Neuraminidase Inhibitors and Hospital Length of Stay: A Meta-analysis of Individual Participant Data to Determine Treatment Effectiveness Among Patients Hospitalized With Nonfatal 2009 Pandemic Influenza A(H1N1) Virus Infection

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(See the Editorial commentary by Monto, on pages 340–2.)

Background.   The effect of neuraminidase inhibitor (NAI) treatment on length of stay (LoS) in patients hospitalized with influenza is unclear.

Methods.   We conducted a one-stage individual participant data (IPD) meta-analysis exploring the association between NAI treatment and LoS in patients hospitalized with 2009 influenza A(H1N1) virus (A[H1N1]pdm09) infection. Using mixed-effects negative binomial regression and adjusting for the propensity to receive NAI, antibiotic, and corticosteroid treatment, we calculated incidence rate ratios (IRRs) and 95% confidence intervals (CIs). Patients with a LoS of <1 day and those who died while hospitalized were excluded.

Results.   We analyzed data on 18 309 patients from 70 clinical centers. After adjustment, NAI treatment initiated at hospitalization was associated with a 19% reduction in the LoS among patients with clinically suspected or laboratory-confirmed influenza A(H1N1)pdm09 infection (IRR, 0.81; 95% CI, .78–.85), compared with later or no initiation of NAI treatment. Similar statistically significant associations were seen in all clinical subgroups. NAI treatment (at any time), compared with no NAI treatment, and NAI treatment initiated <2 days after symptom onset, compared with later or no initiation of NAI treatment, showed mixed patterns of association with the LoS.

Conclusions.   When patients hospitalized with influenza are treated with NAIs, treatment initiated on admission, regardless of time since symptom onset, is associated with a reduced LoS, compared with later or no initiation of treatment.

Keywords.   Neuraminidase inhibitors; pandemic influenza; IPD meta-analysis; length of stay, antivirals.

Seasonal influenza epidemics and pandemics increase pressure on hospital bed capacity. Early initiation of monotherapy with neuraminidase inhibitors (NAIs) reduces illness duration in patients with uncomplicated influenza [1–3]; associated reductions in complications, hospitalizations, and mortality are supported by systematic reviews of observational data [4–8]. The evidence is less clear that NAI treatment reduces length of stay (LoS) in hospitalized patients with influenza, compared with supportive care without antiviral treatment [9–15]. Minimizing the LoS is important in managing hospital surge and limiting healthcare costs due to seasonal influenza epidemics and pandemics. We undertook a one-stage individual participant data (IPD) [16] meta-analysis to explore the association between NAI treatment of patients hospitalized with 2009 pandemic influenza A(H1N1) virus (A[H1N1]pdm09) infection and the LoS during the 2009–2010 influenza pandemic.

METHODS

Details regarding identification of study centers and inclusion of patients have been published previously [6]. Briefly, we requested data from multiple clinical centers worldwide on patients admitted to hospital with laboratory-confirmed or clinically diagnosed A(H1N1)pdm09 infection for whom a minimum data set was available. Of the IPD that we received, we excluded patients who had laboratory-confirmed absence of A(H1N1) pdm09 infection, retaining only patients who had laboratory-confirmed A(H1N1)pdm09 infection and patients with clinically diagnosed pandemic influenza (ie, those for whom the clinical suspicion and working diagnosis was one of pandemic influenza but laboratory confirmation was not performed) [6].

The PRIDE study protocol was registered with the PROSPERO register of systematic reviews (CRD42011001273) prior to data collection [17]. This states that the study will investigate the impact of NAI treatment on multiple outcomes of public health interest in A(H1N1)pdm09-infected patients, using mixed-effects models. After collection and standardization of the data, sufficient data existed to assess 2 indicators of "severe hospital outcomes"—requirement for ventilatory support (ie, intensive care unit [ICU] admission) and LoS. In this article, we present the findings relating to the LoS.

Data Standardization, Exposure, and Outcome

We standardized data from individual data sets before we pooled the data (Supplementary Table 1). The primary outcome was the LoS (in whole days). We excluded patients with known receipt of NAI treatment before admission, to ensure uniform potential for treatment to influence the LoS. We excluded patients with continuing postdischarge NAI treatment; patients with a LoS <1 day, on the grounds that they would have received a maximum of 2 doses of NAI inpatient treatment and that their admission may have been precautionary; and patients with nosocomial influenza (defined as influenza with symptom onset after the hospital admission date; Figure 1). Finally, since rapid deterioration and early death during hospitalization would be an adverse outcome associated with a paradoxically short LoS, those who died in the hospital were excluded from analysis.

The primary exposure variable was in-hospital NAI treatment received on the day of hospital admission, compared with later or no NAI treatment. Additionally, where data were available, we defined 3 further exposure variables: NAI treatment
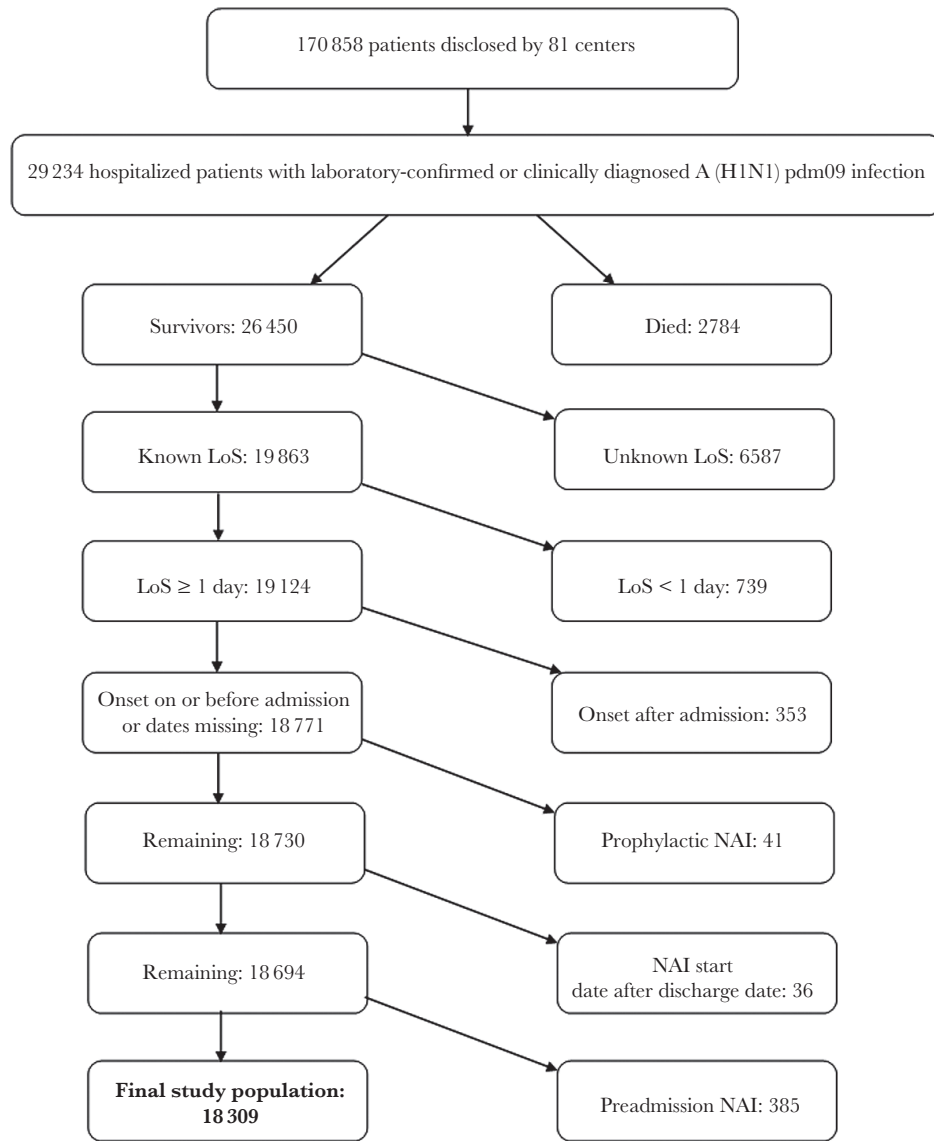
Figure 1. Identification of the study population. A(H1N1)pdm09, 2009 pandemic influenza A(H1N1) virus; LoS, length of stay; NAI, neuraminidase inhibitor.

(at any time) versus no NAI treatment, early NAI treatment (initiated within ≤2 days after symptom onset) versus no NAI treatment, and early NAI treatment versus later treatment (initiated >2 days after symptom onset).

Propensity Scores

We derived propensity scores via multivariable logistic regression for each exposure variable, as described by Hirano and Imbens [18], separately for individual study centers, based on patient characteristics recorded on admission. Propensity score derivation models included, a priori, the following variables: age, sex, comorbidity (yes/no), and an indicator of disease severity, plus any additional covariates (ie, obesity, smoking, pregnancy, asthma, chronic obstructive pulmonary disease, lung disease, heart disease, immunosuppression, neurological

disease, renal disease, and/or diabetes) that remained statistically significant in a regression model. Variables for which data from >25% of participants were missing were excluded from propensity score derivation.

Statistical Analysis

To investigate the impact of NAI treatment on the LoS, we performed a one-stage IPD meta-analysis using a mixed-effects negative binomial regression model, including study center as a random intercept to account for clustering. A negative binomial model was chosen to account for overdispersion in the LoS data (as represented in Supplementary Figure 1). We tested a zero-inflated negative binomial regression model on a subgroup of the data and found that the model fit was inferior to that of a negative binomial regression model.

In our primary analysis, we aimed to quantify the potential benefits of a pragmatic treat-on-admission policy (irrespective of the time elapsed since symptom onset), compared with patients who received no NAI treatment and those whose treatment was delayed until after the day of admission. By way of sensitivity analysis, we restricted the comparator group to patients who did not receive NAI treatment at any point. For both analyses, we adjusted for propensity score quintile, in-hospital antibiotic treatment, in-hospital corticosteroid treatment, and the delay between symptom onset and hospital admission. In addition, we performed secondary analyses for the following exposures: NAI treatment (at any time) versus no NAI treatment, early NAI treatment (≤48 hours after symptom onset) versus later NAI treatment (>48 hours after symptom onset), and early NAI treatment versus no NAI treatment, adjusting for propensity score, in-hospital antibiotic treatment, and corticosteroid treatment.

We performed a priori–specified analyses for the following subgroups: patients with laboratory-confirmed A(H1N1) pdm09 infection, children (age, <16 years), elderly patients (age, ≥65 years), patients with chest radiography–confirmed influenza-related pneumonia (IRP), and patients with confirmed absence of IRP. We looked at pregnant women and obese patients as post hoc subgroups. Furthermore, we investigated, by stratification, the impact of NAI treatment on the total LoS in patients admitted to critical care facilities (ie, ICUs) at any point and patients treated exclusively by using standard ward-based care.

Both unadjusted and adjusted models were run, and results are presented as unadjusted incidence rate ratios (IRRs) or adjusted IRRs (aIRRs) with 95% confidence intervals (CIs). Missing data in the covariates were included in the analysis as dummy variable categories. Using aIRR point estimates, we determined the difference in the LoS (in days) between a treated patient and an untreated patient with similar characteristics by scaling the model prediction for LoS without treatment by (aIRR-1). Repeating this for all patients in our data set gave us a distribution of expected changes in the LoS due to treatment (with timing as defined for each regression analysis). This does not account for error in the estimates of model covariates, which would require a Bayesian approach; however, it offers a clinically relevant interpretation of aIRRs. The statistical analyses were performed using Stata (version 14.2; StataCorp, College Station, TX).

RESULTS

We identified 29 234 patients admitted to the hospital between 2 January 2009 and 14 March 2011 with laboratory-confirmed or clinically diagnosed A(H1N1)pdm09 infection [4]. The analysis population included 18 309 patients (62.6%; Figure 1).

The included patients came from 70 clinical centers in 36 countries across all 6 World Health Organization regions.

The Americas contributed the most data (46.2% of patients), followed by Europe (for 33.3%). The country that contributed the most to the pooled data set was Mexico (28.8% of patients), followed by Spain (8.6%), the United States (7.6%), and the United Kingdom (7.5%). Among patients in the final study population, 67.4% were adults, and 81.1% had laboratory-confirmed A(H1N1)pdm09 infection; general characteristics of the included population are further described in Table 1.

Among the 8621 patients (47.1%) for whom data on the timing of NAI treatment were available, 3678 (42.7%) received early NAI treatment, and 4816 (55.9%) initiated treatment on the day of admission. The median delay from illness onset to hospital admission was 2 days (interquartile range [IQR], 1–5 days), and among patients with data on the timing of treatment, 42.7% presented ≤48 hours after symptom onset; the median LoS was 5 days (IQR, 3–9 days; Supplementary Figure 1). In patients whose NAI treatment was initiated on the day of hospital admission, the median interval between symptom onset and admission was 2 days (IQR, 1–4 days).

Impact of NAI Treatment on LoS

In our primary analysis, we observed that NAI treatment started on the day of admission was associated with a 19% overall reduction in the LoS (aIRR, 0.81 [95% CI, .78–.85]; median decrease, 1.19 days [IQR, 0.85–1.55 days]), compared with no or later initiation of NAI treatment. This association was of similar magnitude and remained significant in all subgroups (Table 2 and Supplementary Table 3).

In the sensitivity analysis, we observed that NAI treatment on the day of hospital admission was associated with an 8% reduction in the LoS among patients not admitted to the ICU (aIRR, 0.92 [95% CI, .85–.98; median decrease, 0.50 days [IQR, 0.43–0.57 days]), a 19% reduction among patients with confirmed absence of IRP (aIRR, 0.81 [95% CI, .73–.90]; median decrease, 1.24 days [IQR, .93–1.38 days]), but a 28% increase among patients with confirmed presence of IRP (aIRR, 1.28 [95% CI, 1.11–1.48]; median increase, 1.73 days [IQR, 1.29–2.07 days]), compared with no NAI treatment.

Secondary Analyses

After adjustment, NAI treatment at any time was associated with an 11% overall increase in the LoS (aIRR, 1.11 [95% CI, 1.07–1.16]; median increase, 0.74 days [IQR, 0.60–1.05 days]), compared with no NAI treatment. By exploring subgroups, we identified corresponding statistically significant findings in patients with laboratory-confirmed A(H1N1)pdm09 infection, children, patients admitted to the ICU, and patients with confirmed IRP but not in the elderly, patients requiring non-ICU care, or patients with confirmed absence of IRP (Table 2). We did not find any evidence of effect modification by pandemic influenza vaccination (P = .68) or by in-hospital antibiotic treatment (P = .20); however, a borderline significant effect modification was observed for in-hospital corticosteroid treatment (P = .05),

Table 1. General Characteristics of the Study Population

Characteristic	Overall	No NAI Treatment	In-Hospital NAI Treatment
Patients	18 309/18 309 (100)	6075/18 309 (33.2)	12 234/18 309 (66.8)
Male sex	9114/18 306 (49.8)	2852 (47)	6262 (51.2)
Age			
Overall (n = 18 238)	26 (10–44)	24 (6–41)	27 (12–46)
≥16 y (adults)	12 331/18 238 (67.4)	3686 (60.8)	8645 (70.7)
<16 y (children)	5907/18 238 (32.3)	2344 (38.6)	3563 (29.1)
≥65 y (elderly individuals)	1035/18 238 (5.7)	304 (5)	731 (6)
Obese	1677/13 695 (12.3)	475 (8.9)	1202 (14.4)
Smoker	1728/12 851 (13.5)	429 (8.2)	1299 (17.1)
Pregnant[a]	1197/5318 (22.5)	380 (21.1)	817 (23.2)
WHO region			
African Region	23/18 309 (0.1)	0/6075 (0)	23/12 234 (0.19)
Region of the Americas	8466/18 309 (46.2)	4606/6075 (75.8)	3860/12 234 (31.6)
Eastern Mediterranean Region	1649/18 309 (9)	41/6075 (0.7)	1608/12 234 (13.1)
European Region	6090/18 309 (33.3)	918/6075 (15.1)	5172/12 234 (42.3)
South-East Asia Region	180/18 309 (1)	107/6075 (1.8)	73/12 234 (0.6)
Western Pacific Region	1901/18 309 (10.3)	403/6075 (6.6)	1498/12 234 (12.2)
A(H1N1)pdm09 infection diagnosis			
Laboratory confirmed	14 844/18 309 (81.1)	3588/6075 (59.1)	11 256/12 234 (92)
Clinically diagnosed	3465/18 309 (18.9)	2487/6075 (40.9)	978/12 234 (8)
Comorbidity			
Any	7017/18 282 (38.4)	1749 (28.8)	5268 (43.2)
Asthma	2461/16 625 (14.8)	607 (10.2)	1854 (17.4)
COPD	792/13 812 (5.7)	187 (3.6)	605 (7.1)
Other chronic lung disease	1393/9800 (14.2)	190 (12.9)	1203 (14.5)
Heart disease	1030/12 146 (8.5)	140 (8.2)	890 (8.5)
Renal disease	401/11 373 (3.5)	44 (3.1)	357 (3.6)
Liver disease	187/9564 (2)	24 (1.7)	163 (2)
Cerebrovascular disease	239/7751 (3.1)	32 (3.2)	207 (3.1)
Neurological disease	743/8929 (8.3)	105 (7)	638 (8.6)
Diabetes	1375/17 377 (7.9)	418 (7.3)	957 (8.2)
Immunosuppression	1051/17 180 (6.1)	245 (4.3)	806 (7)
Chest radiography for influenza-related pneumonia			
Confirmed presence	4591/7611 (60.3)	426 (46.1)	4165 (62.3)
Confirmed absence	3020/7611 (39.7)	498 (53.9)	2522 (37.7)
A(H1N1)pdm09 vaccination	292/5371 (5.4)	33 (4.7)	259 (5.5)
Time from symptom onset to hospital admission, d (n = 16 736)	2 (1–5)	2 (1–5)	2 (1–5)
NAI used			
None	6075/18 309 (33.2)	6075/6075 (100)	…
Any	12 234/18 309 (66.8)	…	12 234/12 234 (100)
Treated with oral oseltamivir	11 082/12 234 (90.6)	…	11 082 (98.8)
Treated with intravenous/inhaled zanamivir	295/12 234 (2.4)	…	295 (4.3)
Treated with intravenous peramivir	13/12 234 (0.1)	…	13 (0.2)
Early NAI initiation (≤2 d after symptom onset)	3678/8621 (42.7)	…	3678/8621 (42.7)
Later NAI initiation (>2 d after symptom onset)	4943/8621 (57.3)	…	4943/8621 (57.3)
Time from symptom onset to antiviral treatment, d (n = 7433)	3 (2–5)	…	3 (2–5)
Treated with any NAI on day of hospital admission	4816/12 234 (39.4)	…	4816/12 234 (39.4)
Treated with antibiotics	9153/14 599 (62.7)	2981 (52.2)	6172 (69.5)
Treated with corticosteroids	2024/8075 (25.1)	165 (15.3)	1859 (26.6)
Hospital LoS, d[b] (n = 18 309)	5 (3–9)	4 (2–6)	6 (3–10)
Admitted to critical care unit	4243/17 348 (24.5)	411 (6.9)	3832 (33.7)

Data are proportion (%) of patients or median value (interquartile range).

Abbreviations: A(H1N1)pdm09, 2009 pandemic influenza A(H1N1) virus; COPD, chronic obstructive pulmonary disease; LoS, length of stay; NAI, neuraminidase inhibitor; WHO, World Health Organization.

[a]Proportions were calculated as a percentage of pregnant patients among female patients of reproductive age (13–54 years). The broader age range was selected in preference to the WHO definition (age, 15–44 years) after consultation with data contributors, to reflect the actual fertility experience of the sample. This also includes data from a hospital obstetrics unit (n = 72)

[c]The LoS in the NAI-treated group is the overall LoS in this group. Precise NAI administration dates were not uniformly available to work out the LoS after NAI administration in the NAI-treated group.

Table 2. Results From Mixed-Effects Negative Binomial Regression Analyses

Variable	Unadjusted, IRR (95% CI)	Adjusted,[a] IRR (95% CI)
Primary analysis: NAI treatment on day of hospital admission vs later/no NAI treatment[b]		
Overall	0.83 (.79–.87)[c]	0.81 (.78–.85)[c]
Laboratory-confirmed A(H1N1)pdm09 infection	0.83 (.79–.86)[c]	0.81 (.77–.85)[c]
Children (age <16 y)	0.90 (.83–.97)[c]	0.85 (.78–.92)[c]
Elderly (age ≥65 y)	0.78 (.67–.91)[c]	0.78 (.67–.91)[c]
Patients requiring standard ward-based care only	0.81 (.77–.85)[c]	0.81 (.78–.86)[c]
ICU-admitted patients only[d]	0.80 (.73–.88)[c]	0.79 (.72–.87)[c]
Confirmed absence of influenza-related pneumonia	0.71 (.66–.77)[c]	0.73 (.68–.79)[c]
Confirmed presence of influenza-related pneumonia	0.91 (.84–.98)[c]	0.85 (.79–.93)[c]
Sensitivity analysis: NAI treatment on day of hospital admission vs no NAI treatment[b]		
Overall	1.14 (1.07–1.22)[c]	1.06 (.99–1.13)
Laboratory-confirmed A(H1N1)pdm09 infection	1.15 (1.07–1.22)[c]	1.04 (.97–1.12)
Children (age <16 y)	1.09 (.98–1.20)	0.98 (.88–1.09)
Elderly (age ≥65 y)	0.84 (.67–1.06)	0.83 (.65–1.07)
Patients requiring standard ward-based care only	0.93 (.87–.99)[c]	0.92 (.85–.98)[c]
ICU-admitted patients only[d]	1.14 (.96–1.36)	1.08 (.90–1.31)
Confirmed absence of influenza-related pneumonia	0.83 (.75–.92)[c]	0.81 (.73–.90)[c]
Confirmed presence of influenza-related pneumonia	1.28 (1.12–1.47)[c]	1.28 (1.11–1.48)[c]
Secondary analyses		
NAI anytime vs no NAI treatment		
Overall	1.21 (1.17–1.26)[c]	1.11 (1.07–1.16)[c]
Laboratory-confirmed A(H1N1)pdm09 infection	1.31 (1.25–1.37)[c]	1.17 (1.12–1.23)[c]
Children (age <16 y)	1.18 (1.11–1.25)[c]	1.11 (1.04–1.18)[c]
Elderly patients (age ≥65 y)	1.00 (.86–1.17)	0.98 (.83–1.14)
Patients requiring standard ward-based care only	1.06 (1.02–1.10)[c]	1.02 (.98–1.05)
ICU-admitted patients only[d]	1.33 (1.19–1.49)[c]	1.26 (1.13–1.41)[c]
Confirmed absence of influenza-related pneumonia	0.98 (.90–1.07)	0.97 (.89–1.06)
Confirmed presence of influenza-related pneumonia	1.36 (1.24–1.49)[c]	1.28 (1.16–1.40)[c]
Early NAI treatment vs later NAI treatment		
Overall	0.70 (.68–.73)[c]	0.77 (.74–.80)[c]
Laboratory-confirmed A(H1N1)pdm09 infection	0.70 (.68–.73)[c]	0.77 (.74–.80)[c]
Children (age <16 y)	0.80 (.74–.86)[c]	0.87 (.81–.93)[c]
Elderly patients (age ≥65 y)	0.71 (.62–.81)[c]	0.71 (.62–.82)[c]
Patients requiring standard ward-based care only	0.78 (.75–.81)[c]	0.83 (.79–.86)[c]
ICU-admitted patients only[d]	0.69 (.64–.74)[c]	0.74 (.69–.80)[c]
Confirmed absence of influenza-related pneumonia	0.80 (.75–.86)[c]	0.84 (.78–.90)[c]
Confirmed presence of influenza-related pneumonia	0.84 (.78–.90)[c]	0.82 (.77–.88)[c]
Early NAI treatment vs no NAI treatment		
Overall	1.04 (.98–1.11)	0.93 (.87–.99)[c]
Laboratory-confirmed A(H1N1)pdm09 infection	1.05 (.98–1.11)	0.93 (.87–.99)[c]
Children (age <16 y)	1.00 (.91–1.10)	0.92 (.83–1.01)
Elderly patients (age ≥65 y)	0.82 (.67–1.01)	0.79 (.63–.997)[c]
Patients requiring standard ward-based care only	0.93 (.87–.99)[c]	0.88 (.82–.94)[c]
ICU-admitted patients only[d]	1.01 (.86–1.20)	0.93 (.79–1.10)
Confirmed absence of influenza-related pneumonia	0.79 (.71–.89)[c]	0.76 (.68–.85)[c]
Confirmed presence of influenza-related pneumonia	1.09 (.95–1.24)	1.01 (.88–1.16)

Abbreviations: A(H1N1)pdm09, 2009 pandemic influenza A(H1N1) virus; CI, confidence interval; IRR, incidence rate ratio; NAI, neuraminidase inhibitor.

[a]Adjusted for propensity scores (quintiles) for receiving treatment, antibiotic treatment received in the hospital, and steroid treatment received in the hospital.

[b]The IRR was further adjusted for time from onset to admission.

[c]Statistically significant ($P < .05$).

[d]Data are for patients admitted to the ICU at any point. The IRR was calculated for the total length of hospital stay, not time in the ICU. Our sensitivity analyses and secondary analyses must be interpreted with caution because they may be affected by various time-dependent biases

with NAI treatment plus corticosteroid treatment associated with a marginally increased LoS (aIRR, 1.17 days; 95% CI, 1.00–1.36).

In contrast, early NAI treatment was associated with a 7% overall reduction in the LoS (aIRR, 0.93 [95% CI, .87–.99]; median decrease, 0.40 days [IQR, 0.36–0.45 days]), compared with no NAI treatment. Similar or larger reductions were observed in most subgroups; however, this association was not statistically significant in children, patients admitted to the ICU,

and patients with confirmed IRP (Table 2). Early NAI treatment was associated with an 23% overall reduction in the LoS (aIRR, 0.77 [95% CI, .74–.80]); median decrease, 1.78 days [IQR, 1.34–2.49 days]), compared with later NAI treatment; the reduction varied across all a priori–specified subgroups but remained statistically significant (Table 2).

In subgroups of pregnant women and obese patients, early NAI treatment was associated with statistically significant reductions of 39% (aIRR, 0.61 [95% CI, .52–.70]; median decrease, 3.10 days [IQR, 2.34–4.56 days]) and 27% (aIRR, 0.73 [95% CI, .65–.83]; median decrease, 2.11 days [IQR, 1.62–3.10 days]) in the LoS, respectively, compared with later NAI treatment. NAI treatment at any time and early NAI treatment were not statistically significantly associated with LoS, compared with no NAI treatment (Supplementary Table 3).

DISCUSSION

Our study extends the existing literature by offering data on the association between NAI treatment and the LoS in >18 000 adult and pediatric patients, of whom >80% had a laboratory-confirmed diagnosis of A(H1N1)pdm09 infection. We found a mixed pattern of association between NAI treatment and LoS, depending on the delay to initiation of treatment, age, and case severity.

The most pragmatic and important question is whether NAI treatment, started on admission, irrespective of delay since symptom onset, reduces the LoS in hospitalized patients with influenza. Clinically, this is important because there can be significant uncertainty in ascertaining symptom onset, even by the attending physician. The uncertainty in ascertaining symptom onset could mean prescribing NAI treatment outside the recommended (licensed) window of ≤48 hours after symptom onset. However, there is evidence pointing to the effectiveness of NAI therapy, albeit reduced, even when given >48 hours after symptom onset [6]. Statistically, by defining our exposure variable on the basis of treatment decisions made on admission, we avoided introducing correlations between exposure and LoS that can lead to survivorship bias in linear regression models of time-to-event data [19, 20]. Additionally, this approach ensures that the propensity scores, modeled on symptom severity at admission, should appropriately correct for treatment bias [21]. However, this choice of exposure variable also reflects the clinical reality that patients present to the hospital at varying intervals after symptom onset (ranging from 0–20 days in our study) and that clinicians and policy makers want to know whether a so-called treat-at-the-door policy applied to patients admitted to the hospital with clinically recognized influenza will be beneficial, compared with no NAI treatment or a watch-and-see approach. This was addressed by our primary analysis, which revealed that initiation of NAI treatment on the day of admission was associated with a 19% reduction in the LoS (median decrease, 1.19 days), compared with later or no treatment, with similar statistically significant findings across all patient subgroups including children, pregnant women, and obese patients. These findings emphasize the importance of presumptive NAI treatment in patients admitted to the hospital with suspected influenza, coupled with early diagnosis using standard laboratory or rapid diagnostic tests.

In our sensitivity analysis, we found a significant reduction of 19% in the LoS (median decrease, 1.24 days) among patients with confirmed absence of IRP and a reduction of 8% (median decrease, 0.5 days) among patients who required supportive ward-based care. In contrast, NAI treatment (compared with no treatment) was associated with a 28% increase in the LoS (median increase, 1.73 days) among patients with IRP. These data suggest that NAIs may be more effective in reducing the LOS when patients do not have IRP and are consistent with the fact that NAIs have no known antibacterial properties.

In secondary analyses, we observed an 11% overall increase in the LoS associated with NAI treatment, equivalent to a median increase of about 0.74 days and irrespective of the time between symptom onset and initiation of therapy. Compared with no treatment, NAI treatment initiated within 48 hours after symptom onset was associated with a 7% overall reduction in the LoS, equivalent to a median decrease of 0.40 days; this effect was not observed in children and patients requiring ICU care. This finding is clinically important because it suggests that rapid access to antiviral treatment after symptom onset may influence the LoS in adults and elderly individuals; nevertheless, we did not observe the same result among patients requiring ICU care. Our results in children may be influenced by a higher A(H1N1)pdm09 viral load in children [22] than in adults, leading to prolonged hospital stay, suboptimal dosing in very young children [23], increased likelihood of antiviral resistance emergence in children [24], secondary bacterial infections, confounding by indication related to baseline illness severity [25], or a combination of these factors. Although we attempted to adjust for influenza severity by using propensity scores, we found ICU care to be very strongly associated with a prolonged LoS (IRR, 2.96; 95% CI, 2.84–3.09) and NAI treatment to be associated with a higher likelihood of requiring ICU care (adjusted odds ratio, 3.11; 95% CI, 2.42–3.98). Furthermore, we found that patients who presented to the hospital >2 days after symptom onset were 73% more likely to eventually require ICU care than patients who presented earlier (odds ratio, 1.73; 95% CI, 1.53–1.95). In addition, patients requiring ICU care have frequently developed extrapulmonary manifestations of influenza and multiorgan decompensation; therefore, inhibition of virus replication may not correspond with rapid clinical recovery.

We noted no association between NAI treatment and LoS among hospitalized children with influenza when considering early treatment versus no treatment. The study may have been underpowered in children, but other factors might have contributed to our findings. The LoS is typically shorter

among children, compared with adults; mortality and serious outcomes are less common among hospitalized children with influenza, compared with adults; and different discharge policies and thresholds for children could also influence the findings. In addition, vomiting is a recognized side effect of oseltamivir in children [3], and this may have prevented discharge in some cases.

Previous studies examining whether use of NAIs in patients hospitalized with influenza affects the LoS have generally been of smaller size (<1300 individuals) as compared to our study and reached variable conclusions. Of note, 8 studies [11–15, 26–28] (of which one [12] was a randomized trial) assessed NAI treatment of hospitalized children, but only 2 (both with an observational design) concluded that the total number of hospital days in the NAI-treated hospital cohort was reduced (by 18% [8.3 days]) [11, 28], with the other 6 reporting no differences [12–15, 26, 27]. Only 4 studies have addressed the same question in adults. In Hong Kong, a study of 356 adult patients hospitalized with laboratory-confirmed seasonal influenza showed that early oseltamivir treatment was associated with a reduced LoS in both unadjusted and multivariable analyses [9], compared with no or later treatment, with the median LoS decreasing from 6 to 4 days; this accords with our primary analysis. A Canadian study of adult patients with seasonal influenza found that oseltamivir treatment was not associated with the LoS among surviving patients [29]. A further study in 13 Spanish hospitals involving 538 patients with laboratory-confirmed A(H1N1)pdm09 infection noted that the LoS increased by 7% (odds ratio, 1.07), after adjustment for confounders, if NAI treatment was instigated <48 hours after symptom onset; however, this was of borderline statistical significance [10]. A recent American study analyzed data on 201 adult patients with laboratory-confirmed seasonal influenza, reporting that NAI treatment was not associated with the LoS overall but was associated with a reduced LoS among vaccinated individuals (hazard ratio of discharge, 1.6; 95% CI, 1.0–2.4; $P = .04$) [30]. Finally, 2 studies included patients of all age groups. One of them, performed in 813 hospitalized patients with A(H1N1)pdm09 infection in Spain, found that early NAI treatment reduced the LoS by 1.9 days ($P = <.001$) [31]. The other, an American study using insurance claims data from patients with seasonal influenza, reported that patients treated with NAIs spent fewer days in the hospital ($P = <.0001$) [32].

This study has a number of strengths and weaknesses. We combined data from geographically diverse centers, offering broad generalizability of our findings. We used propensity scores to adjust for major confounders. By excluding patients who died (10%), we removed the paradoxical possibility that a short LoS (a positive outcome in our analyses) was associated with an extremely unfavorable clinical outcome. However, a limitation of this approach is that it does not explain the impact of NAI treatment on the relationship between LoS and in-hospital mortality. In our primary analysis, we adjusted for the delay between illness onset and admission, to address length bias [20], and chose our exposure variable to avoid time-dependent/survivorship bias [19, 21]. However, our secondary analyses, which used time since onset to define the exposure variable, are subject to time-dependent biases and must therefore be interpreted with caution. Indeed, the benefit of early versus late treatment (Table 2) will be partially driven by this bias [19]. All of our analyses may be subject to residual competing risk bias, which was not removed through adjustment; for example, we found a significant difference between propensity scores to receive NAIs in the hospital for surviving and nonsurviving patients in the data set ($P < .05$, by the Kruskal-Wallis test), signaling that our removal of nonsurviving patients altered the aggregate presenting patient characteristics for which our results hold.

Our data, generated during the 2009–2010 influenza pandemic, contained relatively few elderly patients and children, consistent with patterns of A(H1N1)pdm09 infection [33], and differs in profile from seasonal influenza A(H3N2) virus infection, for which patients admitted to the hospital tend to be much older and to have a median LoS higher than the LoS of 5 days we observed [34, 35]. In addition, the prevalence proportions of clinically recorded obesity (12%) and pregnancy (23%) were both comparatively high.

Optimally, clinicians wish to treat patients with influenza within 48 hours after symptom onset, yet in many cases patients with influenza do not seek medical care during this therapeutic window. Our data show that 57.3% of included patients were hospitalized >48 hours after symptom onset. What then matters is whether initiation of treatment upon hospitalization (on the day of admission), irrespective of the time elapsed since symptom onset, is effective and whether this is preferable to nontreatment or further delays in treatment. We revealed a 19% reduction in the LoS (median decrease, 1.19 days) among patients who were treated with an NAI upon admission, compared with those who received no or later treatment; the trend was observed across all subgroups, including children. This treatment approach would avoid the uncertainties associated with ascertaining the symptom onset date.

Our data support current recommendations to treat adults hospitalized with clinically suspected influenza with NAIs as soon as possible upon admission; furthermore, this approach appears to be superior to no treatment or delayed treatment in terms of a reduced LoS. If used consistently, this strategy would contribute to the management of surge pressures and healthcare costs during seasonal influenza epidemics and pandemics.

STUDY GROUP MEMBERS

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Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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