DOI: 10.17816/KMJ2020-775 

# Problems and prospects of studying hemorrhagic fever with renal syndrome in the Republic of Tatarstan

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## Abstract

The paper presents the history of the study of hemorrhagic fever with renal syndrome (HFRS) at the Kazan Research Institute of Epidemiology and Microbiology from the beginning of the 50s to the present. The accumulated information allows to draw up general conceptions about the main source of infection, the biological structure of natural foci of infection, nosoarea and the main clinical forms of the disease, the nature and seasonality of the disease, the sex and age composition of patients, and the types of natural foci of HFRS. The stages of improving the methods of laboratory diagnosis of HFRS, development of a specific immunoglobulin against the serum of the Puumala virus are described. A significant contribution to the study of HFRS was the landscape-epidemiological ranking of the territory of the Republic of Tatarstan and the Middle Volga endemic for HFRS, with the identification of zones of special risk of human infection and the main factors that form them. At present, a reference center for monitoring HFRS has been created based on the Kazan Research Institute of Epidemiology and Microbiology, and the study of the properties of HFRS pathogens at the current molecular-genetic level continues.
**Keywords**: hemorrhagic fever with renal syndrome, natural foci of infection, the epidemiological situation of HFRS, landscape and epidemiological zoning.

**For citation**: Boyko V.A., Savitskaya T.A., Trifonov V.A. et al. Problems and prospects of studying hemorrhagic fever with renal syndrome in the Republic of Tatarstan. *Kazan Medical Journal.* 2020; 101 (5): 775–785. DOI: 10.17816/KMJ2020-775.

Hemorrhagic fever with renal syndrome (HFRS) is a zoonosis caused by a pathogen that is widespread in Europe and Asia. In Russia, HFRS has a leading position in the incidence rate among natural focal infections.

In 1935, V.A. Targanskaya first described the clinical characteristics of HFRS based on the results of a survey conducted in 1934 on patients hospitalized at the clinic of the Far Eastern Medical University in Khabarovsk, Russia. She observed an unusual appearance of acute nephritis in three patients.

As noted by E.A. Tkachenko and A.A. Ishmukhametov [1], Soviet scientists and doctors, for a long time, considered that the spread of HFRS was only in the Russian Far East as all its descriptions in those years were based only on cases observed in the Khabarovsk and Primorsky territories and the Amur region. This thought was due to the fact that the People's Commissariat of Health of the USSR sent scientific expeditions to the Far East to study the new disease. These expeditions were under the leaderships of Professor V.I. Terskikh in 1937, Professor S.I. Tarasov in 1938, and Professor I.I. Rogozin in 1939. The expedition of the Gorky All-Union Institute of Experimental Medicine led by Professor A.A. Smorodintsev was undertaken in 1940. As a result of these studies, systematic description of the clinical features and experimental materials on the etiology of hemorrhagic nephrosonephritis in the Far East were identified in the early 40s [2–5]. In Japan, the first description of cases of HFRS in Manchuria was provided by M. Kitano in 1940 [6].

In 1976, H.W. Lee, P.W. Lee, and K. Johnson discovered the HFRS virus antigen in the blood of HFRS patients and tissue culture cells using the fluorescent antibody technique, and in the serum and plasma of HFRS patients and rodents from foci of infection using the complement binding reaction, indirect hemagglutination reaction, and gel diffusion–precipitation [7–9].

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Received 22.04.2020; accepted 08.06.2020.

*Beginning of the study of HFRS in the Volga region*. In the Middle Volga region, HFRS was first diagnosed in the early 50s by military doctors G.I. Yudin (1955) and T.A. Bashkirev (1957) (Fig. 1).

From 1955 to 2018, specialists of the Kazan Research Institute of Epidemiology and Microbiology (KRIEM); the Kazan State Institute of Advanced Medical Training; the Institute of Poliomyelitis and Viral Encephalitis of the USSR Academy of Medical Sciences; the sanitary-epidemiological and medical services in the Tatar, Mari, and Chuvash ASSR; a mobile sanitary-epidemiological detachment; and the medical service of the Volga military district actively participated in complex researches. As a result of these researches, voluminous material on etiology, epizootology, epidemiology, pathogenesis, and clinical features of this new nosological form of natural focal infections in the region was accumulated and analyzed [8,9]. The accumulated information provided a general idea about the main source of infection, biological structure of natural focal infections, nosoarea and main clinical forms of HFRS, nature and seasonality of incidence, sex and age compositions of patients, and types of nosofoci of HFRS [8]. The polyhostality (multihost ability) of the pathogen and the leading role of the bank vole in the epidemiology of HFRS were proved, and a correlation was found between the increase in incidence and the early onset of intensive reproduction of populations of this small mammal species. The results of these works were summarized in the collection of scientific works of the KRIEM in 1980 [9].

However, the database was formed in the absence of specific diagnostic methods. For example, incidence rates were calculated only based on the diagnosis of infectious diseases from clinical signs, which could lead to hypo- or overdiagnosis in almost half of the cases due to polymorphism of the disease, especially in mild cases. In fact, there was no knowledge about the nature of the epizootic process of HFRS among natural carriers, and the interpretation of the connection between the epidemic and epizootic processes was empirical because the correlation had to be estimated only by the presence of small mammals and their numbers in places where people were infected. It was difficult to identify the threatened populations because their differentiation was based on risk indicators of infection, where the immune layer is of great importance along with the incidence. The lack of objective information about the risk of infection in certain socioprofessional groups of the population limited non-specific prevention of HFRS to general (undifferentiated) measures.

*Improvement in methods of laboratory diagnostics of HFRS*. In 1979, the KRIEM learned and successfully applied the indirect fluorescent antibody technique, developed by H.W. Lee, P.W. Lee, and K. Johnson in 1976, for the detection of the HFRS virus antigen and antibodies (M.A. Zakharova, S.B. Bogdanova, and M.E. Ermolaeva). Later, a method for obtaining sufficient number of highly concentrated HFRS virus antigens from naturally infected bank voles was developed and applied in practice. Since 1980, this method helped to conduct all studies under the control of a specific diagnostic test. The fluorescent antibody technique and the enzyme immunoassay were successfully applied in the study of biological structure of natural foci in the Middle Volga region, nature of the epizootic process in populations of the main carrier of the pathogenic agent—bank vole, immune layer, and outbreaks; the diagnosis of acute, erased, and atypical forms of diseases and retrospective diagnostics; and so on.

**Fig. 1**. Timofey Antonovich Bashkirev, Director of the Kazan Research Institute of Epidemiology and Microbiology from 1970 to 1983, was the first to conduct research in the field of etiology, diagnosis, epidemiology, and prevention of hemorrhagic fever with renal syndrome.

Studies on etiology, diagnostics, epidemiology, and prevention of HFRS was initiated at the KRIEM under the leadership of T.A. Bashkirev, the head of the laboratory of natural focal infections (V.A. Boiko), and staff of the laboratory of natural focal infections, including I.N. Gavrilovskaya, Y.P. Kovalenko, L.G. Sultanbekova, S.B. Bogdanova, N.G. Konovalov, B.E. Barkan, V.A. Abasheva, V.G. Ivliev, and M.A. Zakharova (Fig. 2). The drug culture was obtained from the antigen of studied biological properties of the virus, isolated from the foci of HFRS in the Middle Volga region [8].

*Development of a specific immunoglobulin against Puumala virus serotype*. Since 1986, the KRIEM has been preparing a series of immunoglobulins against the Puumala virus serotype. The raw material used for the research was the serum from individuals with HFRS from then endemic areas of the Republic of Tatarstan (RT). The Cohn process was used for the purification and concentra-

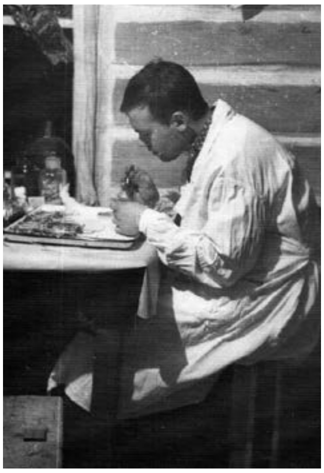

**Fig. 2**. A laboratory investigation of the zoological material by V. G. Ivliev, September 1976, the Almetyevsky area, Tatar ASSR.

tion of immunoglobulin without the loss of specific drug activity. The antibody titer was from 1:640 to 1:1280 and remained at 4°C–6°C for 5 years.

Clinical trials of immunoglobulins were conducted on 61 patients with HFRS at the infectious diseases clinics of Samara and Kazan Medical Institutes based on the data of a high virus-neutralizing activity of the obtained drug. In 1990, A. A. Suzdaltsev, V. S. Potapov, I. N. Gavrilovskaya, and O. A. Alekseev obtained the author's certificate for the invention (No. 1814903) dated 02.01.1990 (Fig. 3). In the trial, immunoglobulin was injected to patients in an interval of 2 to 9 days from the beginning of the disease. It was found that the optimal period for the injection of the drug was 2 to 6 days from the beginning of the disease at a dose of 0.5 mL/kg of body weight, which was recommended for practical use (6 mL 2 times a day intramuscularly for 1–2 days, a course dose of 12–24 mL). However, later, the production of the drug was interrupted due to the liquidation of the company.

Furthermore, a number of research works were carried out jointly with the Institute of Poliomyelitis and Viral Encephalitis of the USSR Academy of Medical Sciences. In one such research, under the academic leadership of M. P. Chumakov, attempts were made to create an experimental model of HFRS. From the study of materials from the foci of HFRS (Tula, Yaroslavl region, and Tatar and Bashkir ASSR), it was observed that the lungs of bank voles containing the antigen can be used for experimental infection of vivar bank voles, field mice, and pied wagtails, which could serve as model for passing the HFRS virus. At the same time, the authors found that the occurrence of animals with a significant accumulation of the antigen in their organs is rare, which makes it difficult to use them widely as a laboratory model.

Since 1957, many years of comprehensive research have been conducted under the guidance of Professor V. A. Boiko to study the epizootological activity and epidemic appearances of HFRS foci in the Middle Volga region [9–13]. The information base was based on long-term (1955–2018) personal materials of field observations of elements of focal complexes in expeditions to municipal districts of the RT (Fig. 4–6), in the order of stationary research in key natural and territorial complexes, as well as during targeted business trips to score group diseases and breakouts of HFRS among civil and military contingents.

In total, 156,250 trap nights were worked out in the forested areas with different species and age and composition of the stand, and 24,603 small mammals of 10 species were caught and processed, including 17,505 bank voles (*Myodes glareolus*). Organs (lungs) of 4,184 individuals were examined for the presence of HFRS antigen, including 2,907 bank voles, the leading species in the population of small forest mammals and the main source of human infection with the HFRS virus. Blood serum of 1,646 people was tested for the presence of specific antibodies (Ab) to the HFRS pathogen [14].

The following was also used in the analysis:

a) Calculated data on the biotopic preference of the bank vole; their dominance in the population of small forest mammals; and results of determining the spontaneous infection of the bank vole with the HFRS pathogen during the sporadic, epizootic, and panzootic courses of the infectious process in the populations of the species

b) Forest inventory information on the species and age and composition of the stand in the local forest areas of the State Forest Fund of the RT

c) Physical–geographical and landscape zoning of the territory of the RT

d) Data on population density (people/km$^2$) in municipal districts of the Republic (State Statistics Committee of the Republic of Tatarstan)

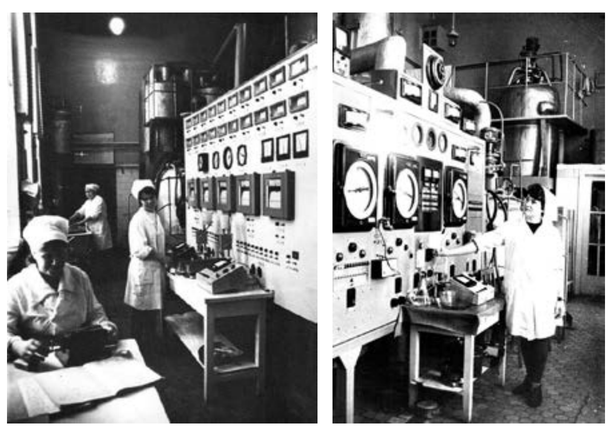

**Fig. 3**. Production of antibody against hemorrhagic fever with renal syndrome for a healthcare practice.

**Fig. 4**. Loading the GAZ-69 with straw for use in nesting sites of small forest mammals in the winter of 1976. On the right is the head of the laboratory of natural focal infections, Senior Staff Scientist (SSC), V. A. Boiko.

e) Information on incidence of HFRS for the entire period of the registration (the Rospotrebnadzor office of the RT)

Capture of small forest mammals and withdrawal of blood serum from the population and organs from animals to examine the presence of Ag or Ab was carried out according to the generally accepted methods (Gero crushers, live traps, enzyme immunoassay, polymerase chain reaction with standard test systems, binocular optics, including a dark field microscope, and so on).

We may include 12 species to the number of small mammals identified in HFRS foci. The bank vole was the dominant species everywhere (the dominance index was 69.1%–72.2%). The positional application of small mammals depends on the forage and size of the territories. Therefore, deciduous forests with a predominance of linden and aspen were indicative. They have the most stable stocks of basic (tree seeds) and seasonal (berries) feed. The bank vole forms the basic population of small mammals in linden and aspen forests, and the importance of wood and yellow-throated mice increases in oak forests.

The HFRS epizootic processes in bank vole populations have different forms of appearance on a large scale. The sporadic nature of the process is observed when the number of animals is low (up to 10 individuals per unit of account). With an increase in the population layer of older age groups (2–4 months), the process becomes epizootic, and up to 50% of animals are involved in the circulation of the virus. Finally, the panzootic process develops when almost the entire animal population has been infected. This process was observed in places of temporary concentration of migrant animals from breeding sites to border areas: omets, haystacks, straw, burts of root crops (potatoes, beets, and so on), human buildings (warehouses, schools, dugouts, and so on), with vivar content of bank voles.

**Fig. 5**. The arrangement of the stack over the nest. On the right is the head of the laboratory of natural focal infections, SSC, V. A. Boiko (1976).

**Fig. 6**. V. G. Ivliev removing the snow cover from the stack for further manipulations to catch animals and remove a collective nest with ectoparasites (1976).

The seasonal dynamics of the number of three rodent species in all landscape provinces does not differ in principle. From April to August/September, there is a gradual increase in the number of animals. The autumn population density is 3–16 times higher than its spring level.

Unfavorable weather conditions of the autumn period—significant downfall in October, an early establishment of a snow cover with its subsequent melting and freezing with the formation of an ice crust, and freezing of the soil—cause a mass migration of bank voles outside forest stations to field lands and human settlements, concentration of migrants in limited territories, and active dissemination of the HFRS pathogen among animals. Generally, these animals leave temporary stations after winter and migrate to their natural habitat.

A distinctive feature of the long-term dynamics of the number of animals in the island forests of the Middle Volga region is the lack of synchronicity of these processes in different territories (removal of forests by 60–80 km). The spatial disunity of woodlands determines the independence of reproduction processes in populations of small rodents.

A study conducted under the supervision of experts from the Institute of Poliomyelitis and Viral Encephalitis of the USSR Academy of Medical Sciences—A. D. Bernstein, Y. A. Myasnikov, and others—to study the link between the incidence of HFRS and peculiarities of epizootic process showed that the occurrence of the epizootic situation in the foci of HFRS was due to the increase in number of bank voles; intensive early breeding (February to March); its multiplication, leading to the spread of the virus among the young; and sharp increase in the number by the middle of summer. The snow-covered reproduction of the bank vole and the survival of young animals were affected by a good supply of seed food and weather conditions.

The incidence of HFRS in the forest centers of the European part of Russia largely depends on the state of the population of the main carrier, in particular, the increase in the incidence of the population followed by the early start of intensive breeding of bank voles. The incidence rate of the population and the emergence of epidemic foci are affected by the intensity of contacts between the population sources of the pathogen on the territory of the natural focus, which is reduced in years with low temperatures in the spring and summer and in years with high rainfall but increases under favorable climatic conditions.

During the period of 1959–2018, more than 25,800 cases of HFRS were officially registered among residents of urban and rural settlements in the RT with an average long-term intensive indicator of 13.2 per 100 thousand population.

In nosogeographic terms, major number of patients (68.4% ± 0.3%) was noted in the Zakamsky physical and geographical region of the national incidence rate with an average long-term indicators of intensive care of 20.2 per 100 thousand. Moreover, the immune layer among the forestry workers reached 35.0% ± 1.9%.

In the pre-Kama physical and geographical region, the proportion of cases was 29.5% ± 0.3% of the total incidence, with an average long-term intensive indicator of 7.9 per 100 thousand. Finally, in the pre-Volga physical and geographical region for the entire period of a registration, the diagnosis of HFRS was established in 2.1% ± 0.1% of all patients with an average long-term intensive indicator of 4.2 per 100 thousand.

Sporadic diseases prevail in the Republic (48.8%) and can be spread during short-term visits to forest areas (picking berries, mushrooms, nuts, fishing, hunting, haymaking, harvesting of twig food, brushwood, and so on.).

Nosofocus of this “forest” type of HFRS is formed mainly in the summer and autumn period with various infection conditions and transmission mechanisms.

Intensive development of the oil and gas industry in the RT has identified the formation of production type of nosofocuses of HFRS (18.3%), and a large-scale agricultural sector resulted in a relatively high incidence of agricultural type of nosofocus of HFRS (16.6%). The household type of nosofocus accounts for 11.7%; the garden-dacha type, 4.0%; and the camp type, 0.6% of all HFRS infections.

*Landscape epidemiological ranking of the territory of the RT and the Middle Volga region endemic for HFRS with the allocation of zones of special risk of human infection and the main factors that form them*. The accumulation of long-term representative materials in natural foci, etiology, pathogenesis, clinic, and epidemiology allowed us to formulate different approaches in typifying and zoning natural foci of infectious zooanthroponoses. All developments were carried out by the authors who studied this issue mainly on natural (landscape) and epidemiological (incidence) indicators [15, 16]. Some work in the field of landscape and epidemiological zoning of territories for HFRS enzootic processes was also performed by specialists of the Middle Volga region.

The main task of epizootic and epidemiological ranking is to identify natural and territorial complexes with a potentially high (relatively stable in time and space) risk of infection of the population. This method increases the effectiveness of epidemiological surveillance, as well as anti-epidemic and preventive protection measures.

Studies of the landscape features of the biological structure of HFRS nosofocus and their epidemiological appearances were carried out by employees of the laboratory of especially dangerous infections of the Mari El Republic, sanitary and epidemiological stations, and the laboratory of natural focal infections at the KRIEM under a creative agreement for 26 years. The analysis of the incidence and examination of the sites of HFRS infection (based on the anamnestic data of patients) allowed us to distinguish four groups of nosocomial foci with different potential (epizootic activity): I, high; II, medium; III, low; and IV, extremely low.

Nosofocus with a relatively high potential (I) coincided with broad-leaved fir forests, as well as to 25-year-old cuttings with a natural renewal of the native stand. These are the most optimal phytocenoses for feeding and harness for bank voles, whose populations can reach the maximum indicators here both in relative numbers (up to 90 individuals per unit of accounting) and in the specific weight of the species in the population of small forest mammals (up to 85% in groups). This group of nosofocus is characterized by a relatively active epizootic process with a high level (up to 50%) of spontaneous infection of hosts with the HFRS virus. The presence of persistent natural foci was confirmed by annual infections of people that ended in sporadic, group diseases, and outbreaks (up to two to three dozen people).

Nosofocus with an average potential (II) are localized mainly in small-leaved forests (birch, aspen, and so on), as well as in fir forests with a linden undergrowth, grass-marsh alders, and coupes with a natural renewal of reduced broad-leaved and small-leaved forests. The average long-term population of the bank vole is 2 times lower than the previous group of nosofocuses but with a fairly expressed specific weight in the population of small mammals (up to 75.0%). The spontaneous infection with the bank vole virus did not exceed 25.0%. Human incidence is only sporadic and has not been recorded every year.

Nosofocus with low potential (III) can develop in the fir forests of wet grassland and birch or aspen forests, having replaced in the secondary succession of wet fir forest. The average long-term relative number of bank vole did not exceed five individuals per unit of an account, and attempts to determine spontaneous infection with the HFRS virus did not give a positive result. However, as a rare exception, the disease can be spontaneous in humans.

Nosofocus with extremely low potential or absence of lesions (IV) can be located in moss pine forests or fresh coupes of natural stands. The average long-term relative number of bank vole does not exceed three individuals per unit of an account. Animals infected with the HFRS virus were not discovered, and diseases among people were not registered.

The landscape shape of the RT is original and determined by its geographical position: on the border of a changing boreal landscape zone (the area of 14,655 km$^2$) to the Subboreal north semihumid zone (48,998 km$^2$) with the formation of the so-called “boreal ecotone” [17]. The percentage of forest areas is 17.4%. In this zone, the authors distinguish the South taiga and subtaiga subzones; they are 2.4% and 97.6% of the zone’s territory, respectively.

Coniferous and small-leaved forests (about 90%) dominate in the Predkamie subtaiga landscape subzone, with only 10% being broad-leaved forests. In average, the percent forest cover is slightly higher than the 16.0% for the subzone.

The Subboreal north semihumid landscape zone is divided into broad-leaved and forest-steppe subzones (24.0% and 75.0%, respectively) of the territory of the zone within the Republic.

The Southwestern territory forms a transitional broad-leaved landscape subzone along the right and left banks of the Kuybyshev Reservoir, with percentage of forest areas reaching 16.0%. The territories of the Drozhzhanovsky and Buinsky municipal districts of the Republic (bordering the Republic of Chuvashia and the Ulyanovsk region in the extreme southwest of the RT) form a section of the southern and typical forest-steppe landscape subzone.

The observed variations in the epidemiological appearances of natural foci of HFRS in three physical and geographical regions of the Republic are primarily due to a number of natural and social factors. Among the natural factors, the following should be noted:

a) The percent forest cover of three regions: the smallest (4.6%) in the Predvoljie region, more expressed (18.8%) in the Predkamie region, and the largest (21.5%) in the Zakamie region

b) The forest productivity (in terms of feeding capacity for mammals): the forests of the Predvoljie and Predkamie regions are characterized by little discernible productivity (65.7% and 68.8%, respectively). In the Zakamie region, the productivity reaches 85.0% due to the predominance of broad-leaved species (oak, maple, linden, and elm).

In 2014, the KRIEM started research on the second stage of a landscape and epidemiological zoning—a ranking of forest-covered territories in the format of regional forest areas of the State Forest Fund of the RT with different phytocenotic composition—a standard for assessing the potential risk of infection with the HFRS pathogen [18].

*The study of genetic variants of Hantavirus HFRS*. In recent years, genetic variants of Hantavirus HFRS have been studied, taking into account the infection rate of bank vole populations in the regions of the RT located in various landscape zones, which are characterized by a high level of HFRS incidence. Rodents were caught in spring–summer and autumn periods of 2015–2019 in the areas where the bank vole lives near settlements in 11 districts of the RT. These districts were Laishevsky, Pestrechinsky, Mamadysh, and Zelenodolsk areas belonging to the area of the Predkamie; Subboreal north semihumid landscape area (broad-leaves area); and Nizhnekamsk, Almetyevsk, Tukayevsky, Leninogorsk, Menzelinsk, and Yelabuga regions belonging to the Zakamie region, Subboreal north semihumid landscaped area (typical and southern forest-steppe subzone). Moreover, Verkhneuslonsky area in the Predvoljie region belongs to the Subboreal north semihumid landscape zone (a typical forest-steppe subzone) [19].

It was found that genetic variants of PUUV virus were circulating among bank voles in various landscape and geographical areas of the RT, the studies of lung tissue samples for the content of Hantaviruses TULV and DOBV showed a negative result.

The infection rate of the bank vole with PUUV virus was high and averaged at 14.16% ± 1.81% over the follow-up period, varying over the years with a downward trend. The variability of bank vole infection rates within landscape–geographical zones was also noted.

Organs (lungs) of 4,183 small forest mammals were examined by fluorescence and immunofermentation methods for spontaneous infection of small mammals with HFRS virus. Seropositive results were obtained in four animal species: a forest mouse, a red mouse, a bank vole, and an ordinary vole, which confirmed the polyhostality of the HFRS virus. At the same time, the frequency of findings and the antigen titer were significantly higher (from 3 to 14 times) for the bank vole compared to other animal species. Therefore, the average number of infected individuals among the bank vole was 15.0%, and the part of seropositive results with titers 1:8–1:512 reached 74.0%. In ordinary and bank voles, these indicators were 3.4% and 4.1%, respectively, and based on seropositive results, titers were 1:4 and 1:16. Finally, the proportion of seropositive samples with titers from 1:2 to 1:4 did not exceed 1.5% among the forest mouse.

These facts indicate an expressed ecological adaptation of the virus to the body of the bank vole and allow us to determine this species as the main reservoir of the HFRS pathogen, as well as the main source of human infection with the pathogen in the natural foci of the Middle Volga region.

In view of the above, the bank vole should be considered the most numerous species in the community of small forest mammals. Moreover, a certain pattern (biotopic preference) in the population of certain groups of forest formations by this species should be noted, which can be ranked into four groups according to the degree of preference.

1. Formations with the largest number (the abundance of bank vole reaches 39 individuals per unit of account, the part in total collections is up to 83.0%): broad-leaved, mixed forests, ripening, ripe and over-mature, and high-density with developed undergrowth and grass, with a significant amount of dead wood and rotting stumps.

2. Formations with smaller numbers (abundance of up to 10 individuals per unit of account, specific weight sets up to 70.0%): small-leaved forests and multi-row forest belts in the agricultural landscape.

3 and 4. Formations with low numbers (abundance of bank vole up to three individuals per unit of account with the part of the species sets up to 40.0%): coniferous forests couping with the renewal of coniferous and deciduous species (young growth of I–II age classes).

The stations that are occasionally populated by bank voles have a certain epidemiological significance. Animals can appear here in the unfavorable autumn–winter period as a result of migration from breeding sites due to lack of food and overpopulation. Populated areas include straw dumps, haystacks, beekeeping sheds, gardening buildings that are empty in the autumn and winter, warehouses, vegetable stores, tourist bases, remote control bunkers on air defense sites, school premises, summer recreation complexes for children (camps) and adults (rest homes) located on the outskirts of settlements, and guard boxes at drilling wells or car parks located near or on wooded territories.

The concentration of bank voles in restricted areas stimulates the dissemination of the HFRS pathogen, increasing the risk of infection for humans and leading to the emergence of group and outbreak diseases.

Long-term observations conducted by KRIEM on the dynamics of the number and distribution of small mammals in their main habitats and the study of factors affecting the level structure and dynamics of the incidence of HFRS allowed us to draw a few important conclusions:

– In the second half of the twentieth century, the trend of the long-term population of small mammals showed a significant increase (linear regression $R^2 = 0.606$), which continues to the present day.

– The abundance of bank vole in forest stations has increased significantly ($R^2 = 0.624$), and its part in the population of small forest mammals has also increased significantly ($R^2 = 0.623$).

– Since the 70s of the twentieth century, especially in recent decades, a winter snow-covered breeding of the bank vole has become a relatively frequent phenomenon in the region, both in time and space.

– Factors that caused the above-mentioned trends in the life of small forest mammals in general and the bank vole in particular: intensive pollination of forest territories in the second half of the twentieth century, dismemberment (fragmentation) of woodlands (construction of highways, power lines, gas and oil infrastructure), the growth of areas of border zones (ecotones), where the fringe effect positively appeared in the life of flora and fauna; creation of the most favorable biotopes for the reproduction of small forest mammals due to high feeding and harness of habitats.

– An important factor affecting the reproductive activity of small mammals was the change in

**Fig. 7**. The staff of the reference center for monitoring hemorrhagic fever with renal syndrome. From left to right: an epidemiologist, I. V. Serova; the head of the reference center, T. A. Savitskaya; and leading research associate V. A. Trifonov (June 2019).

climatic conditions, which in the region are expressed by an increase in the average annual temperature of the surface layer of the atmosphere; these climate changes increase the number of years with favorable conditions for wintering small forest mammals and their reproduction in this season of the year.

*Formation of a reference center for monitoring HFRS*. In December 2017, in accordance with Rospotrebnadzor Order No. 1116 dated 01.12.2017 "On improving the system of monitoring, laboratory diagnostics of infectious and parasitic diseases and indication of pathogenic biological agents in the Russian Federation," a reference center for monitoring HFRS was established by the KRIEM.

The main activities of the reference center are:

– monitoring of the epidemiological situation on HFRS throughout the Russian Federation as a whole and in individual subjects;

– preparation of reviews and short-term and long-term forecasts on the epidemiological situation;

– study of circulating varieties of HFRS viruses using modern laboratory research methods;

– conducting serological monitoring among the population of endemic territories;

– preparation and publication of information and analytical materials on epidemiology, diagnosis, and prevention of HFRS; and

– improvement in epidemiological surveillance, preventive and anti-epidemic measures, and methods of laboratory diagnostics of HFRS.

Currently, the reference center for monitoring HFRS (Fig. 7) monitors the epidemiological situation of HFRS in the Russian Federation and in the whole country, sends monthly reports to the Federal Service of Rospotrebnadzor on the results of monitoring, prepares reviews and forecasts of the epidemiological situation, provides with advice and practical assistance in the laboratory diagnosis of HFRS, conducts laboratory studies on rodents infected with HFRS virus, carries out serological studies on immunity stress that is endemic among the population of the Russian Federation, and participates in the development of normative documents [20, 21].

**Author contributions**. V.A.B. —the head of a study; T.A.S., B.A.T., I.V.S. и G.Sh.I. collected and processed information from archival materials.

**Funding**. The study had no external funding.

**Conflict of interest**. The authors declare no conflict of interest.

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