

Antiviral Treatment of Human Influenza A(H5N1) Infection: Treatment Timing, Clinical Outcomes, Virological Outcomes, and Antiviral Resistance: A Systematic Review

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ABSTRACT

Human influenza A(H5N1) infection remains a clinically important zoonotic disease, but evidence on antiviral effectiveness is limited by observational designs, heterogeneous treatment timing, and potentially overlapping patient populations. This systematic review synthesized evidence on antiviral regimens, treatment timing, clinical and virological outcomes, and antiviral resistance in laboratory-confirmed human A(H5N1) infection. A systematic search of PubMed, Scopus, and ScienceDirect was conducted from database inception to 1 July 2026. Methodological quality was assessed using the Newcastle–Ottawa Scale and the JBI Case Series Checklist. The clinical and methodological characteristics varied across studies; consequently, the findings were synthesized narratively. Potential population overlap was considered when synthesizing findings across publications to avoid duplicate aggregation of patient data. Of 2,329 records identified, 22 publications were included. Oseltamivir treatment was associated with a lower hazard of death than no documented anti-influenza antiviral treatment (adjusted hazard ratio 0.51, 95% confidence interval 0.34–0.77). Treatment within 2 days showed lower odds of death, although the overall estimate was not statistically significant (adjusted odds ratio 0.17, 95% confidence interval 0.03–1.04). Among patients without respiratory failure at treatment initiation, earlier treatment was associated with lower mortality (adjusted odds ratio 0.17, 95% confidence interval 0.03–0.89). Evidence for other antivirals was limited, and one confirmed treatment-emergent H274Y neuraminidase resistance event was identified. Overall, oseltamivir, particularly when initiated early and before advanced respiratory failure, was associated with improved clinical outcomes, although causal inference remains limited by confounding, heterogeneity, and potentially overlapping study populations.

Keywords: influenza A(H5N1); oseltamivir; antiviral therapy; treatment timing; antiviral resistance

INTRODUCTION

Highly pathogenic avian influenza A(H5N1) remains an important zoonotic concern because the virus continues to circulate in animal populations and can sporadically infect humans [1,2]. A(H5N1) has spread globally through migratory birds, and contemporary clade 2.3.4.4b viruses have caused infections in poultry and terrestrial and marine mammals [1]. As of 7 August 2026, 1,002 laboratory-confirmed human A(H5N1) infections, including 479 deaths, had been reported from 25 countries worldwide [3].

The clinical spectrum of human A(H5N1) infection is heterogeneous. The reports of human A(H5N1) infection frequently described viral pneumonia progressing to respiratory failure and acute

respiratory distress syndrome, with multiorgan dysfunction, including renal and occasionally cardiac involvement, also commonly reported [4]. More recent reports of clade 2.3.4.4b infection in the United States documented predominantly mild illness, frequently involving conjunctivitis [5]. Four patients were hospitalized, three had pneumonia, and one died [6]. Most patients in these recent U.S. reports received antiviral treatment [5,6].

Antiviral treatment is central to current management recommendations for suspected or confirmed human A(H5N1) infection. CDC guidance recommends empiric oseltamivir as soon as possible when A(H5N1) infection is suspected and states that treatment should not be delayed while awaiting test

results; hospitalized patients are recommended to receive oseltamivir regardless of time since illness onset [7]. WHO guidance conditionally recommends oseltamivir for patients with suspected or confirmed severe influenza, with treatment administered as early as possible. This recommendation also applies to novel influenza A virus infections associated with high mortality or an unknown risk of severe disease [8]. Observational studies have reported that earlier oseltamivir initiation was associated with better clinical outcomes than later treatment [9–11].

Interpretation of the available evidence is complicated by several methodological limitations. No adequately powered randomized controlled trials have established the clinical effectiveness of antiviral treatment specifically in human A(H5N1) infection, and the available treatment evidence is predominantly observational [9]. Studies vary in treatment timing, disease severity, comparator structure, supportive care, and outcome reporting, limiting direct comparison across reports. Oseltamivir resistance further complicates interpretation: resistant A(H5N1) variants have emerged during treatment, and H274Y and N294S are among the principal neuraminidase substitutions reported in resistant human infections [12,13]. This systematic review aimed to synthesize evidence on antiviral regimens, treatment timing, clinical and virological outcomes, and resistance in laboratory-confirmed human influenza A(H5N1) infection.

METHODS

Study Design and Reporting

This systematic review evaluated antiviral treatment, treatment timing, clinical and virological outcomes, and antiviral resistance in laboratory-confirmed human A(H5N1) infection. This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The protocol was not prospectively registered. Narrative synthesis followed the principles of Synthesis Without Meta-analysis (SWiM).

Eligibility Criteria

Reports including both laboratory-confirmed and probable cases were eligible only if data for the laboratory-confirmed cases could be identified and extracted separately. The comparisons analysed included antiviral treatment versus no documented antiviral treatment, early versus delayed initiation of treatment, and comparisons between regimens, dosages, or treatment durations. Clinical outcomes of interest included mortality or survival; severity of illness, particularly respiratory involvement, including respiratory failure, acute respiratory distress syndrome, mechanical ventilation, and intensive care unit admission; and length of hospital stay. Virological outcomes included viral clearance or shedding, while antiviral resistance was also assessed.

Randomized controlled trials, cohort studies, registry or surveillance analyses, outbreak investigations, and case series reporting relevant treatment or outcome data were eligible. Only articles published in English

were included. Animal studies, in vitro or laboratory-only studies, case reports, reviews, editorials, guidelines, and studies without A(H5N1)-specific antiviral treatment or outcome data were excluded. Potentially overlapping reports were retained when they provided unique information not available in the other study, such as treatment timing, antiviral regimen, virological outcomes, or antiviral resistance.

Search Strategy and Study Selection

A systematic literature search was conducted across PubMed, Scopus, and ScienceDirect from database inception to 1 July 2026. The search strategy combined terms related to influenza A(H5N1), avian influenza, antiviral treatment, human infection, and relevant clinical outcomes, with syntax adapted to the requirements of each database. All retrieved records were imported into Mendeley, and duplicate records were removed before screening. Two reviewers independently screened all titles and abstracts against the predefined eligibility criteria and subsequently assessed the full texts of potentially eligible reports. Disagreements were resolved through discussion and consensus; when consensus could not be reached, a third reviewer served as adjudicator. The study-selection process was reported in accordance with the PRISMA 2020 guidelines.

Data Extraction and Assessment of Potential Population Overlap

Data were extracted using a standardized extraction form. One reviewer performed the primary extraction of all included publications, and a second reviewer verified the extracted data against the original full-text reports for accuracy and completeness. Any discrepancies were resolved by re-examination of the source publication and discussion between the two reviewers; unresolved discrepancies were adjudicated by a third reviewer. Extracted variables included study characteristics, population, antiviral agent, dose and duration when available, treatment timing, clinical and virological outcomes, comparative effect estimates, and antiviral resistance-associated substitutions. Potential population overlap between publications was assessed based on the reported study setting, recruitment period, source population, and patient characteristics. When substantial population overlap between two or more reports was considered likely, reports providing more comprehensive data or additional information were retained.

Critical Appraisal and Data Synthesis

Methodological quality was appraised using design-appropriate tools. Cohort studies and comparative observational analyses were assessed using the Newcastle–Ottawa Scale (NOS), whereas case series and descriptive outbreak reports were evaluated using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Series. Detailed study-level assessments are presented in Supplementary Tables S1A and S1B. Appraisals were performed by one reviewer and subsequently verified by a second reviewer. Disagreements were resolved through discussion and consensus; when consensus could not be reached, a third reviewer served as adjudicator.

For comparative studies, reported odds ratios (ORs), risk ratios (RRs), and hazard ratios (HRs), with corresponding 95% confidence intervals (CIs), were extracted, and adjusted estimates were prioritized when available. Meta-analysis was not performed because of methodological and clinical heterogeneity, including differences in study population definitions, outcome measures, disease severity, and treatment timing. The obtained data were therefore synthesized narratively according to antiviral exposure, timing of antiviral treatment initiation, clinical outcomes, virological outcomes, and antiviral resistance.

RESULTS

Study Selection and Characteristics

The database search identified 2,329 records: 1,557 from PubMed, 572 from Scopus, and 200 from ScienceDirect. After removal of 320 duplicates, 2,009 records underwent title and abstract screening; 1,957 were excluded due to wrong study design, wrong population, and wrong intervention. Fifty-two reports were sought for retrieval; one was not retrieved, and 51 full texts were assessed. Twenty-nine reports were excluded at full-text review (28 wrong study design and one wrong population), leaving 22 publications to be included (Figure 1).

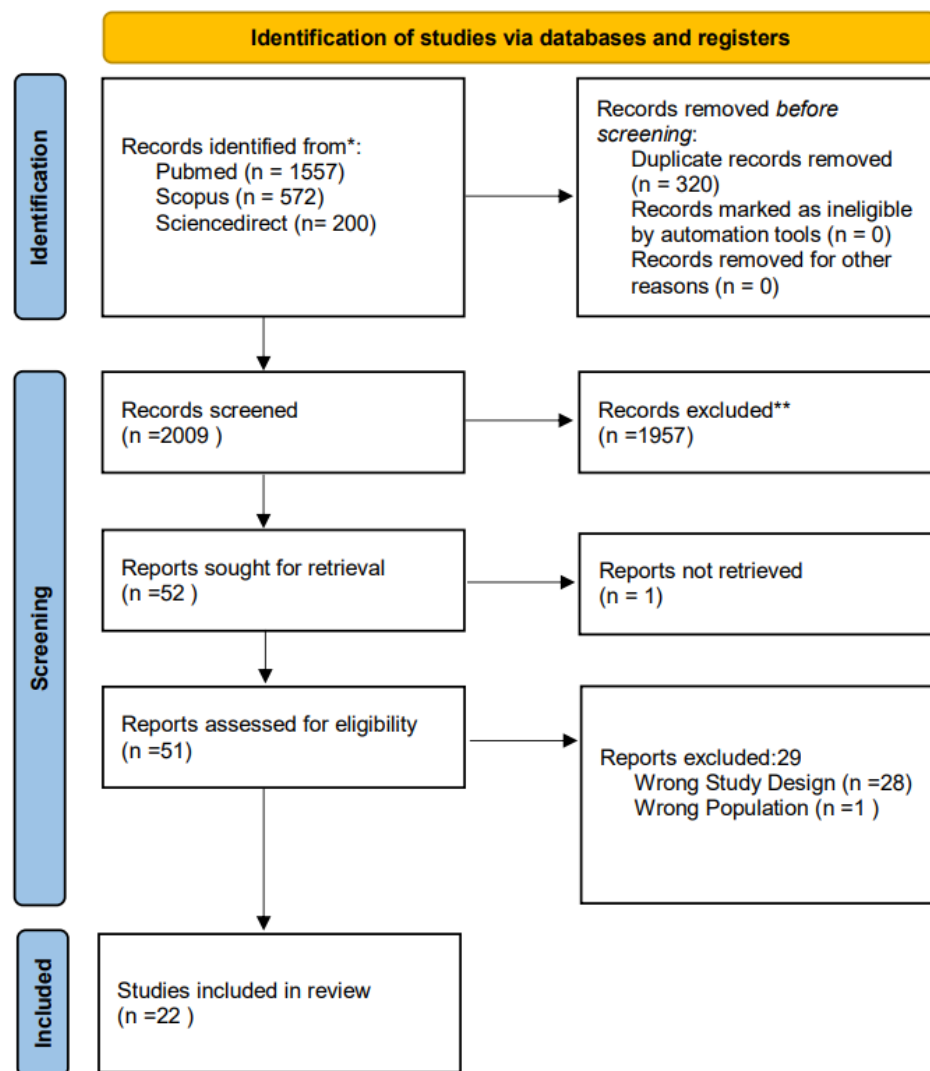


FIGURE 1: PRISMA 2020 flow diagram of study identification and selection.

Study-level antiviral treatment, treatment timing, and reported clinical, virological, and resistance outcomes are summarized in Table 1. A concise overview of study characteristics and each publication's principal contribution to the synthesis is provided in Supplementary Table S2.

The evidence base spanned 2004–2026 and consisted entirely of observational reports, including case series, retrospective cohorts, outbreak investigations, and registry/surveillance analyses. Geographically, the included publications were concentrated in Southeast Asia (n=11), East Asia (n=2), North America (n=3), and Turkey and Egypt (n=2); four publications were derived from multinational registry populations (Figure 2).

TABLE 1: Characteristics, antiviral treatment, and reported outcomes of included publications.

Study Population	N	Antiviral(s)	Treatment timing	Clinical outcome(s)	Virological outcome(s)	Antiviral resistance
Peiris 2004 Case series Hong Kong SAR, China; 2003 family cluster	2	Oseltamivir; amantadine	Oseltamivir ~day 6; amantadine timing NR	1/2 died	NR	M2 S31N; emergence indeterminate
de Jong 2005 Case series Vietnam; 2004–2005	8	Oseltamivir	Days 2–8	4/8 died; 4/8 survived	RNA undetectable in all 4 survivors; persistent in 3/6 evaluable at end of treatment	H274Y in 2 fatal cases; 1 treatment-emergent, 1 indeterminate
Kandun 2006 Case series Indonesia; 2005 family clusters	7	Oseltamivir	Days 5, 7, and 10	3/7 died; 4/7 recovered	NR	NR
Oner 2006 Case series Turkey; 2005–2006	8	Oseltamivir	Approx. illness days 1–10	4/8 died; 4/8 survived	NR	NR
Kandun 2008 Case series Indonesia; Jun 2005–Feb 2008	127	Oseltamivir	Median 7 d (0–21); <2, 2–4, 5–6, ≥7 d	103/127 died; survival decreased with later treatment	NR	NR
Taylor 2008 Case series Vietnam; 2007	2	Oseltamivir	Illness days 7–8	1/2 died; 1/2 survived	Survivor RT-PCR negative by treatment day 5	No phenotypic oseltamivir resistance detected
Yu 2008 Retrospective cohort China; 2005–2008	26	Oseltamivir; amantadine; rimantadine; ribavirin	Illness days 4–12	17/26 died; 4/12 treated vs 13/14 untreated died	NR	NR
Adisasmito 2010 Multinational Registry 12 countries, 1997–2009	308	Oseltamivir; /unspecified antivirals	0–2 to ≥12 d; median NR	174/308 died; 60/150 oseltamivir vs 102/134 no documented antiviral	NR	NR
Kandeel 2010 Retrospective cohort Egypt; 2006–2009	63	Oseltamivir	0–2 vs >2 d; 3–4, 5–6, >7 d	24/63 died; 1/25 early vs 19/33 later (timing subset, n=58)	NR	N294S in 2 cases; baseline resistance; both died
Soepandi 2010 Case series Indonesia; 2005–2008	22	Oseltamivir	Median day 7; range 2–12 d	18/22 died; 15/19 treated vs 3/3 untreated died	Clearance within 24–72 h in 3 survivors	NR
Shinde 2011 Retrospective cohort Thailand; 2004–2006	25	Oseltamivir	Median 7 d (4–21)	17/25 died; 8/25 survived	NR	NR
Chan 2012 Multinational registry 10 countries, 2003–2011	215	Oseltamivir	0–2 vs >2 d; 3–5, 6– 8, ≥9 d	100/215 died; 4/22 early vs 81/129 later	NR	NR

Study Population	N	Antiviral(s)	Treatment timing	Clinical outcome(s)	Virological outcome(s)	Antiviral resistance
Kudo 2012 Case series Vietnam; 2007–2010	8	Oseltamivir	Illness days 2–9	3/8 died; days 2–6: 5/5 survived; days 7–9: 3/3 died	NR	NR
Oner 2012 Multinational registry Pediatric registry; 1997–2010	193	Oseltamivir	Per-day delay model (N=44); median/range NR	94/193 died; 99/193 survived	NR	NR
Adisasmito 2013 Retrospective study Indonesia; 2005–2010	124	Oseltamivir	Median 5 d (2005–2007) vs 7 d (2008–2010)	107/124 died; 17/124 survived	NR	NR
Humphries-Waa 2013 Case series Cambodia; 2005–2011	18	Oseltamivir	Median 9 d; range 5–26 d (n=5 treated)	16/18 died; 2/18 survived	NR	NR
Zaman 2014 Multinational registry Azerbaijan, Indonesia, Pakistan, Turkey; 2005–2011	153	Oseltamivir	Median 7 d; 0–2, 3–5, 6–8, 9–11, ≥12 d	CFR 79.1%; survival 5/8 at 0–2 d, 6/18 at 3–5 d	NR	NR
Pawestri 2020 Retrospective cohort Indonesia; 2005–2017	180	Oseltamivir	Median 7 d (0–18); ≤4 vs >4 d; <7 vs ≥7 d	153/180 died	Median –0.55 log cDNA copies/mL at day 2; RNA commonly remained detectable	No major NA resistance; M2 substitutions 131/153 (V27A 119, S31N 14)
Drehoff 2024 Outbreak investigation United States; Colorado poultry facilities, Jul 2024	5	Oseltamivir	Start day NR; testing median 2 d after onset	0/5 deaths	4/4 retested cases negative on follow-up	NR
Garg 2025 Case series United States; Mar–Oct 2024	46	Oseltamivir	Median 2 d (0–8) among treated cases	0/46 deaths	NR	NR
Rolfes 2025 Case series United States; Mar 2024–May 2025	70	Oseltamivir; baloxavir; peramivir; amantadine; rimantadine	Median 2 d (–1 to 11); hospitalized median 6 d	1/70 died	NR	S247N (n=3), PA I38M (n=1), M2 S31N (n=1); emergence not established
Chin 2026 Outbreak investigation, Cambodia; Feb–Mar 2023 family cluster	2	Oseltamivir	Day 7 and day 10	1/2 died; 1/2 recovered	Two consecutive negative NP/OP tests before discharge	NR

Abbreviations: CFR, case-fatality rate; M2, matrix protein 2; NA, neuraminidase; NP/OP, nasopharyngeal/oropharyngeal; NR, not reported; PA, polymerase acidic protein; RT-PCR, reverse-transcription polymerase chain reaction.

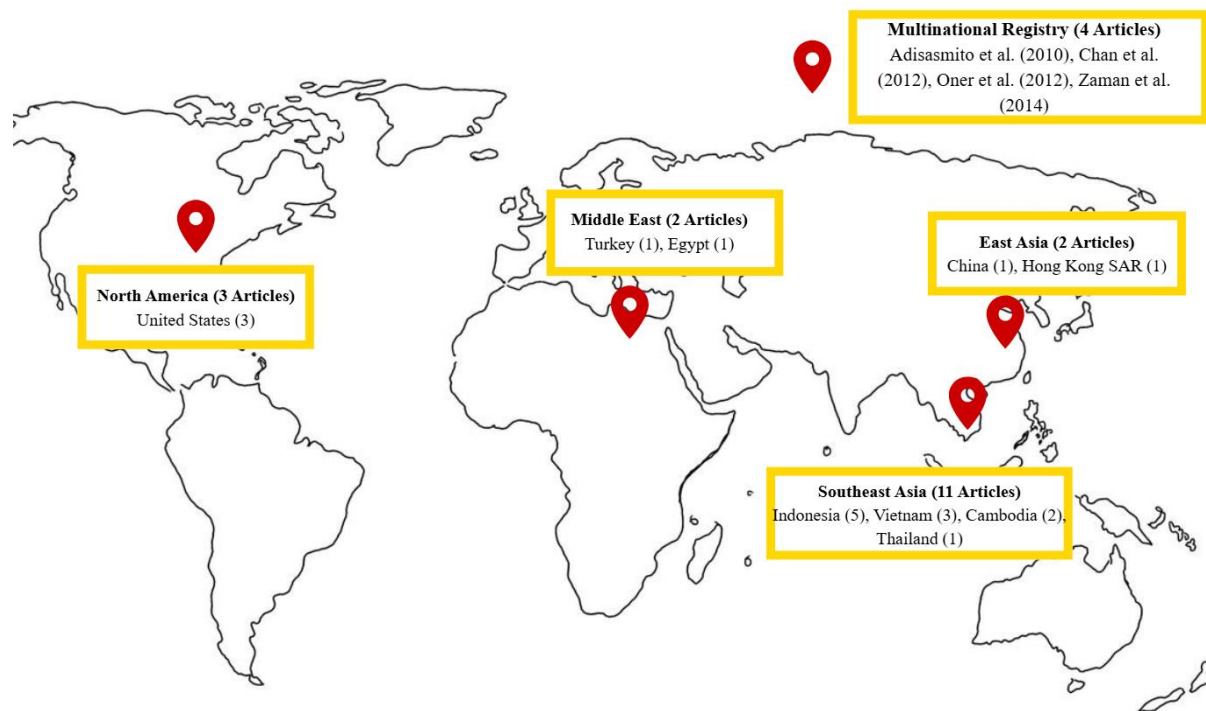


FIGURE 2: Geographic distribution of the 22 included publications.

Potential Overlap Among Study Populations

Potentially overlapping patient populations were identified across several included publications. For overlapping populations, the most informative report was prioritized for each clinical outcome or comparison, while complementary findings from other publications were retained. Sample sizes and event counts from potentially overlapping populations were not aggregated as independent patient data. Adisasmito et al. [11], Chan et al. [10], Oner et al. [14], and Zaman et al. [15] analyzed populations derived from the Global Avian Influenza Registry. Adisasmito et al. [11] provided the principal treatment-versus-no-documented-antiviral analysis, whereas Chan et al. [10] provided the principal early-versus-later treatment analysis. Oner et al. [14] and Zaman et al. [15] provided complementary pediatric and delayed-entry timing analyses.

Potential population overlaps were also identified among: (1) the Indonesian populations reported by Kandun et al. [16], Kandun et al. [17], Soepandi et al. [18], Adisasmito et al. [19], and Pawestri et al. [20]; (2) the Vietnamese populations reported by Taylor et al. [21] and Kudo et al. [22]; and (3) the United States populations represented by Garg et al. [5], Rolfes et al. [6], and Drehoff et al. [23]. Across studies with potential population overlap, outcome data for the same clinical endpoint were preferentially assigned to the most informative report, while overlapping studies were retained when they provided additional information.

Antiviral Treatment

Oseltamivir was the predominant antiviral used across the included studies. The standard adult dose was 75 mg twice daily, with pediatric dosing adjusted according to age or body weight. Higher doses were used in some critically ill patients; 150 mg every 12 hours by nasogastric tube was

administered to two patients with severe H5N1 infection [21], while doses of up to 300 mg/day were reported in another clinical series of patients with ARDS [22].

The principal adjusted comparative evidence for oseltamivir treatment was derived from the multinational registry analysis [11]. Mortality occurred in 60/150 patients (40.0%) receiving oseltamivir alone compared with 102/134 patients (76.1%) with no documented anti-influenza antiviral treatment. Oseltamivir treatment was associated with a lower hazard of death in the propensity-score-adjusted Cox analysis (adjusted HR 0.51, 95% CI 0.34–0.77). In the Chinese cohort, mortality occurred in 4/12 patients (33.3%) receiving antiviral treatment compared with 13/14 patients (92.9%) receiving no antiviral treatment [24]. In a Thai surveillance cohort, 17 of 25 patients (68.0%) died, while oseltamivir receipt did not differ significantly between fatal and nonfatal cases (71% vs 57%; $P=0.65$) [25]. In the Cambodian series, 3/5 oseltamivir-treated patients (60.0%) died compared with 13/13 patients (100%) who did not receive oseltamivir [26].

Observational evidence on oseltamivir treatment was reported in Indonesian cohorts. In the Indonesian tertiary-referral series, 15/19 oseltamivir-treated patients (78.9%) died, whereas all three patients who did not receive oseltamivir (100%) died within hours of referral before antiviral treatment could be administered [18]. A larger Indonesian cohort reported survival in 22/123 oseltamivir-treated patients (17.9%), compared with no survivors among 57 patients who did not receive oseltamivir [20].

Among 70 U.S. H5N1 cases, antiviral treatment status was available for 67 patients; 54/67 (81%) received antiviral treatment, all with oseltamivir,

whereas 13/67 did not receive antiviral treatment. Most infections were mild (66/70, 94%), four patients were hospitalized, and one patient died [6]. Because clinical outcomes were not stratified by antiviral treatment status, comparative effectiveness could not be assessed. Other antivirals, including amantadine, ribavirin, baloxavir, and peramivir, were used infrequently, often in combination, without suitable comparator groups [6,11,24].

Treatment Timing and Clinical Outcomes

Earlier oseltamivir initiation was generally associated with better survival across observational analyses. In the principal timing analysis, mortality was 4/22 patients (18.2%) when oseltamivir was initiated within 2 days of symptom onset compared with 81/129 patients (62.8%) when treatment was initiated later [10]. Early treatment was associated with lower odds of death (adjusted OR 0.17, 95% CI 0.03–1.04). Among patients without respiratory failure at treatment initiation, early treatment was associated with lower mortality (adjusted OR 0.17, 95% CI 0.03–0.89). Adjusted for the timing of first presentation for medical care, early oseltamivir treatment was associated with lower odds of death (adjusted OR 0.13, 95% CI 0.03–0.56) [10]. Respiratory failure requiring mechanical ventilation at or before treatment initiation was strongly associated with mortality (adjusted OR 19.5, 95% CI 4.19–90.84) [10].

Country-specific analyses showed similar patterns with earlier treatment. In Egypt, among 58 patients with complete oseltamivir treatment data, mortality was 1/25 (4.0%) in those treated within 0–2 days compared with 19/33 (57.6%) in those treated after

day 2 [27]. Mortality increased across later treatment intervals, from 3/14 (21.4%) on days 3–4 to 5/7 (71.4%) on days 5–6 and 11/12 (91.7%) after day 7 [27]. In a Cambodian family cluster, oseltamivir was initiated on illness days 7 and 10 in two confirmed cases, with one fatal outcome and one recovery [28]. In Indonesia, survival was reported in 1/1 patient treated before day 2, 4/11 patients (36.4%) treated on days 2–4, 6/16 (37.5%) treated on days 5–6, and 10/54 (18.5%) treated on or after day 7 [17].

Analyses from the multinational registry evaluated treatment delay. Among treated children, each additional day of delay in oseltamivir initiation was associated with higher odds of death (adjusted OR 1.75 per day, 95% CI 1.17–2.61; $n=44$) [14]. In a separate delayed-entry analysis, survival was 5/8 patients (62.5%) treated within 0–2 days compared with 11/97 (11.3%) in the corresponding no-antiviral comparison group (RR for survival 5.51, 95% CI 2.54–11.94; $P=0.002$) [15]. For treatment initiated on days 3–5, survival was 6/18 (33.3%) versus 13/97 (13.4%) (RR for survival 2.49, 95% CI 1.09–5.68; $P=0.076$) [15]. Indonesian cohort reported survival in 8/16 patients (50.0%) treated within 4 days compared with 19/106 (17.9%) treated after day 4, and in 16/51 patients (31.4%) treated before day 7 compared with 11/71 (15.5%) treated on or after day 7 [20]. A separate Indonesian health-system analysis documented median symptom-onset-to-oseltamivir intervals of 5 days in 2005–2007 and 7 days in 2008–2010 ($P=0.012$), without a comparative treatment-timing effect estimate [19]. Key comparative estimates for antiviral treatment and treatment timing are summarized in Table 2.

TABLE 2: Comparative estimates of antiviral treatment and treatment timing in human A(H5N1) infection.

Study	Comparison	Outcome	Event data	Effect estimate (95% CI)
Adisasmito 2010	Oseltamivir vs no documented antiviral	Mortality	60/150 vs 102/134 deaths	Adjusted HR 0.51 (95% CI 0.34–0.77)
Chan 2012	Oseltamivir ≤ 2 d vs > 2 d	Mortality	4/22 vs 81/129 deaths	Adjusted OR 0.17 (0.03–1.04)
Chan 2012	≤ 2 d vs later; no respiratory failure at treatment	Mortality	NR	Adjusted OR 0.17 (0.03–0.89)
Chan 2012	≤ 2 d vs later; additionally adjusted for first presentation	Mortality	NR	Adjusted OR 0.13 (0.03–0.56)
Oner 2012	Each additional day of delay in treated pediatric patients	Mortality	Model $N=44$	Adjusted OR 1.75 (1.17–2.61)
Kandeel 2010	Oseltamivir 0–2 d vs > 2 d	Mortality	1/25 vs 19/33	No adjusted estimate reported
Pawestri 2020	Oseltamivir ≤ 4 d vs > 4 d	Mortality	8/16 vs 87/106	Unadjusted
Pawestri 2020	Oseltamivir < 7 d vs ≥ 7 d	Mortality	35/51 vs 60/71	Unadjusted
Zaman 2014	Oseltamivir 0–2 d vs eligible no-antiviral risk set	Survival	5/8 vs 11/97 survived	RR 5.51 (2.54–11.94)

CI, confidence interval; d, days; HR, hazard ratio; NR, not reported; OR, odds ratio; RR, risk ratio.

Virological Outcomes

Serial virological data showed variable changes in H5N1 viral RNA during oseltamivir treatment. In a Vietnamese case series, H5N1 virus was isolated from admission throat swabs in 6/7 patients, and serial measurements showed a rapid decline to undetectable levels in all four survivors. In contrast, viral RNA remained detectable at the completion of oseltamivir treatment in two patients who died, while another patient died on the second day after admission with an increase in viral RNA load [12]. Additional virological observations were reported in two critically ill patients with H5N1 infection. In the survivor, the first respiratory sample obtained 3 days after oseltamivir initiation remained positive, but the tracheal aspirate became negative by treatment day 5. In the second patient, who died of progressive respiratory failure, H5N1 RNA was detected in tracheal aspirate, pleural fluid, stool, and plasma one day after treatment initiation; no subsequent virological samples were available to assess viral clearance [21]. In an Indonesian tertiary-referral series, viral clearance occurred within approximately 24–72 hours in all three survivors with serial throat-swab sampling [18].

Quantitative virological data from a larger Indonesian cohort showed frequent H5N1 RNA detection at admission, including 142/163 nasal specimens (87.1%), 144/157 pharyngeal specimens (91.7%), and 85/92 lower-respiratory-tract specimens (92.4%) [20]. Admission viral loads were higher in fatal cases than in survivors, with median nasal viral loads of 4.3 versus 3.6 log cDNA copies/mL ($P=.0135$) and pharyngeal viral loads of 5.3 versus 4.5 log cDNA copies/mL ($P=.041$). Among patients with serial pharyngeal sampling, viral RNA decreased by a median of 0.55 log cDNA copies/mL after 2 days of oseltamivir treatment; however, viral RNA remained detectable in 42/44 patients (95.5%) at the same time point [20]. Overall, viral RNA declined or became negative during oseltamivir treatment in several survivors, whereas persistent or increasing viral RNA was reported in some fatal cases.

Antiviral Resistance

Antiviral resistance was reported in several studies, with findings ranging from treatment-emergent neuraminidase resistance to pre-existing resistance-associated substitutions. In Vietnamese patients with H5N1 infection, H274Y neuraminidase resistance was detected in two fatal cases receiving oseltamivir [12]. In one patient, H274Y was detected during treatment and persisted after treatment completion, but emergence could not be confirmed because a pretreatment sequence was unavailable, whereas in the second patient, wild-type 274H was detected at admission and after 2 days of treatment, followed by H274Y detection three days after treatment completion. Viral load increased in the first patient, whereas in the second patient it declined during treatment but remained detectable and subsequently increased after treatment. Both patients died. In contrast, viral RNA declined rapidly to undetectable levels in all four survivors, and H274Y was not reported in these patients [12].

Oseltamivir resistance was identified in two related Egyptian cases, both of whom died. The N294S neuraminidase substitution was present in the initial diagnostic specimens and was associated with a 12–15-fold reduction in oseltamivir susceptibility; therefore, the resistance was present before treatment rather than emerging during therapy [27]. In a larger Indonesian cohort, no H275Y was detected in admission specimens from 155 patients or in 168 post-treatment pharyngeal specimens from 78 oseltamivir-treated patients [20]. R293K and N295S were also not detected in the principal tested subsets. In contrast, M2 substitutions associated with adamantane resistance were common, occurring in 131/153 patients (85.6%); V27A was the most frequent substitution (119/153, 77.8%), followed by S31N (14/153, 9.2%). M2 resistance-associated substitutions were more frequent among fatal cases than survivors (117/132 [88.6%] vs 14/21 [66.7%], $P=.015$) [20].

Resistance-associated markers were reported in recent U.S. H5N1 infections. NA S247N was identified in three viruses and was associated with reduced oseltamivir susceptibility; however, paired baseline specimens were unavailable and treatment-emergent selection could not be established [6]. PA I38M, associated with reduced baloxavir susceptibility, was detected in one patient with mild illness who had received only oseltamivir, while M2 S31N was detected in another mildly ill patient who had also received only oseltamivir [6]. In an earlier Hong Kong H5N1 case, M2 S31N was identified in an amantadine-treated child who recovered, but the absence of a susceptible pretreatment sequence prevented confirmation of treatment-emergent resistance [29].

Critical Appraisal

All the evidence included was observational. Thirteen descriptive or case-series reports were appraised using the JBI Critical Appraisal Checklist for Case Series, and nine cohort or comparative observational analyses were assessed using the Newcastle–Ottawa Scale. In the JBI assessments, uncertainty was concentrated mainly in consecutive participant inclusion, which was unclear in 9 of 13 reports, and complete inclusion, which was unclear in 6 of 13. Diagnostic ascertainment, demographic and clinical reporting, and statistical analysis were otherwise generally adequate. Among NOS-assessed studies, methodological limitations were concentrated in comparability and control of confounding: only 4 of 9 analyses received the first Comparability star and none received the second. Exposure ascertainment, absence of outcome at baseline, outcome assessment, and adequacy of follow-up duration were generally well addressed. Detailed item-level assessments are provided in Supplementary Tables S1A and S1B.

DISCUSSION

This systematic review found that oseltamivir treatment was consistently associated with better clinical outcomes in human A(H5N1) infection, particularly when initiated earlier in the course of

illness. The strongest comparative analysis showed lower mortality among patients receiving oseltamivir than among those with no documented anti-influenza antiviral treatment (adjusted HR 0.51, 95% CI 0.34–0.77) [11]. However, the evidence was observational, and treatment allocation was closely related to disease severity, healthcare access, and the opportunity to receive therapy.

Treatment timing appeared to be an important modifier of outcome. In the principal timing analysis, treatment within 2 days showed lower odds of death, although the 95% CI included the null (adjusted OR 0.17, 95% CI 0.03–1.04) [10]. Among patients without respiratory failure at treatment initiation, early treatment was associated with lower mortality (adjusted OR 0.17, 95% CI 0.03–0.89), while respiratory failure at or before treatment initiation was strongly associated with mortality [10]. Similar patterns were observed in pediatric, Egyptian, and Indonesian analyses [14,17,20,27]. Although timing thresholds differed across studies, the overall direction of evidence suggests that shorter treatment delay is associated with better outcomes, particularly before advanced respiratory failure develops.

Virological findings were broadly consistent with the clinical observations but provided supportive rather than causal evidence. Viral RNA declined or became undetectable in several survivors during oseltamivir treatment, whereas persistent or increasing viral RNA was observed in some fatal cases [12,18,20,21]. In the larger Indonesian cohort, viral RNA remained detectable in most patients after 2 days of treatment despite a reduction in viral load [20]. These findings suggest that persistent viral replication may accompany severe disease, but the absence of appropriate untreated virological comparators prevents attribution of viral clearance directly to oseltamivir.

Neuraminidase inhibitor resistance was identified in a small number of fatal cases, whereas confirmed treatment-emergent resistance was documented in only one patient. Both patients with H274Y reported in the Vietnamese series died, although treatment-emergent resistance could be confirmed in only one because pretreatment sequencing was unavailable in the other [12]. In contrast, pre-existing M2 resistance-associated substitutions were common in some viral populations. Similarly, both Egyptian patients with baseline N294S resistance died [27]. In the larger Indonesian cohort, M2 resistance-associated substitutions were more frequent among fatal cases than survivors (88.6% vs 66.7%, $P=.015$) [20]. However, these observations do not establish that antiviral resistance caused mortality, because the number of neuraminidase-resistant cases was very small and M2 substitutions were largely pre-existing viral characteristics rather than treatment-emergent mutations. Contemporary U.S. resistance-associated markers were identified mainly in mild infections or without sufficient paired specimens to relate the mutations to treatment response [6].

Thus, resistance may contribute to treatment failure in individual cases, but the available evidence is insufficient to quantify its independent effect on clinical outcomes.

Earlier evidence predominantly involved hospitalized patients with severe disease and high mortality, whereas contemporary U.S. clade 2.3.4.4b infections were mostly mild [5,6]. Differences in clinical phenotype, viral characteristics, and case ascertainment limit direct extrapolation of historical mortality and treatment-effect estimates to contemporary infections. Evidence for antivirals other than oseltamivir was insufficient for comparative assessment because exposures were limited and appropriate comparator groups were generally unavailable [6,11,24,29].

Overall, oseltamivir treatment was associated with better outcomes, particularly when initiated earlier and before advanced respiratory failure, although the magnitude of benefit remains uncertain. Future studies should use standardized treatment and severity definitions, patient-level deduplication, and integrated clinical and virological data to better define antiviral effectiveness in contemporary A(H5N1) infection.

CONCLUSION

Available human evidence suggests that oseltamivir treatment, particularly when initiated early and before the onset of advanced respiratory failure, is associated with improved clinical outcomes in A(H5N1) infection. However, the evidence remains predominantly observational and is limited by confounding, heterogeneous treatment timing and disease severity, incomplete exposure data, and potential overlap among several study populations. Confirmed treatment-emergent antiviral resistance was infrequently documented in the available clinical literature. These findings support current recommendations to initiate oseltamivir promptly and highlight the need for prospective clinical and virological data to better define treatment effectiveness across contemporary A(H5N1) infections.

Disclosure of Potential Conflicts of Interest

Declaration of Interest: The authors declare that they have no conflicts of interest related to this work.

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Contributors: HAMRM conceptualized the study, developed the methodology and search strategy, conducted the literature search and screening, performed data extraction and narrative synthesis, and drafted the manuscript. RRM independently performed screening, verified the extracted data, and reviewed the manuscript. KGH adjudicated disagreements, evaluated the methodology, and critically edited the manuscript. J supervised the study, validated the data, and critically revised the manuscript. All authors read and approved the final manuscript.

REFERENCES

- [1] Ison MG, Marrazzo J (2025). The emerging threat of H5N1 to human health. *New England Journal of Medicine*, 392(9), 916-918. <https://doi.org/10.1056/NEJMe2416323>
- [2] Pan American Health Organization. (2026). Avian influenza in the Americas: animal outbreaks decline, but PAHO calls for continued vigilance. <https://www.paho.org/en/news/27-8-2026-avian-influenza-americas-animal-outbreaks-decline-paho-calls-continued-vigilance>. Accessed September 6, 2026.
- [3] World Health Organization. (2026). Cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003-2026, 7 August 2026. [https://www.who.int/publications/m/item/cumulative-number-of-confirmed-human-cases-for-avian-influenza-a\(h5n1\)-reported-to-who--2003-2026--7-august-2026](https://www.who.int/publications/m/item/cumulative-number-of-confirmed-human-cases-for-avian-influenza-a(h5n1)-reported-to-who--2003-2026--7-august-2026). Accessed September 6, 2026.
- [4] Beigel JH, Farrar J, Han AM, Hayden FG, Hyer R, de Jong MD, et al. (2005). Avian influenza A (H5N1) infection in humans. *New England Journal of Medicine*, 353(13), 1374-1385. <https://doi.org/10.1056/NEJMra052211>
- [5] Garg S, Reinhart K, Couture A, Kniss K, Davis CT, Kirby MK, et al. (2025). Highly pathogenic avian influenza A(H5N1) virus infections in humans. *New England Journal of Medicine*, 392(9), 843-854. <https://doi.org/10.1056/NEJMoa2414610>
- [6] Rolfes MA, Kniss K, Kirby MK, Garg S, Reinhart K, Davis CT, et al. (2025). Human infections with highly pathogenic avian influenza A(H5N1) viruses in the United States from March 2024 to May 2025. *Nature Medicine*, 31(11), 3889-3898. <https://doi.org/10.1038/s41591-025-03905-2>
- [7] Centers for Disease Control and Prevention. (n.d.). Clinical guidance for evaluating patients and treatment and post-exposure prophylaxis (PEP) of influenza A(H5N1) virus infection. <https://www.cdc.gov/bird-flu/hcp/clinicians-evaluating-patients/clinical-guidance-treatment.html>. Accessed September 7, 2026.
- [8] World Health Organization. (2024). Clinical practice guidelines for influenza. World Health Organization.
- [9] Uyeki TM, Belser JA (2025). Antivirals for Novel Influenza A Virus Infections. *The Journal of Infectious Diseases*, 232(Suppl 3), S191-S209. <https://doi.org/10.1093/infdis/jiaf296>
- [10] Chan PKS, Lee N, Zaman M, Adisasmito W, Coker R, Hanshaoworakul W, et al. (2012). Determinants of antiviral effectiveness in influenza virus A subtype H5N1. *The Journal of Infectious Diseases*, 206(9), 1359-1366. <https://doi.org/10.1093/infdis/jis509>
- [11] Adisasmito W, Chan PKS, Lee N, Oner AF, Gasimov V, Aghayev F, et al. (2010). Effectiveness of antiviral treatment in human influenza A(H5N1) infections: analysis of a Global Patient Registry. *The Journal of Infectious Diseases*, 202(8), 1154-1160. <https://doi.org/10.1086/656316>
- [12] de Jong MD, Tran TT, Truong HK, Vo MH, Smith GJD, Nguyen VC, et al. (2005). Oseltamivir resistance during treatment of influenza A(H5N1) infection. *New England Journal of Medicine*, 353(25), 2667-2672. <https://doi.org/10.1056/NEJMoa054512>
- [13] Abed Y, Boivin G (2026). Oseltamivir resistance in human influenza A(H5N1) and A(H7N9) infections: a mini review. *Open Forum Infectious Diseases*, 13(7), ofag393. <https://doi.org/10.1093/ofid/ofag393>
- [14] Oner AF, Dogan N, Gasimov V, Adisasmito W, Coker R, Chan PKS, et al. (2012). H5N1 avian influenza in children. *Clinical Infectious Diseases*, 55(1), 26-32. <https://doi.org/10.1093/cid/cis295>
- [15] Zaman M, Gasimov V, Oner AF, Dogan N, Adisasmito W, Coker R, et al. (2014). Recognizing true H5N1 infections in humans during confirmed outbreaks. *The Journal of Infection in Developing Countries*, 8(2), 202-207. <https://doi.org/10.3855/jidc.3329>
- [16] Kandun IN, Wibisono H, Sedyaningsih ER, Yusharmen, Hadisoedarsuno W, Purba W, et al. (2006). Three Indonesian clusters of H5N1 virus infection in 2005. *New England Journal of Medicine*, 355(21), 2186-2194. <https://doi.org/10.1056/NEJMoa060930>
- [17] Kandun IN, Tresnaningsih E, Purba WH, Lee V, Samaan G, Harun S, et al. (2008). Factors associated with case fatality of human H5N1 virus infections in Indonesia: a case series. *The Lancet*, 372(9640), 744-749. [https://doi.org/10.1016/S0140-6736\(08\)61125-3](https://doi.org/10.1016/S0140-6736(08)61125-3)
- [18] Soepandi PZ, Burhan E, Mangunnegoro H, Nawas A, Aditama TY, Partakusuma L, et al. (2010). Clinical course of avian influenza A(H5N1) in patients at the Persahabatan Hospital, Jakarta, Indonesia, 2005-2008. *CHEST*, 138(3), 665-673. <https://doi.org/10.1378/chest.09-2644>

- [19] Adisasmito W, Aisyah DN, Aditama TY, Kusriastuti R, Trihono, Suwandono A, et al. (2013). Human influenza A H5N1 in Indonesia: health care service-associated delays in treatment initiation. *BMC Public Health*, 13, 571. <https://doi.org/10.1186/1471-2458-13-571>
- [20] Pawestri HA, Eggink D, Isfandari S, Thanh TT, van Doorn HR, Setiawaty V, et al. (2020). Viral factors associated with the high mortality related to human infections with clade 2.1 influenza A/H5N1 virus in Indonesia. *Clinical Infectious Diseases*, 70(6), 1139-1146. <https://doi.org/10.1093/cid/ciz328>
- [21] Taylor WRJ, Thinh BN, Anh GT, Horby P, Wertheim H, Lindegardh N, et al. (2008). Oseltamivir is adequately absorbed following nasogastric administration to adult patients with severe H5N1 influenza. *PLOS ONE*, 3(10), e3410. <https://doi.org/10.1371/journal.pone.0003410>
- [22] Kudo K, Binh NG, Manabe T, Co DX, Tuan ND, Izumi S, et al. (2012). Clinical preparedness for severe pneumonia with highly pathogenic avian influenza A (H5N1): experiences with cases in Vietnam. *Respiratory Investigation*, 50(4), 140-150. <https://doi.org/10.1016/j.resinv.2012.08.005>
- [23] Drehoff CC, White EB, Frutos AM, Stringer G, Burakoff A, Comstock N, et al. (2024). Cluster of influenza A(H5) cases associated with poultry exposure at two facilities—Colorado, July 2024. *Morbidity and Mortality Weekly Report*, 73(34), 734-739. <https://doi.org/10.15585/mmwr.mm7334a1>
- [24] Yu H, Gao Z, Feng Z, Shu Y, Xiang N, Zhou L, et al. (2008). Clinical characteristics of 26 human cases of highly pathogenic avian influenza A (H5N1) virus infection in China. *PLOS ONE*, 3(8), e2985. <https://doi.org/10.1371/journal.pone.0002985>
- [25] Shinde V, Hanshaoworakul W, Simmerman JM, Narueponjirakul U, Sanasuttipun W, Kaewchana S, et al. (2011). A comparison of clinical and epidemiological characteristics of fatal human infections with H5N1 and human influenza viruses in Thailand, 2004-2006. *PLOS ONE*, 6(4), e14809. <https://doi.org/10.1371/journal.pone.0014809>
- [26] Humphries-Waa K, Drake T, Huszar A, Liverani M, Borin K, Touch S, et al. (2013). Human H5N1 influenza infections in Cambodia 2005-2011: case series and cost-of-illness. *BMC Public Health*, 13, 549. <https://doi.org/10.1186/1471-2458-13-549>
- [27] Kandeel A, Manoncourt S, Abd el Kareem E, Ahmed ANM, El-Refaie S, Essmat H, et al. (2010). Zoonotic transmission of avian influenza virus (H5N1), Egypt, 2006-2009. *Emerging Infectious Diseases*, 16(7), 1101-1107. <https://doi.org/10.3201/eid1607.091695>
- [28] Chin S, Soputhy C, Seng H, Mom S, Sar B, Finlay A, et al. (2026). Investigation of a family cluster of human infections with highly pathogenic avian influenza A(H5N1) virus, clade 2.3.2.1e, in Cambodia, February 2023. *Influenza and Other Respiratory Viruses*, 20(2), e70231. <https://doi.org/10.1111/irv.70231>
- [29] Peiris JSM, Yu WC, Leung CW, Cheung CY, Ng WF, Nicholls JM, et al. (2004). Re-emergence of fatal human influenza A subtype H5N1 disease. *The Lancet*, 363(9409), 617-619. [https://doi.org/10.1016/S0140-6736\(04\)15595-5](https://doi.org/10.1016/S0140-6736(04)15595-5)
- [30] Oner AF, Bay A, Arslan S, Akdeniz H, Sahin HA, Cesur Y, et al. (2006). Avian influenza A (H5N1) infection in eastern Turkey in 2006. *New England Journal of Medicine*, 355(21), 2179-2185. <https://doi.org/10.1056/NEJMoa060601>