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RABIES IN UKRAINE: PATHOGENESIS, DIAGNOSTICS, AND EPIDEMIOLOGICAL TRENDS IN THE LVIV REGION

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Abstract. *Rabies is an acute infectious zoonotic disease caused by the neurotropic Rabies virus (RABV), a member of the Lyssavirus genus. This review focuses on the pathogenesis, diagnostics, and epidemiological trends of rabies, with a particular emphasis on the Lviv region of Ukraine. The RABV exhibits remarkable pathogenicity, driven by its structural and functional genomic characteristics, immune evasion strategies, and ability to persist in diverse ecological conditions. Rabies pathogenesis involves local replication in muscle cells, followed by retrograde axonal transport to the central nervous system, leading to severe neurological symptoms and inevitable fatality without timely intervention. Domestic dogs (Canis lupus familiaris) remain the primary global reservoir of rabies, responsible for over 99% of human cases, particularly in resource-limited regions. In Ukraine, domestic dogs and cats (Felis catus), alongside wildlife such as red foxes (Vulpes vulpes) contribute significantly to the disease’s epidemiology. Epidemiological data from the Lviv region between 2021 and 2024 indicate a sharp rise in rabies cases, with infections increasing fivefold over the study period. The ongoing large-scale war of russia against Ukraine has exacerbated the situation by disrupting vaccination campaigns and veterinary services, further amplifying the spread of the virus among wild and domestic animals. Molecular diagnostics, including DFA test, PCR, and vaccination programs targeting wildlife and domestic animals are critical for rabies control. This review highlights the need for integrated strategies, including vaccination, surveillance, wildlife population management, and public education, to mitigate rabies transmission. The findings underscore the importance of collaborative efforts to address the escalating challenges of rabies in the Lviv region and provide a foundation for future preventive measures in Ukraine and beyond.*

Key words: rabies virus, epidemiology, pathogenesis, Lviv region, rabies virus reservoirs, vaccination programs.

Rabies is a well-known acute infectious disease that affects both animals and humans. Globally, the disease is referred to as "rabies" in animals and "hydrophobia" in humans. This zoonotic disease is reported in over 150 countries, posing a significant public health challenge (Nychyk, 2006; Nychyk, 2008; Kopcha, 2023; Vynohrad, 2024). According to the World Health Organization (WHO), rabies ranks among the top five most dangerous zoonoses, causing immense social and economic harm (Malyi, 2015). Annually, over 1 million animals and approximately 70,000 people succumb to rabies worldwide, with 40% of cases occurring in children under 15 years old. An estimated 15 million people receive post-exposure prophylaxis

(PEP) after being bitten by potentially rabid animals (Kalinina, 2005). The World Organization for Animal Health (WOAH) emphasizes the substantial economic and social impact of rabies globally (WHO, FAO, & WOAH, 2018; WOAH, n.d.).

The epidemiology of rabies is shaped by a complex interplay between wildlife, domestic animals, and humans. This dynamic requires the implementation of effective prevention and control measures (Coertse, 2017). According to the Law of March 11, 2004, "On Animal Health Protection and the Control of Infectious Animal Diseases," rabies is classified as one of the infectious animal diseases subject to mandatory control within the territory of Ukraine. In Ukraine, rabies remains enzootic, with both natural (wildlife-associated) and anthropogenic (dog-mediated) foci. Cases are regularly reported among wild, domestic, and livestock animals, as well as sporadically in humans. The diversity of rabies reservoirs and sources in Ukraine includes 19 species of wild animals and 10 species of domestic and livestock animals, highlighting the intricate epidemiological network sustaining the disease (Korniyenko, 2019).

Despite advancements in diagnostics, vaccines, and public awareness campaigns, rabies continues to challenge global and regional public health systems. In Ukraine, efforts to combat rabies are complicated by insufficient vaccination coverage in some areas, limited access to diagnostics in rural regions, and ecological factors influencing wildlife transmission. The ongoing war exacerbates these issues, disrupting healthcare infrastructure, vaccination programs, and surveillance, while displacement of people and animals increases exposure risks. For instance, the Lviv region has witnessed significant variations in rabies cases over the years, reflecting regional epidemiological trends that require tailored strategies for control.

This review explores the biological and molecular mechanisms underpinning the rabies virus's pathogenesis, emphasizing its structural and functional genomic characteristics, clinical features, immune evasion strategies, genetic diversity, and environmental persistence. Furthermore, it examines modern frameworks for rabies control, including diagnostic advances, therapeutic approaches, and preventive measures such as vaccination and education. Lastly, the review delves into the transmission dynamics, reservoirs, and epidemiological patterns of rabies, with a particular focus on comparative data from the Lviv region between 2021 and 2024.

The **aim of this review** is to provide a comprehensive synthesis of the current knowledge on rabies, integrating global insights with regional data from Ukraine. By addressing the disease's pathogenesis, control measures, and epidemiology, this work seeks to highlight the progress made in combating rabies while identifying gaps and challenges that warrant further investigation and intervention.

Molecular features underpinning rabies virus pathogenesis

Structural and functional characteristics of the rabies virus genome and proteins. Rabies is caused by the *Rabies virus* (RABV), a neurotropic virus classified under the family *Rhabdoviridae* and the genus *Lyssavirus* (Jackson & Wunner, 2010; Carter & Saunders, 2007). The virus's genome comprises a single-stranded, negative-sense RNA approximately 12 kb in length (Carter & Saunders, 2007). This genome encodes five structural proteins, each playing a pivotal role in the virus's pathogenicity and replication. These proteins include the nucleoprotein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G), and the large polymerase protein (L), each contributing uniquely to the virus's lifecycle (Finke, 2005; Jackson, 2010).

The nucleoprotein (N) is central to encapsidating the viral RNA, forming a ribonucleoprotein complex that is indispensable for genome replication and protection from host degradation mechanisms (Jackson, 2010). The phosphoprotein (P) acts as a critical cofactor for the viral RNA-dependent RNA polymerase (L protein), facilitating the transcription and replication of the viral genome (Chenik, 1998; Jackson, 2010). It also interferes with host interferon pathways, effectively evading the immune response (Chelbi-Alix, 2006). The matrix protein (M) is essential for virus assembly and budding, ensuring the efficient packaging and release of newly formed virions (Jackson, 2010). Glycoprotein (G), located on the viral surface, mediates attachment to host cell receptors such as nicotinic acetylcholine receptors and neural cell adhesion molecules (NCAMs), initiating infection by facilitating viral entry via endocytosis (Jackson, 2010; Finke, 2005). Finally, the large polymerase protein (L) catalyzes the synthesis of viral RNA, driving genome replication and transcription necessary for the production of new virions (Jackson, 2010).

Replication occurs exclusively in the cytoplasm, where transcription generates five distinct mRNA species corresponding to the structural proteins. A positive-sense RNA intermediate serves as the template for synthesizing new negative-sense genomic RNA, ensuring precise control over the production of viral components. This tightly regulated process enables efficient assembly and release of infectious virions, perpetuating the infection cycle (Finke, 2005; Albertini, 2008; Jackson, 2010).

The virus's distinctive bullet-shaped morphology, measuring approximately 180 nm in length and 75 nm in diameter, is a hallmark feature that aids in its identification via electron microscopy (Jackson, 2010).

The RABV exemplifies a masterful pathogen, combining structural simplicity with sophisticated molecular mechanisms for replication, immune evasion, and host cell invasion. Its ability to target neurons underscores the critical need for continued research into its molecular biology, paving the way for novel therapeutic and preventive strategies.

Pathogenesis of rabies: neurological and systemic progression. The pathogenesis of rabies involves a series of well-defined stages, each contributing to the progression of the disease. Following inoculation through a bite or scratch, the virus initially replicates locally in muscle cells at the entry site. This early phase allows the virus to amplify without triggering significant immune responses. The RABV then enters peripheral nerves by binding to nicotinic acetylcholine receptors or NCAMs on neuronal surfaces. This interaction facilitates its migration toward the central nervous system (CNS) via retrograde axonal transport, effectively evading systemic immune detection (Finke, 2005; Carter, 2007; Jackson, 2010; Saini, 2024).

Once within the CNS, the virus spreads rapidly, causing encephalitis characterized by neuronal dysfunction, inflammation, and tissue damage. The clinical manifestations of rabies, including hydrophobia, paralysis, and aggression, are direct consequences of this neurological involvement. Later in the infection, the virus migrates centrifugally to peripheral tissues, including the salivary glands, enabling its transmission to new hosts through saliva (Carter, 2007; Jackson, 2010; Saini, 2024).

Clinical features of rabies. Rabies presents well-defined progression through distinct clinical stages, each characterized by specific symptoms and pathophysiological changes. The disease's course begins with an incubation period, which typically lasts 1–3 months but can range from several days to years (Giesen, 2015; WHO, n.d.a). The length of this phase is influenced by various factors, including the location and severity of the bite, proximity to the CNS, and the viral load introduced during exposure (Greene, 2006; Singh, 2017). During this asymptomatic period, the virus replicates locally in muscle cells and begins its migration toward the CNS via peripheral nerves (Hemachudha, 2002; Singh, 2017).

The prodromal phase, which follows the incubation period, is marked by nonspecific symptoms that can make early diagnosis challenging. These symptoms include fever, malaise, headache, and paresthesia or pain at the bite site, which is often a critical diagnostic clue. This phase tends to run from 2 to 10 days on average and reflects the virus's initial invasion of the peripheral nervous system and early effects on host tissues (Fooks, 2017).

The acute neurological phase typically spans two to ten days and almost always results in death. The nature and intensity of symptoms during this stage largely depend on the severity of the initial exposure. This phase is the hallmark of rabies and is classified into two distinct forms: furious rabies and paralytic rabies. Furious rabies, which occurs in approximately 80% of cases, is characterized by episodes of hyperactivity, agitation, hydrophobia (fear of water), and aerophobia (fear of air movement). These symptoms result from severe encephalitis and the disruption of brainstem functions (Mahadevan, 2016). Paralytic rabies, observed in 20% of cases, progresses more insidiously, with gradual muscle weakness and paralysis (Jackson, 2018; WHO, n.d.a). This form is less dramatic but equally fatal, as paralysis extends to vital muscles, ultimately leading to respiratory failure and coma (Mahadevan, 2016; Jackson, 2010). Additionally, atypical rabies is also distinguished, that is most linked to bat bites, and can exhibit a combination of symptoms characteristic of both the furious and paralytic forms of the disease. This variability in clinical presentation and severity often complicates the accurate identification of rabies cases (Bokade, 2019).

All forms inevitably progress to coma and death without intervention (Mahadevan, 2016). The clinical manifestations of rabies underscore the importance of early recognition and post-exposure prophylaxis to prevent progression to the neurological phase.

Molecular mechanisms of adaptation and immune evasion by the rabies virus. The RABV demonstrates sophisticated mechanisms to evade host immune defenses, ensuring its survival and propagation. Central to this is the viral phosphoprotein (P), which disrupts the host's interferon (IFN) response. The P protein inhibits the activation of signal transducer and activator of transcription 1 (STAT1) and STAT2, key players in the IFN signaling pathway. By blocking the induction of interferon-stimulated genes, RABV effectively suppresses the antiviral state in host cells, facilitating viral replication and spread (Chelbi-Alix, 2006; Kiflu, 2024).

RABV also takes advantage of the immune-privileged CNS. Neurons, the primary target of the virus, have limited innate immune responses, allowing the virus to evade detection and replicate with minimal immune interference. The viral glycoprotein (G) facilitates neuron-specific attachment by binding to neural cell adhesion molecules, ensuring targeted entry while reducing immune recognition (Jackson, 2010; Finke, 2005).

Another critical strategy is RABV’s low replication rate and limited release of viral components, which minimize activation of pattern recognition receptors and subsequent immune responses (Lafon, 2005; Kiflu, 2024).

These immune escape mechanisms demonstrate the virus’s evolutionary adaptations for persistence and pathogenicity, offering valuable insights for developing therapeutic interventions targeting these pathways.

Approaches to rabies control through diagnostics, treatment, and prevention frameworks

Advances in rabies diagnostics: techniques and applications. Accurate and timely diagnosis of rabies is essential for effective control and prevention. Early diagnosis remains a significant global challenge due to the nonspecific nature of initial symptoms, which often mimic other neurological disorders. Clinical observation alone, even with characteristic signs such as behavioral changes or difficulty swallowing, cannot definitively diagnose rabies. This makes confirmatory laboratory tests, as the WHO and the WOAH recommended, the gold standard for reliable diagnosis, particularly in resource-limited settings where access to advanced diagnostic tools may be restricted (Rupprecht, 2018a, 2018b).

Detection of rabies antigen. The fluorescent antibody test (FAT) is the most widely used and reliable diagnostic method for detecting rabies antigen in both humans and animals. FAT is based on antigen detection using fluorescein isothiocyanate-labeled anti-rabies serum or globulin. Brain tissue impression smears, the preferred post-mortem specimen, are treated with these labeled antibodies, and the presence of rabies virus antigen is confirmed by observing fluorescence under a fluorescence microscope. The test is highly accurate, sensitive, and rapid, typically providing results within 1–2 hours. Due to these attributes, FAT is considered the gold standard for rabies diagnosis (Rupprecht, 2018a, 2018b; Hegazy, 2023; WHO, n.d.b).

For situations where fluorescence microscopy is unavailable, the direct rapid immunohistochemistry test (dRIT) serves as an alternative. The dRIT employs streptavidinbiotin peroxidase staining, achieving sensitivity and specificity comparable to FAT. This method is particularly valuable in resource-limited settings where conventional diagnostic infrastructure is lacking (Rupprecht, 2018a, 2018b; WOAH, 2018; Madhusudana, 2012; WHO, n.d.b).

Lateral flow devices (LFDs) have been developed for rapid rabies antigen detection under field conditions. While these devices show promise, their sensitivity and specificity currently fall short of the standards set by FAT and dRIT. Further validation and refinement are necessary for their integration into rabies surveillance programs in underserved regions (Kimitsuki, 2020; WOAH, 2023; WHO, n.d.b).

Detection of rabies virus replication. In cases where antigen-based methods yield inconclusive results, virus isolation techniques can confirm infection and characterize the viral strain. Neuroblastoma cell culture and mouse inoculation tests (MIT) are traditional methods for detecting rabies virus replication. In cell culture, rabies virus replicates without cytopathic effects, requiring confirmation via FAT. Similarly, in mouse models, intracranial inoculation induces characteristic clinical signs of rabies, verified through antigen detection (WOAH, 2012; Mani, 2013; Dacheux, 2015).

While the MIT has historically been used, it is being phased out in favor of cell culture techniques due to ethical considerations, cost efficiency, and faster results. Establishing cell culture facilities in diagnostic laboratories is a critical step toward modernizing rabies diagnostics (WHO, n.d.b).

Detection of rabies virus RNA. Molecular diagnostics, particularly reverse transcriptase polymerase chain reaction (RT-PCR) and real-time PCR, have revolutionized rabies diagnostics. These techniques amplify specific fragments of the rabies virus genome, enabling highly sensitive and rapid detection. RT-PCR is especially valuable for intra-vitam diagnosis in humans, as it can detect viral RNA in saliva, skin biopsies, or hair follicles. However, due to the risk of false positives or negatives, PCR should complement conventional diagnostic methods rather than replace them (Rupprecht, 2018a, 2018b; WHO, n.d.b; Marston, 2019).

Serological tests. Serological assays are not suitable for diagnosing acute rabies infections, as virus-specific antibodies appear late or are absent during the clinical stage. Instead, serological tests primarily evaluate immune responses to rabies vaccines. The gold standard for serological testing is the virus neutralization test, which directly correlates virus-neutralizing antibody titers with protection levels. The Fluorescent Antibody Neutralization Test (FAVN) and Rapid Fluorescent Focus Inhibition Test (RFFIT) are internationally approved methods for determining antibody titers in pets for trade and travel (Ciconello, 2022; Moore, 2010; WOAH, 2021; WHO, n.d.).

Enzyme-linked immunosorbent assays (ELISAs) offer a faster alternative to traditional serological tests, eliminating the need to handle live rabies virus. These assays detect antibodies specific to rabies virus antigens, such as glycoprotein and nucleoprotein, and are increasingly utilized for post-vaccination monitoring (Ma, 2012; Feyssaguet, 2007; Realegeno, 2018; WHO, n.d.b).

Rabies diagnostics in Ukraine. In Ukraine, rabies diagnosis is conducted in accordance with DSTU 7053:2009 "Veterinary medicine. Methods for diagnosing rabies." The primary laboratory diagnostic method is the FAT, which allows for the detection of rabies virus antigens in the brain tissue of animals (Polupan, 2021).

To enhance rabies diagnostics in Ukraine, modern molecular-genetic methods, such as PCR, are being introduced. In June 2024, the WHO in Ukraine organized an online webinar titled "PCR in rabies diagnosis and basics of biosafety and biosecurity" for specialists from the SSUFSCP. This highlights the gradual integration of PCR into rabies diagnostics, which is expected to improve the accuracy and speed of virus detection (Polupan, 2021; SSUFSCP, n.d.).

Additionally, the FAVN test is widely used in Ukraine, especially for determining the titer of rabies antibodies. This test is essential for preparing animals for international travel and is conducted by institutions such as the State Scientific-Research Institute for Laboratory Diagnostics and Veterinary-Sanitary Expertise (SRILDVSE) and several private veterinary laboratories.

While the use of FAT and PCR methods dominate, other diagnostic tests like dRIT, LFDs, MIT, and RFFIT are currently less prevalent. However, specialists from the SSUFSCP are actively exploring these techniques in collaboration with international reference laboratories to enhance diagnostic capabilities.

Advances in rabies diagnostics have significantly improved the accuracy and efficiency of detecting this fatal zoonotic disease. Techniques such as FAT, dRIT, RT-PCR, and serological assays cater to diverse diagnostic needs, ranging from post-mortem confirmation to evaluating vaccine efficacy. However, despite these advancements, accessibility to molecular diagnostic tools like PCR remains a challenge, particularly in underserved regions. Addressing this requires further investment in diagnostic infrastructure and training to enhance early rabies detection, including across Ukraine. Continued validation, standardization, and the adoption of innovative diagnostic tools will be crucial for global rabies control and prevention efforts.

Post-exposure prophylaxis and experimental therapies for rabies. Rabies treatment is highly time-sensitive. Once clinical symptoms appear, the disease is almost invariably fatal, underscoring the importance of early intervention.

Post-Exposure Prophylaxis (PEP) is the cornerstone of rabies treatment. This approach includes immediate wound washing, administration of rabies immunoglobulin (RIG), and a series of rabies vaccines. Globally, PEP has proven highly effective in preventing disease onset when administered promptly (Jackson, 2010; CDC, n.d.). In Ukraine, the availability and utilization of PEP vary between urban and rural areas. Urban centers generally have better access to PEP, while rural regions face challenges due to limited healthcare infrastructure and public awareness. For instance, the Lviv Regional Center for Disease Control and Prevention has highlighted the importance of timely PEP administration, noting that delays often result from misconceptions about the risks associated with animal bites and the lack of immediate healthcare facilities (Lviv Regional Center for Disease Control and Prevention, n.d.).

To address these issues, Ukrainian health authorities, in collaboration with international organizations like the WHO, are working to improve rabies control measures. Efforts include increasing public awareness, enhancing healthcare accessibility in rural areas, and ensuring the availability of PEP across the country (WHO, n.d.).

Proactive measures for rabies control: vaccination and education. Rabies prevention strategies globally focus on mass vaccination, public awareness, and pre-exposure prophylaxis (PrEP) for high-risk groups. In Ukraine, these strategies are actively employed but face regional disparities in implementation.

Vaccination programs. Vaccination remains the most effective tool for controlling rabies in both human and animal populations. In recent decades, significant emphasis has been placed on oral immunization programs for wild animals as an effective method of rabies control. Studies conducted in European countries have shown that this strategy has significantly reduced rabies incidence among wild animals, thereby decreasing the risk of transmission to domestic animals and humans. At the same time, in Ukraine, the implementation of such programs depends on funding and organizational capacities, resulting in uneven regional vaccination coverage (Maki, 2017; Korniyenko, 2019; Polupan, 2019). In particular, oral rabies vaccination (ORV) campaigns targeting wild animal reservoirs, such as foxes, are sporadically conducted in Lviv but require sustained funding and organization to achieve long-term efficacy. Additionally, vaccination efforts have been significantly hindered by restrictions on the use of airspace for distributing vaccine-laden baits. Nevertheless, despite these objective challenges, oral vaccination was carried out across 118,710.816 km^2 of Ukraine's territory in 2023, and 4.9 million domestic animals were vaccinated against rabies. In the Lviv region, vaccination covered an area of 1,828 km², where 45.7 thousand vaccine doses were distributed using ground-based methods (SSUFSCP, n.d.).

PrEP is recommended for veterinarians, wildlife handlers, and individuals in high-risk professions. However, the uptake of PrEP in Ukraine remains low due to cost barriers and limited availability, particularly in rural areas.

Public awareness. Public education is a fundamental aspect of rabies prevention, as increasing awareness among at-risk populations is crucial for controlling the spread of this deadly zoonotic disease. In Ukraine, a variety of educational campaigns have been implemented to inform the public about the risks associated with rabies, preventive measures, and the importance of timely medical intervention. Despite these initiatives, significant challenges persist, particularly in rural and remote regions where access to educational resources and healthcare is limited.

At the national level, the SSUFSCP collaborates with international organizations, including the WHO and the EU-funded EU4SaferFood project, to develop and distribute informational materials. These campaigns often target children and adolescents, employing creative and engaging approaches such as animated films and educational handbooks, which emphasize the importance of avoiding contact with unfamiliar animals, understanding the risks of rabies, and seeking immediate medical assistance in case of an animal bite (SSUFSCP, 2023).

Regional campaigns further reinforce national efforts, with localized programs addressing specific community needs. Educational workshops in schools have been organized to inform students about rabies prevention, including proper wound care and the necessity of timely vaccination. Awareness activities linked to World Rabies Day have included multimedia presentations and the distribution of educational materials to promote preventive measures (SSUFSCP, 2023; SSUFSCP, n.d.).

However, significant barriers remain in rural and remote areas, where limited infrastructure and inadequate healthcare services hinder the effectiveness of public education campaigns. In regions such as Kirovohrad, delayed responses to animal bites and low levels of public awareness contribute to the persistence of rabies cases, with 35 animal rabies cases reported in 2024 alone. These challenges highlight the urgent need for targeted interventions to ensure that critical information reaches underserved populations (Oleksandrivska Village Council, n.d.).

Enhancing the reach and effectiveness of public awareness campaigns is essential for bridging knowledge gaps in rural areas. Collaborative efforts with local communities can increase the credibility and impact of educational initiatives, while the integration of digital platforms and mobile applications can make information more accessible, particularly for younger, tech-savvy audiences. Addressing these gaps will not only improve public understanding of rabies prevention but also reduce the incidence of delayed post-exposure prophylaxis, ultimately saving lives and supporting broader public health goals.

Efforts to increase public awareness must continue to evolve, focusing on innovative and inclusive approaches that prioritize rural and underserved regions. By addressing these disparities, Ukraine can make significant progress toward reducing the burden of rabies and achieving its prevention objectives.

Rabies transmission, reservoirs, and regional epidemiology

Routes of rabies transmission. RABV is primarily transmitted through the saliva of infected animals, introduced into the body via bites or scratches (Fooks, 2014; Wallace, 2020). The virus gains access to peripheral nerves through damaged tissue, enabling its neurotropic nature to facilitate progression toward the CNS (Wallace, 2020). While bites and scratches remain the dominant modes of transmission, less common mechanisms include mucosal exposure, inhalation of aerosolized viral particles, and, in sporadic cases, organ transplantation from infected donors (Irons, 1957; Afshar, 1979; Ross, 2015; Saeed, 2017; Wallace, 2020).

The latter poses a risk due to the virus's ability to remain latent in nervous tissue and evade detection in routine donor screenings (Jackson, 2010).

Rabies vectors and reservoirs: global and Ukrainian perspectives. Rabies is a zoonotic disease maintained through various animal reservoirs, which sustain the virus in wildlife populations and facilitate its transmission to domestic animals and humans. These reservoirs are central to understanding rabies epidemiology and developing effective control strategies (Aiyedun, 2017; Jackson, 2010).

Global patterns of rabies reservoirs. All mammals are susceptible to lyssavirus infections; however, the primary reservoirs are specific species within the order *Carnivora*. The global diversity and distribution of lyssaviruses are heavily influenced by a wide variety of bat species (*Chiroptera*) (Makovska, 2020). Among carnivores, domestic dogs (*Canis lupus familiaris*) play a pivotal role in rabies transmission to humans, particularly in developing countries, where limited vaccination coverage and inadequate control of stray dog populations exacerbate the public health burden (WHO, 2023). Specifically, domestic dogs are the primary reservoirs of the RABV, accounting for over 99% of human rabies cases globally, with the highest prevalence in Africa and Asia. In contrast, in developed countries, rabies is predominantly maintained and transmitted by wild animal populations, reflecting fundamental differences in the epidemiology and control strategies of the disease (WHO, 2023).

Typical carnivore reservoirs of RABV could vary by the region. In Africa, domestic dogs, jackals (*Canis adustus* and *C. mesomelas*), and mongooses (*Herpestes* spp.) serve as primary hosts. In the Middle East and Asia, domestic dogs, red foxes (*Vulpes vulpes*), ferret badgers (*Melogale moschata*), and golden jackals (*Canis aureus*) are significant reservoirs. In Europe, red foxes (*Vulpes vulpes*) and raccoon dogs (*Nyctereutes procyonoides*) maintain the virus. In North America, raccoons (*Procyon lotor*), gray foxes (*Urocyon cinereoargenteus*), striped skunks (*Mephitis mephitis*), and coyotes (*Canis latrans*) are key reservoirs. In South America, domestic dogs, crab-eating foxes (*Cerdocyon thous*), and marmosets (*Callithrix jacchus*) play significant roles. On the Caribbean islands, domestic dogs (*Canis lupus familiaris*) and small Indian mongooses (*Herpestes auropunctatus*) are the primary reservoirs. In the Eurasian and American Arctic and subarctic regions, the arctic fox (*Alopex lagopus*) is a major host species (Gilbert, 2018; Wallace, 2020; WHO, 2023).

Rabies reservoirs in Ukraine. In Ukraine, rabies reservoirs include both domestic and wild animals. Among wildlife reservoirs, red foxes (*Vulpes vulpes*) are the most significant contributors to rabies transmission (Polupan, 2019; Picard-Meyer, 2012). Foxes exhibit high seroprevalence rates, particularly in forested and rural areas, where their scavenging behavior often brings them into close proximity to human settlements and livestock (Polupan, 2019). Foxes act as a bridge between wild and domestic reservoirs, transmitting the virus to unvaccinated pets and livestock. In addition to foxes, sporadic cases of rabies have been reported in other wild species, including bats (*Chiroptera*), roe deer (*Capreolus capreolus*), martens (*Martes martes*), rats (*Rattus spp.*), wolves (*Canis lupus*), and raccoon dogs (*Nyctereutes procyonoides*). Although these species are less prominent as reservoirs, they play a role in maintaining the virus within ecosystems and facilitating its spread to domestic animals (Polupan, 2019).

Domestic animals, particularly dogs, and cats (*Felis catus*) are also significant reservoirs of rabies in Ukraine. Cats, due to their frequent interactions with wildlife, often act as intermediaries in virus transmission, while dogs remain a primary source of human exposure, especially in rural areas with limited vaccination coverage (Makovska, 2020; Polupan, 2019). In addition, isolated cases of rabies have been recorded in other domestic species, including cattle (*Bos taurus*), goats (*Capra aegagrus hircus*), horses (*Equus ferus caballus*), and even guinea pigs (*Cavia porcellus*) (Polupan, 2019). These sporadic incidents highlight the potential for spillover from wildlife to less commonly affected domestic animals, underlining the need for comprehensive vaccination strategies across all susceptible species.

Overall, rabies persists as a complex epidemiological challenge in Ukraine, with significant interconnections between wild and domestic animal populations. Effective rabies control requires strengthened vaccination programs for domestic animals, particularly in rural areas, and continued monitoring of wildlife species to better understand their role in maintaining and transmitting the virus.

Genetic variability and host-specific variants of rabies virus. As mentioned above, rabies is caused by a neurotropic virus belonging to the genus *Lyssavirus* within the family *Rhabdoviridae*. Seven distinct genetic lineages have been identified within the *Lyssavirus* genus through cross-protection tests and molecular biological analyses. These include the classical rabies virus (*Rabies virus*, RABV), classified as genotype 1 and serotype 1, along with six additional rabies-related viruses: *Lagos bat virus* (LBV, genotype 2, serotype 2), *Mokola virus* (MOKV, genotype 3, serotype 3), *Duvenhage virus* (DUVV, genotype 4, serotype 4), *European bat lyssavirus 1* (EBLV-1, genotype 5, serotype 5), *European bat lyssavirus 2* (EBLV-2, genotype 6, serotype 6), and *Australian bat lyssavirus* (ABLV, genotype 7), which has not yet been classified into a serotype (Fooks, 2003).

Serotype 1, *Rabies virus*, includes both street and fixed strains that are found worldwide and encompasses strains isolated from rodents in Central Europe. Serotype 2, *Lagos bat virus*, was first isolated from bats in Nigeria, Guinea, and the Central African Republic, as well as from a cat in Zimbabwe (Boulger, 1958). Serotype 3, *Mokola virus*, has been detected in shrews in Nigeria, humans in Cameroon, and both wild and domestic animals in the Central African Republic and Zimbabwe (von Teichman, 1998). Serotype 4, *Duvenhage virus*, was identified in a human bitten by a bat and has been isolated from bats in South Africa and Central Europe (Tignor, 1997). Serotypes 5 and 6, EBLV-1 and EBLV-2, are associated with European bats and have caused rabies in humans bitten by infected bats, particularly in Finland (Fooks, 2003). Genotype 7, ABLV, was first detected in bats in Australia and has been linked to fatal infections in humans following exposure to infected bats (Speare, 1997).

While all seven serotypes exhibit varying degrees of host specificity and geographic distribution, serotypes 1 and 3 through 6 pose the most significant threats to humans due to their zoonotic potential. These serotypes are maintained within specific reservoir hosts and demonstrate distinct ecological and epidemiological patterns (Skrybitskyi, 2005). The rabies-related viruses (serotypes 2–4, EBLV, and ABLV) highlight the global diversity of *Lyssavirus* species and their ability to persist in wildlife populations, particularly bats, further emphasizing the importance of comprehensive surveillance and control measures.

RABV is divided into two primary genetic lineages: the canine lineage and the New World bat lineage. These lineages are further categorized into specific variants based on genetic distinctions and the reservoir species in which they are maintained. RABV variants are classified primarily by their reservoir hosts, reflecting the ecological diversity of the disease. Globally, canine variants dominate in Africa and Asia, accounting for the vast majority of human rabies cases in these regions (WHO, n.d.; CDC, n.d.). In the Americas and parts of Europe, bat variants, including multiple *Lyssavirus* species, are prevalent and contribute significantly to zoonotic transmission. Wild carnivore variants, such as those associated with foxes and raccoons, play a critical role in rabies epidemiology in Europe and North America, further complicating disease control efforts (CDC, n.d.).

Across regions, specific viral variants have adapted to diverse mammalian hosts, persisting in both domestic dogs and wildlife species, including bats, foxes, jackals, mongooses, raccoons, and skunks. This host-specific adaptation underscores the importance of understanding the ecological dynamics of rabies to inform targeted and effective control strategies (CDC, n.d.).

In Ukraine, molecular analyses have identified distinct RABV lineages associated with domestic dogs and wild foxes (Picard-Meyer, 2012).

Factors influencing rabies virus persistence in the environment. The RABV demonstrates significant sensitivity to environmental conditions such as desiccation, ultraviolet light, and exposure to disinfectants, which substantially limit its survival outside the host. However, in cold and moist conditions, the virus can persist for extended periods, directly influencing its epidemiological patterns, particularly in temperate regions (Fooks, 2014). These conditions create a stable environment for the virus, supporting its persistence in wildlife reservoirs and increasing the likelihood of exposure to domestic animals and humans. Researchers have highlighted the seasonality and geographical distribution of rabies cases, noting that peak incidence occurs during the autumn-winter period. This seasonal trend is closely linked to the active migration period of wild animals, further exacerbating the risk of transmission (SSUFSCP, n.d.).

In Ukraine, the temperate climate plays a pivotal role in shaping the seasonal dynamics of rabies outbreaks. During colder months, the environmental stability of the rabies virus increases, aligning with heightened animal interactions driven by food scarcity. This trend is particularly evident in rural and forested areas, such as the Lviv region, where the incidence of rabies is consistently higher during the autumn and winter seasons. These seasonal patterns underscore the critical need for continuous vaccination campaigns and enhanced surveillance during periods of elevated transmission risk.

The ongoing war in Ukraine has introduced additional challenges to rabies control. Displacement of populations, increased interactions between humans and stray animals, and disruptions to veterinary services have exacerbated the spread of rabies. Conflict-affected regions, particularly in eastern and southern Ukraine, report significant reductions in vaccination coverage for domestic and wild animals. Furthermore, logistical challenges in delivering oral vaccines for wildlife and the restricted use of airspace have severely hampered the implementation of effective oral vaccination campaigns.

Comparative analysis of rabies epizootic data in the Lviv region: 2021–2024. Understanding the dynamics of rabies spread in the Lviv region requires a comprehensive analysis of epizootic data for 2021–2024. Such an investigation is essential for evaluating the effectiveness of previously implemented measures and provides critical insights for planning future preventive and anti-epizootic strategies. All the data presented below regarding the epizootic situation of rabies in the Lviv region were obtained from the State Service of Ukraine on Food Safety and Consumer Protection (SSUFSCP).

In the Lviv region, the rabies situation remains highly concerning. According to the analyzed data, there has been a significant increase not only in the number of infected animals but also in the number of localities where rabies cases have been detected over the past four years. Based on the diagram of affected localities regarding rabies cases in 2021, the highest number of infected animals was recorded in Pustomyty, Zhovkva, Kamianka-Buzka, and Busk districts, accounting for 28%, 24%, 14%, and 9% of cases, respectively (Fig. 1).

These findings highlight the necessity of strengthening control and preventive measures in these regions, particularly through active monitoring and vaccination of both wild and domestic animals.

In 2022, the number of affected localities reporting rabies cases increased by 1.4 times compared to 2021. Additionally, new districts—Zhydachiv, Zolochiv, Skole, and Radekhiv—were added to the list of affected areas, contributing 8%, 16%, 8%, and 11% of cases, respectively. This indicates a relative increase in rabies cases among both domestic and wild animals, further underscoring the importance of a comprehensive approach to the prevention and control of the epizootic situation (Fig. 2).

In 2023, the number of localities where animal rabies cases were detected decreased compared to 2022; however, the total number of animals infected with rabies increased. The highest number of infected animals was reported in Drohobych (25%), Sambir (15%), and Stryi districts (23%) of Lviv region (Fig. 3).

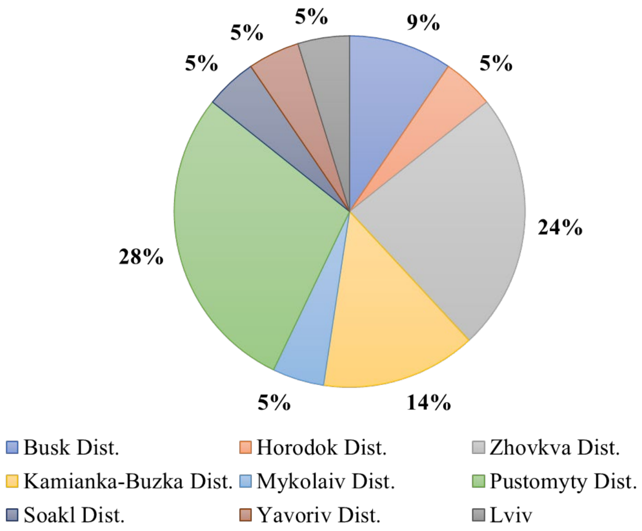

Figure 1. Affected localities with reported rabies cases in 2021

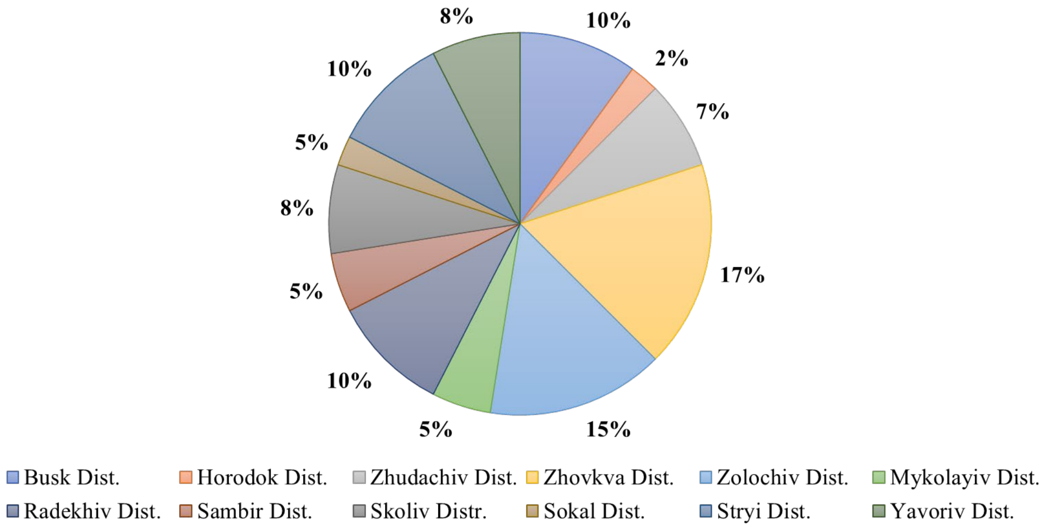

Figure 2. Affected localities with reported rabies cases in 2022

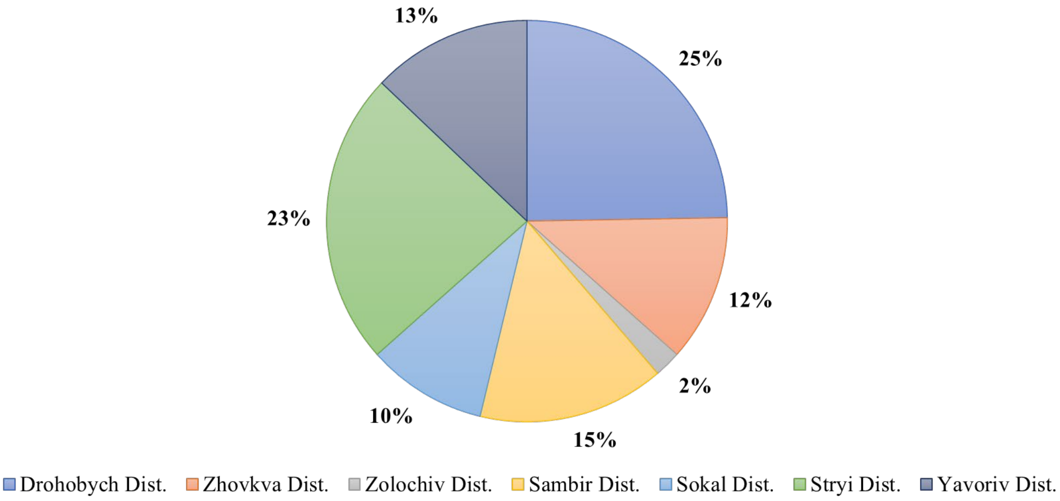

Figure 3. Affected localities with reported rabies cases in 2023

This indicates that despite the reduced territorial coverage, the rabies epizootic continues to progress with an increased intensity of animal infections.

In 2024, the number of localities with reported rabies cases remained at the 2021 level, yet the number of infected animals increased significantly. This trend may be associated with the insufficient effectiveness of preventive measures and underscores the need for enhanced control of wild and domestic animal populations in the region. The highest number of cases was recorded in the Lviv district (33%), followed by Sambir (10%), Stryi (15%), and Zolochiv districts (9%) (Fig. 4).

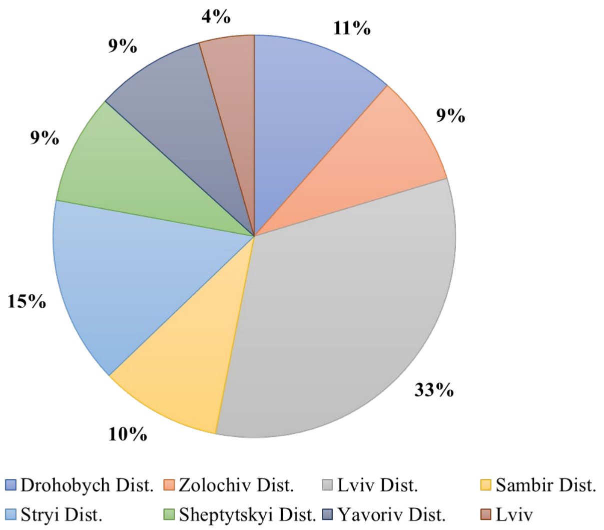

Figure 4. Affected localities with reported rabies cases in 2024

In 2021, a total of 21 infected animals were reported across the districts of the Lviv region (Fig. 5).

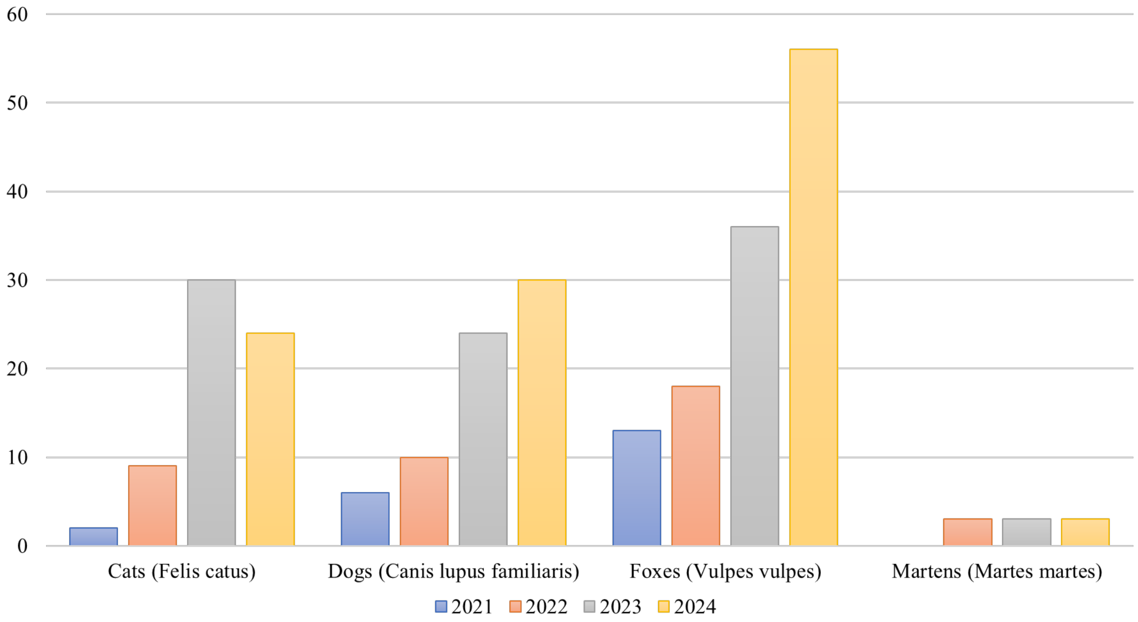

Figure 5. Dynamics of registered rabies-infected animals for the period 2021–2024

Foxes demonstrated a significantly higher disease incidence, with cases surpassing those of cats by 6.5 times and dogs by 3 times. This increase in rabies cases among wild animals highlights the need for detailed investigation and monitoring.

Further analysis of rabies cases in three animal species in 2022 reveals that the number of infections in foxes doubled compared to cats, while cases in dogs increased by 1.8 times.

This upward trend underscores the growing risk of rabies transmission among domestic and wild animal populations.

In 2023, a comparative analysis of rabies cases in domestic and wild animals showed an increasing trend in infections among dogs and cats relative to 2021. However, the number of cases in foxes decreased by 0.7 times compared to cats, which may indicate the initial impact of vaccination programs targeting wild animals.

The year 2024 marked an exceptionally challenging epizootic situation regarding rabies. The total number of infected animals increased by 5.4 times compared to 2021, emphasizing the urgent need for comprehensive control measures and enhanced vaccination campaigns to address the escalating threat of rabies in the region.

Among the infected animals, confirmed cases of rabies were observed not only in foxes but also in martens, indicating an increasing prevalence of the neurotropic rabies virus among wild animals. This trend underscores the growing challenge of controlling rabies within wildlife populations.

Analyzing the number of affected localities based on confirmed rabies cases, the highest numbers were reported in 2022 (Fig. 6).

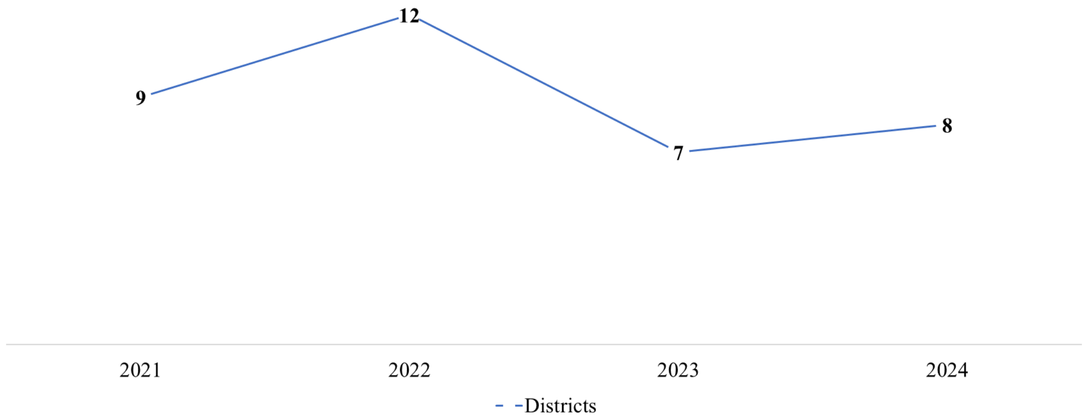

Figure 6. Comparative number of rabies-affected areas for the period 2021–2024

This peak may be linked to the onset of russia's full-scale military invasion of Ukraine, which disrupted public health infrastructure and veterinary services, further exacerbating rabies control efforts.

The ongoing crisis has posed significant challenges for the implementation of vaccination and surveillance programs, highlighting the need for enhanced measures to mitigate the impact of the conflict on rabies elimination efforts. As noted by the WHO, Ukraine has faced unique obstacles in its journey from crisis to control, requiring coordinated international support and innovative strategies to address the escalating risks of rabies transmission in both domestic and wild animal populations.

Comparing the number of reported rabies cases over the analyzed period reveals a consistent upward trend. In 2021, 21 cases of rabies were officially confirmed among dogs, cats, and foxes. This number increased to 40 cases in 2022, 93 cases in 2023, and 113 cases in 2024. Consequently, the number of infected animals in 2022, 2023, and 2024 rose by 1.9, 4.4, and 5.3 times, respectively, compared to 2021 (Fig. 7).

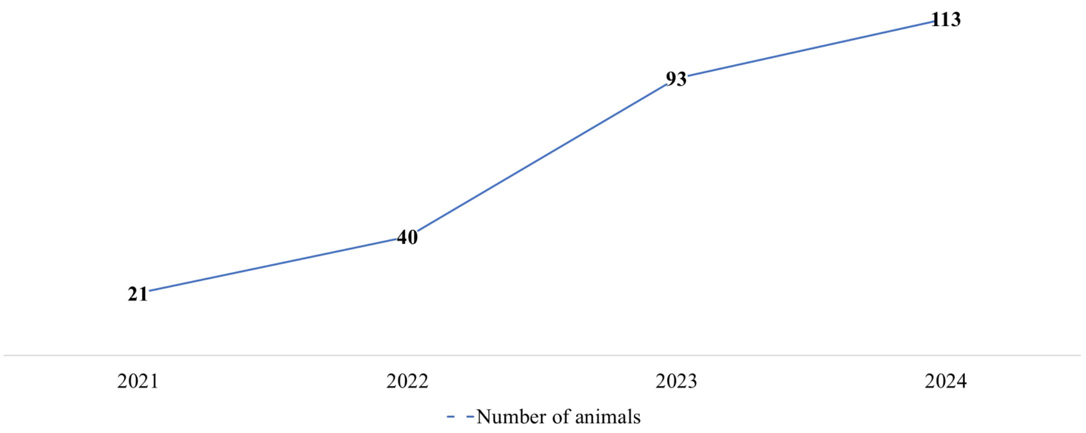

Figure 7. Analysis of animal rabies cases for the period 2021–2024

This growing incidence highlights the escalating challenge of rabies control, necessitating a more robust and targeted approach to vaccination, monitoring, and public awareness campaigns to curb the spread of the disease effectively.

The increase in rabies cases among wild populations poses a threat to ecosystem stability and biodiversity, while simultaneously endangering public health due to the potential for virus transmission to humans. Additionally, rabies outbreaks among domestic animals require attention due to their implications for public health and safety. These findings highlight the urgent need for effective management and prompt action to address this escalating issue.

In light of the challenging epizootic situation regarding rabies in the Lviv region, a specialized commission convened to formulate a plan of anti-epizootic measures aimed at preventing infectious and parasitic diseases in animals for 2025 (Table 1).

Table 1

Anti-epizootic measures for rabies control in the Lviv region

Measure	Details	Objective
Execution of comprehensive rabies plan	Adherence to the 2024–2028 Rabies Control Plan with adjustments for martial law conditions (Protocol No. 1, 24.01.2024).	Systematic implementation of rabies prevention strategies.
Regulation of wild animal populations	Organized culling of foxes, wolves, and raccoon dogs; maintain 200 m distance from residential areas.	Reduce fox density to 0.5–1 individual per 1,000 hectares.
Updating domestic animal records	Record numbers of domestic dogs and cats in local communities and submit to regional veterinary authorities.	Improve tracking and vaccination of domestic animal populations.
Strengthening compliance with regulations	Monitor adherence to pet-keeping rules; enforce penalties for violations.	Ensure responsible pet ownership to reduce rabies transmission.
Enforcing transportation requirements	Verify veterinary documentation for animals during transportation and at border checkpoints.	Enhance control over animal movement and disease spread.

These measures integrate wild and domestic animal management strategies to mitigate the rabies burden in the Lviv region while safeguarding public health and biodiversity.

Conclusion. Rabies remains a pressing global and regional public health challenge, with Ukraine exemplifying its complex epidemiological and ecological dynamics. This review has highlighted the biological and molecular mechanisms of rabies virus pathogenesis, its strategies for immune evasion, and transmission routes. Additionally, it emphasized the critical role of both domestic animals and wildlife reservoirs, such as red foxes (*Vulpes vulpes*), martens (*Martes martes*), and bats, in perpetuating the disease.

The fivefold increase in rabies cases in the Lviv region between 2021 and 2024 underscores the impact of insufficient vaccination coverage, limited diagnostics, and disrupted veterinary services, exacerbated by the ongoing conflict. Seasonal trends in rabies incidence, particularly during autumn and winter, further highlight the need for targeted control strategies during high-risk periods.

The proposed anti-epizootic measures for 2025, including enhanced ORV for wildlife, improved domestic animal vaccination programs, and public education initiatives, reflect a comprehensive approach to rabies control. Addressing logistical and infrastructural challenges, particularly those arising from the conflict, will be essential for safeguarding public health and mitigating the impact of this zoonotic disease in Ukraine and beyond. Integrated efforts and international collaboration remain pivotal in achieving sustainable progress toward rabies elimination.

Conflict of interest. The authors declare that they have no conflicts of interest.

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СКАЗ В УКРАЇНІ: ПАТОГЕНЕЗ, ДІАГНОСТИКА ТА ЕПІДЕМІОЛОГІЧНІ ТЕНДЕНЦІЇ У ЛЬВІВСЬКІЙ ОБЛАСТІ

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Резюме. *Сказ — це гостре інфекційне зоонозне захворювання, спричинене нейротропним вірусом сказу (Rabies virus, RABV), що належить до роду Lyssavirus. У даному огляді розглянуто патогенез, методи діагностики та епідеміологічні тенденції сказу, з особливим акцентом на Львівському регіоні України. Вірус сказу демонструє виняткову патогенність, зумовлену його структурними та функціональними особливостями геному, стратегіями ухилення від імунної відповіді та здатністю зберігатися в різноманітних екологічних умовах. Патогенез сказу включає локальну реплікацію вірусу в м'язових клітинах, подальший ретроградний аксональний транспорт до центральної нервової системи, що призводить до важких неврологічних симптомів і неминучої смерті за відсутності своєчасного втручання. Домашні собаки (Canis lupus familiaris) залишаються основним глобальним резервуаром сказу, відповідальним за понад 99% випадків у людей, особливо у регіонах із обмеженими ресурсами. В Україні вагомий внесок у епідеміологію сказу мають як домашні собаки й коти (Felis catus), так і дикі тварини, зокрема червоні лисиці (Vulpes vulpes). Епідеміологічні дані за 2021–2024 роки у Львівській області свідчать про різке зростання кількості випадків сказу, яке за цей період збільшилося у п'ять разів.*

Триваюча широкомасштабна війна росії проти України загострила ситуацію, порушивши програми вакцинації та ветеринарні послуги, що сприяло поширенню вірусу серед диких і домашніх тварин. Молекулярна діагностика, включаючи прямий метод імунофлуоресценції, полімеразну ланцюгову реакцію та програми вакцинації диких і домашніх тварин, є критично важливими для контролю сказу. У цьому огляді підкреслено необхідність інтегрованих стратегій, що включають вакцинацію, моніторинг, управління популяціями диких тварин і просвітницьку роботу з населенням для зниження рівня передачі сказу. Результати огляду акцентують важливість спільних зусиль у вирішенні зростаючих викликів сказу у Львівському регіоні, що створює основу для майбутніх профілактичних заходів в Україні та за її межами.

Ключові слова: *вірус сказу, епідеміологія, патогенез, Львівська область, резервуари вірусу сказу, програми вакцинації.*

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