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ASSESSMENT OF EPIZOOTIC ACTIVITY AND EPIDEMIC RISK IN HEMORRHAGIC FEVER WITH RENAL SYNDROME FOREST FOCI OF PRIMORSKY KRAI[1]

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In forest foci of hemorrhagic fever with renal syndrome (HFRS) of Primorsky Krai Amur and Hokkaido hantaviruses are circulated in the natural host population, i.e. Apodemus peninsulae and Myodes rufocanus. The indicators of epizootic activity and their threshold values in rodent population dynamics were determined in order to forecast HFRS outbreaks. The material for the research was obtained throughout 2001–2013. The number of trap-nights was 33890. 2737 of A. peninsulae and 1643 of M. rufocanus were investigated. ELISA, RT-PCR, IFA were used for the detection of hantavirus antigen, RNA, antibodies/avidity. The parameters of epizootic activity per 100 TN (N – population, n_i – infected rodents, n_{ai} – individuals with acute infection) were proposed. The results showed that the active foci of Amur viral infection are located on the slopes of the Sikhote-Alin ridge. The epizootic activity in A. peninsulae populations is characterized by the expressed cyclicity: phase I is rise, phase II is high activity, phase III is recession/low activity. Phases I and II are valid up to a year, whereas phase III is valid within a few years, determining the whole epizootic cycle. In phase I the number of rodents with an acute infection increased from summer to late autumn. In phase II the number of rodents with acute infection was considerable in spring/summer and decreased in autumn more than 3 times. In all phases of the cycle the threshold values were considerably higher for A. peninsulae, than for M. rufocanus, thus showing the former's epidemiological role in forest ecosystems. HFRS infection rate in phases I/II of the epizootic cycle in A. peninsulae populations had two peaks: during late autumn – winter (≥ 37% of cases) and spring – first half of summer (≥ 55% of cases).

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The obtained threshold values of Amur hantavirus active circulation in population dynamics of the natural host allows to predict the periods of the increased risk of infection in HFRS forest foci for humans.

Keywords: *hantaviruses; rodents; hemorrhagic fever with renal syndrome (HFRS); natural foci; Primorsky Krai.*

ОЦЕНКА ЭПИЗООТИЧЕСКОЙ АКТИВНОСТИ И ЭПИДЕМИЧЕСКОГО РИСКА В ЛЕСНЫХ ОЧАГАХ ГЕМОРРАГИЧЕСКОЙ ЛИХОРАДКИ С ПОЧЕЧНЫМ СИНДРОМОМ ПРИМОРСКОГО КРАЯ

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В лесных очагах геморрагической лихорадки с почечным синдромом (ГЛПС) Приморского края циркулируют хантавирусы Amur и Hokkaido в популяциях природных хозяев – Apodemus peninsulae и Myodes rufocanus. С целью прогноза подъемов заболеваемости ГЛПС определены индикаторные показатели эпизоотической активности и их пороговые значения в динамике популяций грызунов. Материал получен в 2001–2013 гг. Выставлено 33890 ловушко-ночей (л-н). Исследовано 2737 A. peninsulae и 1643 M. rufocanus. Антиген, РНК хантавируса, специфические антитела / авидность выявляли в ИФА, ОТ-ПЦР, НМФА. Предложены показатели эпизоотической активности на 100 л-н: N – вся популяция; $n_и$ *– все инфицированные;* $n_{ои}$ *– все особи с острой инфекцией. Результаты показали, что активные очаги Amur-вирусной инфекции расположены на склонах хребта Сихотэ-Алинь. Эпизоотическая активность в популяциях A. peninsulae имеет выраженную цикличность: I фаза – подъем, II – высокая, III – спад / низкая активность. I и II фазы длятся не более года, III фаза длится несколько лет, определяя период всего эпизоотического цикла. В I фазу число зверьков с острой инфекцией увеличивалось от лета к поздней осени. Во II число зверьков с острой инфекцией было значительно выше весной/летом, снижаясь осенью более чем в 3 раза. Значения показателей во все фазы цикла были значительно выше у A. peninsulae, чем у M. rufocanus, указывая на ее эпидемическую значимость в лесных экосистемах. В период I и II фаз эпизоотического цикла в популяциях A. peninsulae заболеваемость ГЛПС в крае имела два пика: осенне-зимний (≥ 37% случаев) и весенне-летний (≥ 55% случаев).*

Полученные пороговые показатели активной циркуляции вируса Amur в динамике популяций природного хозяина дают возможность прогнозировать периоды повышенного риска заражения людей в лесных очагах ГЛПС.

Ключевые слова: *хантавирусы; грызуны; геморрагическая лихорадка с почечным синдромом (ГЛПС); природные очаги; Приморский край.*

Introduction

Currently, over 40 genetically and immunologically distinct hantavirus species in the genus *Hantavirus* of the *Bunyaviridae* family have been discovered. Each of them, with few exceptions, is strongly associated with a unique host species, having passed a long way of co-evolution. 22 species of hantaviruses are considered pathogenic to humans, their natural hosts being defined as the rodents of the three families, i.e. *Murinae*, *Cricetinae*, *Sigmodontinae* [1, 2]. Hantaviruses are capable of causing serious diseases in humans, i.e. the so-called hantavirus fevers [3] that are defined as natural focus nontransmissible viral zoonoses. Hemorrhagic fever with renal syndrome (HFRS) is quite widespread in Eurasia, whereas hantavirus pulmonary syndrome (HPS) can be found in both North and South America. Geographic distribution and epidemiology of cases caused by hantaviruses are seen as the consequence of distribution and natural history of their natural hosts [4]. The problem with HFRS, associated with immunologically distinct hantaviruses, seems to be particularly acute on the foci where two or more of its causative agents are present at the same time. In the European part of Russia, the following hantaviruses are HFRS etiologic agents: *Puumala* (reservoir – the *Myodes glareolus* bank vole) and *Dobrava* (the *Kurkino* genetic subtype, the reservoir being a subspecies of the *Apodemus agrarius* field mouse and the *Sochi* genetic subtype, its reservoir being the Caucasian forest mouse *A. ponticus*) [3, 5, 6]. In the Asian part of Russia, the following hantaviruses are HFRS etiologic agents: *Hantaan* (Far East genovariant), *Amur* (Amursk, Khabarovsk, Primorye, and Primorye1-China genovariants) and *Seoul* (VDV genovariant). The natural hosts of *Hantaan*, *Amur* and *Seoul* viruses are the eastern subtype of the *A. agrarius* field mouse, *A. peninsulae* forest Asian mouse and *Rattus norvegicus* gray rat, respectively [7–9]. The forest ecosystems are dominated by *A. peninsulae* – the natural host of the *Amur* pathogenic virus and the source of infection to humans, its co-dominant being the *Myodes rufocanus* gray-sided vole – natural host of the *Hokkaido* hantavirus with an unknown virulence level to humans. Studying of the areas being endemic to HFRS is aimed at establishing biocenotic structures of ecosystems, function and reservoir potential peculiarities of hantavirus natural foci [10, 11]. However, quite a few urgent issues related to natural foci of hantavirus zoonoses have not been thoroughly studied so far, one of them being the mechanism of epizootic activity in the dynamics of rodent population as well as epidemic manifestations of different types of hantavirus infection natural foci within a particular spatial-temporal framework. The purpose of the study was to determine the indicators of epizootic activity and their threshold values in the population dynamics of rodents, being the carriers of the forest areas hantaviruses, in order to predict HFRS incidence rise on the forested territory of Primorsky Krai.

Material and Research methods

For the purposes of the study the research material was obtained during field and stationary research activities (2001–2013) on the HFRS endemic areas in the belt of mixed coniferous-deciduous and deciduous forests in central and southern parts of Primorsky Krai. The epizootological observation and collection of the material was carried out yearly in spring, summer and autumn. During the observation period, 33890 trap-nights (TN) were worked over. 4594 rodents were caught, 2737 of those were identified as *A. peninsulae*, 214 – *A. agrarius*, 1505 – *M. rufocanus*, 114 – *Myodes rutilus* red voles and 24 – *Microtus fortis* reed voles.

Table 1.

Immunological and molecular genetic research techniques

Research techniques	Hantavirus and infection identification in rodents
ELISA (enzyme-linked immunosorbent assay) Hantagnost commercial test-system manufactured by Federal State Unitary Enterprise on Manufacture of Bacterial and Viral Preparations of Chumakov Institute of Poliomyelitis and Viral Encephalitides	**Viral antigen** in 10–20% of the rodents' lungs and excretory organs suspension
RT-PCR (Reverse transcription polymerase chain reaction) RNA extraction, RT and PCR formulation, visual indication of amplification products by gel electrophoresis in agarose gel in the presence of ethidium bromide. Vector-Best, AmpliSens Hantavirus sets.	Hantavirus **RNA** in the animals' organs on ambient substrata
IFAT (Indirect fluorescent antibody technique). Anti-species FITC conjugates manufactured by N.F. Gamaleya Research Institute of Epidemiology and Microbiology. Antibody avidity in seropositive animals by the Hedman technique (1991).	**Antibodies** to culture antigens of hantaviruses Antibodies *avidity*: high, transitional, low.

The animals' hantavirus infection was detected by the presence of antigen/RNA in lungs/excretory organs and/or the presence of specific antibodies in their blood. Hantavirus antigen was identified using the ELISA, whereas viral RNA was identified using the RT-PCR; specific antibodies and their avidity were identified using the indirect fluorescence technique (Table 1).

To characterize hantavirus infection in individuals as well as on the population level of rodents, being hantavirus carriers, the following parameters and indicators were proposed: infection rate; acute infection; relative abundance / infection rate; epizootic activity (Table 2).

Table 2.

Main parameters and indicators of hantavirus infection

Parameters and values	Hantavirus infection in animals and population
Infection rate in rodents	Hantavirus antigen in lungs/organs, specific antibodies in blood.
Acute infection in rodents (hantavirus shedding with the natural host's saliva, urine, faeces into ambient environment).	Hantavirus antigen/RNA in lungs/ secretory and excretory organs, antibodies of low/transitional avidity.
Relative abundance of the species – Relative infection rate – Relatively acute infection –	number of all individuals per 100 TN number of all infected individuals per 100 TN number of all individuals with acute infection per 100 TN
Epizootic activity	Relatively acute infection in population

Research results and discussion

Forest ecosystems occupy about 70% of Primorsky Krai. *Amur* viral infection endemic areas were identified in the parts of the region with mixed coniferous-deciduous forests with a high proportion of cedar and oak, and a well-developed lower tier, being a favorable habitat for the large Japanese field mouse. *Amur* viral infection active natural foci are located on the western and eastern slopes of the Sikhote-Alin ridge occupied by coniferous-deciduous forests that are preferred by the *A. peninsulae*. Long-time average annual values for various rodent species, being hantavirus carriers, in forest communities are shown in Table 3, which proves the fact that all the values obtained are much higher in the *A. peninsulae* species.

According to the obtained data the dynamics of epizootic activity in *A. peninsulae* populations has an expressed cyclic recurrence. Rise and high activity are valid up to a year, from autumn of the current year till autumn of the subsequent year, followed by recession. The phase of recession/low activity lasts for several years, determining the duration of the cycle. Table 4 presents the characteristic of the rodents, being hantaviruses carriers in forest ecosystems, within the phases of rise, high and low epizootic activity in *A. peninsulae* populations.

Table 3.

Long-time average annual values for rodents, being hantavirus carriers, in HFRS forest natural foci

Species of rodents as hantaviruses carriers	Values			
	Species proportion in the trapping (%)	Species proportion of the infected animals in the trapping (%)	Species population (per 100 TN)	The infection rate of the species (per 100 TN)
Apodemus peninsulae	59,6±0,7	**65,5**±1,8	**8,1**	**1,4**
Apodemus agrarius	4,7±0,2	2,5±0,2	0,6	<0,1
Myodes rufocanus	32,7±0,7	29,6±0,5	4,4	0,6
Microtus fortis	0,5±0,1	1,1±0, 4	<0,1	<0,1
Myodes rutilus	2,5±0,2	1,3±0, 4	0,3	<0,1

Table 4.

The characteristic of rodents, being hantaviruses carriers in forest ecosystems, within different phases of the epizootic activity in *A. peninsulae* populations

Phases of the *A. peninsulae* epizootic cycle	Species of rodents as hantaviruses carriers	Values of the species			
		Proportion in the trapping (%)	Proportion of the infected animals in the trapping (%)	Population (per 100 TN)	The infection rate (per 100 TN)
Phase I – activity rise	***A. peninsulae***	**78,3**	**78,9**	**7,45**	**1,58**
	A. agrarius	8,0	5,3	0,76	0,10
	M. rufocanus	13,4	15,8	1,28	1,31
	Microtus fortis	0,0	0,0	0,00	0,00
	M. rutilus	0,4	0,0	0,04	0,00
Phase II– high activity	***A. peninsulae***	**65,2**	**75,6**	**20,52**	**5,62**
	A. agrarius	3,3	1,8	1,04	0,14
	M. rufocanus	31,2	22,3	9,82	1,66
	Microtus fortis	0,2	0,3	0,07	0,02
	M. rutilus	0,1	0,0	0,02	0,00

End of the Table 4.

Phase III–low activity	***A. peninsulae***	**82,5**	**65,4**	**5,35**	**0,31**
	A. agrarius	1,0	0,0	0,06	0,00
	M. rufocanus	13,5	26,9	0,88	0,15
	Microtus fortis	0,3	3,8	0,02	0,02
	M. rutilus	2,6	3,8	0,17	0,02

During a year characterized by the activity rise the relative abundance of mice with acute infection in populations of *A. peninsulae* increased from summer to late autumn to an average value of 2. Within the high activity phase the number of mice with acute infection during a spring and summer season was more than 5 individuals per 100 TN, decreasing to more than 3 times in autumn at a fairly high population rate. Within the phase of low epizootic activity individuals with acute infection were found during all seasons, their number not exceeding the value of 0.3.

As a result of HFRS forest foci long-term monitoring, the parameters of hantaviruses active circulation were determined as well as their threshold values at different phases of the epizootic cycle in populations of rodents, being virus carriers, were defined. As seen in Table 5, within all the cycle phases the epizootic activity values tend to be much higher in *A. peninsulae*, compared to *M. rufocanus*, that proves the epidemiological importance of this species in forest ecosystems of Primorsky Krai.

Table 5

Threshold values of the population parameters within different phases of the *Apodemus peninsulae* and *Myodes rufocanus* epizootic cycle

Parameters	Phases of the cycle		***Apodemus peninsulae***	*Myodes rufocanus*
Relative abundance of the natural host (number of individuals per 100 TN): **N** – whole population $\mathbf{n}_u$ – all infected animals $\mathbf{n}_{ou}$ – animals with acute infection	**Rise** of the epizootic activity	N	≥ 8,0	≥ 1,5
		$\mathbf{n}_u$	≥ 1,8	≥ 0,3
		$\mathbf{n}_{ou}$	**≥ 1,5**	≥ 0,2
	High epizootic activity	N	≥ 20,0	≥ 9,0
		$\mathbf{n}_u$	≥ 7,0	≥ 1,7
		$\mathbf{n}_{ou}$	**≥ 5,0**	≥ 0,8
	Low epizootic activity	N	≤ 6,0	≤ 1,0
		$\mathbf{n}_u$	≤ 0.5	≤ 0,2
		$\mathbf{n}_{ou}$	**≤ 0,3**	≤ 0,1

For the observed period, in forest natural foci of hantavirus infection 39.6% of HFRS cases were reported from May to June. During the years of high epizootic activity in the populations of the large Asian field mouse the bulk of HFRS cases were reported in spring and summer (68.6% of annual incidence). When comparing the long-time annual dynamic pattern of the epizootic activity in populations of rodents, being hantavirus carriers, to HFRS incidence in humans, the following dynamics conjugation was noted, the one of the epizootic process in populations of *A. peninsulae* and the annual and seasonal dynamics of HFRS cases registration. During the rise/high stage of the epizootic activity in populations of *A. peninsulae* two incidence peaks were determined: autumn to winter (≥ 37,5% of cases during a year), and spring to summer (≥ 55,2% of cases).

Another research activity was conducted within the frame of the study regarding the possibility to preserve natural foci of HFRS hantaviruses in the ambient environment, the ones excreted by the infected rodents with urine, saliva, faeces. Environmental substrata samples were taken on forested areas, being enzootic to hantavirus infections (Table 6).

Table 6.

Detection of hantavirus RNA, being external to its natural host, in the ambient environment of HFRS forest foci

Area / Time of sample collection	Research objects	Number of substrara samples	Sample characteristics	RT-PCR results
Kavalerovsky district, June to October	Trap lines in coniferous and cone-bearing forest on a stationary plot	20	Soil with plant litter	4+ RNA assays
Chuguyevsky district, October	Rodents' natural refuges	10	Soil with litter	2+ RNA assays
Olginsky district, Jyne. *HFRS group cases*	Trap lines in coniferous and cone-bearing forest around gamekeepers' dwelling	8	Soil with plant litter	2+ RNA assays

A specific RNA was found in the samples containing soil with plant litter on trap lines as well as in places, where HFRS group cases had been detected, and a certain number of *A. peninsulae* with acute hantavirus infection had been caught as well as traces of their activity detected.

Conclusion

To date, the Eurasian countries have seen the increase in both the amplitude and number of HFRS outbreaks. The risk determinants include reservoir ecology, ecology of the virus and antropogenous factors [12, 13]. Every year, hundreds of thousands of people, who live in the endemic territories or temporarily stay there while at work or having time off, get in contact with HFRS natural foci. Both temporary protection of an individual or a group of people from a pathogen is required, as well as preventive measures aimed at reducing infection rate on specific HFRS endemic territories. HFRS, having all the features of the emerging infection, can lead to a complicated epidemic situation. In some HFRS and HPS outbreaks the mortality rate can reach 12% and 60% respectively [14]. WHO estimates that each year there are between 150000 and 200000 hantavirus disease cases, of which 70 to 90% are detected in parts of China, adjoining the north-eastern border of Primorsky Krai. More and more HFRS cases are reported in Europe [15]. In order to improve the prevention of hantavirus infections, the cooperation of international organizations is required, just as it is done concerning other widespread viral diseases [16].

According to the hypothesis (Vorontsov, 1974), causative agents of viral infections, by integrating fragments of their genome into their natural host's genome, play an important role in their evolution. The strategy to prevent natural foci infection should be aimed at preserving the role of the pathogen in the ecosystem, along with the unconditional protection of humans from infections caused by pathogens, rather than at the elimination of the pathogen [17].

In order to develop effective methods of HFRS protection and prevention, in our opinion, it is necessary to obtain quantitative parameters of hantaviruses circulation in different phases of the epizootic cycle in different types of the natural foci. After long-term monitoring of HFRS forest foci in Primorsky Krai, certain epidemic-significant indicators and their thresholds values were identified that reflect the activity of the epizootic process in its different development phases in populations of *A. peninsulae* and *M. rufocanus*, being natural hosts to *Amur* and *Hokkaido* hantaviruses. It is important to note that the rise, high and low epizootic activity values obtained were significantly higher in *A. peninsulae* compared to *M. rufocanus*, that proves the former's epidemic significance. Within the periods of rise and high epizootic activity in populations of *A. peninsulae* the two HFRS incidence peaks were observed as follows: autumn to winter and spring to summer (≥ 37% and ≥ 55% of the annual incidence). The epizootic activity in populations of *A. peninsulae*, being cyclical, leads to years to year and seasonal differences in the HFRS cases distribution [18, 19]. Detection of hantavirus RNA in ambient environment substrata of HFRS forest natural foci shows the possibility of *Amur* virus survival within a considerably long period, while being external of its natural host organism, which is consistent with the data obtained for *Puumala* hantavirus [20]. Considering the 'hantavirus – rodent' binomial parasitic system the study on the detection of hantavirus in the medium between the natural host and human being seems to be quite significant in determining the factors, time, and areas of HFRS high infection rate concerning humans.

The proposed indicators for assessing the epizootic activity and their threshold values in the population dynamics of the natural host of *Amur* virus makes it possible to predict high-risk periods of human infection in HFRS forest foci within a particular spatial-temporal framework.

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