International Journal of Science and Research Archive
eISSN: 2582-8185
Cross Ref DOI: 10.30574/ijsra
Journal homepage: https://ijsra.net/

(Review Article)

A comprehensive biochemical and epidemiological review of avian influenza: Mechanisms, pharmacology and emerging trends in treatment

Umer Ahmed [1, *], Hafiza Amna Farooq [2], Faiza Bashir [3], Muhammad Haseeb [1], Farzeen Yaseen [2] and Nawal Amin [4]

[1] *Institute of Microbiology, Faculty of Veterinary Sciences, University of Agriculture, Faisalabad, Pakistan.*
[2] *Department of Biochemistry, Faculty of Sciences, University of Agriculture, Faisalabad, Pakistan.*
[3] *Institute of Physiology and Pharmacology, Faculty of Veterinary Sciences, University of Agriculture, Faisalabad, Pakistan.*
[4] *Health Biotechnology Division, National Institute for Biotechnology and Genetic Engineering Faisalabad, Pakistan.*

International Journal of Science and Research Archive, 2024, 13(01), 1148–1164

Publication history: Received on 16 August 2024; revised on 22 September 2024; accepted on 25 September 2024

Article DOI: https://doi.org/10.30574/ijsra.2024.13.1.1811

Abstract

Avian influenza viruses, particularly H5N1, H7N9, and H9N2, pose significant threats to avian and human populations through zoonotic transmission, as they have potential to change their genetic material through mutations. Symptoms of Avian Influenza ranges from mild to severe, mainly respiratory problems in both and muscle aches, fatigue in humans. This review highlights the molecular mechanisms by which the virus infects host cells, emphasizing the roles of hemagglutinin (HA) and neuraminidase (NA) in viral entry and release. Biochemical processes involved in viral replication, immune responses, and cytokine production are discussed, with a detailed examination of how antiviral drugs like neuraminidase and polymerase inhibitors disrupt these processes. Outbreak of AIV can cause mass culling results in massive economic loss, trade disruptions, and consumer reductions. The review also addresses the challenges posed by antiviral resistance and outlines novel therapeutic strategies, including combination therapies, vaccine advancements, and host-directed treatments. With an interdisciplinary "One Health" approach, this paper underscores the need for enhanced biosecurity, international cooperation, and continued research to mitigate the global impact of avian influenza.

Keywords: Avian Influenza; Infectious diseases; Epidemiology; Poultry; Diagnosis

1. Introduction

Avian influenza (AI), also known as bird flu, is a highly contagious viral disease that primarily affects birds, including domestic poultry and wild birds. Avian flu viruses are a global concern due to their widespread and high death rates [1]. Deadly strains like H5N1 have triggered major bird outbreaks. According to data reported by the World Health Organization (WHO, 2023), the cumulative number of H5N1 cases includes 878 confirmed human cases, with 458 deaths across 23 countries (see Table 1). Recent epidemics in various animals, including wild birds, domestic fowl, sea lions, and minks, coupled with genetic changes in H5N1 strains, raise worries about transmission and public health dangers [2]. At the molecular level, Avian Influenza is a negative-sense single-stranded RNA virus from the Orthomyxoviridae family. Hemagglutinin (HA) and neuraminidase (NA) play critical roles in viral entry and release from host cells. The interaction of HA with sialic acid receptors on host cells initiates infection, while NA enables the release of viral particles by cleaving sialic acids on the surface of infected cells, making these proteins critical targets for antiviral drugs [3].

---

[*] Corresponding author: Umer Ahmed

Table 1 Cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003–2023

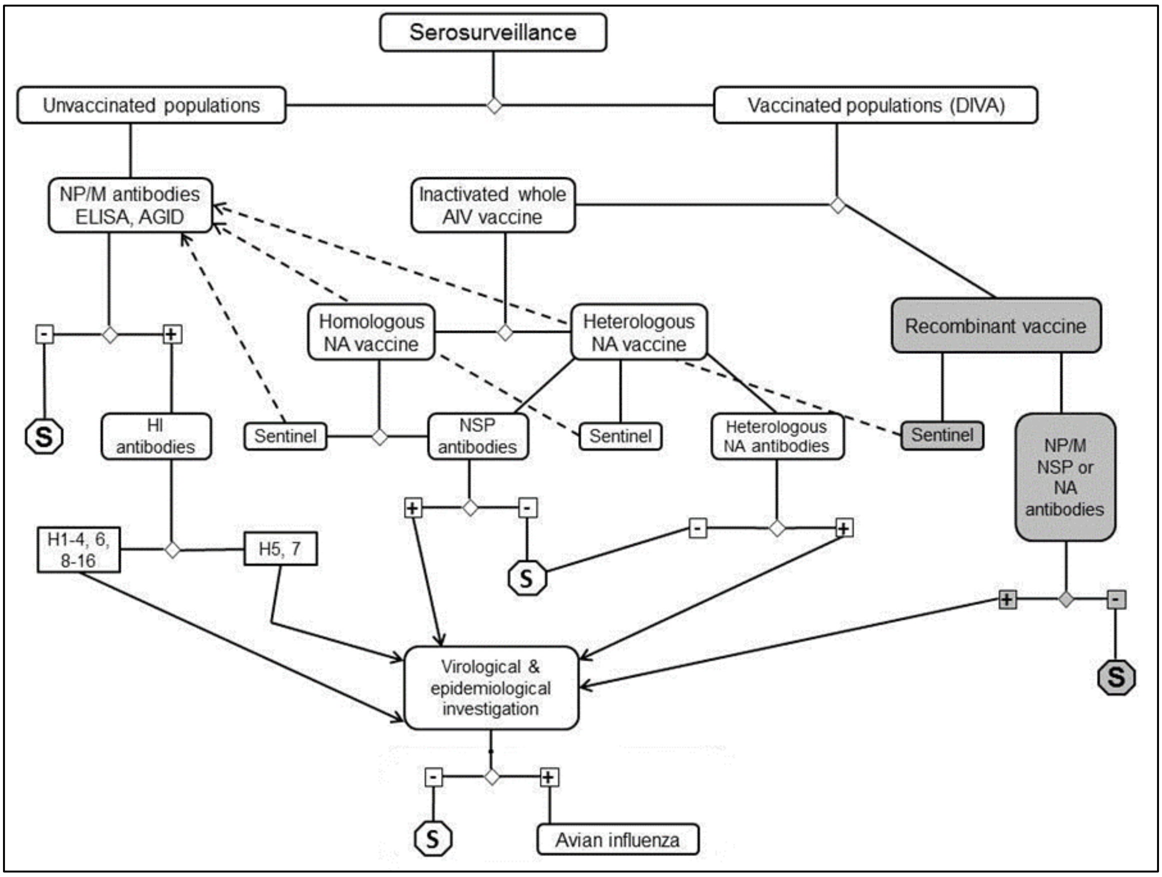
Country	2003-2009 Cases	2003-2009 Deaths	2010-2014 Cases	2010-2014 Deaths	2015-2019 Cases	2015-2019 Deaths	2020-2023 Cases	2020-2023 Deaths	Total Cases	Total Deaths
Azerbaijan	8	5	0	0	0	0	0	0	8	5
Bangladesh	1	0	6	1	1	0	0	0	8	1
Cambodia	9	7	47	30	0	0	2	1	58	38
Canada	0	0	1	1	0	0	0	0	1	1
Chile	0	0	0	0	0	0	1	0	1	0
China	38	25	9	5	6	1	2	1	55	32
Djibouti	1	0	0	0	0	0	0	0	1	0
Ecuador	0	0	0	0	0	0	1	0	1	0
Egypt	90	27	120	50	149	43	0	0	359	120
India	0	0	0	0	1	1	0	0	1	1
Indonesia	162	134	35	31	3	3	0	0	200	168
Iraq	3	2	0	0	0	0	0	0	3	2
Lao PDR	2	2	0	0	1	0	0	0	3	2
Myanmar	1	0	0	0	0	0	0	0	1	0
Nepal	0	0	0	0	1	1	0	0	1	1
Nigeria	1	1	0	0	0	0	0	0	1	1
Pakistan	3	1	0	0	0	0	0	0	3	1
Spain	0	0	0	0	0	0	2	0	2	0
Thailand	25	17	0	0	0	0	0	0	25	17
Turkey	12	4	0	0	0	0	0	0	12	4
United Kingdom	0	0	0	0	0	0	5	0	5	0
USA	0	0	0	0	1	0	0	0	1	0
Vietnam	112	57	15	7	0	0	1	0	128	64
Total	468	282	233	125	160	48	8	1	878	456

Source: World Health Organization, (2023).

However, certain strains of AI viruses have the potential to infect humans, leading to zoonotic transmission. The most notable zoonotic strains include H5N1, H7N9, and H9N2. AI viruses are classified into low pathogenic avian influenza (LPAI) and highly pathogenic avian influenza (HPAI) based on their virulence in poultry. LPAI strains typically cause mild or asymptomatic infections in birds, while HPAI strains can lead to severe outbreaks with high mortality rates [4]. AI viruses primarily spread through direct contact with infected birds or their secretions, as well as through contaminated environments, such as poultry farms and live bird markets [5]. Influenza viruses in natural ecosystems spread through droppings from water birds and contaminated objects, favouring strains with low harm. Certain strains like H5 or H7 can become highly dangerous in poultry farms [6].

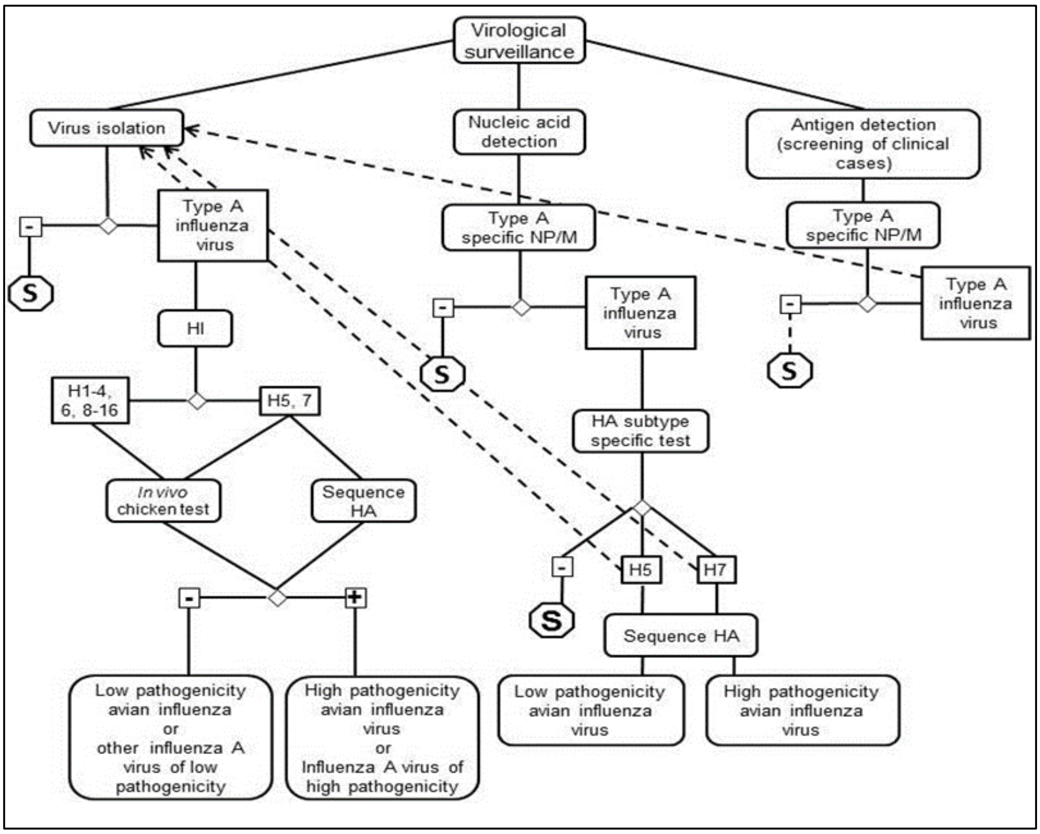
The persistence of highly pathogenic AIV H5N1 worldwide exposes wild birds to infected poultry, enabling the virus to spread over long distances. There's worry that these wild birds could spread these dangerous strains or infect domestic birds. The only current solution to reduce this risk is strict disease control and biosecurity measures on poultry farms [7].

Influenza A viruses (IAVs) have significant potential to spread between animals and humans, infecting various avian and mammalian hosts. They possess the capability to alter their genetic makeup through mutation or recombination when infecting a host cell alongside different AIV strains, leading to a wide range of genetic variations [8]. These evolving AIVvariants pose recurring global health risks to both human and animal populations every year. Human infections usually occur through close contact with infected birds or their contaminated environments, although limited human-to-human transmission has been reported [9]. A virus is a negative-sense single-stranded RNA virus that belongs to the Orthomyxoviridae family. Based on the antigenic characteristics of hemagglutinin (HA) and neuraminidase (NA) influenza viruses are classified into multiple subtypes. **Fig. 1.** H9N2 belongs to the low pathogenic Avian Influenza Viruses (AIVs) and is one of the widely spread viruses in poultry, which can pose a threat to humans by directly infecting or providing internal genes for various zoonotic avian influenza strains [10]. Virological surveillance of the Influenza A virus is a critical process for monitoring the circulation of influenza strains, detecting emerging variants, and informing public health interventions. This process involves a series of steps, beginning with specimen collection from individuals with influenza-like illnesses. The collected specimens are then analyzed using various laboratory techniques, such as virus isolation, nucleic acid detection, and antigen detection. Once the virus is confirmed as Influenza A, its subtype is determined, and its pathogenicity is assessed. This information is essential for understanding the epidemiology of influenza, developing effective vaccines, and implementing appropriate public health measures. **Fig. 1** In birds, AI infection can cause a wide range of clinical signs, including respiratory distress, decreased egg production, and neurological symptoms. In humans, symptoms of AI infection vary from mild respiratory illness to severe pneumonia and acute respiratory distress syndrome (ARDS), with the potential for fatal outcomes [11].



Source: Avian Influenza. *Terrestrial Animal Health Code*, World Organization for Animal Health (WOAH), 2018.

Figure 1 Schematic representation of laboratory tests for determining evidence of avian influenza infection through or following serological surveys



Source: Avian Influenza. *Terrestrial Animal Health Code*, World Organization for Animal Health (WOAH), 2018

Figure 2 Schematic representation of laboratory tests for determining evidence of avian influenza infection using virological methods

Laboratory diagnosis of AI in poultry and humans involves molecular techniques such as reverse transcription polymerase chain reaction (RT-PCR) for viral detection and subtyping. Serological assays are also used to detect antibodies against AI viruses in both birds and humans [12]. Preventive measures for AI in poultry include strict biosecurity practices, vaccination of poultry flocks, and surveillance programs to detect and control outbreaks [13]. In humans, public health interventions such as rapid diagnosis, quarantine measures, and antiviral treatment play a crucial role in preventing the spread of AI. Despite significant progress in AI research and control efforts, several challenges remain, including the ongoing evolution of AI viruses, the emergence of novel zoonotic strains, and the development of effective vaccines and antiviral therapies for both poultry and humans [14]. Future research should address improved surveillance strategies, understanding the mechanisms of transmission of the virus, and an integrated One Health approach to the prevention and control of AI.

2. Epidemiology

In late 2016, a highly contagious bird flu (HPAI H5N6) virus was found in wild birds in South Korea for the first time. Since then, it has spread to domestic poultry and other parts of Asia. This virus is highly deadly to poultry and has caused significant economic damage. It first appeared in China in 2013 and has since spread to other countries in Asia. While the H5N8 strain, which is also part of the same virus family, has not caused any human infections, the H5N6 strain has infected 16 people in China, resulting in six deaths. In South Korea, the H5N6 virus was first detected in wild birds and then spread to poultry farms, likely due to contact with these birds [15].

Avian influenza viruses have mostly been identified in birds, exclusively in wild birds. In rare occurrences, these viruses infect domestic poultry, including chickens, turkeys, ducks, and quail. The occurrence of avian influenza globally and in a country varies from place to place and is regulated by various factors including the geographical position and climatic conditions of the country, the livestock farming practice and the migration pattern of the birds among others [16]. In recent years, highly pathogenic avian influenza (HPAI) outbreaks have occurred in many parts of the world and are causing significant economic losses to the poultry industry. There is a high potential risk to human health in areas of dense poultry populations with poor biosecurity as the virus is present there. Avian influenza viruses are subtyped based on two surface proteins: hemagglutinin and neuraminidase. The H and N proteins are further divided into various subtypes. Some of the most notable subtypes of avian influenza viruses include H5N1, H7N9, H9N2, and H5N8 [17].

While most avian influenza viruses primarily infect birds and do not usually cause illness in humans, some subtypes have demonstrated the ability to infect humans and cause severe respiratory illness. For example, the H5N1 virus has caused sporadic cases of human infection with a high mortality rate, although sustained human-to-human transmission has been limited. Similarly, the H7N9 virus has caused outbreaks of human infection in China, primarily through exposure to infected poultry [18].

2.1. Zoonotic Transmission Routes and Risk Factors

Table 2 Zoonotic Potential of AI Strains

AI Strain	Animal Host	Human Infections	Mortality Rate (%)	Transmission Mode	References
H5N1	Poultry, Wild Birds	878	52.16	Direct Contact, Aerosol	(Charostad et al. 2023)
H7N9	Poultry	Numerous	High	Direct Contact, Live Markets	(Subbarao & Katz, 2000)
H9N2	Poultry, Wild Birds	Limited	Low	Direct Contact, Wild Birds	(Bao et al. 2022)

Direct Contact: The primary route of zoonotic transmission of avian influenza viruses to humans is direct contact with infected birds or their secretions, such as respiratory droplets, faeces, or blood. Individuals involved in poultry farming, live bird markets, or handling sick or dead birds are at increased risk of exposure [19]. Influenza viruses typically replicate in the epithelial cells of the upper respiratory or gastrointestinal tract, leading to varied outcomes ranging from asymptomatic infection to severe respiratory disease and occasionally death [20]. While most avian infections are subclinical, poultry can experience respiratory disease or reduced egg production, with certain strains causing severe disseminated infections and high mortality rates. Interspecies transmission between different hosts, such as chicken-to-human or duck-to-pig, is rare, with sporadic cases documented [21]. In mammals, influenza viruses mainly replicate in the respiratory tract, causing clinical signs like rhinitis, especially in humans, horses, and pigs. Instances of avian influenza transmission to range turkeys via free-flying birds during wild-bird migrations have been observed in Minnesota, highlighting the potential for interspecies spread [22].

Indirect Contact: Indirect transmission can occur through exposure to contaminated environments, such as surfaces or objects contaminated with avian influenza virus particles [22]. This can happen in settings like live poultry markets, where viruses may persist on surfaces and equipment [23]. H5 and H7 avian influenza viruses, following interspecies transmission, can become highly pathogenic in chickens and occasionally transmit directly to humans in various regions. Our study focuses on H7N3 viruses isolated from Pakistani chickens between 1995 and 2002, analyzing their antigenic, sequence, and phylogenetic characteristics. In chickens, these viruses exhibited high pathogenicity but limited transmissibility to contact birds, with prolonged cloacal shedding and widespread tissue dissemination [19].

However, they replicated poorly in mallard ducks. In mammalian hosts, certain H7N3/02 viruses caused weight loss and mortality in mice and showed significant virus multiplication in ferrets' lungs, intestine, and conjunctiva, indicating potential zoonotic transmission. This highlights the importance of ongoing surveillance and understanding of avian influenza virus evolution and transmission dynamics [24].

Risk Factors: factors may increase the risk of zoonotic transmission, including close and prolonged contact with infected birds, poor biosecurity practices, inadequate hygiene measures, and exposure to high concentrations of virus in crowded or poorly ventilated environments [25] Additionally, genetic factors and underlying health conditions in humans may influence susceptibility to severe disease following avian influenza infection. In this way, knowledge of AI virus transmission modes and identifying clinical expressions in poultry and in humans, as well as identification of the routes and modulators of zoonotic transmission, is central to effective surveillance, prevention, and control of outbreaks [26].

2.2. Factors Influencing the Spread and Transmission Dynamics of Avian Influenza

Several factors contribute to the spread and transmission dynamics of avian influenza:

- **Bird Migration:** Wild birds, particularly waterfowl, serve as natural reservoirs for avian influenza viruses and can carry the virus over long distances during migration, introducing it to new regions and populations [27].
- **Poultry Trade and Transport:** The movement of live poultry and poultry products can facilitate the spread of avian influenza within and between countries. Infected birds or contaminated materials can introduce the virus to new areas and farms [28].
- **Biosecurity Measures:** Biosecurity measures are also one of the practices on poultry farms that affect the prevention of the introduction and spread of avian influenza. Good biosecurity includes restricting entry to poultry farms, disinfection, and proper waste handling [29].
- **Contact between Wild Birds and Domestic Poultry:** Close contact between domestic poultry and wild birds, either through water use and sharing watering places or through cohabitation in free-range systems, provides a significant opportunity for transmission of the avian influenza viruses [30].
- **Viral Evolution and Adaptation:** Like most influenza viruses, avian influenza viruses can evolve and reassort genetically into novel strains that are more transmissible or pathogenic. Monitoring viral evolution and understanding the factors that drive adaptation are essential for predicting and controlling future outbreaks [31].

Overall, the epidemiology of avian influenza is complex and determined by a set of ecological, biological, and socio-economic factors. Consequently, good surveillance, biosecurity, and international cooperation are constituents that greatly reduce the risks of avian influenza and protect the health of animals to humans [32].

3. Immunology

3.1. Evasion Mechanisms of AI Virus from Immune systems

Poultry: The avian influenza virus is dangerous to birds and mammals, but wild ducks, gulls, and shorebirds are its natural hosts. In poultry, infections can range from asymptomatic to severe respiratory or systemic diseases, such as highly pathogenic avian influenza (HPAI) [33]. Protective antibodies against viral proteins like hemagglutinin and neuraminidase are crucial for poultry immunity, achievable through various vaccines like killed whole virus or fowl-pox recombinant vaccines. While antigenic drift may not greatly impact vaccine efficacy in poultry, the role of cytotoxic T lymphocyte response in reducing viral shedding is uncertain, and the influence of genes and cytokines on disease protection remains unclear [34].

Avian influenza viruses primarily target the respiratory and gastrointestinal tracts of birds [35]. Infection typically begins when the virus enters the respiratory system through inhalation of contaminated droplets or direct contact with infected birds or surfaces [36].

Once inside the host, the virus replicates in the epithelial cells lining the respiratory tract, causing damage to the cells and triggering an inflammatory response. It will Infect the alveolar Macrophages. This leads to respiratory symptoms and lesions in the respiratory tissues [37].

- **Humans**: Human infection with avian influenza viruses usually occurs through direct contact with infected birds or their secretions, or exposure to contaminated environments such as live bird markets or poultry farms. The virus can enter the human respiratory tract via inhalation of infectious droplets or through contact with mucous membranes [38]. Once inside the body, the virus attaches to respiratory epithelial cells using the viral hemagglutinin protein, initiating viral replication and triggering an immune response. In severe cases, the virus can invade deeper lung tissue, causing pneumonia and potentially leading to systemic complications [39].
- **Insights into IFN Antagonism and Host Interactions:** The circulation of seasonal influenza A viruses (IAVs) in humans depends on their ability to effectively evade and manipulate the host immune response. While the adaptation of seasonal H1N1 and H3N2 viruses to escape humoral immunity is well documented, there is less understanding of how these viruses evolve to counteract innate immune responses [40]. Research indicates that only a small fraction of infected cells triggers the type I and type III interferon (IFN) response during IAV infection, highlighting the need for single-cell analyses to accurately assess the IFN response. We developed a flow cytometry-based technique to investigate transcriptional changes in IFN and interferon-stimulated gene (ISG) expression at the single-cell level [40]. Our findings show that NS segments from seasonal H3N2 viruses are more effective at antagonizing IFN signaling but less adept at suppressing IFN induction compared to the

pdm2009 H1N1 lineage. By comparing various NS segments across the evolutionary history of seasonal IAV lineages, we observed prolonged periods of stability in IFN antagonism, with occasional shifts in phenotype. [40] Our data highlight notable differences in how seasonal and pandemic H1N1 and H3N2 viruses counteract the human IFN response at the single-cell level.

Similarly, upon infection with Avian Influenza Virus (AIV), the virus exploits the host's cellular machinery to replicate its genetic material and produce new viral proteins. The viral RNA-dependent RNA polymerase (RdRp) plays a vital role in this process by replicating the viral RNA genome [41]. For RdRp to operate efficiently, it interacts with various host proteins, such as the nuclear export protein and nucleoprotein, which aid in the transport of viral RNA and proteins within the cell.

In response to AIV infection, the host immune system activates and begins producing cytokines and interferons [42]. These signalling molecules coordinate the body's defense against the infection. Although cytokines and interferons are crucial for fighting the virus, their excessive production can lead to a cytokine storm, a severe and potentially life-threatening condition marked by uncontrolled inflammation [43].

4. Clinical Signs and Symptoms

- **Poultry:** Clinical signs of avian influenza in poultry can vary depending on the virulence of the virus strain and the species affected. Common symptoms include respiratory distress, nasal discharge, coughing, sneezing, lethargy, decreased egg production, and gastrointestinal disturbances such as diarrhoea. In severe cases of highly pathogenic avian influenza (HPAI), birds may exhibit neurological signs, haemorrhages, oedema, and high mortality rates [44].
- **Humans:** Sero epidemiologic and virologic studies dating back to 1889 have indicated that human influenza pandemics were typically caused by H1, H2, and H3 subtypes of influenza A viruses. However, the 1997 avian A/H5N1 outbreak in Hong Kong shifted attention to subtype H2 as a potential candidate for the next pandemic [45]. Unlike previous outbreaks, the currently circulating A/H5N1 genotype Z virus has spread globally from Southern China, possibly facilitated by migratory birds and bird trafficking [46]. Human cases of avian influenza virus infections, mainly due to A/H5, A/H7, and A/H9 subtypes, have been reported, with A/H5N1 infections exhibiting a >50% case fatality rate. The emergence of resistance to antiviral drugs and the uncertain effectiveness of current vaccines highlight the urgent need for research and preparedness at national and international levels [47]. In humans, symptoms of avian influenza can range from mild respiratory illness to severe pneumonia and acute respiratory distress syndrome (ARDS). Early symptoms often resemble those of seasonal influenza and may include fever, cough, sore throat, muscle aches, headache, and fatigue [48]. As the infection progresses, patients may develop severe respiratory symptoms such as dyspnea (difficulty breathing), chest pain, and cyanosis (bluish discolouration of the skin). Complications can include multi-organ failure and death, particularly in cases of HPAI or when there are underlying health conditions [49].

5. Laboratory Methods for AI Virus Detection and Diagnosis

Table 3 Diagnostic Methods for AI in Poultry and Humans

Method	Poultry Application	Human Application	Sensitivity/Specificity	Challenges	References
RT-PCR	Virus detection	Virus detection	High	Resource-intensive	(Suarez et al. 2020)
Serological Assays	Antibody detection	Antibody detection	Moderate	Cross-reactivity	(Capua & Munoz, 2013)
Virus Isolation	Confirmatory Diagnosis	Confirmatory Diagnosis	Very High	Time-consuming	(Shahzad et al. 2020)

- **Poultry Diagnostics:** Poultry diagnostics are mainly based on methods such as isolation of the virus, serological tests including hemagglutination inhibition assay, molecular methods, including RT-PCR, and antigen detection assays, for the identification of the presence of the AI virus in poultry populations and monitoring outbreaks to inform control measures. (e.g., ELISA) [50]. These methods help identify the presence of AI virus in poultry populations, monitor outbreaks, and inform control measures. Human Diagnostics: Human diagnostics involve similar techniques, including RT-PCR, virus isolation, serological assays, and antigen detection tests [51]. Poultry diagnostics are mainly based on methods such as isolation of the virus, serological tests including hemagglutination inhibition assay, molecular methods, including RT-PCR, and antigen detection assays, for the identification of the presence of the AI virus in poultry populations and monitoring outbreaks to inform control measures. Diagnostic procedures in humans are done by almost similar means; these include RT-PCR, virus isolation, serological assays, and antigen detection tests. These methods confirm AI virus infection in humans, particularly in the suspected cases of avian-to-human transmission or human-to-human transmission in rare instances [52]. These methods are used to confirm AI virus infection in humans, especially in cases of suspected avian-to-human transmission or human-to-human transmission in rare instances [53].

- **Human Diagnostics:** Human diagnostics involve similar techniques, including RT-PCR, virus isolation, serological assays, and antigen detection tests [54]. These methods are used to confirm AI virus infection in humans, especially in cases of suspected avian-to-human transmission or human-to-human transmission in rare instances [55]. Recent global outbreaks of avian influenza (AI) highlight the complexity of controlling the infection, especially in densely populated poultry regions or areas with free-range rural poultry. Laboratory testing primarily focuses on tracing viral circulation for early warning systems rather than diagnosing diseased flocks [56].

This necessitates rapid, sensitive, and cost-effective tests adaptable to high throughputs. While molecular biology and biotechnology offer advanced diagnostic techniques, their widespread use is limited by costs and technical expertise, emphasizing the importance of improving conventional methods alongside developing new technologies [57].

6. Advances in Diagnostic Technologies and Tools:

- **Point-of-Care Testing:** The development of rapid diagnostic tests that can be performed at the point of care has advanced, enabling quicker detection and response to AI outbreaks, particularly in remote or resource-limited settings [58].
- **Next-Generation Sequencing (NGS):** NGS technologies allow for high-throughput sequencing of viral genomes, providing detailed genetic information for strain characterization, surveillance, and monitoring of viral evolution. This enables a more comprehensive understanding of AI virus diversity and epidemiology [59].
- **Multiplex Assays:** Multiplex assays capable of detecting multiple viral targets simultaneously have been developed, improving efficiency and cost-effectiveness in surveillance efforts and outbreak investigations by screening for a broader range of pathogens in a single assay [60].
- **Advanced Serological Assays:** Advancements in serological assays, such as microarray-based or multiplex immunoassays, offer enhanced sensitivity and specificity for detecting antibodies against AI viruses, aiding in sero surveillance and vaccine evaluation studies [61].

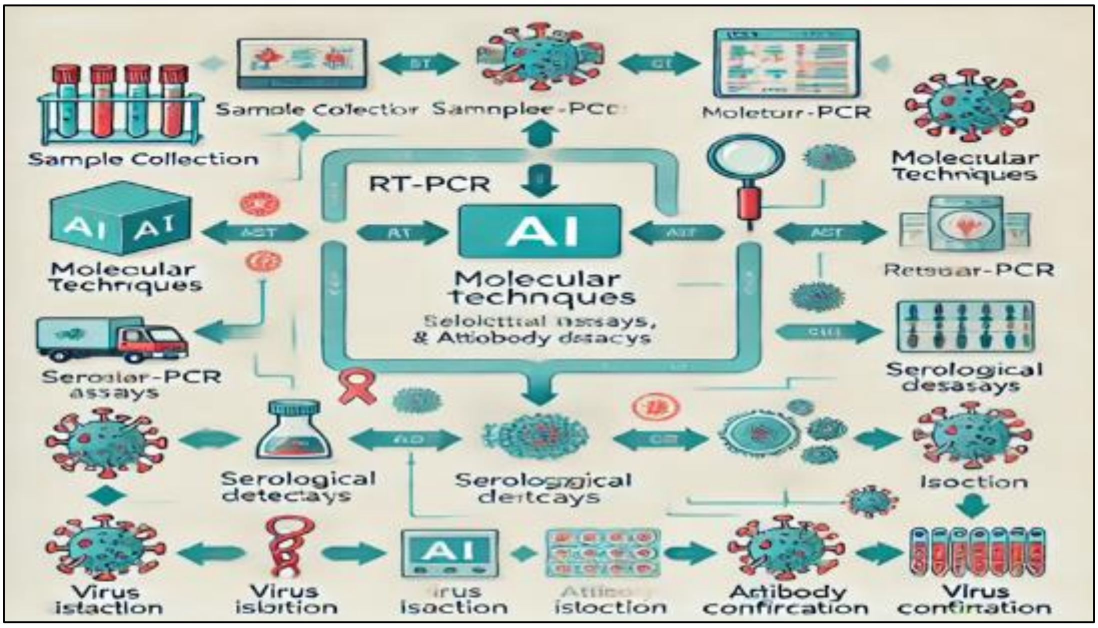


Figure 3 Overview of Molecular and Serological Techniques for Viral Detection and Isolation

7. Challenges and Limitations in AI Diagnostics

- **Specificity and Sensitivity:** Some diagnostic methods may lack specificity or sensitivity, leading to false-positive or false-negative results, respectively. This can complicate accurate detection and surveillance of AI viruses, particularly during low-level or mixed infections [62].
- **Resource Constraints:** Many diagnostic techniques require specialized equipment, reagents, and trained personnel, which may be lacking in resource-limited settings. This can hinder timely and accurate diagnosis, especially in regions with limited access to laboratory facilities [63].
- **Virus Diversity:** The genetic diversity of AI viruses poses challenges for diagnostic assays designed to target specific viral strains or subtypes. Mutations in viral genes can affect primer and probe binding sites, impacting the accuracy of molecular tests [64].
- **Cross-Reactivity:** Cross-reactivity with other respiratory pathogens, such as other influenza virus subtypes or respiratory viruses, can lead to ambiguous results and complicate interpretation, especially in areas where multiple pathogens co-circulate [65].

8. Pharmacology

8.1. Pharmacological Interventions

In Pharmacological interventions, managing avian influenza (AI) involves targeting specific viral proteins with antiviral drugs. For poultry, neuraminidase inhibitors like oseltamivir block the enzyme neuraminidase, preventing the release of new virus particles from infected cells, while M2 ion channel inhibitors such as amantadine obstruct the virus's entry into host cells by interfering with ion channels necessary for viral uncoating [66]. These mechanisms are crucial for controlling AI outbreaks but face challenges from antimicrobial resistance due to the overuse and misuse of these drugs, leading to mutations that diminish their effectiveness. Strategies to mitigate resistance include rotating drug classes, combining therapies, and adhering to dosage guidelines [67]. For humans, neuraminidase inhibitors and polymerase inhibitors (e.g., baloxavir marboxil) similarly target viral replication processes, with ongoing surveillance for resistance and the development of new drugs being essential to maintain effective control of AI across both veterinary and human medicine [68].

Table 4 Pharmacological Interventions for AI

Intervention	Target Host	Drug Class	Mechanism of Action	Resistance Challenges	References
Oseltamivir	Humans	Neuraminidase Inhibitor	Blocks viral particle release	Resistance mutations	(Beigel & Hayden, 2021)
Amantadine	Poultry	M2 Ion Channel Inhibitor	Prevents virus entry into host cells	Resistance emergence	(Conrad et al. 2009)
Baloxavir Marboxil	Humans	Polymerase Inhibitor	Inhibits viral RNA replication	Limited human trials	(Palomba et al. 2021)

- **Poultry:** Pharmacological interventions in poultry focus on antiviral drugs to control avian influenza (AI) outbreaks. Neuraminidase inhibitors like oseltamivir and M2 ion channel inhibitors such as amantadine are commonly used. Neuraminidase inhibitors work by blocking the release of newly formed virus particles from infected cells, while M2 ion channel inhibitors prevent the virus from entering host cells. These drugs can help reduce the severity and spread of AI within poultry populations [69]. However, the emergence of antimicrobial resistance poses a significant challenge. Continued and indiscriminate use of antiviral drugs can lead to the development of resistance, rendering these drugs ineffective over time. Strategies to mitigate resistance include judicious use of antivirals, rotation of drug classes, combination therapy, and strict adherence to dosage regimens [70].
- Additionally, ongoing surveillance for resistance mutations and the development of new antiviral agents with novel mechanisms of action are crucial for effective AI control in poultry [71].
- **Human:** Pharmacological interventions for treating avian influenza (AI) in humans primarily involve antiviral drugs, notably neuraminidase inhibitors (such as oseltamivir and zanamivir) and polymerase inhibitors (like baloxavir marboxil) [72].

9. Pharmacokinetics

- **Neuraminidase inhibitors:** These drugs inhibit the neuraminidase enzyme, essential for the release of newly formed viral particles from infected cells, thus impeding viral spread and reducing the severity and duration of AI symptoms [73]
- **Polymerase inhibitors:** These drugs target the viral RNA polymerase enzyme, crucial for viral replication, thereby hindering the synthesis of viral RNA and halting viral replication, ultimately curbing infection progression [74].
- **Efficacy in AI Treatment:** Neuraminidase inhibitors have demonstrated effectiveness in reducing the severity of AI symptoms and shortening the duration of illness when administered early in the infection. They also aid in preventing complications and reducing mortality rates associated with AI [75]. Baloxavir marboxil, a newer class of antiviral, has shown efficacy in treating influenza A viruses, including some strains of avian influenza. It acts by inhibiting the cap-dependent endonuclease activity of the viral polymerase, thereby disturbing viral RNA transcription and hampering viral replication [76].
- **Challenges of Antiviral Resistance:** The most important challenge in AI treatment is antiviral resistance. Instances of resistance to oseltamivir among the strains of influenza A/H5N1 virus are reported, thus warranting strict surveillance and monitoring for the development of antiviral resistance patterns, it is clear that there is a need for the development of alternative forms of treatment as the resistance to neuraminidase inhibitors emerges, and consequently, combination therapies to fight the drug-resistant strains [77].
- **Development of Novel Antiviral Therapies:** Focus has been set on the development of novel antiviral therapies that have various mechanisms of action to outdo the limitations of the current methods of treatment and fight antiviral resistance. Research involves the identification of new drug targets to develop viral entry inhibitors or host-targeted therapies and the potential of broad-spectrum antiviral agents against multiple strains of influenza viruses, including avian influenza [78].

9.1. Emerging Trends in Treatment

- **Novel Antiviral Drugs:** Research is in progress on novel antiviral drugs with distinctive mechanisms of action for effective control of AIV infections. The targets in the viral replication cycle for these drugs offer a promise as good alternative agents to the available therapies [79].
- **Immunotherapies:** Mono-clonal antibodies against viral epitopes are developed for the effectiveness of virus neutralization and reduction in disease severity. Passive immunization is also being investigated for convalescent plasma from recovered cases [80].
- **Vaccine-Based Approaches**: New developments in vaccination approaches have focused on a method that will improve efficiency and increase the extent of protection from AIV strains. New platforms for vaccine development, like the recombinant protein vaccines, virus-like particles, and vectored vaccines, are increasing the possibilities for broadening a landscape of broadly protective vaccines, which can mediate strong immune responses [81].
- **Host-Directed Therapies:** Treatment intervention goes straight to the host factors, either in the viral replication cycle or in the host immune response. These treatments work through the modulation of host pathways to inhibit viral replication and the reduction of inflammation at the same time as increasing antiviral immunity, which would ameliorate the disease's severity and thus improve clinical outcomes [82].
- **Combination Drug Therapies:** Combination drug therapies involving multiple antiviral agents or combining antiviral drugs with immunomodulatory agents are being explored to enhance treatment efficacy and reduce the risk of antiviral resistance development. Synergistic interactions between different classes of antiviral drugs may provide broader coverage against AIV strains and improve patient outcomes [83].
- **Prevention and Control Strategies:** Prevention and control strategies for avian influenza (AI) encompass various measures aimed at reducing the risk of AI outbreaks, containing viral spread, and mitigating the impact of AI on poultry populations and public health [84].
- **Vaccination Strategies for AI in Poultry:** Vaccination plays a crucial role in preventing AI outbreaks in poultry. Vaccines are made either using inactivated or weakened AI viruses or recombinant viral proteins [81].

These vaccines induce protective immune Such immune responses in poultry reduce the severity of infection, viral shedding, and transmission. The efficacy of vaccination is dependent on several factors, including vaccine formulations, administration protocols, and matching vaccine strains with circulating AI virus subtypes. Routine monitoring of vaccination efficacy and updating vaccine formulation based on circulating AI virus strains are critical steps in maintaining the effectiveness of vaccination programs [85].

- **Biosecurity Measures:** There are some biosecurity measures to avoid outbreaks of AI in a poultry farm. Very tight control of the farm, observance of hygiene practices, avoiding contact between domestic poultry and wild birds, disinfection of equipment, vehicles, and personnel, and a reduction of contact points of manure are done to minimize the chances of viral transmission [29]. Essential elements in effective biosecurity measures include early implemented quarantine measures for newly introduced poultry, biosecurity surveillance for early detection presence of the virus, and observing the biosecurity protocols. Early Detection and Rapid Response Early detection of AI outbreaks is of utmost importance in the early implementation of control measures to prevent the further viral spread [86].
- **Early Detection and Rapid Response:** Active surveillance would include regular testing flocks of poultry populations, the search for clinical signs of AI, and laboratory diagnoses of the presence of AI virus. The rapid response would include the prompt quarantine of affected premises, the culling of infected birds, and the disinfection of infected areas. This would be facilitated through early detection and rapid response by the development of efficient reporting mechanisms, personnel training, and coordination between veterinary and public health authorities [87].

9.2. International Cooperation and Policy Frameworks:

AI control should require international cooperation since the disease spreads from one country to another. International organizations, which include the World Organization for Animal Health (OIE) and the Food and Agriculture Organization of the United Nations (FAO), provide coordination and information exchange between countries. AI control policy frameworks should have the formulation and establishment of national strategies on AI control, legislation of movements and trade of poultry, and agreements for international surveillance, reports, and response to AI outbreaks. Effective control of AIs on a global scale will require inter-country collaboration, and sharing of resources and expertise, but within the recommended international standards and guidelines [88].

9.3. Impact on Public Health and Economy:

- **Human cases of AI:** The impact of avian influenza on public health and the economy is multifaceted, involving human cases, economic losses in the poultry industry, and public health interventions to mitigate the risks of transmission [89].
- **Epidemiology:** Human cases of avian influenza have typically resulted from direct contact with infected poultry or contaminated environments. Influenza viruses have, however, been able to transmit from humans to humans, a relatively rare phenomenon but a potential threat for the onset of a pandemic. Cases are generally clustered in regions with close contact between humans and poultry [90].
- **Clinical Outcomes:** Clinical manifestations of AI in humans are varied and may include self-limited conjunctivitis or a mild respiratory illness and may progress to severe pneumonia and acute respiratory distress syndrome (ARDS). Death rates can be high, especially from highly pathogenic AI viruses such as H5N1, and have been reported to exceed 50% during some outbreaks [91].
- **Mortality Rates:** Mortality rates vary in human AI cases related to different viruses and their subtypes, virulence, and important host and healthcare factors. Highly pathogenic AI viruses cause much more severe disease and higher mortality than low-pathogenic strains.
- **Economic Impact on the Poultry Industry and Global Trade:** Outbreaks of AI have significant economic impacts on the poultry industry because of the direct losses due to mortality in infected birds and the indirect losses due to trade restrictions, closure of markets, and reduced consumer confidence [92].
- **Direct Losses:** An outbreak of highly pathogenic AI often results in mass culling of poultry flocks in a bid to halt the spread of the disease, and this causes massive economic loss to the producers [93].
- **Indirect Losses:** Embargoes by the importing countries to prevent the spread of the AI virus may grind poultry trade to a halt globally, shutting down markets with lower demand and, subsequently, prices of poultry products. These disruptions may be very long-lasting for the poultry industry and the livelihoods that revolve around poultry production and trade [94].
- **Public Health Interventions and Measures to Mitigate AI Transmission Risks:** Public health interventions that are designed to reduce AI transmission risks in poultry populations and the zoonotic risks associated with human exposure [95].

9.4. These measures include:

- **Surveillance and Early Detection**: Surveillance of poultry populations with a view to early detection of infection with AI and implementation of rapid response measures to contain outbreaks [96].
- **Vaccination Programs:** Vaccinating poultry against AI to reduce viral circulation and transmission [85].

- **Biosecurity Measures:** Implementation of highly stringent biosecurity measures at poultry farms to prevent the introduction and the spread of AI viruses [97].
- **Public awareness campaigns:** This shall help create awareness with the general public, poultry workers, and healthcare providers given the risk presented by AI, ways of prevention, and measures of early detection [98].
- **International collaboration:** This shall enable information sharing, research collaboration, and joint action in the event of an AI outbreak with the involvement of key international organizations working in the field such as WHO and OIE [98].
- **One Health Perspective on Avian Influenza:** Avian influenza is a striking example of the interrelation between human, animal, and environmental health [99]. The virus circulates naturally in wild birds, domestic poultry, and, at times, humans, thereby suggesting a complex interface between these sectors. Diverse activities, particularly in livestock keeping such as poultry farming, wildlife trade, and land use change, can impact avian influenza transmission dynamics with effects on animal and human populations. Environmental factors, including climate change and habitat destruction, can affect the distribution and migration patterns of wild bird populations, potentially altering the spread of avian influenza viruses [100].
- **Importance of Interdisciplinary Collaboration:** Effective control and prevention of avian influenza require interdisciplinary collaboration between human health, animal health, and environmental sectors. This involves cooperation between veterinarians, public health professionals, ecologists, and policymakers [100].
- **Integrated Surveillance Systems**: Integrated surveillance systems that monitor AI viruses in animals, humans, and the environment facilitate early detection of outbreaks, prompt response, and informed decision-making. Shared data, information-sharing platforms, and joint research efforts enhance understanding of AI transmission dynamics and support evidence-based interventions across sectors [101].

10. Research Gaps and Future Directions

- **Identification of Gaps in Current Knowledge**: Understanding the mechanisms underlying AI transmission between animals and humans remains incomplete. Knowledge gaps exist regarding the role of environmental factors, viral genetics, and host susceptibility in AI transmission dynamics [102]. Limited information is available on the efficacy of control measures, such as vaccination strategies and biosecurity measures, in different ecological and socio-economic contexts. The impact of emerging AI virus strains, including reassorting and novel subtypes, on human and animal health requires further investigation.
- **Recommendations for Future Research Priorities**: [103] Future research efforts should focus on improving surveillance systems to enhance early detection and response capabilities, particularly in regions where AI is endemic or where zoonotic transmission poses a significant risk. Enhanced genomic surveillance and phylogenetic analysis can provide insights into the evolution and spread of AI viruses, informing the development of targeted control measures and vaccine strategies. Interdisciplinary studies that integrate epidemiological, ecological, and socio-economic factors are needed to address the complex drivers of AI transmission and develop holistic approaches to AI prevention and control [104].

11. Conclusion

In conclusion, this review underscores the essential role of effective surveillance, biosecurity measures, and international collaboration in mitigating avian influenza risks and safeguarding both animal and human health. From a biochemical perspective, understanding the molecular mechanisms of avian influenza viruses—such as their protein structures, replication processes, and interactions with host cellular machinery—can enhance our ability to develop targeted vaccines and antiviral treatments. The document highlights the critical interplay between human, animal, and environmental health within the framework of avian influenza and stresses the need for ongoing biochemical research to uncover the intricacies of viral pathogenesis and resistance mechanisms. Interdisciplinary collaboration, integrating biochemistry with epidemiology and public health, is crucial for bridging knowledge gaps and formulating comprehensive strategies for the prevention and control of avian influenza.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Charostad J, Rukerd MRZ, Mahmoudvand S, Bashash D, Hashemi SMA, Nakhaie M, et al. A comprehensive review of highly pathogenic avian influenza (HPAI) H5N1: An imminent threat at doorstep. Travel Medicine and Infectious Disease. 2023:102638.

[2] Chowdhury S, Hossain ME, Ghosh PK, Ghosh S, Hossain MB, Beard C, et al. The pattern of highly pathogenic avian influenza H5N1 outbreaks in South Asia. Tropical Medicine and Infectious Disease. 2019;4(4):138.

[3] Su S, Bi Y, Wong G, Gray GC, Gao GF, Li S. Epidemiology, evolution, and recent outbreaks of avian influenza virus in China. Journal of virology. 2015;89(17):8671-6.

[4] Gao HaiNv GH, Lu HongZhou LH, Cao Bin CB, Du Bin DB, Shang Hong SH, Gan JianHe GJ, et al. Clinical findings in 111 cases of influenza A (H7N9) virus infection. 2013.

[5] Capua I, Alexander D. Avian influenza infection in birds: a challenge and opportunity for the poultry veterinarian. Poultry science. 2009;88(4):842-6.

[6] Alexander DJ. An overview of the epidemiology of avian influenza. Vaccine. 2007;25(30):5637-44.

[7] Tiensin T, Chaitaweesub P, Songserm T, Chaisingh A, Hoonsuwan W, Buranathai C, et al. Highly pathogenic avian influenza H5N1, Thailand, 2004. Emerging infectious diseases. 2005;11(11):1664.

[8] Alexander D. Should we change the definition of avian influenza for eradication purposes? Avian diseases. 2003;47(s3):976-81.

[9] Yang R, Sun H, Gao F, Luo K, Huang Z, Tong Q, et al. Human infection of avian influenza A H3N8 virus and the viral origins: a descriptive study. The Lancet Microbe. 2022;3(11):e824-e34.

[10] Bao P, Liu Y, Zhang X, Fan H, Zhao J, Mu M, et al. Human infection with a reassortment avian influenza A H3N8 virus: an epidemiological investigation study. Nature Communications. 2022;13(1):6817.

[11] Pantin-Jackwood MJ, Swayne DE. Pathobiology of Asian highly pathogenic avian influenza H5N1 virus infections in ducks. Avian Diseases. 2007;51(s1):250-9.

[12] Capua I, Marangon S. Control of avian influenza in poultry. Emerging Infectious Diseases. 2006;12(9):1319.

[13] Halvorson DA. The control of H5 or H7 mildly pathogenic avian influenza: a role for inactivated vaccine. Avian Pathology. 2002;31(1):5-12.

[14] Abdelwhab E, Hafez HM. An overview of the epidemic of highly pathogenic H5N1 avian influenza virus in Egypt: epidemiology and control challenges. Epidemiology & Infection. 2011;139(5):647-57.

[15] Kim Y-I, Si Y-J, Kwon H-I, Kim E-H, Park S-J, Robles NJ, et al. Pathogenicity and genetic characterisation of a novel reassortant, highly pathogenic avian influenza (HPAI) H5N6 virus isolated in Korea, 2017. Eurosurveillance. 2018;23(7):18-00045.

[16] Subedi D, Farhan MHR, Niraula A, Shrestha P, Chandran D, Acharya KP, et al. Avian Influenza in Low and Middle-Income Countries (LMICs): Outbreaks, Vaccination Challenges and Economic Impact. Pakistan Veterinary Journal. 2024;44(1).

[17] Peng Y, Xie Z-x, Liu J-b, Pang Y-s, Deng X-w, Xie Z-q, et al. Epidemiological surveillance of low pathogenic avian influenza virus (LPAIV) from poultry in Guangxi Province, Southern China. PLoS One. 2013;8(10):e77132.

[18] Subbarao* K, Katz J. Avian influenza viruses infecting humans. Cellular and Molecular Life Sciences CMLS. 2000;57:1770-84.

[19] Capua I, Munoz O. Emergence of influenza viruses with zoonotic potential: open issues which need to be addressed. A review. Veterinary microbiology. 2013;165(1-2):7-12.

[20] Swayne DE, Perdue ML, Beck JR, Garcia M, Suarez DL. Vaccines protect chickens against H5 highly pathogenic avian influenza in the face of genetic changes in field viruses over multiple years. Veterinary microbiology. 2000;74(1-2):165-72.

[21] Qiao C-l, Yu K-z, Jiang Y-p, Jia Y-q, Tian G-b, Liu M, et al. Protection of chickens against highly lethal H5N1 and H7N1 avian influenza viruses with a recombinant fowlpox virus co-expressing H5 haemagglutinin and N1 neuraminidase genes. Avian pathology. 2003;32(1):25-31.

[22] Swayne DE, Garcia M, Beck JR, Kinney N, Suarez DL. Protection against diverse highly pathogenic H5 avian influenza viruses in chickens immunized with a recombinant fowlpox vaccine containing an H5 avian influenza hemagglutinin gene insert. Vaccine. 2000;18(11-12):1088-95.

[23] Aamir UB, Naeem K, Ahmed Z, Obert CA, Franks J, Krauss S, et al. Zoonotic potential of highly pathogenic avian H7N3 influenza viruses from Pakistan. Virology. 2009;390(2):212-20.

[24] Goneau L, Mehta K, Wong J, L'Huillier A, Gubbay J. Zoonotic influenza and human health—part 1: virology and epidemiology of zoonotic influenzas. Current infectious disease reports. 2018;20:1-12.

[25] Aiello R, Beato MS, Mancin M, Rigoni M, Tejeda AR, Maniero S, et al. Differences in the detection of highly pathogenic avian influenza H5N1 virus in feather samples from 4-week-old and 24-week-old infected Pekin ducks (Anas platyrhynchos var. domestica). Veterinary microbiology. 2013;165(3-4):443-7.

[26] Azeem S, Guo B, Sato Y, Gauger PC, Wolc A, Yoon K-J. Utility of Feathers for Avian Influenza Virus Detection in Commercial Poultry. Pathogens. 2023;12(12):1425.

[27] Krauss S, Obert CA, Franks J, Walker D, Jones K, Seiler P, et al. Influenza in migratory birds and evidence of limited intercontinental virus exchange. PLoS pathogens. 2007;3(11):e167.

[28] Moyen N, Hoque MA, Mahmud R, Hasan M, Sarkar S, Biswas PK, et al. Avian influenza transmission risk along live poultry trading networks in Bangladesh. Scientific reports. 2021;11(1):19962.

[29] Guinat C, Comin A, Kratzer G, Durand B, Delesalle L, Delpont M, et al. Biosecurity risk factors for highly pathogenic avian influenza (H5N8) virus infection in duck farms, France. Transboundary and emerging diseases. 2020;67(6):2961-70.

[30] van der Kolk JH. Role for migratory domestic poultry and/or wild birds in the global spread of avian influenza? : Taylor & Francis; 2019. p. 161-7.

[31] Joseph U, Vijaykrishna D, Smith GJ, Su YC. Adaptive evolution during the establishment of European avian-like H 1 N 1 influenza A virus in swine. Evolutionary Applications. 2018;11(4):534-46.

[32] Yee KS, Carpenter TE, Cardona CJ. Epidemiology of H5N1 avian influenza. Comparative immunology, microbiology and infectious diseases. 2009;32(4):325-40.

[33] Swayne DE, Sims LD. Avian influenza. Veterinary vaccines: Principles and applications. 2021:229-51.

[34] Alqazlan N, Astill J, Raj S, Sharif S. Strategies for enhancing immunity against avian influenza virus in chickens: A review. Avian Pathology. 2022;51(3):211-35.

[35] Huang P, Sun L, Li J, Wu Q, Rezaei N, Jiang S, et al. Potential cross-species transmission of highly pathogenic avian influenza H5 subtype (HPAI H5) viruses to humans calls for the development of H5-specific and universal influenza vaccines. Cell discovery. 2023;9(1):58.

[36] Siegers JY, Ferreri L, Eggink D, Veldhuis Kroeze EJ, Te Velthuis AJ, van de Bildt M, et al. Evolution of highly pathogenic H5N1 influenza A virus in the central nervous system of ferrets. PLoS pathogens. 2023;19(3):e1011214.

[37] Veldhuis Kroeze E, Bauer L, Caliendo V, van Riel D. In vivo models to study the pathogenesis of extra-respiratory complications of influenza A virus infection. Viruses. 2021;13(5):848.

[38] Bauer L, Benavides FF, Kroeze EJV, de Wit E, van Riel D. The neuropathogenesis of highly pathogenic avian influenza H5Nx viruses in mammalian species including humans. Trends in Neurosciences. 2023.

[39] Eggink D, Spronken M, van der Woude R, Buzink J, Broszeit F, McBride R, et al. Phenotypic effects of substitutions within the receptor binding site of highly pathogenic avian influenza H5N1 virus observed during human infection. Journal of virology. 2020;94(13):10.1128/jvi. 00195-20.

[40] Bougon J, Kadijk E, Gallot-Lavallee L, Curtis B, Landers M, Archibald J, et al. Influenza A virus NS1 effector domain is required for PA-X mediated host shutoff. bioRxiv. 2023:2023.10. 02.560421.

[41] Vera JC, Sun J, Lin YT, Drnevich J, Ke R, Brooke CB. A common pattern of influenza A virus single cell gene expression heterogeneity governs the innate antiviral response to infection. bioRxiv. 2019:858373.

[42] Muñoz-Moreno R, Martínez-Romero C, García-Sastre A. Induction and evasion of type-I interferon responses during influenza A virus infection. Cold Spring Harbor Perspectives in Medicine. 2021;11(10):a038414.

[43] Yang Q, Elz AE, Panis M, Liu T, Nilsson-Payant BE, Blanco-Melo D. Modulation of Influenza A virus NS1 expression reveals prioritization of host response antagonism at single-cell resolution. Frontiers in Microbiology. 2023;14:1267078.

[44] Germeraad EA, Elbers AR, De Bruijn ND, Heutink R, Van Voorst W, Hakze-Van Der Honing R, et al. Detection of low pathogenic avian influenza virus subtype H10N7 in poultry and environmental water samples during a clinical outbreak in commercial free-range layers, Netherlands 2017. Frontiers in Veterinary Science. 2020;7:237.

[45] Yuen K, Wong S. Human infection by avian influenza A H5N1. Hong Kong Medical Journal. 2005.

[46] To KK, Wong SS, Li IW, Hung IF, Tse H, Woo PC, et al. Concurrent comparison of epidemiology, clinical presentation and outcome between adult patients suffering from the pandemic influenza A (H1N1) 2009 virus and the seasonal influenza A virus infection. Postgraduate medical journal. 2010;86(1019):515-21.

[47] Korteweg C, Gu J. Pathology, molecular biology, and pathogenesis of avian influenza A (H5N1) infection in humans. The American journal of pathology. 2008;172(5):1155-70.

[48] Lycett SJ, Duchatel F, Digard P. A brief history of bird flu. Philosophical Transactions of the Royal Society B. 2019;374(1775):20180257.

[49] Naguib MM, Verhagen JH, Mostafa A, Wille M, Li R, Graaf A, et al. Global patterns of avian influenza A (H7): virus evolution and zoonotic threats. FEMS Microbiology Reviews. 2019;43(6):608-21.

[50] Suarez DL, Miller PJ, Koch G, Mundt E, Rautenschlein S. Newcastle disease, other avian paramyxoviruses, and avian metapneumovirus infections. Diseases of poultry. 2020:109-66.

[51] Shahzad R, Irshad S, Javaid A, Yaqoob T. Mutational analysis of neuraminidase of avian influenza virus H9N2 indicating the cause of hyper pathogenicity in poultry. Pakistan Veterinary Journal. 2020;40(2).

[52] Aslan C. Avian influenza; virus characteristics, clinical symptoms and antiviral drugs. 2022.

[53] Annand EJ, High H, Wong FY, Phommachanh P, Chanthavisouk C, Happold J, et al. Detection of highly pathogenic avian influenza in Sekong Province Lao PDR 2018—Potential for improved surveillance and management in endemic regions. Transboundary and Emerging Diseases. 2021;68(1):168-82.

[54] An S-H, Kim N-Y, Heo G-B, Kang Y-M, Lee Y-J, Lee K-N. Development and evaluation of a multiplex real-time RT-PCR assay for simultaneous detection of H5, H7, and H9 subtype avian influenza viruses. Journal of Virological Methods. 2024:114942.

[55] Al-Bawi FHK, Hussein AA. STUDY OF THE VIRAL PHYLOGENIC DIAGNOSIS OF AVIAN INFLUENZA DISEASE IN BROILER CHICKENS IN BABYLON PROVINCE, IRAQ. Plant Archives. 2020;20(1):2448-52.

[56] Poen MJ, Venkatesh D, Bestebroer TM, Vuong O, Scheuer RD, Oude Munnink BB, et al. Co-circulation of genetically distinct highly pathogenic avian influenza A clade 2.3. 4.4 (H5N6) viruses in wild waterfowl and poultry in Europe and East Asia, 2017–18. Virus Evolution. 2019;5(1):vez004.

[57] El-Khantour A, Soulaymani A, Salek M, Maltouf AF, Darkaoui S, El-Mellouli F, et al. Molecular characterization of the hemagglutinin gene of H9N2 avian influenza viruses isolated from broiler flocks in Morocco from 2016 to 2018. 2020.

[58] Le KT, Okamatsu M, Nguyen LT, Matsuno K, Chu D-H, Tien TN, et al. Genetic and antigenic characterization of the first H7N7 low pathogenic avian influenza viruses isolated in Vietnam. Infection, genetics and evolution. 2020;78:104117.

[59] Barberis A, Boudaoud A, Gorrill A, Loupias J, Ghram A, Lachheb J, et al. Full-length genome sequences of the first H9N2 avian influenza viruses isolated in the Northeast of Algeria. Virology journal. 2020;17:1-16.

[60] Pasick J. Advances in the molecular based techniques for the diagnosis and characterization of avian influenza virus infections. Transboundary and emerging diseases. 2008;55(8):329-38.

[61] Germeraad EA, Sanders P, Hagenaars TJ, de Jong MC, Beerens N, Gonzales JL. Virus shedding of avian influenza in poultry: a systematic review and meta-analysis. Viruses. 2019;11(9):812.

[62] Verdugo C, El Masry I, Makonnen Y, Hannah H, Unger F, Soliman M, et al. Sensitivity and specificity estimation for the clinical diagnosis of highly pathogenic avian influenza in the Egyptian participatory disease surveillance program. Avian diseases. 2016;60(4):805-9.

[63] Spackman E, Suarez DL, Senne DA. Avian influenza diagnostics and surveillance methods. Avian influenza. 2008;1.

[64] Spackman E, Suarez D. Avian influenza virus: Humana Press Totowa, NJ, USA:; 2008.

[65] Umar S, Guerin JL, Ducatez MF. Low pathogenic avian influenza and coinfecting pathogens: a review of experimental infections in avian models. Avian Diseases. 2017;61(1):3-15.

[66] An L, Liu R, Tang W, Wu J-G, Chen X. Screening and identification of inhibitors against influenza A virus from a US drug collection of 1280 drugs. Antiviral research. 2014;109:54-63.

[67] Mahmoud EA. Hemato-biochemical and pathological changes on avian influenza in naturally infected domestic ducks in Egypt. Veterinary world. 2015;8(10):1177.

[68] Watanabe Y, Ibrahim MS, Suzuki Y, Ikuta K. The changing nature of avian influenza A virus (H5N1). Trends in microbiology. 2012;20(1):11-20.

[69] Ross KA, Huntimer LM, Vela Ramirez JE, Adams JR, Carpenter SL, Kohut ML, et al. Vaccine technologies against avian influenza: current approaches and new directions. Journal of biomedical nanotechnology. 2014;10(9):2261-94.

[70] Conrad PA, Mazet JA, Clifford D, Scott C, Wilkes M. Evolution of a transdisciplinary "One Medicine–One Health" approach to global health education at the University of California, Davis. Preventive Veterinary Medicine. 2009;92(4):268-74.

[71] Khetmalis RS, Madhwal A, Supriya K, Pradhan S, Reddy BV, Bera B, et al. Influenza a viruses: Future challenges and opportunities in relation to therapeutics. Indian Journal of Comparative Microbiology, Immunology and Infectious Diseases. 2020;41(2):86-97.

[72] Beigel JH, Hayden FG. Influenza therapeutics in clinical practice—challenges and recent advances. Cold Spring Harbor Perspectives in Medicine. 2021;11(4):a038463.

[73] Bialy D, Shelton H. Functional neuraminidase inhibitor resistance motifs in avian influenza A (H5Nx) viruses. Antiviral Research. 2020;182:104886.

[74] Takashita E. Influenza polymerase inhibitors: mechanisms of action and resistance. Cold Spring Harbor perspectives in medicine. 2021;11(5):a038687.

[75] Palomba E, Castelli V, Renisi G, Bandera A, Lombardi A, Gori A, editors. Antiviral treatments for influenza. Seminars in Respiratory and Critical Care Medicine; 2021: Thieme Medical Publishers, Inc.

[76] Wang Y, Fan G, Salam A, Horby P, Hayden FG, Chen C, et al. Comparative effectiveness of combined favipiravir and oseltamivir therapy versus oseltamivir monotherapy in critically ill patients with influenza virus infection. The Journal of infectious diseases. 2020;221(10):1688-98.

[77] Panyako PM, Lichoti JK, Ommeh SC. Antimicrobial drug resistance in poultry pathogens: Challenges and opportunities. Journal of Agriculture, Science and Technology. 2022;21(1):62-82.

[78] Sarker A, Gu Z, Mao L, Ge Y, Hou D, Fang J, et al. Influenza-existing drugs and treatment prospects. European Journal of Medicinal Chemistry. 2022;232:114189.

[79] Hayden F. Developing new antiviral agents for influenza treatment: what does the future hold? Clinical Infectious Diseases. 2009;48(Supplement_1):S3-S13.

[80] Lukosaityte D. Development of antibody therapeutic approaches for poultry diseases using avian influenza as a disease model. 2022.

[81] Ninyio NN, Ho KL, Omar AR, Tan WS, Iqbal M, Mariatulqabtiah AR. Virus-like particle vaccines: A prospective panacea against an avian influenza panzootic. Vaccines. 2020;8(4):694.

[82] Kumar N, Sharma S, Kumar R, Tripathi BN, Barua S, Ly H, et al. Host-directed antiviral therapy. Clinical microbiology reviews. 2020;33(3):10.1128/cmr. 00168-19.

[83] Batool S, Chokkakula S, Song M-S. Influenza treatment: limitations of antiviral therapy and advantages of drug combination therapy. Microorganisms. 2023;11(1):183.

[84] Abbas G, Yu J, Li G. Novel and alternative therapeutic strategies for controlling avian viral infectious diseases: Focus on infectious bronchitis and avian influenza. Frontiers in Veterinary Science. 2022;9:933274.

[85] Dey P, Ahuja A, Panwar J, Choudhary P, Rani S, Kaur M, et al. Immune control of avian influenza virus infection and its vaccine development. Vaccines. 2023;11(3):593.

[86] Oladipo FO, Bello OG, Daudu AK, Kayode AO, Kareem OW, Olorunfemi OD, et al. Adoption of bio-security measures against avian-influenza outbreaks among poultry farmers in Jigawa State, Nigeria. Journal of Agricultural Extension. 2020;24(1):85-94.

[87] Verhagen JH, Fouchier RA, Lewis N. Highly pathogenic avian influenza viruses at the wild–domestic bird interface in Europe: Future directions for research and surveillance. Viruses. 2021;13(2):212.

[88] Goldizen FC. From SARS to Avian influenza: The role of international factors in China's approach to infectious disease control. Annals of global health. 2016;82(1):180-8.

[89] Gashaw M. A review on avian influenza and its economic and public health impact. Int J Vet Sci Technol. 2020;4(1):15-27.

[90] Perdue ML, Swayne DE. Public health risk from avian influenza viruses. Avian diseases. 2005;49(3):317-27.

[91] Dudley JP. Public health and epidemiological considerations for avian influenza risk mapping and risk assessment. Ecology and Society. 2008;13(2).

[92] Yu H, Cowling BJ, Feng L, Lau EH, Liao Q, Tsang TK, et al. Human infection with avian influenza A H7N9 virus: an assessment of clinical severity. The Lancet. 2013;382(9887):138-45.

[93] Akunzule A, Koney E, Tiongco M. Economic impact assessment of highly pathogenic avian influenza on the poultry industry in Ghana. World's Poultry Science Journal. 2009;65(3):517-28.

[94] Djunaidi H, Djunaidi AC. The economic impacts of avian influenza on world poultry trade and the US poultry industry: a spatial equilibrium analysis. Journal of Agricultural and Applied Economics. 2007;39(2):313-23.

[95] You L, Diao X. Assessing the potential impact of avian influenza on poultry in West Africa: a spatial equilibrium analysis. Journal of Agricultural Economics. 2007;58(2):348-67.

[96] Gonzales J, Boender G, Elbers A, Stegeman J, de Koeijer A. Risk based surveillance for early detection of low pathogenic avian influenza outbreaks in layer chickens. Preventive veterinary medicine. 2014;117(1):251-9.

[97] Ssematimba A, Hagenaars T, De Wit J, Ruiterkamp F, Fabri T, Stegeman J, et al. Avian influenza transmission risks: analysis of biosecurity measures and contact structure in Dutch poultry farming. Preventive veterinary medicine. 2013;109(1-2):106-15.

[98] Barennes H, Harimanana AN, Lorvongseng S, Ongkhammy S, Chu C. Paradoxical risk perception and behaviours related to Avian Flu outbreak and education campaign, Laos. BMC Infectious Diseases. 2010;10:1-7.

[99] Ryu S, Kim C-K, Kim K, Woo SH, Chun BC. Serosurveillance of avian influenza A/H5N6 virus infection in poultry farmers, Gyeonggi Province, Republic of Korea, 2016–2017. International Journal of Infectious Diseases. 2018;75:49-51.

[100] Wedari NLPH, Sukrama IDM, Budayanti NNS, Sindhughosa DA, Prabawa IPY, Manuaba IBAP. One Health concept and role of animal reservoir in avian influenza: a literature review. Bali Medical Journal. 2021;10(2):515-20.

[101] Okello AL. Beyond avian influenza: policy considerations for the implementation of a “one health” approach in developing countries. 2013.

[102] Klaassen M, Hoye BJ, Roshier DA. Identifying crucial gaps in our knowledge of the life-history of avian influenza viruses–an Australian perspective. Emu. 2011;111(2):103-12.

[103] Auewarakul P, Hanchaoworakul W, Ungchusak K. Institutional responses to avian influenza in Thailand: Control of outbreaks in poultry and preparedness in the case of human-to-human transmission. Anthropology & Medicine. 2008;15(1):61-7.

[104] He J, Kam Y-W. Insights from Avian Influenza: A Review of Its Multifaceted Nature and Future Pandemic Preparedness. Viruses. 2024;16(3):458.