



Association between predator species richness and human hantavirus infection emergence in Brazil

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ABSTRACT

Hantavirus infection is a rodent-borne disease (RBD) transmitted by urine or feces (as the natural reservoirs) with an annual estimated worldwide incidence of ~150,000 cases. Previous ecological studies suggested that higher species richness of rodents could decrease the risk of RBDs in humans, because the regulatory pressure of predators could reduce contact among rodents, and between humans and rodents. Using surveillance data, we investigated the association of predator species richness with hantavirus infection emergence in 5562 Brazilian inland municipalities between 2007 and 2017. Multivariable logistic regression models were used for the analyses. Diurnal and non-diurnal predator species were independent explanatory variables in the models. Rodent species richness and demographic, socioeconomic, and environmental factors were used as covariates. During the study period, 1084 cases were reported in 429 municipalities. The results showed a reverse-U-shaped association between diurnal predator species richness and hantavirus infection emergence (odds ratio [OR] 0.463, 0.688, and 0.553 for the first [lowest], third, and fourth [highest] quartiles, respectively, using the second quartile as a reference), while higher non-diurnal predator species richness tended to be associated with higher emergence risk (OR 0.134, 1.065, and 2.708 for the first, third, and fourth quartiles, respectively). The difference in these associations illustrates the complexity of the effects of predator species richness on human RBDs, which require further investigation in follow-up studies. The results showed a close link between environmental factors and public health, emphasizing that the One Health concept should be employed to understand the dynamics of RBDs.

1. Introduction

Hantavirus is a rodent-borne disease (RBD) transmitted by aerosolized urine, feces or saliva of infected rodents [1,2] with an annual worldwide incidence of ~150,000 cases [3]. Various types of hantavirus have been discovered, including Hantaan virus (China and South Korea), Seoul virus (worldwide), and Sin Nombre virus (North America). New World hantavirus is related to hantavirus pulmonary syndrome (HPS), and Old World hantavirus causes hemorrhagic fever with renal syndrome (HFRS) [3]. HPS is the main concern in Brazil; its clinical presentation includes fever, dyspnea, myalgia, cough, and tachycardia, and the case fatality rate varies by region (33–100%) [4].

Previous studies have suggested various drivers of hantavirus

infection. Deforestation (or forest fragmentation) [5] and anthropogenic changes in land use were reported to promote hantavirus infection [6] by increasing the likelihood of contact between the reservoir species and humans. The resilience of reservoir rodents, which survive and even thrive in environments of anthropogenic defaunation as generalist species [7], also contributes to the association between anthropogenic pressure and disease incidence. Climatic and meteorological factors also affect disease dynamics through their effects on rodent habitats [6]. Prist et al. reported that rising temperature by climate change could increase the risk by 1.6–1.7% due to its effects on increasing rodent population and virus survival time in environment [8]. Higher agricultural practices such as sugarcane production in Brazil could increase disease incidence [8]. Economic status may affect the incidence [9], from its associations

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with common practices and public awareness to minimize human–rodents contact.

The effects of wildlife diversity on disease dynamics have also been studied. For example, higher natural host reservoir diversity was suggested to decrease the risk of spillover to humans due to reduced contact between natural hosts (and thus lower disease incidence in the natural host population) [10]. This phenomenon, termed the dilution effect, is supported by field experiments, observational studies [11,12], and theoretical modelling studies [13,14]. However, discussion is ongoing, and contradictory results regarding the association between host diversity and disease transmission have been reported [15].

On the other hand, the effects of predators on spillover transmission from prey species has been neglected [16], although the potential protective effect by predators' top-down regulation has been suggested for many years [17]. For example, there is evidence that a greater number of predator species may reduce the activity levels of reservoir rodents [18,19]. By decreasing contact among reservoir rodents, or between these rodents and humans, higher predator species richness could protect humans through regulation of zoonotic transmission. These hypotheses have been supported by some empirical evidence for tick-borne disease [20] and hantavirus infection [21]. However, additional evidence is required to bolster the link between predator species richness and zoonotic transmission to human populations. Because the two studies mentioned above used disease prevalence among vectors or reservoir species as outcome measures, studies directly concerned with disease outcomes in humans are needed. In addition, studies covering larger geographical areas are required for generalizability, as previous studies focused on relatively small areas.

In this regard, we investigated the association of predator species richness with human hantavirus infection to examine the effect of the species richness of predators on regulating spillover transmission. The study area was in Brazil, which has a high degree of wildlife diversity and a systematic surveillance system for infectious diseases, including hantavirus. As the major reservoirs for hantavirus are rodents [22], *Carnivore* (e.g., wolves, foxes, cats), *Accipitridae* (e.g., hawks), *Falconidae* (e.g., falcons), and *Strigidae* (e.g., owls) families were included as predator species of interest. Diurnal and non-diurnal predator species richness were examined separately, because the effect of predator species richness on transmission risk could differ according to circadian rhythm. Among rodents with diurnal circadian rhythm, *Necromys lasiurus* [23] is a major reservoir species for hantavirus [22] with high abundance in Brazil [24,25]. On the other hand, the relative abundance of non-diurnal reservoirs, such as *Oligoryzomys nigripes*, *Oligoryzomys fomesi*, *Oligoryzomys utariensis*, *Oligoryzomys microtis*, *Holochilus sciurus*, *Akodon montensis*, and *Calomys callidus* [22], among non-diurnal rodents could not be high as relative abundance of *Necromys lasiurus* among diurnal rodents, considering that majority of rodents species are non-diurnal [26]. Because the predation pressure tends to concentrate on prey species with relatively higher abundance [27], the regulatory effects from non-diurnal predator species richness could be lower than those from diurnal predators.

2. Materials and methods

2.1. Data acquisition and preprocessing

Various types of data were acquired to examine the association between predator species richness and human hantavirus emergence in Brazil (Table 1). The incidence of hantavirus between 2007 and 2017 was the main outcome variable. The diurnal and non-diurnal two predator species richness were the main explanatory variables. Rodent species richness, and sociodemographic, climatic, land use, agricultural, and geographical factors were also acquired to adjust association between human hantavirus emergence and predator species richness.

The study area consisted of 5562 inland municipalities in Brazil (second administrative level). The geographical locations of each

Table 1

Variables included to investigate the association between predator species richness and hantavirus emergence risk in Brazil.

Variable	Data source ^a	Reference
Hantavirus incidence	SINAN	[29,30]
<i>Carnivora</i> distribution	IUCN	[33]
<i>Accipitridae</i> distribution	Birdlife	[32]
<i>Falconidae</i> distribution	Birdlife	
<i>Strigidae</i> distribution	Birdlife	
<i>Rodentia</i> distribution	IUCN	
Population	IBGE	[35]
Urban population	IBGE	[35]
Gross domestic product	IBGE	[34]
Annual total precipitation	Worldclim	[37]
Annual mean temperature	Worldclim	
Agricultural land use	Tuanmu et al	[38]
Urban area land use	Tuanmu et al	
Forest land use	GFC	[39]
Deforestation	GFC	
Corn	IBGE	[36]
Soya	IBGE	[36]
Sugarcane	IBGE	[36]
Elevation	Hastings et al	[41]
Latitude		

^a SINAN: Brazilian Notifiable Diseases Information System; IUCN: International Union for Conservation of Nature; IBGE: Brazilian Institute of Geography and Statistics; GFC: Global Forest Change.

municipality were obtained from the Global Administrative Areas Database (GADM) [28]. The number of human hantavirus cases between 2007 and 2017 was obtained for each municipality from the Notifiable Diseases Information System (SINAN) database [29,30], which was used to determine whether there has been human hantavirus infection emergence in each municipality.

Species richness values for predators and rodents were calculated using the International Union for Conservation of Nature (IUCN) [31] and Birdlife international database [32]. These two databases provide geographical ranges for mammalian and avian species, including the *Carnivore*, *Accipitridae*, *Falconidae*, and *Strigidae* families and *Rodentia* order [33]. Data on total population size, proportion of urban population, gross domestic product (GDP), and annual corn, soy, and sugarcane production by municipality were acquired from the Brazilian Institute of Geography and Statistics (IBGE) [34–36]. Climate data were acquired from WorldClim [37], which provides monthly temperature and precipitation data for the period 1970–2000 in raster format. The mean temperature and annual precipitation for each municipality were calculated from the raster data. Three types of land use/land cover data were acquired in this study: agricultural, urban, and forest. The agricultural and urban area land use were obtained from Tuanmu et al. [38] which were derived from DISCover, GLC2000, MODIS2005, and GlobCover. Forest land cover variable was acquired from Global Forest Change (GFC) [39]. These land use data were also in raster format, with the probability of land use for each raster cell ranging from 0 to 100. We used a threshold value of 50 when calculating the land use type proportions for each municipality. Regarding deforestation, we used forest land cover and tree-loss data from the GFC database. Tree loss, a binary raster variable, was calculated for each municipality. The details of the analysis procedure are provided elsewhere [40]. Global elevation data (at the 1-km scale) were obtained from David et al. [41], in a raster format, and the mean elevation was calculated for each municipality. All spatial data preprocessing was conducted using R software (v. 3.5.0) [42]. The 'getValue' function of the raster R package [43] and 'gIntersection' function of the rgeos R package [44] were used to extract values from raster data and calculate the number of species in each municipality, respectively.

2.2. Statistical analysis

Descriptive statistics were generated to provide an overview of differences in general characteristics between municipalities with and without human hantavirus emergence between 2007 and 2017. Means and standard deviations for the main explanatory variables and covariates were calculated, and choropleth maps with deciles for each variable were generated to illustrate the geographical distribution of hantavirus.

Multivariable logistic regression models were used to examine the associations between predator species richness and human hantavirus emergence. Both diurnal and non-diurnal predator species richness data are provided as quartiles. Two multivariable models were generated. In Model 1, we calculated the species richness for all acquired species, whereas species under threat of extinction were not included in Model 2. The IUCN Red List divides species into five categories based on risk of extinction, including least concern (LC), near-threatened (NT), vulnerable (VN), endangered (EN), and critically endangered (CR). Species in all five categories were included in Model 1, whereas species in the VN, EN, CR categories were excluded from Model 2. List of predator species were described in Table S1-4. The odds ratios (ORs) and 95% confidence intervals (95% CIs) were estimated for each variable. To avoid multicollinearity in the multivariable models, covariates with a generalized variance inflator factor (GVIF $^{(1/(2*DF))}$) value >2 were excluded [45]. Considering the potential for spatial autocorrelation, which generally exaggerates associations, Moran's I statistic [46] was estimated for the residuals of the fitted logistic regression model. Conditional autoregressive (CAR) models were to be used if spatial autocorrelation was detected.

3. Results

3.1. Descriptive analysis

Between 2007 and 2017, 1084 human cases of hantavirus infection in Brazil were reported to SINAN (average of 98.5 cases per year). The number of hantavirus cases was higher in the southern region (369 cases). At the first administrative level, Mato Grosso (206 cases) showed the highest number of cases, followed by Santa Catarina (180 cases) and Minas Gerais (152 cases). Fourteen states did not report cases during this period (Table 2). At the second administrative level, 429 of 5562 municipalities reported cases of hantavirus during the study period. The geographical distribution of hantavirus infection and reservoir rodent species were shown in Fig. S1. Diurnal predator species richness distribution in Brazil is wide and involves parts of all five main regions, whereas non-diurnal predator species richness is more concentrated in southeastern and southern regions (Fig. 1).

Descriptive analysis results (means and standard deviations of the municipalities with and without human hantavirus emergence, for the main explanatory variables and covariates) are shown in Table 3. The annual mean temperature, annual soy production, and municipality size were excluded from the analysis, as these variables all showed GVIF values >2 (Table S5).

The species richness values of diurnal and non-diurnal predators, and of rodents, were higher in regions with hantavirus emergence (35.97, 16.76, and 28.56, respectively) than in those without hantavirus emergence (34.52, 12.82, and 26.87, respectively). In terms of the demographic and socioeconomic factors, the proportion of urban population and GDP per capita were also higher in the regions with hantavirus emergence (70.86% and US\$29,290, respectively) than in those without hantavirus emergence (63.23% and US\$18,780, respectively).

With regard to the environmental factors, regions with hantavirus emergence showed greater annual precipitation (1609.23 mm) than those without hantavirus emergence (1360.04 mm). The total area of agricultural land use was greater in the regions with hantavirus emergence (485.40 km²) than in those without hantavirus emergence

Table 2

Number of municipalities with hantavirus infection cases and total number of cases in each region and state in Brazil.

Categories	Region	Number of municipalities	Number of municipalities with cases	Total number of cases between 2007 and 2017
Total		5562 ^a	429	1084
Regions	South	1188	197	369
	Center-west	466	82	336
	Southeast	1667	137	301
	North	449	11	76
	Northeast	1792	2	2
States	Mato Grosso	141	36	206
	Santa Catarina	293	102	180
	Minas Gerais	853	60	152
	Sao Paulo	644	77	149
	Parana	399	41	115
	Goias	246	42	76
	Rio Grande do Sul	496	54	74
	Para	143	6	69
	Distrito Federal	1	1	47
	Mato Grosso do Sul	78	3	7
	Rondonia	52	4	5
	Maranhao	217	2	2
	Amazonas	62	1	2

Note: 1910 missing municipalities are distributed in the States where no cases were registered.

^a Among 5564 Brazilian municipalities, 5562 inland municipalities were included in this study.

(316.12 km²). The extent of deforestation was also greater in regions with than without hantavirus emergence (44.71 vs. 21.43 km², respectively). Crop production levels were higher in regions with hantavirus emergence (36.86 and 284.84 kt for corn and sugarcane production, respectively) than in those without hantavirus emergence (9.22 and 113.68 kt for corn and sugarcane production, respectively). Elevation was higher in the regions with than without hantavirus emergence (469.90 vs. 326.60 m, respectively). The regions of hantavirus emergence were at lower latitudes than those without hantavirus emergence (−22.29 vs. −15.96, respectively). The covariates data in this study are presented by municipality in Fig. S2.

3.2. Association between hantavirus emergence and predator species richness

Table 4 shows the results of the logistic regression analysis of the association between hantavirus emergence and predator species richness. The direction and significance of this association was the same in Models 1 and 2. The association of diurnal predator species richness showed a reverse-U-shape. Higher species richness for non-diurnal predators was associated with a higher risk of hantavirus emergence.

The area under the receiver operating characteristic curve (AUC) was 0.845 for both Models 1 and 2, indicating that the models showed a reasonable fit to the data. Moran's I test revealed a lack of evidence for spatial autocorrelation; both *p*-values were > 0.05 and the Moran's I statistic was small. Therefore, CAR models were not used in this study.

4. Discussion

In this study, we examined the hypothesis that higher predator

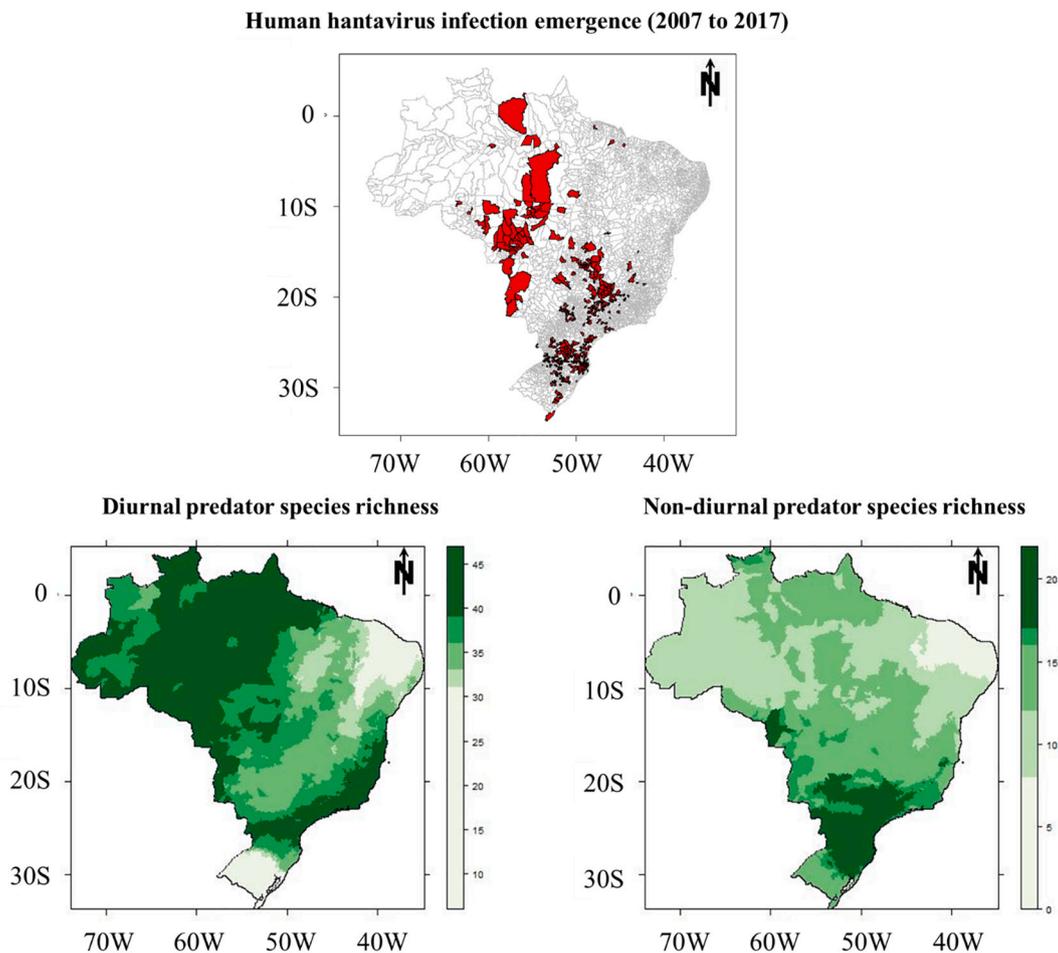


Fig. 1. Distribution of human hantavirus emergence from 2007 to 2017 (top), and diurnal (bottom-left) and non-diurnal predator species richness (bottom-right).

species richness suppresses activities of reservoir rodents and thereby reduces the risk of hantavirus spillover to humans. The association of diurnal predator species richness with hantavirus infection emergence had a reverse-U-shape, indicating that municipalities with low or high species richness tended to have a lower risk of hantavirus infection emergence. On the other hand, non-diurnal predator species richness showed a linear positive association with hantavirus infection emergence, indicating that municipalities with higher species richness tended to have a higher risk of emergence. The results of two logistic regression models using different measures for predator species richness were consistent, indicating the robustness of the models.

For both predator species richness indicators, the lowest species richness showed a lower hantavirus emergence risk than second lowest species richness, in contrast to our hypothesis. The lower risk in the lower predator species richness regions could elicit from lower reservoir abundance. Although relevant evidence is lacked, we found that mean abundance of *N. lasiurus* (a main reservoir species) tend to be low in the region with low predator species richness (Fig. S3), using rodent survey data from Mendonca et al. [47], 2018). Considering that there is no rodent survey for whole Brazilian regions, we cannot adjust the abundance in the model. Further longitudinal studies on temporal trends between predator species richness and prey abundance could shed further light on this finding.

Higher diurnal predator species richness was associated with low emergence risk, which supported our hypothesis, while non-diurnal predator species richness showed the opposite association. The difference in relative abundance of different rodents with the same circadian rhythm could explain these differential associations. Despite regional

differences, high predator diversity generally increases prey diversity [48] possibly via predatory pressure on prey animals with high relative abundance [27]. As *N. lasiurus* is generally abundant [22,24,25] and shows diurnal activity, and where the majority of rodents are nocturnal [26], the relative abundance of hantavirus reservoirs among diurnal rodents could be high, while among non-diurnal rodents could be low. Therefore, the regulatory pressure exerted by diurnal predator species richness could effectively reduce reservoir species abundance, whereas that exerted by non-diurnal predator species richness would mainly affect non-reservoir species, including mammals other than rodents, which in turn could increase the activity of reservoir species. However, *N. lasiurus* has been considered as a main reservoir for hantavirus in Brazil [49], and we also found that distribution of *Necromys lasiurus* matches the highest concentration of hantavirus cases (Fig. S1). In addition, a recent study suggested that the range of *Necromys lasiurus* would expand [50]. Therefore, the protective effect of diurnal predators can be important in public health perspective.

This study had several limitations that should be taken into consideration when interpreting the results. First, we did not account for temporal variation in species richness during the study period (2007–2017). As recent anthropogenic land cover changes and the climate crisis could rapidly alter wildlife assemblages, temporal changes in species richness should be taken into consideration in future studies. Second, there are possible reservoir species other than rodents, such as *Chiroptera* and *Insectivora* [22], although their role in human hantavirus incidence have not been fully studied. The effect of predators on these species could be different and future studies are recommended to elaborate on this issue. Third, the abundance and relative abundance of

Table 3
Difference in general characteristics between municipalities with and without hantavirus report in Brazil.

Variable (unit)	Mean (\pm SD)		p value (t-test)
	With Hantavirus (N = 429)	Without Hantavirus (N = 5133)	
Diurnal predator SR	35.97 \pm 3.7	34.52 \pm 4.7	<0.001
Non-diurnal predator SR	16.76 \pm 2.5	12.82 \pm 4.4	<0.001
Rodent SR	28.56 \pm 4.9	26.87 \pm 7.4	<0.001
Population density (per km ²)	132.52 \pm 547.7	114.05 \pm 610.4	0.506
Urban population (%)	70.86 \pm 23.4	63.23 \pm 21.8	<0.001
GDP per capita ($\times 10^3$ US\$)	29.29 \pm 17.8	18.78 \pm 19.8	<0.001
Annual total precipitation (mm)	1609.23 \pm 240.4	1360.04 \pm 429.2	<0.001
Agricultural land use (km ²)	485.40 \pm 790.4	316.12 \pm 511.3	<0.001
Urban area land use (km ²)	6.28 \pm 41.7	1.34 \pm 10.8	0.015
Forest land use (km ²)	1486.87 \pm 9436.9	803.54 \pm 4686.4	0.138
Deforestation (km ²)	44.71 \pm 172.93	21.43 \pm 94.32	0.006
Corn production (kilotons)	36.86 \pm 111.3	9.22 \pm 32.4	<0.001
Sugarcane production (kilotons)	284.84 \pm 742.5	113.68 \pm 388.6	<0.001
Elevation (m)	469.90 \pm 262.3	326.60 \pm 252.9	<0.001
Latitude	-22.29 \pm 5.8	-15.96 \pm 8.3	<0.001

SR: species richness (number of species), GDP: gross domestic product. Note: significance level was 0.05 for t-test.

Table 4
Results of logistic regression analysis of human hantavirus infection emergence between 2007 and 2017 in Brazil.

Variable	Odds Ratio (95% CI)	
	Model 1	Model 2 (LC)
Diurnal predator species richness (Q1)	0.463 (0.296–0.717)	0.460 (0.291–0.722)
Diurnal predator species richness (Q3)	0.688 (0.497–0.952)	0.679 (0.497–0.928)
Diurnal predator species richness (Q4)	0.553 (0.368–0.831)	0.442 (0.282–0.687)
Non-diurnal predator species richness (Q1)	0.134 (0.021–0.474)	0.122 (0.019–0.432)
Non-diurnal predator species richness (Q3)	1.065 (0.708–1.620)	0.874 (0.571–1.348)
Non-diurnal predator species richness (Q4)	2.708 (1.617–4.590)	2.193 (1.295–3.749)
AUC	0.845	0.845
Moran'I statistics (p-value)	0.009 (0.126)	0.008 (0.147)

Note: Predator species richness was calculated using all species of interest in Model 1, while species under threat of extinction were excluded from Model 2. Both diurnal and non-diurnal predator species richness were included as categorical variables based on quartiles: Q1, 1st quartile (lowest); Q2, 2nd quartile; Q3, 3rd quartile, Q4, 4th quartile (highest). The 2nd quartile was used as the reference for both predator species richness variables. Deforestation, urban population, GDP per capita, population density, annual precipitation, agricultural land use, urban area land use, forest land cover, corn production, sugarcane production, elevation, and latitude were also included in the model as covariates.

predators and reservoir rodents were not modeled due to a lack of data. Although there have been several local field surveys in Brazil, no national systematic investigation on wildlife abundance has been performed. Abundance data could facilitate examination of the association of species evenness (another indicator of diversity, incorporating both species richness and relative abundance) with zoonotic transmission.

Fourth, the analysis was conducted at the municipality level. An analysis conducted at the 1 km² scale, for example, would yield different sample sizes and explanatory variable values (i.e., the modifiable area unit problem). Fifth, underreporting of hantavirus infection may have occurred because we used national surveillance databased only on official reports of disease incidence. Sixth, future studies can improve the analysis using advanced variables. For example, we used GDP per capita as a covariate in the model. However, as GDP cannot fully represent municipality level income, other economic status related variable, such as sum of household income could be used as a sensitivity analysis. In addition, time-varying variables for agricultural land use or urban land use can be used rather than fixed value. Seventh, the predatory pressure from each predator species can be different, but the heterogeneous predatory pressure was not considered in the models, due to lack of available data.

Nevertheless, the results of this study have important implications for public health. Although further studies are needed to explain the causal association between predators and disease risk in humans, our results could facilitate prediction of disease outbreaks. Although current vaccines for hantavirus are not highly effective [51], various efforts have been made to improve the effectiveness [52]. The prediction of hantavirus emergence can be used to prioritize vaccine distribution. As a pragmatic measure, previous studies often used total mammalian species richness in global-scale prediction models of infectious disease outbreaks [53,54]. However, our results showed that the effects of wildlife species richness could differ according to their trophic relationships with other species, suggesting that considering wildlife species as homogenous could be an oversimplification. Furthermore, the results of this study implied a close association between wildlife ecology and human disease risk, thus supporting the One Health concept [55,56]. As suggested in previous reports, the One Health approach is important to improve knowledge and understanding of disease dynamics, which can in turn promote the health of human populations, animals, and the environment for better sustainability [57].

In this study, we found a nonlinear association of diurnal predator species richness, and a linear association of non-diurnal predator species richness, with human hantavirus infection emergence. Although additional studies are required to confirm the complicated associations, the results suggest that the intricate trophic networks among wildlife should be taken into consideration when analyzing human disease risk in association with zoonotic transmission. The close associations of environmental factors with disease emergence emphasized that the One Health concept should be applied to better understand the dynamics of RBDS.

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Declaration of competing interest

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.onehlt.2020.100196>.

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