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EDITORIAL

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Converging threats: The intersection of seasonal influenza surges and zoonotic highly pathogenic avian influenza

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Abstract: The global landscape of influenza is becoming increasingly complex. In the Northern Hemisphere, seasonal influenza activity is exhibiting a pattern of "early onset, high intensity". At the same time, highly pathogenic avian influenza (HPAI) continues to circulate widely among wild birds and poultry, with a growing tendency to spillover into mammals, including dairy cattle, thereby substantially increasing the zoonotic risk. This convergence exposes the limitations of control systems that manage human and animal influenza separately. Given the ongoing cross-species adaptive evolution of influenza viruses at the human–animal–environment interface, global strategies need to pivot toward a fully integrated One Health paradigm as the organizing principle for preparedness and response. By synthesizing surveillance data and research capacity across human, animal, and environmental health sectors, the international community can build a more resilient defense network that both reduces the current disease burden and helps pre-empt the emergence of novel pandemic strains arising from viral reassortment.

Keywords: seasonal influenza, highly pathogenic avian influenza (HPAI), One Health, zoonoses, pandemic preparedness

1. Changing epidemiology of human seasonal influenza

Seasonal and zoonotic influenza are increasingly interacting within a shared respiratory viral ecosystem, creating new challenges for global health security. Against this backdrop, the epidemiology of human seasonal influenza itself is undergoing important changes.

Since 2020, the B/Yamagata lineage has almost disappeared from global surveillance networks (*1,2*). This presumed "functional extinction" is generally attributed to its slower antigenic evolution, accumulated population immunity from past epidemics, and the suppressive effects of non-pharmaceutical interventions (NPIs) during the COVID-19 pandemic (*3*). Currently, influenza A viruses, together with the B/Victoria lineage, are predominantly circulating, and many countries report influenza A as the predominant strain (*4,5*). Within this broader context, the 2025–2026 Northern Hemisphere season has followed an "early start, high intensity" trajectory: Early peaks have been observed in China and Japan, placing substantial strain on healthcare systems (*6,7*).

Early surveillance data suggest that a novel influenza A(H3N2) virus variant, designated "Subclade K", has emerged as a major driver of transmission this season (*8,9*). Antigenic drift appears to have diminished the match between circulating viruses and current vaccine strains, while several years of relatively low influenza circulation have led to an "immunity gap", thereby enhancing transmission and disproportionately affecting school-aged children, resulting in increased demands on healthcare system (*9,10*). Data from the WHO Global Influenza Surveillance and Response System (FluNet) indicate that many Northern Hemisphere countries are experiencing the concurrent circulation of influenza, SARS-CoV-2, and respiratory syncytial virus (RSV) (*11,12*). The co-circulation observed reflects a shift in population immunity and changes in viral ecological dynamics, thereby complicating clinical diagnosis and posing challenges for health system planning. Rapid urbanization and high population density contribute to increased transmission efficiency in urban environments (*13,14*). Concurrently, disparities in surveillance capacity and unequal access to vaccines in low- and middle-income countries may enable emerging variants to spread undetected, underscoring the necessity of a genuinely global approach to influenza risk management (*15,16*).

2. Cross-species transmission and global threat of highly pathogenic avian influenza (HPAI)

Highly pathogenic avian influenza (HPAI) H5N1 (clade 2.3.4.4b) continues to serve as the primary driver of a global panzootic, spreading through migratory bird flyways and demonstrating enhanced adaptability to mammalian hosts (*17,18*). The virus has repeatedly crossed species barriers, including causing infections in North American dairy cattle, thereby significantly elevating the risk of zoonotic transmission (*19-21*). Since 2024, a novel genotype (B3.13) has become established in U.S. dairy cattle, leading to outbreaks within dairy herds, while H5N1 viruses responsible for outbreaks in poultry, dairy cows, and other animal populations have been associated with approximately 70 reported human infections in the United States between 2024 and early 2025, predominantly among individuals with occupational exposure (*22,23*). Recent outbreaks in poultry in Ontario, Canada, further highlight the ongoing geographic expansion and severity of HPAI (*24*). Of particular concern is the diversification of H5 subtypes through cross-species transmission, exemplified by the first reported human case of H5N5 in the United States, which underscores both the genetic diversity among H5 viruses and their potential for spillover into humans (*25*).

Clinical and experimental evidence indicates genotype-specific differences in host adaptation and disease severity (*22,26*). Although D1.1 retains preferential binding to avian-type α-2,3-linked sialic acid receptors, its pronounced pathogenicity in humans warrants heightened vigilance (*26,27*). Mechanistically, avian influenza virus polymerases, such as the PB1 subunit, are adapted for efficient replication at the higher core body temperatures of birds (40–42°C) (*28*), a trait that may impair the protective efficacy of the human febrile response. This underscores the need for rapid diagnosis and early, aggressive clinical management in suspected zoonotic influenza cases.

A central virological concern is the potential for seasonal influenza viruses and HPAI viruses to undergo genetic reassortment in co-infected hosts such as swine, humans, or potentially dairy cattle, thereby generating novel reassortant strains that combine high intrinsic pathogenicity with efficient human-to-human transmissibility. Although no such reassortant has yet been detected in nature, experimental studies demonstrate both the feasibility and potentially severe consequences of such events, underscoring the need for high sensitivity and genomic resolution in global surveillance systems (*29-33*). In parallel, surveillance of H5N1 viruses — particularly clade 2.3.4.4b — has already identified mutations associated with reduced susceptibility or resistance to oseltamivir and baloxavir (*34,35*), highlighting the urgency of incorporating resistance monitoring in clinical decision-making and diversifying the antiviral toolbox beyond a small number of drug classes. Against this backdrop, the concurrent high-level circulation of human seasonal influenza and HPAI is not only overburdening surveillance and laboratory capacities but is also increasing opportunities for reassortment in intermediate hosts, raising concerns about the emergence of novel strains with pandemic potential (*36,37*). These converging dynamics at the human–animal–environment interface underscore the need for a One Health oriented approach to surveillance and control.

3. Building a resilient One Health surveillance and defense system

To effectively address the compounded risks posed by seasonal influenza and HPAI, a shift from a narrow focus on "seasonal influenza management" to a resilient, One Health oriented risk governance framework is increasingly recognized as necessary (*38,39*). Central to this transition is an integrated system for surveillance, early warning, and intervention that spans human, avian, and other mammalian hosts and encompasses influenza and other major respiratory viruses, enabling a shift from reactive seasonal responses to a proactive approach to "viral ecosystem management". Figure 1 presents a conceptual framework of the dual viral threats at the human–animal–environment interface and outlines strategic future directions for influenza control under a One Health paradigm (Figure 1).

3.1. Establishing a multidimensional, integrated surveillance and early-warning network

We recommend moving beyond single-pathogen surveillance toward a multidimensional, integrated system capable of detecting human respiratory pathogens (*e.g.*, influenza, SARS-CoV-2, RSV) and monitoring infections in livestock, wildlife, and key environmental reservoirs, such as wastewater. Strengthening whole-genome sequencing and bioinformatics capacity, coupled with modelling approaches and real-time digital data-sharing, would enable continuous tracking of the evolutionary trajectories, transmission chains, and resistance mutations of high-risk viruses such as H5N1 and facilitate earlier, risk-stratified interventions (*38,40,41*). Linking existing platforms (*e.g.,* national influenza centers, FluNet, and wastewater surveillance systems) within a unified analytic framework could substantially increase the sensitivity and timeliness of global early warning.

3.2. Implementing cross-sectoral, One Health oriented governance

Anchored in a One Health framework, global influenza control should include systematic upgrading of biosecurity standards in animal production and the phasing out of high-risk farming practices. At the national and regional level, joint risk assessment and emergency response mechanisms should be implemented across the agriculture,

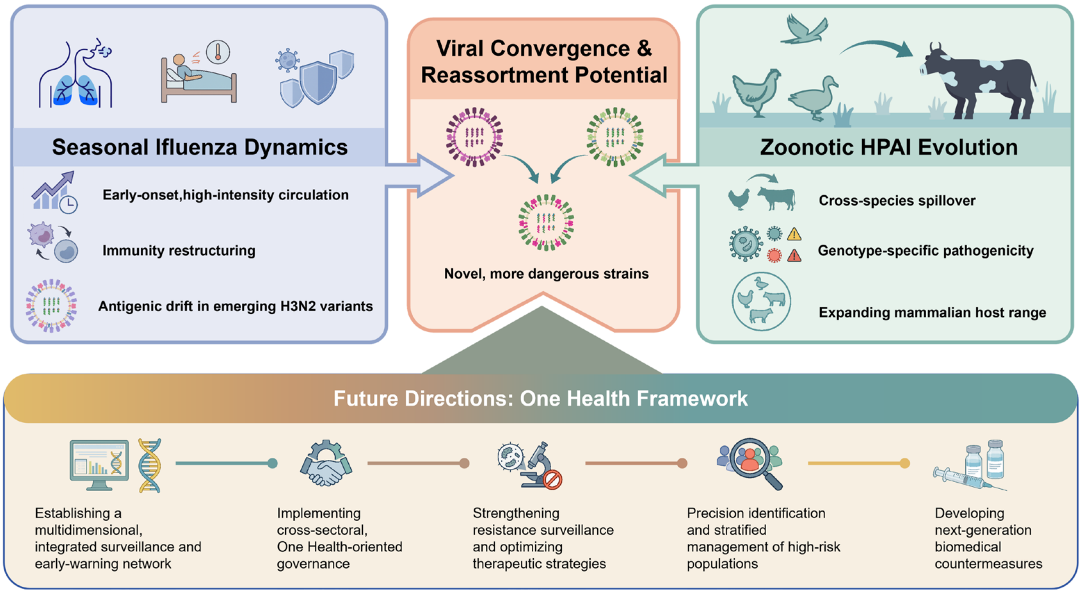

Figure 1. Conceptual framework of dual viral threats at the human–animal–environment interface and strategic future directions under the One Health paradigm. This schematic illustrates the compounding risks posed by the concurrent circulation of human and animal influenza viruses and outlines a comprehensive, integrated response strategy. (Top left) This box characterizes current seasonal influenza dynamics in human populations, highlighting challenges such as early-onset, high-intensity circulation, immunity restructuring, and antigenic drift in emerging variants (*e.g.*, H3N2). (Top right) This box depicts the ongoing evolution of zoonotic highly pathogenic avian influenza (HPAI), emphasizing the risks of cross-species spillover into novel hosts (including ruminants), genotype-specific pathogenicity, and an expanding mammalian host range. (Center) The box in the center illustrates viral convergence and reassortment potential, whereby the interface between human and animal reservoirs functions as a "mixing vessel", increasing the risk of novel, highly virulent strains emerging. (Bottom) The box at the bottom outlines five strategic pillars in the "Future Directions" panel within a One Health framework: (1) establishing a multidimensional, integrated surveillance and early-warning network; (2) implementing cross-sectoral, One Health oriented governance; (3) enhancing antiviral resistance surveillance and optimizing therapeutic strategies; (4) enabling precision identification and stratified management of high-risk populations; and (5) developing next-generation biomedical countermeasures to enhance global health security.

healthcare, and environmental sectors, along with routine occupational health surveillance and protection for high-risk workers (*39,42*). Legal and regulatory measures should be used to overcome data silos and to establish mandatory, transparent international platforms for information sharing and joint notification, in line with existing frameworks such as the International Health Regulations and One Health Joint Plan of Action. These measures are essential to close the "surveillance–decision–action" loop from animals and the environment to human populations.

3.3. Enhancing resistance surveillance and optimizing therapeutic strategies

Future influenza control should be underpinned by an integrated resistance surveillance system linking frontline clinical care with pathogen genomics. Sequencing-based assessment of susceptibility to oseltamivir, baloxavir, and other antivirals should be integrated into routine care pathways to facilitate the dynamic optimization of first-line and combination regimens, particularly in severe and high-risk patients. In parallel, therapeutic strategies that combine direct-acting antivirals with targeted immunomodulation (*43*), together with forward-looking pipelines focused on novel viral targets and critical host factors, are needed to build a multi-target therapeutic armamentarium to combat the continued emergence of resistant variants.

3.4. Precision identification and stratified management of high-risk populations

Next-generation influenza control will require the refined, evidence-based definition of high-risk groups. Recent data indicating that chronic hepatitis B virus carriers are more prone to severe liver injury when co-infected with influenza support their inclusion in priority tiers for surveillance and vaccination (*44*). Mechanistically complementary combination antiviral regimens should be prioritized for severe and high-risk patients (*45*), while aging-related biomarkers in older adults can be incorporated into risk-stratification tools to enable earlier identification of those at highest risk of severe outcomes (*46*). These approaches can guide targeted prevention, timely antiviral initiation, and intensified follow-up and better align clinical practice with population-level risk.

3.5. Developing next-generation biomedical countermeasures

There is a strategic need to invest in adaptable, platform-based technologies, with priority given to universal influenza vaccines targeting conserved epitopes and rapidly updatable mRNA vaccine platforms capable of covering multiple subtypes, including HPAI viruses (*47,48*). In parallel, enhanced basic and translational research on cross-species transmission mechanisms, host immune response profiles, and host-targeted interventions will be essential to advancing mucosal immunization strategies, broadly neutralizing antibodies, and host-directed antivirals. Together, these efforts can build an expandable toolkit of biomedical countermeasures for future pandemic-scale influenza threats.

4. Conclusion

The world is confronting not isolated seasonal peaks or sporadic avian outbreaks, but an evolving viral ecosystem at the human–animal–environment interface. Siloed control models divided by host or sector are poorly suited to this reality. Strategic investment in One Health surveillance, adaptable vaccines and therapeutics, and cross-sectoral collaboration can strengthen early warning and response capacities, thereby improving global resilience to the next influenza pandemic.

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