

# Effectiveness of Antiviral Treatment in Human Influenza A(H5N1) Infections: Analysis of a Global Patient Registry

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(See the editorial commentary by Couch and Davis, on pages 1149–1151.)

**Background.** Influenza A(H5N1) continues to cause infections and possesses pandemic potential.

**Methods.** Data sources were primarily clinical records, published case series, and governmental agency reports. Cox proportional hazards regression was used to estimate the effect of treatment on survival, with adjustment using propensity scores (a composite measure of baseline variables predicting use of treatment).

**Results.** In total, 308 cases were identified from 12 countries: 41 from Azerbaijan, Hong Kong SAR, Nigeria, Pakistan, and Turkey (from clinical records); 175 from Egypt and Indonesia (from various sources); and 92 from Bangladesh, Cambodia, China, Thailand, and Vietnam (from various publications). Overall crude survival was 43.5%; 60% of patients who received  $\geq 1$  dose of oseltamivir alone (OS<sup>+</sup>) survived versus 24% of patients who had no evidence of anti-influenza antiviral treatment (OS<sup>-</sup>) ( $P < .001$ ). Survival rates of OS<sup>+</sup> groups were significantly higher than those of OS<sup>-</sup> groups; benefit persisted with oseltamivir treatment initiation  $\leq 6$ –8 days after symptom onset. Multivariate modeling showed 49% mortality reduction from oseltamivir treatment.

**Conclusions.** H5N1 causes high mortality, especially when untreated. Oseltamivir significantly reduces mortality when started up to 6–8 days after symptom onset and appears to benefit all age groups. Prompt diagnosis and early therapeutic intervention should be considered for H5N1 disease.

Although the world was challenged in 2009 by a pandemic caused by influenza A(H1N1), human infections

with H5N1 virus continue to be reported and remain a threat. The existence of an extensive avian reservoir makes it likely that the H5N1 virus will continue to pose a threat to human health. The high mortality rate associated with H5N1 (reported by the World Health Organization [WHO] as 59% [1, 2]) and the novelty of the virus to humans give cause for concern that, should the virus acquire increased capacity to transmit from human to human, it might trigger a pandemic that exacts a very high human and economic cost.

Currently, patients infected with H5N1 are treated with supportive care, often at intensive care unit level, and with specific antiviral drugs. There are 2 major classes of antiviral drugs with anti-influenza activity in clinical use: the neuraminidase inhibitors oseltamivir and zanamivir and the adamantane M2 inhibitors rimantidine and amantadine; ribavirin has also been used occasionally [3]. Oseltamivir, which is orally administered and systemically bioavailable, has been the main-

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stay of antiviral treatment in H5N1 infections [4]; inhaled zanamivir possesses minimal systemic bioavailability. Resistance to the M2 inhibitors is not infrequent and tends to emerge rapidly during use [5]. Although there are reports of resistance or reduced susceptibility by clinically isolated H5N1 viruses [6–9], a recent genotyping study predicted oseltamivir susceptibility in >99% of circulating H5N1 strains [10], a finding pointing to continued attention on oseltamivir's clinical effectiveness.

To date, although most reports have demonstrated benefit from intervention with oseltamivir, especially if given early during the course of illness, there have been reports that have questioned treatment efficacy, the benefits of delayed treatment, and the optimum regimen [11, 12]. To better understand the course of H5N1 infection in humans and the effectiveness of various treatments, a pooled analysis of H5N1 cases was conducted, drawn from a specially designed registry containing individual case data from many countries [13]. To our knowledge, this is the first pooled, systematic analysis of multicountry data and the largest series of human cases of confirmed H5N1 infection analyzed.

## METHODS

**Patients and procedures.** Cases were drawn from an ongoing, specially designed patient registry that allows for online data entry of clinical presentation, all treatments, and all outcomes, using a secure information platform (<http://www.avianfluregistry.org>), and conforms to the most recent guidance for high-quality registries [14]. The registry protocol has been reviewed and approved by ethical review committees in study countries, as required, and in the US. Informed consent was not required because data were obtained from record review, without patient contact, and then made anonymous; all data are protected with strong security.

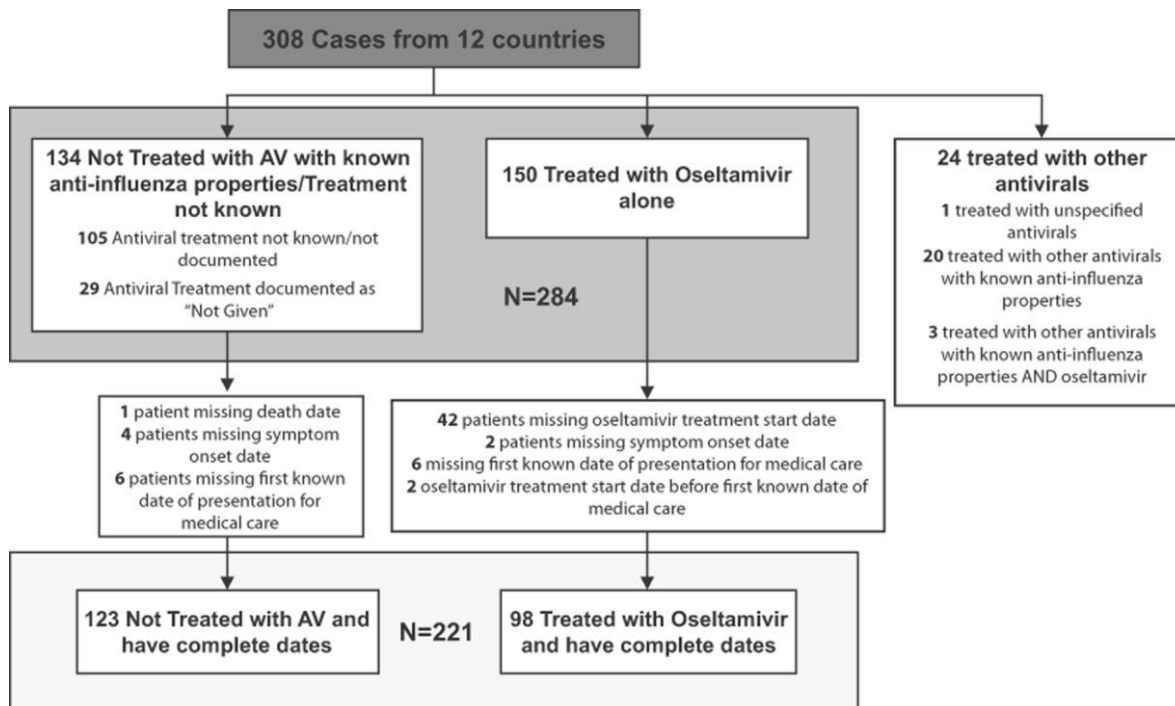
Patients with laboratory confirmation of infection with influenza A(H5N1) who survived long enough to present for medical care were identified from 3 sources: (1) by in-country reporters, who helped abstract clinical data; (2) through clinical records and reports from governmental health institutions at the national, regional, and district levels; and (3) from published case series; some additional data elements were obtained from ProMED. Published case reports were included only if age, sex, country, symptoms, exposure or viral testing, and outcome were reported for each case. Medline was searched by PubMed for cases between 1997 and August 2009 using the following medical subject heading search terms: influenza, human; influenza A virus, H5N1 subtype; influenza in birds/epidemiology; influenza in birds/transmission; case reports; treatment outcome; and country (for any country where avian influenza cases have been reported to WHO). Published reports that provided additional information about cases already in the registry were used to supplement and verify data abstracted in

the field [6, 15–24]. Duplicate cases were eliminated by comparing all cases by age, sex, country of origin, and date of symptom onset (within 30 days).

Core data for all cases include the information available on demographics, dates of symptom onset and presentation for treatment, characteristics of initial disease manifestation, infection outcome (survived or deceased), and the results of laboratory confirmation for influenza A(H5N1), if available. Additional details, as available, were included for symptoms, clinical presentation, all treatments used once a patient had sought medical attention, and other laboratory investigations. Antiviral treatments were classified by whether they had anti-influenza properties (AV<sup>+</sup>); acyclovir, an antiherpetic, and qing kai ling, an antipyretic, were not considered to have anti-influenza properties. Use of any antiviral was recorded if it had been documented in any record source. In some situations, it was specifically noted that antivirals were not given, but because this information was not systematically recorded or available, the absence of documentation about antivirals, as well as notes confirming that no antivirals were given, were analyzed together as “antiviral treatment not documented (AV<sup>-</sup>).” Because oseltamivir was the most commonly used antiviral, additional analyses were performed comparing treatment with oseltamivir only (OS<sup>+</sup>); this group included all patients who received  $\geq 1$  dose of oseltamivir. Treatment effectiveness was examined in the context of time to treatment from onset of symptoms and from presentation for medical care.

**Statistical analysis.** Data were analyzed using  $2 \times 2$  tables, with relative risks used to describe the risk of death in the treated patients compared with the same risk in untreated patients, with probability determined by use of a mid-*P* test [25]. Statistical significance was determined with  $\alpha$  set at .05.

A delayed cohort entry analysis was used to calculate survival per day because deaths prior to presentation for medical attention were not available for analysis [26]. Survival analyses were performed using the Kaplan-Meier procedure for estimating survival over time. Cox proportional hazards regression were performed for estimation of the hazard ratio of death associated with oseltamivir treatment among a subset of patients with either oseltamivir treatment or no antiviral treatment recorded, from countries with both treated and untreated patients. Because missing data are not a rarity in observational studies derived from existing records, we chose to impute missing dates for Cox proportional hazards analyses, blinded to treatment status of patients. Patients reported as alive at last contact were assumed to have lived  $\geq 30$  days after presentation for medical care. Two of 150 patients reported as deceased did not have a recorded date of death; for these 2 patients the mean time to death of 8 days was imputed. For 148 patients with information about date of symptom onset but not date of presentation for treatment, the date of presentation for treat-



**Figure 1.** Availability of data on medication and dates of presentation for medical care.

ment was imputed as 2 days after symptom onset for all patients, on the basis of the overall mean observed time from symptom onset to presentation for treatment. For one patient who survived <1 day, the survival time was estimated to be 0.5 days for analysis. No other missing data were imputed.

Stepwise logistic regression was used to estimate the propensity score, or predicted probability of receiving treatment with oseltamivir. Probability of oseltamivir treatment was the dependent variable, and factors including age, sex, country, exposure to poultry, exposure in the home or healthcare setting to other H5N1 patients, history of respiratory or immunologic disorders, pregnancy, time from symptom onset to first known time of presentation for treatment, type of healthcare setting where patient presented for treatment, and symptoms at presentation were included as independent variables. A backward selection process was used, with a *P* value of .20 as the criterion for retaining a variable in the model. Countries with no variability in treatment (either 100% or 0% of patients treated) were not included (Bangladesh, Cambodia, Hong Kong SAR, Nigeria, and Turkey). In total, 258 patients representing 7 countries remained available for the propensity score analysis. The estimated propensity score was used for statistical adjustment in the Cox model.

All statistical analyses were performed using SAS software, version 9.2 (SAS Institute), except mid-*P* tests, which were performed using Episheet software (<http://krothman.byethost2.com/Episheet.xls>), and propensity score modeling, which was performed using STATA software (version 11.0; StataCorp).

## RESULTS

This report is based on 308 cases of human avian influenza occurring from 1997 to 2009 from 12 countries in the Pandemic/Avian Influenza Registry: Azerbaijan (7 cases), Bangladesh (1 case), Cambodia (6 cases), China (20 cases), Egypt (82 cases), Hong Kong (18 cases), Indonesia (99 cases), Nigeria (1 case), Pakistan (4 cases), Thailand (12 cases), Turkey (11 cases), and Vietnam (47 cases) [13]. All cases have laboratory confirmation of H5N1 infection, 228 cases meet the WHO criteria for a confirmed case [27], 4 cases are known to have been confirmed only by local laboratories, and WHO status for the other 111 lab-confirmed cases was not recorded. Forty-one cases (13%) were abstracted from clinical records in Azerbaijan, Hong Kong, Nigeria, Pakistan, Turkey; 175 cases (57%) in Egypt and Indonesia were obtained from governmental records, other clinical data, and from public Web sites [28, 29] complemented by matching cases in ProMED [30]. And 92 cases (30%) were obtained from detailed publications about cases in Bangladesh, Cambodia, China, Egypt, Thailand, Vietnam, and other regions in Indonesia [6, 7, 11, 18, 24, 31–40]. Figure 1 illustrates the availability of data on medication and dates of presentation for medical care and highlights the 2 main analytic subgroups.

Overall, the median age of patients was 17 years (range, 1–75 years); 46% were under 16 years; 39% were aged 16–34, and 15% were aged  $\geq 35$  years. Nearly half (45%) of patients were male. The overall mortality rate was 56.5%. Analysis by study period showed the lowest mortality in 2009 (27%), followed by 1997 (33%); mortality ranged from 48% to 78% during 2003–2008. Of 173 patients who were treated with oseltamivir or another antiviral with known anti-influenza properties ( $AV^+$ ), 102 patients (59%) survived. Eighty-seven percent (150/173) of those  $AV^+$  patients were treated only with oseltamivir; 2 were also treated with ribavirin, and 1 also received rimantidine.

Of the 284 patients with known age and outcome who received either oseltamivir alone or no anti-influenza antiviral, the crude overall survival rate of patients who received at least 1 dose of oseltamivir alone ( $OS^+$ ) was 60% (90/150), whereas survival among  $AV^-$  patients was 24% (32/134) ( $P < .001$ ). Figure 2 shows survival rates by age and receipt of oseltamivir for 3 age groups for these patients. For all age groups, a significantly higher survival rate was observed for  $OS^+$  patients than  $AV^-$  patients. For patients  $< 16$  years of age, 68% (49/72) of  $OS^+$  patients survived compared with 40% (23/58) of  $AV^-$  patients ( $P < .001$ ). For patients  $\geq 16$  years but  $< 35$  years, 48% (28/58) of  $OS^+$  patients survived compared with 9% (5/55) of  $AV^-$  patients ( $P < .001$ ). The comparison of survival rates of patients  $\geq 35$  years of age was 65% survival (13/20) for the  $OS^+$  patients and 19% survival (4/21) for the  $AV^-$  patients ( $P < .004$ ).

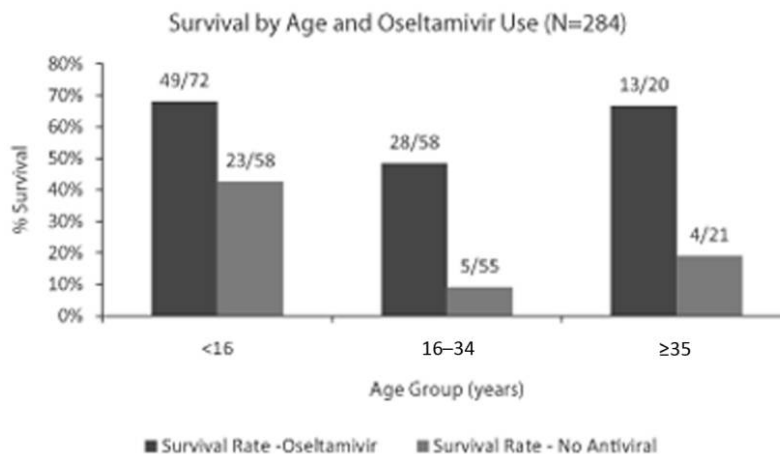
Survival by interval from symptom onset to first dose of oseltamivir was analyzed by comparing the survival rate of  $OS^+$  patients with that of the  $AV^-$  patients: 221 patients had information available on symptom onset, survival, and oseltamivir use. The survival rate of  $OS^+$  patients who received treatment within 2 days of symptom onset was 83%, compared with 20% of  $AV^-$  patients who received no treatment in the interval, giving a survival difference of 63% for  $OS^+$  patients. Survival

difference for  $OS^+$  patients decreased to 21% for treatment initiated 3–5 or 6–8 days after symptom onset. No statistically significant benefit was seen when the first dose of oseltamivir was administered  $> 8$  days after symptom onset. Relative risks, risk differences, and confidence intervals for the survival benefit of oseltamivir are presented in Table 1. The full set of  $AV^-$  and  $OS^+$  patients are shown with the Kaplan-Meier survival curves (Figure 3).

A propensity score model was developed as a summary measure of factors associated with oseltamivir treatment, as described above in the section on statistical analysis. Variables retained in the final propensity score model included age, country (Vietnam), direct exposure to live poultry, indirect exposure to poultry, exposure to a case of avian influenza in the home, a history of respiratory compromise, symptoms of unexplained respiratory disease, rhinorrhea, sore throat, fatigue, and myalgia at onset, presentation at an emergency room for treatment, and presentation at a rural health center for treatment. The *c* statistic for the final propensity score model was 0.85, indicating that the model is highly predictive of treatment with oseltamivir. The estimated propensity score was then used as a covariate in a multivariate analysis to adjust for potential confounding by factors associated with treatment.

Results of a Cox regression analysis including only oseltamivir treatment as an independent variable yielded a hazard ratio of death of 0.34 (95% confidence interval [CI], 0.25–0.48). Inclusion of the propensity score as a covariate changed the estimate to 0.51 (95% CI, 0.34–0.77). Additional covariates, including sex and the first known time of presentation for treatment, to the Cox model including the propensity score, did not change the adjusted hazard ratio estimate by 10% or more.

We examined the sensitivity of the findings to variations in country-specific mortality and to secular trends. Comparing the countries with high and low mortality rates,  $\geq 50$  cases, and



**Figure 2.** Survival rates by age and receipt of oseltamivir for 3 age groups.

**Table 1. Relative Risk of Survival of Patients Treated with Oseltamivir, Compared with Patients Who Did Not Receive Antiviral Treatment (N = 221)**

Treatment initiation from symptom onset, days	Oseltamivir treatment, survived/total (%)	No antiviral treatment, survived/total (%)	Difference in survival, %	Relative risk	95% CI	P
0–2	15/18 (83)	19/95 (20)	63	4.17	2.65–6.55	<.001
3–5	15/31 (48)	32/117 (27)	21	1.77	1.11–2.83	.032
6–8	16/32 (50)	31/108 (29)	21	1.74	1.10–2.75	.031
9–11	3/8 (38)	30/70 (43)	–5	0.88	0.34–2.23	.797
≥12	3/9 (33)	29/45 (64)	–31	0.52	0.20–1.34	.105
Any time	52/98 (53)	29/123 (24)	29	2.25	1.56–3.25	<.001

**NOTE.** Relative risk of survival by interval from symptom onset and first dose of oseltamivir, compared with risk of survival of individuals who presented for medical care during the interval, were alive in the interval, and did not receive any antiviral treatment during the interval. CI, confidence interval.

sustained outbreaks lasting for >3 years, the relative risk of survival from oseltamivir treatment within 6 days of symptom onset was 1.75 (95% CI, 1.13–2.72) in the country with low mortality rate and 3.45 (95% CI, 1.2–10.1) in the country with high mortality rate.

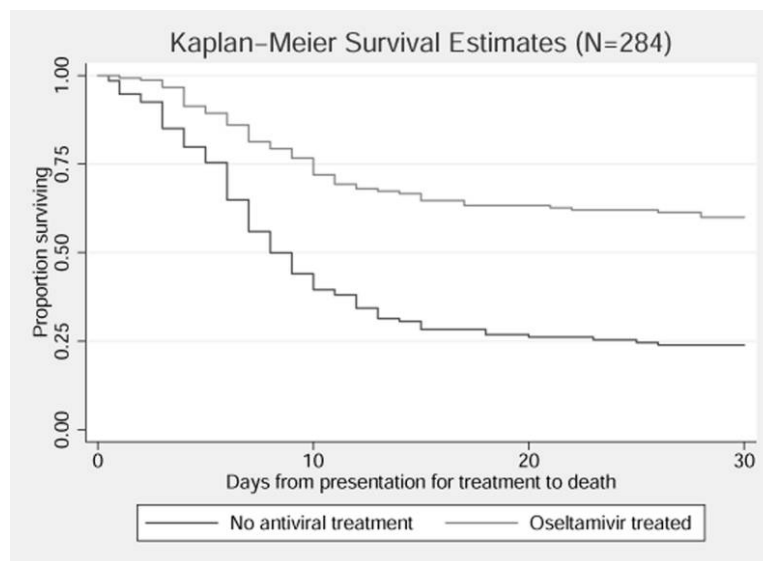
Survival in patients who received oseltamivir for longer than the standard 5-day duration of treatment usually given for seasonal influenza was available for 20 patients; other patients may have been treated for >5 days but treatment start and stop dates were not available in the records. The median duration was 7 days (range, 6–26 days); 75% (15/20) of these patients survived. Two patients stopped oseltamivir therapy after 8 days: one patient on multiple medications exhibited hepatomegaly and had all medications withdrawn; a second patient had oseltamivir withdrawn following a complaint of severe headache and vomiting. Both of these patients survived.

Fourteen patients received doses higher than those routinely used for the treatment of seasonal influenza: 50% (7/14) sur-

vived; one patient stopped oseltamivir at day 8 of therapy, due to severe headache and vomiting (the same patient mentioned in the preceding paragraph).

## DISCUSSION

This study represents the largest multinational repository of data on cases of avian influenza. Cases were selected without regard to treatment and are likely to represent typical cases that present for medical attention, as is common practice with patient registries [14]. We observed that infection with H5N1 carries a high mortality rate (56.5%) and is lower in older age groups. Mortality reaches 76% in the absence of antiviral treatment; receipt of oseltamivir reduces crude overall mortality to 40%. Multivariate modeling, which incorporated all statistically significant measured treatment predictors, showed an overall benefit of a 49% reduction in mortality risk from treatment with oseltamivir.



**Figure 3.** Kaplan-Meier survival curves showing receipt of oseltamivir compared with no antiviral treatment.

These data were abstracted from various sources, some data were missing, and the data that were obtained reflect the various recording conventions of individual clinicians and institutions. Because all subjects did not have detailed information on the number of doses of oseltamivir received, patients who received even a single dose of oseltamivir before death were classified as having been treated with oseltamivir. One can speculate that these were patients in extremis, and their inclusion may understate the clinical utility of oseltamivir in patients who are not immediately moribund. Sensitivity analyses were performed to examine the extent to which our findings were dependent on recorded source, country, and background mortality from H5N1. The survival benefit from treatment with oseltamivir up to 6 days after symptom onset was evident in all record sources and also was evident ( $P \leq .05$ ) in countries with high and low survival rates from H5N1.

A clear benefit was evident from treatment with oseltamivir, even when treatment was delayed, with maximum benefit accruing when therapy was administered within 2 days of onset of illness. The fact that 75% of patients die when they are not treated with appropriate antivirals indicates that H5N1 is a highly virulent virus, which in turn proffers suggestions as to both pathogenesis and additional lines of treatment to explore.

Progressive infections associated with multiorgan dysfunction and a high lethality suggest immune dysfunction [41]; indeed, previous work points strongly to cytokine dysregulation playing a role in the pathogenesis of H5N1 mortality [42, 43]. This is compatible with the notion that early intervention with antivirals prevents viral load accumulating to a level that it triggers an injurious and ongoing immune response, including hypercytokinemia. Direct support for the role of cytokine dysregulation comes from work showing that H5N1 infection induces high levels of proinflammatory cytokines, including interferons, tumor necrosis factor  $\alpha$ , interferon- $\gamma$ -induced protein 10, and interleukin 6, among others [42]. De Jong et al [43] showed a correlation between H5N1 viral load and a number of immune parameters and found higher cytokine and chemokine levels in H5N1 patients than those detected patients with seasonal influenza, and especially so in H5N1 patients who died. The immune response to H5N1 infection is doubtless complex, with Deng et al [44] having reported finding quite different cytokine response patterns in 2 lethal cases of infection. Whatever type of hypercytokinemia results, however, the trigger is likely to be a high viral load, underpinning the argument in favor of early antiviral therapy in human H5N1 infections.

Prolonged viral shedding and a high viral reproduction rate, as seen with H5N1, suggest that higher doses and longer durations of antiviral therapy may be needed, and registry cases treated with nonstandard regimens did not appear to suffer adverse outcomes and may have benefited. The missing part of the

puzzle required to reduce mortality even further, once higher antiviral exposures have been fully explored, may be therapies directed at blunting detrimental inflammatory responses.

Although this registry represents the largest global detailed patient data set on H5N1 cases, many questions remain unanswered. For example, it has been suggested that oseltamivir be used in combination with other antivirals, principally amantadine, where resistance patterns make this a rational combination, in that such combination therapy may promote efficacy and retard emergence of transmissible resistant virus strains. The very small number of patients in this study who had received a combination that contained oseltamivir, 3 in all, unfortunately precludes the drawing of any conclusions on the clinical efficacy of such combinations. Nonetheless, these registry data, by virtue of their numbers and scope, provide important information on treatment patterns and outcomes for a wide variety of patients treated under a variety of conditions across the world.

These findings have important implications for clinical management. These data show that humans infected with H5N1 face near certain death unless prescribed effective antiviral treatment, preferably within 2 days of symptom onset, although benefit remains even with treatment initiation up to about 5–6 days after symptom onset, possibly a reflection of prolonged viral replication in human H5N1 infection. Thus, there is still benefit from initiating treatment with oseltamivir in patients who present relatively late in the course of their illness, and clinicians should be mindful not to assume that all is lost in such patients.

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