ISSN 1067-4136, Russian Journal of Ecology, 2013, Vol. 44, No. 3, pp. 267–270. © Pleiades Publishing, Ltd., 2013.
Original Russian Text © O.A. Zhigalskii, A.D. Bernshtein, I.A. Kshnyasev, N.S. Apekina, 2013, published in Ekologiya, 2013, No. 3, pp. 237–240.

BRIEF COMMUNICATIONS

Ecological Mechanism of HFRS Activity in European Foci: Prognosis of Incidence

O. A. Zhigalskii[a], A. D. Bernshtein[b], I. A. Kshnyasev[a], and N. S. Apekina[b]

[a] *Institute of Plant and Animal Ecology, Ural Branch, Russian Academy of Sciences, ul. Vos'mogo Marta 202, Yekaterinburg, 620144 Russia*
e-mail: zig@ipae.uran.ru

[b] *Institute of Poliomyelitis and Viral Encephalites, Russian Academy of Medical Sciences, Leninskii raion, Moscow oblast, 142782 Russia*
e-mail: centrglps@rambler.ru

Received March 11, 2012

Keywords: Puumala virus, hantaviruses, hemorrhagic fever with renal syndrome (HFRS), epizootic process, zoonoses, prognostic model, bank vole *Myodes glareolus*, incidence, population cycles, population dynamics, winter breeding, winter food supply

DOI: 10.1134/S1067413613020124

Hemorrhagic fever with renal syndrome (HFRS) is a nontransmissible viral zoonosis that is widespread in Europe and ranks first among infections with natural focality in Russia. The agents of HFRS belong to the genus *Hantavirus* of the family Bunyaviridae, which currently comprises more than 30 geno- and serotypes. Natural reservoir hosts for all hantaviruses pathogenic for humans are some small mammals of the families Muridae and Cricetidae, with virus–host relationships having been established in the course of long-term coevolution (Plyusnin and Morzunov, 2001). In the two-component parasitic system of hantaviral zoonoses, the main warm-blooded hosts become directly involved in horizontal virus transmission and are the only source of infection for humans.

The absolute majority of HFRS cases in Russia are caused by Puumala virus (>95%), whose main reservoir host (and source of human infection) in nature is the bank vole (*Myodes glareolus*), a species widespread in the forest and forest–steppe zones of Europe, European Russia, and Transural region. The most active foci of Puumala HFRS concentrate in the optimum of *M. glareolus* range. This optimum lies in broadleaf and conifer–broadleaf forest with a large proportion of linden, which, in particular, are characteristic of the Middle Volga and Cisural regions (Bashenina et al., 1981b; Bernshtein, Gavrilovskaya, and Apekina, 2010).

More than 30 years have passed since the agent of HFRS was identified, and abundant data on the genetic structure, distribution, and evolution of different hantaviruses and their phylogenetic relationships with warm-blooded hosts have been obtained during this period/ However, the mechanisms of functioning of natural hantavirus foci in forest subzones have not been studied adequately, and the task of making a reliable forward prognosis of morbidity from zoonotic infections often remains unsolved (Zhigalski, 2012). Therefore, the purposes of our research were (1) to identify the main factors determining the activity of forest foci of HFRS associated with Puumala virus, and (2) to develop a prognostic model of the functioning of HPRS foci and verify it with reference to the data of long-term monitoring of HFRS endemic areas in the Republic of Udmurtia.

This paper is based on the results of integrated studies on HRFS foci in the Republic of Udmurtia, including zoological and epidemiological monitoring for 38 years (1973–2010) and epizootiological monitoring performed in all seasons for 15 years (1981–1995) and then in August for 10 years (1981–2005). Annual data on meteorological parameters and seed production in the main tree species were available for the entire observation period. Trap-line censuses of bank voles were regularly taken four times a year by standard methods (Karaseva, Telitsina, and Zhigalski, 2008), recording animal age and reproductive status. The starting date of the breeding season was estimated from the reproductive status of females and the age composition of population in April. Animals with viral antigen in the lungs (active virus carriers) were identified by an immunoenzyme assay (Bernshtein, Gavrilovskaya, and Apekina, 2010). On the whole, field work in sample plots amounted to about 20000 trap–days, and more than 10000 bank voles were examined. Analysis of HFRS incidence was based on the absolute numbers of confirmed human cases recorded per epidemiological season. This parameter was also used to estimate epidemic activity in the endemic area of the

Results from model selection procedures to explain the number of HFRS cases in the Udmurt Republic (1973–2002), $\log(N_{HFRS}) = \Sigma x_i b_i$

Model	Predictors			−2LL	LR	k	CAIC	ΔCAIC	w
1	X_1	X_2	X_3	496.6	88.0	4	515.1	0.0	0.995
2	X_1	X_4	X_3	507.4	77.2	4	526.0	10.9	0.004
3	X_1	X_5	X_3	515.5	69.1	4	534.1	19.0	8.E-05
4	X_2	X_3		521.3	63.3	3	535.2	20.1	4.E-05
5	X_1	X_3		521.5	63.1	3	535.4	20.3	4.E-05

Note: X_1 is the variable accounting for the offset in the long-term average annual number of HFRS cases after 1985; X_2, std logit of bank vole abundance in April; X_3, winter breeding (1, yes; 0, no); X_4 – std logit of bank vole abundance in June; X_5, std logit of bank vole abundance in August; w, the weight of model.

republic. On the whole, more than 23 500 HFRS cases were recorded over 38 years.

The bank vole dominates in broadleaf and conifer–broadleaf forests of the Ural region and neighboring territories, where the proportion of these rodents in catches reaches 70–80% (Bashenina et al., 1981a; Zhigalski, 2002). Their abundance in the optimum of the range is not subject to long-term declines or deep depression, unlike at the periphery, and its long-term average value has increased significantly since 1985 (Bernshtein, Gavrilovskaya, and Apekina, 2010).

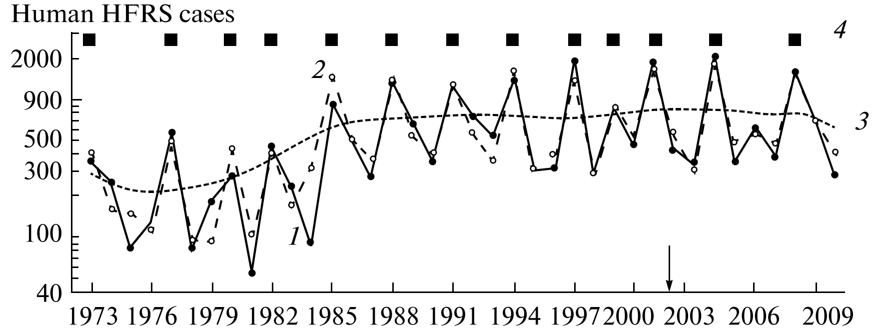
Our experimental and field studies have made it possible to reveal factors determining the dynamics of closely interrelated epizootic and epidemic processes. Among them, the state of the reservoir host population plays the main role. It is noteworthy that hemorrhagic fever in bank voles is symptomless and does not affect their reproduction rate and population growth (Bernshtein et al., 1999, 2001; Bernshtein, Gavrilovskaya, and Apekina, 2010).

To evaluate the roles of different factors in the dynamics of HFRS foci, we have analyzed data on more than 10 demographic and epizootiological characteristics of bank vole population and 24 monthly average meteorological parameters and indices of seed production in spruce and linden. At the first stage, we calculated rank correlation coefficients (γ) between the number of human HFRS cases and various characteristics of bank vole population, winter food supply for these rodents, and meteorological parameters. Among all these factors, human HFRS incidence proved to correlate most strongly with winter breeding of voles under snow ($\gamma = 1.0$, $Z = 5.39$), linden seed yield in the previous year ($\gamma = 0.61$, $Z = 4.39$), and vole population abundance in April ($\gamma = 0.5$, $Z = 3.75$).

Using the model selection procedure (Burnham and Anderson, 2002), we tested the optimality of regression models for describing the dynamics of morbidity and estimated the relative importance of predictors ($w^+ = \Sigma w_i$) and their coefficients (table). The time series of observations was divided into two parts: the first (1973–2002) was used for the evaluation of the coefficients, and the second (2003–2010) for the verification of prognosis.

The results showed that winger breeding of bank voles, which occurs in Udmurtia once in 2–3 years (Zhigalski, 2012), is the most important predictor for describing (forecasting) HFRS morbidity. The “weight” of other predictors is lower, and therefore their role in the activity of HFRS foci is less significant. Regular winter breeding following the years with an abundant yield of linden seeds is a characteristic feature of bank vole populations in optimal habitats, such as linden–spruce forests of Udmurtia (figure). The first litters of winter-breeding voles are born under snow, sometimes as early as January but no later than March to early April (Bernshtein, Gavrilovskaya, and Apekina, 2010; Hansson, Jebrzejewska, and Jebrzejewski, 2000). The role of winter reproduction of bank voles in activation of HFRS foci is accounted for by specific features of virus circulation in the body and the population of the host. As shown in our previous studies (Bernshtein et al., 1999; Bernshtein, Gavrilovskaya, and Apekina, 2010; Tersago et al., 2012), voles during the first month after being infected are the main source for horizontal transmission of virus, and such animals occur most frequently among recently matured voles. In case of winter reproduction, the frequency of contacts between voles of either sex from older age groups and rapidly maturing young of the year (born before May) increases already at the beginning of the breeding season, which enhances the risk of infection spreading among the animals (Mikhailova, 1999; Bernshtein et al., 1999). While the animals remain within the endemic area, the risk of being infected increases with time. This provides for intergenerational continuity in horizontal virus transmission within the bank vole population and, therefore, for the maintenance of the epizootic process. In such a situation, this process reaches its peak already in summer, which creates conditions for large-scale human infection.

In years when the offspring are born later (late April to May), the proportion of active virus carriers remaining in the population at the beginning of the



Log-scale plot of HFRS incidence in the Republic of Udmurtia, 1973–2010: (*1*) observed and (*2*) predicted values, (*3*) trend, (*4*) years of winter breeding. Annual data over the period from 1973 to 2002 (indicated with an arrow) were used to parameters estimation; subsequent data (1973–2002) were used for verification only.

breeding season is relatively small, and prevents epizootic and epidemic outbreaks in the spring–autumn period (Mikhailova, 1999; Bernshtein et al., 2001). The role of an early start of bank vole breeding in HFRS epidemic outbreaks has been shown in studies performed in conifer–broadleaf and broadleaf forests of Tatarstan, Marii El, and Samara, Ulyanovsk, and Tula oblasts (Bernshtein et al., 1980; Apekina et al., 2007). Similar trends have been observed in the activity of Amur hantavirus foci in the Russian Far East: the epidemiological situation in the region flares up only in years when Korean field mice (*Apodemus peninsulae*) breed under snow (Simonova et al., 2006).

The epizootic and epidemic processes, as well as the bank vole population dynamics in Udmurtia, are obviously cyclic (Zhigalski and Kshnyasev, 2000; Zhigalski, 2011), which is illustrated in the figure. Activation of HFRS foci takes place every 2–4 years (in most cases, 3 years) against the background of high abundance of bank voles but always following the early onset of breeding after a year with an abundant yield of linden seeds. The breeding season in the subsequent 1–3 years starts no earlier than mid-April, with the activity of the focus inevitable decreasing even when the abundance of bank voles (ind./100 trap–days) reaches or exceeds the threshold for an epidemic outbreak: 7.2 in April and 22.0 in August before 1985 and 22.0 and 35.0, respectively, after 1985. Over the 38-year observation period, such abundance values were recorded 22 times in spring and 24 times in late summer, whereas sharp peaks of HFRS morbidity occurred only 13 times. The high abundance of the main host in the optimum of its range is not itself the cause of an outbreak, unlike the situation in less productive taiga forests (Kallio et al., 2010). Therefore, phases of epizootic and epidemic activity of the foci does not always concur with bank vole population cycles in the same area. In some cases, periods of decline in their activity may occur in years of population peak, provided it was not preceded by early breeding (e.g., 1974, 1983, 1989), while years of outbreaks may be not coincident with the peak phase (1973, 1988, 1999).

Our statistical model for predicting HFRS incidence in Udmurtia has been constructed on the basis of data presented in the figure and the proposed mechanism of the functioning of HFRS foci. Several different equations could be used for this purpose, but we have selected the simplest model that nevertheless adequately describes the processes of interest:

$$N_{\mathrm{HFRS}} = 43 + \exp(5.9 + 0.95X_1 + 0.02X_2),$$

where X_1 is winter breeding (1, yes; 0, no), and X_2 is the abundance of bank voles in April, ind./100 trap–days.

The predicted and observed values of HFRS morbidity are almost identical (figure), and the removal of data on bank vole abundance from the model only slightly affects the accuracy of prognosis (by about 10%). Error in predicting HFRS incidence for the 2011 epidemiological season was only 6% (1140 predicted vs. 1078 observed cases).

Thus, our results has shown that future human HFRS incidence in endemic area may be accurately predicted as early as spring, solely by the some demographic parameters of the carrier species (starting date of breeding and bank vole abundance in April) even without any knowledge about hantavirus activity in the host population.

ACKNOWLEDGMENTS

This study was supported by the research program of the Ural Branch, Russian Academy of Sciences (project nos. 12-S-4-1012 and 12-P-4-1068).

REFERENCES

Apekina, N.S., Bernshtein, A.D., Mikhailova, T.V., et al., Characteristics of Areas Endemic for Hemorrhagic Fever with Renal Syndrome in Different Landscape Zones of Tula Oblast, *Med. Virusol.*, 2007, vol. 24, pp. 99–107.

Bashenina, N.V., Bernshtein, A.D., Voronov, G.A., et al., Population Dynamics, in *Evropeiskaya ryzhaya polevka*

(The European Bank Vole), Moscow: Nauka, 1981a, pp. 245–268.

Bashenina, N.V., Bernshtein, A.D., Voronov, G.A., et al., Habitat Conditions, Distribution, and Biocenotic Relationships, in *Evropeiskaya ryzhaya polevka* (The European Bank Vole), Moscow: Nauka, 1981b, pp. 143–157.

Bernshtein, A.D., Gavrilovskaya, I.N., and Apekina, N.S., Specific Features of Natural Focality of Hantavirus Zoonoses, *Epidemiol. Vaktsinoprofilakt.*, 2010, no. 2, pp. 5–13.

Bernshtein, A.D., Myasnikov, Yu.A., Abasheev, V.A., et al., Activity of the Foci of Hemorrhagic Fever with Renal Syndrome and Population Dynamics of Basic Hosts: An Attempt at Epidemiological Prognosis, in *Gemorragicheskaya likhoradka s pochechnym sindromom v Srednem Povolzh'e i Predural'e* (Hemorrhagic Fever with Renal Syndrome in the Middle Volga and Cisural Regions), Leningrad, 1980, pp. 58–68.

Bernshtein, A.D., Apekina, N.S., Mikhailova, T.V., et al., Dynamics of Puumala Hantavirus Infection in Naturally Infected Bank Voles (*Clethrionomys glareolus*), *Arch. Virol.*, 1999, vol. 144, pp. 2415–2428.

Bernshtein, A.D., Apekina, N.S., Mikhailova, T.V., et al., Hantavirus Infection in Bank Voles in a Natural HFRS Focus: 2. Infection Prevalence in Voles of Different Age and Functional Groups, *Med. Parazitol.*, 2001, no. 4, pp. 55–58.

Burnham, K.P. and Anderson, D.R., *Model Selection and Multimodel Inference: A Practical Information–Theoretic Approach*, New York: Springer, 2002.

Clement, J., Maes, P., and Van Ranst, M., Hantaviruses in the Old and New World, in *Perspectives in Medical Virology*, vol. 16: *Emerging Viruses in Human Population*, Tabor, E., Ed., London: Elsevier, 2006, pp. 161–177.

Hansson, L., Jebrzejewska, B., and Jebrzejewski, W., Regional Differences in Dynamics of Bank Vole Populations in Europe, *Pol. J. Ecol.*, 2000, vol. 48, pp. 163–177.

Kallio, E.R., Begon, M., Henttonen, H., Koskela, E., Mappes, T., Vaheri, A., and Vapalahti, O., Hantavirus Infections in Fluctuating Host Populations: The Role of Maternal Antibodies, *Proc. Roy. Soc. B: Biol. Sci.,* 2010. doi 10.1098/rspb.2010.1022

Karaseva, E.V., Telitsina, A.Yu., and Zhigalski, O.A., *Metody izucheniya gryzunov v polevykh usloviyakh* (Methods of Studies on Rodents in the Field), Moscow: LKI, 2008.

Mikhailova, T.V., Bank Vole Population Dynamics and Their Relationships with the Epizootic Process in a Focus of Hemorrhagic Fever with Renal Syndrome, *Extended Abstract of Cand. Sci. (Biol.) Dissertation*, Moscow, 1999.

Plyusnin, A. and Morzunov, S., Virus Evolution and Genetic Diversity of Hantaviruses Rodent Hosts, *Curr. Top. Microbiol. Immunol.,* 2001, vol. 256, pp. 47–75.

Simonova, T.L., Kushnareva, T.V., Simonov, S.B., et al., Zoogeographic Characteristics of *Apodemus peninsulae* Population and Its Role in the Maintenance of Hantavirus Infection in Southern Primorye, *Zh. Mikrobiol. Epidemiol. Immunol.*, 2006, no. 3, pp. 81–84.

Tersago, K., Crespin, L., Verhagen, R., and Leirs, H., Impact of Puumala Virus Infection on Maturation and Survival in Bank Voles: A Capture–Mark–Recapture Analysis, *J. Wildl. Dis.*, 2012, vol. 48, no. 1, pp. 148–156.

Zhigalski, O.A., Analysis of Population Dynamics in Small Mammals, *Zool. Zh.*, 2002, vol. 81, no. 9, pp. 1078–1106.

Zhigalski, O.A., Structure of the Bank Vole (*Myodes glareolus*) Population Cycles in the Center and Periphery of Its Distribution Area, *Biol. Bull.* (Moscow), 2011, no. 6, pp. 629–641.

Zhigalski, O.A., Analysis of Methods for Predicting Morbidity from Zoonotic Infections, *Epidemiol. Vaktsinoprofilakt.*, 2012a, no. 3 (64), pp. 26–31.

Zhigalski, O.A., Dynamics of Abundance and Population Structure in the Bank Vole, *Myodes (Clethrionomys) glareolus*, after the Winter or Spring Onset of Breeding, *Zool. Zh.*, 2012b, vol. 91, no. 5, pp. 619–628.

Zhigalski, O.A. and Kshnyasev, I.A., Population Cycles of the Bank Vole in the Range Optimum, *Russ. J. Ecol.*, 2000, vol. 31, no. 5, pp. 345–352.