Neuraminidase inhibitors and hospital length of stay: an individual participant data (IPD) meta-analysis of treatment effectiveness in patients hospitalised with non-fatal A(H1N1)pdm09 virus infection

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Running title: NAI treatment & hospital length of stay

Abstract word count: 199 words

Manuscript word count: 3,255 words

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Abstract

Background: The effect of neuraminidase inhibitors (NAI) treatment on length of stay (LoS) in patients hospitalised 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 hospitalised with influenza A(H1N1)pdm09. Using mixed-effects negative binomial regression, adjusting for propensity to receive NAIs, antibiotic and corticosteroid treatment, incidence rate ratios (IRRs) and 95% confidence Intervals (95% CI) were calculated. Patients with LoS <1 day, and in-hospital deaths were excluded.

Results: We analysed data on 18,309 patients from 70 clinical centres. After adjustment, NAI treatment initiated at hospitalisation, compared to later or no NAI treatment, was associated with a 19% reduction in LoS in patients with clinically suspected or laboratory-confirmed influenza A(H1N1)pdm09 virus infection (IRR: 0.81; 95% CI: 0.78-0.85). Similar statistically significant associations were seen in all clinical sub-groups. NAI treatment (any time) compared to no NAI treatment, and NAI treatment initiated <2 days of onset compared to later/no NAI treatment showed mixed patterns of association with LoS.

Conclusions: When patients hospitalised with influenza are treated with NAIs, treatment initiated on admission regardless of time since illness onset, is associated with reduced LoS compared with later or non-treatment.

Key words: Neuraminidase inhibitors, pandemic influenza, IPD meta-analysis, length of stay, antivirals

Introduction:

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, hospitalisation 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 hospitalised influenza patients, compared with supportive care without antiviral treatment.[9-15] Minimising 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 hospitalised with influenza A(H1N1)pdm09 and length of inpatient stay during the 2009-10 influenza pandemic.

Methods:

Details regarding identification of study centres and inclusion of patients have been published previously.[6] Briefly, we requested data on patients admitted to hospital with laboratory-confirmed or clinically diagnosed influenza A(H1N1)pdm09 virus infection for whom a minimum dataset was available, from multiple clinical centres worldwide. Of the individual participant data that we received, we excluded patients who had a laboratory-confirmed absence of A(H1N1)pdm09 virus infection, retaining only those patients who had laboratory-confirmed A(H1N1)pdm09 virus infection and patients with clinically diagnosed pandemic influenza (i.e. 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 NAI impact on multiple outcomes of public health interest in A(H1N1)pdm09-infected patients using mixed-effects models. After collection and standardisation of the data, sufficient data existed to assess two indicators of “severe hospital outcomes” – requirement for ventilatory support (ICU admission) and hospital LoS. In this manuscript, we present the findings relating to hospital LoS.

Data Standardisation, Exposure and Outcome

We standardised data from individual datasets prior to pooling (Supplementary Table 1). Primary outcome was length of hospital stay (in whole days). We excluded patients with known pre-admission NAI treatment to ensure uniform potential for treatment to influence LoS. We excluded patients with continuing post-discharge NAI treatment; patients with length of hospital stay <1 day on the grounds that they would have received a maximum two doses of NAI inpatient treatment and their admission may have been precautionary; and also patients with nosocomial influenza (symptom onset after hospital admission date, see Figure 1). Finally, since rapid deterioration and early death in hospital would be an adverse outcome associated with paradoxically short LoS, those who died in hospital were excluded from analysis.

The primary exposure variable was in-hospital NAI treatment received on the day of hospital admission, compared to later NAI treatment or no NAI treatment. Additionally, where data were available, we defined three further exposure variables: NAI treatment (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 centres, based on patient characteristics recorded on admission. Propensity score derivation models included, *a priori*: age, sex, comorbidity (yes/no) and an indicator of disease severity, plus additional covariates that remained statistically significant in a regression model, from: obesity, smoking, pregnancy, asthma, chronic obstructive pulmonary disease, lung disease, heart disease, immunosuppression, neurological disease, renal disease, and diabetes. Variables with >25% missing data were excluded from propensity score derivation.

Statistical analysis

To investigate the impact of NAI treatment on length of hospital stay, we performed a one-stage IPD meta-analysis using a mixed effects negative binomial regression model, including study centre 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 sub-group 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 to 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 and in-hospital corticosteroid treatment, and the time 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 (≤48h from symptom onset) versus later NAI treatment (>48h from symptom onset), and early NAI treatment versus no NAI treatment, adjusting for propensity score, in-hospital antibiotic and corticosteroid treatment.

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

Both unadjusted and adjusted models were run, and results are presented as unadjusted or adjusted incidence rate ratios (IRR/aIRR) with 95% confidence intervals (95% CI). Missing data in the covariates were included in the analysis as dummy variable categories. Using aIRR point estimates, we calculated the difference in LoS (in days) between a treated and untreated patient with similar characteristics by scaling the model prediction for LoS without treatment by (aIRR-1). Repeating this for all patients in our dataset gave us a distribution of expected changes in 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 LP, College Station, TX, USA).

Results:

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

The included patients came from 70 clinical centres in 36 countries across all six World Health Organization regions. The Americas contributed most data (46.2%), followed by Europe (33.3%). The country that contributed the most to the pooled dataset was Mexico (28.8%), followed by Spain (8.6%), USA (7.6%) and the UK (7.5%). The majority of the patients in the final study population were adults (67.4%), with laboratory-confirmed influenza A(H1N1)pdm09 virus infection (81.1%); general characteristics of the included population are further described in Table 1.

Among the 8,621 patients (47.1%) for whom data on timing of NAI treatment were available, 3,678 (42.7%) received early NAI treatment and 4816 (55.9%) had treatment started on the day of admission. The median delay from illness onset to hospital admission was 2 days (interquartile range (IQR): 1-5) and, where data on timing of treatment were available, 42.7% presented ≤48h after symptom onset; median LoS was 5 days (IQR: 3-9) (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).

Impact of NAI treatment on length of stay

In our primary analysis, we observed that NAI treatment started on the day of admission, compared with no treatment or later initiation of NAI treatment, was associated with an overall 19% reduction in LoS [aIRR:0.81 (0.78-0.85)], median decrease 1.19 days (IQR: 0.85-1.55). 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 LoS compared to no NAI treatment, in non-ICU cases [aIRR: 0.92 (0.85-0.98) median decrease: 0.50 days (IQR: 0.43-0.57)], a 19% reduction in patients with a confirmed absence of IRP [aIRR: 0.81 (0.73-0.90) median decrease: 1.24 days (0.93-1.38)], but a 28% increase in LoS in patients with confirmed presence of IRP [aIRR: 1.28 (1.11-1.48) median increase: 1.73 days (1.29-2.07)].

Secondary analyses

After adjustment, NAI treatment at any time was associated with an overall 11% increase in LoS [aIRR: 1.11, (1.07-1.16), median increase: 0.74 days (0.60-1.05)], when compared to no NAI treatment. By exploring subgroups we identified corresponding statistically significant findings in laboratory-confirmed cases, children, ICU patients and in patients with confirmed IRP, but not in the elderly, patients requiring non-ICU care, or in patients with a confirmed absence of IRP (Table 2). We did not find any evidence for effect-modification by pandemic influenza vaccination (p-value: 0.68) or by in-hospital antibiotic treatment (p-value: 0.20); however, a borderline significant effect-modification was observed for in-hospital corticosteroid treatment (p-value: 0.05), with NAI treatment plus corticosteroids being associated with marginally increased LoS [aIRR: 1.17 days (1.00-1.36)].

In contrast, early NAI treatment compared to no NAI treatment was associated with a 7% overall reduction in LoS [aIRR: 0.93 (0.87-0.99), median decrease: 0.40 days (0.36-0.45)]. Similar or larger reductions were observed in most sub-groups; however, this association was not statistically significant in children, ICU patients, and in patients with confirmed IRP (Table 2). Early NAI treatment compared to later NAI treatment was associated with an overall 23% reduction in

LoS [aIRR: 0.77 (0.74-0.80), median decrease: 1.78 days (1.34-2.49)], which varied across all *a priori* specified sub-groups but remained statistically significant (Table 2).

In pregnant women and obesity subgroups, early NAI treatment compared to later NAI treatment was associated with statistically significant reductions in LoS by 39% [aIRR: 0.61 (0.52-0.70), median decrease: 3.10 days (2.34-4.56)] and 27% [aIRR: 0.73 (0.65-0.83), median decrease: 2.11 days (1.62-3.10)] respectively. NAI treatment at any time and early NAI treatment, when compared to no NAI treatment, were not statistically significantly associated with LoS (Supplementary table 3).

Discussion

Our study extends the existing literature by offering data on the association between NAI treatment and LoS in over 18,000 adult and paediatric patients, of whom >80% had a laboratory confirmed diagnosis of A(H1N1)pdm09 virus 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 LoS in hospitalised influenza patients. Clinically, this is important as 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 from symptom onset. However, there is evidence pointing to NAI effectiveness, albeit reduced, even when given >48 hours from symptom onset.[6] Statistically, by defining our exposure variable based on treatment decisions made on admission, we avoid introducing correlations between exposure and

LoS which can lead to survivorship bias in linear regression models of time-to-event data.[19,20] Additionally this approach ensures that the propensity scores, modelled 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 hospital with varying delays since symptom onset (in our study, ranging from 0-20 days); and that clinicians and policy makers want to know if a 'treat at the door' policy, applied to patients admitted to hospital with clinically recognised influenza will be beneficial compared with no NAI treatment or a 'watch and see' approach. This was addressed by our primary analysis which revealed NAI treatment started on the day of admission, compared to later or no treatment, was associated with an 19% reduction in LoS (median 1.19 days), with similar statistically significant findings across all patient subgroups including children, pregnant women and obese patients. These findings emphasise the importance of presumptive NAI treatment in patients admitted to hospital with suspected influenza, coupled with early diagnosis using standard laboratory or rapid diagnostic tests.

In our sensitivity analysis we found a significant reduction in LoS of 19% (median 1.24 days) in patients with a confirmed absence of IRP and reduction in LoS of 8% (median 0.5 days) in patients who required supportive ward-based care. In contrast, NAI treatment (compared with none) was associated with an increase in LoS by 28% (median 1.73 days) in patients with IRP. These data suggest that NAIs may be more effective in reducing LOS when patients do not have IRP and is consistent with the fact that NAIs have no known antibacterial properties.

In secondary analyses, we observed an 11% increase in LoS associated with NAI treatment, equivalent to about 0.74 days, irrespective of the time between symptom onset and initiation of therapy in the overall study population. NAI treatment initiated within 48h of symptom onset, compared with no treatment,

was associated with an overall 7% reduction in LoS, equivalent to a median reduction by 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 LoS in adults and the elderly; nevertheless, we did not observe the same in patients requiring ICU. Our results in children may be influenced by higher influenza A(H1N1)pdm09 viral load in children[22] than 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, and confounding by indication related to baseline illness severity,[25] or a combination of these factors. Although we attempted to adjust for severity using propensity scores, we found ICU care to be very strongly associated with 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 (aOR: 3.11; 95% CI: 2.42-3.98). Furthermore, we found that patients who presented to hospital >2 days from symptom onset were 73% more likely to eventually require ICU care than patients who presented earlier (OR: 1.73; 95% CI: 1.53-1.95). In addition, patients requiring ICU care have frequently developed extra-pulmonary manifestations of influenza, and multi-organ decompensation, therefore inhibition of virus replication may not correspond with rapid clinical recovery.

We noted no association between NAI treatment and LoS in hospitalised 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. LoS is typically shorter in children than in adults, mortality and serious outcomes are less common in hospitalised children with influenza compared with adults; different discharge policies and thresholds for children could also influence the findings. In addition, vomiting is a recognised

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 hospitalised with influenza affects LoS have generally been of smaller size (n<1300) in comparison to our own, and reached variable conclusions. Of note, eight studies[11-15,26-28] (of which one was a randomised trial)[12] assessed NAI treatment of hospitalised children, but only two (observational) concluded that total hospital days in the NAI treated hospital cohort were reduced (by 18% and 8.3 days respectively),[11,28] the other six reporting no differences.[12-15,26,27] Only four studies have addressed the same question in adults. In Hong Kong, a study of 356 adult patients hospitalised with laboratory confirmed seasonal influenza showed that early oseltamivir treatment, compared with none or later treatment, was associated with reduced LoS in both unadjusted and multivariable analyses,[9] median LoS was reduced from six to four days and accords with our primary analysis. A Canadian study of adult patients with seasonal influenza found oseltamivir treatment was not associated with LoS in surviving patients.[29] A further study in 13 Spanish hospitals, in 538 patients with laboratory confirmed A(H1N1)pdm09, noted LoS increased by 7% (OR =1.07) after adjustment for confounders, if NAI treatment was instigated <48h after symptom onset; however this was of borderline statistical significance.[10] A recent American study analysed data on 201 adult patients with laboratory-confirmed seasonal influenza reporting that NAI treatment was not associated with LoS overall, but was associated with a reduced LoS in vaccinated individuals [hazard ratio of discharge: 1.6 (1.0-2.4), p-value:0.04].[30] Finally, two studies included patients of all age groups. One of them, performed in 813 hospitalised patients with A(H1N1)pdm09 virus infection in Spain, found that early NAI treatment reduced LoS by 1.9 days (p-value: <0.001).[31] The other, an American study using insurance claims data from

seasonal influenza patients reported that patients treated with NAI spent fewer days in hospital (p-value: <0.0001).[32]

This study has a number of strengths and weaknesses. We combined data from geographically diverse centres, offering broad generalisability of our findings. We used propensity scores to adjust for major confounders. By excluding patients who died (10%), we removed the paradoxical possibility that short LoS (a positive outcome in our analyses) was associated with an extremely unfavourable clinical outcome. However, a limitation of this approach is that it does not explain NAI impact on the relationship between LoS and in-hospital mortality. In our primary analysis, we adjusted for delay from illness onset to admission to address length bias[20] and have chosen our exposure variable to avoid time-dependent/survivorship bias.[19,21] However, our secondary analyses, which use 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 vs 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 has not been removed through adjustment; for example, we found a significant difference between propensity scores to receive NAIs in hospital for surviving and non-surviving patients in the data set (Kruskall-Wallis: $p<0.05$), signalling that our removal of non-surviving patients alters the aggregate presenting patient characteristics for which our results hold.

Our data, generated during the 2009-10 pandemic, contained relatively few elderly patients and children, consistent with patterns of A(H1N1)pdm09 virus infection,[33] and differs in profile from seasonal influenza (A(H3N2)) where patients admitted to hospital tend to be much older, and median LoS higher than the five days we observed.[34,35] In addition, the prevalence of clinically recorded obesity (12%) and pregnancy (23%) were both comparatively high.

Optimally, clinicians wish to treat influenza patients within 48h of symptom onset, yet in many cases influenza patients do not seek medical care during this therapeutic window. Our data show that 57.3% of included patients were hospitalised >48h after symptom onset. What then matters is whether initiation of treatment upon hospitalisation (on the day of admission) irrespective of the time elapsed since symptom onset is effective, and whether this is preferable to non-treatment or further delays in treatment. We reveal a 19% reduction in LoS (median 1.19 days) in patients treated with an NAI upon admission, rather than remaining untreated or being treated later on; the trend is 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 hospitalised with clinically suspected influenza with NAIs as soon as possible upon admission; furthermore, this approach appears superior to no-treatment or delayed treatment in terms of reduced LoS. If applied consistently, this strategy would contribute to the management of surge pressures and healthcare costs during seasonal influenza epidemics and pandemics.

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Author contributions: JSN-V-T, PRM, SV, and SGM conceived and designed the study. Alcl authors, apart from SV, KJB, and SGM, contributed to the acquisition and local preparation of constituent datasets. SV, PRM, KJB and SGM contributed to data set amalgamation and standardisation, design of statistical analyses, and data analysis. JSN-V-T, PRM, KJB, and SV interpreted the data and wrote the manuscript. All authors contributed to critical examination of the paper for important intellectual content and approval of the final report. Each author acted as the guarantor of data from their individual study centre. SV had full access to the pooled dataset in the study and takes responsibility for the accuracy of the data analysis. JSN-V-T acts as overall guarantor of the manuscript.

Funding: The PRIDE study is funded via an unrestricted educational grant from F. Hoffmann-La Roche, Switzerland (the manufacturers of Oseltamivir (Tamiflu®)). The Funder has had no role in protocol design, no opportunity to comment on it, and no opportunity to see it other than via the PROSPERO website; no access to any data (and no rights to future access); no role in analysis or interpretation; no opportunity to preview results/findings before entry into the public domain; no opportunity to contribute to, preview or comment on manuscripts and presentations arising from this work. The research contract between the University of Nottingham and the Funder is freely available for

inspection (commercial details redacted) at:
http://www.nottingham.ac.uk/research/groups/healthprotection/projects/pride.aspx

No data were provided or funded for collection by pharmaceutical companies.

Acknowledgements: We would like to thank Dr. Jerome Tokars and Dr. Alicia Fry from CDC Atlanta, USA, for their comments on the manuscript.

Declaration of interests: GM reports grants and other funding from Pfizer, MSD and Gilead outside the submitted work; KGIM reports personal fees from Sanofi-Aventis Norway AS outside the submitted work; DT reports grants from Canadian Institutes of Health Research/SickKids Foundation New Investigator Grant XG08-049R, grants from Canadian Institutes of Health Research Catalyst Grant CAT86860, grants from University of Toronto Dean's Fund Pilot Study Grant, during the conduct of the study. WV reports grants from Canadian Pediatric Society during the conduct of the study. KJB reports funding from a University of Nottingham Anne McLaren Fellowship. JSN-V-T reports grants from F. Hoffmann-La Roche for the conduct of this study, and personal fees from Shionogi Ltd. (in 2016) outside the submitted work. He is currently on secondment to the Department of Health and Social Care, England. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the UK Government or the United States Centers for Disease Control and Prevention. All other authors report no conflicts of interests.

Preliminary results from this paper were presented at the Sixth ESWI Influenza Conference, Riga, Latvia, held between 10th and 13th of September 2017.

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Figure 1. Identification of the study population

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Table 1. General Characteristics of study population (n= 18,309)

Characteristic (denominator)*	Total study population n (%)	No NAI treatment n (%)	In-hospital NAI treatment n(%)
Number of patients	18,309 (100)	6,075 (33.2)	12,234 (66.8)
Number of male cases (n=18,306)	9,114 (49.8)	2,852 (47)	6,262 (51.2)
Age: median (IQR) in years (n=18,238)	26 (10-44)	24 (6-41)	27 (12-46)
Adults (≥16 years)	12,331 (67.4)	3,686 (60.8)	8,645 (70.7)
Children (<16 years)	5,907 (32.3)	2,344 (38.6)	3,563 (29.1)
Elderly (≥65 years)	1,035 (5.7)	304 (5)	731 (6)
Patients with obesity (n=13,695)	1,677 (12.3)	475 (8.9)	1,202 (14.4)
Smoking (n=12,851)	1,728 (13.5)	429 (8.2)	1,299 (17.1)
Pregnant women‡ (n=5,318)	1,197 (22.5)	380 (21.1)	817 (23.2)
WHO Regions (n=18,309)			
African Region	23 (0.1)	0 (0)	23 (0.19)
Region of the Americas	8466 (46.2)	4,606 (75.8)	3,860 (31.6)
Eastern Mediterranean Region	1649 (9)	41 (0.7)	1,608 (13.1)
European Region	6090 (33.3)	918 (15.1)	5,172 (42.3)

South-East Asia Region	180 (1)	107 (1.8)	73 (0.6)
Western Pacific Region	1901 (10.3)	403 (6.6)	1,498 (12.2)
A(H1N1)pdm09 diagnosis (n=18,309)			
Laboratory confirmed	14,844 (81.1)	3,588 (59.1)	11,256 (92)
Clinically diagnosed	3,465 (18.9)	2,487 (40.9)	978 (8)
Comorbidities			
Any comorbidity (n=18,282)	7,017 (38.4)	1,749 (28.8)	5,268 (43.2)
Asthma (n=16,625)	2,461 (14.8)	607 (10.2)	1,854 (17.4)
COPD (n=13,812)	792 (5.7)	187 (3.6)	605 (7.1)
Other chronic lung disease (n=9,800)	1,393 (14.2)	190 (12.9)	1,203 (14.5)
Heart disease (n=12,146)	1,030 (8.5)	140 (8.2)	890 (8.5)
Renal disease (n=11,373)	401 (3.5)	44 (3.1)	357 (3.6)
Liver disease (n=9,564)	187 (2)	24 (1.7)	163 (2)
Cerebrovascular disease (n=7,751)	239 (3.1)	32 (3.2)	207 (3.1)
Neurological disease (n=8,929)	743 (8.3)	105 (7)	638 (8.6)
Diabetes (n=17,377)	1,375 (7.9)	418 (7.3)	957 (8.2)
Immunosuppression (n=17,180)	1,051 (6.1)	245 (4.3)	806 (7)
Chest radiograph-confirmation of influenza-related pneumonia (n=7,611)			

Confirmed presence of influenza-related pneumonia	4,591 (60.3)	426 (46.1)	4,165 (62.3)
Confirmed absence of influenza-related pneumonia	3,020 (39.7)	498 (53.9)	2,522 (37.7)
Pandemic H1N1 vaccination (n=5,371)	292 (5.4)	33 (4.7)	259 (5.5)
Time from symptom onset to hospital admission (days), median (IQR) (n=16,736)	2 (1-5)	2 (1-5)	2 (1-5)
Antiviral agents used			
No NAI treatment	6,075 (33.2)	6075 (100)	-
Any NAI	12,234 (66.8)	-	12,234 (100)
Treated with oral oseltamivir (n=12,234)	11,082 (90.6)	-	11,082 (98.8)
Treated with intravenous/inhaled zanamivir (n=12,234)	295 (2.4)	-	295 (4.3)
Treated with intravenous peramivir (n=12,234)	13 (0.1)	-	13 (0.2)
Early NAI (≤2 days of symptom onset) (n=8,621)	3,678 (42.7)	-	3,678 (42.7)
Later NAI (>2 days after symptom onset) (n=8,621)	4,943 (57.3)	-	4,943 (57.3)
Time from symptom onset to antiviral treatment, days, median (IQR) (n=7,433)	3 (2-5)	-	3 (2-5)
Treated with any NAI on the day of hospital admission (n=12,234)	4,816 (39.4)	-	4,816 (39.4)
Antibiotics (n=14,599)	9,153 (62.7)	2,981 (52.2)	6,172 (69.5)
Corticosteroids (n= 8,075)	2,024 (25.1)	165 (15.3)	1,859 (26.6)
Hospital LoS, days†, median (IQR) (n=18,309)	5 (3-9)	4 (2-6)	6 (3-10)

Admission to critical care (n=17,348)	4,243 (24.5)	411 (6.9)	3,832 (33.7)

*IQR: Interquartile range; *Percentages have been calculated using the individual denominators (brackets) for each table row.*

‡*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 (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)*

†LoS in the NAI treated group is the overall LoS in this group; precise NAI administration dates were not uniformly available to work out LoS after NAI administration in the NAI-treated group

584 **Table 2.** Results from mixed effects negative binomial regression analyses

	Unadjusted	**Adjusted**[a]
	IRR (95%CI)	IRR (95%CI)
Primary analysis: NAI treatment on the day of hospital admission vs Later/No NAI treatment[b]		
Overall	**0.83 (0.79-0.87)**	**0.81 (0.78-0.85)**
Laboratory-confirmed A(H1N1)pdm09	**0.83 (0.79-0.86)**	**0.81 (0.77-0.85)**
Children (age <16 years)	**0.90 (0.83-0.97)**	**0.85 (0.78-0.92)**
Elderly (age ≥65 years)	**0.78 (0.67-0.91)**	**0.78 (0.67-0.91)**
Patients requiring standard ward-based care only	**0.81 (0.77-0.85)**	**0.81 (0.78-0.86)**
ICU patients only[c]	**0.80 (0.73-0.88)**	**0.79 (0.72-0.87)**
Confirmed absence of Influenza-related pneumonia	**0.71 (0.66-0.77)**	**0.73 (0.68-0.79)**
Confirmed presence of Influenza-related pneumonia	**0.91 (0.84-0.98)**	**0.85 (0.79-0.93)**
Sensitivity analysis: NAI treatment on the day of hospital admission vs No NAI treatment[b]		
Overall	**1.14 (1.07-1.22)**	1.06 (0.99-1.13)
Laboratory-confirmed A(H1N1)pdm09	**1.15 (1.07-1.22)**	1.04 (0.97-1.12)
Children (age <16 years)	1.09 (0.98-	0.98 (0.88-

	1.20)	1.09)
Elderly (age ≥65 years)	0.84 (0.67-1.06)	0.83 (0.65-1.07)
Patients requiring standard ward-based care only	**0.93 (0.87-0.99)**	**0.92 (0.85-0.98)**
ICU patients only[c]	1.14 (0.96-1.36)	1.08 (0.90-1.31)
Confirmed absence of Influenza-related pneumonia	**0.83 (0.75-0.92)**	**0.81 (0.73-0.90)**
Confirmed presence of Influenza-related pneumonia	**1.28 (1.12-1.47)**	**1.28 (1.11-1.48)**
Secondary Analyses		
NAI anytime vs No NAI treatment		
Overall	**1.21 (1.17-1.26)**	**1.11 (1.07-1.16)**
Laboratory-confirmed A(H1N1)pdm09	**1.31 (1.25-1.37)**	**1.17 (1.12-1.23)**
Children (age <16 years)	**1.18 (1.11-1.25)**	**1.11 (1.04-1.18)**
Elderly (age ≥65 years)	1.00 (0.86-1.17)	0.98 (0.83-1.14)
Patients requiring standard ward-based care only	**1.06 (1.02-1.10)**	1.02 (0.98-1.05)
ICU patients only[c]	**1.33 (1.19-1.49)**	**1.26 (1.13-1.41)**
Confirmed absence of Influenza-related pneumonia	0.98 (0.90-1.07)	0.97 (0.89-1.06)
Confirmed presence of Influenza-related pneumonia	**1.36 (1.24-1.49)**	**1.28 (1.16-1.40)**

Early NAI treatment vs Later NAI treatment		
Overall	**0.70 (0.68-0.73)**	**0.77 (0.74-0.80)**
Laboratory-confirmed A(H1N1)pdm09	**0.70 (0.68-0.73)**	**0.77 (0.74-0.80)**
Children (age <16 years)	**0.80 (0.74-0.86)**	**0.87 (0.81-0.93)**
Elderly (age ≥65 years)	**0.71 (0.62-0.81)**	**0.71 (0.62-0.82)**
Patients requiring standard ward-based care only	**0.78 (0.75-0.81)**	**0.83 (0.79-0.86)**
ICU patients only[c]	**0.69 (0.64-0.74)**	**0.74 (0.69-0.80)**
Confirmed absence of Influenza-related pneumonia	**0.80 (0.75-0.86)**	**0.84 (0.78-0.90)**
Confirmed presence of Influenza-related pneumonia	**0.84 (0.78-0.90)**	**0.82 (0.77-0.88)**
Early NAI treatment vs No NAI treatment		
Overall	1.04 (0.98-1.11)	**0.93 (0.87-0.99)**
Laboratory-confirmed A(H1N1)pdm09	1.05 (0.98-1.11)	**0.93 (0.87-0.99)**
Children (age <16 years)	1.00 (0.91-1.10)	0.92 (0.83-1.01)
Elderly (age ≥65 years)	0.82 (0.67-1.01)	**0.79 (0.63-0.997)**
Patients requiring standard ward-based care only	**0.93 (0.87-0.99)**	**0.88 (0.82-0.94)**
ICU patients only[c]	1.01 (0.86-	0.93 (0.79-

	1.20)	1.10)
Confirmed absence of Influenza-related pneumonia	**0.79 (0.71-0.89)**	**0.76 (0.68-0.85)**
Confirmed presence of Influenza-related pneumonia	1.09 (0.95-1.24)	1.01 (0.88-1.16)

IRR: Incidence Rate Ratio; 95%CI: 95% Confidence Interval (bold font indicates statistical significance at the 5% level (p<0.05); a) IRR adjusted for propensity scores (quintiles) for receiving treatment, antibiotic treatment received in hospital, steroid treatment received in hospital; b) IRR further adjusted for time from onset to admission; c) patients admitted to ICU at any point – IRR calculated for total length of hospital stay, not time on ICU.

Our sensitivity analyses and secondary analyses must be interpreted with caution as they may be affected by various time-dependent biases