Epidemiology and Health System Journal
doi:10.34172/ehsj.26493 2025 Autumn;12(4):243-247 http://ehsj.skums.ac.ir

Mini Review

H5N1 at the Pandemic Threshold: Military-Grade Preparedness for an Avian Influenza Crisis

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Abstract

Background and aims: The rapid evolution of highly pathogenic avian influenza H5N1, with recent spillover to mammals and sporadic human cases, may pose a serious pandemic risk. This study focused on examining how integrating CBRNe principles can address critical gaps in traditional preparedness frameworks.

Methods: This narrative review comprehensively synthesized evidence from virological research (2003-2025), WHO outbreak reports, and military-civilian biosecurity collaborations.

Results: H5N1's pandemic potential is escalating through key mutations, such as HA-T160A and PB2-E627K, which enhance mammalian airway replication. Current surveillance systems remain inadequate, particularly at animal-human interfaces. Crucially, CBRNe adaptations demonstrated superior containment in simulations. NATO's 2023 Global BioLock exercise achieved a 63% reduction in cross-border transmission through spectral biosensor checkpoints and coordinated alert protocols. Moreover, military-civilian partnerships proved effective in the rapid deployment of field hospitals, as observed in Spain's establishment of a 72-hour biocontainment unit.

Conclusion: In general, the convergence of H5N1's virological risk factors and CBRNe's operational capabilities suggests the necessity of a paradigm shift. Thus, it is proposed that an international task force be established to standardize CBRNe protocols for avian influenza, prioritizing environmental biosurveillance and dual-use training for health workers. This strategic integration offers a tangible solution to mitigate the most probable pandemic threat, as the WHO considers it to be.

Keywords: Public health, Influenza a virus, Epidemiology, Population health management, Disease outbreaks

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Received: May 23, 2025
Revised: December 12, 2025
Accepted: December 13, 2025
ePublished: December 30, 2025

Introduction

The H5N1 virus has long been recognized as a leading candidate for triggering the next global pandemic. Since its first detection in humans in 1997, this virus has evolved into multiple clades, with the 2.3.4.4b strain now demonstrating unprecedented mammalian adaptation. Recent outbreaks, from poultry farms in Southeast Asia to marine mammals off South American coasts, underscore its expanding ecological footprint.[1,2] Moreover, the World Health Organization (WHO) has documented a case-fatality rate of over 50% in humans, a stark reminder of the virus's virulence once it breaches the species barrier.[3]

The dual capacity of H5N1 for rapid mutation and zoonotic spillover makes it uniquely threatening. Unlike seasonal influenza, HPAI viruses possess molecular machinery that favors high pathogenicity, including polybasic cleavage sites in hemagglutinin (HA) and mutations in polymerase basic protein 2 (PB2) that enhance replication in mammalian cells.[4] These virological traits, combined with increasing human-animal interactions in agriculture and wildlife trade, create a perfect storm for cross-species transmission.[3,4] Despite two decades of warnings, global preparedness remains fragmented. In addition, traditional pandemic frameworks, designed for human-adapted influenza, fail to address the logistical challenges posed by a pathogen that emerges at the intersection of animal health, environmental surveillance, and rapid military-grade containment.[5]

This review argues that a CBRNe (Chemical, Biological, Radiological, Nuclear, and Explosive) approach, refined through collaboration with NATO and WHO, can bridge these gaps. By repurposing early-warning biosensors, mobile biocontainment units, and crisis communication protocols from CBRNe systems, health agencies might preempt the worst-case scenario: a highly lethal, globally disseminated H5N1 strain.[6,7]

As H5N1 continues its silent evolution in avian and mammalian reservoirs, the question is no longer *if* a

pandemic will occur, but *how well* we will respond. Accordingly, this review synthesizes virological insights, epidemiological trends, and CBRNe innovations in order to propose an actionable strategy before the subsequent spillover becomes a catastrophe.[6]

Virological, Clinical, and Epidemiological Aspects of HPAI H5N1

The pandemic potential of H5N1 lies embedded within its genetic blueprint, a constellation of molecular adaptations that have progressively enhanced its ability to cross species barriers and evade immune defenses.[3, 4] Two pivotal viral components are at the core of this threat: HA, which is the key that unlocks host cells, and PB2, which is the engine driving viral replication. Overall, these components orchestrate a pathogenic profile distinct from seasonal influenza, marked by systemic invasion and catastrophic immune dysregulation. Moreover, the HA protein of H5N1 has demonstrated a concerning capacity for human adaptation.[8] Furthermore, mutations such as T160A and H103Y gradually shift their binding preference from avian-specific receptors to those prevalent in the human upper respiratory tract.[9] While still inefficient for sustained human-to-human transmission, these changes mirror evolutionary steps observed in past pandemic strains. Similar adaptations in PB2, particularly the E627K substitution, enable efficient viral replication at the temperature characteristic of human nasal passages. Generally, such mutations lower the genetic barrier to a transmissible, high-mortality pandemic strain.[9, 10]

Clinical data from confirmed human cases reveal a disease trajectory that is markedly different from seasonal influenza. Rapid progression to acute respiratory distress syndrome typically occurs within six days of symptom onset, with mortality rates exceeding 50%.[11] The propensity of the virus to trigger cytokine storms leads to multi-organ failure, while its neurotropic potential manifests in encephalitis in nearly one-third of cases. These severe outcomes are compounded by diagnostic limitations, especially in resource-limited regions where surveillance infrastructure is the weakest.[11]

The evolutionary trajectory of H5N1 hinges on its ability to navigate the complex ecological bridge between birds, intermediate hosts, and human populations. Due to their unique biological susceptibility to both avian and human influenza strains, pigs have long been recognized as potential "mixing vessels" for viral reassortment. Their respiratory epithelium expresses both α-2,3 and α-2,6 sialic acid receptors, creating an environment in which avian-adapted viruses, such as H5N1, can exchange genetic material with human-adapted strains.[12-14] Recent surveillance data from China's swine populations demonstrate troubling evidence; between 2021 and 2023, H5N1 clade 2.3.4.4b was detected in 4.7% of pigs sampled in Guangdong province, with the co-infections of seasonal H1N1 observed in 11% of the positive cases.[13, 14] This biological overlap raises the specter of novel reassortants, viruses that could combine the high pathogenicity of avian strains with the transmissibility of human-adapted influenza viruses.[12] The spillover cascade from birds to pigs to humans follows a predictable though perilous path. Human exposure events occur with alarming frequency in rural farming communities where backyard poultry and swine production overlap.[13] A 2023 study in Vietnam documented H5N1 antibodies in 8.3% of swine workers compared to 0.2% in urban populations. These agricultural hotspots serve as evolutionary testing grounds, where each interspecies jump presents the virus with new opportunities to refine its adaptability. However, the surveillance net remains full of holes.[15, 16] Only 17 countries currently mandate H5N1 testing in swine, and even fewer sequence isolates systematically. This blind spot leaves the world vulnerable to what virologists refer to as "silent spread," which is undetected viral circulation that can produce a pandemic strain without warning (Table 1).[17]

This convergence of virological risk factors and epidemiological vulnerabilities demands preparedness strategies of proportional sophistication. It should be noted that traditional public health measures, while necessary, may prove insufficient against a pathogen capable of simultaneous high lethality and rapid dissemination.[6, 7, 17, 20] The following section will examine how principles from CBRNe response frameworks, honed through decades of security applications, could provide the missing link in pandemic defense, offering scalable solutions for early detection, rapid containment, and crisis coordination in the face of an H5N1 pandemic.

A Chemical, Biological, Radiological, Nuclear, and Explosive Framework for Pandemic Avian Influenza: Opportunities and Implementation Challenges

The evolving threat of H5N1 avian influenza necessitates a critical re-evaluation of traditional public health preparedness paradigms.[6, 7, 20-22] This section investigates the potential integration of CBRNe frameworks, initially developed for high-consequence security threats, into pandemic response strategies.[23, 24] While these approaches offer promising innovations, their implementation presents serious challenges that require careful consideration.[25, 26]

CBRNe systems bring three potentially transformative capabilities to pandemic management: advanced early warning, rapid containment protocols, and interoperable crisis coordination.[21-24] Environmental biosurveillance technologies (e.g., NATO's Joint Biological Agent Identification and Diagnostic System) can detect airborne pathogens within minutes rather than days.[27] During the 2023 White Swan exercise, a simulated H5N1 scenario, these systems identified aerosolized viral particles in under forty minutes, suggesting potential for early outbreak detection at high-risk animal-human interfaces. Similarly, mobile treatment units derived from military CBRNe deployments (e.g., Spain's Unidad Militar de Emergencias prototype) demonstrated the ability to

Table 1. Global Spread and Evolution of HPAI H5N1 (2003-2025): Key Epidemiological Transitions

Time Period	Geographic Epicenter	Affected Hosts	Documented Cases	Epidemiological Significance	Predominant Clade	References
2003-2005	Southeast Asia	Avian/human	400+human cases (CFR: 60%)	First sustained human transmission	2.1/2.2	[18,19]
2006-2007	Europe/Near East	Wild birds	1,200 poultry outbreaks	First intercontinental spread via migratory birds	2.2.1	
2014-2015	South Korea	Commercial poultry	30 M+culled birds	Largest agricultural impact to date	2.3.2.1c	
2020-2021	South Africa	Ostriches	24,000 affected birds	First detection of clade 2.3.4.4b in Africa	2.3.4.4b	
2022	North America	Wild birds	50 M+wild bird mortalities	Unprecedented panzootic scale	2.3.4.4b	
2023	Pacific South America	Marine mammals	20,000+sea lion deaths	First mass mammalian die-off	2.3.4.4b	
2024	United States	Bovine/human	12 affected herds (4 human cases)	Novel cross-species transmission to cattle	2.3.4.4b	
2025	Eurasia	Poultry	80+active outbreaks (preliminary)	Emerging reassortants with H9N2	2.3.4.4b+	

Note. CFR: Case fatality rate.

establish biocontainment facilities within seventy-two hours in controlled exercises.[27-29]

The logistical advantages of CBRNe approaches were further illustrated in Operation Global Biolock (2024), where standardized crisis communication protocols enabled coordinated response across eighteen nations. Based on simulation data, spectral biosensor checkpoints could reduce cross-border transmission by approximately 63% compared to conventional screening methods. However, it is crucial to emphasize that these findings are derived from exercise scenarios rather than real-world H5N1 outbreaks.[30]

The translation of CBRNe capabilities to civilian health contexts faces substantial operational limitations. Implementation requires essential financial resources, specialized equipment, and highly trained personnel; these resources are disproportionately available in high-income countries.[6, 7, 23, 24, 26] The estimated cost of deploying advanced biosurveillance systems in low-resource settings could exceed local health budgets, potentially creating preparedness disparities that mirror existing global health inequities. Furthermore, legal and governance frameworks for military-civilian health collaboration remain underdeveloped in various regions.[31,32]

Recent advances in modeling software (e.g., the Spatiotemporal Epidemiological Modeler) offer opportunities to enhance CBRNe planning through quantitative scenario analysis. These tools can help optimize resource allocation by projecting transmission dynamics under a wide variety of intervention strategies. Nevertheless, such models require validation against empirical data from actual outbreaks.[33,34]

In summary, while CBRNe frameworks offer valuable innovations for pandemic preparedness, their implementation must be contextualized within practical constraints.[6, 7,23,24,26,35-38]

Conclusion

This study explored the integration of CBRNe principles into H5N1 pandemic preparedness, an approach that represents a significant paradigm shift in how we conceptualize biological threat management. While the WHO currently assesses the risk to the general population as low, the proactive development of advanced response capabilities offers valuable insurance against potential escalation scenarios.

It was revealed that the CBRNe framework's primary contribution lies in its potential to enhance early detection through military-grade biosurveillance, accelerate containment through mobile medical units, and improve coordination through standardized protocols. However, these advantages must be balanced against serious implementation challenges, including high costs, technical requirements, and the need for cross-sector collaboration. It is noteworthy that much of the evidence presented here was obtained from simulation exercises rather than real-world applications, indicating the need for validation during actual public health emergencies.

Accordingly, future research should prioritize three key areas: (1) the development of scalable CBRNe adaptations for low-resource settings, (2) the integration of quantitative modeling tools (e.g., Spatiotemporal Epidemiological Modeler) to refine intervention strategies, and (3) the strengthening of surveillance at human-animal interfaces where spillover risks are the highest. Additionally, more studies are needed to evaluate the cost-effectiveness of CBRNe approaches compared to conventional public health measures.

Rather than presenting a complete solution, this review highlighted the innovative potential of merging security and health paradigms. Overall, the CBRNe framework offers a promising avenue for strengthening global health security, but its ultimate value will depend on careful adaptation to diverse contexts and continuous evaluation against evolving threats. By approaching pandemic preparedness as a dynamic, interdisciplinary challenge, the global health community can build more resilient systems that are capable of responding to emerging threats.

Authors' Contribution

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Competing Interests
The authors declare no conflict of interests.

Ethical Approval
Not Applicable.

Funding
The authors received no financial support for this work.

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