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Hantavirus infection in Europe: the implied strains and their epidemiology – A short review

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Abstract: Rodents make up about 40% of all mammal species and can be found in various habitats around the world, except for Antarctica. They are known to play an essential role in transmitting various diseases with zoonotic potential. Throughout history, there have been numerous infectious episodes, starting from the Bubonic Plague pandemic, produced by *Yersinia pestis*, transmitted to humans through fleas previously fed on rats, and up to the viroses and bacterioses that currently manifest themselves globally. This category includes Typhus (infections caused by *Rickettsia species*), Rat-bite fever, Yersiniosis, Leptospirosis, Tularemia, as well as Tick-borne encephalitis, Hantavirus, Hepatitis E, Borna virus, Lassa fever, Omsk hemorrhagic fever or even Cowpox. In 1978, the causative agent of Korean hemorrhagic fever was isolated from infected small field rodents, *Apodemus agrarius*, near the Hantan River in South Korea. The virus was named the *Hantaan* virus after the nearby river. Its electron microscope images soon revealed that the virus was a new member of the *Bunyaviridae* family. It has been observed that hantaviruses, unlike other members of this family, do not have an arthropod vector and cause a persistent infection in the population of their specific rodent hosts. The genus includes the viruses that cause hemorrhagic fever with renal syndrome (HFRS) in Europe and eastern Asia and hantaviral cardiopulmonary syndrome (HCPS) in the Americas. Currently, the genus includes more than 21 species and exceeds 30 genotypes, expanding to multiple territories in the world. A good knowledge of the epidemiology, symptomatology, but above all, of the main species of rodents that can be involved in the transmission of zoonoses, plays an important role in preventing potential outbreaks of infection and narrowing the area of diseases. **While most countries in Europe report Hantavirus infections in humans, such data is very limited in Romania due to the lack of studies or official reports. In this review, we aim to update the data on the spread of Hantaviruses in Europe.**

INTRODUCTION

Hantaviruses have evolved for millions of years through their natural reservoirs represented by rodents and insectivores. Natural reservoirs include both *Cricetidae* rodents (subfamilies *Arvicolinae, Neotominae* and *Sigmodontinae*) and *Muridae* rodents (subfamily *Murinae*). *Cricetidae* rodents include individuals widespread in the northern hemisphere and American territory. *Muridae* rodents include mice and rats distributed throughout the rest of the globe. Hantavirus phylogeny closely follows that of their rodent hosts, suggesting long-term coevolution, although there has been evidence of occasional changes in hosts. The phylogenetic tree suggests that the interbreeding of hantaviruses with hosts from four different rodent subfamilies appears to influence their ability to cause a specific clinical manifestation in humans. For example, it is known that most viruses affecting the *Neotominae* and *Sigmodontinae* subfamilies cause severe HCPS with a high mortality rate (40-50%). These viruses are widespread in North and South America in different species of *Neotominae* and *Sigmodontinae* rodents. The hantaviruses which evolved alongside *Murinae* rodents cause severe HFRS, which primarily affects kidney function, resulting in a rate of mortality of 0-15%. Although the disease caused by viruses found in *Murinae* has a lower mortality rate, it still poses a significant threat to human health because of the disease severity and the ability of viruses to cause epidemics.

RODENT SPECIES OF INTEREST

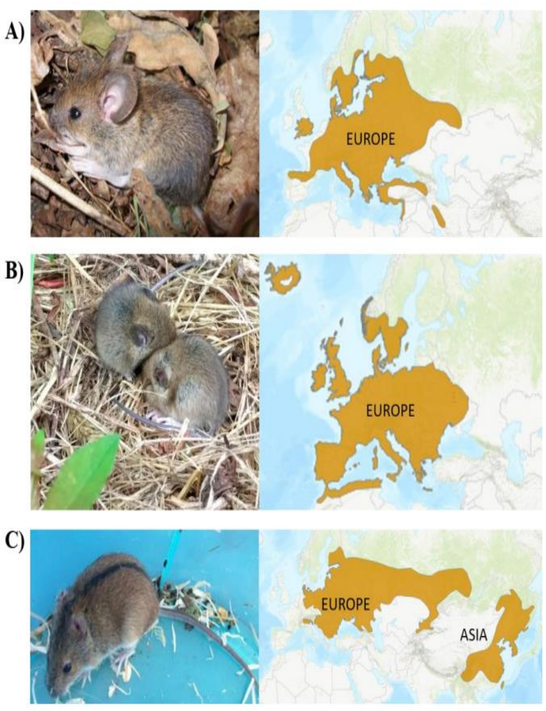
Important rodent species of the *Muridae* family with a wide distribution in Europe include, in addition to rats and house mice, members of the *Apodemus* genus:

(a) The collared mouse (*Apodemus flavicollis*) (Fig. 1A) is widespread in European forests, especially at their edges.

b) The wood mouse (*Apodemus sylvaticus*) (Fig. 1B) also lives in forests, but also in meadows.

c) The striped field mouse (*Apodemus agrarius*) (Fig. 1C) lives in forest margins and woodland areas. This rodent is found in two separate populations: in central Europe and Eastern Europe to Russia and China, as well as in parts of Southeast Asia.

In addition to the *Muridae* family, the *Cricetidae* family with the *Arvicolinae* subfamily is of great importance as it carries a large number of zoonotic agents. Some species of mice and rats in this family are restricted to small geographical areas, such as *Microtus lusitanicus* (Fig. 2A) in Portugal and north-western Spain and *Microtus subterraneus* in central Europe (Fig. 2B). Other species, such as the field mouse (*Microtus arvalis*) (Fig. 2C) and *Microtus agrestis* (Fig. 2D) are found in larger geographical areas such as Europe and parts of Asia. In particular, the tundra mouse (*Microtus oeconomus*) can be detected in areas of three continents (Asia, Europe and North America) (Fig. 2E). The mouse (*Myodes glareolus*) (Fig. 2F) is found in most parts of Europe, up to western parts of Russia, living in mixed and coniferous forests and preferring vegetation from the ground level. The virus is spread through the urine, faeces and the saliva of infected animals. Hantavirus infection in rodents is thought to be asymptomatic, but changes in health status have been observed.



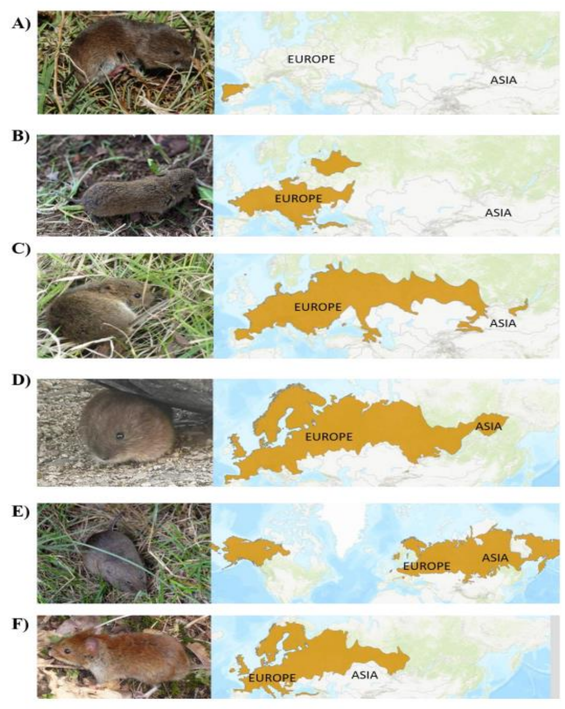


Fig. 1 - The main rodent species of the *Muridae* family found in Europe (left)
Fig. 2 – The main rodent species of the *Cricetidae* family found in Europe (right)
(source: Jeske K., 2021)

DIAGNOSIS FOR THE HANTAVIRUS INFECTION

The most frequently used serological test is the indirect ELISA or rapid tests. Hantavirus infection can also be confirmed by detecting the hantavirus genome in samples of blood or serum by RT-PCR. Both classical and quantitative RT-PCR are used for viremia detection. When testing for the detection of the virus in rodents, it is recommended that the collected samples are of blood and thoracic fluid. Furthermore, these may be tested through ELISA for a rapid result. For a more precise diagnosis, RT-qPCR or conventional PCR followed by a Nested-PCR assay should be applied on lung, kidney and urinary bladder samples previously collected from the rodents.

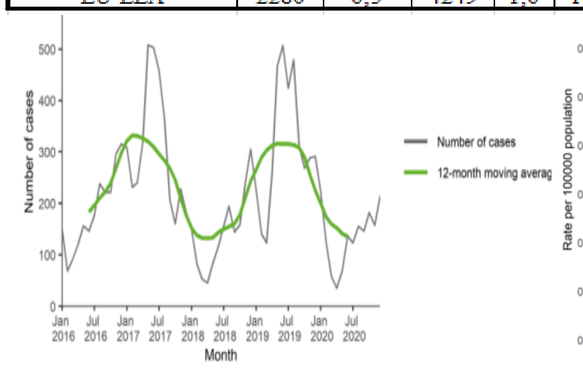
HANTAVIRUS EPIDEMIOLOGY

The geographical distribution of hantavirus hosts reflects the epidemiology and distribution of infection. Hantavirus infection in humans is considered to be an infection causing two types of serious disease, HFRS and HCPS. The main route of infection for both syndromes is inhalation of the virus. In general, people become infected with hantavirus by the direct contact with infected rodents or their droppings in aerosolised form. In Europe, most HFRS cases are reported in Russia, Finland and Sweden. The majority of HFRS patients are men aged between 20 and 50. The mortality rate for HFRS depends on the type of virus and generally ranges from 0.1% to 10%. Patients with HRFS mainly come from rural areas, where rodent hosts are very widespread. **Regarding Romania, the literature mentions the existence of 27 clinical cases of HFRS, reported between 1956 and 1977. Subsequently, the disease seems to have died out, until the National Reference Laboratory was able to analyse 6 suspected cases of leptospirosis dating from 2005-2007, thus allowing the diagnosis of HFRS. Afterwards, ECDC reported a total number of 18 cases of Hantavirus infection only in Romania, between 2016 and 2020 (Table 1).** Moreover, the same platform signals the disease occurring more in men than in women. The professional environment that implies contact with rodents is mainly occupied by men rather than women, which explains the cases' occurrence. According to the table and the two figures, the reported cases are expanded on the whole European continent, but most of these occurred in countries that have a large forest area and in the ones located in the Eastern region, where economic issues play a major role in daily life. **Because all of Romania's neighboring countries have reported Hantavirus infections in humans, it is important to maintain proper hands and working environment hygiene, especially for the workers who have a higher risk of disease (farmers, lumberjacks, hunters, foresters etc.).**

Table 1

Number of Hantavirus cases reported in Europe between 2016-2020 (ecdc.com)

Country	2016		2017		2018		2019		2020	
	No.	Rate	No.	Rate	No.	Rate	No.	Rate	No.	Rate
Austria	30	0,3	90	1,0	24	0,3	276	3,1	30	0,3
Belgium	38	0,3	123	1,1	85	0,7	57	0,5	9	0,1
Bulgaria	10	0,1	8	0,1	7	0,1	6	0,1	1	0,4
Croatia	31	0,7	389	9,4	18	0,4	191	4,7	17	0,4
Cyprus	0	0,0	0	0,0	0	0,0	0	0,0	0	0,0
Czechia	10	0,1	17	0,2	4	0,0	15	0,1	5	0,0
Estonia	11	0,8	26	2,0	15	1,1	26	20	17	1,3
Finland	1663	30,3	1246	22,6	999	18,1	1256	22,8	1164	21,1
France	58	0,1	236	0,4	55	0,1	131	0,2	26	0,0
Germany	282	0,3	1731	2,1	235	0,3	1535	1,8	229	0,3
Greece	1	0,0	2	0,0	3	0,0	1	0,0	1	0,0
Hungary	7	0,1	16	0,2	6	0,1	13	0,1	4	0,0
Italy	0	0,0	0	0,0	0	0,0	0	0,0	0	0,0
Latvia	8	0,4	4	0,2	3	0,2	5	0,3	3	0,2
Lithuania	0	0,0	0	0,0	0	0,0	0	0,0	0	0,0
Luxembourg	1	0,2	15	2,5	0	0,0	8	1,3	0	0,0
Netherlands	2	0,0	6	0,0	1	0,0	0	0,0	0	0,0
Norway	10	0,2	26	0,5	21	0,4	1 1	0,2	12	0,2
Poland	8	0,0	14	0,0	11	0,0	9	0,0	3	0,0
Portugal	0	0,0	0	0,0	0	0,0	0	0,0	0	0,0
Romania	***0***	***0,0***	***12***	***0,1***	***1***	***0,0***	***4***	***0,0***	***1***	***0,0***
Slovakia	6	0,1	53	1,0	88	1,6	94	1,7	50	0,9
Slovenia	12	0,6	76	3,7	12	0,6	252	12,1	14	0,7
Spain	0	0,0	1	0,0	0	0,0	0	0,0	0	0,0
Sweden	92	0,9	158	1,6	243	2,4	155	1,5	61	0,6
UK	No data	No rate	No data	No rate	No data	No rate	3	0,0	No data	No rate
EU-EEA	2280	0,5	4249	1,0	1831	0,4	4048	0,8	1647	0,4



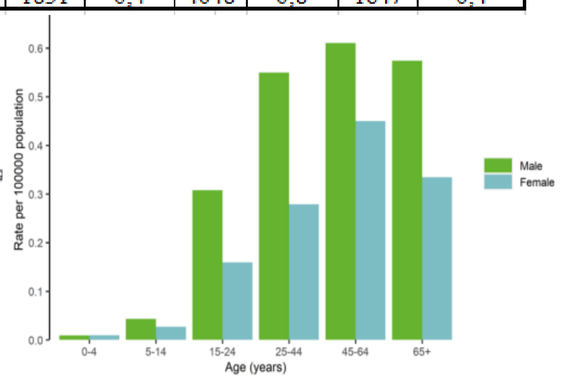


Fig. 4 - Distribution of hantavirus infection cases by month, EU/EEA, 2016–2020 (left)
Fig. 5 - Distribution of hantavirus infection rate per 100 000 population, by age and gender, EU/EEA (right)
(ecdc.com)

CONCLUSIONS

Rodent-borne infections belong to the group of emerging zoonotic diseases. The extent and magnitude of hantavirus outbreaks have increased, and thiscould be explained by improved clinical awareness, the development of specific diagnostic tests, research on natural reservoirs and changing climatic conditions. Until official up-to-date reports are to be offered to the public, further research is needed on pathogenesis, diagnosis, development of antimicrobial and antiviral drugs and vaccines, in order to prevent and control rodent-borne infections. **Thus, we aim to study more the occurrence of rodent-borne zoonoses in Romania, through officially reported database, but also using laboratory testing on rodent and human samples.**