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Stopping the Next Spillover: A Comprehensive Review of Viral Transmission from Wildlife to Humans

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Abstract

Zoonotic spillover, the transmission of viral pathogens from animal reservoirs to human hosts, has caused the majority of emerging infectious disease events in the past century, including HIV, Ebola, Zika, SARS, MERS, and SARS-CoV-2. Understanding the mechanisms that drive spillover is essential for pandemic prevention and preparedness. This comprehensive review synthesizes evidence from 150 studies (2000–2025) examining the ecological, virological, host, and behavioral determinants of viral spillover. We analyze the multi-step process: viral circulation in reservoir hosts (bats, rodents, non-human primates, birds, livestock), mechanisms of cross-species transmission (receptor binding, host restriction factors, viral polymerase fidelity), bridging factors that bring reservoir and human populations into contact (land use change, deforestation, wildlife trade, livestock intensification, bushmeat hunting), and within-human transmission potential (R_0, antigenic novelty, pre-existing immunity). Spillover is not a random event but a predictable consequence of anthropogenic environmental change and viral evolution. Key findings: bats are the reservoirs for coronaviruses, filoviruses, henipaviruses, and lyssaviruses; rodents for hantaviruses and arenaviruses. Land use change is the dominant driver, increasing human-wildlife contact. We recommend One Health surveillance at human-animal interfaces, targeted viral discovery in high-risk reservoirs, land use policy reforms, wildlife trade regulation, and early warning systems for spillover hotspots.

Keywords: Zoonotic spillover; viral emergence; reservoir hosts; land use change; pandemic prevention; One Health; cross-species transmission

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Introduction

The majority of emerging infectious diseases affecting humans are zoonotic, originating in animal reservoirs (Jones *et al.*, 2008). Over the past 50 years, viral pathogens including HIV, Ebola virus, Nipah virus, Hendra virus, SARS-CoV, MERS-CoV, Zika virus, and most recently SARS-CoV-2 have spilled over from wildlife or livestock into human populations, causing epidemics and pandemics with catastrophic consequences (Morens and Fauci, 2020). The COVID-19 pandemic, caused by SARS-CoV-2 (likely originating in bats with an intermediate mammalian host), resulted in over 7 million confirmed deaths (excess mortality estimates exceed 20 million) and trillions of dollars in economic losses (WHO, 2024). Yet despite the predictable pattern of viral spillover events, the underlying mechanisms remain incompletely understood, and prevention efforts remain chronically underfunded (Dobson *et al.*, 2020). Understanding spillover mechanisms is an existential necessity for pandemic prevention.

Zoonotic spillover is a multi-step process involving the convergence of ecological, virological, host, and behavioral factors (Plowright *et al.*, 2017; Morse *et al.*, 2012). First, a viral pathogen must circulate endemically in a reservoir host population, typically bats, rodents, non-human primates, birds, or livestock (Olival *et al.*, 2017). Second, the virus must possess or acquire the genetic capacity to infect human cells: binding to human receptors, replicating at human body temperature, evading human innate immune responses, and using human cellular machinery (Letko *et al.*, 2020). Third, an ecological bridging event must bring the reservoir host and humans into proximity for transmission, often driven by land use change, wildlife hunting and trade, livestock intensification, or habitat fragmentation (Wilkinson *et al.*, 2018; Plowright *et al.*, 2021). Fourth, following spillover, the virus must achieve sustained human-to-human transmission ($R_0 > 1$) to cause an epidemic or pandemic (Lloyd Smith *et al.*, 2022). Most spillover events are dead ends; the rare events that achieve sustained transmission become pandemics. This review argues that spillover is a predictable consequence of human environmental encroachment, requiring One Health interventions rather than just reactive response.

General Review

2.1 The Viral Zoonotic Landscape: Reservoirs, Families, and Hotspots

Not all viral families or animal reservoirs pose equal spillover risk. Bats (order Chiroptera) are the most important reservoir for emerging viral pathogens, harboring more zoonotic viruses per species than any other mammal order (Olival *et al.*, 2017). Bats are reservoirs for coronaviruses (including SARS-CoV-1, MERS-CoV, SARS-CoV-2 precursors), filoviruses (Ebola, Marburg), henipaviruses (Nipah, Hendra), lyssaviruses (rabies), and others (Letko *et al.*, 2020). Bats' unique immune systems, including tolerance of high viral loads without disease, allow persistent viral carriage (Brook and Dobson, 2024). High species diversity (>1,400 bat species), large colony sizes, and flight facilitate viral maintenance and spread (Plowright *et al.*, 2017). Rodents (order Rodentia) are the second most important reservoir, harboring hantaviruses (Sin Nombre, Andes, Seoul), arenaviruses (Lassa, Junin, Machupo), and orthopoxviruses (monkeypox/mpox), among others (Han *et al.*, 2015). Rodents' high reproductive rates, synanthropic behavior, and population density fluctuations drive spillover risk. Non-human primates (NHPs) are reservoirs for HIV, yellow fever virus, Zika virus, and Ebola virus (Wolfe *et al.*, 2007). Birds (particularly waterfowl) are reservoirs for influenza A viruses (avian influenza: H5N1, H7N9, H9N2) (Webster *et al.*, 2024). Livestock (pigs, camels, cattle, poultry) act as intermediate or amplifying hosts for spillover to humans (Lloyd Smith *et al.*, 2022). Spillover hotspots are geographic regions with high viral diversity, high human-wildlife contact, and high population density. These include Central and West Africa (Ebola, HIV, monkeypox, Lassa fever), Southeast Asia (Nipah, SARS, avian influenza), South Asia (Nipah, rabies), and the Amazon (yellow fever, arenaviruses) (Allen *et al.*, 2017). Land use change hotspots (deforestation frontiers in the Amazon, Congo Basin, Southeast Asia) are also spillover hotspots (Wilkinson *et al.*, 2018).

2.2 Virological Determinants of Cross-Species Transmission

For a virus to spill over from its reservoir host to humans, it must overcome multiple species barriers. Receptor binding is the first barrier. For coronaviruses, spike protein binding to human ACE2 (for SARS-CoV-1 and SARS-CoV-2) or DPP4 (for MERS-CoV) is essential (Letko *et al.*, 2020).

For filoviruses, binding to the conserved NPC1 receptor facilitates cross-species transmission (Ng *et al*., 2022). For henipaviruses (Nipah, Hendra), binding to ephrin B2/B3 receptors enables broad host range (Lee *et al*., 2024). Host restriction factors are the second barrier. Zoonotic viruses must encode antagonists of interferon signaling (e.g., Ebola VP35, SARS-CoV-2 ORF6) (García Sastre, 2023). TRIM proteins, Mx proteins, tetherin, and APOBEC3 further restrict viral replication; successful spillover requires viral antagonists for these factors in human cells. Viral polymerase fidelity influences adaptation. Low-fidelity RNA-dependent RNA polymerases generate high mutation rates, enabling rapid adaptation to new hosts (Duffy, 2024). Coronaviruses have proofreading capability that paradoxically allows larger genomes and adaptation without lethal mutagenesis (Denison *et al*., 2025). Recombination and reassortment generate novel genomes with new host range properties (Li *et al*., 2024).

2.3 Ecological and Anthropogenic Drivers of Spillover

Land use change is the dominant driver (Wilkinson *et al*., 2018; Plowright *et al*., 2021). Deforestation, agricultural expansion, mining, and urbanization fragment wildlife habitat, increase human-wildlife contact, and stress wildlife, increasing viral shedding (Bloomfield *et al*., 2023). For Nipah virus in Bangladesh, deforestation drives fruit bats to forage in date palm orchards, leading to annual spillover through contaminated sap collection (Luby *et al*., 2006). For Ebola virus, deforestation in Central Africa increases bat-human contact through bushmeat hunting (Rulli *et al*., 2017). Wildlife trade and bushmeat hunting are direct bridges. HIV spillover occurred via bushmeat hunting of chimpanzees and sooty mangabeys (Sharp and Hahn, 2011). Live animal markets (wet markets) in Asia bring diverse wildlife species into close contact with humans and livestock, creating mixing vessels for viral recombination and spillover (Li *et al*., 2024). Livestock intensification increases viral amplification and spillover risk; pigs are mixing vessels for influenza A viruses (Webster *et al*., 2024). Climate change alters wildlife distribution and viral ecology, forcing wildlife into human settlements (Hassell *et al*., 2023).

2.4 Bat Origin Viruses: Coronaviruses, Filoviruses, Henipaviruses, Lyssaviruses

Coronaviruses are among the most significant spillover risks. Bats are the ancestral reservoirs for SARS-CoV-1, MERS-CoV, and SARS-CoV-2 (Letko *et al.*, 2020). Filoviruses (Ebola and Marburg) spill over via human contact with bat guano or handling of infected bushmeat (Plowright *et al.*, 2017; Muyembe Tamfum *et al.*, 2022). Henipaviruses (Nipah and Hendra) spill over via bat-contaminated date palm sap or fruit dropped into pig pens (Field *et al.*, 2014; Luby *et al.*, 2006). Lyssaviruses (rabies) spill over to humans via bat bites (García Sastre, 2023).

2.5 Rodent Borne Viruses: Hantaviruses, Arenaviruses, and Others

Hantaviruses spill over via inhalation of aerosolized rodent excreta, causing hemorrhagic fever with renal syndrome or hantavirus pulmonary syndrome (Jonsson *et al.*, 2010; Krüger *et al.*, 2024). Arenaviruses, including Lassa virus (100,000–300,000 annual cases in West Africa), spill over via contact with rodent excreta (Radoshitzky *et al.*, 2024; McCormick and Fisher Hoch, 2025).

2.6 Livestock, Poultry, and Intermediate Hosts

Influenza A viruses circulate in wild waterfowl and spill over to humans via direct contact with infected poultry; pigs act as mixing vessels for reassortment (Webster *et al.*, 2024; Smith *et al.*, 2009). MERS-CoV spills over from camels to humans (Dudas *et al.*, 2024). Nipah virus spilled over from bats to pigs to humans in Malaysia (Field *et al.*, 2014).

2.7 Spillover Hotspots and Early Warning Systems

Predicting spillover hotspots using spatial risk modeling has advanced substantially (Allen *et al.*, 2017). Land use change is the most important predictor, increasing spillover risk 2- to 10-fold (Wilkinson *et al.*, 2018). Viral discovery programs like PREDICT have discovered >1,000 novel viruses (Carroll *et al.*, 2024). The Global Virome Project aims to characterize viral diversity of all bat, rodent, and primate species (Dobson *et al.*, 2020; Olival *et al.*, 2017). Early warning systems integrate viral discovery, wildlife surveillance, ecological risk modeling, and human sentinel surveillance (Plowright *et al.*, 2017).

2.8 One Health Prevention and Interventions

Preventing spillover requires One Health interventions. Land use policy reforms should protect intact forests and maintain buffer zones (Plowright *et al*., 2017, 2021). Wildlife trade regulation should ban high-risk species in live animal markets (Rulli *et al*., 2017). Bushmeat hunting reduction can be achieved through alternative protein sources (Muyembe Tamfum *et al*., 2022). Livestock biosecurity includes exclusion fencing and vaccination (Field *et al*., 2014; Webster *et al*., 2024). Community engagement (e.g., bamboo skirts on date palm sap collection) reduced Nipah spillover in Bangladesh (Luby *et al*., 2006).

2.9 The Spillover to Pandemic Continuum: Sustained Transmission

Most spillover events are dead ends; sustained transmission requires $R_0 > 1$, sufficient human population density, absence of pre-existing immunity, and viral adaptation for airborne transmission (Lloyd Smith *et al*., 2022). SARS-CoV-2 has $R_0 \approx 3–5$, enabling a global pandemic (Peacock *et al*., 2025). WHO criteria for high-priority pathogens include high CFR, human-to-human transmission, and lack of countermeasures (WHO R&D Blueprint, 2024).

2.10 Gaps and Future Research Directions

Critical gaps remain, including incomplete viral sampling in under-sampled hotspots, correlational rather than causal drivers, and operationalizing real-time surveillance in low-resource settings (Peacock *et al*., 2025). Intervention effectiveness has rarely been rigorously evaluated. Current funding for spillover prevention is <1% of pandemic response spending (Dobson *et al*., 2020).

Conclusion

Zoonotic spillover is not an unpredictable act of nature but a predictable consequence of human environmental encroachment. This review has demonstrated that spillover requires convergence of virological capacity, ecological bridging, and human population connectivity. Bats, rodents, non-human primates, birds, and livestock are the major reservoir hosts; coronaviruses, filoviruses, henipaviruses, hantaviruses, arenaviruses, and influenza A viruses are the highest-risk viral families. Deforestation, agricultural expansion, wildlife trade, and live animal markets are the dominant anthropogenic drivers. Most spillover events are dead ends, but rare events achieving sustained human-to-human transmission become pandemics. Spillover is preventable through One

Health interventions, yet the global community chronically underinvests in prevention. The next pandemic virus is already circulating; we know where hotspots are and what interventions work. The only missing ingredients are political will and sustained funding.

Recommendations

Based on the evidence synthesized in this review, the following recommendations are offered for governments, international organizations (WHO, FAO, OIE, UNEP), researchers, and policymakers:

1. Implement One Health surveillance platforms integrating wildlife virology, ecological risk monitoring, livestock health surveillance, and human febrile illness surveillance in spillover hotspots (Central/West Africa, Southeast Asia, South Asia, Amazon).
2. Protect intact forests and halt deforestation in high-priority spillover hotspots (Congo Basin, Amazon, Southeast Asia). Implement health impact assessments for all development projects.
3. Regulate wildlife trade: ban commercial trade of high-risk species (bats, primates, rodents, civets, pangolins, wild birds) in live animal markets. Enforce CITES. Close wet markets selling wildlife.
4. Reduce bushmeat hunting through alternative protein programs, provision of processing facilities, and community-led conservation.
5. Improve livestock biosecurity: separate livestock from wildlife habitat (exclusion fencing, netting for pig farms); implement all-in-all-out production; require hygiene measures at slaughterhouses and markets.
6. Establish a Global Spillover Prevention Fund (target $10–30 billion over 10 years) to finance surveillance, prevention, and early warning in low- and middle-income countries.
7. Ratify and implement the WHO Pandemic Treaty (2024) with specific provisions for spillover prevention, including mandatory reporting of unusual wildlife die-offs.
8. Expand viral discovery in under-sampled hotspots through the Global Virome Project, with

open data sharing and biosafety protocols.

9. Develop vaccines and therapeutics for high-priority zoonotic viruses without licensed countermeasures (Nipah, Lassa, MERS, Marburg, Hantavirus, H5N1/H7N9 avian influenza).
10. Train frontline healthcare workers in zoonotic syndrome recognition, isolation protocols, PPE use, and diagnostic sample collection.
11. Conduct intervention effectiveness research: randomized trials and interrupted time series of land use policies, wildlife trade bans, and livestock biosecurity.
12. Establish international accountability mechanisms with independent monitoring, reporting, and consequences for non-compliance.

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