REVIEW

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CLINICAL AND MUTAGENIC SPECTRUM OF HIGHLY PATHOGENIC AVIAN INFLUENZA A(H5N1) CLADE 2.3.4.4B: A NARRATIVE REVIEW

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Abstract. *Avian influenza A(H5N1) is a highly pathogenic virus causing significant outbreaks in birds and sporadic human infections since 1997. The virus is classified into various clades based on genetic characteristics, and recently, concerns have been raised over the risk of clade 2.3.4.4b becoming widespread and infecting humans. Since 1997, more than 1,000 infections with highly pathogenic avian influenza A(H5N1) virus among humans have been reported globally. Given ongoing A(H5N1) outbreaks in animals, understanding the frequency of A(H5N1) virus infections among asymptomatic persons can inform public health risk assessments and infection prevention guidance. We performed a literature search focusing on reported infections among humans with Highly Pathogenic Avian Influenza (HPAI). This study was conceived as a narrative review focusing on clade 2.3.4.4b H5N1, but was expanded to all reported H5Nx and other zoonotic subtypes (H5N6, H6N1, H7N9, H10N3) when clade-specific data were sparse. Although not a formal systematic review, the search, screening, and appraisal followed the PRISMA 2020 Checklist for search reporting where applicable.*

Key words: *avian influenza A(H5N1), global spread, pathogenesis, mortality*

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INTRODUCTION

Avian influenza A(H5N1) is a highly pathogenic virus causing significant outbreaks in birds and sporadic human infections since 1997 [1]. The virus is classified into various clades based on genetic characteristics, and recently, concerns have been raised over the risk of clade 2.3.4.4b becoming widespread and infecting humans.

Highly pathogenic avian influenza (HPAI) viruses of clade 2.3.4.4 first drew global attention in 2014 because of their remarkable capacity for reassortment and rapid spread. This led to the emergence of multiple A(H5Nx) subtypes, including A(H5N2), A(H5N5), A(H5N6), and A(H5N8) – each characterized by distinct gene constellations and associated with extensive outbreaks across several continents. While these A(H5Nx) viruses have historically been largely restricted to wild and domestic birds, clade 2.3.4.4b A(H5N1) viruses have recently exhibited an increased ability to infect mammalian hosts [2].

The broad geographic distribution of A(H5N1) viruses, now detected in birds on five continents, combined with their documented spillover into a growing number of mammalian species — including humans — poses an escalating global public health concern. Although frequent human infections and sustained human-to-human transmission have not been observed, the increasing adaptability of clade 2.3.4.4b H5 viruses to mammals, together with the presence of mammalian adaptation markers in many mammalian isolates, underscores the urgency of strengthening surveillance efforts. Enhanced monitoring of the genetic evolution and pathobiological properties of these viruses is essential to identify changes that could enable efficient replication in the human respiratory tract and facilitate onward transmission, thereby heightening the risk of a future pandemic.

We performed a literature search focusing on reported infections among humans with Highly Pathogenic Avian Influenza (HPAI). This study was conceived as a narrative review focusing on clade 2.3.4.4b H5N1, but was expanded to all reported H5Nx and other zoonotic subtypes (H5N6, H6N1, H7N9, H10N3) when clade-specific data were sparse. Although not a formal systematic review, the search, screening, and appraisal followed the PRISMA 2020 Checklist for search reporting where applicable. The search was performed in PubMed and Web of Science from 1 January 1997 to 30 April 2025 using the following terms (adapted per database): ("avian influenza" OR "highly pathogenic avian influenza" OR HPAI) AND ("H5N1" OR "clade 2.3.4.4b") AND (human* OR patient* OR case* OR outbreak* OR infection). No language limits were applied. Non-English articles were screened by machine translation. To capture grey literature and real-time surveillance, we searched the World Health Organization (WHO) Disease Outbreak News, and rapid risk assessments and reports of the Centers for Disease Control and Prevention (CDC) and the European Centre for Disease Prevention and Control (ECDC). Reference lists of all eligible papers and key reviews were cross-checked to identify additional reports. Each article or report was screened by at least one reviewer. We included reports of laboratory-confirmed or WHO/ECDC-probable human infections with any HPAI subtype, accepting case series (≥ 10 patients), single-case reports describing distinctive phenotypes, and WHO surveillance summaries for mortality, while excluding animal, molecular, duplicate, or abstract-only studies. Symptom frequencies and case-fatality rates were summarised descriptively, and notable single cases were integrated narratively to illustrate atypical presentations.

Epidemiology and Global Spread

Since its emergence in 2020, highly pathogenic avian influenza (HPAI) A(H5N1) clade 2.3.4.4b has exhibited an unprecedented global spread, affecting avian and mammalian species across multiple continents [3]. In Europe, clade 2.3.4.4b became predominant by late 2020, leading to outbreaks in wild birds and poultry [4]. The virus's persistence in wild bird populations has facilitated its continuous circulation and reassortment with local low-pathogenic avian influenza viruses [1, 5]. In North America, the virus was first detected in 2021; subsequent outbreaks have affected wild birds, poultry, and various mammalian species, including seals and foxes. In 2024, H5N1 was detected in dairy cattle in the United States, marking the first such occurrence and raising concerns about cross-species transmission. H5N1 reached South America for the first reported case in late 2022, leading to high mortality in wild bird populations and marine mammals. In 2023, significant mortality among sea lions and elephant seals was reported along the coasts of Peru, Chile, and Argentina. Finally, in 2023, H5N1 was detected in the Antarctic region for the first time, with cases confirmed in brown skuas and other seabirds. This development raises concerns about the virus's potential impact on previously unexposed wildlife and the increasing risk of pandemic spread to humans [6].

Transmission and Pathogenesis

At the end of 2021, an H5N1 virus belonging to clade 2.3.4.4b was detected in North America [7]. This lineage has demonstrated an exceptional ability to infect a broad spectrum of avian species, as well as numerous mammalian hosts, including both marine and terrestrial mammals and, in rare cases, humans [8]. In early 2024, the first human infection associated with the bovine-adapted H5N1 virus was reported in Texas.

The rapid and extensive spread of clade 2.3.4.4b is largely attributed to migratory birds, which serve as natural reservoirs and facilitate long-distance dissemination of the virus [7]. Genetic changes supporting viral adaptability have broadened its host range, enabling infection across multiple mammalian species [9]. Its increasing presence in domestic animals – particularly cats, poultry, and cattle – further elevates the risk of human exposure, especially among individuals in direct contact with infected animals [10]. Although sustained human-to-human transmission has not been observed, the ongoing evolution of this virus underscores the need for robust surveillance and preparedness to mitigate potential pandemic threats.

A major barrier to efficient transmission of avian influenza viruses to humans lies in the receptor specificity of hemagglutinin (HA), which binds to sialic acid receptors [11, 12]. Avian influenza HA preferentially recognizes "avian" receptors featuring sialic acid in an α2-3 linkage (Neu5Acα2-3Gal), whereas human influenza viruses primarily bind to "human" receptors with an α2-6 linkage (Neu5Acα2-6Gal), which are abundantly expressed in the upper respiratory tract [12]. Acquisition of human-type receptor specificity is therefore considered a prerequisite for human-to-human transmission and is a central criterion used by the CDC in evaluating the pandemic potential of emerging animal influenza strains [11].

Sporadic human infections with H5 viruses have heightened global concern that these viruses may evolve the ability to alter their receptor-binding preferences. Over the past decade, studies have shown that amino acid substitutions, such as Gln226Leu and Gly228Ser in H5 HA, can promote binding to human-type receptors while retaining partial affinity for avian receptors [13]. Ferret aerosol transmission studies further indicate that additional mutations, when combined with Leu226 or Ser228, can enhance human receptor binding and reduce avian receptor binding [13, 14]. However, none of the tested variants have demonstrated a complete shift to exclusive human receptor specificity.

MATERIALS AND METHODS

Receptor specificity of H5 HA and mutants

Previous studies investigating receptor specificity and transmission of H5N1 strains have shown that multiple HA mutations are required to shift receptor preference toward the human type [15]. In one study, the mutation Asn224Lys occurred together with Gln226Leu [14]. When Asn224Lys was introduced into the Texas HA in combination with either Leu226 alone or the double mutation Leu226/Ser228, binding to elongated linear α2-6-sialosides (measured by SPR) and to both elongated linear and biantennary N-glycosidically linked α2-6-sialosides (measured by ELISA) increased, with the strongest effect observed for the Lys224/Leu226 combination. In contrast, the double mutant Leu226/Ser228 displayed negligible binding to α2-3-sialosides, whereas the triple mutant Lys224/Leu226/Ser228 retained weak α2-3 binding.

Additional combinations of Leu226 with previously reported mutations – such as Asn193Thr, Asn193Lys, Arg227Asn, Arg227Ser, and Arg227Gln – had also been suggested to enhance human-type receptor binding in H5 HA [16]. However, when these mutations were introduced together with Leu226 in the Texas HA background, none produced a notable increase in α2-6 binding. Instead, they resulted in a complete loss of α2-3 binding. Collectively, these findings indicate that substitution of Gln226 with Leu226 is a key determinant for initiating a shift in receptor preference from avian to human type in the Texas H5 HA.

A switch from avian to human receptor specificity is regarded as a major risk factor for increased transmissibility in humans [12]. Thus, the observation that a single mutation – Gln226Leu – can alter receptor specificity in the Texas H5 HA is concerning. The respiratory and mammary gland epithelium of cattle predominantly expresses avian receptors and only small amounts of human receptors, which imposes relatively weak selective pressure for human-type receptor adaptation. In contrast, infection of dairy workers, who express abundant human-type receptors, may create stronger selective pressure favoring mutations that enhance human receptor specificity.

Additionally, co-infection of humans with bovine H5N1 and seasonal influenza viruses during the flu season could provide an opportunity for reassortment, potentially generating hybrid viruses with improved adaptation to human hosts [11, 12].

Spectrum of Human Infection

The clinical spectrum of H5N1 infection in humans ranges from mild symptoms to severe, sometimes fatal, disease. The case definition is presented in Table 1 [17, 18].

Human clinical experience with highly pathogenic avian influenza (HPAI) A(H5) clade 2.3.4.4b is still limited – only 20 documented infections between 2022 and early 2025 – but the published case series show a broad clinical spectrum.

Across reported cases, incubation was short (median one day, range 1-8 days), and illness tended either to remain mild or to evolve quickly into severe, sometimes fatal, lower-respiratory or neuroinvasive disease [19]. Host factors, such as chronic lung disease, cancer, or concurrent viral infection, appear to increase severity, whereas otherwise healthy exposed workers usually experience self-limited conjunctivitis.

The largest clusters have come from the United States. Four Texas dairy workers and nine poultry depopulation workers in Colorado all acquired genotype B3.13 viruses within the 2.3.4.4b clade [19, 20]. Every patient in these two outbreaks developed acute conjunctivitis with profuse tearing and, in some cases, subconjunctival haemorrhage. Systemic or respiratory complaints were absent or mild – only six

Table 1. Case Definitions for Human Infection with HPAI A (H5)

Criteria	ECDC	WHO
Clinical Criteria	– Fever AND signs/symptoms of acute respiratory infection (e.g., cough, sore throat, shortness of breath) OR – Death from unexplained acute respiratory illness	– Clinical symptoms not required for reporting if lab-confirmed Common symptoms may include: ● Fever ● Cough ● Sore throat ● Shortness of breath ● Conjunctivitis ● Severe cases: pneumonia, ARDS, organ failure, or death
Laboratory Criteria	At least one of the following: ● Isolation of influenza A/H5N1 virus ● Detection of A/H5 nucleic acid ● Four-fold or higher antibody titre to A/H5	At least one of the following: ● PCR or virus isolation from a respiratory specimen ● Paired sera with ≥ 4-fold rise in neutralizing antibodies to A(H5) ● Single convalescent serum (≥ 21 days post-onset/exposure) with: – Neutralizing antibody ≥ 1:40 – Positive result on second assay (e.g., HI, ELISA) – Antigenic match to virus – Epidemiological link to confirmed human case
Epidemiological Criteria	At least one of the following: ● Close contact (< 1 m) with probable/confirmed human case ● Lab exposure ● Contact with infected animal (e.g., cat, pig) ● Visited outbreak area AND – Contact with sick/dead poultry – OR lived/farmed near recent poultry deaths	Only required when using a single serum sample for serologic confirmation (no requirement if PCR or paired sera are used) ● Close physical contact with confirmed human case (e.g., caregiver, family, cohabitation)
Case Classification	– Possible case: Clinical + epidemiological criteria – Probable case: Lab-positive (non-EU ref lab) – Nationally confirmed: Lab-positive (EU reference lab) – WHO confirmed: Confirmed by the WHO Collaborating Centre	– Confirmed case: Meets WHO lab confirmation (PCR, paired sera, or validated single serum + epidemiological link) – All confirmed cases must be reported under IHR (2005) if caused by novel influenza A virus with pandemic potential (e.g., A(H5))

of the nine Colorado workers noted fever or chills, while throat ache or cough were uncommon. All cases were managed as outpatients with oseltamivir, symptoms resolved within a week, and no secondary transmission was documented. Interestingly, conjunctival swabs were positive in eight of the nine Colorado cases, whereas nasopharyngeal swabs were negative in five. Therefore, the eye appears to be a favoured site of replication for this clade and should always be sampled in suspected infections.

Outside North America, the disease has generally been more severe. The first Chilean patient progressed from a mild cough and sore throat to fulminant bilateral pneumonia requiring mechanical ventilation, though he ultimately survived [21]. Another Chilean case involved a 53-year-old man infected with clade 2.3.4.4b who progressed from mild upper-respiratory symptoms to severe dyspnea requiring mechanical ventilation. H5N1 was confirmed only on bronchoalveolar lavage after the initial nasopharyngeal swabs were negative [22, 23]. Two Chinese case reports describe fulminant respiratory failure with fatal outcomes: a 52-year-old woman and a 40-year-old man with metastatic nasopharyngeal carcinoma both died within weeks of symptom onset, which also initially included cough and congestion [24]. A third Chinese patient with chronic bronchiectasis experienced a 44 – day intensive care course complicated by respiratory failure. She was coinfected with SARSCoV2, but survived after prolonged ICU treatment [25].

Clade 2.3.4.4b can also invade the central nervous system. A 2022 Chinese case presented as acute encephalitis – fever, headache, seizures, and coma – without any respiratory features [26]. The patient recovered after aggressive antiviral, steroid, and intensive supportive therapy. Finally, a fatal 2025 H5N6 infection in Changsha, China, with reassortant 2.3.4.4b viruses was linked to infection at livepoultry markets. While detailed symptoms were not reported, the patient passed away as well [27].

Due to the limited data for clade 2.3.4.4b, we expanded our search to cases of HPAI (H5N1) infection. Based on published observational studies with more than 10 patients, we present the symptom profile of confirmed and probable HPAI A(H5N1) infections

in humans. The profile varies but shows consistent patterns across outbreaks based on available studies in the US [28, 29, 30]. As presented in Table 2, eye irritation, or conjunctivitis, is by far the most commonly reported symptom, especially in occupational exposures on dairy farms or in poultry settings. Respiratory symptoms, such as cough, sore throat, and shortness of breath, as well as systemic symptoms like fever, myalgia, and headache, are also frequently observed. Gastrointestinal symptoms were less common, and severe cases requiring hospitalization were rare. Unilateral conjunctivitis and no respiratory or systemic complaints have also been reported [31]. Asymptomatic infection is also possible, and subclinical carriage can occur even in older adults with high-risk exposure [32].

Outside the H5N1, we review the clinical presentation in other reported HPAI cases. H5N6 infections have been reported to begin with influenza-like illness – high fever, cough, and myalgia – before rapidly advancing to severe pneumonia and acute respiratory distress syndrome (ARDS), yet presentations ranged from an aggressively progressive adult case requiring ECMO and showing multi-organ laboratory abnormalities to a self-limited febrile rhinitis in a toddler who recovered at home and a fulminant respiratory failure with ARDS in a middle-aged man [33, 34, 35]. The single documented H6N1 patient manifested typical upper-respiratory symptoms (fever, non-productive cough, sore throat), but added progressive dyspnoea and bilateral infiltrates on imaging [36]. H7N9 cases broaden the symptomatic spectrum still further: one patient's earliest – and previously unreported – symptom was occipital neuralgia [37]. Others developed organizing pneumonia after apparent virologic clearance or deteriorated because of unrecognised *Mycoplasma* co-infection [38, 39]. In larger and clustered series, fever, cough, dyspnoea, and rapid progression to ARDS predominated [40, 41]. Finally, H10N3 infection seems to follow a similar pattern – initial fever and cough progressing within a week to type-I respiratory failure and multi-organ dysfunction, requiring prolonged intensive care [42]. Collectively, these reports underscore that while febrile respiratory illness is the common entry point, clinicians must also recognise atypical warning signs – isolated neurological pain, refractory organising pneumonia, or unexpectedly mild rhinitis – when evaluating patients with potential avian-influenza exposure.

Mortality

Due to limited clade 2.3.4.4b data, we looked into any HPAI H5N1 data. The cumulative global data from the World Health Organization (2003–2024) reports a total of 954 confirmed human cases of H5N1 avian influenza, resulting in 464 deaths, representing a case fatality rate (CFR) of approximately 49% [43]. The highest number of fatal cases has occurred in Indonesia, followed by Egypt, Vietnam, and Cambodia, all of which have had recurring outbreaks linked to close contact with poultry.

Indonesia remains the country with the highest recorded fatalities, with a CFR exceeding 80%, predominantly between 2005 and 2012. Egypt, while having the highest number of total cases, showed a lower fatality rate (~33%) likely due to improved surveillance and healthcare access during later outbreaks.

Table 2. Reported clinical symptoms and signs in confirmed HPAI A(H5N1) cases

Symptom	Zhu et al. (2025) (n = 38)	Mellis et al. (2024) (n = 115)	Garg et al. (2024) (n = 45)	Overall Range
Systemic				
Fever/Chills	29%	37%	49%	29-49%
Muscle aches (Myalgia)	34%	45%	42%	34-45%
Headache	26%	45%	44%	26-45%
Fatigue	18%	50%	22%	18-50%
Rash	–	10%	–	10%
Eye irritation/Conjunctivitis	97%	62%	93%	62-97%
Respiratory				
Cough	16%	31%	18%	16-31%
Sore throat	16%	57%	29%	16-57%
Shortness of breath	11%	17%	16%	11-17%
Runny nose/Congestion	–	48%	–	48% (Mellis only)
Sneezing	–	31%	25%	25-31%
Gastrointestinal				
Diarrhea	5%	15%	4%	4-15%
Nausea/Vomiting	5%	10%	4%	4-10%

In recent years, attention has shifted to North and South America. The United States has recorded 59 cases since 2022, all without fatalities – many of which were mild or asymptomatic, suggesting possible changes in either virus behavior or detection practices [30].

Table 3. HPAI H5N1 Human Infections by Country (2003–2024)

Country	Total Cases	Total Deaths	Case Fatality Rate (%)
Indonesia	200	168	84%
Egypt	359	120	33%
Vietnam	129	65	50%
Cambodia	72	43	60%
China	56	32	57%
United States	59	0	0%
Azerbaijan	8	5	63%
Bangladesh	8	1	13%
Thailand	25	17	68%
Turkey	12	4	33%

Outside of H5N1, we also looked into mortality data about other HPAI cases. In a series of 24 H5N6 cases from China (2014-2023), Li et al. (2024) calculated a 52% case-fatality rate overall and an alarming 100% mortality among patients whose exposure involved handling sick or dead birds, implying that exposure dose may directly influence outcome [44]. Survivors often endured severe long-term sequelae – irreversible pulmonary fibrosis or posterior cerebral atrophy. A systematic review of 30 pregnancies complicated by avian influenza infection (reported as H5N1 or H7N9) found maternal death in 90% of cases and near-universal fetal loss when the mother died. Even surviving neonates were premature, low-birth-weight, and frequently required intensive neonatal care [45]. A review of 85 H5N6 cases revealed a 40% case-fatality proportion, with 95% of patients hospitalised and a median of only four days between symptom onset and admission [46]. Among H7N9 infections, three of eight ICU patients in Shanghai died, and additional fulminant fatalities occurred in a young surgeon and a migrant worker lacking early antiviral therapy [40, 47, 48]. No deaths have yet been recorded in the small number of documented H6N1 and H10N3 cases, but the prolonged critical illness of the Kunming H10N3 patient warns that emerging subtypes can exact substantial morbidity even when ultimately non-fatal [42].

Treatment and Management

Due to the scarcity of data but easy access, early administration of antiviral medications, specifically oseltamivir, is recommended, as it may reduce disease severity and mortality. Early oseltamivir therapy was common to all survivors in the above-mentioned clade 2.3.4.4b cases, but its precise impact remains uncertain in the absence of randomized data. Supportive care, including oxygen therapy and management of complications, is another critical factor [49, 50].

In summary, while human infections with H5N1 clade 2.3.4.4b are uncommon, they pose significant health risks due to their potential severity and high mortality rate [1, 43]. Continued surveillance, prompt diagnosis, and appropriate clinical management are essential to mitigate the impact of these infections.

CONCLUSION

Clade 2.3.4.4b HPAI H5N1 viruses have triggered unprecedented global outbreaks since October 2020. These viruses have been detected extensively in wild birds, domestic poultry, and an expanding range of mammalian species. In this review, we summarize current knowledge on the evolution, host range, molecular markers, host determinants, and vaccine-mediated control of clade 2.3.4.4b H5N1 viruses [8, 9].

Despite significant advances, key questions remain unresolved. The factors driving the extraordinary geographic spread and the virus's ability to infect diverse hosts are not fully understood. Moreover, the potential risks posed by the virus's rapid evolution – both to animal populations and to human health – remain uncertain [51].

Continued surveillance and comprehensive risk assessment are, therefore, essential to evaluate emerging threats. At the same time, the development of effective vaccines and additional control strategies is urgently needed to mitigate the impact of these viruses on public health and the agricultural sector.

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