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Детерминанты проявлений эпидемического процесса геморрагической лихорадки с почечным синдромом в Приморском крае

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АННОТАЦИЯ

Обоснование. Роль случайных и закономерных факторов в эпидемическом процессе геморрагической лихорадки с почечным синдромом до сих пор не изучена, и потому является актуальной темой для исследователей. Причины формирования тяжёлых и летальных случаев требуют конкретизации.

Цель исследования — на основе заболеваемости геморрагической лихорадкой с почечным синдромом в Приморском крае за длительный интервал времени установить роль основных детерминант эпидемического процесса, продемонстрировать причинную обусловленность локальных проявлений в эпидемических очагах у пациентов с геморрагической лихорадкой с почечным синдромом.

Материалы и методы. Проведено комплексное дескриптивное эпидемиологическое и клиническое исследование. Эпидемиологический анализ заболеваемости геморрагической лихорадкой с почечным синдромом и данных обследований очагов инфекции. Клиническое наблюдение (case study) за случаем геморрагической лихорадки с почечным синдромом с летальным исходом. Объект исследования: статистические данные по официально зарегистрированным случаям геморрагической лихорадки с почечным синдромом в Приморском крае с 1995 по 2021 год; случай геморрагической лихорадки с почечным синдромом с летальным исходом у пациентки, госпитализированной в ГБУЗ «Краевая клиническая инфекционная больница» в марте 2022 года.

Результаты. Доля случайных факторов в эпидемическом процессе геморрагической лихорадки с почечным синдромом в рассматриваемый период составила 28,7%. Они формировали отклонения от типовой кривой, но не участвовали в формировании цикличности в многолетней динамике. Переменные факторы, формирующие цикличность и случайные отклонения, вместе определяли 53,4% заболеваемости. Они полностью относятся к сезонной заболеваемости (67,8%). Более того, оставшиеся 14,4% сезонности формируются постоянными для каждого месяца факторами. Постоянные для всех месяцев года факторы формируют круглогодичную форму, которая составляет 32,2% заболеваемости.

В клинико-эпидемиологическом наблюдении летального случая геморрагической лихорадки с почечным синдромом присутствовало заражение в условиях пылеобразования: при наведении порядка в закрытом помещении при отрицательной температуре (подметание). Среди индивидуальных факторов риска — высокие титры специфических антител как результат многократных встреч с возбудителем при жилищном и профессиональном типах заболеваемости; сопутствующие заболевания.

Заключение. Изучение заболеваемости геморрагической лихорадкой с почечным синдромом продемонстрировало высокую разрешающую способность эпидемиологического анализа с использованием бинарного метода при зоонозах. Закономерности и особенности заболеваемости человека контролируются природными и социальными факторами более строго, чем биологическими. Детерминанты социально-экологической системы при геморрагической лихорадке с почечным синдромом в Приморском крае позволяют конкретизировать тактику и стратегию реализации эпидемиологического надзора.

Ключевые слова: геморрагическая лихорадка с почечным синдромом; ГЛПС; бинарный метод анализа; летальность; типы заболеваемости.

Как цитировать

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Determinants of manifestations of the epidemic process of epidemic hemorrhagic fever in Primorsky Krai

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ABSTRACT

BACKGROUND: The contribution of random and regular factors in the process of epidemic hemorrhagic fever is unknown, which necessitates the search for the reasons for the formation of severe and fatal cases.

AIM: Based on the incidence of epidemic hemorrhagic fever in Primorsky Krai over a long period, we aimed to establish the role of the main determinants of the epidemic process and to demonstrate the causality of local manifestations in epidemic foci in patients with epidemic hemorrhagic fever.

MATERIALS AND METHODS: In this comprehensive descriptive epidemiological and clinical study, we undertook the epidemiological analysis of the incidence of epidemic hemorrhagic fever and data from examinations of the foci of infection. We performed a clinical observation (case study) of a case of epidemic hemorrhagic fever with a fatal outcome at the Regional Clinical Infectious Diseases Hospital in March 2022. The object of the study is statistical data on officially registered cases of epidemic hemorrhagic fever in Primorsky Krai from 1995 to 2021.

RESULTS: The proportion of random factors in the epidemic process of epidemic hemorrhagic fever in the period under review was 28.7% of the incidence, which formed deviations from the typical curve, but did not participate in the formation of cyclicity in the long-term dynamics. Variable factors that formed cyclicity and random deviations together determined 53.4% of the incidence. They were fully related to seasonal morbidity (67.8%). Moreover, the remaining 14.4% of seasonality was formed by constant factors for each month. Factors constant for all months of the year form a year-round form, that is, 32.2% of the incidence.

In the clinical and epidemiological observation of a lethal case of epidemic hemorrhagic fever, infection was noted under conditions of dust formation, such as when restoring order in a closed room at a negative temperature (sweeping) and high titers of specific antibodies resulting from repeated encounters with the pathogen in residential and occupational types of morbidity and the accompanying illnesses.

CONCLUSIONS: The study of the incidence of epidemic hemorrhagic fever demonstrated a high resolution of epidemiological analysis by using a binary method in zoonoses. The patterns and features of human morbidity were controlled by natural and social factors more strictly than by biological ones. The determinants of the socio-ecological system in epidemic hemorrhagic fever in Primorsky Krai make it possible to specify the tactics and strategy for the implementation of epidemiological surveillance.

Keywords: epidemic hemorrhagic fever; binary method of analysis, lethality, types of morbidity.

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ECO•VECTOR

BACKGROUND

Haemorrhagic fever with renal syndrome has a high profile among zoonotic infections [1]. It is of high clinical significance. The proportion of severe cases ranges from 7.5 to 21.9% in the federal districts [2]. Mortality in different types of orthochantavirus infections ranges from 1–10% (haemorrhagic fever with renal syndrome) to 50% (hantavirus cardiopulmonary syndrome) [3, 4].

In Primorsky Krai, as in many areas of the Russian Federation, the incidence of haemorrhagic fever with renal syndrome is consistently low and has been thoroughly studied by epidemiologists [5, 6]. In contrast, epizootics are highly dynamic but labour-intensive to visualize and model [7, 8]. The methodological problem arises of the intersection of low human morbidity with a potent zoonotic reservoir of infection. Assessing the ratio of accidental and regular factors in the epidemic process of hemorrhagic fever with renal syndrome has not been solved. From a clinical point of view, it is relevant to study the causes of severe and fatal cases, the regularity of the manifestations of the epidemic process in foci of this infection.

The aim of the study was to establish the role of the main determinants of the epidemic process in the long-term incidence of hemorrhagic fever with renal syndrome in Primorsky Krai, and to demonstrate the causality of local manifestations in an epidemic focus based on clinical observation of a fatal case of hemorrhagic fever with renal syndrome.

MATERIALS AND METHODS

Research design

A comprehensive descriptive epidemiological study.

Terms and conditions

The article used statistical data from the FBUZ Center for Hygiene and Epidemiology in Primorsky Krai on officially registered cases of hemorrhagic fever with renal syndrome from 1995 to 2021 (Form No. 2, monthly, annual). Data on cases of hemorrhagic fever with renal syndrome from infectious disease registers (Form No. 60) for the period from 2017 to 2021: age, sex, occupation, position, residence, organization (in children). Data from the Annex to Decree of the Chief State Sanitary Doctor of Russia dated 21.10.2010 N 133 "Act of epidemiological investigation of foci of infectious (parasitic diseases) with establishment of causal relationship"[1] to study transmission routes and types of morbidity.

This is a clinical description of a fatal case of hemorrhagic fever with renal syndrome in a patient hospitalized at the Regional Clinical Infectious Disease Hospital in March 2022. The epidemiological surveillance method of a single case outbreak was used to discuss risk factors.

Statistical analysis

Spatial characterization of the distribution in hemorrhagic fever with renal syndrome was performed for the last complete cycle of multiyear dynamics (2017–2021) by administrative-territorial entities of Primorsky Krai. Given the low incidence of the disease, Poisson distribution statistics of rare events were used and the average multi-year absolute number of cases was calculated, which allowed an objective assessment of the epidemiological situation.

Epidemiological analysis of socio-ecological factors in haemorrhagic fever with renal syndrome (determinants of the epidemic process) was carried out using the binary method [9]. The role of biological factors (cyclic and basal components) was studied for periods from 1995 to 2010 and from 2011 to 2021. The structure of natural (seasonal and year-round components) and social (random and regular manifestations) factors was studied for the period from 2011 to 2021.

RESULTS

Structure of biological factors

Two periods can be distinguished in the long-term dynamics of the incidence of hemorrhagic fever with renal syndrome among the population of Primorsky Krai from 1995 to 2021. The first, from 1995 to 2010, had an average incidence of 3.5 per 100,000 population, with a weak downward trend of 2.2% per year (Fig. 1). Cyclical variations accounted for 25.2% of morbidity and the baseline part for 74.8%. Cycles were formed with a duration of 2 to 4 years with moderate to weakly pronounced amplitude. The second period of multi-year incidence, from 2011 to 2021, had an average level of 2.5 cases per 100,000 population and a pronounced downward trend with an annual rate of 10.0%. The cyclical component of morbidity was 24.7% and the baseline component was 75.3%. Two cycles with a moderate amplitude of 4–5 years were formed.

Thus, the structure of biological factors did not differ between the periods in question (common determinants or predictors). It manifested itself integrally in the same proportion of the variable component of morbidity, formed by changes in immunity and susceptibility of reservoir animal species, virulence and antigenicity of pathogen populations. The cyclicality of the long-term dynamics of human morbidity is formed secondary to the cyclicality of the epizootic process. In contrast, the difference in trend expression between the two periods (2.2% and 10.0%) can hardly be explained by a biological factor. It was probably determined by social factors: a reduction in the probability of contact with a reservoir of infection or an increase in the effectiveness of anti-epidemic work.

[1] Resolution of Chief State Sanitary Doctor of Russian Federation of 21 October 2010 N 133 "On optimisation of anti-epidemic work and approval of form of certificate of epidemiological investigation of focus of infectious (parasitic) disease with establishment of causal relationship". Access mode: https://base.garant.ru/12180676/.

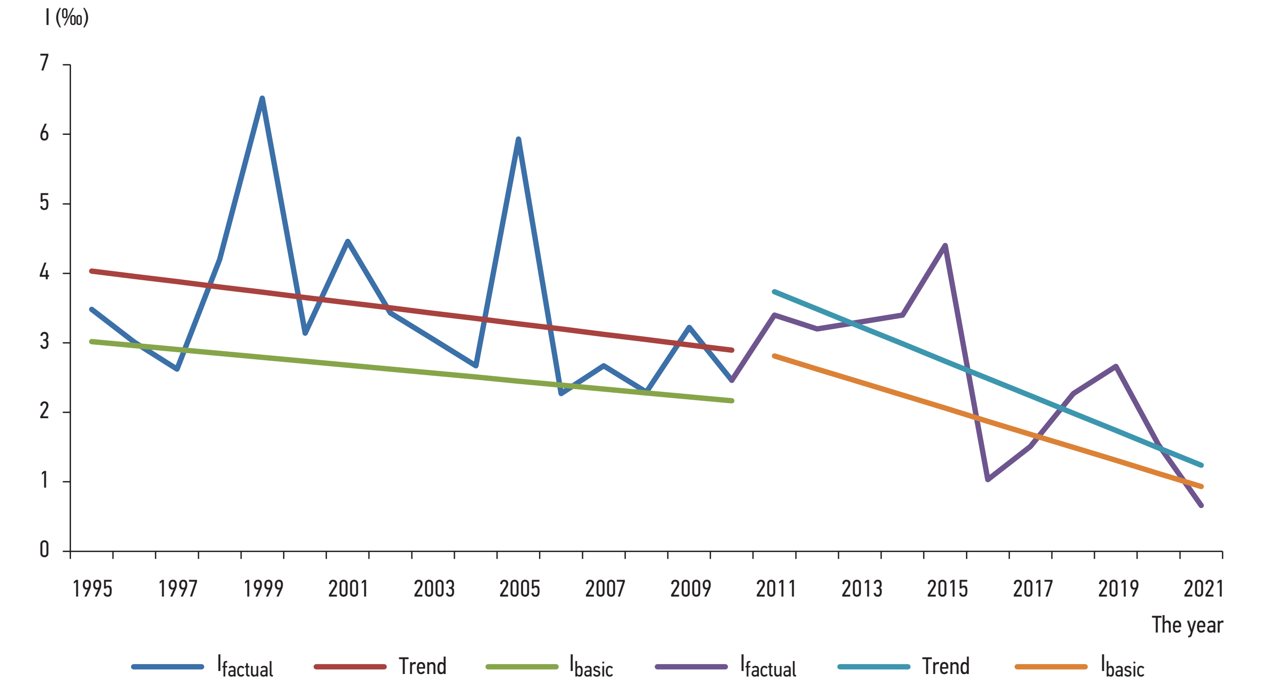

Fig. 1. Long-term dynamics of the incidence of hemorrhagic fever with renal syndrome in Primorsky Krai from 1995 to 2021 (on the "X" axis — years, on the "Y" axis — incidence per 100,000 population; $I_{factual}$ — actual incidence; trend — trend line; I_{basic} — baseline incidence).

We chose the second period as the object of our analysis. A typical curve of annual morbidity dynamics was characterised by two peaks (Fig. 2): the spring-summer epidemic period (May-June) and the autumn-winter upswing (October-December). The proportion of morbidity above the year-round level, which was controlled by seasonal factors, was 67.8%, while constant year-round factors accounted for 32.2%. February and September had the lowest levels.

The contribution to morbidity of the infectious-immunological mechanism was higher than the upper limit of year-round morbidity, calculated according to the method of I.P. Paltyshev and A.N. Gerasimov [10], and amounted to

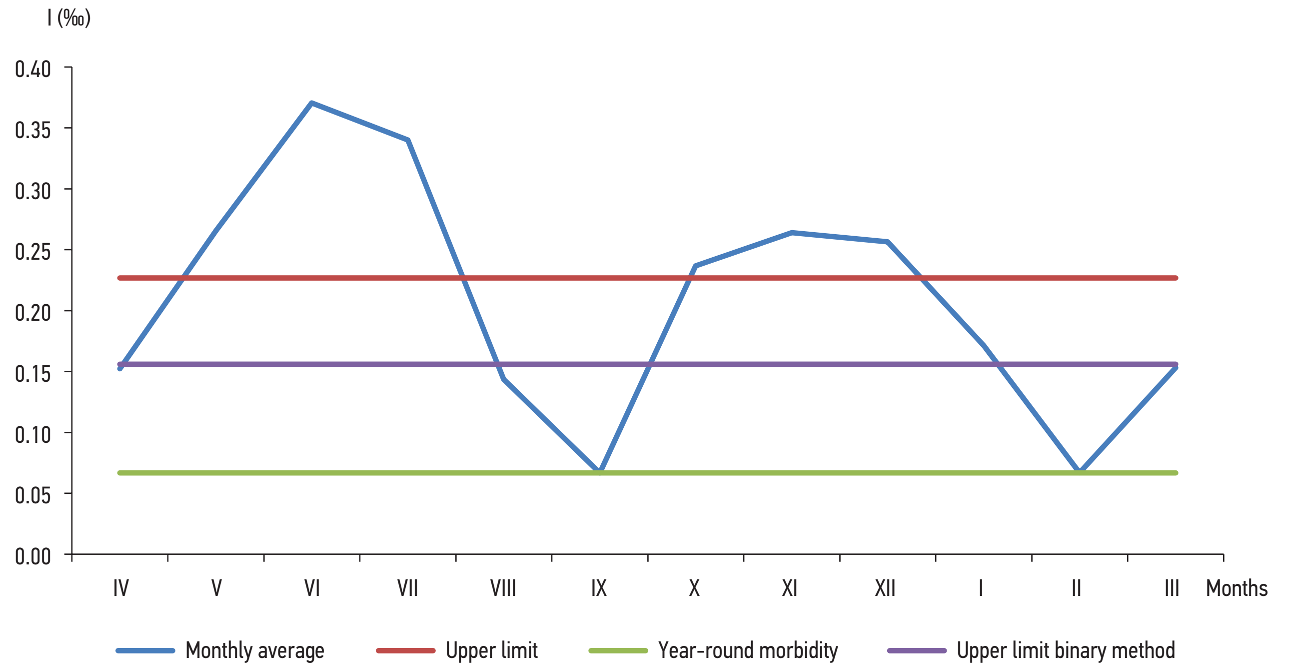

Fig. 2. A typical curve of the annual dynamics of the incidence of hemorrhagic fever with renal syndrome from 2011 to 2021 (on the "X" axis — the months from April to March, on the "Y" axis — the incidence per 100,000 population).

15.0%. In anthropogenic infections, it usually coincides with the proportion of cyclical morbidity in the structure of the multiannual dynamics. In the example of haemorrhagic fever with renal syndrome in Primorsky Krai, the cyclical component of the multiyear trend was almost 10% higher. Consequently, this method of upper limit determination has a large margin of error, which is due to the low absolute number of cases of hemorrhagic fever with renal syndrome in Primorsky Krai in the years considered and the wide confidence interval in the statistics of rare events for a small number of cases. The use of the binary method to calculate the upper limit of year-round morbidity eliminated error and made the estimation and characterization of epidemic manifestations objective [9].

The proportion of incidental factors in the epidemic process of haemorrhagic fever with renal syndrome during the period under review was 28.7%. They formed deviations from the type curve, but did not participate in the cyclicity in the multiyear dynamics. Consequently, this is the basal part of the morbidity (a non-cyclical add-on to the multiannual rates), and it is manifested and assessed through the participation of seasonal factors. Theoretically, when the proportion of year-round morbidity is high, accidental factors can also shape it. However, on the one hand, this contradicts the notion of constant factors; on the other hand, variable factors forming cyclicality and random deviations together determine 53.4% of morbidity. This proportion refers entirely to seasonal morbidity (67.8%). Moreover, 14.4% is left to seasonality formed by factors constant for each month (this is not much). They are both regular and basic. And the factors constant for all months of the year form a year-round pattern, similarly regular and basic, which accounts for 32.2% of the morbidity. Human association with natural and anthropogenic foci of haemorrhagic fever with renal syndrome — close and continuous throughout the calendar year — forms almost 1/3 of the morbidity.

Thus, the seasonal increase in morbidity has a very complex pattern of formation (Table 1); however, despite the seeming randomness and chaotic nature of morbidity in individual years, the epidemic process of haemorrhagic fever with renal syndrome in Primorsky Krai is strictly deterministic.

Structure of patients with haemorrhagic fever with renal syndrome

In the structure of hemorrhagic fever with renal syndrome patients in Primorsky Krai (from 2017 to 2021), children under 17 years (inclusive) were represented by single cases (1–2), which were not registered every year. Persons aged 51 years and older had a significant proportion ranging from 10.7% (2017) to 39.3% (2020). The main proportion was in the 18–50 age group, ranging from 53.6% (2020) to 89.3% (2020). This is a typical age distribution for zoonotic infections with a natural foci.

Professional risk groups (forestry, agriculture, transport) accounted for 10.6% (2019) to 20.0% (2021) of adult cases by employment. Unemployed people had the highest proportion of cases of haemorrhagic fever with renal syndrome: they accounted for 40.0% (2021) to 57.7% (2020) of cases. Other occupational groups and pensioners accounted for 26.9% (2020) to 46.2% (2018).

The study of infection conditions (occupation, position, place of work, conditions and place of residence, employment, pastime) in patients with hemorrhagic fever with renal syndrome allowed us to create a working model of disease types by sphere of vital activities (Table 2). The basic one is a house type (family, household) of morbidity (34.6%): infection occurs during service of a household, house property with outbuildings in the private sector. Dacha and horticultural types are closely related (9.8%). The socio-biological sphere (home) thus accounts for 44.4% of the incidence.

The occupational types (transport, agriculture) can account for 14.3% of the incidence, and another 19.4% of the incidence is the occupational type (conditions of infection in the unemployed, marginalised and retired people when extracting income and food through occupational activities). Together, these types belong to the social sphere (work) and

Table 1. Analysis of the incidence of hemorrhagic fever with renal syndrome from 2011 to 2021 by factors of parasitic and socio-ecological systems (binary analysis)

Medium		**2,5%ooo**					
Biological[1]		**Social**		**Biological[2]**		**Natural**	
Basic	75.3	Random	28.7		28.7	Seasonal	28.7
		Legitimate	46.5	Basic	46.5	Year-round	32.2
						Seasonal	14.4
Cyclical	24.7	Legitimate	24.7	Epidemic	15.0	Seasonal	24.7
	-			Error	9.8	-	-
Total (%)	100	-	100		100	-	100

Note: [1] — the upper limit was calculated using the binary method; [2] — the upper limit was calculated according to I.P. Paltyshev and A.N. Gerasimov [10].

Table 2. Structure of morbidity of the population by types and spheres of life activity from 2016 to 2021

Sphere	Type of morbidity	*P*, %
Home	Housing	34.6
	Gardening and gardening	9.8
Work	Professional industrial	7.3
	Vocational agriculture	7.0
	Fishing	19.4
Consumption	Recreational	19.4
Not established		2.5
Total		100

account for 33.7% of the incidence. The socio-cultural sphere (consumption), in the field of leisure activities (recreational, tourist types) account for 19.4% of the incidence.

Thus, the formation of the epidemic process at the expense of the three spheres of human activity leads to a stable situation. The downward trend in the incidence of the disease may be determined by the loss of relevance of the residential and horticultural types of disease (the home sphere), which previously accounted for up to 59.1% [8].

Territorial structure

The spatial distribution of haemorrhagic fever with renal syndrome in Primorsky Krai is characterized by zonal features (Fig. 3). Areas with persistent morbidity are linked to the Razdolnaya and Ussuri river basins. These are the western, often border areas with the People's Republic of China, and the cities of Primorsky Krai. The maximum annual average number of cases of haemorrhagic fever with renal syndrome was as follows: Vladivostok — 10.8, an incidence

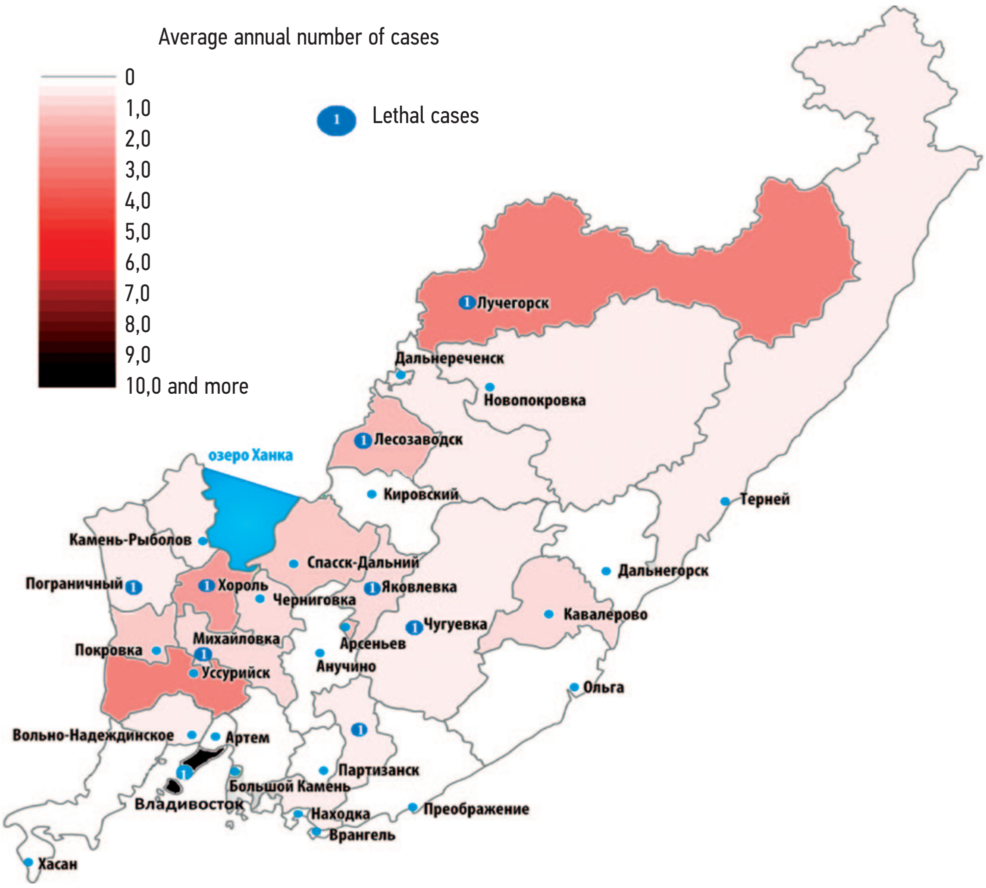

Fig. 3. Territorial distribution of the average annual number of cases of hemorrhagic fever with renal syndrome by cities and administrative territories of Primorsky Krai; data for 2017–2021 (total deaths).

of 1.7 prosantimille (‰); Ussuriisk — 2.8 (1.4‰); Pozharsky district — 2.8 (10.0‰); Khorolsky District, 2.0 (7.4‰); Arseniev, 1.4 (2.7‰); Lesozavodsk, 1.4 (3.3‰); Spassk-Dalny, 1.2 (1.7‰); Oktyabrsky District, 1.2 (4.4‰). Lethal outcomes were predominantly observed in endemic areas, and no significant statistical correlation with the number of cases of GLPS, correlation of morbidity and mortality was found.

Description of a fatal case of haemorrhagic fever with renal syndrome

To assess conditions of clinical manifestations in patients with haemorrhagic fever with renal syndrome in epidemic foci, we used individual case-fatality surveillance.

About the patient. A 38-year-old patient was admitted to the Regional Clinical Infectious Disease Hospital on 20 March 2022.

Past medical history. She fell ill on 15 March 2022, experienced weakness, malaise, pain in the muscles of the lumbar region and trunk, chills with sweating. On the day of admission to hospital (20 March 2022) she had fever of 39°C, stopped urinating. On examination by emergency physician — jaundice of skin, diffuse changes of parenchymatous organs on ultrasonic examination. The patient was taken to an infectious diseases hospital with suspicion of viral hepatitis. Blood and urine tests (Table 3) and tests for coronavirus antigens (Ag SARS CoV-2), hepatitis B surface antigen (HBsAg) and hepatitis C virus specific immunoglobulins classes M and G (anti-HCV) were performed in the emergency room, all negative. Preliminary diagnosis: Haemorrhagic fever with renal syndrome.

Past medical history. Was treated for post-traumatic encephalopathy at age 16 (2000). The same year she was diagnosed with grade II hypertension, risk 2. She was on perindopril and bisoprolol for a long time.

Lived in a well-appointed flat in Vladivostok on the 1st floor. Worked in the storage room of an office where she noted the presence of rodents and cleaned (swept) their products.

Results of laboratory and instrumental investigations. On 20.03.2022 at 23:50 a.m. the patient was admitted to the intensive care unit for clinical indications. Progressive decline in blood pressure and development of shock. Norepinephrine vasopressor support (6 ml/h, 0.4 μg/kg per minute) was connected. Blood pressure increased to 112/65 mmHg. A 500 ml of concentrated urine was obtained: colour of meat slop, dark. Urine and blood tests were carried out (see Table 3).

On 21.03.2022, indirect fluorescent antibody detection revealed hantavirus antibodies in titer 1:256. The haemodynamic parameters remained stable. Against a background of vasopressor support with norepinephrine (6 ml/h, 0.4 μg/kg per minute), 1025 ml of urine was obtained (hourly diuresis was 0.6 ml/kg per hour).

On 22.03.2022 she complained of abdominal pain throughout the abdomen, marked weakness, malaise, dry mouth and thirst. She had no appetite, vomiting and nausea. Body mass index 30.46 kg/m^2. General condition was severe. Body temperature did not exceed 37°C. Jaundice of skin and sclerae increased. Stools were delayed, gas was not excreted. Oliguria (250 ml of urine). Increasing bilirubin,

Table 3. Dynamics of clinical and laboratory parameters of the patient

Analysis	Indicator	20.03; 17:35	21.03	22.03
Blood	Hyperbilirubinemia	9 norms	13 norms	18 norms
	Transaminase activity	3 norms	-	-
	Azotemia	3 norms	3 norms	Creatinine clearance — 19 ml/min
	Cytolysis	-	5–6 norms	9–14 norms
	Hypercoagulation, ng/ml	-	D-dimer — 6959	>6000
	Procalcitonin, ng/ml	-	8.5	-
	Hv, g/l	15.9	15	14.9
	Erythrocytes	5.2×10 /l^{12}	5.0×10 /l^{9}	4.94×10 /l^{12}
	White blood cells	10.5×10 /l^{9}	10.1×10 /l^{9}	5.6×10 /l^{9}
	Platelets	48×10 /l^{9}	38×10 /l^{9}	38×10 /l^{9}
	Erythrocyte sedimentation rate, mm/h	18	-	30
Urine	Specific weight	1025	1030	-
	pH	-	5	-
	Protein, g/l	0.1	1.5	-
	White blood cells, in the field of view	2–3	10	-
	Erythrocytes, in the field of view	10–15	15–50	-

cytolysis (predominantly aspartate aminotransferase; de Ritis coefficient 1.14) in tests. Increasing azotemia (see table 3). Chest radiograph shows increased pulmonary pattern in all pulmonary cords, infiltration of pulmonary tissue in S_3 on the right. Ultrasound of the abdominal organs, kidneys showed diffuse changes in the liver, pancreas, kidneys, splenomegaly, thickening of the gallbladder walls.

Outcome. No haemodialysis was carried out due to the severity of the condition, impossibility of transport and low platelet count. On 23.03.2022, despite intensive care, death occurred at 02:00.

Study of an epidemic outbreak. Epidemiological investigation of a fatal outbreak of haemorrhagic fever with renal syndrome showed that it was a local case with infection at the place of work (Vladivostok). The route of infection was aspiration. The source of infection was rodents inhabiting the storage rooms of the office. In view of many years of work in the office and marked character of immune response, it is possible to assume, that there were repeated contacts with contaminated material. Dry cleaning of the storage rooms after the winter season was accompanied by the formation of a concentrated aerosol.

DISCUSSION

In the socio-ecological system, which forms the morbidity of hemorrhagic fever with renal syndrome, the seasonal component of natural factors (67.8%) stands out, including 24.7% of the cyclic component (infection-immunological mechanism), 28.7% of the random component (social activity), and 14.4% of factors constant for each month (activating transmission mechanism). The cyclical and random components have a high proportion in the parasitic system, which determines the great variability of manifestations in individual calendar years.

Random factors are realised in fishing (work) and recreational (consumption) types of morbidity [11]. A causal chain is possible: weather-calendar-social human behaviour. The participation of the unemployed, marginalized populations, pensioners determines the specificity of the socio-ecological system by social factors. Probably at the expense of participation of these contingents is formed 28,7% of morbidity by casual factors (weather, yield of wild-growing products, requirements of the population).

Of the stable components of the socioecological system, the proportion of year-round (32.2%) and constant seasonal (14.4%) morbidity is high. Consequently, in haemorrhagic fever with renal syndrome we are dealing with a stable (zoonotic) reservoir. The contribution of the infectious-immunological mechanism, determined by the size of the susceptible animal population, fluctuations in their population size, which depends on breeding and feeding grounds, is 24.7%.

The spatial distribution of hemorrhagic fever with renal syndrome cases in Primorsky Krai for the years under consideration most closely corresponds to the habitat of the field mouse (*Apodemus agrarius*) and the Far Eastern vole (*Microtus fortis*), with only *Apodemus agrarius* considered as a significant reservoir of hemorrhagic fever with renal syndrome pathogens [7]. It is the biological features of the field mouse [12], such as reproduction from 3–4 to 5–6 times a year, absence of hibernation, and the semi-synanthropic behavior (it inhabits populated areas in autumn and winter with 24-hour activity), that ensure the established pattern of disease incidence in Primorsky Krai.

From a theoretical perspective, it is of interest to discuss the mechanism of transmission in hemorrhagic fever with renal syndrome in the epizootic in field mice (according to V.D. Belyakov, a non-transmissible mechanism of transmission). Field mice feed on plant (seeds, berries, plant parts) and animal (insects) food. In the absence of vector-borne transmission, both fecal-oral and aerosol transmission are possible. In our opinion, since the virus is present in the respiratory organs, there is reason to assume an aerosol transmission mechanism not characteristic of zoonoses.

Biological characteristics of rodents, in particular living in burrows, warehouses, barns (anthropocenoses and agrocenoses), family formation, reproduction up to 5–6 times per year, food stockpiling, cohabitation and feeding, are capable of spreading the pathogen through respiration. The aerosol transmission mechanism is realised by two main routes, airborne and aspiration (with urine, to a lesser extent with faeces), and an additional route, foodborne. The arguments against the faecal-oral mechanism of transmission are the lack of conclusive evidence for the relevance in humans of the aquatic route and the low frequency of foodborne outbreaks.

Based on the survey of epidemic foci from 2017 to 2021, the aspiration route of human infection accounted for 85.7% (2017) to 100% (2021). The case of haemorrhagic fever with renal syndrome with fatal outcome considered also corresponds to the aspiration route of infection. The low activity of food and waterborne transmission is indicated, firstly, by the low proportion of infected children (and children should be involved much more frequently with the waterborne route). Secondly, the small absolute number of cases among marginalized populations (the unemployed) engaged in hunting in natural foci (providing markets in the region with wild-growing products), and the incomparable size of the zoonotic reservoir and the number of group cases of the disease (single cases).

The main argument for an aerosol transmission mechanism is the morphological structure and taxonomic characteristics of the pathogen. Hantavirus belongs to the order Bunyavirales, which was distinguished in 2016 [13]. Most of its representatives are transmissible viruses, which allows this mechanism of transmission to be considered basic. However, in the family *Hantaviridae,* viruses have non-transmissible pathways: these are RNA viruses with a spherical virion covered by a lipid shell [14], characteristic of many pathogens with an aerosol transmission mechanism [15].

In scientific sources, "contamination in a dusty environment" and a high viral load are noted as individual risk factors for severe clinical presentation and lethal outcomes. This is realised by tidying up closed rooms (sweeping), especially in sub-zero temperatures. Another individual risk factor is the high titres of specific antibodies in the urine of patients [16], which may result from repeated encounters with the pathogen in residential and occupational types of infection. Both individual risk factors are present in the clinical and epidemiological case report of haemorrhagic fever with renal syndrome with a fatal outcome.

CONCLUSION

The study of the incidence of hemorrhagic fever with renal syndrome demonstrates the high resolution of epidemiological analysis using the binary method in zoonoses. The incidence of hemorrhagic fever with renal syndrome is strictly determined by the epizootic process, but the patterns and characteristics of human morbidity are controlled by natural and social factors more strictly than biological ones.

The analysis shows the basic structure of the socio-environmental system in haemorrhagic fever with renal syndrome in Primorsky Krai, which should be used to develop tactics and strategies for epidemiological surveillance.

ADDITIONAL INFORMATION

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REFERENCES

1. Morozov VG, Ishmukhametov AA, Dzagurova TK, Tkachenko EA. Clinical manifestations of hemorrhagic fever with renal syndrome in Russia. *Meditsinskiy sovet*. 2017;(5):156–161. (In Russ).

2. Savitskaya TA, Ivanova AV, Isaeva GS, et al. Assessment of epidemiological situation on hemorhhagic fever with renal syndrome around the world and in Russia: Forecast for 2020. *Problems of particularly dangerous infections*. 2020;(2):62–70. (In Russ). doi: 10.21055/0370-1069-2020-2-62-70

3. Kruger DH, Figueiredo LT, Song JW, Klempa B. Hantaviruses: Globally emerging pathogens. *J Clin Virol*. 2015;(64):128–136. doi: 10.1016/j.jcv.2014.08.033

4. Kompanets GG, Iunikhina OV. To the history of the discovery and research in to hemorrhagic fever with renal syndrome. *Public health and life environment*. 2021;(5):33–38. (In Russ). doi: 10.35627/2219-5238/2021-338-5-33-38

5. Kiriakov VY, Reshetnyak EA. Peculiarities of some of the epidemic hemorrhagic fever with renal syndrome in Primorsky region. *Health. Medical Ecology. Science*. 2015;(4):118–121. (In Russ).

6. Iunichina OV. Features incidence of hemorrhagic fever with renal syndrome among certain groups of Primorsky Region. *Health. Medical Ecology. Science*. 2016;(2):57–59. (In Russ). doi: 10.18411/hmes.d-2016-080

7. Slonova RA, Simonov SB, Kompanets GG, et al. Hantavirus infection in Primorsky Krai. Medical-geographical atlas. Vladivostok; 2007. 46 p. (In Russ).

8. Zakharova GA, Prosyannikova MN, Burukhina YG, Khomichuk TF. On the epidemiological situation of hemorrhagic fever with renal syndrome in Primorsky Krai in 2009–2010. *National priorities of Russia*. 2011;(2);101–102. (In Russ).

9. Kolpakov SL. Binary method of the epidemiological analysis of infectious incidence. *Epidemiology and Infectious Diseases*. 2018;23(5): 212–219. (In Russ). doi: 10.18821/1560-9529-2018-23-5-212-219

10. Paltyshev IP, Gerasimov AN. Methodology for determining the timing of the beginning and end of seasonal rises. In: Theoretical problems of epidemiology and infectious immunology at the present stage: Abstracts of reports for the conference. Ed. by V.I. Pokrovsky. Nalchik: B.i.; 1986. P. 52–55. (In Russ).

11. Yanovich VA, Kolpakov SL. Systematization of types of infectious morbidity in the study of epidemic process. *The Far eastern journal of infectious pathology*. 2020;(38):104–111. (In Russ).

12. Gromov IM, Yerbayeva MA. Mammals of the fauna of Russia and adjacent territories. Lagomorphs and rodents. Saint-Petersburg; 1995. 522 p. (In Russ).

13. Briese T, Alkhovskiy SV, Beer M, Calisher CH. Create a new order, Bunyavirales, to accommodate nine families (eight new, one renamed) comprising thirteen genera. ICTV [International Committee for Taxonomy of Viruses] Proposal (Taxoprop) No. 2016.030a-vM. doi: 10.13140/RG.2.2.27230.2336813

14. Jonsson CB, Figueiredo LT, Vapalahti OA. Global perspective on hantavirus ecology, epidemiology, and disease. *Clin Microbiol Rev*. 2010;23(2):412–441. doi: 10.1128/CMR.00062-09

15. Kolpakov SL. The mechanism of parasite transmission as a tool of evolution and a criterion for a taxonomy of infectious disease. *Pacific Med J*. 2022;(3):24–31. (In Russ). doi: 10.34215/1609-1175-2022-3-24-31

16. Iunikhina OV, Maksema IG, Savko SA, Kompanets GG. The level of specific antibodies in biological fluids as a criterion for the severity of clinical manifestations of hemorrhagic fever with renal syndrome. *Young Sci*. 2020;(50):376–378. (In Russ).

СПИСОК ЛИТЕРАТУРЫ

1. Морозов В.Г., Ишмухаметов А.А., Дзагурова Т.К., Ткаченко Е.А. Клинические особенности геморрагической лихорадки с почечным синдромом в России // Медицинский совет. 2017. № 5. С. 156–161.

2. Савицкая Т.А., Иванова А.В., Исаева Г.Ш., и др. Оценка эпидемиологической ситуации по геморрагической лихорадке с почечным синдромом в мире и России: прогноз на 2020 г. // Проблемы особо опасных инфекций. 2020. № 2. С. 62–70. doi: 10.21055/0370-1069-2020-2-62-70

3. Kruger D.H., Figueiredo L.T., Song J.W., Klempa B. Hantaviruses — globally emerging pathogens // J Clin Virol. 2015. N 64. P. 128–136. doi: 10.1016/j.jcv.2014.08.033

4. Компанец Г.Г., Иунихина О.В. К истории открытия и изучения геморрагической лихорадки с почечным синдромом // Здоровье населения и среда обитания. 2021. № 5. С. 33–38. doi: 10.35627/2219-5238/2021-338-5-33-38

5. Киряков В.Ю., Решетняк Е.А. Некоторые особенности протекания эпидемического процесса геморрагической лихорадки с почечным синдромом в Приморском крае // Здоровье. Медицинская экология. Наука. 2015. № 4. С. 118–121.

6. Иунихина О.В. Особенности заболеваемости геморрагической лихорадкой с почечным синдромом среди отдельных групп населения Приморского края // Здоровье. Медицинская экология. Наука. 2016. № 2. С. 57–59. doi: 10.18411/hmes.d-2016-080

7. Слонова Р.А., Симонов С.Б., Компанец Г.Г., и др. Хантавирусная инфекция в Приморском крае. Медико-географический атлас. Владивосток, 2007. 46 с.

8. Захарова Г.А., Просянникова М.Н., Бурухина Е.Г., Хомичук Т.Ф. Об эпидемиологической ситуации по геморрагической лихорадке с почечным синдромом в Приморском крае в 2009–2010 гг. // Национальные приоритеты России. 2011. № 2. С. 101–102.

9. Колпаков С.Л. Бинарный метод эпидемиологического анализа факторов эпидемического процесса // Эпидемиология и инфекционные болезни. 2018. № 5. С. 212–219. doi: 10.18821/1560-9529-2018-23-5-212-219

10. Палтышев И.П., Герасимов А.Н. Методика определения сроков начала и окончания сезонных подъемов // Теоретические проблемы эпидемиологии и инфекционной иммунологии на современном этапе: тезисы докладов к конференции / под общ. ред. В.И. Покровского. Нальчик: Б. и., 1986. С. 52–55.

11. Янович В.А., Колпаков С.Л. Систематизация типов инфекционной заболеваемости в изучении эпидемического процесса // Дальневосточный журнал инфекционной патологии. 2020. № 38. С. 104–111.

12. Громов И.М., Ербаева М.А. Млекопитающие фауны России и сопредельных территорий. Зайцеобразные и грызуны. Санкт-Петербург, 1995. 522 с.

13. Briese T., Alkhovskiy S.V., Beer M., Calisher C.H. Create a new order, Bunyavirales, to accommodate nine families (eight new, one renamed) comprising thirteen genera. ICTV [International Committee for Taxonomy of Viruses] Proposal (Taxoprop) No. 2016.030a-vM. doi: 10.13140/RG.2.2.27230.23368

14. Jonsson C.B., Figueiredo L.T., Vapalahti O.A Global perspective on hantavirus ecology, epidemiology, and disease // Clin Microbiol Rev. 2010. Vol. 23, N 2. P. 412–441. doi: 10.1128/CMR.00062-09

15. Колпаков С.Л. Механизм передачи паразита как механизм эволюции и критерий систематики инфекционных болезней // Тихоокеанский медицинский журнал. 2022. № 3. С. 24–31. doi: 10.34215/1609-1175-2022-3-24-31

16. Иунихина О.В., Максема И.Г., Савко С.А., Компанец Г.Г. Уровень специфических антител в биологических жидкостях как критерий тяжести клинических проявлений геморрагической лихорадки с почечным синдромом // Молодой ученый. 2020. № 50. С. 376–378.

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