as hemorrhagic fever with renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS) in humans. HFRS occurs in Eurasia, is caused by at least four antigenically and genetically different hantaviruses, and is classified by the serotypes *Hantaan*, *Seoul*, *Dobrava/Belgrade*, and *Puumala* (Schmaljohn et al., 1985). HPS occurs in America and is caused by the *Sin Nombre* virus in North America, and the *Andes* virus in South America (Nichol et al., 1993). Hantavirus infections are of increasing concern in terms of public health, with an incidence of approximately 30,000 cases annually in humans and an increasing distribution worldwide (Watson et al., 2014). They are of great importance because of their severity, high lethality rate (up to 15% for HFRS and 50% for HPS) (Avšič-Županc et al., 2019), and because of their little-known history (Jonsson et al., 2010). The first outbreak of HFRS occurred in the 1950s among American soldiers during combat in the Korean War and was attributed to the high level of contact between rodents and soldiers in wild environments (Sheedy et al., 1954). HPS was first recognized in 1993 in the Four Corners region of the United States (southwestern corn of Colorado, sotheastern corner of Utah, northeastern corner of Arizona, and northwestern corner of New Mexico) and in the second half of 1993 in South America (Nichol et al., 1993).

Considering that rodents are the main hosts of hantaviruses, the occurrence of hantavirus is essentially influenced by the geographic distribution of these rodents (Watson et al., 2014). In Eurasia, these viruses are called *Old World* hantaviruses and are transferred by four genera of rodents: *Myodes, Microtus*, *Apodemus*, and *Rattus* (Avšič-Županc et al., 2019). In America, they are called *New World* hantaviruses, belong to the subfamily *Sigmodontinae,* and are endemic to the American continent (Nichol et al., 1993). The rodents *Necromys lasiurus, Peromyscus maniculatus, Peromyscus leucopus, Oligoryzomys nigripes*, and *Akodon montensis* are considered having generalist habitat, therefore, with relatively high abundance (Palma et al., 2012).

Hantaviruses are spread to humans through aerosols present in environments where infected rodents excrete saliva, urine, and feces containing viruses, especially where there are agricultural activities and urban areas (Oliveira et al., 2014). The spread tends to worsen when intense anthropogenic changes occur. The removal of native vegetation and the consequent creation of disturbances in the original habitat may promote the replacement of specialist species by generalist species of rodents with a high potential for hantavirus transmission (McKinney, 2006). Changes in the landscape cause the rodents to move habitats, increasing interspecies contact, which in turn generates increased competition and the probability of transferring the virus from the infected individual to uninfected members of the reservoir population (Langlois et al., 2001). In this sense, the pressures of anthropogenic origin in the landscape cause the introduction of new pathogens in native ecosystems and reduce the resilience in these environments. Because of this, changes of anthropogenic origin are related to specific zoonoses such as hantavirus (Ostfeld et al., 2005).

There is a significant gap in studies on the relationship between the hantavirus and landscape configuration, temperature, humidity, as well as between disease and interaction with climatic variables and land use (Prist et al., 2017a). Studying the link between ecological factors and specific changes in the landscape can contribute to identify of the most critical variables in the risk-analysis of zoonoses under specific circumstances. The present study presents a careful bibliographic review of scientific publications that address the increase of hantavirus caused by human changes of the landscape.

2.2 Material and Methods

The first stage of this research involved a systematic bibliographic search of the topic of interest, following the recommendations of the platform called Main Items for Reporting Systematic Reviews and Meta-Analyzes (PRISMA) (Moher et al., 2009). This platattorn indicates procedures for systematic reviews to be reproducible and to avoid methodological biases in the search for revised publications. Searches were carried out in three scientific literature databases (*PubMed, Scopus,* and *Web of Science*) to find publications with association between hantavirus and land use or landscape. The search covered the combination of the following descriptive terms: (hantavirus* OR hantaan* OR hantavirus pulmonary syndrome* OR hemorrhagic fever with renal syndrome*) AND (“land use*” OR “land cover*"OR landscape*). The search took place between 22 to 25 August 2019, covering the title, summary, and keywords.

The bibliographic search involved only articles in English, without date restriction. Articles that did not directly assess the relationship between hantavirus and land use and/or landscape or those that presented analyzes without specifying a methodological approach were excluded. The selection of publications was made by two independent technicians who analyzed the title and summary of the articles. All articles that were classified as “to be excluded” by the two technicians were removed. For those articles with divergence between the two technicians, a third reviewer was consulted for final decision-making. After this stage, the authors carefully read the articles to see whether they all met the eligibility criteria. The following information was extracted from the selected articles: first author; year of publication; institution; goals; study area; study period; predictive methods; response variable; and effects found (Appendix I).

The data extracted from the articles included the number of publications per year, the variables studied, and the countries involved in the studies. After this step, the *ggplot2* package (Wickham, 2016) was used to generate the graphics. From the locations of the samples from each publication, a global map was generated with the support of the *QGIS* geographical information system (GIS) program (QGIS Development Team, 2019), identifying the regions with high sample densities.

2.3 Results

We identified 64 articles in the PubMed database, 69 in the Scopus, and 75 in the Web of Science and added two additional articles identified by other databases. After removing 111 duplicate publications, we selected 99 publications, of which 42 were removed after analyzing the titles and abstracts. Of the 57 eligible articles, one was excluded because it did not directly assess hantavirus and land use, or landscape. Only 56 articles remained for further analysis. Figure 1 sumarizes the selection process of articles and eligibility criteria. The earliest three articles dealing with the relationship between hantavirus and analysis of landscape and land use were published in 2000 (Utrera et al., 2000) and 2001 (Calisher et al., 2001; Langlois et al., 2001). There were no publications between 2002 and 2005. The years with the highest number of publications were 2007 (7 publications), 2016 (5 publications) and 2017 (9 publications) (Figure 2).

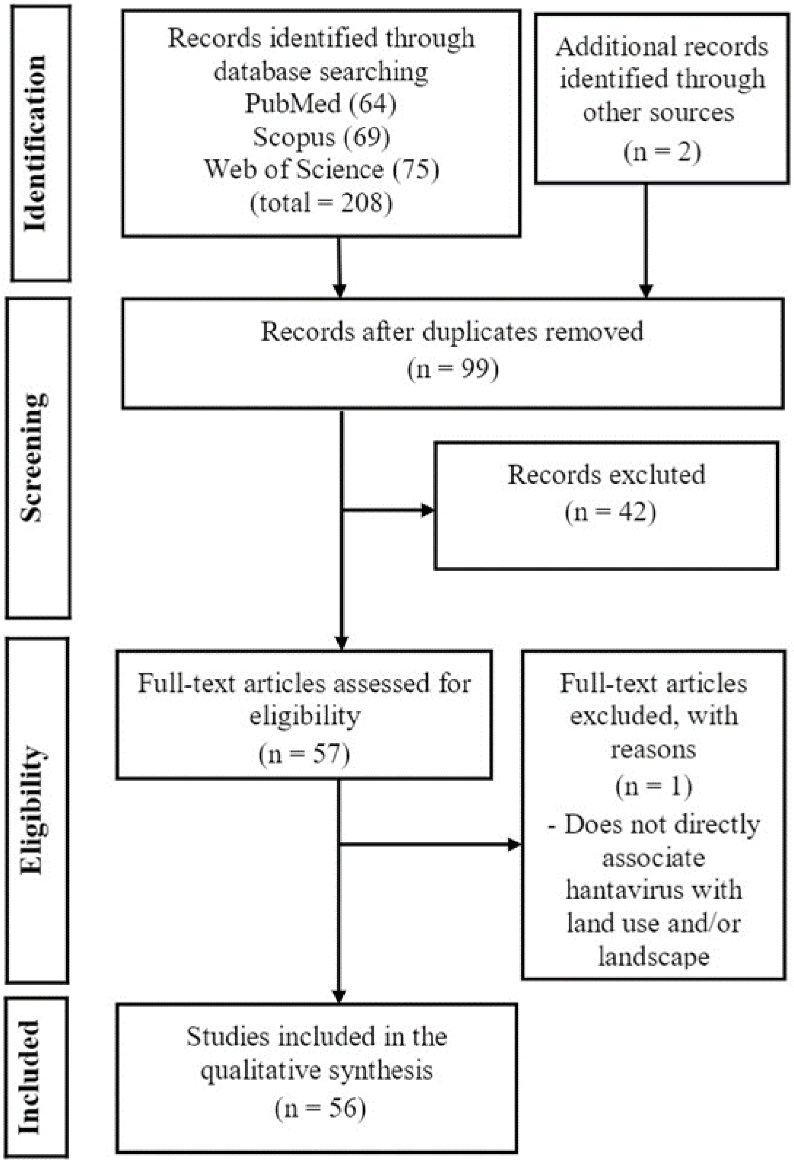

Fig. 1 Flow chart of the process of publication selection that were included in the systematic review.

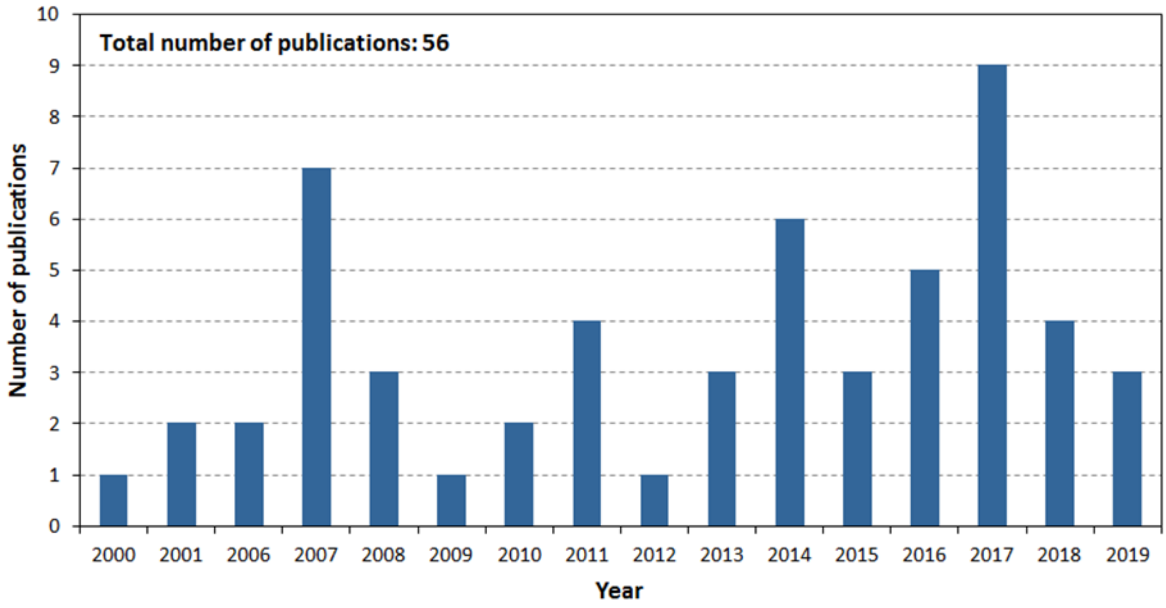

Fig. 2 Number of publications per year of studies associating hantavirus with land use or landscape.

The countries with the highest number of publications, according to the first author, were Argentina and Brazil (6 publications, 11%), Belgium (7 publications, 13%) China (10 publications, 18%) and USA (8 publications, 14%). The countries where most studies were carried out (Figure 3) were China (10 publications, 15%), Belgium (7 publications, 12%), Brazil (10%), Argentina and France (6 publications, 9%) (Figure 3). Four articles (Haredasht et al., 2013; Zeimes et al., 2015; Blasdell et al., 2016; Milholland et al., 2017) analyzed coverage and land use or landscape and their relationship to hantavirus in spaces that spanned more than one country. In total, there were 23 countries (Argentina, Austria, Belgium, Brazil, Cambodia, Canada, Chile, China, Czech Republic, Finland, France, French Guiana, Germany, Italy, Mexico, Netherlands, Norway, Panama, Paraguay, Sweden, Switzerland, USA, and Venezuela) studied in the 56 analyzed scientific articles.

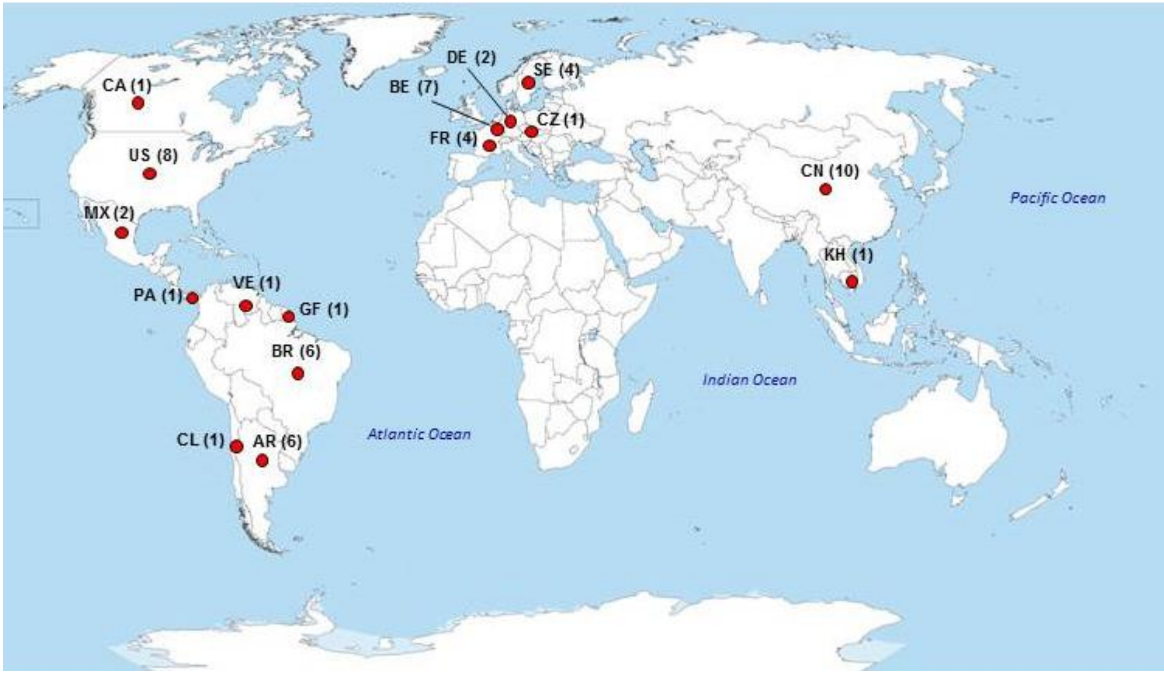

Fig. 3 Number of publications (in parenthesis) involving the association between hantavirus and land use or landscape per country. AR = Argentina; BE = Belgium; BR = Brazil; CA = Canada; CL = Chile; CN = China; CZ = Czechia; DE = Denmark; FR = France; GF = French Guiana; KH = Cambodia; MX = Mexico; PA = Panama; SE = Sweden; US = United States; and VE = Venezuela.

The most studied variables related to land use or landscape were rodents (32 publications, 57%), rodents and HFRS (8 publications, 14%), rodents and HPS (3 publications, 5%), HFRS (8 publications, 14%) and HPS (5 publications, 9%) (Figure 4a). Two hundred eighteen rodent species were studied in association with land use or landscape (Appendix I). Some studies considered more than one species of rodent, while others looked exclusively at the same group. The ten species that appeared in the most significant number of studies were from the family Cricetidae (41 publications, 73%) and Muridae (15 publications, 21%). The ten most studied rodent species (Figure 4b) were: *Myodes glareolus* (13 publications, 23%), *Mus musculus* (8 publications, 14%), *Zygodontomys brevicauda* (6 publications, 11%), *Oligoryzomys fulvescens* (5 publications, 9%), *Oligoryzomys longicaudatus* (5 publications 9%), *Oligoryzomys nigripes* (5 publicationsosts, 9%), *Sigmodon hirsutus* (4 publications, 7%), *Apodemus agrarius* (4 publications, 7%), *Necromys Lasiurus* (3 publications, 5%) and *Rattus rattus* (3 publications, 5%).

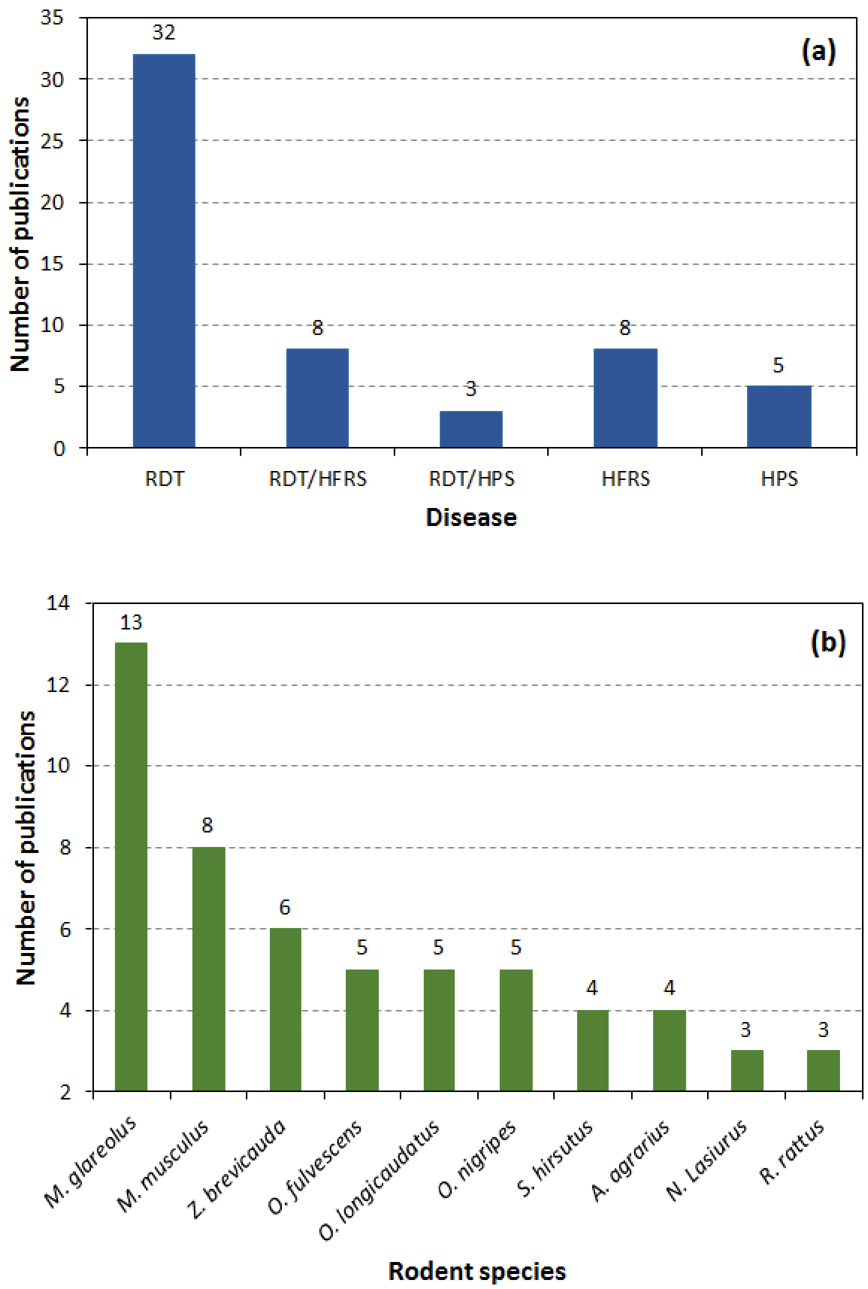

Fig. 4 (a) Number of publications associating hantavirus and land use or landscape considering the variables studied: rodent (RDT); RDT and hemorrhagic fever with renal syndrome (HFRS); RDT and hantavirus pulmonary syndrome (HPS); HFRS; and HPS. (b) number of publications using hantavirus association methods and land use or landscape use considering the rodent species studied.

In general, the studies aimed to analyze the dynamics of the incidence of HPS and HFRS, as well as the dynamics, abundance, and seroprevalence of rodents associated with the risk and the spatial and seasonal patterns of distribution of hantavirus in the landscape of the studied areas. The studies evaluated a wide variety of methods and techniques that related hantavirus to the landscape and land use. The most common methods were: normalized difference vegetation index (NDVI, 11 publications, 20%); Bayesian analyzes

(8 publications, 14%); generalized linear mixed effect model (GLM, 8 publications, 14%); spatial distribution (8 publications; 14%); logistic regression (8 publications, 14%); spatial correlation (7 publications, 13%); landscape characteristics (7 publications, 13%); land cover classification (7 publications, 13%); landscape structure (6 publications, 13%); multiple linear regression (6 publications; 13%) (Appendix I).

2.4 Discussion

We found that Brazil, Belgium, China, and the United States are significant hubs for research in the field of hantavirus, landscape, and land use, which is reflected in the number of first authors from these countries. Regarding the publication date, there is no constant pattern over the years. We observed that rodent species was the most studied response variable, showing the importance of understanding the dynamics of rodents for risk analysis of hantavirus in a landscape.

2.4.1 Rodents

The expansion of hantavirus is sensitive to ecological changes. Environmental changes, such as the decrease in rodent diversity, cause an increase in interactions between rodent species. This subsequently increases aggressive encounters within a single species which generates exposure to saliva and excrement. The result is an increase in the prevalence of viruses in rodents and the risk of hantavirus transmission in humans. Land cover plays an important role in the prevalence of positive cases. Agricultural land coverage is associated with a greater presence of seropositive rodents and human disturbances in the distribution of rodents that are or have been exposed to hantavirus (Goodin et al., 2006). In addition, the significant spatial changes in land use influence hantavirus hosts at the landscape level (Suzán et al. 2006; Muylaert et al. 2019). The components of the structure (Monjeau et al., 2011), composition, and configuration of the landscape determine the spatial distribution of the hantavirus reservoirs (Langlois et al., 2001).

Among the variables related to landscape and land use, it was observed that rodents were the most studied, with emphasis on the subfamilies *Arvicolinae, Murinae,* and *Sigmodontinae*, since only murine rodents are involved with hantavirus (Musser, 1993). These animals are associated with a group of hantavirus species and their geographic distributions, which explains why some geographic regions are studied more than others. The rodents of the subfamily *Arvicolinae* are distributed in Eurasia and North America, while those of the subfamily *Murinae* have their original distribution in Eurasia. Those of the subfamily *Sigmodontinae* occur exclusively in the American continent (Pereira, 2006).

Studies in the USA and Mexico (Milholland et al., 2017), and Paraguay (Goodin et al., 2006) show that the diversity of species does not influence the prevalence of hantavirus in rodents, whereas, in Panama (Suzán et al., 2008) and Brazil (Oliveira Santos et al., 2018), increased diversity influences the transmission of the virus. Anthropogenic activities such as deforestation, agricultural development, and urbanization impact the complexity of ecosystems and affect the density of rodents. The most studied rodents: *Zydontomys brevicauda* - Panama (Suzán et al., 2006; 2008), French Guiana (Thoisy et al., 2014) and Venezuela (Utrera et al., 2000) and *Necromys lasiurus* - Brazil (Prist et al., 2017b; Oliveira Santos et al., 2018), *Apodemus agrarius* and *Mus musculus* - China (Zhang et al., 2009; Wei et al., 2011; Xiao et al., 2013a, 2018; Wang et al., 2016) and *Rattus* spp. Tailandia and Cambodia (Blasdell et al., 2016), are species that benefit from land use change. The species *Sigmodon hirsutus* - USA (Walsh et al., 2007); *Olygoryzomys longicaudatus* - Argentina (Andreo et al., 2014) and Chile (Lazo-Cancino et al., 2017); *Olygoryzomys negripes* - Paraguay (Goodin et al., 2006) and *Myodes glareolus* - France (Guivier et al., 2011, 2014; Haredasht et al., 2013), Belgium (Linard et al., 2007a; Haredasht et al., 2013; Laenen et al. 2019); Switzerland (Haredasht et al., 2013), Germany (Haredasht et al., 2013; Cunze et al. 2018); Sweden (Khalil et al., 2016; Ecke et al., 2017) Italy (Haredasht et al., 2013); Austria (Haredasht et al., 2013); Czech Republic (Heroldová et al., 2010); Finland (Zeimes et al., 2015); Norway (Zeimes et al., 2015); and Holland (Zeimes et al., 2015), are species that are best adapted to environments with natural vegetation cover.

Except for *Rattus novergicus*, *Rattus rattus*, and *Mus musculus*, which are habitually anthropized, all rodents of the subfamilies *Arvicolinae*, *Murinae*, and *Sigmodontinae* are rural, mostly wild and have a regional distribution (Pereira, 2006). The rodents of the *Sigmodontinae* subfamily, in turn, are species with more significant adaptation, being therefore generalists. Rodents tend to benefit from land conversion to agriculture (Blasdell et al., 2016) in Southeast Asia, where the change in the natural environment resulting from forest fragmentation is increasing the abundance and distribution of species that are reservoirs of the hantavirus in tropical areas (Suzán et al., 2008a, 2008b).

Populations of different rodent species may have different patterns of seasonal variation, as they depend on different resources and can respond to variations in extrinsic factors distinctly. In this context, the rodent *Myodes glareolus* maintains a complicated relationship between its predators and landscape structure (Khalil et al., 2017). Broad-leaved forests are the favorite habitat of this rodent, with the density of rodents being high where urbanization is low (Linard et al., 2007b). The rodent species *Oligoryzomys fulvescens* showed a distinct spatial pattern over time, associated with seasonality and anthropogenic pressures that occurred with agricultural activities (Armién et al., 2016). The rodent *Apodemus agrarius* avoids humid habitats, extreme drought conditions, and urban areas. These conditions act as a barrier to the gene flow of the species (Jo et al., 2018). The rodent *Oligoryzomys longicaudatus* prefers humid habitats with hight cover (Andreo et al., 2012). The *Olygoryzomys negripes* species showed low density in warmer months. Intra-annual population fluctuations in tropical ecosystems, showed to be regulated by the availability of food, and influenced by the dynamics of the rains (Galiano et al., 2013). Rodents *Zygodontomys brevicauda* are opportunists who prefer habitats with dense cover and sparse tree vegetation (Utrera et al., 2000). The species *Necromys lasiurus* are better adapted to heterogeneous habitats, in agricultural lands, and in low altitude regions, close to water bodies (Oliveira Santos et al., 2018) as observed in sugarcane plantations (Muylaert et al., 2019). Geographical extension and the quality of the vegetation influence the dispersion of the rodents of the species *Sigmodon hirsutus.* They prefer moderate temperatures and avoid temperatures above 34 °C (Walsh et al., 2007).

2.4.2 Methods

We found that the application of GIS, together with spatial statistical techniques, provides explicit ways to quantify and identify fluctuations in rodent reservoir abundance and other environmental variables responsible for the increased risk of hantavirus (Yu et al. 2017). Most studies have combined an epidemiological approach to the landscape with GIS and remote sensing techniques to increase understanding of the dynamics of hantavirus and its relationship with landscape elements. For example, disease predictions using different proxies have led to a wide variation in the results in their sensitivity and specificity in predicting new cases of HPS (Prist et al., 2017c).

Several studies have used vegetation index (NDVI) as a way to reflect the amount of vegetation cover in a specific region. NDVI was related to the quantity and productivity of vegetation and crops, which are the food source of rodents (Wei et al., 2011) (Calisher et al. 2001; Yan et al., 2007; Viel et al., 2011; Xiao et al., 2013; Andreo et al., 2014), and correlated significantly with the rodent density in the cities of Changsha (Xiao et al., 2013) and Shandong Province (Wei et al., 2011). In the Dongting Lake District, NDVI (62.7%), and the type of land use (7.9%) were dominant factors for the incidence of cases of HFRS (Liu et al., 2014).

The Bayesian models were adequate and important not only to identify variables for improving prevalence estimates in specific locations (local landscape associated with an increased likelihood of infection (Walsh et al., 2007) but also in observing the set of landscape attributes and risk disease as common and specific risk factors for HFRS (Barrios et al., 2013). The Bayesian regression approach showed an association between biomass and the incidence of HFRS (Viel et al., 2011).

The logistic regression model accurately indicated the coverage area for the risk of HPS (Eisen et al., 2007) and HFRS, predicting the locations where hantavirus infections can occur among rodent populations (Zhang et al., 2009). Niche modeling provides a useful tool to predict the spatial and temporal risk of hantavirus (Liu et al., 2014), helping to identify both potential habitat areas of *M. glarerolus* with possible risk to humans and the significant environmental factors involved in defining the suitable habitat areas of species based on environmental conditions (Haredasht et al. 2013).

Modeling the distribution of a specific species is challenging in several tropical areas due to variations in land use. Generalist species such as *Sigmodon hispidus*, *Z. brevicauda*, and *Oligoryzomys fulvens*, researched in Venezuela (Utrera et al., 2000), United States (Diffendorfer et al., 1995), Paraguay (Meserve et al., 2001) and Costa Rica (Daily et al., 2003) dominate anthropic landscapes that have a mosaic of various successional stages and forest patches. The landscape structure, more than other ecological variables, such as climate and seasonal changes, can affect the distribution pattern of the rodent population and the risk of hantavirus infection in humans (Langlois et al., 2001; Xiao et al., 2013). The multiple linear regression model, for example, predicted the highest abundance of *Z. brevicauda* in flat areas, where humans also dominate (Suzán et al., 2006). In recent years, in China, the geographically weighted regression (GWR) model has shown that the frequency of HFRS has been affected mainly by human activities (Li et al., 2014).

The SARIMAX model was used as a predictive model for HFRS in almost real-time (He et al., 2018). In turn, object-based classification methods have proved useful in specific applications, such as studies related to the epidemiological landscape. The classification of object-based land use/cover metrics corresponds to 84% of the overall occurrence of classification, compared to only 43% who used the per pixel method. The Kappa statistics was also significantly higher for the object-based classification (Koch et al., 2007).

According to our systematic review, one can take as a base the list of study descriptions to formulate proposals for methodologies in future publications in the field of research into landscape epidemiology. As expected, geospatial analysis technologies have been applied in most of the studies analyzed, demonstrating that they are useful for understanding the mechanisms of transmission of hantavirus and their interactions with the environment.

We restricted our study to publications that had, in their methodology, the assessment of land use and landscape associated with hantavirus. Therefore, we may have missed studies that used relevant methodologies, but that were not explicitly defined in the title, abstract, or keywords. Despite these limitations, following the PRISMA protocol of systematic review, the strength and direction of research in the reviewed studies were rigorously examined. The results strengthen the existing evidence for associations between hantavirus, land use, and landscape and provide research models and methodological implications for future studies on landscape epidemiology.

2.5 Conclusions

The selected articles reinforce the significance and effects of disturbing ecological niches with the anthropic activities of agricultural production and settlement for social housing. They identify the spread of hantavirus among rodents as its repercussions for human health. The characteristics of the landscape and the understanding of the dynamics of rodents are essential mechanisms for identifying the risks of hantavirus, predicting future outbreak, and providing guidance for monitoring strategies and epidemiological surveillance in public health.

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Appendix I Description of studies associating hantavirus with land use and landscape.

Reference	Institution	Objective	Predictive method	Variable response	Effect found	Study local	Period
Langlois et al. (2001)	Carleton University, Ottawa, Canada	To analyze the risk ratio of a deer rodent carrying the Sin Nombre virus with the variables that define the structure of the landscape and other factors likely to affect the incidence of the virus	landscape structure, composition, and configuration, multiple logistic regression analyses	Rodent (*Penomysens moniculatus*)	The landscape structure, more than other environmental variables such as climate and seasonal change, can affect the pattern of distribution of a virus in its host population	Canada	Two years
Calisher et al. (2001)	Colorado State University, Fort Collins, USA	To investigate population and community dynamics with a rodent occurring in a disturbed micro-habitat	Floral composition assessed by an ocular estimate based on past line intercept studies	Rodent (*Peromyscus maniculatus* and *Reithrodontomys megalotis*)	In environments with natural vegetation cover, more typical shortgrass prairie and canyon habitats, the prevalence of infection was higher than in urban environments with disturbed habitat	The Pinõn Canyon Maneuver Site (PCMS), Las Animas County, southeastern Colorado/USA	1995-1997
Utrera et al. (2000)	Universidad Nacional Experimental de Los Llanos, Colonia Guanare, Venezuela	To characterize the general structure of rodent assemblages with emphasis on agroecosystems	Landscape characteristics and land use composition	Rodent (*Dildelphis marsupialis*, *Marmosa robinsoni*, *Monodelphis brevicaudata*, *Heteromys anomalus*, *Rattus rattus*, *Holochilus sciureus*, *Oecomys speciosus*, *O. trinitatis*, *Oligoryzomys fulvescens*, *Sigmodon alstoni*, *S. hispidus*, *Zygodontomys brevicauda*, and *Proechimys guairae*)	The structure of small-mammal assemblages in agricultural and pastoral areas of the western llanos varied among natural vegetative types, habitat types or land-use categories, and specific agricultural systems. Alteration of the environment for human use has resulted in significant changes in those environments	Western Llanos/Venezuela	1994-1997

Blasdell et al. (2016)	Institut Pasteur du Cambodge, Phnom Penh, Cambodia	To analyze the relationship between habitat structure and the prevalence of hantavirus infection in rodents	Spatial distribution, Land-cover and configuration metrics, SPOT-DEM, Logistic regression (GLM with logit function) and autocorrelation test (Moran's test)	Rodent (*Bandicota indica*, *B. savilei*, *Bandicota sp.*, *Berylmys berdmorei*, *B. bowersi*, *Leopoldamys edwardsi*, *Maxomys surfer*, *Mus caroli*, *M. cervicolor*, *M. cookii*, *Mus sp.*, *Niviventer fulvescens*, *Rattus andamanensis*, *R. argentiventer*, *R. exulans*, *R. sakaretensis*, *R. nitidus*, *R. norvegicus*, and *R. tanezumi*)	The relation between hantavirus seropositivity and agriculture is significant. Generalist rodents tend to benefit from converting land to agriculture.	Buriran, Champasak, Luang Prabang/Thailand e Preai Sihanouk, Mondolkiri/Cambodia	2008-2009
Haredasht et al. (2013)	University of Leuven, Leuven, Belgium	To predict the geographic distribution of the rat population based on spatial climate information, using ecological niche modeling	Land cover fractions based on the CORINE land cover and Ecological Niche Modeling (GARP)	Rodent (*Myodes glareolus*)	The habitat preference of rats is linked to climatic factors, and they prefer habitats with moderate temperatures. Areas habitable by rats in broadleaf forests, coniferous and mixed forests, and natural fields; agricultural areas and artificial areas, to a lesser extent, are habitable by rats	Belgium, Switzerland, West/Germany, North/France, North/Italy, West/Austria	1885-2005
Milholland et al. (2017)	Texas State University, San Marcos, USA	To determine if rodent assemblage structure differed between sylvan and disturbed site and if species richness are different in hantavirus seroprevalence	Spatial autocorrelation (LISA), Student's test, Generalized Linear Mixed Effect Model	Rodent (*Baiomys musculus*, *B. taylori*, *Hodomys alleni*, *Neotoma albigula*, *N.floridana*, *N.mexicana*, *N.micropus*, *Ochrotomys nuttali*, *Onychomys arenicola*, *O. leucogaster*, *Peromyscus attwateri*, *P. boylii*, *P. difficilis*, *P. furvus*, *P. gossypinus*, *P. leucopus*, *P. levipes*, *P. maniculatus*, *P. melonophrys*, *P. mexicanus*, *P. ochraventer*, *P. pectoralis*, *P. species*, *Reithrodontomys fulvencens*, *Oryzomys couesi*,	The increase in species diversity is not necessarily a driver of the decrease in the prevalence of hantavirus, and habitat disturbance has a low predictive value in estimating prevalence.	Texas/ USA and Chihuahua, Hidalgo, Morelos, Tamaulipas, Veracruz/ Mexico	2011-2016

				O. paulustris, *O. species*, *Sigmodon hispidus*, *S. toltecus*, *Chaetodipus hispidus*, *C. penicillatus*, *Dipodomys merriami*, *D. ordii*, *D. spectabilis*, *Liomys irroratus*, *Perognathus flavus*, *P. merriami*, *Mus musculus*, *Rattus rattus*, *Glaucomys volans*, *Spermophillus variegatus*, and *Cryptotis parva*)			
Zeimes et al. (2015)	Université Catholique de Louvain, Louvain-la-Neuve, Belgium	To analyze how landscape factors contribute to the spatial distribution of hantavirus infection in rodent hosts.	Logistic regression on ecoregions, overall niche modeling (environmental, climatic, land use, soil, human distribution variables, and vegetation indices)	HFRS incidence	The highest risk of infection in well-connected with places forests, more intense vegetation activity, low soil water content, mild summers, and cold winters.	Belgium, Finland, France and Netherlands, Norway and Sweden	1950-2012
Goodin et al. (2006)	Kansas State University, Manhattan, USA	To classify the defined ground cover with a mapping resolution of 1 km² and associate it possessing rodents with antibodies to hantavirus	Land cover classification and statistical analysis (relationships between land cover and frequency of seropositivity), Poisson regression analysis	Rodent (*Akodon azarae*, *A. montensis*, *Bibimys chacoensis*, *Graomys griseoflavus*, *Holochilus chacarius*, *Nectomys squamipes*, *Olgoryzomys chacoensis*, *O. fornesi*, *O. nigripes*, and *Oryzomys* sp.)	Land cover plays a role in the prevalence of positive cases. There was a higher prevalence of positive cases in areas of agricultural coverage associated with a more significant presence of seropositive rodents, while	Eastern/Paraguay	1996-1998
Suzán et al. (2006)	University of New Mexico, Alburquerque, USA	To relate the characteristics of the landscape and the distribution of reservoirs on geographic scales	Landscape metrics, classification, and characteristics, spatial model (multiple linear regression model)	Rodent (*Zygodontomys brevicauda*, *Liomys adspersus*, *Oryzomys talamancae* and *Sigmodon hispidus*)	*Z. brevicauda* showed a higher infection rate. Its density may be associated with the specific structure of the vegetation, or it may depend on specific plant species	The Azuero Peninsula, South/Panama	2003

Eisen et al. (2007)	Centers for Disease Control and Prevention, Fort Collins, USA	To create spatial risk models at a precise scale for pest and HPS using an epidemiological approach and identify areas of high risk of exposure for both pathogens	Logistic regression and GIS-based modeling	HPS incidence	Areas that presented the highest risk were those that were close to the ecotone of intermountain basin juniper savannah and Colorado piñon juniper woodland. Areas with higher annual precipitation were more likely to be classified as suitable than relatively drier areas	Southeast/USA	1965-2000
Glass et al. (2007)	Centers for Disease Control and Prevention, Fort Collins, USA	To uncover the places where the cold meets the criteria for refuges and indicate their physical characteristics intending to monitor local rodent populations	MODIS NDVI, land-cover characteristics, DEM, logistic regression analysis (Komolgorov-Smirnov two-sample test and Watson's U2 test), multivariate analyses (Multivariate Poisson regression, Monte Carlo analysis), SARIMA models, ELISA	HPS incidence	Areas with more significant vegetation and natural forest cover were related to higher risk of infected rodents. In contrast, areas with cleared ground or shrublands were less often associated with high risk.	New Mexico/USA	1992-1994
Koch et al. (2007)	Kansas State University, Manhattan, USA	To represent automated land cover classification methods using SR data for studies of infectious disease dynamics	TDI, Land use classification based on objects (IDOS model assuming an Angstrom exponent of 2), FNEA, land-use metrics (GLCM), Cohen's Kappa statistics	HPS incidence	The object-based method achieves 84% overall occurrences, compared to only 43% using the per-pixel method. Producer's and user's occurrences for the object-based map were higher for every class compared to the per-pixel classification. The Kappa statistic was also significantly higher for the object-based classification	Mbaracayú Forest Nature Reserve between Paraíba and Paraná/Brazil	2003

Linard et al. (2007d)	Université Catholique de Louvain, Louvain-la-Neuve, Belgium	To associate environmental and socio-economic factors with the spatial distribution of the incidence of *Puumala* virus disease and *Lyme borreliosis*	Land cover classification based on the CORINE land cover 2000, Statistical distribution analysis and spatial autocorrelation	HFRS incidence	*Puumala* virus infection risk is more prevalent in remote, low-income areas with extensive forests	Belgium	1994 - 2004
Linard et al. (2007b)	Université Catholique de Louvain, Louvain-la-Neuve, Belgium	To understand the cause and effect relationship between the environmental characteristics and prevalence of the Puumala virus in a rat population and associate it with the risk of human transmission	NDVI, landscape configuration, multivariable regressions, logistic model with logit link function and binomial distribution	HFRS incidence e rodent (*Myodes glareolus*)	The proportion of broad-leaved forests is high where urbanization is low. Broad-leave forests are the rodent's favorite habitat; they use small areas and rarely leave the forests. The highest risk of acquiring HFRS is in the ecological habitat of bank rats.	Northern and southern/Belgium	1994-2005
Walsh et al. (2007)	Johns Hopkins Bloomberg School of Public Health, Baltimore, USA	To present the empirical Bayesian approach to estimate the prevalence of Black Creek Canal Virus Infection in trapped hispid cotton rats	Logistic regression, Bayesian models performed using MCMC, landscape structure	Rodent (*Sigmodon hispidus*)	Aggressive males facilitate the transmission of the virus, and older ones have a higher prevalence. Vegetation type and thermal indexes were related to an increased likelihood of infection.	Dade County, Florida/USA	1994
Yan et al. (2007)	State Key Laboratory of Remote Sensing Science, IRSA/CAS, Beijing, People's Republic of China	To identify the relationship between the incidence of HFSR, hantaan, and landscape elements	NDVI, soil type, land use, univariate analysis (χ^2), Odds ratio, multivariate logistic analysis	HFRS incidence	Agricultural activities, timber forest, and orchard land provide food for reservoir rodents, increasing the density of rodents which contributes to the high incidence of HFRS	Rural areas with demographic density <1000/km² of China	1994-1998
Deter et al. (2008)	INRA, UMR CBCP, Campus international de Baillarguet, Montferrier-sur-Lez Cedex, France.	To characterize the dynamics of hantavirus in a rodent community	Logistic regression, spatial and temporal distribution	Rodent (*Myodes glareolus, Clethrionomys glareolus*, and *Microtus arvalis*)	Sex, age, and landscape characteristics play a significant role in the spatial distribution of infections in rats	East/France	2004-2006

Suzán et al. (2008b)	Facultad de Medicina Veterinaria y Zootecnia, Universidad Nacional Autónoma de México, México D.F, México	To determine the correlation between hantavirus infection and the spatial attributes of the landscape	Landscape characteristics and multiple linear regressions to produce spatial model	Rodent (*Oligoryzomys fulvescens* and *Zygodontomys brevicauda*)	Loss of habitat and fragmentation and species diversity loss are altering hantavirus infection dynamics	Azuero Peninsula/Panamá	2003
Suzán et al. (2008a)	The University of New Mexico, Albuquerque, USA	To correlate communities of small mammals in different habitats with different degrees of anthropogenic fragmentation	ANOVA, cluster analyses and Jaccard similarity index	Rodent (*Oligoryzomys fulvescens* and *Zygodontomys brevicauda*)	Rodent hosts of hantavirus were frequent in pasture landscapes, agricultural areas, and border areas of small fragments of continuous forest.	Panama	2001-2002
Zhang et al. (2009)	Beijing Institute of Microbiology and Epidemiology, Beijing, People's Republic of China	To identify landscape factors that contribute to the spatial distribution of hantavirus infection in rodent hosts	Land use classification, spatial elevation model, NDVI, logistic regression model, univariate and multivariate logistic analysis	Rodent (*Rattus norvegicus, Mus musculus, Apodemus agrarius, A. peninsulae, Niviventer confucianus, Sciurotamias davidianus, Cricetus triton,* and *C. rufocanus*)	Rice agriculture and orchards were suitable habitats for host rodents. Infection with SEOV in rodents occurred mainly in the rural-urban fringe of Beijing.	Beijing/China	2005-2007
Heroldová et al. (2010)	Institute of Vertebrate Biology, AS CR, Brno, Czech Republic	To evaluate the prevalence of hantavirus and its relationship to demographic structure, population dynamics, and type of habitat	Population index based on the counts of active burrow entrance per hectare, ELISA hanta agnostic sets and generalized linear models	Rodent (*Apodemus flavicollis, A. sylvaticus, A. uralensis, Mus musculus, Micromys minutus, Myodes glareolus, Microtus arvalis, M. subterraneus*, *Sorex araneus* and *S. minutus*)	There is a direct relationship between the increased prevalence the TUVL antigen and the density of rodents. The highest number of TULV antigen-positive common voles was found in set-aside plots and winter crops, such as rape and winter wheat	Southern Moravia/ Czech Republic	2000-2004
Polop et al. (2010)	Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Buenos Aires, Argentina	To examine spatial heterogeneity and seasonal variation in the predominance of the rodent population	Estimate rodent abundances values as RDI, ELISA test, χ^2 test	Rodent (*Olygoryzomys longicaudatus*, *Akodon olivaceus*, and *A. longipilis*)	There was a greater abundance of *O. longicaudatus* and low rodent richness in an area of anthropogenic activity. The infection has a persistent regional spatial pattern, but the risk to humans in a landscape would be localized	Southern/Argentina	2003-2006

Guivier et al. (2011)	INRA, UMR CBCP, Campus international de Baillarguet, Montferrier-sur-Lez Cedex, France.	To demonstrate how landscape genetics can contribute to understanding hantavirus epidemiology and the influence of landscape characteristics on rodent dynamics and dispersion	landscapes genetics, landscape configuration, the spatial distribution of Puumala virus	Rodent (*Myodes glareolus*)	The immigration of large populations in small continuous isolates could be an essential process for the occurrence of PUUV in fragmented landscapes	French Ardennes/France	2008
Monjeau et al. (2011)	Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Argentina	To investigate the habitat suitability of the four species acknowledged as potential reservoirs of hantavirus using different satellite tools	Landscape structure, NDVI combined with DEM, parallelepiped classification, maximum likelihood classification method	Rodent (*Oligoryzomys longicaudatus*, *Abrothrix longipilis*, *A. olivaceus*, and *Loxodontomys micropus*)	The components of the landscape structure determine the spatial distribution of the hantavirus reservoirs, regardless of the floristic composition of the vegetation patches.	Nahuel Huapi National Park and surrounding areas, Patagonia/Argentina	1984-1997
Viel et al. (2011)	Chrono-Environment, Besancon, France	To determine the space-time distribution of HFRS and evaluate the association between HFRS, incidence, and environmental factors that potentially influence PUUV reservoir abundance	NDVI, cluster of cases, scan test, Bayesian hierarchical models and odds ratios	HFRS incidence	There is an association between the incidence of HFRS in humans and biomass. Coniferous forest was the most significant soil cover variable, but it is not a preferred habitat for rats. Broadleaf forests were not associated with the risk of HFRS	Franche-Comte´, East/France	1999-2008
Wei et al. (2011)	Beijing Institute of Microbiology and Epidemiology, Beijing, People's Republic of China	To identify risk factors and areas affected by hantavirus infections by rodent hosts	NDVI, ecologic niche modeling	HFRS incidence and rodent (*Apodemus agrarius*, *Mus musculus*, *Rattus norvegicus* and *R. rattus*)	Coverage and landscape were associated with the distribution of reservoir rodents. The vegetation index correlated with the quantity and productivity of vegetation and crops, which are the food source of rodents, and also significantly effected the presence of infected rodents	Shandong Province/China	2005-2008

Andreo et al. (2012)	Consejo Nacional de Investigaciones Científicas y Técnicas (CONICET), Buenos Aires, Argentina	To analyze rodent abundance and distribution in the landscape.	Estimation of rodent abundance value density index, comparison between temperature and precipitation using ANOVA, Tukey, variance homogeneity assumptions and Kruskal-Wallis and Mann-Whitney tests	Rodent (*Abrothrix longipilis, Olygoryzomys longicaudatus, Loxodontomys micropus, Abrothrix olivaceus, Eligmodontia morgani, Reithrodon auritus, Phyllotis xanthopygus, Geoxus valdivianus, Chelemys macronyx*, and *Ctenomys* sp.)	There is a risk of cases of hantavirus pulmonary syndrome in humans in forest, scrub, and steppe habitat. Sweetbriar shrublands can play an essential role in HPS dynamics	Northwestern Chubut Province/Argentin a	2007-2009
Barrios et al. (2013b)	Universiteit Leuven, Belgium	To characterize the landscape and associate it with risk of the HFRS.	Land cover classes and metrics, spatial correlation (Moran's I), local Bayesian method	HFRS incidence	Mixed forests are a determining component of the landscape for HFRS. Peri-urban areas can host critical ecological processes that can influence the risk of disease	Belgium	2000-2010
Xiao et al. (2013b)	Junan Normal University, Changsha, China	To analyze the distribution of HFRS and identify risk factors and the relationship between HFSR occurrences and rodent hosts	NDVI and ecological niche modeling (GARP), Markov chain, Monte Carlo approach	HFRS incidence and rodent (*Apodemus agrarius, Mus musculus, Rattus norvegicus*, and *R. flavipectus*)	Cultivated urban areas are sources of food for rodents. The occurrence of HFRS is closely related to biomass. The incidence of HFRS increases with the density of rodents and vice versa. The risk of incidence of HFRS is concentrated in urban and cultivated areas	Changsha/China	2005-2009
Andreo et al. (2014)	Instituto de Altos Estudios Espaciales "Mario Gulich", Centro Espacial Teófilo Tabanera, CONAE, Falda del Carmen, Córdoba, Argentina	To associate the occurrence of hantavirus cases with environmental variables and estimated risk	Landscape classification, GLM with binomial error, MaxEnt algorithm	HPS incidence e rodent (*Oligoryzomys longicaudatus*)	The area with the highest probability of occurrence of HPS is 28% higher in the most sensitive habitat for the occurrence of *O. longicaudatus*. This is also the case with forest, shrubland, shrubby peridomestic settings and sylvan areas of steppe habitats	Southern/Argentin a	1995-2009

Guivier et al. (2014)	INRA, UMR CBCP, Campus international de Baillarguet, Montferrier-sur-Lez Cedex, France.	To analyze the role of landscape characteristics and co-infection on the spatial immune heterogeneity of the wild rat population	Generalized linear model (habitat fragmentation and geographic area)	Rodent (*Myodes glareolus*)	The expression of Tnf-a and Mx2 genes showed a negative correlation with the PUUV virus and the expression of these immune genes in bank voles. Mx2 levels were higher in fragmented forests than in extensive forests. The interactions between landscape characteristics, co-infection, and immune gene expression are narrow and can shape the epidemiology of PUUV	French Ardennes/France	2008
Thoisy et al. (2014)	Laboratoire des Interactions Virus-Hôtes, Institut Pasteur de la Guyane, Cayenne, French Guiana	To identify areas of higher rodent prediction.	Environmental descriptors of trapping sites (vegetation, landscape units, rain, and human disturbance, a maximal entropy-based species distribution model)	Rodent (*Oligoryzomys fulvescens* and *Zygodontomys brevicauda*)	The emergence of hantavirus is associated with the proliferation of rodents locally and when temporarily restricted. These proliferations are caused by small ecological events that the model may not be able to detect.	Amazonian region/French Guiana	2008
Liu et al. (2014)	College of Resources and Environment Science, Junan Normal University, Changsha, China	To create HFRS risk predictions with models using human HFRS records and environmental variables.	Normalized difference vegetation index (NDVI); Ecological Niche Modeling based in GARP; Maximum Entropy Models; Logistic Regression Models; and the DOMAIN model together	HFRS incidence	The highest incidence of HFRS occurs in the spring and winter. Seasonal variations can affect rodent activities. Locations with higher levels of vegetation can provide shelters for breeding, food, and increased activity of rodents		

Li et al. (2014)	Chinese Academy of Sciences, Beijing, China	To characterize the spatiotemporal dynamics of FHSR epidemics and identify the impact of environmental and socio-economic factors for spatiotemporal heterogeneity with the GWR model	Spatial autocorrelation (Moran's global and LISA), GWR model	HFRS incidence	The incidence of HFRS showed a spatiotemporal heterogeneity and was influenced by climatic, landscape, land use, and geographic factors. In recent years, the frequency of HFRS has been affected by human activities.	China	2005-2012
Wu et al. (2014)	Department of Epidemiology and Statistics, Jilin University, Changsha, China	To investigate the spatial and seasonal patterns of HFRS distribution for different epidemic phases and analyze the relationship between HFRS incidence, livestock, climatic factors, and soil cover.	Spatial distribution and Poisson regression analyses.	HFRS incidence	The incidence of HFRS was significantly associated with livestock husbandry and climate factors, particularly with deer cultivation.	Changchun, Northeast/China	1998-2012
Armién et al. (2016)	Department of Research in Emerging and Zoonotic Infectious Diseases, Gorgas Memorial Institute for Health Studies, Panama City, Panama	To characterize the spatiotemporal distribution of the rodent in the landscape	Non-spatial analyses (box plots) and explicit spatial statistical tests (correlograms, SADIE, and LISA)	Rodent (*Zygodontomys brevicauda, Sigmodon hirsutus, Oligoryzomys fulvescens, Liomys adspersus, Mus musculus*, and *Oecomys concolor*)	*Oligoryzomys fulvescens* showed a well-defined spatial pattern over time, causing a change in the aggregation pattern. The hot spot showed a general shifting pattern, and this variation was associated with the seasonality and anthropic pressures that occurred with agricultural activities	Southern coast of Azuero/Panama	2006-2009

Galetti et al. (2015)	Universidade Estadual Paulista (UNESP), São Paulo, Brazil	To evaluate the ecological responses of rodents to the functional extinction of a dominant terrestrial mammal in the Atlantic Forest	Monte Carlo resampling, abundance, and SECR, stable isotope analysis	Rodent (*Akodon montensis*, *Blarinomys breviceps*, *Brucepattersonius soricine*, *Calomys tener*, *Euryoryzomys russatus*, *Juliomys pictipes*, *Nectomys squanipes*, *Oecomys spp.*, *Oligoryzomys nigripes*, *Rhipidomys mastacalis*, *Sooretamys angouya*, *Thaptomys nigrita*, and *Trinomys ihering*i)	Large herbivores can serve to maintain a greater diversity of rodent species, suppressing dominant rodent populations via competition for resources with granivores and interfering with fossorial insectivorous habitat. *A. montensis* and *O. nigripes* increase their abundance in forests	Serra do Mar State Park/ Brazil	Not informed by the author
Magnusson et al. (2015)	Swedish University of Agricultural Sciences, Sweden	To detect core habitats and suitable landscapes where winter survival is good and where the virus survives low bottleneck phases of vole cycles	Landscape structure, characteristics, and metrics, analysis (χ^2), Student's test, generalized linear mixed-effects model with or without binomial errors	Rodent (*Myodes glareolus*)	The occurrence of PUUV-infected rats in the spring was negatively related to the proportion of cut-over forest in the surrounding landscape, suggesting that the change in land use changed the occurrence of rats with positive antibodies.	Sweden	1979-1986
Khalil et al. (2016)	University of Agricultural Sciences, Skogmarkgrand, Sweden	To analyze if the Puumala virus seroprevalence in cached voles is higher than seroprevalence in the population as reflected in trapped voles	Landscape properties and characteristics	Rodent (*Myodes glareolus*)	The higher density of bank vole in isolated forest fragments may have caused seroprevalence patterns	Sweden	2014

Laenen et al. (2016)	Rega Institute for Medical Research, Leuven, Belgium	To investigate the distribution of the *Nova* virus in the population	Spatial-temporal analysis (Bayesian evolutionary inference techniques)	Rodent (*Arvicola amphibius* and *Talpa europaea*)	The *Nova* virus has a high prevalence and wide distribution in Belgium. There has been no decrease in the spread of the Nova Virus across Belgium's main waterways. This heterogeneity of the landscape does not limit the *Nova* virus, which can quickly infect new host animals	Belgium	2013-2015
Ortiz et al. (2017)	CONICET and Universidad Nacional de Córdoba, Córdoba, Argentina	To characterize the populatious genetic structure at different spatial scales	Geographic distribution, indexes for estimating the degree of polymorphism in each population, AMOVA, genetic clusters, modeling approach using partial Mantel tests, landscapes classification, Euclidean geographic distances	Rodent (*Olygoryzomys longicaudatus*)	The dispersion of *O. longicaudatus* seems to be restricted by the combination of landscape features - lakes, rivers, cities, settlements, and roads	Patagonia/ Argentina	2006-2009
Prist et al. (2016)	University of São Paulo, São Paulo, Brazil	Quantify and analyze population risk and its relationship between the incidence of HPS and landscape structure variables, climate and social factors	Bayesian model (climate, variables, structure metrics, social factors)	HPS incidence	The increase in sugarcane plantations was the most critical predictor of hantavirus infection in the Cerrado biomes and the Atlantic Forest	São Paulo/Brazil	1993-2012
Prist et al. (2017a)	University of São Paulo, São Paulo, Brazil	Compare two different proxies and predict the risk of hantavirus	Landscape metrics, Bernoulli distribution, baseline model, spatial analyst multivariate	HPS incidence and rodent (*Oligoryzomys nigripes* and *Necromys lasiurus*)	The areas that had a reservoir with greater abundance was associated with a higher risk of infection	São Paulo/Brazil	1993-2012

Drewes et al. (2017)	Institute for Novel and Emerging Infectious Diseases, Greifswald - Insel, Germany	To associate the rat bank, PUUV records in rodents and humans and beech mast/oak in the forest by districts with and without historical cases of PUUV in humans	Odds ratio and multiple linear regression model	HFRS incidence and rodent (*Myodes glareolus*, *Sorex* spp., *Microtus* spp. And *Apodemus flavicollis*)	The heterogeneous distribution of cases was caused by the abundance of RNA-positive PUUV bank rats, as well as the interaction of beech mast/oak and the proportional coverage of beech mast forest by the district	Germany	2012-2013
Ecke et al. (2017)	University of Agricultural Sciences, Skogmarkgrand, Sweden	To analyze the association between changing boreal landscapes with changes in biodiversity in small mammal communities and understanding the possible effects of changes in the community to increase the risk of PUUV transmission	Landscape structure, diversity metrics with correlation analysis, Wilcoxon matched pairs test, Spearman's rank correlation, first-order polynomial regression in cases of nonlinearity	Rodent (*Myodes glareolus, M. rufocanus*, *Microtus agrestis, Sorex araneus, S. caecutiiens, S. minutus*, *Neomys fodiens*, *Mycopus schisticolor*, and *Apodemus flavicollis*)	Long-term changes in the boreal landscape explain the decrease in biodiversity and changes in the structure of small mammal communities. The decrease in the diversity at small mammals has knock-on effects on the dynamics of infectious diseases among small mammals with potential implications for the transmission of the disease to humans	Northern/Sweden	1971-2013
Khalil et al. (2017)	University of Agricultural Sciences, Skogmarkgrand, Sweden	To identify whether cover and food-rich forests are a determinant for the presence of infected rats and develop a spatial predictive model that assesses the seasonal risk of PUUV	Boosted regression trees	Rodent (*Myodes glareolus*)	Moist and mesic old spruce forest, with abundant cover such as large holes and bilberry shrubs that, also provide food, were most likely to harbor infected bank voles	Northwestern/Sweden	2003-2015

Lazo-Cancino et al. (2017)	Universidad de Concepción, Concepción, Chile	To evaluate the effects of landscape fragmentation and matrix structure on the genetic diversity and genetic structure of rodents	Landscape structure, baseline model, clusters, landscape matrix (IBD, LCP analysis, IBR)	Rodent (*Oligoryzomys longicaudatus*)	*O. longicaudatus* moved with preference through young and all growth native forest, and grassland with arborescent shrublands to connect patch pairs. Dispersion through ideal routes and their associated habitats increases the likelihood of finding resources and escaping predation	Curirruca,Panguipulli/Chile	2007
Prist et al. (2017b)	University of São Paulo, São Paulo, Brazil	To verify how cane expansion and temperature changes under two climate scenarios can influence HCPS risk	Landscape composition, configuration metrics, Bernoulli distribution, baseline model	HCPS incidence	Conversion of native vegetation to agriculture, in the case of sugar cane, can alter the abundance of generalist rodent species that are reservoir hosts for HPS	São Paulo/Brazil	1993-2012
Yu et al. (2017)	Shaanxi Provincial Centre for Disease Control and Prevention, China	To analyze the relationships between A. agrarius population dynamics and environmental conditions of land cultivation	NDVI, LAI, fAPAR, net photosynthesis, PsnNet, GPP, surface temperature, Pearson's correlation, SEM, normalized χ^2 test	HFRS incidence and rodent (*Apodemus agrarius*)	There is a higher correlation between the population density of *A.* *agrarius* and PsnNet than between the population density of *A. agrarius* and NDVI. Primary productivity can influence rodent demographics with a time lag	China	2005-2012
Cunze et al. (2018)	Goethe University Frankfurt, Frankfurt, Germany	To create spatial and temporal patterns of human hantavirus infection caused by PUUV	Spatial, temporal and seasonal patterns, landscape structure, GLM, EG, correlation analysis	HFRS incidence and rodent (*Myodes glareolus*)	The areas with a higher risk of human infections by PUUV are concentrated in areas with high forest cover (spatial pattern); in the years following mast years (temporal pattern) and in early summer (seasonal pattern)	Germany	2001-2015

He et al. (2018)	Zhejiang University, Zhoushan, China	To model the variability of HFRS cases between HFRS incidence and environmental factors.	NDVI, SARIMA with exogenous variables model	HFRS incidence	Current HFRS cases are closely related to previous HFRS cases. The transmission of HFRS is non-stationary and indicates local characteristics. NDVI is closely related to HFRS transmission	China	[illegible]
Santos et al. (2018)	Instituto Oswaldo Cruz/FIOCRUZ, Brazil	To map the occurrence of the rodent and its potential as a reservoir of the hantavirus Araraquara	Niche model (MaxEnt model), species distribution model	Rodent (*Necromys lasiurus*)	The replacement of the original open-floor Atlantic Forest may be favorable for *N. lasiurus*. The distribution of *N. lasiurus* is restricted to the highlands, Northern, and Coastal lowlands regions, with high densities being observed only in the region of the REBIO Poço das Antas	Rio de Janeiro/Brazil	2016-2017
Xiao et al. (2018)	Junan Normal University, Changsha, China	To investigate how the community composition of reservoirs influences the risk of HFRS across different landscapes	Land cover classification and statistical analysis (R matrix)	HFRS incidence and rodent (*Apodemus agrarius, Mus musculus, Rattus norvegicus*, and *R. flavipectus*)	The highest risk of HFRS infection was in urban areas for Mus musculus, while for other rodents in areas of cultivated land	Shaoyang, Loudi/China	2006-2013
Laenen et al. (2019)	Rega Institute for Medical Research, Leuven, Belgium	To evaluate the impact of several landscape factors on the rate of PUUV spread	Landscape configuration and Bayesian continuous phytogeographic method	Rodent (*Myodes glareolus*)	Land-use type defines the dispersal dynamics of PUUV, with forests facilitating and croplands impeding virus spread	Belgium	1984-1986 and 2006-2016

Muylaert et al. (2019)	Universidade Estadual Paulista (UNESP), Rio Claro, Brazil	To investigate how patterns of landscape structure, climate, and biodiversity within mammalian communities influence potential hantavirus hosts	GWR models	Rodent (*Necromys lasiurus, Oligoryzomys nigripes, O. moojeni, O. flavescens, O. fornesi, Calomys callidus, C. laucha, C. tener, C. callosus, Akodon paranaensis, A. cursor, A. azarae, A. serrensis* and *Oxymycterus nasutus*)	1. The quantities at the level of the cane landscape and tree plantations positively influence the genotype of potentially pathogenic hantavirus hosts. 2. There is a positive global influence of habitat diversity and rainfall in the proportion of pathogenic hosts in the community. 3. The reservoir proportions of hantavirus in rodent communities are positively influenced by the number of local species in most of the Atlantic Forest	Atlantic Forest/Brazil	Not informed by the author
Vadell et al. (2019)	Universidad de San Martín, San Martín, Argentina	To analyze the risk of HPS in an endemic province	Linear models (climate, vegetation, landscape, reservoir, population, community)	HPS incidence and rodent (*Olygoryzomys flavescens, O. nigripes, Holochilus chacarius, Scapteromys aquatics, Cavia aperea, Rattus* spp.and *Mus musculus*)	The risk of occurrence of HPS increased with tree cover and decreased with distance from rivers	Entre Ríos Province/ Argentina	2004-2015

Acronyms: AMOVA = Analysis of Molecular Variance; ANOVA = Analysis of Variance; DEM = Digital elevation model; ELISA = Enzyme-Linked Immunosorbent Assay; fAPAR = Fraction of Photosynthetically Active Radiation; FNEA = Fractal Net Evolution Approach; GARP = Genetic Algorithm for Rule-Set Prediction; GIS = Geographical Information System; GLCM = Grey-Level Co-Occurrence Matrix; GLM = Generalized Linear Model; GPP = Gross Primary Productivity; GWR = Geographical weighted regression; HFRS = Hemorrhagic Fever with Renal Syndrome; HPS = Hantavirus Pulmonary Syndrome; IBD = Isolation by Distance Test; IBR = Isolation by Resistance; LAI = Leaf Area Index; LCP = Last-Cost Path; LISA = Local Indicators of Spatial Association; MaxEnt = Maximum Entropy; MCMC = Markov Chain Monte Carlo; MODIS = Moderate Resolution Imaging Spectroradiometer; NDVI = Normalized Difference Vegetation Index; PUUV = Puumala virus; RDI = Relative Density Index; SARIMA = Seasonal Autoregressive Integrated Moving Average; SECR = Spatially Explicit Capture-Recapture; SEM = Structure Equation Modeling; SR = Remote sensing; TDI = Transformed Divergence Index.

CAPÍTULO 3 - INFLUENCE OF ENVIRONMENTAL FACTORS ON THE INCIDENCE OF HANTAVIROSIS IN THE FEDERAL DISTRICT, BRAZIL

Abstract: Hantavirus is highly lethal. Different causes are associated with the occurrence or increase of disease outbreaks. Among other factors, land use and vegetation cover significantly influence the potential distribution of hosts. For this reason, studies that address the link between land cover and hantavirus have been increasing in the field of landscape epidemiology. However, there are gaps in research about relationship between hantavirus and landscape configuration, given that most studies are aimed at people affected by this disease. To fill these gaps, the present study explains how environmental factors contribute to the incidence of Hantavirus in the Federal District at the regional and local levels. For this, a spatial analysis of the probable sites of infection from 2007 to 2017 in the Geographic Information System (GIS). Was conduced we made use at the Global and local Moran Index, Getis-Ord Gi *, and by the environmental modeling in the EGO Dynamics to indicate the areas of highest risk and the environmental variables that most predispose the disease in the DF region. In DF, the Global Moran Index obtained was 0.28. The analysis of Hotspots using the Getis-Ord Gi * algorithm pointed out that the Administrative Regions (AR) of Paranoá, Planaltina, and São Sebastião are critical regions for the occurrence of Hantavirose. In the calculations of weights and evidence, the altitude, categories of transition, land use, and geomorphology were the ones that showed the greatest likehood for the occurrence of the disease. The variables examined by Crammer's criterion showed that the variables of altitude and average temperature show a correlation of 73% among themselves, which shows a significant relationship. This study provides information on the effects of landscape and climatic factors on the incidence of Hantavirus. The information can be used to better understand how Hantavirus Cardiopulmonary Syndrome (HCPS) behaves in the Federal District and provides subsidies for the guidance of monitoring strategies and epidemiological surveillance in public health.

Keywords: Hantavirus, zoonoses, rodent, land use, landscape, geospatial analysis, systematic review, environmental modelin

3.1 Introduction

The hantavirus (family *Bunyaviridae*) causes diseases in humans, as is the case of hemorrhagic fever due to renal syndrome (HFRS) and hantavirus pulmonary and cardiovascular syndrome (HPCS). HFRS occurs more frequent by Eurasia and is caused by at least four antigenically and genetically different hantaviruses classified by serotypes: *Hantaan* (HTNV), *Seoul* (SEOV), *Dobrava* / *Belgrade* (DOBV), and *Puumala* (PUUV) (Schmaljohn et al ., 1985). Hantavirus pulmonary syndrome (HPS), on the other hand, has a higher incidence in the Americas and is associated with sigmodontine, such as the *Sin Nombre virus* (SNV), in North America, and the *Andes virus* (ANDV), in South America (Nichol et al., 1993). Both are very lethal and little-studied diseases (Barrios et al., 2013). Hantavirus infections are a growing concern in terms of public health, with an incidence of approximately 30,000 cases annually in humans and a growing distribution worldwide (Watson et al. 2014). They are of great importance due to their severity, high lethality rate - up to 15% (HFRS) (Avsic-Zupanc et al., 2019), and 50% (HPS) - and relatively unknown natural history (Jonsson et al., 2010).

The first outbreak of HFRS occurred in the 1950s among Americans when soldiers in combat in the Korean War had a high level of contact between rodents and others soldiers who resided outdoors (Sheedy et al., 1954). HPS was first recognized in 1993 in the Four Corners region of the United States, and during from the second half of 1993, in South America (Nichol et al., 1993). In Brazil, in the state of São Paulo (Juquitiba) in 1993 and the Federal District in 2004 had their first cases of the disease. In Brazil, outbreaks in São Paulo and the Federal District were due to two factors; the rat phenomenon and the deforestation of rats’ native habitats (Ferreira, 2003).

The pressures of anthropogenic origin on the landscape cause the introduction of new pathogens into native ecosystems and reduces of resilience of these environments. Because of this, changes of anthropogenic origin are somehow related to specific zoonoses such as hantavirus. The epidemiological landscape proposed by Pavlovsky (1966) is based on the understanding of how the disease occurs in spatial patterns that derive from underlying changes in the characteristics of space and in the relevant factors that influence the dynamics and distribution of the populations of hosts, pathogens, and vectors. These patterns can be represented on maps (Ostfeld et al., 2005).

For Goodin et al. (2006), efforts to detect outbreaks of the disease should focus on disturbed human landscape regions, primarily agricultural areas. Once identified, hotspots should be analyzed at a higher resolution using remote sensing tools or perhaps by environmental surveillance at ground level. Remote sensing (RS) and geographic information systems (GIS) are geospatial analysis technologies that provide tools for analyzing data from epidemiological landscape studies. These can be related to research on transmitted diseases by vectors and zoonoses with environmental cofactors (Beck et al., 2000). The analysis of land use and cover is usual in RS, as well as in landscape epidemiology. This information converges to identify and map the hosts' vectors and habitats (Kazmi and Usery, 2001).

According to Linard et al. (2007), the spatial distribution of the hantavirus (*Puumala* virus) in Belgium was explained by the combination of environmental and socioeconomic factors. Land use was used as a variable for the hosts' spatial distribution and determined the prevalence of the disease, controlling the degree of exposure of people in the contact with the hosts.

To understand how the hantavirus behaves in the Federal District, it is useful to study aspects of landscape analysis. These variables can provide guidance for monitoring strategies and epidemiological surveillance in public health, given that the exploitation of natural resources without planning and without investigating the presence of pathogens leads the population of the habitat to adjust to new hosts and new environmental conditions.

Because of the above, the present study aims to spatially analyze the cases of hantavirus in the Federal District between 2004 to 2017 to verify the dependence and spatial correlation of these occurrences and to statistically assess the influence of land-use variables. The intention is to generate information on critical points that may be the center of future epidemics, in addition to filling possible gaps in knowledge about how the disease behaves in the Federal District.

3.1 Material and Methods

3.1.1 Study area

The Federal District is part of the Central Plateau in the Center-West Region of Brazil, extends between the parallels 15 ° 47 'south latitude and 47 ° 56' west longitude and occupies an area of 5,779 km² (Codeplan, 2017).

The topography is flat to hilly, with altitudes ranging from approximately 950 m to approximately 1,400 m. Predominant forms of relief evolved by the erosion process, characterized by plateaus (Codeplan, 2017).

In this region are the headwaters of the tributaries of three of the largest Brazilian rivers - the Maranhão River (tributary of the Tocantins River), the Rio Preto (tributary of the São Francisco) and the São Bartolomeu and Descoberto rivers (tributaries of the Paraná River) (Codeplan , 2017).

The region's climate is humid tropical savanna with a dry winter, defined by intense climatic seasonality (dry winters and rainy summers), with an average annual rainfall of 1,500 mm and an average annual temperature between 20 ° C and 22 ° C (Silva et al. , 2008). The forest, savannas, and countryside formations of its vegetation are verified (Ribeiro and Walter, 2008).

The Federal District is composed of 31 Administrative Regions (AR), of which only 19 were recognized according to the 2010 IBGE census (Figure 1). The DF has an estimated population of 2,974,703 inhabitants (IBGE, 2018) and a demographic density of 444.66 inhab./km² (IBGE, 2016).

The population arrangement of the Federal District has 45.5% continuity of the urbanized center. The urban morphology is dispersed and not very dense, combined with still-strong population growth. The urban agglomeration of Brasília has excellent potential for urban growth (Codeplan, 2018).

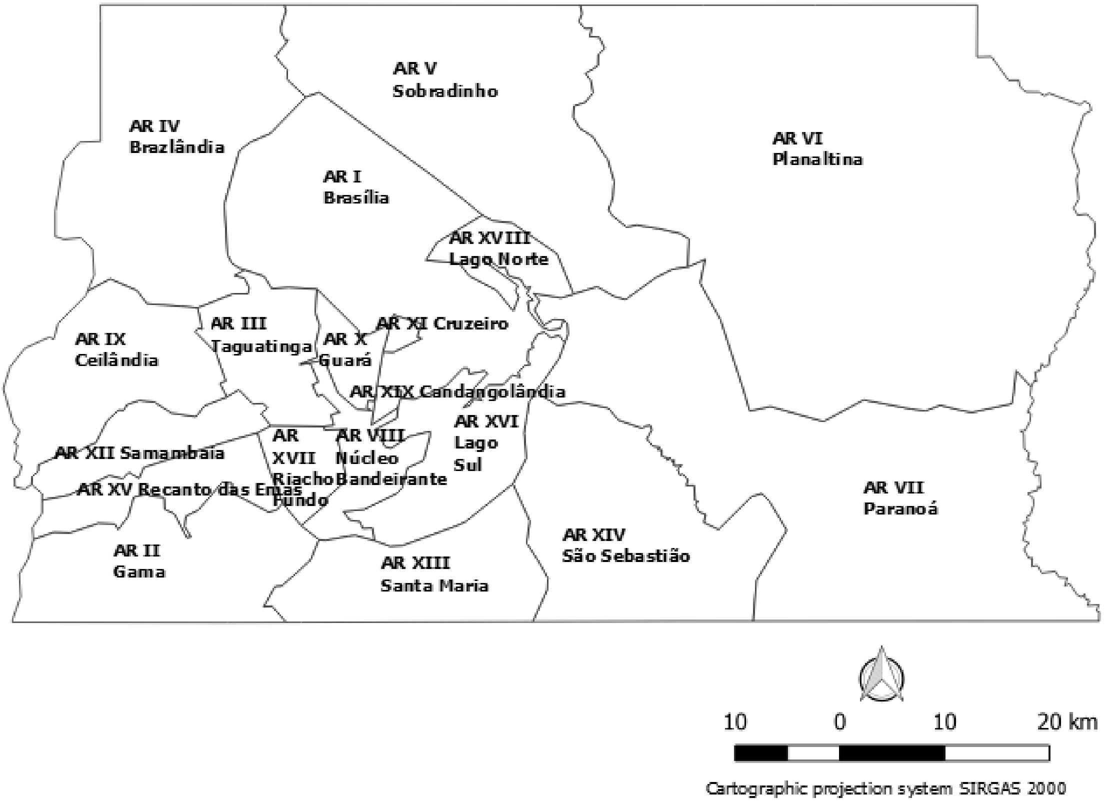

Figure 1: Administrative Regions of the Federal District, according to the 2010 census of the Brazilian Institute of Statistics and Geography (IBGE).

3.1.1.1 Spatialization of indigenous confirmed cases of Hantavirus for spatial statistics

The geographic coordinates (latitude and longitude) of the 43 home addresses of confirmed and indigenous cases came from the Information System for Notifiable Diseases records of the Federal District Environmental Surveillance System from 2007 to 2017. They were obtained using the free software Google Earth to generate a map of cases of Hantavirus in the territory. The cases used in the study were classified as indigenous when the probable infection sites (PIS) were located in the DF area. For the digital mapping elaboration, the PIS data superimposed of the Administrative Regions of the Federal District map were used according to the sense of 2010, constant in the bases of the Brazilian Institute of Statistics and Geography (IBGE). The Land Use Coverage map elaboration for the year 2016 was based on the Ministry of the Environment.

3.1.1.1.1 Spatial statistics

In spatial statistics, we use the digital mapping of the data from the overlapping residential addresses in the IBGE bases and the use and occupation of the Federal district's land. The first analysis we performed was Moran's Global Index, which demonstrated spatial autocorrelation and observed spatial data similarity in addition to quantitatively investigating the characteristics of spatial distribution in spatial units (MORAN, 1950). Moran's global index aimed to estimate spatial dependence, showing how the values are correlated in space. This index ranges from -1 to +1, indicating a positive correlation when the value is > 0 in a statistically significant level. Negative correlations are treated in a similar way when the index is <0 (Marques et al., 2010).

The Moran local spatial association indicator (LISA MAP) analyzed the degree of spatial dependence from a second-order estimate, a type of spatial covariance between the polygons. The local Moran coefficient GI represents four different modes of spatial grouping: High-High (HH) (hotspots), Low-Low (LL) (colds), High-Low (HL) and Low-High (LH). The spatial autocorrelation analysis was performed using the univariate Moran's tool (local) using ArcGis software. The significance level was set at $p < 0.05$ and a 95% confidence level with the number of simulations at 999. While the Moran global index indicated the level of spatial interdependence between all polygons studied, Moran's local index calculated the covariance between a given polygon and a specific neighborhood defined as a function of a distance d (Anselin, 1995).

The Getis-Ord Gi * algorithm (Getis, 1995) is a spatial indicator that allows cluster studies to take into account the predicted statistics of a polygon and its neighbors compared to the average of all checks. Getis-Ord Gi is a local data indicator for which it is feasible to calculate the degree of significance for values that are below or above the expected average for a given variable.

For spatial statistics, we used the digital mapping generated from the georeferenced point of the residences of the confirmed hantavirose cases to the nearest location of the conservation unit. These distances were calculated for the analyzes. For elaborating the cartograms layouts, we adopted techniques: neighborhood matrix, calculation of the spatial correlation of Moran, and the Getis-Ord Gi of the ArcGis software. At the end of this stage, we generate the global spatial association (Moran index) and local (LISA MAP), considering each variable individually.

3.1.1.2. Spatialization of indigenous confirmed cases of hantavirus for environmental modeling

The geographical coordinates (latitude and longitude) of the 108 probable infection sites (PIS) of the confirmed and indigenous cases in the Federal District, came from the Information System for Notifiable Diseases records of the Federal District Environmental Surveillance System from the years 2004 to 2017. They were obtained through the free software Google Earth for the spatialization of Hantavirus cases in the territory. For the EGO Dynamics model, we used the coordinates of the PIS overlaid on the Federal District map, contained in the Geoportal of the Federal District.

3.1.1.2.1 Environmental modeling

The models generate a global picture of the totality of the systems and determine the degree of knowledge about the components and interactions between the elements and interactive functioning between the system's inputs and outputs (Christofoletti, 1999). The spatially explicit model is based on a two-dimensional representation of the initial landscape configuration, the function of the change in land cover composed of its quantification and allocation and also of the output map, corresponding to the simulated landscape for the analyzed event (Soares -Filho et al., 2007). Dinâmica EGO is free software that develops space-time models, in which geographic surface changes respond to a set of factors in time, which proves to be an adequate and essential tool for environmental modeling, as it makes possible the reproduction of phenomena (Soares-Filho et al., 2009).

According to Lima (2013), in modeling processing, the first step for future analysis is the identification of the study transition. From the maps of the observed landscape, the software quantifies the land cover changes through estimates, based on Markovian chains, converting it into a transition matrix comprising the change rates to be used in the simulation. The transition matrix calculation used the time interval of 14 years between the beginning of the disease in 2004 and 2017.

In the calibration process, tests are carried out on the system to identify, in a given period, parameters that better define the model's fit and the reality observed on the map. Based on this, the Bayes conditional probability theorem (Bonham-Carter, 1994) applies the probabilities conditioned to these data to employ the correlation between the presence/absence of change (Lima et al., 2013).

For this study, we used the Dynamic Software EGO as a platform for simulating the land cover model to observe the variables that most contributed to the occurrence of hantavirus in the Federal District between 2004 and 2017 to simulate the probability of occurrence in the areas of the Federal District. The representation of the database set was the Federal District region. We employed nine variables (Table 01) in environmental modeling, include: altimetry, drainage network, highways, conservation units, geomorphology, LPIs from 2004 to 2017, the transition from land use, average precipitation and average temperature. These maps represent the explanatory variables. For data on the drainage network, urban area, highways, conservation units, and PIS, we generated maps of Euclidean distances to understand the relevance of these factors in terms of proximity.

Table 01: Database used in the land cover change model.

Database	Variable	Type	Format	Year	Source
Altimetry	Altitude	Static	Continuous	2000	MAPA
Drainage network	Distance from a drainage network	Static	Continuous	2017	SIEG
Highways and roads	Distance from highways and roads	Dynamic	Continuous	2017	Open Street Map
Federal District conservation áreas	Distance from natural habitats	Static	Contínuous	2017	IBRAM
Geomorphology	Soils	Static	Categorical	2006	SIEG
Probable infection sites	Distance from probable infection sites from 2004 until 2017	Static	Contínuous	2004 from 2017	DIVAL e DIVEP Federal District
Land-use transition	Vegetation transition	Static	Categorical	2001 from 2016	MAPBIOMAS
Average rainfall	Average rainfall	Static	Contínuous	1970 from 2000	WorldClim
Average temperature	Average temperature	Static	Continuous	1970 from 2000	WorldClim

We analyzed the spatial association between the explanatory variable with Hantavirus's presence, using the method of weights and evidence. In this phase, we used the initial disease (2) and the final disease (1) as input data considering the absence of the disease and the incidence sites as the final landscape. The variables were weighted. Each variable received a favorable weight (W +) or not favorable (W-) to the probable site of infection. This allowed the calculation of the probability of hantavirus occurrence in the Federal District as well as identifying which factors most influence the proliferation of the disease.

The distributions of the weights of evidence by categorical variable were as follows: Land use and cover transition: 03 - Forest Formation, 04 - Savanna Formation, 12 - Country Formation, 15 - Pasture, 33 - River, Lake and Ocean, 300 - Mining, 303 - Forest Formation for Forest Formation, 304 - Forest Formation for Savanic Formation, 309 - Forest Formation for Savanic Formation, 312 - Forest Formation for Campestre Formation, 315 - Forest Formation for Pasture, 319 - Forest Formation for Annual and Perennial Culture , 324 - Forest Formation for Urban Infrastructure, 325 - Forest Formation for Another Non-

Vegetated Area, 330 - Forest Formation for Mining, 333 - Forest Formation for River, Lake and Ocean, 400 - Savanica Formation, 403 - Savanica Formation for Forest Formation, 404 - Savanic Formation for Savanic Formation, 409 - Savanic Formation for Planted Forest, 412 - Savanic Formation for Campestre Formation, 415 - Savanic Formation for Pasture, 419 - Savanic Formation for Annual and Perennial Culture, 424 - Savanic Formation for Urban Infrastructure, 425 - Savanic Formation for Another Non-Vegetated Area, 430 - Savanic Formation for Mining, 433 - River, Lake and Ocean, 903 - Planted Forest for Forest Formation, 904 - Planted Forest for Savanna Formation, 909 - Planted Forest for Planted Forest, 912 - Planted Forest for Country Formation, 915 - Planted Forest for Pasture, 919 - Planted Forest for Annual and Perennial Culture, 924 - Planted Forest for Urban Infrastructure, 1200 - Country Formation, 1203 - Country Formation for Forest Formation, 1204 - Country Formation for Savanic Formation, 1209 - Country Formation for Planted Forest, 1212 - Country Formation for Country Formation, 1215 - Country Formation for Pasture, 1219 - Country Formation for Annual and Perennial Culture, 1224 - Country Training for Urban Infrastructure, 1225 - Country Formation for Another Non-Vegetated Area, 1230 - Country Formation for Mining, 1233 - River, Lake and Ocean, 1500 - Pasture, 1503 - Pasture for Forest Formation, 1504 - Pasture for Savanic Formation, 1509 - Pasture for Planted Forest, 1512 - Pasture for Country Formation, 1515 - Pasture for Pasture, 1519 - Pasture for Annual and Perennial Culture, 1524 - Pasture for Urban Infrastructure, 1525 - Pasture for Other Non-Vegetated Area, 1530 - Pasture for Mining, 1533 - Pasture for River, Lake and Ocean, 1903 - Annual and Perennial Culture for Forest Formation, 1904 - Annual and Perennial Culture for Savanna Formation, 1912 - Annual and Perennial Culture for Countryside Formation, 1915 - Annual and Perennial Culture for Pasture, 1919 - Annual and Perennial Culture for Annual and Perennial Culture, 1924 - Annual and Perennial Culture for Urban Infrastructure, 1925 - Annual and Perennial Culture for Another Non-Vegetated Area, 1933 - Annual and Perennial Culture for River, Lake and Ocean, 2403 - Urban Infrastructure for Forest Formation, 2409 - Urban Infrastructure for Planted Forest, 2412 - Urban Infrastructure for Rural Training, 2415 - Urban Infrastructure for Pasture, 2419 - Urban Infrastructure for Annual and Perennial Culture, 2424 - Urban Infrastructure for Urban Infrastructure, 2425 - Infrastructure Urban to Another Non-Vegetated Area, 2430 - Urban Infrastructure for Mining, 2433 - Urban Infrastructure for River, Lake and Ocean, 2500 - Another Non-Vegetated Area, 2503 - Another Non-Vegetated Area for Forest Formation, 2504 - Another Non-Vegetated Area for Formation Savânica, 2509 - Another non-vegetated area for planted forest, 2512 - Another Non-Vegetable Area for Rural

Training, 2515 - Another Non-Vegetable Area for Pasture, 2519 - Another Non-Vegetable Area for Annual and Perennial Culture, 2524 - Another Non-Vegetable Area for Urban Infrastructure, 2525 - Another Non-Vegetable Area for Another Area Non-Vegetated Area, 2530 - Other Non-Vegetated Area for Mining, 2533 - Other Non-Vegetated Area for River, Lake and Ocean, 3003 - Mining for Forest Formation, 3004 - Mining for Savanna Formation, 3012 - Mining for Contry Formation, 3015 - Mining for Pastagem, 3024 - Mining for Urban Infrastructure, 3025 - Mining for Other Non-Vegetated Area, 3030 - Mining for Mining, 3033 - Mining for River, Lake and Ocean, 3300 - River, Lake and Ocean, 3303 - River, Lake and Ocean for Planted Forest, 3312 - River, Lake and Ocean for Countryside Formation, 3315 - River, Lake and Ocean for Pasture, 3319 - River, Lake and Ocean for Annual and Perennial Culture, 3324 - River, Lake and Ocean for Urban Infrastructure, 3325 - Rio, L ago and Ocean to Another Non-Vegetated Area, 3330 - River, Lake and Ocean for Mining, 3333 - River, Lake and Ocean to River, Lake and Ocean.

Distribution for the geomorphological categories: 7 - Alluvial Strip (FA), 15 - Water mass, 27 - Fluvial Plain with Meandriform Pattern (PFm), 34 - Regional Planing Surface IIA with dimensions between 900 and 1100 m, with strong dissection , developed on Precambrian rocks (SRAIIA (fo)), 35 - Regional Planing Surface IIA with elevations between 900 and 1100 m, with weak dissection, developed on Precambrian rocks (SRAIIA (fr)), 36 - Superficie Regional of Planing IIA with elevations between 900 and 1100 m, with medium dissection, developed on Precambrian rocks (SRAIIA (m)), 65 - Receding Erosion Zone with very strong dissection, related to the generation of SRAIIA and erosion dominant to SRAIIA: Associated with hills and with Strong Structural Control (ZER-SRAIIA-MC-FCE / IIA (mfo)), 92 - Retreating erosion zone with strong dissection, dominating erosion (SRAIIA ZER / IIA (fo))..

3.2 Results

3.2.1 Spatial Analyses

In the years 2007 to 2018, 838 Federal District hospitals visits were made due to suspected contamination by hantavirus, of which 680 cases were discarded, 95 undetermined, and only 63 confirmed. In the Federal District, 43 indigenous cases of hantavirus were confirmed. The Administrative Regions of São Sebastião (8 cases), Planaltina (7 cases), and Paranoá (6 cases), presented the highest number of occurrences.

The Administrative Regions with the highest incidence rate for every 100,000 inhabitants were: Paranoá (13.34), Fercal (12.07) and Varjão (11.83).

The majority of human hantavirus cases are located less than 1,000 m from probable habitat (Occupation in Country Areas, Country Vegetation, Pasture with Management, Silviculture, Forest Vegetation, Public Forests and Permanent Conservation Units) of wild rodents (virus"reservoirs") (Figure 2).

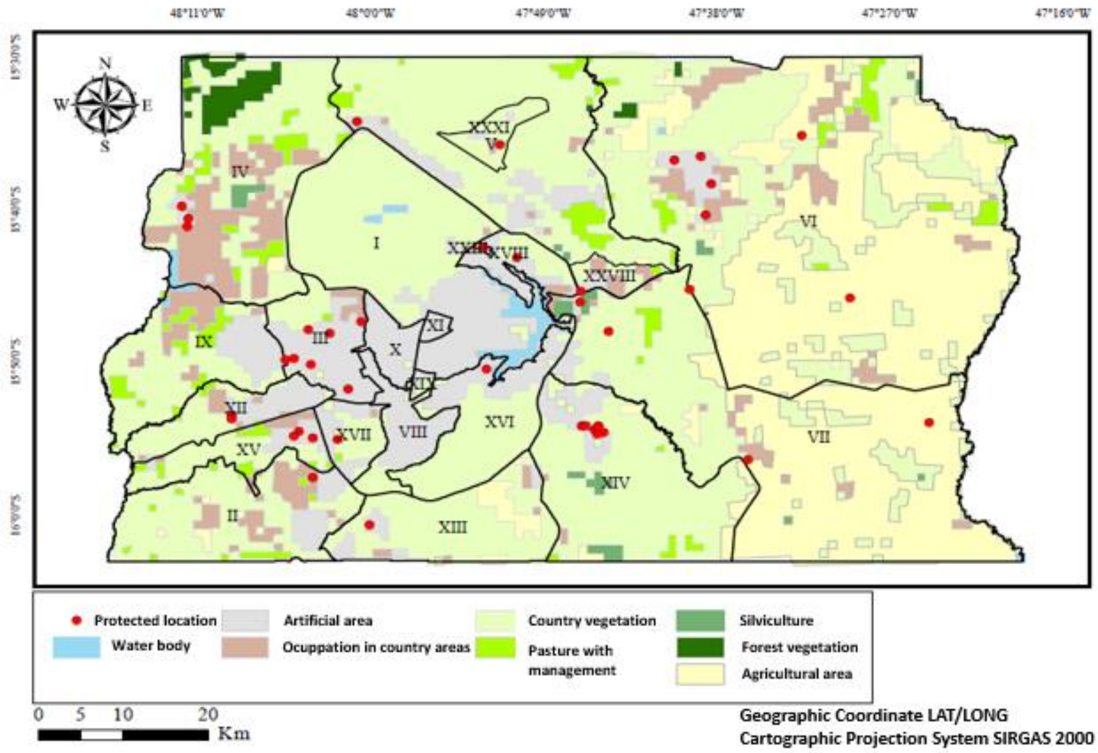

Figura 02: Residencies of cases confirmed by Hantavirus and classes of land use and occupation for the years 2007 to 2017 in the Administrative Regions (Roman numbers) in the Federal District, Brazil.

According to the Moran Index, given the z score of 4.93, there is less than 1% probability that this high cluster pattern is random. This gaves high confidence that there is positive autocorrelation between the observed distance values; that is, the proximity of the infected patient's residence with the wild rodent habitat is related to the contraction of the disease (figure 03).

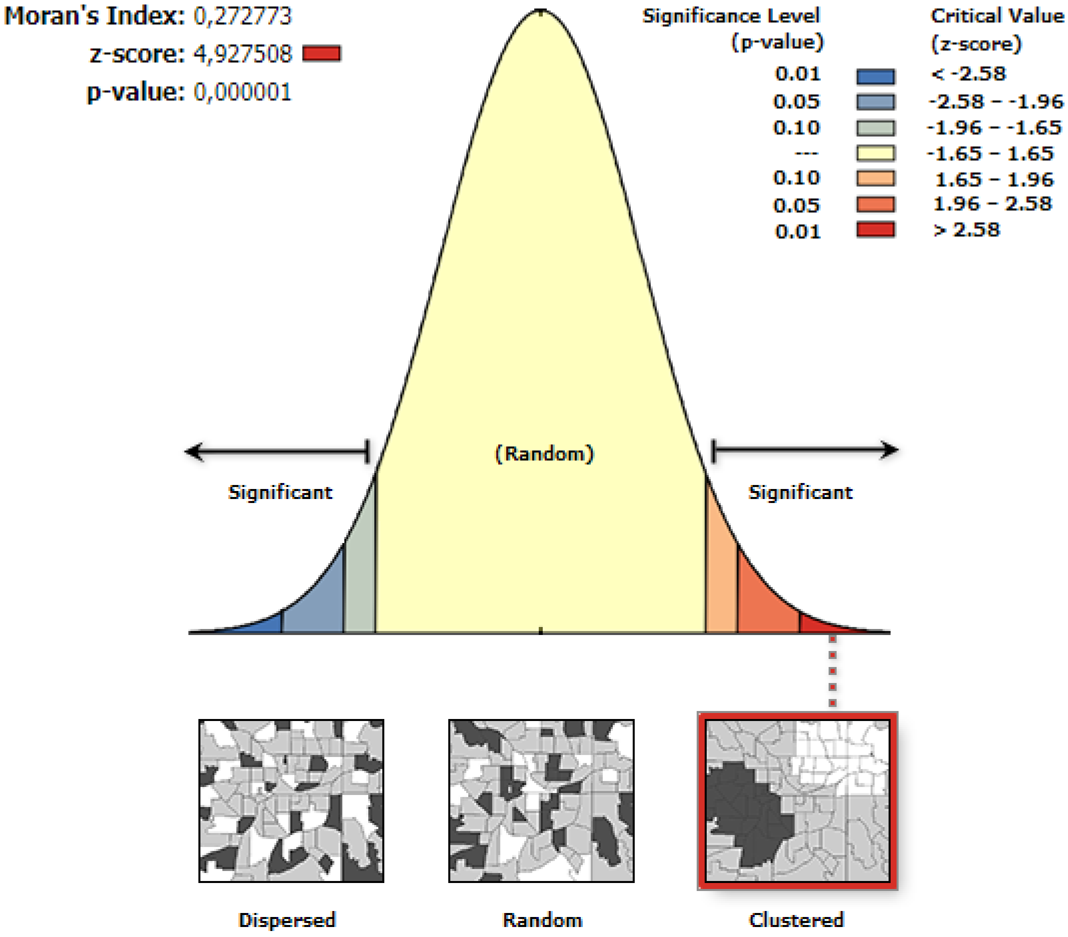

Figura 3: Moran's Index

According to the GI coefficient, given the z score of 4.06, there is less than a 1% probability that this high cluster pattern is random. Which means to say with high confidence that there is positive autocorrelation between the observed distance values; that is, the proximity of the infected patient's residence with the wild rodent habitat is related to the contraction of the disease (figure 04).

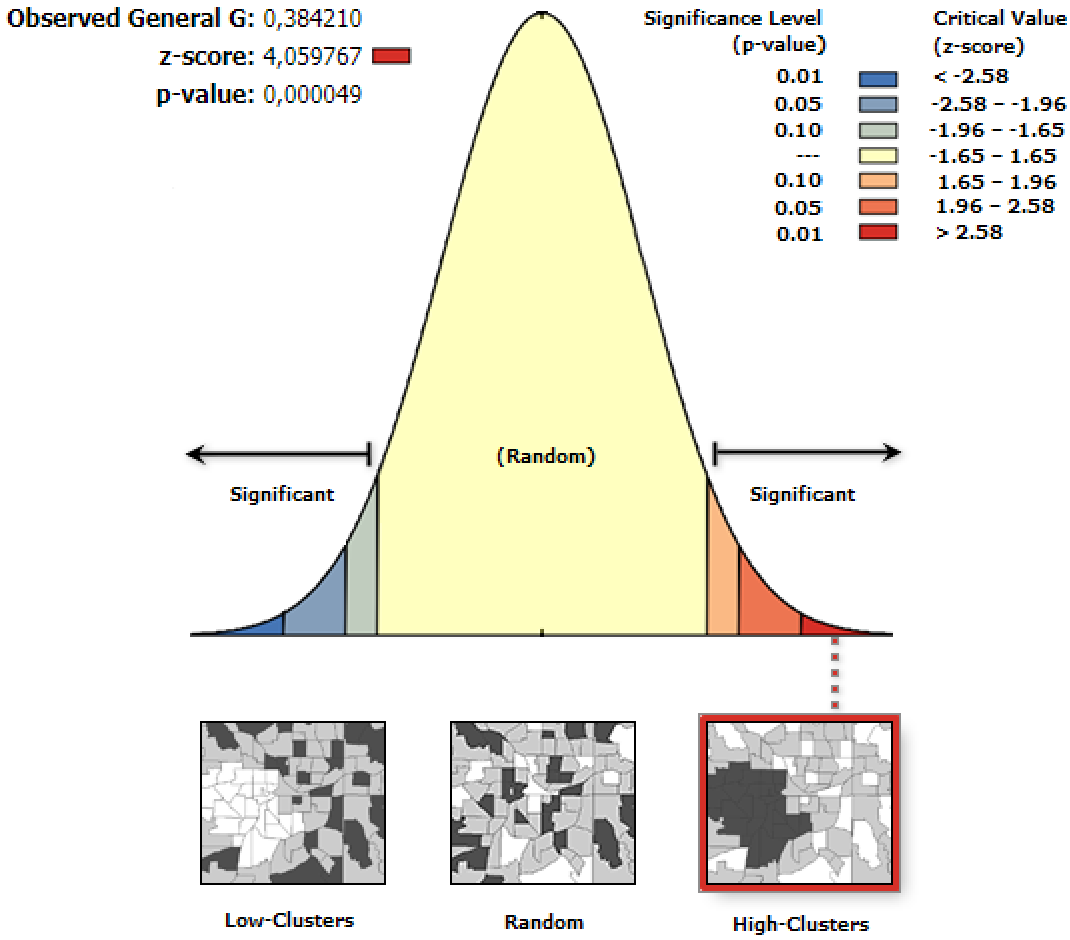

Figure 04: GI coefficient

In AR VII (Paranoá), the contagious values are high, above average and are surrounded by values in other regions that are also above the average. Thus, possibly the contagion in the referred AR influences the neighboring areas (AR). In Taguatinga (ARIII), it can be inferred that the contagious values are high, above average, but are surrounded by values below the number of infected in the neighboring regions (figure 05).

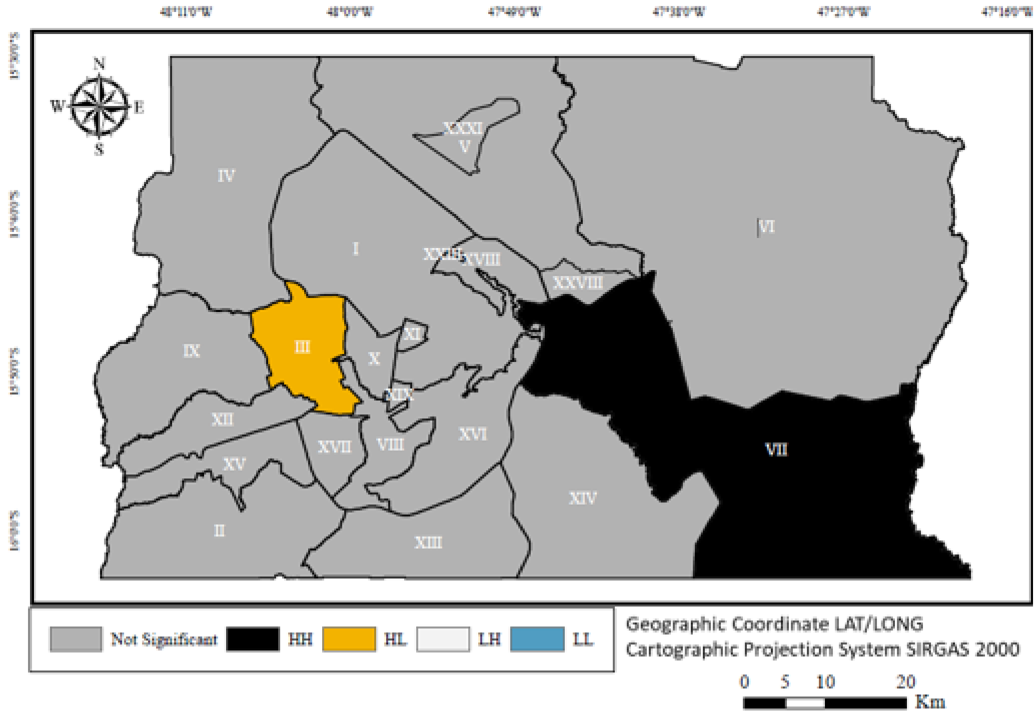

Figure 05: Statistics Anselin Local Morans I for the number of people infected by Hantavirus for the years 2007 to 2017 in the Administrative Regions (AR) of the Federal District, Brazil.

In Paranoá (AR VII), it is possible to affirm with high reliability based on the number of contagion, the tendency to form homogeneous groups. The homogeneous also occurs, although with less reliability in AR's VI, XIV, II, and IV, as well as in AR's III, XII, and XV. In the AR's XVII, XI, XVIII, and XXIII there is little probability of the formation of homogeneous groups of confirmed cases. This can be stated with a minimum confidence of 90% probability (figure 06).

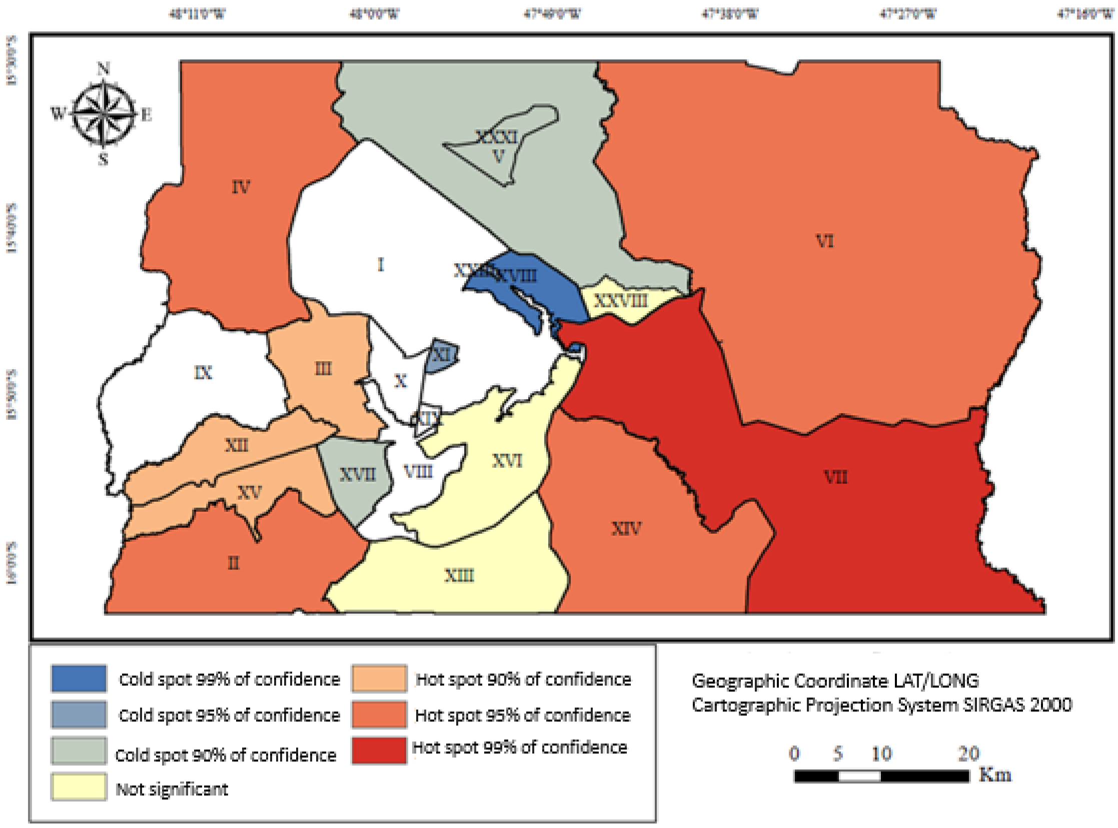

Figure 06: Hot spot and Could spot statistics (Getis-ord * statistics) for the number of people infected by Hantavirus for the years 2007 to 2017.

3.2.2 Environmental modeling

The analysis weights and evidence, figure 07, shows the relationships between the variables and the transitions according to the occurrence, or not, of the disease. We noticed that all the variables presented classes of retraction and attraction to the disease, except for the variable distance of highways and back roads that indicated only a refraction. The disease is more likely to occur at elevations of 1134 m and less likely at altitudes of 1292 m. Concerning hantavirus, it is likely to occur in places close to natural habitats, close to watercourses, and likely places of infection; however, the drainage distance and likely places of infection are characteristics that are seen only in the first meters of analysis. Regarding the average temperature and average precipitation, the actual data are given in lower temperatures and precipitations, with retraction in higher temperatures and precipitations.

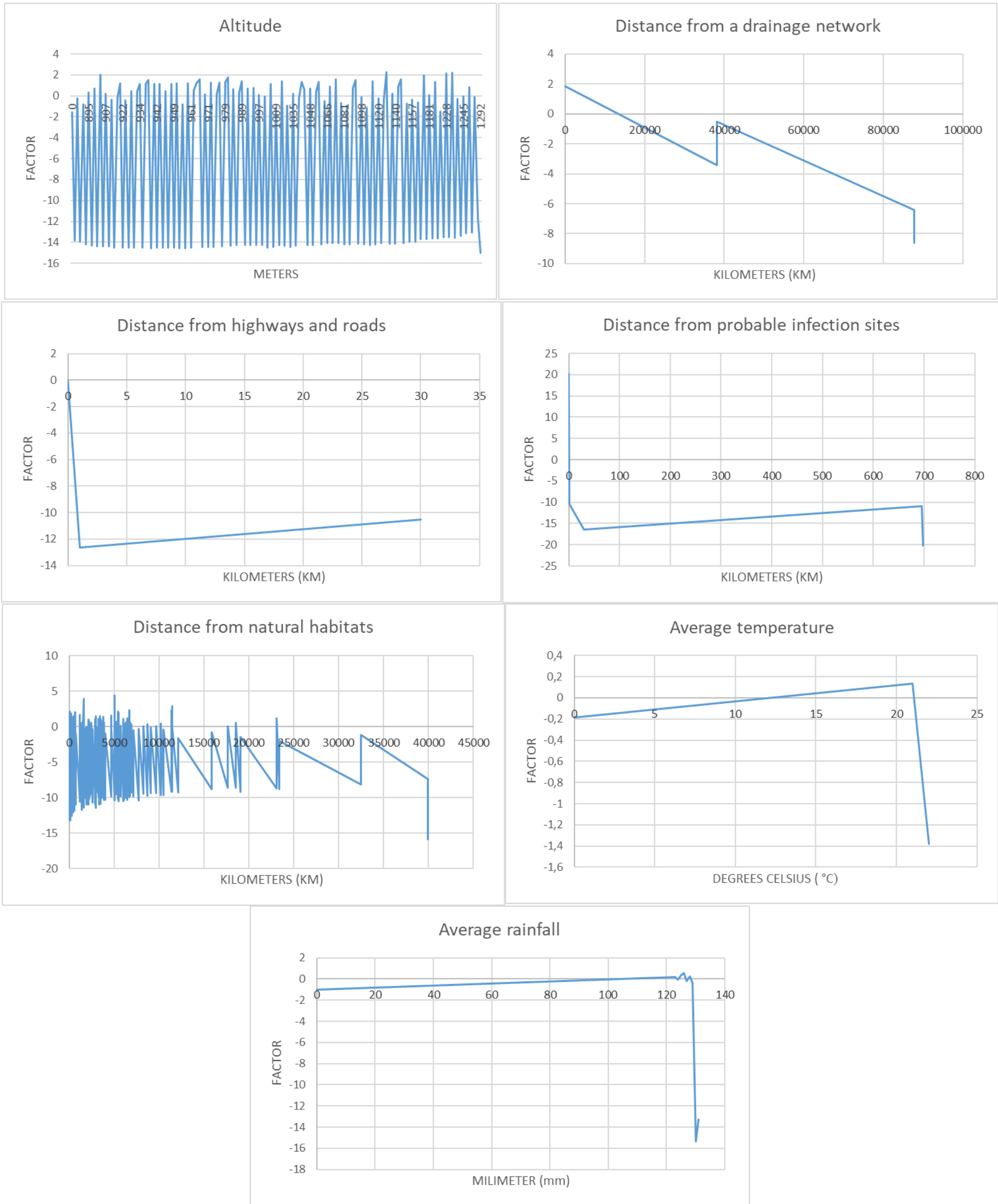

Figure 07: Distribution of weights of evidence for continuous variables

Categorical variables (figure 08), demonstrated well-defined behavior. About land use and cover transitions, most of them are refractory to the occurrence of the disease, the most influential being: river and lake environments, forest formation for savanna formation and field formation for annual and perennial culture, and annual and perennial for annual and perennial culture. The transitions that indicated more attraction were: another non-vegetated area for savanna formation, another non-vegetated area for pasture, urban infrastructure for pasture, annual and perennial culture for pasture. The analysis of the geomorphological variable showed retraction for all categories, except the area of Receding Erosion Zone with strong dissection, predominantly eroding the (SRAIIA ZER / IIA (fo)) which presented attraction.

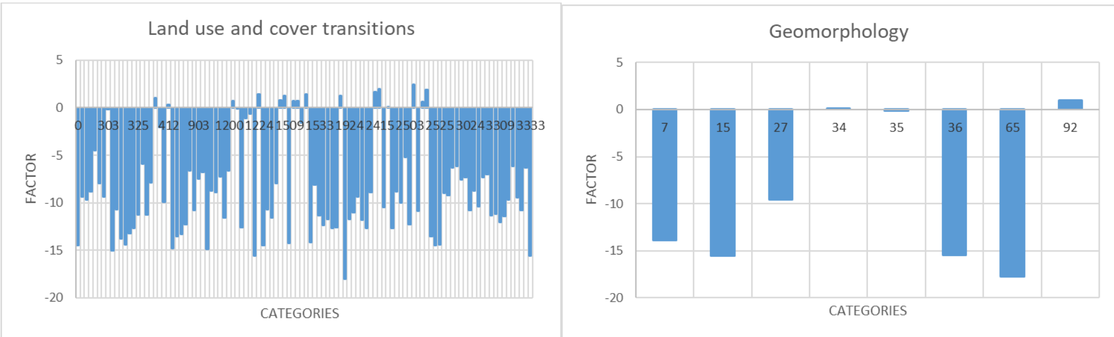

Figure 08: Distribution of the weights of evidence by categorical variable. a) land use and cover transition and b) geomorphology

For more efficient analysis of the model, we studied the correlation between the variables to reduce duplicate information in the research. The matrix generation (Crammer's criterion), table 02, showed for most variables a data correspondence with low inter-correlation, which pointed to independent elements. Exceptionally, the Altitude and Temperature variables showed a correlation of 73% among themselves, which shows a significant relationship.

Table 02: Correlation obtained between variables used by the Crammer criterion.

	Altitude	Distance of drainage network	Distance from natural habitats	Distance from PIS	Distance from highways and roads	Land-use transition	Average rainfall	Average temperature
Geomorphology	0,2601	0,3333	0,2394	0,1709	0,0199	0,3413	0,2474	0,5020
Altitude		0,2291	0,0642	0,1318	0,2275	0,0629	0,3405	0,7350
Distance of drainage network			0,2739	0,1985	0,0000	0,1347	0,1399	0,2480
Distance from natural habitats				0,1412	0,0498	0,0805	0,2443	0,3078
Distance from PIS					0,0147	0,0758	0,1656	0,3038
Distance from highways and roads						0,0776	0,0062	0,0009
Land use transition							0,1759	0,2266
Average rainfall								0,4130

3.3 Discussions

The Global Moran Index showed a significant autocorrelation between the confirmed cases of hantavirus and the natural habitats of wild rodents in the spatial analysis of hantavirus disease. This result suggests that infected people possibly live near rodent habitats. The *Necromys lasiurus*, can live close to urban areas, agricultural expansion, rural settlements and condominiums in Federal District. (Oliveira et al. 2013). This rodent can adapt to small fragments of vegetation in areas of interface with the wild environment, the rural environment, and the home environment (plantations), therefore the importance of analyzing the risk of possible infections in urban and peri-urban areas (Pereira, 2006).

Moran Local's analysis showed the formation of homogeneous groups in the administrative region of Paranoá, which shows high occurrences of the disease. It is noticed that this scenario can be influenced by the regions of Planaltina and São Sebastião, which are neighboring regions with strong spatial dynamism. These regions have diversified agricultural activities, rural settlements and areas with a transition from rural to urban areas. The proximity of residences to areas of native forest and pasture facilitates contact with reservoir rodents that move in search of new spaces to obtain food (Penna, 2003). In Taguatinga, there was also a significant occurrence of Hantavirus. However, the surrounding regions did not present relevant data. It can be assumed that the contagion in the Taguatinga region is a problem mainly due to internal environmental issues within its perimeter.

We observed that the spatial statistics in the Gi * algorithm shows a behavior similar to the Moran Index, since the Paranoá region has statistically relevant clusters, determining a pattern of distribution of hantavirus in the Federal District. The central areas of the Federal District did not present outliers in the model. However, according to the map, we observed that this central area is surrounded by areas that present cases of hantavirus infections or areas of favorable habitats for rodents carrying hantavirus.

In the analysis of weights and evidence, we noticed that the results confirm the study's spatial statistics results. We observed that the risk of the disease occurring is more likely in places of natural habitats of the rodent that hosts the hantavirus. It can be seen that infection risk increases with the non-length of the minimum distance of 40 meters for the construction of houses, silos, pigsties, farms, waterfalls, sheds, garages and others in these environments, which perform the natural function corridors, facilitating the entry of rodents in urban environments. According to Santos (2011), cities' natural expansion has promoted the construction of houses towards rural, agricultural, and wild regions that surround the municipalities. In the Federal District, the natural growth of the urban area leads to the emergence of new condominiums and satellite cities, which are usually situeted on old farms. These land invasious of areas with abandoned planting or stretches of wild vegetation, which are habitats of the rodent, allow occasional contact with man, with the possibility of transmitting the disease to humans.

Considering the analysis of categorical variables, the relation of land use and cover transitions, the areas that showed the greatest significance for the disease's occurrence were the transition areas for pastures. In the Federal District, the cultivation of grasses of the *Brachiaria* genus is conventional, in which beef cattle breeding in acidic and low-fertility soils is prevalent, predominant in the cerrados region (Papini, 2009). According to Pereira (2006), in field studies 70.3% of the catches occurred in the area of *brachiaria* grass. It is noticed that the rodent *Necromys lasiurus* is adapted to live inside the *brachiaria* pasture, in which it feeds on the seeds and water of its roots, mainly during the dry periods, which promotes the maintenance of the high-density rodent population (Alvin & Xavier, 2002). The only geomorphological category that showed attraction was those of Receding Erosion Zones (ZER), which present irregular relief, strongly dissected, less favorable to agriculture and pasture practices, where high rates of arboreal and forest strata are located (Carvalho, et al. 2002).

Altitude and temperature, as examined by Crammer's criterion, showed a significant correlation for the occurrence of hantavirus. The climate in the Federal District is predominantly tropical in altitude, according to the Köppen classification, where there are two well-defined seasons; are hot and humid, the orther cold and dry (Cardoso, et al. 2014). We found in the study that the variables are more representative when analyzed together with other parameters and not in isolation. The model confirmed Santos (2011) observations that point out the relationship between average temperature and average precipitation in the incidence of the disease in the Federal District, where the cases are concentrated in the dry season between April and September. The regions of rainy weather with dry winter, as in the case of the cerrado in Federal District change agricultural production dynamics. These changes can make food available in large quantities in naturally limited periods, interfering with the rodent population's dynamics and abundance (Klemba, 2009). Generalist species, such as *Necromys lasiurus*, adapt better to anthropized habitats. The reproduction period of these rodents occurs between October and January, reaching adulthood around March. Adult rodents are the significant agents of transmission of Hantavirus, due to the increased probability of exposure to the virus, contracted in fights and disputes, a fact observed in several species associated with hantavirus (Childs, 1995). In the dry season between May and October, *Necromys lasiurus* presents its highest density, which corresponds to the harvest period (Vieira, 1997).

3.4 Conclusions

The Federal District territory represents an intense anthropization of rural areas. These modifications of the habitat, contribute to the dynamics of the rodents reservoirs of hantavirus due to the increase of the urban spaces on the rural areas and agricultural activities. Through the analysis of the referred distance and considering the spatial autocorrelation given by the Moran Global Index and the Getis statistics, we verified that the proximity of the infected patient's residence - the contagion at or near the dwelling with the wild rodent habitat - it is related to the contraction of the disease, making it possible to form homogeneous groups.

We can see that the problem of transmission may be associated with the supply of food attractive to wild rodents, given by the waste generated in urban areas and newly occupied natural areas close to unoccupied natural areas, and by food from agricultural activities, such as cultivation of grains in places bordering natural areas. Furthermore, the application of modeling as a tool for predicting the occurrence of disease shows realistic results. It can also provide guidance for the analysis of risks of the disease and promote strategies for monitoring and epidemiological surveillance of public health in the Federal District.

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