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REVIEW

Hantavirus infections in Southeastern Europe – Epidemiology, outbreak dynamics, and One Health preparedness: A narrative review

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Human-pathogenic orthohantaviruses are significant rodent-bornezoonotic pathogens in Europe. Southeastern Europe (SEE) is a distinct endemic region where Dobrava-Belgrade virus (DOBV) and Puumala virus (PUUV) co-circulate, causing hemorrhagic fever with renal syndrome (HFRS) of varying severity. This narrative review synthesizes the epidemiology, transmission dynamics, clinical characteristics, ecological drivers, and public health challenges of hantavirus infections across SEE, identifying priorities for regional preparedness. We searched PubMed, Scopus, and Web of Science from their inception through June 2026, supplementing with reference screening. Regional epidemiological patterns were assessed descriptively using national surveillance data, European surveillance reports, published studies, and available population-based incidence estimates. Long-term surveillance reveals persistent endemic transmission with significant geographic and interannual heterogeneity. Slovenia and Croatia exhibit the highest cumulative burden and most pronounced periods of increased HFRS activity. Several years—2008, 2012, 2014, 2017, 2019, 2021, and 2023—showed partially synchronized increases across multiple neighboring countries. These patterns align with shared ecological influences, including rodent population fluctuations, mast-seeding events, and climatic variability. However, local ecology, human exposure, and differences in surveillance capacity modify their magnitude. The coexistence of generally milder PUUV-associated disease and more severe DOBV-associated HFRS further distinguishes SEE's clinical landscape. Therefore, hantavirus epidemiology in SEE is best understood as an interconnected regional ecological system. Integrated human, animal, environmental, and genomic surveillance within a coordinated One Health framework is crucial for improving outbreak prediction, cross-border preparedness, and future disease control.

Keywords: Orthohantavirus, hemorrhagic fever with renal syndrome, Dobrava–Belgrade virus, Puumala virus, Southeastern Europe, zoonoses, One Health approach.

Introduction

Human-pathogenic orthohantaviruses (family *Hantaviridae*) are prominent rodent-borne zoonotic viruses globally, causing a range of clinical syndromes known collectively as hantavirus disease [1, 2]. In this review, "orthohantavirus" refers to viral taxonomy, while "hantavirus disease" and related clinical terms maintain consistency with established medical nomenclature. In Eurasia, hantavirus infections primarily manifest as hemorrhagic fever with renal syndrome (HFRS), whereas in the Americas, they lead to hantavirus cardiopulmonary syndrome (HCPS), also known as hantavirus pulmonary syndrome (HPS) [3, 4].

The public health significance of hantaviruses extends beyond their clinical impact, reflecting their remarkable capacity to persist silently in specific small-mammal reservoir hosts. They amplify under favorable ecological conditions and periodically emerge as geographically focused outbreaks in human populations [5–7]. Consequently, hantavirus disease exemplifies a zoonotic pathogen shaped by intricate interactions among viral biology, reservoir ecology, land use, and climatic

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conditions [6–8]. In Europe, Old World orthohantaviruses, particularly Puumala virus (PUUV) and Dobrava–Belgrade virus (DOBV), dominate the epidemiological and public health landscape. These viruses vary in reservoir associations, ecological niches, geographical distribution, and typical disease severity, yet collectively account for the majority of the regional HFRS burden [4, 9, 10].

Southeastern Europe (SEE) holds a unique position within the European orthohantavirus landscape. It is not merely a southern extension of the PUUV-dominated ecosystems of Central and Northern Europe. Instead, SEE represents one of the few European macro-regions where highly pathogenic DOBV lineages and less virulent PUUV strains coexist in shared ecological and clinical spaces. This contributes to a heterogeneous regional risk signature that cannot be fully understood using only Northern European *nephropathia epidemica* models [4, 9]. For this review, SEE encompasses Albania, Bosnia and Herzegovina (BiH), Bulgaria, Croatia, Greece, Kosovo, Montenegro, North Macedonia, Romania, Serbia, and Slovenia, as no single definition of SEE exists. SEE countries have significantly contributed to hantavirus research, with DOBV first identified in the former Yugoslavia [10]. The region continues to be characterized by the endemic circulation of orthohantaviruses in both human populations and rodent reservoirs, exhibiting marked geographic heterogeneity and localized transmission foci. Human infections and evidence of viral circulation have been documented across all countries in the study [11–16]. Although clinical reporting remains limited in some parts of the region, evidence of ongoing viral circulation is widespread.

Renewed interest in hantavirus disease across SEE stems from climatic variability, changing reservoir ecology, land-use changes, and evolving human exposure patterns, all contributing to dynamic transmission risk [5, 17–19]. Therefore, hantavirus disease in SEE should be viewed not as a static endemic problem but as a dynamic interplay between reservoir ecology, environmental change, and human activities. Accordingly, this review synthesizes current evidence on hantavirus epidemiology, clinical characteristics, ecological drivers, and public health challenges across SEE, with a particular emphasis on regional outbreak patterns and cross-border epidemiological dynamics.

Search strategy and data sources

This review is based on a structured search of PubMed, Scopus, and Web of Science to identify literature relevant to orthohantavirus disease in SEE. Searches covered publications from database inception until June 2026 and combined terms such as “hantavirus,” “orthohantavirus,” “hemorrhagic fever with renal syndrome,” “Southeastern Europe,” “Balkans,” and the names of individual countries within the study region. Additional relevant publications were identified by manually screening the reference lists of eligible articles. The review focuses on the epidemiology, clinical manifestations, transmission dynamics, and public health implications of human hantavirus infections in SEE. As this is a narrative review, studies were selected based on their relevance to the manuscript’s scope rather than through formal systematic review methodology.

The epidemiological data used for the comparative regional analysis were compiled from multiple complementary sources, including annual surveillance reports from the European Centre for Disease Prevention and Control (ECDC), official national public health reports, and country-specific datasets provided or verified by collaborating public health experts where available. Given the heterogeneity of surveillance systems, reporting practices, and laboratory confirmation procedures across countries, epidemiological data were interpreted descriptively. The primary data source for each country is summarized in Table S1.

For countries with ECDC-derived data, EU-level surveillance through The European Surveillance System (TESSy) is available from 2008 onward; therefore, our comparative analysis covers 2008–2024, with earlier years reported as N/A. Heyman et al. independently documented laboratory-diagnosed hantavirus infections in Greece, Slovenia, Romania, and Bulgaria during 2005–2007 [20]. We cite these findings as evidence of earlier hantavirus activity but do not combine them with ECDC or national data because the two sources are based on different surveillance approaches.

Annual incidence rates were calculated as: Incidence (per 100,000 population) = (annual number of reported HFRS cases / corresponding annual mid-year population estimate) × 100,000.

Annual country-specific mid-year population estimates were obtained from the World Bank DataBank, World Development Indicators (indicator SP.POP.TOTL) and matched to the corresponding surveillance year for each country. World Bank data were accessed on July 9, 2026 [21].

Epidemiology of hantavirus infections in SEE

HFRS has been recognized in SEE for over half a century, establishing the region as an endemic area characterized by sporadic cases each year punctuated by periodic epidemics [9]. A distinct north-south gradient is evident across the region, with PUUV being relatively more common in the northern part, and DOBV predominating in the southern Balkans [9, 22]. SEE is also the origin of DOBV taxonomy: the prototype Dobrava strain was recovered from a yellow-necked mouse (*Apodemus flavicollis*) in Slovenia, while Belgrade virus was isolated from a fatal HFRS case in Serbia, with both subsequently confirmed as genetically identical [10, 23]. DOBV and PUUV widely co-circulate across the Balkans, with generally moderate reported regional incidence but subject to marked interannual variability driven by multi-annual rodent population cycles [19]. Outbreaks typically follow mast-seeding events and favorable climatic conditions, including winters that enhance rodent survival and reproduction [4, 6, 7].

Subclinical infections are common, with estimated subclinical-to-clinical ratios ranging from 5:1 to 20:1, leading to substantial under-ascertainment, particularly of mild PUUV-associated disease [19, 24, 25]. Seroepidemiological surveys indicate significant background exposure with a clear geographic gradient: overall seroprevalence has been estimated at approximately 6% in BiH, approximately 4% in Greece (ranging from 0% to 14% by county), 3.1% in Bulgaria,

Table 1. Epidemiological overview of hantavirus infections in Southeastern Europe

Country	Predominant hantaviruses	First documented human case(s)	Current epidemiological status	Main endemic areas	Principal reservoirs	Key public health challenges
Slovenia	PUUV, DOBV	1950s–1970s	Highly endemic with recurrent large outbreaks	Alpine and central regions	*M. glareolus*, *A. flavicollis*	Climate-associated outbreak prediction
Croatia	PUUV, DOBV	1950s	Endemic with recurrent outbreaks	Lika, Gorski Kotar, Central Croatia, Western Slavonia, with recent expansion toward the Adriatic coast	*M. glareolus*, *A. flavicollis*	Regional heterogeneity and ecological monitoring
Bosnia and Herzegovina	PUUV, DOBV	First probable case (1952)	Endemic with recurrent outbreaks	Central and northeastern Bosnia, with evidence of wider circulation	*M. glareolus*, *A. flavicollis*	Underrecognition, fragmented surveillance, and the estimation of the true burden and geographic extent
Serbia	DOBV	1950s–1960s	Endemic with sporadic outbreaks	Western and central Serbia	*A. flavicollis*	Harmonized surveillance and reporting
Montenegro	DOBV	1990s	Endemic with recurrent transmission	Northern mountainous areas	*A. flavicollis*	Limited diagnostic capacity
Kosovo	DOBV	1990s	Probable endemicity with limited surveillance data	Central and western Kosovo	*A. flavicollis*	Limited epidemiological data
North Macedonia	DOBV	1980s	Endemic with sporadic reported cases	Mountainous regions	*A. flavicollis*	Limited laboratory capacity and surveillance coverage
Albania	Suspected DOBV predominance	1987	Poorly characterized endemicity	Northern, northeastern and southeastern Albania	*A. flavicollis*	Underdiagnosis and insufficient surveillance
Greece	DOBV	1980s	Low-level endemic transmission	Northern Greece (Rhodope and Pindos regions)	*A. flavicollis*	Geographic variability and outbreak prediction
Bulgaria	DOBV	1950s	Low-level endemic transmission	Southwestern mountain regions	*A. flavicollis*	Reporting consistency and sustained surveillance
Romania	DOBV, PUUV	1990s	Endemic with increasing recognition and detection	Northeastern and central regions	*M. glareolus*, *Apodemus* spp.	Uneven surveillance and diagnostic coverage

The epidemiological status and public health challenges are understood through published literature and national surveillance data. **Abbreviations:** *A. flavicollis*, *Apodemus flavicollis*; DOBV, Dobrava–Belgrade virus; *M. glareolus*, *Myodes glareolus*; PUUV, Puumala virus; spp., species.

1.7% in Slovenia, and 1.6% in Croatia, with higher rates reported among occupationally exposed populations and in local foci [9, 14, 25–29]. Evidence of viral circulation has been documented across the SEE region, although the dominant virus and disease burden vary according to local ecology, rodent-host distribution, and surveillance intensity (Table 1). Albania and Kosovo were not included in the comparative surveillance analysis presented in Table 2 because continuous annual surveillance data were not publicly available; therefore, the information presented for these countries is based primarily on available published evidence.

BiH has been a major endemic focus of hantavirus infections in Europe for over 50 years. Outbreaks have been documented since 1967, including large epidemics in the former Yugoslavia during 1986–1987 and 1989, involving over 1,000 reported cases, and further outbreaks in 1995 and 2002. The latter implicated PUUV, DOBV, and untyped serotypes [30–34]. Following the 2002 epidemic, hantavirus infections continued to occur regularly in BiH, with at least one confirmed case reported annually between 2005 and 2024 (Table 2). Although annual case numbers were generally low, pronounced peaks were observed in 2014, 2017, and 2021, supporting the persistence of endemic circulation with periodic outbreaks. While the majority of reported cases originate from central and northeastern Bosnia, the distribution of rodent reservoirs and serological evidence of exposure indicate that hantavirus circulation extends

Table 2. Annual reported hantavirus infections and incidence rates in Southeastern Europe, 2005–2024.

Year	Slovenia *n* (I)*	Croatia *n* (I)**	Bosnia and Herzegovina *n* (I)**	Serbia *n* (I)**	Montenegro *n* (I)**	Kosovo *n* (I)	North Macedonia *n* (I)**	Albania *n* (I)	Greece *n* (I)*	Bulgaria *n* (I)**	Romania *n* (I)*	Total cases per year
2005	N/A	0 (0.00)	12 (0.29)	8 (0.11)	5 (0.81)	N/A	0 (0.00)	N/A	N/A	N/A	N/A	25
2006	N/A	0 (0.00)	7 (0.17)	42 (0.57)	4 (0.65)	N/A	0 (0.00)	N/A	N/A	N/A	N/A	53
2007	N/A	26 (0.60)	10 (0.25)	14 (0.19)	6 (0.97)	N/A	0 (0.00)	N/A	N/A	N/A	N/A	56
2008	45 (2.24)	40 (0.93)	23 (0.58)	11 (0.15)	12 (1.94)	N/A	0 (0.00)	N/A	2 (0.02)	4 (0.05)	4 (0.02)	**141**
2009	5 (0.25)	13 (0.30)	6 (0.15)	17 (0.23)	4 (0.65)	N/A	0 (0.00)	N/A	2 (0.02)	5 (0.07)	9 (0.05)	61
2010	17 (0.83)	16 (0.37)	3 (0.08)	8 (0.11)	1 (0.16)	N/A	0 (0.00)	N/A	1 (0.01)	3 (0.04)	4 (0.02)	53
2011	17 (0.83)	22 (0.51)	6 (0.16)	8 (0.11)	1 (0.16)	N/A	0 (0.00)	N/A	3 (0.03)	3 (0.04)	4 (0.02)	64
2012	182 (8.86)	154 (3.61)	25 (0.68)	21 (0.29)	10 (1.61)	N/A	0 (0.00)	N/A	1 (0.01)	3 (0.04)	3 (0.02)	**399**
2013	6 (0.30)	6 (0.14)	9 (0.25)	8 (0.11)	6 (0.96)	N/A	0 (0.00)	N/A	2 (0.02)	15 (0.21)	4 (0.02)	56
2014	25 (1.20)	209 (4.97)	133 (3.73)	52 (0.73)	43 (6.89)	N/A	0 (0.00)	N/A	2 (0.02)	9 (0.12)	14 (0.07)	**487**
2015	8 (0.40)	10 (0.24)	13 (0.37)	10 (0.14)	8 (1.28)	N/A	0 (0.00)	N/A	1 (0.01)	1 (0.01)	6 (0.03)	57
2016	12 (0.60)	32 (0.78)	9 (0.26)	15 (0.21)	2 (0.32)	N/A	1 (0.06)	N/A	1 (0.01)	10 (0.14)	0 (0.00)	82
2017	77 (3.73)	389 (9.63)	114 (3.32)	28 (0.40)	6 (0.96)	N/A	16 (0.84)	N/A	2 (0.02)	8 (0.11)	12 (0.06)	**652**
2018	12 (0.60)	18 (0.45)	9 (0.27)	9 (0.13)	5 (0.80)	N/A	3 (0.16)	N/A	3 (0.03)	7 (0.10)	1 (0.01)	67
2019	252 (12.07)	197 (4.99)	29 (0.87)	13 (0.19)	10 (1.60)	N/A	3 (0.16)	N/A	1 (0.01)	6 (0.09)	4 (0.02)	**515**
2020	14 (0.70)	11 (0.28)	1 (0.03)	3 (0.04)	1 (0.16)	N/A	0 (0.00)	N/A	1 (0.01)	1 (0.01)	1 (0.01)	33
2021	569 (27.00)	334 (8.61)	73 (2.25)	10 (0.14)	10 (1.60)	N/A	3 (0.16)	N/A	4 (0.04)	11 (0.16)	12 (0.06)	**1026**
2022	7 (0.30)	6 (0.16)	5 (0.16)	5 (0.07)	4 (0.64)	N/A	2 (0.11)	N/A	0 (0.00)	1 (0.01)	7 (0.04)	37
2023	64 (3.00)	65 (1.68)	21 (0.66)	31 (0.47)	2 (0.32)	N/A	3 (0.16)	N/A	1 (0.01)	6 (0.09)	6 (0.03)	**199**
2024	0 (0.00)	14 (0.36)	4 (0.13)	11 (0.17)	3 (0.48)	N/A	0 (0.00)	N/A	0 (0.00)	2 (0.03)	0 (0.00)	34
Total (2005–2024)	**1312**	**1562**	**512**	**324**	**143**	**N/A**	**31**	**N/A**	**27**	**95**	**91**	**4097**

*Data were extracted from the European Centre for Disease Prevention and Control (ECDC) annual surveillance reports. **Data were obtained from national public health surveillance reports and/or aggregated national surveillance datasets, which were provided or verified by collaborating public health experts. Primary data sources for each country are summarized in Table S1. Annual national surveillance data for Albania and Kosovo were not publicly available and thus could not be included in this study. Data are presented as n (I). "N/A" indicates that national surveillance data were unavailable for the respective year, while "0" signifies that surveillance data were available but no cases were reported. The "Total" row reports only cumulative case counts and does not aggregate incidence. Light grey shading indicates annual incidence rates of 0.50–0.99 per 100,000 population, whereas dark grey shading indicates annual incidence rates ≥1.00 per 100,000 population. These shadings highlight periods of moderate and high national hantavirus activity, respectively. Bold values in the "Total cases per year" column identify years with the highest cumulative regional burden and highlight major outbreak years across Southeastern Europe. **Abbreviations:** ECDC, European Centre for Disease Prevention and Control; I, incidence rate per 100,000 population; N/A, not available.

beyond these recognized endemic foci [27, 35]. Consequently, the geographic distribution of infection may be broader than indicated by routine surveillance data.

In Croatia, both DOBV and PUUV contribute to the disease burden, with a notable military outbreak in 1995, and large epidemics in 2002, 2012, 2014, 2017, and 2021. Notably, the 2012 Medvednica outbreak was linked to exceptionally high PUUV infection rates in bank voles, while the 2017 (≈389 notified cases) and 2021 (≈334 cases) outbreaks were the largest on record and extended into Adriatic-coastal and other areas previously considered non-endemic [18, 36, 37].

Serbia has reported HFRS since 1961, with Belgrade virus characterized during a 1989 epidemic and subsequent molecular confirmation of DOBV circulation foci in western and central regions [10, 38, 39]. Serbian national surveillance demonstrates persistent endemic HFRS activity, with generally low annual incidence punctuated by occasional increases in reported cases.

In Greece, serological evidence for HFRS dates back to 1981, with 0–4 cases reported annually in recent years. The estimated case-fatality rate among hospitalized patients is approximately 9%, a figure derived from severely ill cases and thus an overestimate of the overall rate [14, 40]. DOBV, genotype Dobrava, hosted by *A. flavicollis*, predominates, causing 80% of all cases. These cases primarily occur in endemic foci within the Rhodope and Pindos mountains near the northern borders, with no cases reported from southern Greece or the islands. While PUUV is also endemic, it accounts for far fewer recognized cases [10, 14]. Despite relatively low annual notification rates, the persistence of endemic foci and serological evidence of exposure indicate continuous viral circulation, underscoring the importance of sustained surveillance in northern Greece.

Bulgaria has recorded HFRS since the 1950s, primarily across the Rila-Pirin-Rodopi massifs in the southwest. Here, phylogenetically related DOBV strains circulate in *Apodemus* mice, confirming local rodent reservoirs [9, 10, 16]. Although reported incidence has remained consistently low, the continued detection of DOBV in both rodents and human cases supports persistent endemic transmission rather than sporadic viral introduction.

Albania has also confirmed hantavirus circulation through genetic detection in rodent hosts [12, 41–43]. Similarly, Kosovo reports severe DOBV-associated HFRS, with documented population seroconversion in endemic zones and severe sporadic cases [15, 44, 45].

Slovenia is one of the most affected countries in SEE, experiencing recurrent large-scale outbreaks and the highest incidence rates in the region, particularly in 2012, 2019, and 2021. In contrast, Montenegro reports relatively few cases but periodically reaches some of the highest annual incidence rates in SEE due to its small population size. This highlights the importance of interpreting incidence in conjunction with absolute case numbers [46]. North Macedonia has reported only sporadic cases in recent years, though limited surveillance coverage makes it difficult to determine the true extent of endemic circulation [11].

Hantavirus infections in Romania remain rare but endemic, with sporadic cases reported over the past two decades, primarily caused by DOBV [4, 13]. Despite the low number of reported cases, increasing recognition through improved diagnostics and surveillance suggests that hantavirus infections may be more widespread than previously appreciated.

A comparative analysis of 20-year surveillance data, presented in Table 2, draws from long-term national surveillance data, ECDC surveillance reports, and published national epidemiological studies. This analysis further illustrates the heterogeneous yet interconnected epidemiological landscape of hantavirus infections in SEE. Slovenia and Croatia experienced the highest cumulative burden and the most pronounced increases in reported HFRS activity, while BiH showed recurrent but less intense outbreaks during the same periods. These differences may partly reflect variations in surveillance systems, reporting practices, and the availability of standardized national-level epidemiological data [11, 19]. Montenegro, despite reporting relatively few absolute cases, reached some of the highest annual incidence rates in the region due to its small population size. Conversely, Bulgaria, Greece, Romania, Serbia, and North Macedonia generally maintained lower levels of reported disease despite evidence of persistent viral circulation.

These findings highlight considerable heterogeneity in the long-term epidemiology of hantavirus infections across SEE. In this review, heterogeneity refers to country-specific differences in reported disease burden, outbreak magnitude, incidence patterns, predominant orthohantavirus species, and surveillance characteristics. Countries with the highest cumulative case numbers also experienced the largest increases in reported HFRS activity, while others maintained persistent low-level endemic transmission with only occasional increases in incidence. Collectively, these observations suggest that while ecological drivers operate across the region, their impact is substantially modified by local environmental conditions, rodent host dynamics, surveillance intensity, and healthcare infrastructure.

Importantly, a descriptive comparison of the temporal distribution of reported cases suggests that several years, including 2008, 2012, 2014, 2017, 2019, 2021, and 2023, were characterized by increased reported HFRS activity across multiple neighboring countries (Table 2). This partially synchronized regional activity is consistent with the influence of shared ecological drivers, although differences in surveillance intensity, reporting practices, and local ecological conditions should also be considered. Rather than demonstrating a progressive increase in disease burden over time, the regional surveillance data reveal an epidemiological pattern characterized by alternating periods of low endemic transmission and periods of partially synchronized increased reported activity. Despite the apparent temporal alignment of regional outbreak years, epidemic intensity varied considerably between countries, indicating that shared regional transmission patterns coexist with substantial local ecological and epidemiological heterogeneity.

Interpretation of the regional surveillance data should be undertaken with caution. Surveillance systems, laboratory confirmation practices, reporting completeness, and case definitions differ between countries and have evolved over time.

Consequently, variations in reported incidence may partly reflect differences in surveillance sensitivity and diagnostic capacity rather than true epidemiological differences. Furthermore, mild and subclinical infections, particularly those caused by PUUV, are likely to remain underdiagnosed. Therefore, the surveillance data presented in this review should be interpreted as a descriptive synthesis of the available evidence rather than as a formal comparative epidemiological analysis.

Transmission dynamics and emerging drivers

North–South and West–East gradients have previously been described across Europe, where outbreak magnitude is largely driven by ecological conditions influencing rodent abundance rather than by intrinsic viral characteristics [4, 6, 9]. Despite these ecological differences, human infection occurs through a common transmission pathway: predominantly via inhalation of aerosolized particles derived from rodent urine, feces, or saliva in environments where infected reservoir hosts feed, nest, or overwinter. In SEE, the principal human pathogenic orthohantaviruses are PUUV, maintained by the bank vole (*Myodes glareolus*), and DOBV, primarily associated with *Apodemus* spp. mice [5, 9, 10].

The coexistence of multiple reservoir hosts and orthohantavirus species contributes to the complex epidemiology of hantavirus infections in SEE. The risk of PUUV is most closely tied to bank vole ecology in humid forested landscapes, whereas severe disease caused by DOBV is primarily associated with *A. flavicollis* in deciduous Balkan woodlands [10, 47]. The epidemiology of DOBV is further complicated by the circulation of multiple host-associated genotypes that differ in their geographic distribution and pathogenic potential. Transmission is also enabled by the biology of the host reservoir: infection persists, virus shedding may continue for life, and the infectious virus survives in the environment long enough to enable indirect transmission through contaminated material [48, 49]. For clinicians and epidemiologists in SEE, this translates into practical, everyday exposure risks, including visiting rodent-infested outbuildings, cleaning enclosed rural structures, agricultural and forestry work, military field training, and recreational activities in endemic rural areas [28, 29].

The available epidemiological data suggest that the partially synchronized outbreak patterns observed across SEE are best explained by fluctuations in established ecological drivers rather than the emergence of novel transmission routes. Periods of increased reported hantavirus activity observed across the region closely correspond to mast-seeding events, increases in rodent population density, and favorable climatic conditions that enhance reservoir survival and virus transmission [19]. Conversely, prolonged periods of low notification likely reflect both genuine reductions in transmission and underrecognition of mild infections, particularly those associated with PUUV.

The 2021 Croatian outbreak illustrates how increased rodent activity and occupational exposure may coincide with heightened transmission risk [36]. Extreme weather events, including flooding and heavy precipitation, may further increase human–rodent contact by displacing reservoir hosts and contaminating human environments [50]. However, quantitative evidence linking these factors to outbreak occurrence in SEE remains limited and should be interpreted cautiously [7, 8, 48, 50–52]. Land-use change, agricultural restructuring, and expansion of human activities into rodent habitats create additional modifiers of risk by altering the spatial interface between humans and rodent reservoirs. Agricultural activities, forest management practices, land abandonment, and seasonal population movements may increase opportunities for peridomestic and occupational exposure beyond traditionally recognized forest-associated settings [28]. Emerging evidence from Europe also highlights the relevance of synanthropic rodent-associated orthohantaviruses such as Seoul virus. Although not yet established as a major regional pathogen in the Balkans, documented pet-associated and urban rat-associated infections elsewhere indicate that urban monitoring gaps may represent an underrecognized vulnerability within predominantly sylvatic PUUV/DOBV systems [47, 53–55].

Human-to-human transmission of hantaviruses has only been definitively observed with the Andes virus in South America. Genomic and epidemiological studies in this region indicate limited secondary transmission and occasional transmission clusters [56, 57]. However, this phenomenon should not be generalized to SEE orthohantaviruses. There is no evidence of sustained person-to-person transmission for PUUV or DOBV in SEE. Therefore, suspected clusters should be interpreted primarily in the context of shared environmental exposure or common rodent-contaminated sources rather than interpersonal spread [19]. This distinction is crucial for outbreak response strategies, which should prioritize rodent control, environmental decontamination, and occupational risk mitigation over measures targeting respiratory transmission in healthcare settings [4, 58].

Clinical spectrum and diagnostic challenges of hantavirus infections

Hantavirus infections present a wide clinical spectrum, from asymptomatic or subclinical cases to severe multisystem disease, categorized into two primary syndromes:

- **HFRS:** Primarily caused by orthohantaviruses found in Europe and Asia, including Puumala, Dobrava-Belgrade, Hantaan and Seoul viruses.
- **HCPS:** Mainly caused by orthohantaviruses found in the Americas, such as Sin Nombre, Black Creek Canal, New York, Bayou Andes, Laguna Negra, Choclo, and Rio Mamoré viruses [1].

While HFRS and HCPS are recognized as distinct syndromes, they share significant overlaps in clinical manifestations, laboratory findings, and underlying pathogenic mechanisms [3]. For HCPS, patient outcomes are heavily influenced by early disease recognition, the availability of rapid diagnostic tests or reliable presumptive protocols, and timely referral to intensive care-equipped facilities [59, 60].

Table 3. Comparison of epidemiological, ecological, and clinical characteristics of the two predominant hantaviruses in Southeastern Europe

Feature	Puumala virus (PUUV)	Dobrava–Belgrade virus (DOBV)
Primary reservoir	*M. glareolus* (bank vole)	*A. flavicollis* (yellow-necked mouse)
Geographic distribution in Europe	Northern Europe, Central Europe and parts of SEE	Predominantly SEE and the Balkans
Distribution in SEE	Slovenia, Croatia, Bosnia and Herzegovina, Romania	Predominant hantavirus in most countries of SEE
Typical clinical syndrome	Mild to moderate HFRS (*nephropathia epidemica*)	Moderate to severe HFRS
Common clinical manifestations	Fever, thrombocytopenia, acute kidney injury, transient proteinuria	Fever, hemorrhagic manifestations, hypotension, acute kidney injury, shock
Renal involvement	Moderate	Often severe
Hemorrhagic manifestations	Usually mild or absent	More frequent and pronounced
Case-fatality rate	Usually <1%	Approximately 5–15%, depending on viral lineage and outbreak setting
Outbreak pattern	Periodic outbreaks associated with bank vole population dynamics	Localized outbreaks linked to *Apodemus* abundance and ecological conditions
Main ecological drivers	Beech mast, mild winters, bank vole population cycles	Forest habitats, climatic variability and *Apodemus* population density
Public health relevance in SEE	Major contributor to HFRS burden in Slovenia, Croatia and Bosnia and Herzegovina	Predominant hantavirus across most countries of SEE and responsible for the most severe HFRS cases

Clinical characteristics represent the typical spectrum of disease associated with each virus and may vary according to viral lineage, host factors and outbreak setting. **Abbreviations:** *A. flavicollis*, *Apodemus flavicollis*; DOBV, Dobrava–Belgrade virus; HFRS, hemorrhagic fever with renal syndrome; *M. glareolus*, *Myodes glareolus*; PUUV, Puumala virus; SEE, Southeastern Europe.

In SEE, HFRS, caused by PUUV and DOBV, constitutes the predominant clinical burden. Table 3 compares their principal epidemiological, ecological, and clinical characteristics. Unlike Northern and Central Europe, where PUUV-associated *nephropathia epidemica* is common, the coexistence of PUUV and the more pathogenic DOBV in SEE leads to a broader clinical spectrum. Consequently, clinicians in the region encounter both the generally milder PUUV-associated disease and severe DOBV-associated HFRS. The latter is linked to more pronounced renal impairment, hemorrhagic complications, dialysis requirements, and higher case fatality rates [3, 9, 10]. These differences reflect viral pathogenicity rather than distinct clinical syndromes and are a defining clinical characteristic of hantavirus disease in SEE. Regardless of the infecting orthohantavirus, the disease primarily results from non-cytolytic infection of vascular endothelial cells, leading to endothelial dysfunction, increased vascular permeability, thrombocytopenia, and the characteristic clinical manifestations of HFRS [3].

After an incubation period of 1–6 weeks (most commonly 2–3 weeks), HFRS typically progresses through five clinical phases: febrile (toxic), hypotensive, oliguric, polyuric, and convalescent [3]. The febrile phase is marked by non-specific symptoms such as fever, malaise, headache, myalgia, arthralgia, gastrointestinal issues, and occasionally back pain, blurred vision, conjunctival hemorrhages, and petechiae. This is followed by a hypotensive phase, characterized by low blood pressure, early renal dysfunction, and laboratory abnormalities including leukocytosis, thrombocytopenia, proteinuria, and elevated serum creatinine and urea levels [61]. During the oliguric phase, acute kidney injury reaches its peak severity, potentially necessitating hemodialysis in severe cases. Hemorrhagic manifestations range from petechiae and mucosal bleeding to major hemorrhages, while electrolyte disturbances, hypertension, and pulmonary edema can complicate the clinical course. This phase transitions into a polyuric phase with significant diuresis and gradual normalization of renal function. Recovery occurs during the convalescent phase, although complete renal function restoration may take several weeks [40, 62].

Diagnosing HFRS in SEE remains challenging due to its non-specific early clinical presentation, which can mimic other acute febrile illnesses like leptospirosis, acute pyelonephritis, sepsis, and other causes of acute kidney injury [3, 40]. Clinical suspicion should therefore be guided by epidemiological history, particularly residence in or travel to endemic areas, occupational or recreational exposure to rodent habitats, and seasonal disease occurrence [9, 28]. Laboratory confirmation primarily relies on serological testing, as hantavirus-specific IgM and IgG antibodies are usually detectable at or soon after symptom onset. Acute infection is indicated by the presence of specific IgM antibodies, seroconversion, or a significant increase in IgG titers in paired serum samples [3]. Reverse transcription polymerase chain reaction (RT-PCR) is most effective during the early viremic phase before antibody development but has limited sensitivity later in the disease course due to

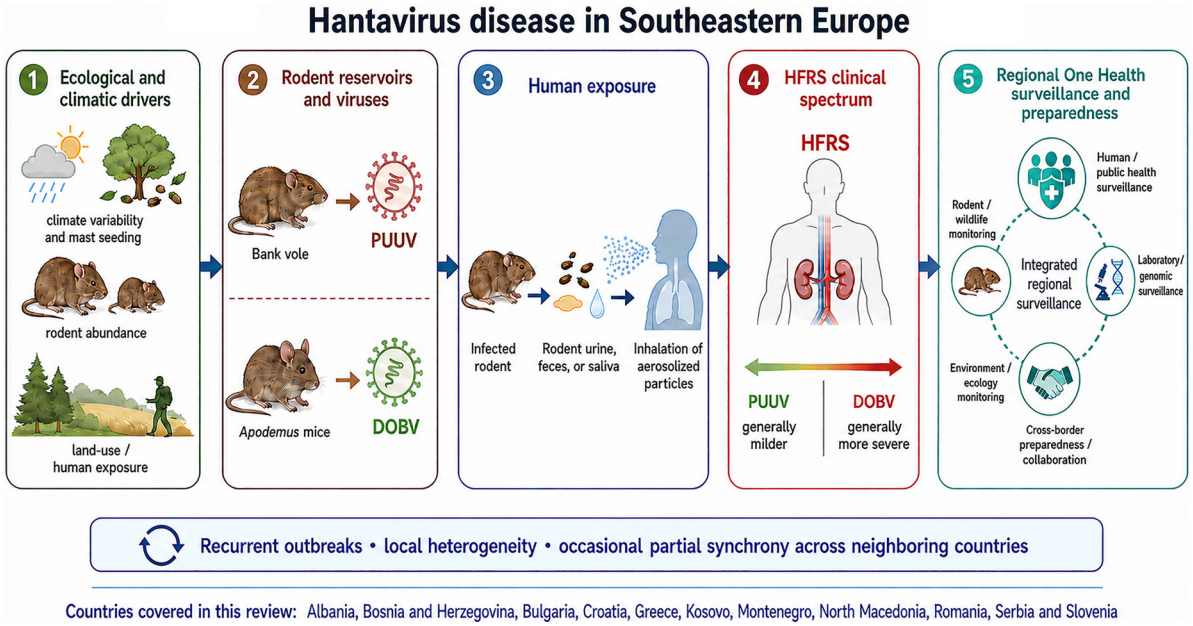

Figure 1. Ecological drivers, transmission pathway, clinical spectrum, and One Health preparedness for hantavirus disease in SEE. Climatic variability, mast seeding, rodent abundance, land-use patterns, and human activities collectively shape hantavirus transmission risk. PUUV is maintained primarily by the bank vole (*Myodes glareolus*), whereas DOBV is mainly associated with *Apodemus* spp. mice. Human infection occurs predominantly through the inhalation of aerosolized particles derived from infected rodent urine, feces, or saliva. The resulting HFRS encompasses a broad clinical spectrum, with PUUV generally causing milder disease and DOBV being associated with a more severe clinical course. Across SEE, endemic transmission is characterized by recurrent, locally heterogeneous outbreaks that may be partially synchronized across neighboring countries. Effective preparedness requires integrated One Health surveillance encompassing human cases, rodent and wildlife reservoirs, environmental and ecological drivers, and laboratory and genomic data, supported by coordinated cross-border collaboration. The review covers Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Greece, Kosovo, Montenegro, North Macedonia, Romania, Serbia, and Slovenia. **Abbreviations**: DOBV, Dobrava–Belgrade virus; HFRS, hemorrhagic fever with renal syndrome; PUUV, Puumala virus; SEE, Southeastern Europe.

transient viremia [63]. Consequently, timely diagnosis depends on integrating epidemiological exposure, characteristic clinical findings, and appropriate laboratory testing. In endemic areas of SEE, clinicians should consider DOBV infection in patients presenting with rapidly progressive renal impairment, hemorrhagic manifestations, or shock, as these features are generally associated with a more severe clinical course than PUUV infection [9, 10].

Disease severity also correlates strongly with the causative virus. Approximately 90% of PUUV infections are asymptomatic, and symptomatic cases typically present as a milder, influenza-like illness. This significant difference in virulence largely explains the greater variability in disease severity observed in SEE compared to European regions where PUUV predominates. The fatality rate in HFRS ranges from less than 1% for PUUV infections to 10%–15% for severe DOBV infections [3]. About one-third of deaths occur from shock at the end of the febrile stage, while the remaining two-thirds result from cerebrovascular accidents and pulmonary edema during the renal stages of the illness [16, 42, 62]. Therefore, clinicians in SEE must routinely consider both relatively mild PUUV-associated *nephropathia epidemica* and severe DOBV-associated HFRS within the same endemic setting—a clinical scenario encountered less frequently in regions where a single orthohantavirus predominates.

Several biomarkers, including lipocalin-2, endothelin-1, and N-terminal pro-B-type natriuretic peptide (NT-proBNP), have been linked to disease severity and acute kidney injury in HFRS [64]. While these biomarkers enhance our understanding of disease pathophysiology, their routine clinical utility in SEE is currently limited and requires further validation.

Emerging risk: Is SEE prepared for hantavirus?

While hantavirus infections have long been present in SEE, several emerging factors could elevate their public health significance in the coming decades. Ecological disruptions from deforestation, land-use changes, urban expansion, and biodiversity loss may alter rodent population dynamics, increasing human exposure to infected reservoir hosts. Additionally, climate variability, including warmer winters, altered precipitation patterns, and extreme weather events, could influence rodent abundance and viral transmission cycles, potentially leading to more frequent or geographically expanded outbreaks [19].

Orthohantaviruses are closely linked to specific rodent reservoir species, a result of long-term host-pathogen co-evolution that has led to distinct viral lineages tied to particular rodent groups (Figure 1). A notable example of environmental factors influencing hantavirus transmission is the 1993 Four Corners outbreak in the United States. Increased precipitation from the El Niño phenomenon boosted vegetation growth, expanding deer mouse populations and heightening human exposure to Sin Nombre virus [65]. Similarly, in Europe, fluctuations in bank vole abundance correlate strongly

with PUUV infection outbreaks. Increased human mobility could introduce infections into regions with low clinical suspicion. Furthermore, the non-specific clinical presentation of hantavirus disease and limited diagnostic capacity suggest that outbreaks may be underrecognized, especially in areas lacking systematic surveillance [19, 40].

A potential future concern for Europe is the introduction and establishment of Andes virus, a hantavirus endemic to South America. Unlike European hantaviruses, which are almost exclusively transmitted through contact with infected rodent excreta, Andes virus can spread person-to-person. While there is currently no evidence of sustained Andes virus circulation in Europe, increasing international travel and globalization raise the possibility of imported cases [57, 66]. If introduced into a susceptible population, the combination of severe disease, high case-fatality rates, and potential for secondary transmission could pose significant public health challenges. Moreover, ecological changes that alter host distributions or facilitate orthohantavirus adaptation to novel reservoir species cannot be ruled out. These considerations underscore the importance of preparedness for timely recognition and management of imported cases.

Future perspectives

The future burden of hantavirus disease in SEE will likely be shaped more by ongoing ecological, environmental, and societal transformations than by changes in viral biology. These transformations may lead to outbreaks that are more frequent, geographically expanded, and less predictable than historical patterns. Such anticipated changes highlight the need for surveillance systems capable of detecting shifts in transmission patterns before they escalate into large-scale outbreaks. Concurrently, land-use changes, agricultural transformation, urban expansion, and increased human mobility are likely to modify human-rodent interaction patterns. These developments could increase exposure not only among traditional high-risk groups like forestry and agricultural workers but also among populations in peri-urban environments or those visiting endemic areas for recreation. The potential emergence of rat-associated orthohantaviruses, including Seoul virus, emphasizes the need to broaden surveillance beyond the traditional sylvatic reservoirs that have historically dominated SEE's epidemiology [53, 54].

Future preparedness efforts should prioritize integrated monitoring of rodent reservoirs, systematic genomic surveillance, harmonized regional reporting systems, standardized laboratory protocols, and improved clinician awareness. These measures are crucial for early detection of outbreaks and changes in viral circulation. Developing shared regional databases and predictive ecological models would further strengthen cross-border surveillance and facilitate more timely public health responses. Particular attention should be given to cross-border collaboration, as ecological drivers and reservoir populations frequently transcend national boundaries. Ultimately, improving preparedness in SEE requires recognizing that hantavirus epidemiology is best understood at the regional rather than the national level. Integrating human, animal, environmental, and genomic surveillance within a coordinated One Health framework will be essential for enhancing outbreak prediction, strengthening preparedness, and reducing the future burden of hantavirus disease across SEE.

Conclusion

Hantavirus infections remain a significant and dynamic public health challenge in SEE. The region presents a unique ecological setting where highly pathogenic DOBV and the generally milder PUUV coexist. This coexistence leads to marked regional variations in disease burden, differing from patterns observed elsewhere in Europe. While the overall incidence of HFRS remains moderate, long-term surveillance indicates that endemic transmission is periodically interrupted by recurrent, partially synchronized periods of increased hantavirus activity affecting multiple neighboring countries. The evidence synthesized in this review demonstrates that hantavirus epidemiology in SEE is best understood as the product of interconnected ecological processes operating across shared landscapes, rather than as a series of independent national epidemiological events. Recognizing these regional patterns has important implications for surveillance, outbreak preparedness, and future research.

Strengthening integrated surveillance of human cases, wildlife reservoirs, environmental drivers, and viral genomic diversity within a coordinated One Health framework will be essential for improving outbreak prediction, facilitating cross-border preparedness, and reducing the future burden of hantavirus disease across SEE.

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Supplemental data

Table S1. Primary sources of epidemiological data for Table 2

Country	Primary data source	Type of data	Notes
Slovenia	ECDC annual surveillance reports [67]	Annual surveillance data	-
Croatia	Croatian Institute of Public Health [68]	Croatian Health Statistics Yearbook	Reviewed by national co-author
Bosnia and Herzegovina	The Institute for Public Health of the Federation of BiH [69], Public Health Institute of the Republic of Srpska [70]	Annual national surveillance	Reviewed by national co-authors
Serbia	Institute of Public Health of Serbia "Dr Milan Jovanović Batut", Belgrade, Serbia [71]	Annual national surveillance	Aggregated annual national surveillance data provided and verified by a collaborating national public health expert
Montenegro	Institute of Public Health of Montenegro, Podgorica, Montenegro	Annual national surveillance	Aggregated annual national surveillance data provided and verified by a collaborating national public health expert
Kosovo	Not available	Annual national surveillance data not publicly available	Not included in Table 2
North Macedonia	Institute of Public Health of the Republic of North Macedonia, Skopje, North Macedonia	Annual national surveillance	Aggregated annual national surveillance data provided and verified by a collaborating national public health expert
Albania	Not available	Annual national surveillance data not publicly available	Not included in Table 2
Greece	ECDC annual surveillance reports [67]	Annual surveillance data	Reviewed by national co-author
Bulgaria	NCIPD, Sofia, Bulgaria [72]	Annual reports of the acute infectious diseases in Bulgaria (main epidemiological indicators)	Reviewed by national co-author
Romania	ECDC annual surveillance reports [67]	Annual surveillance data	Reviewed by national co-author

Table 2 was compiled using aggregated annual surveillance data from the sources listed above. Annual incidence estimates were not calculated where national surveillance data were unavailable. **Abbreviations:** ECDC, European Centre for Disease Prevention and Control; NCIPD, National Centre of Infectious and Parasitic Diseases.