Review Articles

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Cross-Species Defense: Transmission Mechanisms of Zoonotic Diseases and Systematic Prevention Strategies Based on the "One Health" Approach

John Sum, Say Yong Hui, Poon Cheng Hao, Vince Chiam Kew Chiu*

Department of Public Health, Faculty of Medicine, Universiti Cyberjaya, 63000 Cyberjaya, Selangor Darul Ehsan, Malaysia

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ABSTRACT

Zoonotic diseases represent one of the most critical threats to global public health security. More than 70% of emerging infectious diseases are zoonotic in origin, with pathogens capable of crossing species barriers to complete transmission cycles at the animal–environment–human interface. Accelerating globalization, ongoing ecological degradation, and expanding wildlife trade have further intensified cross-species transmission risk. Traditional single-discipline control models suffer from fundamental blind spots: clinical medicine focuses exclusively on human case diagnosis and treatment; veterinary medicine manages livestock and poultry diseases in isolation; and environmental health departments monitor ecological risks independently. These disciplinary silos produce severe data fragmentation and widespread surveillance gaps, often triggering emergency responses only after extensive community-level transmission has already occurred. This article systematically examines the scientific rationale and operational framework of the "One Health" strategy, analyzing how it integrates human medicine, veterinary science, and environmental science to elucidate the molecular adaptation mechanisms, host interaction dynamics, and ecological drivers of cross-species transmission—and to construct a full-chain prevention system encompassing pathogen surveillance, early risk warning, source-level intervention, and cross-sectoral governance. Breaking down disciplinary silos and establishing cross-sectoral collaborative mechanisms is the key pathway to addressing future pandemic threats. Only by embedding human, animal, and environmental health within a unified decision-making framework can the next pandemic be blocked at its source.

1. Introduction

In many respects, the history of human civilization is also a history of struggle against zoonotic diseases. From the Black Death that swept across Eurasia in the fourteenth century, to the 1918 Spanish influenza (H1N1) that claimed over 50 million lives [1], to the successive emergence in the twenty-first century of severe acute respiratory syndrome (SARS), Middle East Respiratory Syndrome (MERS), Ebola hemorrhagic fever, and Coronavirus Disease 2019 (COVID-19), the threat of pathogen spillover from animal reservoirs into human populations has never abated [2][3]. Between 2022 and 2023, the mpox (Mpox) virus spread rapidly across 112 non-endemic countries, with over 87,000 confirmed cases [4]; the World Health Organization declared it a Public Health Emergency of International Concern (PHEIC) on two separate occasions, underscoring the acute and contemporary nature of this risk.

Epidemiological evidence reveals the systemic character of this threat. Jones et al. (2008) [5] analyzed 335 emerging infectious diseases between 1940 and 2004 and found that 60.3% were zoonotic in origin, of which 72% derived from wildlife. Woolhouse and Gowtage-Sequeria (2005) [6] identified that among the 1,415 pathogens known to infect humans, 61% are zoonotic. In 2024, highly pathogenic avian influenza H5N1 achieved sustained transmission among dairy cattle herds across multiple US states, causing infections in over 60 farm workers—the first documented sustained spread of this strain in cattle—signaling an elevated pandemic risk that cannot be ignored [7].

Cross-species transmission is not random. It is the inevitable product of the convergence of pathogen adaptive evolution, expanded host contact interfaces, and human-driven ecosystem degradation [8][9]. The "One

* *Corresponding author: Vince Chiam Kew Chiu*
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Health" concept—jointly championed by the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO), and the World Organisation for Animal Health (WOAH)—responds directly to this systemic challenge [10]: human health, animal health, and environmental health are interdependent and inseparable, and addressing zoonotic diseases requires an integrated approach that transcends disciplinary, sectoral, and national boundaries. This article systematically reviews the key mechanisms of cross-species transmission, dissects the structural deficiencies of traditional control models, and details the pathways for constructing a comprehensive prevention system within the One Health framework.

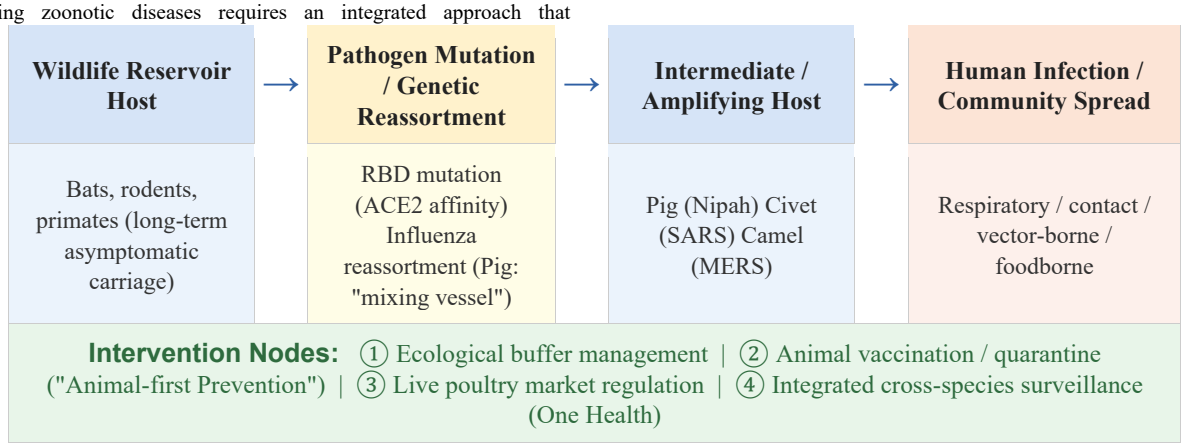

Fig. 1 - Zoonotic Spillover Pathway and Key "One Health" Intervention Points

2. Key Mechanisms of Cross-Species Transmission

2.1. Pathogen-Level Mechanisms

2.1.1 High mutation rates and genetic reassortment in RNA viruses

Whether a pathogen can successfully cross a species barrier depends critically on its genetic plasticity. RNA viruses rely on an RNA-dependent RNA polymerase (RdRp) that lacks proofreading capacity, generating error rates of approximately 10^{-4} to 10^{-6} per replication cycle—several orders of magnitude higher than DNA viruses (~10^{-8} to 10^{-10}). As a result, RNA virus populations exist as quasispecies: heterogeneous ensembles of closely related yet genetically diverse mutants. When a virus encounters the immune selection pressures of a novel host, rare adaptive variants within the quasispecies rapidly expand to become the dominant strain, enabling host switching.

In influenza viruses, host tropism is governed by the affinity of the hemagglutinin (HA) surface protein for host-cell receptors. Avian influenza viruses (H5N1, H7N9) preferentially bind α-2,3-linked sialic acid receptors (predominant in avian intestines and the human lower respiratory tract), while human seasonal influenza viruses favor α-2,6-linked sialic acid receptors (dominant in the human upper respiratory tract). Pigs co-express both receptor types, making them ideal "mixing vessels": when avian-origin and human-origin influenza viruses co-infect a single porcine cell, their eight genome segments can undergo random reassortment, generating novel reassortant strains with new antigenic configurations. The 1957 H2N2 Asian flu and 1968 H3N2 Hong Kong flu pandemics both arose through this mechanism.

2.1.2 Adaptive evolution of the coronavirus receptor-binding domain

The receptor-binding domain (RBD) of SARS-CoV-2 shares 96.2% whole-genome sequence identity with RaTG13, a coronavirus isolated from Rhinolophus affinis bats. Its binding affinity for human ACE2 is substantially higher than that of known bat coronaviruses [3][11]. Cryo-electron microscopy studies by Wrapp et al. (2020) [11] confirmed that key RBD contact residues including Tyr501 and Lys417 confer a binding affinity for human ACE2 approximately 10- to 20-fold greater than that of SARS-CoV. Species-specific variation in ACE2 further shapes the viral host range. Mink, domestic cats, tigers and lions carry ACE2 sequences that closely match the human form and all experienced natural infections during the COVID-19 pandemic. Poultry show greater divergence at key binding sites and comparatively lower susceptibility to infection.

2.2. Host-Level Mechanisms

2.2.1 Reservoir, Intermediate, and Amplifying Hosts

In most zoonotic disease transmission chains, spillover to humans does not occur directly from the wildlife reservoir but proceeds through a multi-stage transition involving reservoir hosts (which maintain the pathogen through long-term, often asymptomatic carriage), amplifying hosts (in which the pathogen achieves high-titer viremia), and intermediate hosts (which bridge the gap between the reservoir and human populations). The Nipah virus (NiV) transmission chain is paradigmatic [12]: Pteropus fruit bats serve as reservoir hosts with no apparent clinical disease; during the 1998–1999 Malaysian outbreak, pigs functioned as amplifying hosts, with Nipah virus transmitted through bat excreta contaminating pig enclosures, ultimately infecting 265 people with a case fatality rate of approximately 40%. In contrast, subsequent outbreaks in Bangladesh have involved direct human infection through consumption of raw date palm sap contaminated with bat secretions. No intermediate host is required for this transmission route. This divergence highlights how the presence or absence of an amplifying host fundamentally alters exposure pathways and shapes intervention priorities.

2.2.2 Bat Immune Tolerance and Immunopathological Mismatch in Novel Hosts

Bats serve as reservoir hosts for numerous highly pathogenic viruses including SARS coronaviruses, Marburg virus, and Hendra virus, owing to a distinctive immune architecture. Interferon-stimulated genes (ISGs) are constitutively expressed at baseline levels; the activation threshold of the NF-kB signaling pathway is elevated; and pro-inflammatory cytokine secretion is substantially attenuated [13]. This anti-inflammatory immune tolerance permits viral replication at low levels without triggering the acute inflammatory damage that would be lethal to the host, enabling a stable co-evolutionary equilibrium between bat and pathogen. When these same viruses infect humans whose immune systems have no prior evolutionary adaptation, the response is often dysregulated and catastrophic. The pathological overactivation of IL-6, IL-1b, and TNF-a observed in severe COVID-19 patients is a direct consequence of this immunological mismatch, and is the central mechanism driving acute respiratory distress syndrome (ARDS) and multi-organ failure. This phenomenon illuminates a fundamental truth about cross-species transmission: pathogenicity in a novel host reflects not only intrinsic viral virulence factors, but also the depth of the mismatch between the pathogen's evolutionary adaptation and the host's immune architecture.

2.3. Ecological Drivers: Expanding Human–Wildlife Contact Interfaces

2.3.1 Land-use change and biodiversity loss

Human encroachment on natural ecosystems is among the most powerful macroscale drivers of increasing zoonotic spillover risk. Deforestation and agricultural expansion destroy the ecological buffer zones that once maintained geographic separation between wildlife and human populations, dramatically expanding the human–wildlife contact interface. A meta-analysis by Gottdenker et al. (2014) [14] found that in tropical regions, greater levels of anthropogenic disturbance are associated with higher diversity and transmission risk of zoonotic pathogens in wildlife. This pattern represents an inverse expression of the dilution effect. As biodiversity declines, non-reservoir species that would otherwise dilute pathogen transmission are lost. This elevating the relative density of reservoir hosts and amplifying spillover risk. Live poultry markets epitomize this dynamic at a micro-scale: dense mixed-species housing and repeated turnover provide continuous opportunities for genetic reassortment among influenza viruses of different subtypes. Epidemiological data from China demonstrate that closure of live poultry markets was followed by a substantial decline in human H7N9 cases, directly confirming the role of these high-risk contact nodes.

2.3.2 Climate change and the spatial reshaping of transmission risk

Global warming is systematically expanding the geographic distribution of disease vectors. Aedes aegypti and Aedes albopictus, the primary vectors for dengue fever, Zika virus disease, and chikungunya, are spreading into higher latitudes and elevations, with sustained Ae. albopictus colonization now documented across southern Europe and mid-latitude North America. Within the temperature range of 26°C to 30°C, the extrinsic incubation period (EIP) of dengue virus in Aedes mosquitoes is approximately 50% shorter than at 20°C, substantially increasing the proportion of an infected mosquito's lifespan during which it is infectious. El Niño-driven alternations of extreme precipitation and drought alter rodent population dynamics, and these shifts correlate significantly with the cyclical emergence of hantavirus pulmonary syndrome, Lassa fever, and other rodent-borne zoonoses.

3. Structural Limitations of Conventional Control Models

3.1. Disciplinary silos and data fragmentation

Clinical medicine, veterinary science, and environmental health operate within separate academic disciplines, administrative frameworks, and professional accreditation systems. These divisions create severely limited mechanisms for knowledge exchange and real-time data sharing. The Nipah virus outbreak in Malaysia offers a stark illustration of the consequences. During the early weeks of the 1998 epidemic, human encephalitis cases were misclassified as Japanese encephalitis. This diagnostic error persisted for nearly four months. Meanwhile, veterinary reports documenting an unusual respiratory syndrome in pigs—marked by a distinctive "barking cough" and high mortality—failed to reach public health decision-makers. This four-month delay allowed the virus to spread across pig farms in multiple states, ultimately resulting in 265 human infections and 105 deaths. The episode remains one of the most compelling demonstrations of the lethal cost of the information barrier between human and veterinary medicine.

3.2. Temporal lag and reactive surveillance

Conventional surveillance systems based on clinical case reporting are inherently reactive. The timeline from initial spillover to the accumulation of sufficient confirmed cases for an epidemiological alert typically requires weeks to months, depending on the disease. This timeline encompasses incubation, clinical presentation, case confirmation, contact investigation, and cluster recognition. During this interval, cryptic transmission may already be widespread and the optimal window for early containment irretrievably closed. Retrospective genomic analyses of H7N9 avian influenza provide a clear illustration. The novel reassortant virus responsible for the 2013 outbreak in China had been circulating silently in poultry at live bird markets for at least several weeks before the first confirmed human case was identified. This signal was entirely missed by conventional surveillance systems.

Human Health Domain	Environmental Health Domain	Animal Health Domain
• Clinical case surveillance & reporting	• Wastewater epidemiology	• Poultry/livestock sentinel surveillance
• Hospital/CDC early warning systems	• Vector species distribution tracking	• Wildlife metagenomics surveys
• Seroepidemiological surveys	• Land-use & ecological risk assessment	• Animal vaccination & culling/quarantine
• IHR notification mechanisms	• Climate change adaptation management	• Live animal market risk regulation

Core Integration Layer: Cross-sectoral data-sharing platform · Joint inter-agency committees · Multidisciplinary risk assessment · International intelligence cooperation (WHO / FAO / WOAH)

Fig. 2 - One Health Three-Domain Integrated Prevention and Control Framework

4. Comprehensive Prevention Strategies Under the One Health Framework

4.1. Building an integrated cross-species surveillance system

One Health Surveillance (OHS) aims to replace fragmented parallel monitoring with a systems-integrated architecture that enables real-time sharing and joint analysis of human, animal, and environmental surveillance data. Core elements include: multi-host coordinated sentinel networks, cross-agency data standardization interfaces, multidisciplinary joint risk assessment mechanisms, and rapid information relay and response-trigger protocols [15]. Metagenomics methods allow comprehensive genetic profiling of samples from wildlife, livestock, and environmental matrices without requiring pre-specified detection targets, extending surveillance reach into the realm of "unknown unknowns." The PREDICT program (2009–2020), funded by the EcoHealth Alliance across 31 high-risk countries, discovered over 1,100 novel viruses in wildlife, constructing the largest zoonotic virus database to date [16]. Thailand's integrated One Health surveillance, which combines human febrile illness monitoring with poultry and wild bird surveillance and leverages rapid sequencing capabilities, has substantially shortened the time to initial signal detection compared with conventional systems. This accelerated detection window is critical for timely early intervention and outbreak containment.

4.2. Environmental risk surveillance and ecological health management

Systematic environmental sampling in high-risk ecotones where human settlement, agricultural production, and wildlife habitat overlap can provide early warning before pathogen spillover occurs. Wastewater epidemiology demonstrated its value during the COVID-19 pandemic. Multiple studies confirmed that SARS-CoV-2 nucleic acid signals in wastewater preceded clinical case confirmation in corresponding communities by approximately four to seven days. Ecological buffer zone management offers a spatial-scale tool for reducing human–wildlife contact frequency. Post-SARS market regulations in Guangdong Province, China, which curtailed trade in high-risk wildlife species, directly reduced human exposure to bats and civets as potential reservoir hosts. Critically, however, intervention strategies must be grounded in a thorough understanding of local ecosystem structure and community livelihoods. Indiscriminate culling of reservoir host species can disrupt population immune structure and age distribution. This may paradoxically increase the proportion of highly-infectious young animals and elevate overall community viral shedding.

4.3. "Animal-first prevention": shifting the control frontier upstream

Implementing proactive interventions at the animal level represents one of the core innovations of the One Health approach, as it exchanges relatively modest veterinary prevention costs for substantial improvements in human health outcomes. Brucellosis control stands as the most well-documented proof of this concept. Israel implemented a comprehensive strategy combining mandatory vaccination of cattle and sheep with culling of seropositive animals, which reduced annual human brucellosis case reports from thousands to just tens over a 20-year period. China's mandatory H5/H7 bivalent avian influenza vaccination program, launched nationwide in 2017 with an immunization coverage rate exceeding 95%, combined with periodic closure and disinfection of live poultry markets, led to a dramatic decline in human H7N9 infections after 2018. This outcome provides robust evidence that upstream animal-level immunization can effectively break the transmission chain between avian and human populations.

4.4. Institutionalizing cross-sectoral governance

Technical surveillance and intervention capabilities can only achieve their full potential within a supporting institutional framework. Effective One Health governance requires a normalized institutional architecture rather than merely ad hoc emergency coordination. It includes standing inter-agency joint committees with regular cross-sectoral risk reviews and emergency exercises, a unified data-sharing platform that integrates surveillance outputs from health, agriculture, forestry, and environment agencies with standardized formats and open access interfaces, and explicit notification obligations with defined response-trigger thresholds.

In terms of human capital, joint degree programs between medical schools, veterinary schools, and schools of public health, cross-institutional collaborative research, and inter-professional exchange placements are essential vehicles for cultivating the interdisciplinary competencies that One Health demands at the field level.

At the international level, the International Health Regulations (2005) provide a legal foundation for global event notification, but enforcement mechanisms require strengthening. The WHO–FAO–WOAH Tripartite Collaboration framework must be further operationalized into a binding global zoonotic intelligence-sharing platform [10].

5. Challenges and Prospects

5.1. Implementation barriers

Three interconnected obstacles impede the real-world translation of One Health principles: bureaucratic fragmentation, chronic underfunding, and weak baseline capacity in high-risk settings. On the financial dimension, Bernstein et al. (2022) [17] estimated that a globally comprehensive One Health prevention system would require approximately USD 22 billion annually—a figure dwarfed by the multi-trillion-dollar economic losses attributable to a major pandemic, yet one that consistently struggles for political priority because its benefit takes the form of pandemics that do not occur. On the operational dimension, the regions of highest zoonotic spillover risk—tropical and subtropical forest-edge ecotones, intensive livestock production areas—coincide systematically with the areas of lowest public health and veterinary service capacity, creating a fundamental equity challenge for any strategy premised on universal surveillance coverage.

5.2. Enabling potential of emerging technologies

Artificial intelligence and large-scale data analytics are transforming the horizons of zoonotic risk prediction. Machine-learning-based viral host-range prediction models integrate viromics data, host trait matrices, and ecological-geographic parameters. These models can probabilistically screen for high-risk viruses with cross-species transmission potential before any human cases emerge. Johnson et al. (2020) [16] estimated the existence of approximately 35,000 undescribed coronaviruses in bats alone, a subset of which may harbor pandemic potential. This underscores the enormous value of systematic virome surveillance coupled with AI-assisted prioritization. Advances in portable nanopore sequencing are making point-of-care whole-genome sequencing a practical reality even in resource-limited settings. This technology has the potential to close the global surveillance capacity gap that currently leaves the highest-risk regions effectively blind.

5.3. Policy framework development

Translating One Health from scientific consensus into legally binding policy architecture is the most urgent implementation priority. At the national level, enshrining One Health principles in public health law or biosecurity legislation provides the legal authority and enforcement mechanisms needed to sustain cross-sectoral coordination over the long term. At the international level, the ongoing negotiation of a Pandemic Treaty offers a historic opportunity: mandating zoonotic disease surveillance and notification obligations, and embedding One Health surveillance standards as core metrics within global health security capacity assessments, would represent a transformative shift in the legal architecture of pandemic preparedness.

6. Conclusion

Cross-species transmission of zoonotic pathogens is fundamentally the systemic product of interactions among pathogen adaptive evolution, host ecological contact dynamics, and human-transformed natural environments. Mechanisms operate across multiple levels, from the molecular precision of receptor-binding domain mutations and the immunological mismatch between bat-adapted viruses and the naive human immune system, to the macro-ecological erosion of species-boundary buffer zones driven by land-use change and climate disruption. Each tier of mechanism must be fully understood before effective interventions can be designed. Single-discipline, single-agency control models cannot address this complexity due to their inherent structural limitations.

The defining value of the One Health strategy lies in its transformation of fragmented, reactive surveillance into a proactive, integrated architecture spanning the animal–environment–human interface. The case studies examined here, including brucellosis elimination, H7N9 suppression through poultry vaccination, and wastewater-based SARS-CoV-2 early warning, collectively demonstrate that this transformation is achievable and delivers measurable public health returns. The global spread of mpox during 2022–2023 and the emergence of H5N1 in U.S. dairy cattle in 2024 serve as stark contemporary reminders that spillover risk is not receding.

Only by converting One Health from an aspirational framework into a system with institutional grounding, sustained resourcing, and binding international commitments can humanity build a durable cross-species defense against the next pandemic threat. This transition requires deepening the science of cross-species transmission, constructing intelligent integrated surveillance networks, strengthening cross-sectoral governance, and operationalizing global health security cooperation.

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