IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 5, Issue 2, June 2025
Impact Factor: 7.67

Recent Advances in The Prevention and Control of Highly Pathogenic Avian Influenza A (H5N1): A Review of Vaccine, Therapeutic and Surveillance Strategies

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Abstract: *H5N1 is a highly pathogenic avian influenza virus with significant zoonotic and pandemic potential due to its high fatality rate, rapid mutation, and cross-species transmission. This review summarizes recent advances in H5N1 vaccine development for humans and poultry, including novel adjuvants and viral vectors. It also explores therapeutic options such as broadly neutralizing antibodies and small-molecule antivirals, with a focus on viral pathogenesis and host interactions involving the NS1 protein. Genomic surveillance highlights global spread via migratory birds and mutations linked to mammalian adaptation. The review also addresses food safety and innovative neuraminidase-based virus-like particle vaccines. Emphasizing a One Health approach, it calls for coordinated international efforts to monitor and control H5N1 threats..*

Keywords: H5N1, Highly-pathogenic avian influenza (HPAI), Zoonosis, Viral vectors, Adjuvants, NS1 protein, Genomic surveillance, Mammalian adaptation, Virus-like particle (VLP) vaccines, Neuraminidase, One-Health, Cross-species transmission, Panzootic, Influenza pathogenesis

I. INTRODUCTION

Influenza Bird flu, also referred to as virus subtype H5N1 (A/H5N1), is a highly virulent strain of avian influenza that seriously endangers the health of both humans and animals. The virus, which was initially limited to animals, especially poultry, has subsequently shown that it can infect mammals, including people, with frequently serious or lethal consequences. The virus is now panzootic, impacting a wide range of animal species over large geographic areas, but it was first enzootic in bird populations.[1]

The disease spreads rapidly among wild and domesticated birds via contact with contaminated fluids such as saliva, mucus, waste product, and respiratory droplets. Human infections are uncommon, but they are frequently caused by close contact with polluted surroundings or unhealthy birds. The H5N1 virus's high human case fatality rate is more than 50% in reported cases which points to the virus's potential for pandemic outbreaks.[2]

Since its inception, H5N1 has resulted in the extinction of hundreds of millions of birds globally and caused extensive ecological harm, particularly among wild bird populations. In recent years, worrying developments including the first reported mammal-to-human transmission and cases in people with no known animal exposure which have revived concerns about the virus's increasing threat.[3]

Considering its high lethality, zoonotic potential, and ability to rapidly evolve, H5N1 avian influenza continues to be a major worldwide health concern. Several strategies have been investigated since its inception to lessen its effects on both human and animal populations. Recent findings on viral etiology, antibody therapies, vaccination effectiveness, and surveillance techniques are included in this review.[4]

DOI: 10.48175/IJARSCT-27460

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2. Viral Pathogenesis and Host Interaction

The influenza virus membrane contains two key glycoproteins: hemagglutinin (HA) and neuraminidase (NA), both of which interact with sialic acid. HA initiates infection by binding to sialic acid on host cell surfaces, while NA facilitates virus spread by cleaving sialic acid, allowing newly formed viruses to exit infected cells. Both proteins are targets of neutralizing antibodies, and under immune pressure, they undergo antigenic changes, necessitating periodic vaccine updates.[5] Influenza A viruses are classified into 16 HA (H1–H16) and 9 NA (N1–N9) subtypes, grouped phylogenetically into two lineages for each glycoprotein. All subtypes are found in birds, especially waterfowl. Historical pandemics in 1918, 1957, 1968, 1977, and 2009 were caused by different combinations of HA and NA subtypes, with most originating from avian or swine reservoirs.[6]

Sheng et al. explored the role of the NS1 protein (Non-Structural Protein) in modulating host signaling pathways via Transforming growth factor-β-activated kinase 1 (TAK1) activation. Inhibition of TAK1 reduced Jun N-terminal kinase (JNK) activation, autophagy, and viral replication, revealing a potential antiviral target.[7] This mechanistic insight advances our understanding of H5N1's manipulation of host immunity.

3. Human Vaccine Development and Efficacy

A modified mRNA-LNP vaccine using a novel ionizable lipid induced strong immunity and reduced side effects in mice against H5N1 influenza. It offered better cross-protection and caused less inflammation and fewer adverse reactions than conventional mRNA-LNPs, suggesting a safer alternative to improve vaccine acceptance.[8]

Studies have shown that adjuvants play a critical role in enhancing immune responses in humans. Feldstein et al. demonstrated that vaccines adjuvanted with AS03 (squalene, polysorbate 80 & α-tocopherol) significantly outperform MF59 (squalene & triterpene hydrocarbon) and unadjuvanted vaccines in eliciting immune protection, particularly after two doses, achieving theoretical efficacies above 90%. This supports dose-sparing strategies critical during vaccine shortages. Reinforcing this, virtual screening studies emphasized the need for rational vaccine design targeting conserved viral regions, especially during pandemics with limited supply.[9]

4. Poultry Vaccine Innovations

Poultry vaccination remains a frontline defense against H5N1 spread. Kim et al. assessed a live and inactivated Newcastle disease virus (NDV)-vectored vaccine expressing clade 2.3.4.4b H5 HA. Both forms offered complete protection across chickens, broilers, and ducks, even under maternally derived antibody interference.[10]

Similarly, Chen et al. developed a duck enteritis virus (DEV)-vectored vaccine effective against H5N1, H5N6, and H5N8 strains, demonstrating cross-clade protection and long-term immunity. These innovations align with DIVA (Differentiating Infected from Vaccinated Animals) principles, facilitating disease control and trade continuity.[11]

5. Antibody-Based Therapeutics and Immunogen Design

Understanding immune responses post-infection is vital for therapeutic antibody development. Wang et al. identified a conserved, vulnerable hemagglutinin (HA) surface (VS1) targeted by neutralizing antibodies. Structural mapping revealed key residues involved in antibody binding, supporting their inclusion in universal vaccine targets.[12]

Sun et al. further isolated cross-neutralizing antibodies from H5N1-infected patients, targeting conserved stem epitopes and exhibiting antibody dependent cellular cytotoxicity (ADCC) functions. These findings highlight the therapeutic potential of monoclonal antibodies and inform future vaccine designs that elicit broadly protective responses.[13]

6. Antiviral Drug Development

Yu et al. introduced furan-carboxamide derivatives as novel inhibitors of H5N1, identifying lead compound *2,5-dimethyl-N-(2-((4-nitrobenzyl)thio)ethyl)-furan-3-carboxamide* with promising in vitro efficacy.[14] These small molecules, targeting conserved viral mechanisms, may serve as next-generation antivirals, especially amidst resistance concerns.

Taurolidine (TRD), a taurine derivative known for antibacterial and antitumor properties, was found to significantly inhibit H5N1 influenza virus replication in MDCK cells (EC_{50} = 34.45 μg/mL). In a mouse model, TRD improved

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survival rates (86% protection), reduced lung damage and viral titers, and modulated immune response by lowering neutrophils and increasing lymphocytes. Mechanistically, TRD suppressed the NF-κB signaling pathway, reducing inflammatory cytokine expression. These results suggest TRD as a promising candidate for anti-influenza therapy pending further clinical evaluation.[15]

7. Genomic Surveillance and Outbreak Characterization

Recent H5N1 outbreaks in Peru (Sevilla et al.) and Brazil (Rivetti Jr. et al.) were linked to clade 2.3.4.4b, showing genetic ties to strains in North America and Europe. These findings underscore the transcontinental spread through migratory birds and emphasize the need for real-time genomic surveillance. Mutations associated with host adaptation (e.g., PB2-D701N, Q591K) raise concerns over mammalian transmission. These studies advocate for One Health approaches and robust monitoring systems.[16][17]

8. Food Safety and Public Health Assurance

In March 2024, H5N1 avian influenza virus was found in U.S. dairy cows, and infectious virus was detected in some raw milk samples. A study tested whether standard pasteurization (72°C for 15 seconds) would kill the virus. No live virus was found after pasteurization, even in high-virus samples. This confirms that pasteurized milk is safe and does not pose a risk of H5N1 transmission.[18]

Luchansky et al. addressed public concerns about H5N1 transmission via food. They confirmed that cooking ground beef patties to USDA-recommended temperatures (71.1°C) completely inactivates the virus, supporting current food safety practices.[19]

9. Innovate Platforms

Smith et al. developed a neuraminidase (NA)-based virus-like particle (VLP) vaccine that provided strong protection in ferrets. NA immunity, often overlooked compared to hemagglutinin (HA), showed promise in reducing viral shedding and disease severity, suggesting NA-based vaccines as complementary tools in pandemic preparedness.[20]

10. Conclusion and Future Directions

H5N1 avian influenza remains a serious threat at the human-animal environment interface, with its high pathogenicity, cross-species transmission potential, and capacity for rapid evolution raising persistent global health concerns. The advances in vaccine development-both for humans and poultry have demonstrated promising efficacy, mainly with the combination of novel adjuvants and viral vectors. Simultaneously, the identification of and new antiviral compounds provides hope for improved therapeutic interventions.

The mechanistic studies continue to unravel the complex host-virus interactions that support H5N1 pathogenesis, offering new antiviral targets. While, the genomic surveillance has proven essential in tracing viral spread and detecting mutations associated with mammalian adaptation. A One Health strategy that integrates virology, immunology, ecology, and public health is crucial in the face of changing dangers, especially in light of recent zoonotic incidents.

A sustained investment in research, surveillance, and vaccine innovation-alongside public education and international cooperation will be critical to mitigating the current and future impacts of H5N1 and preparing for its pandemic potential.

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