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Zoonotic Spillover Mechanisms of Emerging Viral Pathogens at the Wildlife–Livestock Interface

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Abstract

The wildlife–livestock interface (WLI) serves as a critical hotspot for zoonotic spillover of emerging viral pathogens, facilitating the transmission of viruses from wildlife reservoirs to livestock (as intermediate or bridge hosts) and subsequently to humans. This review synthesizes the multi-scale mechanisms underpinning viral spillover, including ecological drivers (such as habitat fragmentation, deforestation, intensive farming, wildlife trade, and climate change), genetic plasticity of RNA viruses (high mutation rates, quasi-species diversity, and recombination), cellular compatibility (receptor usage and tissue tropism), and viral evasion of innate immune responses (interferon antagonism via proteins like NS1, V, VP35). Special emphasis is placed on how livestock act as amplification or mixing vessels, enabling adaptation before human infection. Key case studies illustrate these processes: Henipaviruses (Nipah and Hendra viruses) demonstrate bat-to-pig/horse-to-human pathways or direct bat-to-human routes influenced by strain-specific pathogenesis and cultural practices; MERS-CoV highlights source-sink dynamics in dromedary camels with seasonal spillover linked to calving cycles. The document also explores the debated biodiversity-disease relationship (dilution vs. amplification effects), network ecology for identifying bridge hosts (rodents in human-dominated landscapes), and anthropogenic factors amplifying risk. Effective mitigation requires a One Health approach integrating surveillance in biodiversity hotspots, biosecurity at interfaces, predictive AI modeling, and global data sharing to anticipate and prevent future spillovers of viruses with pandemic potential.

Keywords: Zoonotic Spillover, Wildlife–Livestock Interface, Emerging Viral Pathogens, Henipaviruses, MERS-CoV, Viral Genetic Plasticity, Interferon Antagonism, Receptor Tropism, One Health, Biodiversity Dilution Effect, Anthropogenic Drivers

1. Introduction

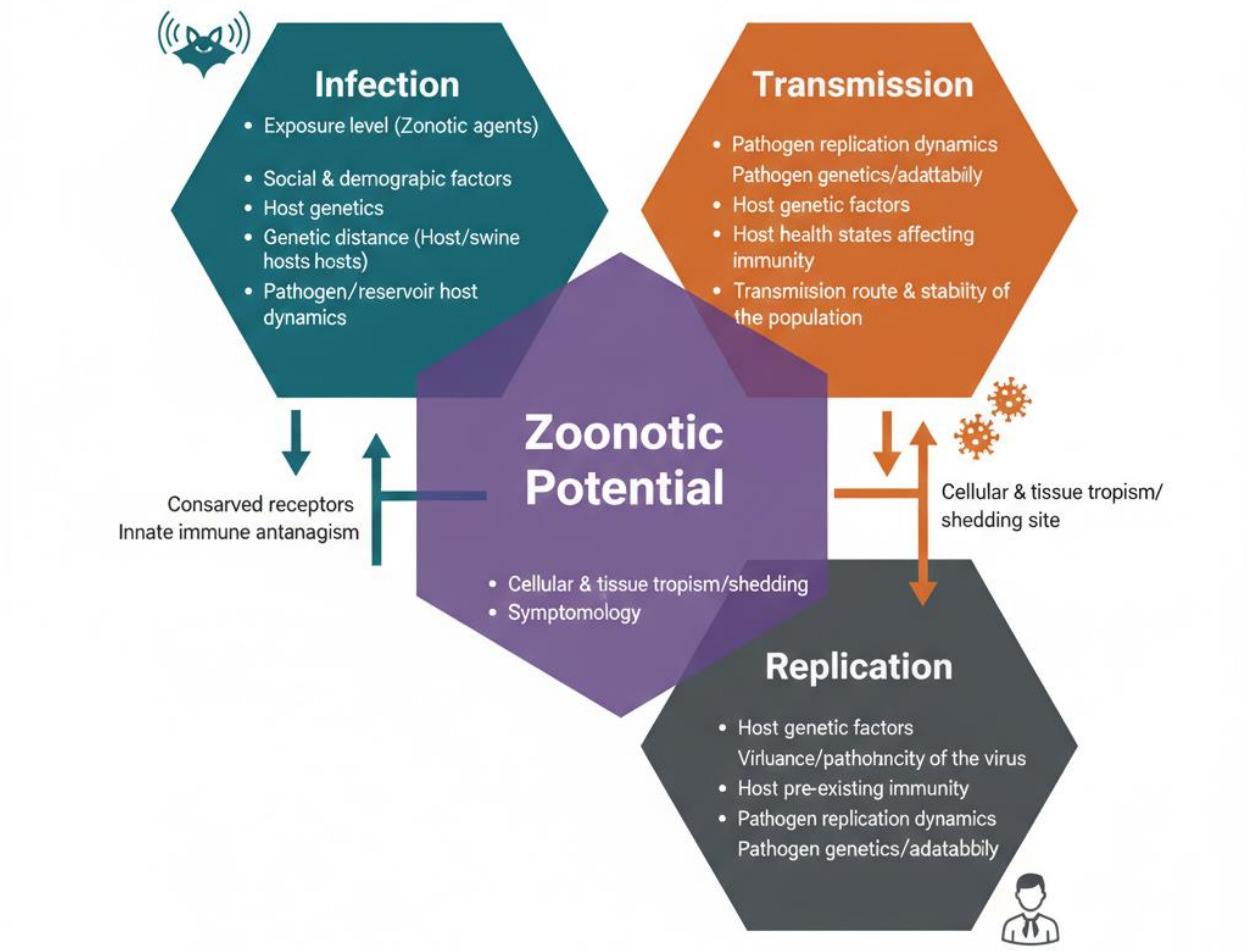
The contemporary landscape of global health is increasingly defined by the permeable boundaries between wild ecosystems, agricultural production systems, and human settlements. Zoonotic spillover, the process by which a pathogen is transmitted from a vertebrate animal to a human host, serves as the fundamental mechanism for the emergence of novel infectious diseases (Ellwanger & Chies, 2021). Quantitative assessments indicate that between 60% and 75% of all human

infectious diseases are derived from pathogens that originally circulated in non-human animal species (Zoonotic spillover and pandemic risk, 2025). This phenomenon is not a singular event but a complex, multi-stage ecological and biological process that requires the alignment of various favorable conditions across different host species and environments (Plowright et al., 2017). The wildlife–livestock interface (WLI) represents a critical nexus in this process, functioning as a high-density zone where pathogens can amplify, adapt, and eventually jump into human populations (Vercauteren et al., 2021).

2. Conceptualizing the Mechanisms of Viral Spillover

The mechanisms driving viral spillover are inherently hierarchical, requiring a pathogen to overcome a series of barriers that start at the landscape level and conclude at the molecular level within the recipient host cell (Pauciullo et al., 2024). At the broadest level, ecological factors dictate the exposure of humans or livestock to reservoir hosts (Borremans et al., 2019). These factors are heavily influenced by the prevalence and intensity of infection within the reservoir population, which are themselves products of the host's immunological condition and inter-species interactions such as prey-predator dynamics and habitat sharing (Escudero-Pérez et al., 2023).

Figure 1: Multi-stage Process of Zoonotic Spillover, Pathogen Adaptation, and Human Emergence



Spillover is often characterized as a stochastic and "imperfect" process from the perspective of the pathogen's success; the majority of mammalian viruses do not possess the capacity to infect humans, and most spillover events that do occur fail to establish a sustained chain of transmission

(Purushotham et al., 2025). To understand why certain viruses, succeed where others fail, it is necessary to examine the stages of emergence. The framework proposed by Wolfe and others delineates these stages, beginning with agents found only in animals and progressing through primary human infection, limited outbreaks, and sustained transmission, finally resulting in a pathogen that circulates exclusively among humans (Gangopadhayya et al., 2023).

Table 1: Stages of Viral Emergence and Pathogen Distribution Dynamics

Stage of Viral Emergence	Pathogen Distribution and Transmission Dynamics	Evolutionary Relevance
Stage I	Agent present only in animal reservoirs; no human exposure.	Reservoir maintenance
Stage II	Primary infection in humans; no secondary human-to-human spread.	Evolutionary dead-end
Stage III	Limited human-to-human transmission; short chains (R0 < 1).	Transient outbreaks
Stage IV	Sustained human-to-human transmission; established outbreaks.	Potential pandemic
Stage V	Exclusive human pathogen; no longer requires animal reservoir.	Endemic human agent

The wildlife–livestock interface significantly complicates this hierarchy by introducing intermediate hosts that can act as "mixing vessels" or "bridge hosts" (O'Reilly et al., 2025). Livestock often occupy an ecological space that overlaps with both wild reservoirs and dense human populations, facilitating a two-step spillover process where pathogens first adapt to domestic animals before jumping to humans (Wiethoelter et al., 2015).

3. Genetic Variability and Evolutionary Constraints of Emerging Viruses

The ability of a virus to traverse species boundaries is largely a function of its genetic plasticity. RNA viruses are disproportionately represented among emerging zoonotic pathogens, a trend driven by their high mutation rates and rapid replication cycles (Mechanism driving zoonotic spillover, 2024). The mutation rate for RNA viruses is estimated to be between 0.1 and 1.0 mutations per genome per replication cycle, which is approximately six times higher than the rates observed in eukaryotes. This high rate of error is primarily due to the lack of proofreading activity in RNA-dependent RNA polymerases (RdRp) (Nolting, 2018).

This inherent instability leads to the formation of "quasi-species" populations of genetically diverse variants within a single host. This diversity provides a reservoir of variants that may, by chance, possess mutations allowing them to bind to receptors in a novel host species (Mokalla et al., 2025). However, there is an "error threshold" that limits the size of most RNA viral genomes to approximately 10 kb; beyond this size, the accumulation of lethal mutations would compromise the fitness of the virus (Leung, 2024). Coronaviruses are a notable exception to this rule, maintaining genomes of approximately 30 kb through an exonuclease-mediated proofreading mechanism that enhances replication fidelity while still allowing for significant recombination and mutation (Hickler, 2009).

The substitution rate of specific viruses highlights the speed of this adaptation; for example, the pandemic Influenza A/H1N1 virus has an estimated substitution rate of 5 x 10^-3 substitutions per site per year (Zhang et al., 2021). While many mutations are lethal estimates suggest 40% to 80% of mutations in RNA viruses result in a loss of fitness the surviving variants are often those best suited for the selective pressures of a new host environment (Vilain et al., 2025).

Table 2: Genetic Characteristics and Mutation Rates of Major Virus Categories

Virus Category	Genome Size (kb)	Mutation Rate (subst./site/year)	Proofreading Mechanism
Standard RNA Viruses	2–15	10^-3 to 10^-5	Absent
Coronaviruses	approx. 30	Variable (higher than DNA)	Present (Exonuclease)
DNA Viruses	5–300+	10^-6 to 10^-8	Present (DNA Polymerase)
H1N1 (Influenza A)	approx. 13	5 x 10^-3	Absent

4. Biological Barriers and Cellular Compatibility

The transition from a reservoir host to a recipient human host requires a high degree of molecular compatibility. The primary barrier at the cellular level is the presence and accessibility of host cell receptors that facilitate viral entry (Key host-pathogen interactions, 2023). Viruses that utilize highly conserved receptors those involved in essential biological functions that vary little across mammalian species possess a higher potential for broad host range spillover (Johnson et al., 2020). The Hendra and Nipah viruses utilize the Ephrin B2 ligand as their main entry receptor. Ephrin B2 is involved in vasculogenesis, embryogenesis, and neurogenesis, and is highly conserved across all mammals, which explains why these viruses can infect a wide range of species including bats, pigs, horses, dogs, and humans (Letko et a., 2020). In contrast, other viruses target receptors that are more species-restricted. For instance, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) utilizes dipeptidyl peptidase-4 (DPP4) and alpha 2,3-sialic acids for attachment (Host factors in MERS-CoV pathogenesis, 2019). In human lungs, DPP4 expression is primarily concentrated in Type II pneumocytes, which can limit the efficiency of infection unless the virus adapts or the host has pre-existing conditions (like smoking or COPD) that upregulate the receptor in other tissues like Type I pneumocytes (Drucker, 2020).

Table 3: Host Cell Receptors and Tissue Tropism of Key Zoonotic Viruses

Virus	Host Receptor	Tissue Tropism (Human)	Spillover Relevance
Nipah Virus	Ephrin B2	Endothelial cells, neurons	High conservation across mammals
SARS-CoV-2	ACE2	Nasal/lung epithelium	High affinity for human ACE2
MERS-CoV	DPP4	Alveolar Type II cells	Camel-to-human jump
Influenza A (Avian)	alpha 2,3-Sialic Acid	Lower respiratory tract	Requires switch to alpha 2,6
Influenza A (Human)	alpha 2,6-Sialic Acid	Upper respiratory tract	Human adaptation marker

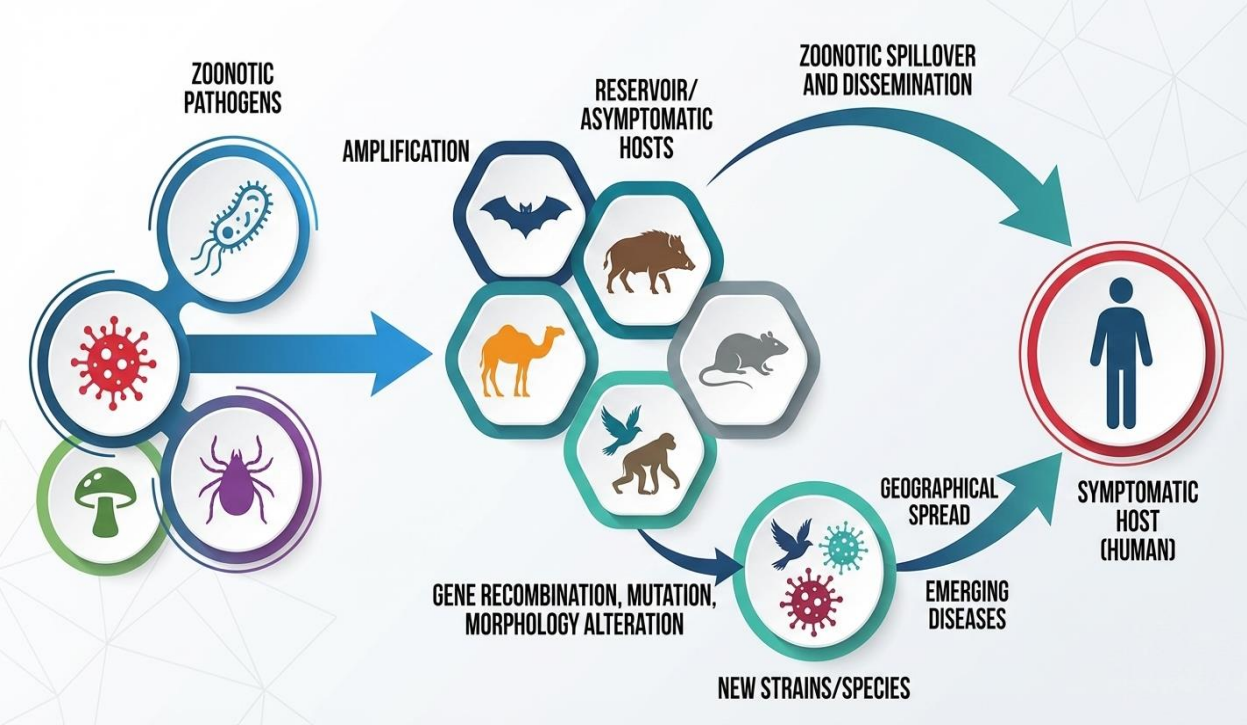
The phenomenon of tissue tropism also dictates the clinical manifestation and transmissibility of the virus. In the case of coronaviruses, most human infections begin in the nasal epithelium. Endemic coronaviruses like HCoV-229E primarily infect non-ciliated cells, while others like HCoV-OC43 and HCoV-HKU1 target ciliated cells (Hua et al., 2023). The high expression of receptors like TMPRSS2 and ACE2 in the nasal and pharyngeal mucosa facilitates initial establishment, while the progression to the lower respiratory tract where alveolar Type II cells are infected leads to severe disease like acute respiratory distress syndrome (ARDS) (Breugem et al., 2025).

5. Evasion of the Innate Immune System and Interferon Antagonism

Successful spillover is not merely a matter of entry; the virus must also effectively derail the host's innate immune defenses (Wu et al., 2020). The production of Type I interferons (IFN-alpha/beta) is the primary intracellular defense mechanism against viral infection. This response is initiated when pattern recognition receptors (PRRs), such as RIG-I-like receptors (RLRs) or the cGAS-STING axis, detect viral nucleic acids (Viral interferon antagonism, 2024).

Viral evasion strategies are often species-specific, creating "interspecies barriers". A viral protein may successfully inhibit the IFN response in its natural reservoir but fail to do so in a novel host because the target host protein (ortholog) has slightly different amino acid sequences (Wang et al., 2022). For example, the NS1 protein of Influenza A Virus (IAV) binds to the central coiled-coil (CCD) region of human TRIM25 to block the activation of RIG-I (Lee et al., 2020). While NS1 from human, swine, and mouse-adapted strains interacts effectively with human TRIM25, it fails to interact with murine TRIM25 due to specific residues in the mouse ortholog, thereby limiting the virus's ability to replicate in mice without further adaptation (Wei et al., 2024).

Figure 2: Biological and Ecological Determinants of Pathogen Infection, Replication, and Transmission Success



Similarly, the V protein of Nipah virus targets STAT1 and STAT2 proteins to prevent their translocation to the nucleus, effectively silencing the interferon-stimulated gene (ISG) response (Mechanism of Viral Immune Evasion, 2025). Unlike many other viral antagonists, the NiV V protein is capable of inhibiting IFN signaling across a wide range of species, which facilitates its broad tropism (Evseev et al., 2022). In contrast, the NS protein of Severe Fever with Thrombocytopenia Syndrome Virus (SFTSV) interacts with human STAT2 but fails to interact with murine STAT2, which likely explains why the virus is pathogenic in humans but not in mice (Lamotte et al., 2021).

Table 4: Molecular Mechanisms of Viral Interferon Antagonism

Viral Antagonist	Host Target	Molecular Mechanism	Effect on Immunity
IAV NS1	TRIM25	Blocks ubiquitination of RIG-I	Inhibits IFN production
NiV V Protein	STAT1/STAT2	Sequesters STATs in the cytoplasm	Blocks ISG expression
EBOV VP35	RIG-I/MDA5	Competes for RNA binding	Inhibits sensor activation
EBOV VP24	Karyopherin alpha	Blocks nuclear transport of STAT1	Blocks IFN signaling
HSV-1 UL37	RIG-I	Deamidation of N495 residue	Inactivates RIG-I sensor

6. Ecological Drivers of Spillover at the Interface

The ecological context of the wildlife–livestock interface provides the necessary exposure for spillover to occur (De Garine-Wichatitsky et al., 2021). Anthropogenic activities, including deforestation, urbanization, and the intensification of agriculture, have significantly disrupted natural ecosystems and increased the frequency of human–wildlife–livestock interactions (Ellwanger & Chies, 2021).

Habitat fragmentation often forces wildlife out of their natural ranges and into human-dominated landscapes. For instance, the destruction of natural forest buffers in states like Kerala and Maharashtra in India has been linked to increased zoonotic spillover events (Vercauteren et al., 2021). When wildlife, livestock, and humans share resources such as food and water, the risk of transmission through indirect contact such as environmental pollution with saliva, urine, or feces rises dramatically (Vicente et al., 2021).

Intensive animal husbandry and "mixing vessels" like live animal markets further amplify these risks. In these environments, different species are often confined in crowded, unsanitary conditions that facilitate interspecies transmission and viral recombination (Caron et al., 2021). Livestock production accounts for significant global economic losses; over 20% of global animal production is lost annually due to infectious diseases, many of which are shared with wildlife (Wiethoelter et al., 2015).

Table 5: Anthropogenic and Ecological Drivers of Viral Spillover

Ecological Driver	Impact on Spillover Mechanism	Resulting Risk Factor
Deforestation	Habitat loss forces reservoirs into farmland.	Increased inter-species contact
Intensive Farming	High density of susceptible hosts.	Viral amplification and mutation
Wildlife Trade	Mixing of taxonomically diverse species.	Novel recombination opportunities
Urban Expansion	Encroachment of settlements into sylvan areas.	Direct human-reservoir interaction
Climate Change	Altered distribution of hosts and vectors.	Range expansion of pathogens

7. Biodiversity and the Disease-Risk Debate: Dilution vs. Amplification

The relationship between biodiversity and zoonotic disease risk remains a central and debated

topic in disease ecology. Two primary hypotheses dominate the literature: the "dilution effect" and the "amplification effect" (Reappraisal of the Dilution and Amplification Effect, 2025).

The dilution effect hypothesis suggests that higher vertebrate species diversity can lead to decreased disease transmission and prevalence in the reservoir host, thereby reducing the risk of spillover to humans (Luis et al., 2018). This typically occurs in systems where the primary reservoir is a generalist species that dominates low-diversity communities. In these scenarios, when biodiversity is lost, the species that remain tend to be the most competent reservoirs for the pathogen (Cantonati et al., 2020). For example, Lyme disease research has shown that increased vertebrate diversity can reduce the density of infected ticks by providing "sink" hosts that are less competent for transmission (Keesing et al., 2021).

Conversely, the amplification effect occurs when increased species diversity leads to increased infection prevalence or higher spillover risk. This can happen if diversity increases the density of hosts, the frequency of contact rates, or the overall transmissibility within the community (Rohr et al., 2020).

Detailed mathematical modeling of Sin Nombre Hantavirus (SNV) in deermice populations indicates that both effects can occur concurrently. High small mammal diversity was found to decrease the population density of deermice, which in turn decreased the prevalence of SNV a net dilution effect (Warner, 2020). However, when controlling for density, researchers found that the transmission rate actually increased at sites with higher diversity a "component amplification effect" (Miglio, 2021). This suggests that the net relationship between biodiversity and disease is a balance between these competing drivers (Williams, 2021).

Table 6: Mechanisms of the Dilution and Amplification Effects in Disease Ecology

Biodiversity Mechanism	Effect on Pathogen Transmission	Resulting Phenomenon
Competition/Predation	Reduces reservoir host population density.	Dilution effect
Host Diversity	Vectors waste meals on incompetent hosts.	Dilution effect
Generalist Vectors	High diversity provides more feeding opportunities.	Amplification effect
Resource Sharing	Increases inter-species contact rates.	Amplification effect
Density-Dependence	Low density leads to reduced viral circulation.	Net Dilution (e.g., SNV)

8. Case Study: Henipaviruses at the Wildlife–Livestock Interface

Nipah virus (NiV) and Hendra virus (HeV) are archetypal examples of spillover at the interface, though they demonstrate distinct transmission pathways, Nipah virus has caused repeated outbreaks in Malaysia, Bangladesh, and India, with case fatality rates (CFR) often exceeding 70% (Spatio-temporal dynamics of Hendra virus, 2024).

In the 1998 Malaysian outbreak, the virus spilled over from Pteropus fruit bats to domestic pigs, which then acted as bridge hosts, amplifying the virus and transmitting it to thousands of pig farmers (Patterns of transmission and shedding of Nipah virus, 2016). In contrast, the Bangladeshi and Indian outbreaks involve direct bat-to-human transmission through the consumption of raw date palm sap contaminated with bat excreta (Shanta et al., 2023). Genomic analysis shows that the Malaysia (NiV-MY) and Bangladesh (NiV-BD) strains share 91.8% nucleotide sequence homology but exhibit notable differences in pathology and transmission (Khan et al., 2025).

Experimental studies using ferrets have revealed that NiV-BD replicates more rapidly and to higher levels in the respiratory tract compared to NiV-MY, which likely contributes to the person-to-person respiratory transmission observed in Bangladesh but not in Malaysia (Cimaroli, 2024).

However, transmission risk is also heavily underpinned by social and environmental factors. In the ferret model, transmission did not occur during simple cohabitation but occurred 100% of the time when there was direct, assisted exposure to oronasal fluids (Yeasmin et al., 2025). This suggests that the intensive care provided by family members to NiV patients in Bangladesh is a primary driver of the observed human-to-human spread (Dhivahar et al., 2023).

Table 7: Comparative Pathogenesis and Transmission of Nipah Virus Strains

Feature	Nipah Malaysia (NiV-Mal/MY)	Nipah Bangladesh (NiV-Ban/BD)
Primary Spillover Route	Bat to Pig to Human	Bat to Human (Date palm sap)
Case Fatality Rate (CFR)	approx. 40%	approx. 75%
Primary Symptoms	Acute Encephalitis	Encephalitis + Severe Respiratory
Human-to-Human Spread	Rare/Absent	Frequent
Viral Shedding	Lower in respiratory secretions	Significantly higher in secretions
Target (Lung Histopath)	Bronchi and BALT	Alveolar pneumocytes

Hendra virus spillover in Australia follows a similar pattern involving flying foxes and horses as intermediate hosts (Lunn, 2021). Research into HeV genomic diversity has revealed four distinct clades circulating in bat populations, with no strong spatial or temporal structuring, suggesting that viral shedding events are not necessarily driven by the introduction of new lineages but by the physiological stressors on the bat populations themselves (Linnegar et al., 2026).

9. Case Study: MERS-CoV and the Camel Reservoir

Middle East Respiratory Syndrome Coronavirus (MERS-CoV) provides a different perspective on the wildlife–livestock interface, where the virus is maintained in a domestic animal population with frequent jumps to humans. Since 2012, MERS-CoV has caused significant morbidity and mortality in the Arabian Peninsula, though its spread between humans remains limited (Dudas et al., 2018).

Structured coalescent modeling indicates that long-term MERS-CoV evolution occurs exclusively in dromedary camels. In this "source-sink" dynamic, camels serve as the stable source and humans act as "evolutionary dead-ends" or transient sinks (Wasik et al., 2025). Analysis of 174 human genomes estimated a median of 56 separate camel-to-human transmission events, suggesting that the human epidemic is sustained by hundreds of individual jumps from camels rather than endemic circulation in humans (Hill et al., 2023).

Seasonality plays a major role in these spillover events. The odds of zoonotic transfer increase significantly during April, May, June, and July. This peak follows the camel calving season (October to February) (Kandeel et al., 2022). As maternal antibody levels in calves decline, the virus sweeps through the new generation of susceptible young camels, increasing the overall viral load in the population and thus the risk of transmission to humans (Tulu et al., 2024).

Table 8: Source-Sink Dynamics of MERS-CoV in Camel and Human Populations

Parameter	Camel Population (Source)	Human Population (Sink)
Role in Evolution	Exclusive site of long-term evolution	Transient, terminal host
Scaled Effective Pop. Size (Ne tau)	3.49 years	0.24 years

Cross-Species Migration	Frequent (Camel to Human)	Negligible (Human to Camel)
Reproductive Number (R0)	greater than 1 (Efficient transmission)	less than 1 (Transient chains)
High Risk Season	Post-calving (Spring/Summer)	Linked to Camel Epizootics

10. Livestock Production and Global Health Security

The interface between wildlife and livestock is not only a biological risk but a significant economic one. Outbreaks of transboundary animal diseases like African Swine Fever (ASF) and Avian Influenza (AI) have devastating impacts on food security and international trade (Yadav et al., 2020). ASF, caused by a DNA virus, affects domestic pigs and wild boar and is transmitted through direct contact or vectors like ticks (Clemmons et al., 2021).

Biosecurity measures are essential for managing these risks at the WLI. These strategies include preventing direct contact (bites, fluids) and indirect contact (contaminated surfaces, shared water) between domestic and wild species (Evseev et al., 2022). Herd immunity through vaccination and rigorous sanitary surveillance are critical tools for disrupting the chain of transmission (Grace et al., 2020). The World Organisation for Animal Health (WOAH) provides guidelines for managing these interfaces, advocating for a customized approach that considers local geography and production systems (Thompson et al., 2024).

11. The Role of Network Ecology in Pathogen Sharing

Understanding the structure of host-pathogen networks at the wildlife–livestock–human interface allows for a more targeted approach to surveillance. Community ecology studies have shown that the sharing of parasites between species is not random (Hua et al., 2023). For example, rodent species that reside in human settlements and rice fields share a significantly higher proportion of their parasite diversity than those living in primary forests (Emerging infectious diseases' hotspots, 2008). (Vicente et al., 2021).

In tropical ecosystems, these networks are characterized by high Jaccard index values a measure of similarity between sample sets (Yeasmin et al., 2025). Rodent species like Bandicota indica and Bandicota savilei in human-dominated landscapes show Jaccard indices as high as 0.48 and 0.5 respectively when compared to human-shared parasites (Breugem et al., 2025). This high degree of overlap identifies these species as critical bridge hosts for the transmission of rodent-borne viruses to humans (Emerging infectious diseases' hotspots, 2008).

Table 9: Rodent-Human Pathogen Sharing and Jaccard Index Values in Tropical Landscapes

Host Species (Rodent)	**Habitat Preference**	**Parasite Diversity**	**Jaccard Index (with Humans)**
Bandicota indica	Human settlements/Rice fields	High	0.48
Bandicota savilei	Human settlements/Rice fields	High	0.50
Rattus exulans	Human settlements	High	0.43
Rattus tanezumi	Human settlements	High	0.42
Mus caroli	Primary/Secondary Forest	Low	Low

12. Future Directions: One Health and Predictive Modeling

Addressing the increasing frequency of zoonotic spillover requires a "One Health" strategy an

integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals, and ecosystems (Caron et al., 2021). This approach recognizes that the health of humans is inextricably linked to the health of animals and the environment (Keesing et al., 2021).
Current research identifies several critical gaps in our response to these threats (Zoonotic spillover and pandemic risk, 2025). There is a significant need for the integration of ecological data into public health frameworks to better understand how environmental changes drive spillover events (Linnegar et al., 2026). Surveillance must be shifted towards biodiversity "hotspots" where the risk of novel pathogen emergence is highest. Furthermore, global data-sharing barriers often political or economic must be overcome to allow for rapid response to emerging threats (Williams, 2021).
The application of Artificial Intelligence (AI) and predictive modeling represents a promising frontier in zoonotic surveillance. AI-driven models can synthesize vast amounts of genomic, ecological, and human mobility data to anticipate where and when the next spillover might occur (Vicente et al., 2021). Initiatives such as the Global Virome Project aim to proactively identify the estimated 10,000 viral species with zoonotic potential, providing a library of threats that can be used to develop "pre-exposure" prophylactics and rapid diagnostic tools (Carlson et al., 2019).

13. Conclusions

Zoonotic spillover at the wildlife–livestock interface represents a complex, hierarchical process driven by ecological disruption, viral evolutionary adaptability, molecular compatibility barriers, and immune evasion strategies. The increasing encroachment of human activities into natural ecosystems, combined with intensive livestock production and wildlife trade, has amplified the frequency and risk of cross-species transmission events. Case studies of Nipah, Hendra, and MERS-CoV viruses underscore the pivotal role of intermediate hosts and environmental/social factors in determining spillover success and subsequent transmission chains. While RNA viruses dominate due to their mutational capacity, overcoming interspecies barriers often requires specific adaptations that are stochastic yet increasingly probable under current global changes. Addressing these threats demands an integrated One Health framework that bridges ecology, virology, epidemiology, and policy. Future efforts should prioritize proactive surveillance in high-risk interfaces, biodiversity conservation to potentially modulate dilution effects, advanced predictive modeling, and international collaboration to close data and response gaps ultimately safeguarding global health security against the next emerging zoonotic threat.

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