Determinants of Antiviral Effectiveness in Influenza Virus A Subtype H5N1

Article *in* The Journal of Infectious Diseases · August 2012

DOI: 10.1093/infdis/jis509 · Source: PubMed

Journal of Infectious Diseases Advance Access published September 12, 2012

MAJOR ARTICLE

Determinants of Antiviral Effectiveness in Influenza Virus A Subtype H5N1

Paul K. S. Chan,[1] Nelson Lee,[1] Mukhtiar Zaman,[3] Wiku Adisasmito,[4] Richard Coker,[5] Wanna Hanshaoworakul,[7] Viktor Gasimov,[8] Ahmet Faik Oner,[9] Nazim Dogan,[10] Owen Tsang,[2] Bounlay Phommasack,[11] Sok Touch,[12] Ebun Bamgboye,[13] Anna Swenson,[14] Stephen Toovey,[6] and Nancy A. Dreyer[14]

[1]Faculty of Medicine, Chinese University of Hong Kong, and [2]Hospital Authority Infectious Disease Centre, Princess Margaret Hospital, Kowloon, Hong Kong Special Administrative Region; [3]Khyber Teaching Hospital, Peshawar, Pakistan; [4]Department of Health Policy and Administration, University of Indonesia, Depok, Indonesia; [5]London School of Hygiene and Tropical Medicine, and [6]Department of Infection and Immunity, Academic Centre for Travel Medicine and Vaccines, Royal Free and University College Medical School, London, United Kingdom; [7]Ministry of Public Health, Nonthaburi, Thailand; [8]Azerbaijan Ministry of Health, Baku, Azerbaijan; [9]Yuzuncu Yil University, Van, and [10]Ataturk University Medical School, Erzurum, Turkey; [11]Ministry of Health, Lao People's Democratic Republic; [12]Ministry of Health, Cambodia; [13]Nephrology, St Nicholas Hospital, Lagos, Nigeria; and [14]Quintiles Outcome, Cambridge, Massachusetts

Background. Oseltamivir is widely used as treatment for influenza virus A subtype H5N1 (hereafter, "H5N1") infection but, like any intervention, is not always effective.

Methods. We used Avian Influenza Registry data from 10 countries to examine the risk of death in 215 patients with confirmed H5N1 infection who were treated with oseltamivir, according to viral clade, age, respiratory failure, and adjunctive treatment with corticosteroids or antibiotics.

Results. The median age of infected individuals was 18 years, and 50% were male. The highest fatality rate occurred in a country with clade 2.1 virus circulation, and the lowest occurred in countries with clade 2.2 virus circulation ($P < .001$). In univariate analyses, age of ≤5 years and treatment ≤2 days after symptom onset were protective against fatality. When accounting for all risk factors, early initiation of oseltamivir was found to be particularly effective in individuals without respiratory failure (odds ratio, 0.17; $P = .04$). Patients who had advanced respiratory failure requiring ventilatory support at the time of oseltamivir initiation were more likely to die from the episode of H5N1 infection than patients who did not ($P < .001$). Adjunctive therapy did not improve the likelihood of surviving the episode.

Conclusions. Oseltamivir is especially effective for treating H5N1 infection when given early and before onset of respiratory failure. The effect of viral clade on fatality and treatment response deserves further investigation.

Human cases of influenza virus A subtype H5N1 (hereafter, "H5N1") infection continue to be reported, with outbreaks in Bangladesh, Cambodia, Indonesia, and Egypt in 2011 [1]. Additionally, a large and ineradicable avian reservoir of H5N1 remains ready to seed further human outbreaks. Oseltamivir is the current de facto antiviral of choice for treatment of H5N1 infection, but, as with any intervention, it is not equally effective in all situations and for all patients. Most data on human H5N1 infection come from case series and meta-analyses of country-specific data [2]. While these provide a useful overview of issues and trends, they cannot substitute for systematic analyses of pooled data, which should provide more accurate information, especially for subgroups. For this reason, the global Avian Influenza Registry (hereafter, the "Registry"; available at: http://ww.avianfluregistry.org) was created in 2006 to collect systematic information on human cases for pooled analysis.

The benefits of oseltamivir, compared with no treatment, on survival from H5N1 infection have been reported previously [3]. The purpose of this analysis is to examine cases of H5N1 infection treated with oseltamivir, to understand the factors (demographic, virologic, and clinical) that influence the treatment's

Received 26 January 2012; accepted 25 April 2012.

Correspondence: Nancy A. Dreyer, PhD, MPH, Quintiles Outcome, 201 Broadway, Cambridge, MA 02139 (ndreyer@outcome.com).

The Journal of Infectious Diseases

DOI: 10.1093/infdis/jis509

effectiveness, which may provide useful information to guide clinical management.

METHODS

The Registry is a systematic program for accruing data on human cases of H5N1 infection. Data were abstracted from clinical records, published case series, and governmental agency reports, using a standardized data collection form. When information from the same cases was available from both publications and medical records and discrepancies were detected, the medical record was used as the primary source. Information was recorded about exposures, clinical signs, symptoms, treatments, and outcomes; case ascertainment and data collection methods are described elsewhere in detail [3, 4]. As of 8 March 2012, the Registry contained 407 laboratory-confirmed cases of H5N1 infection from 13 countries.

Altogether, 229 patients received oseltamivir treatment, and 178 did not. For the purpose of these analyses, all 229 patients who received oseltamivir treatment were eligible for inclusion in this study. Six patients who received another antiviral in addition to oseltamivir (ribavirin for 2 patients and rimantadine, amantadine, acyclovir, and methisoprinol for 1 patient each) and 8 who received a subtherapeutic dose of oseltamivir (defined as at least 1 dose less than the standard recommended dose) were excluded from analysis (Figure 1). For the purpose of this analysis, patients were assumed to have received standard doses if their records indicated neither suboptimal dosing nor suboptimal therapy duration (n = 147). Thus, the analysis population consisted of 215 patients who received oseltamivir.

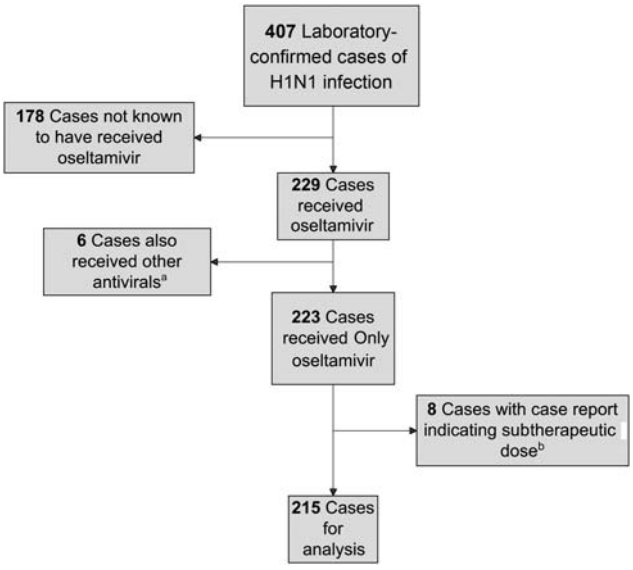

Figure 1. Selection of cases of influenza virus A subtype H5N1 infection for analysis. [a]Other antivirals included ribavirin (for 2 patients), amantadine (for 1), rimantadine (for 1), acyclovir (for 1), and methisoprinol (for 1). [b]A subtherapeutic dose was defined as anything less than the standard dose, defined as follows: age ≥13 years: 75 mg twice daily; age 1–12 years: 30 mg twice daily for individuals weighing ≤15 kg or less, 45 mg twice daily for those weighing >15 to 23 kg, 60 mg twice daily for those weighing >23 to 40 kg, and 75 mg twice daily for those weighing >40 kg. No standard dosing is available for children <1 year old.

Patients who also received corticosteroids and/or antibiotic treatment were compared with oseltamivir-treated patients who had not received these comedications under examination. Patients whose source documents did not include any information about the comedications of interest were excluded from these analyses. The timing of initiation of each medication was also examined in relation to case fatality.

Presumed viral clade for each case was assigned on the basis of location and year of infection with reference to the known clade in circulation at the time [2, 5–11]. When 2 clades were reported from the same country in a given year, clade was determined by successfully matching the case to published case reports that included information about the specific clade [12–14].

Patients were categorized by age (0–5, 6–13, and ≥14 years) to investigate possible age-related outcome effects. Fourteen years of age was chosen as the cut point between children and adults to reflect the approximate maturation of the immune system, and ≤5 years of age was selected to highlight effects in children [15–17]. Age was analyzed categorically, not as a continuous variable, because earlier reports have shown a nonlinear relationship between age and fatality [18].

Respiratory failure, defined as a requirement for intubation and mechanical ventilation, was included as a measure of illness severity. We assumed that respiratory failure did not occur unless there was specific documentation of intubation and mechanical failure. Respiratory parameters, including degree of oxygen desaturation and supplemental oxygen requirement (ie, data on the fraction of inspired O_2), were rarely available and thus were not analyzed.

The study's primary outcome of interest was death. Univariate associations of fatality with demographic, epidemiologic, and treatment variables were examined. χ^2 or Fisher exact tests were used for comparisons between categorical variables. The Wilcoxon rank-sum test was used to examine continuous variables if they were not normally distributed. Kaplan-Meier curves were used to analyze survival. The log-rank test was used to compare median time to death between groups.

All variables significant at an α level of 0.20 in the univariate models were included in a multivariate logistic regression model. Variables for which >50% of cases were missing data were not included in the multivariate model, regardless of significance level; thus, time from symptom onset to first presentation for any medical care, use of antibiotics, and use of corticosteroids were omitted from multivariate analyses. The

group with the highest fatality rate was chosen as the reference group for comparison of categorical variables. All analyses were conducted using SAS, version 9.2 (SAS Institute, Cary, NC).

RESULTS

The analysis population comprised 215 oseltamivir-treated patients from 10 countries: Azerbaijan (6 patients), Cambodia (6), China (5), Egypt (77), Indonesia (46), Laos (2), Pakistan (3), Thailand (17), Turkey (8), and Vietnam (45). Registry cases from 3 other countries were not treated with oseltamivir and were therefore excluded. All cases were diagnosed between 2003 and 2011. The median age was 18 years (range, 0.7–75 years), and 50% of patients were male. Case-fatality rates (CFRs) by country and presumed viral clade are shown in Table 1. The highest CFR among clades (ie, those for which >1 case was reported) was observed in Indonesia, where clade 2.1 was circulating; the lowest CFRs were observed in countries where clade 2.2 was circulating ($P < .001$).

The independent effects of age, sex, and timing of oseltamivir initiation on fatality are shown in Table 2. Although there was little difference in survival between sexes, children aged ≤5 years had lower fatality rates than older patients. The CFR among patients who received treatment ≤2 days after symptom onset was 18.2%, compared with 62.8% for those receiving treatment later; the CFR was 23.4% for 64 patients who were missing data on the timing of oseltamivir initiation.

Table 1. Case-Fatality Rate (CFR) Among Patients Who Received Oseltamivir for Treatment of Influenza Virus A Subtype H5N1 Infection, by Presumed Virus Clade and Country

Virus Clade, Country	CFR, Proportion (%) of Patients
Overall	100/215 (46.5)
Clade 1	28/59 (47.5)
Cambodia	4/6 (66.7)
Thailand	12/17 (70.6)
Vietnam	12/36 (33.3)
Clade 2.1	
Indonesia	39/46 (84.8)
Clade 2.2	23/94 (24.5)
Azerbaijan	3/6 (50.0)
Egypt	17/77 (22.1)
Pakistan	1/3 (33.3)
Turkey	2/8 (25.0)
Clade 2.3	9/15 (60.0)
China	1/4 (25.0)
Lao	2/2 (100)
Vietnam	6/9 (66.7)
Clade 7	
China	1/1 (100)

Table 2. Demographic and Treatment Characteristics Among Patients Who Received Oseltamivir for Treatment of Influenza Virus A Subtype H5N1 Infection, by Patient Outcome

Characteristic	Proportion (%) of Patients Who Died (n = 100)	Who Survived (n = 115)	P[a]
Male sex	44/100 (44.0)	64/115 (55.7)	.088
Age, y			<.001
0–5	12/100 (12.0)	43/115 (37.4)	<.001
6–13	17/100 (17.0)	14/115 (12.2)	.315
≥14	71/100 (71.0)	58/115 (50.4)	.002
Pharmacologic treatment, initiation time			
Oseltamivir, ≤2 days after symptom onset[b]	4/85 (4.7)	18/66 (27.3)	<.001
Corticosteroids and oseltamivir, any	37/58 (63.8)	13/30 (43.3)	.066
Antibiotics and oseltamivir, any[c]	53/53 (100)	26/27 (96.3)	.338[d]

[a] By the χ^2 test, unless otherwise indicated.

[b] A total of 64 patients were missing data on timing of oseltamivir initiation.

[c] Only 1 patient with documented medications did not receive antibiotics.

[d] By the Fisher exact test.

Adjunctive treatment with antibiotics did not affect survival, whereas corticosteroid comedication may have been associated with a higher CFR. Review of the range of times to initiation of treatment with oseltamivir among patients with information on date of presentation for medical care (Figure 2) revealed that the probability of surviving the infection decreased with the delay in starting oseltamivir and was significantly

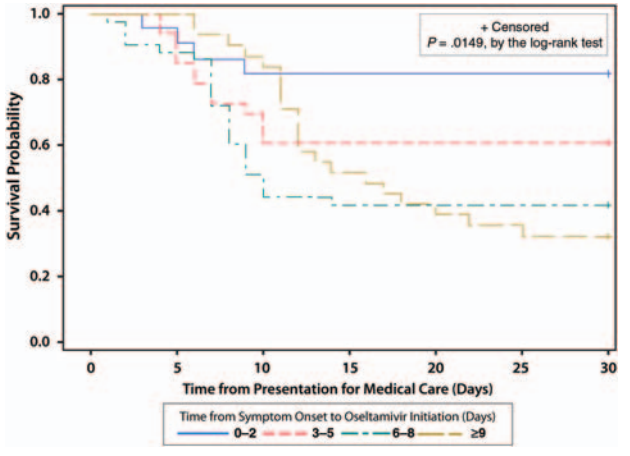

Figure 2. Survival among 129 patients with influenza virus A subtype H5N1 infection, by interval between oseltamivir initiation and symptom onset. A total of 86 patients for whom data on the time of first presentation for medical care or the time from symptom onset to oseltamivir initiation were excluded from the analysis.

Table 3. Times to Presentation for Medical Care and Initiation of Treatment Among Patients Who Received Oseltamivir for Treatment of Influenza Virus A Subtype H5N1 Infection, by Patient Outcome

Variable	No. of Patients	Days, Median (Range)		*P*
		Patients Who Died (n = 100)	Patients Who Survived (n = 115)	
Time from symptom onset to				
To first presentation for medical care	92	1 (−2 to 10[a])	2 (0–20)	.039
To hospital admission	207	6 (0–20)	3 (0–20)	<.001
Time from symptom onset to treatment with				
Oseltamivir alone or in combination	151	7 (0–23)	5 (0–20)	<.001
Corticosteroid	28[b]	6 (1–16)	7 (2–9)	.762
Antibiotic	65[b]	5 (0–11)	4.5 (1–15)	.560
NSAID	31[b]	4 (0–11)	3 (0–7)	.393

Abbreviation: NSAID, nonsteroidal antiinflammatory drug.

[a] One case presented for prophylaxis 2 days before onset of symptoms. Note: Wilcoxon rank-sum test was used to test the difference in median days between fatal and surviving cases.

[b] Includes patients for whom timing of corticosteroids, antibiotics, or NSAID initiation is known, whether or not timing of oseltamivir initiation is known.

Table 4. Timing of Respiratory Failure and Death in Relationship to Symptom Onset and Oseltamivir Initiation Among 215 Patients Who Received Oseltamivir for Treatment of Influenza Virus A Subtype H5N1 Infection

Variable	No. of Patients	Days, Median (Range)
Time from symptom onset to		
Respiratory failure	54[a]	7 (4 to 15)
Death	96	10 (3 to 32)
Oseltamivir treatment in patients with respiratory failure	71[b]	7 (1 to 21)
Oseltamivir treatment in patients without respiratory failure	80	5 (0 to 23)
Time from oseltamivir initiation to		
Respiratory failure	52	0 (−10 to 11)
Death	85	4 (1–19)

[a] Data are for patients for whom the time of respiratory failure was known.

[b] Data are for patients with known respiratory failure and for whom the time of oseltamivir initiation was known.

different for intervals of 0–2 days (for 22 patients), 3–5 (for 33), 6–8 (for 43), and ≥9 days (for 31; $P = .015$).

Table 3 shows the differences in survival by time of presentation for medical care and treatment initiation among 151 patients with information on timing for both variables. Patients who died presented to the hospital substantially later after symptom onset than survivors (median interval, 6 vs 3 days; $P < .001$) and received oseltamivir later (median interval, 7 vs 5 days; $P < .001$). There was no significant difference between patients who died and those who survived with regard to the timing of initiation of corticosteroids, antibiotics, and/or nonsteroidal antiinflammatory drugs.

The CFR was much higher among the 137 patients who developed respiratory failure and required mechanical ventilation, compared with patients who did not (89.7% vs 21.9%). The median time from symptom onset to respiratory failure was 7 days, and the median time to death was 10 days (Table 4). Patients who had respiratory failure at the time of treatment initiation were more likely to die from H5N1 infection than patients who did not require ventilation when oseltamivir was initiated ($P < .001$). The median time from oseltamivir initiation to respiratory failure was 0 days (range, −10 to 11 days), indicating that, for most patients who developed respiratory failure, oseltamivir was not initiated until their illness had reached an advanced stage. In addition, the time to first oseltamivir treatment was shorter for patients who did not develop respiratory failure, compared with those who did, although the difference was not statistically significant (median interval, 5 vs 7 days).

When predictors of fatality were examined using a multivariate logistic regression model, viral clade, absence of respiratory failure at or before the time of oseltamivir initiation, and initiation of oseltamivir treatment ≤2 days after symptom onset were the strongest predictors of survival (Table 5). It is worth noting that, after adjustment for confounders, analysis revealed that patients aged ≤5 years had a 66% lower fatality risk than patients aged ≥14 years, although the difference was not statistically significant (odds ratio [OR], 0.34; 95% CI, .08–1.34). Infection with clade 1 viruses (OR, 0.09; 95% CI, .03–.33), clade 2.2 viruses (OR, 0.20; 95% CI, .04–.89), and clade 2.3 viruses (OR, 0.03; 95% CI, .01–.40) were associated with a greater odds of surviving the episode, compared with clade 2.1 viruses. Oseltamivir treatment initiated ≤2 days after symptom onset was shown to be associated with an 83% lower fatality risk, compared with treatment initiated later (OR, 0.17; 95% CI, .03–1.04), in analyses that adjusted for respiratory failure, age, sex, clade, and time from symptom onset to hospitalization. In contrast, patients with respiratory failure before or on the same day as oseltamivir initiation showed an almost 20-fold increased risk of death due to H5N1 infection (OR, 19.50; 95% CI, 4.19–90.84), compared with patients who never developed respiratory failure or developed it after starting oseltamivir therapy. In a separate subgroup analysis of 178

Table 5. Multivariate Analyses of Mortality Among Patients Who Received Oseltamivir for Treatment of Influenza Virus A Subtype H5N1 Infection

	Unadjusted Analysis		Adjusted Analysis[a]	
Variable	No. of Subjects	OR (95% CI)	OR (95% CI)	*P*
Age, y	215			
0–5		0.23 (.11–.47)	0.34 (.08–1.34)	.122
6–13		0.99 (.45–2.18)	0.97 (.24–3.99)	.965
≥14		Reference	Reference	
Male sex	215	0.63 (.37–1.07)	0.68 (.27–1.72)	.417
Viral clade (country)	215			
Clade 1 (Thailand, Vietnam, Cambodia)		0.16 (.06–.42)	0.09 (.03–.33)	<.001
Clade 2.1 (Indonesia)		Reference	Reference	
Clade 2.2 (Azerbaijan, Egypt, Pakistan, Turkey)		0.06 (.02–.15)	0.20 (.04–.89)	.035
Clade 2.3 (Vietnam, China, Laos)		0.27 (.07–1.00)	0.03 (.01–.40)	.007
Clade 7[b] (China)	NA	…	…	
Time from symptom onset to hospital admission, per day	207	1.26 (1.13–1.40)	1.02 (.88–1.17)	.813
Early oseltamivir treatment (≤2 d vs >2 d after symptom onset)	151	0.13 (.04–.41)	0.17 (.03–1.04)	.055
Respiratory failure/mechanical ventilation at time of initiating oseltamivir	189	27.82 (8.12–95.31)	19.50 (4.19–90.84)	<.001

Abbreviations: CI, confidence interval; NA, not available; OR, odds ratio.

[a] Data are for 130 patients and are adjusted for all other variables in the table.

[b] The 1 patient with clade 7 infection could not be included in the model because of quasi-complete separation of data points.

patients who did not have respiratory failure when initiating oseltamivir treatment (113 patients had enough information to be retained in the model), early oseltamivir treatment (ie, treatment initiated ≤2 days after symptom onset) showed a strong survival benefit (OR, 0.17; 95% CI, .03–.89; $P = .04$), after adjustment for confounders.

DISCUSSION

Our analysis showed that oseltamivir, when initiated ≤2 days after symptom onset, has the strongest impact on survival among H5N1-infected patients, even after adjustment for other factors that influence survival. There is some evidence to suggest an increased survival likelihood when treatment was initiated as late as 3–5 days after symptom onset, before respiratory failure occurred; this finding was particularly apparent when treated patients were compared with untreated patients [3]. The consistent evidence that prompt initiation of antiviral therapy confers a significant survival benefit to individuals with H5N1 infection supports the need to improve access to antivirals and to start empirical treatment for patients for whom H5N1 infection is strongly suspected, even prior to virological confirmation [3, 17, 19]. In settings without ready recourse to virological tests, this may be especially important.

Age, development of respiratory failure, and viral clade are also shown to be important determinants of survival. In this case series, children aged ≤5 years showed greater survival than older cases [16], consistent with reports from smaller case series [18, 20–23]. A plausible explanation for this finding might be that children in this age group mount a less flamboyant inflammatory response, but whether it is related to less prior exposure to influenza viruses or to age-related immunological immaturity is unclear. Respiratory failure at time of treatment initiation carries a graver prognosis, which suggests that severe inflammatory damage in association with H5N1 pneumonias can be difficult to reverse, again highlighting the need for early therapeutic intervention. Our data on clade should be interpreted with caution, in part because clade was extrapolated but not virologically determined. However, this grouping might contribute to understanding some geographical variations in patient outcomes. Published variations in in vitro strain sensitivity to oseltamivir generally show sensitivities to drug concentrations well below the minimum in vivo concentrations achieved during therapy [12, 24–27]. Clade 2.1, with the highest mortality worldwide, was reported only from Indonesia. Since the circulating virus clade and country are intractably intertwined, the higher mortality associated with clade 2.1 may also be due to differences in access to or delivery of healthcare services, oseltamivir availability, or other factors. Interestingly, Indonesian cases generally presented for medical care sooner (median interval between symptom onset and presentation, 0 days), compared with all other countries (median interval, 2 days). However, oseltamivir treatment was typically not initiated in Indonesia until a median of 7 days after

symptom onset, compared with a median of 6 days for all other countries. This line of reasoning is supported by the finding that, looking only at the Indonesian cases, early treatment with oseltamivir still appears to have been associated with reduced mortality (OR, 0.11; 95% CI, .01–1.05), indicating the effectiveness of this agent against clade 2.1 in Indonesia.

Like all rigorous observational studies drawn from existing data, these registry data were abstracted following a standard protocol. Nonetheless, the original data were not recorded for the purpose of this study, making it sometimes difficult to determine whether an event did not occur, whether treatment was not given, or whether these events occurred without having been recorded. For example, for "respiratory failure," we assumed that this event did not occur unless there were specific notations documenting intubation and mechanical ventilation. We tested the sensitivity of our analyses to this assumption by comparing 24 patients whose records clearly documented "no respiratory failure" with 113 patients whose records had no information indicating the presence of respiratory failure. The CFR among patients with unknown information on respiratory failure (12.5%) was lower than that among patients with documented absence of respiratory failure (32.3%). Both CFRs were quite different from the CFR for patients with respiratory failure (89.7%), suggesting that it was reasonable to combine the 2 groups and unlikely that respiratory failure was misclassified for patients who required mechanical ventilation and intubation but did not receive these services because facilities were unavailable.

Limited information available on the timing of events resulted in small numbers in some subgroup analyses of treatment combinations and timing. For instance, only 10% of patients (22) received oseltamivir ≤2 days after symptom onset, and timing of oseltamivir treatment was unavailable for 30% of patients (64). The date of hospitalization was available for 96% of patients, but the date of first presentation for medical attention was often missing (in 57% of patients). We examined the effect of missing data on early treatment by conducting an analysis restricted to patients with "known" dosage, and the results were similar to those conducted using all oseltamivir-treated patients. Also a previous investigation of missing data showed that the survival benefits of oseltamivir and timing of treatment initiation were essentially unchanged after augmentation by multiple imputation of missing data [28, 29].

For cases that included information on the timing of key events, it remained challenging to disentangle the effects of related timing of events, namely, presentation for medical care and initiation of oseltamivir treatment. Because early treatment was defined as initiation ≤2 days after symptom onset and because late presentation for medical care was defined as presentation >2 days after symptom onset, these categories are mutually exclusive, and it would not be possible for a case to have presented "late" for medical attention and to have been treated ≤2 days after symptom onset. An interaction term for early treatment and timing of hospitalization was introduced into our model, but it was not significant ($P = .957$) and was excluded from the final model.

We conducted 2 sensitivity analyses to examine the potential for treatment effectiveness to be confounded or modified by the timing of presentation for medical care, since this variable was excluded from the multivariate model because >50% of cases were missing this information. In the first sensitivity analysis, we conducted a stratified Mantel-Haenszel analysis of survival, early oseltamivir treatment, and early presentation for medical care (≤2 days after symptom onset); however, because a patient presenting late for medical care *cannot* receive early oseltamivir treatment (unless treatment/prophylaxis was given as part of a public health campaign), the OR of death could not be calculated because of 0 cell counts. A logistic regression model containing only early oseltamivir treatment and the time from symptom onset to first presentation for medical care, as well as an interaction term between the two, did not result in a significant interaction ($P = .431$; n = 83). The same model, in which time from symptom onset to oseltamivir (continuous) was substituted for early oseltamivir treatment, also did not result in a significant interaction term ($P = .790$). In the second sensitivity analysis, when simultaneous adjustment was performed for early oseltamivir treatment and timing of presentation, early oseltamivir treatment was strongly associated with improved survival (OR, 0.13; 95% CI, .03–.56). Thus, the small number of cases precluded extensive modeling for interaction, even though our study represents the largest H5N1 series available anywhere, yet it appears that the timing of first presentation for medical care does not explain the relationship observed here between early oseltamivir treatment and survival. While the absence of data is always disappointing, having missing data was not a correlate of poor treatment or poor prognosis (CFR, 51.9% for patients with complete data and 38.1% for patients with incomplete data). Rather, the pattern of missing data largely reflects variations in source documents, which differed by country and information type (eg, medical records vs data reported to public health departments), and appears to be unrelated to any particular patient characteristics.

Overall, our analyses provide further evidence of the effectiveness of treating H5N1 infection with oseltamivir, especially early after symptom onset. These data do not support a benefit of adding either corticosteroids or antibiotics to oseltamivir therapy. However, although corticosteroids might negatively impact survival, this observation may simply reflect "last ditch" therapy for moribund individuals. Corticosteroid use in severe cases of non-H5N1 infection is associated with prolonged viral shedding, which might also explain our findings;

increased corticosteroid-associated mortality has also been reported in smaller case series of H5N1 infection [30–33]. For patients presenting late in the course of their illness with respiratory failure, newer therapeutic approaches in addition to oseltamivir treatment should be studied.

Notes

Acknowledgment. N. A. D. had full access to all the data in the study and made the final decision to submit for publication.

Disclaimer. F. Hoffmann-La Roche provides scientific collaboration and has rights to nonbinding review of manuscripts but does not have the right to choose authors or manuscript topics; nor does it have the right to final approval of the wording of any manuscripts.

Financial support. This work is funded by a contract to Quintiles Outcome from F. Hoffmann-La Roche.

Potential conflicts of interest. W. A., M. Z., N. D. and A. F. O. received modest support to facilitate data collection and review. R. C. has received funding from F. Hoffmann-La Roche, the manufacturer of oseltamivir. P. K. S. C. and N. L. received funding support from F. Hoffmann-La Roche for an investigator-initiated study. P. K. S. C. received a consultant fee from F. Hoffmann-La Roche. N. A. D and A. S. are employed by Quintiles Outcome, a company that specializes in patient registries and which received funding from F. Hoffmann-La Roche to create and conduct the registry study. S. T. is a former employee and a paid consultant to F. Hoffmann-La Roche and has been reimbursed by a number of influenza vaccine manufacturers. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. World Health Organization. Cumulative number of confirmed human cases for avian influenza A(H5N1) reported to WHO, 2003–2011. 10 October **2011**. http://www.who.int/influenza/human_animal_interface/EN_GIP_20111010CumulativeNumberH5N1cases.pdf. Accessed 15 December 2011.
2. Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza A(H5N1) Virus. Update on avian influenza A(H5N1) virus infection in humans. N Engl J Med **2008**; 358:261–73.
3. Adisasmito W, Chan PKS, Lee N, et al. Effectiveness of antiviral treatment in human influenza H5N1 infections: analysis from a global patient registry. J Infect Dis **2010**; 202:1154–60.
4. Dreyer N, Starzyk K, Wilcock K, Toovey S. A global Registry for understanding clinical presentation, treatment outcomes and survival from human avian influenza. Bangkok, Thailand: BIOTEC, **2008**:155.
5. World Health Organization. Continuing progress towards a unified nomenclature system for the highly pathogenic H5N1 avian influenza viruses—full tree, January, **2009**. March 2009. http://www.who.int/csr/disease/avian_influenza/guidelines/nomenclature/en/index.html. Accessed 28 September 2011.
6. World Health Organization. Antigenic and genetic characteristics of influenza A(H5N1) and influenza A(H9N2) viruses and candidate vaccine viruses developed for potential use in human vaccines. 17 February **2011**. http://www.who.int/csr/disease/avian_influenza/guidelines/h5n1virus/en/index.html. Accessed 28 September 2011.
7. Uyeki TM. Human infection with highly pathogenic avian influenza A(H5N1) virus: review of clinical issues. Clin Infect Dis **2009**; 49:279–90.
8. World Health Organization. Evolution of H5N1 avian Influenza viruses in Asia. Emerg Infect Dis **2005**; 11:1515–21.
9. Puthavathana P, Sangsiriwut K, Korkusol A, et al. Avian influenza virus (H5N1) in human, Laos. Emerg Infect Dis **2009**; 15:127–9.
10. Kitphati R, Pooruk P, Lerdsamran H, et al. Kinetics and longevity of antibody response to influenza A H5N1 virus infection in humans. Clin Vaccine Immunol **2009**; 16:978–81.
11. Zaman M, Ashraf S, Dreyer N, Toovey S. An extended review of human infection with influenza H5N1 virus in North West Frontier Province (NWFP), Pakistan, in 2007. Emerg Infect Dis **2011**; 17: 1056–9.
12. Le MTQ, Wertheim HFL, Nguyen HD, et al. Influenza A H5N1 clade 2.3.4 virus with a different antiviral susceptibility profile replaced clade 1 in humans in Northern Vietnam. PLoS One **2008**; 3: e3339.
13. Nguyen TD, Nguyen TV, Vijaykrishna D, et al. Multiple sublineages of influenza A virus (H5N1), Vietnam, 2005–2007. Emerg Infect Dis **2008**; 14:632–6.
14. Le QM, Ito M, Muramoto Y, et al. Pathogenicity of highly pathogenic avian H5N1 influenza A viruses isolated from humans between 2003 and 2008 in northern Vietnam. J Gen Virol **2010**; 91: 2485–90.
15. Janeway C Jr, Travers P, Walport M, Capra JD. Immunobiology: The immune system in health and disease. Fourth ed. London: Taylor & Francis Inc.; **1999**.
16. Mahon BP. The rational design of vaccine adjuvants for mucosal and neonatal immunization. Curr Med Chem **2001**; 8:1057–75.
17. Oner AF, Dogan N, Gasimov V, et al. H5N1 avian influenza in children. Clin Infect Dis **2012**; 55:26–32.
18. Abdel-Ghafar AN, Chotpitayasunondh T, Gao Z, et al. Update on avian influenza A(H5N1) virus infection in humans. N Engl J Med **2008**; 358:261–73.
19. de Jong MD, Simmons CP, Thanh TT, et al. Fatal outcome of human influenza a (H5N1) is associated with high viral load and hypercytokinemia. Nat Med **2006**; 12:1203–7.
20. Chan PKS. Outbreak of avian influenza A(H5N1) virus infection in Hong Kong in 1997. Clin Infect Dis **2002**; 34(Suppl 2):S58–64.
21. Update: WHO—confirmed human cases of avian influenza A(H5N1) infection, 25 November 2003–24 November 2006. Wkly Epidemiol Rec **2007**; 82:41–8. http://www.who.int/wer/2007/wer8206.pdf. Accessed 15 December 2011.
22. Yuen KY, Chan PKS, Peiris M, et al. Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. Lancet **1998**; 351:467–71.
23. Liem NT, Tung CV, Hien ND, et al. Clinical features of human influenza A(H5N1) infection in Vietnam: 2004–2006. Clin Infect Dis **2009**; 48:1639–46.
24. Hurt AC, Lowther S, Middleton D, Barr IG. Assessing the development of oseltamivir and zanamivir resistance in A(H5N1) influenza viruses using a ferret model. Antiviral Res **2010**; 87:361–6. Epub 2010 Jul 21.
25. Hurt AC, Selleck P, Komadina N, Shaw R, Brown L, Barr IG. Susceptibility of highly pathogenic A(H5N1) avian influenza viruses to the neuraminidase inhibitors and adamantanes. Antiviral Res **2007**; 73:228–31. Epub 2006 Nov 10. PubMed PMID: 17112602.
26. Earhart KC, Elsayed NM, Saad MD, et al. Oseltamivir resistance mutation N294S in human influenza A(H5N1) virus in Egypt. J Infect Public Health **2009**; 2:74–80. Epub 2009 May 27.
27. Boltz DA, Douangngeun b, Phommachanh P, et al. Emergence of H5N1 avian influenza viruses with reduced sensitivity to neuraminidase inhibitors and novel reassortants in Lao People's Democratic Republic. J Gen Virol **2010**; 91:949–59.
28. Adisasmito W, Chan PKS, Lee N, et al. Strengthening observational evidence for antiviral effectiveness in H5N1. J Infect Dis **2011**; 204:810–11.
29. Dreyer NA, Toovey S, Adisasmito W, et al.. Handling missing data in prospective registries. In: Abstract presented at Agency for Healthcare Research and Quality 3rd Symposium on Comparative Effectiveness Research Methods; 2011 Jun 6–7; Rockville, MD.

30. Lee N, Chan PK, Hui DS, et al. Viral loads and duration of viral shedding in adult patients hospitalized with influenza. J Infect Dis **2009**; 200:492–500.
31. Brun-Buisson C, Richard JC, Mercat A, Thiébaut AC, Brochard L; REVA-SRLF A/H1N1v 2009 Registry Group. Early corticosteroids in severe influenza A/H1N1 pneumonia and acute respiratory distress syndrome. Am J Respir Crit Care Med **2011**; 183:1200–6.
32. Abdel-Ghafar AN, Chotpitayasunondh T, et al. Writing committee of the second world health organization consultation on clinical aspects of human infection with avian influenza A(H5N1) virus. Update on avian influenza A(H5N1) virus infection in humans. N Engl J Med **2008**; 358:261–73.
33. Lee N, Hui DSC. Dexamethasone in community-acquired pneumonia. Lancet **2011**; 378:979–80.