Impact of outpatient neuraminidase inhibitor treatment in patients infected with influenza A(H1N1)pdm09 at high risk of hospitalization: an Individual Participant Data (IPD) meta-analysis

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Running Head: NAIs & Influenza related hospitalization

Short summary of main findings (38 words)**:**

Our findings suggest that in populations at a high risk for hospital admission, patients with laboratory-confirmed or clinically diagnosed A(H1N1)pdm09 infection, NAI treatment in the community or outpatient settings is associated with reduced likelihood of subsequent hospital admission.

ABSTRACT

Background: While evidence exists to support the effectiveness of neuraminidase inhibitors (NAIs) in reducing mortality when given to hospitalized patients with A(H1N1)pdm09 virus infection, the impact of outpatient treatment on hospitalization has not been clearly established. The objective of this work was to investigate the impact of outpatient NAI treatment on subsequent hospitalization in patients with A(H1N1)pdm09 virus infection.

Methods: We assembled general community and outpatient data from nine clinical centers in different countries collected between January 2009 and December 2010. We standardized data from each study center to create a pooled dataset, then used mixed-effects logistic regression modeling to determine the effect of NAI treatment on hospitalization. We adjusted for NAI treatment propensity and pre-admission antibiotic use, including 'study centre' as a random intercept to account for differences in baseline hospitalization rate between centers.

Results: We included 3,376 patients with influenza A(H1N1)pdm09 of whom 3,085 (91.4%) had laboratory-confirmed infection. 873 patients (25.8%) received outpatient or community-based NAI treatment, 928 of 2,395 (38.8%) with available data had dyspnea or respiratory distress, and 1,705 (50.5%) hospitalizations occurred. After adjustment for pre-admission antibiotics and NAI treatment propensity, pre-admission NAI treatment was associated with decreased odds of hospital admission compared to no NAI treatment (adjusted OR =0.24; 95% CI: 0.20 to 0.30).

Conclusions: In a population with confirmed or suspected A(H1N1)pdm09, and at high risk of hospitalization, outpatient or community-based NAI treatment significantly reduced the likelihood of requiring hospital admission. These data suggest that community patients with severe influenza should receive NAI treatment.

Key words: Influenza; neuraminidase inhibitors; individual participant data meta-analyses; hospitalization; pandemic

INTRODUCTION

Neuraminidase inhibitors (NAIs) were widely deployed in hospitals, outpatient clinics and primary care settings during the influenza A(H1N1) pandemic in 2009-10. Although licensed on the basis of symptom reduction, deployment in 2009-10 was mainly targeted towards reducing complications, hospital admissions and deaths. Data from randomized trials pertaining to important public health outcomes, such as reductions in mortality and hospital admissions, for patients with A(H1N1)pdm09 influenza are lacking. In otherwise healthy patients with seasonal influenza, low case severity and low frequency of severe outcomes contribute to a lack of statistical power in randomized studies [1-3]. Notwithstanding, summaries of observational data suggest that NAIs reduced mortality in hospitalized patients during the 2009-10 pandemic [4, 5]. Likewise, a meta-analysis of observational data on seasonal influenza prior to 2009, also suggests that NAIs given to high-risk community patients with influenza may reduce subsequent hospitalization [6]. To the best of our knowledge, similar data on hospitalization during the 2009-10 pandemic period are absent. We therefore performed a global individual participant data (IPD) meta-analysis to address this question.

METHODS

The PRIDE research consortium

Research centers participating in the Post-pandemic Review of anti-Influenza Drug Effectiveness (PRIDE) study were identified while conducting a meta-analysis of published studies on the effectiveness of NAI treatment in hospitalized patients [4]. A detailed description of the PRIDE study has been published previously [5]. In total, the PRIDE consortium obtained data on 170,858 potentially eligible patients from 81 research centers in 38 countries across six World Health Organization (WHO) regions; a subset of these centers provided community or outpatient data, which were then used for the current analysis. No data were provided or funded for collection by

pharmaceutical companies. The protocol for this study was registered with the PROSPERO register of systematic reviews, number CRD42011001273 [7].

Data standardization, exposure, outcome and covariates

Data were available on community patients or those attending outpatient clinics with laboratory-confirmed or clinically diagnosed influenza A(H1N1)pdm09 from nine centers (Argentina, Canada, France, Germany, Israel, Saudi Arabia, Singapore, Slovenia and the UK). These were standardized using a data dictionary (Supplementary Table 1) before pooling for analysis. The primary outcome variable was influenza-related hospital admission as determined by case records linking admission to the influenza illness episode. The primary exposure variable was treatment with an NAI initiated in any community or outpatient setting as compared to no NAI treatment in the community or outpatient setting. If data were available we further distinguished early treatment (NAI started ≤2 days after symptom onset) versus later treatment (>2 days after symptom onset). We excluded from all our analyses those patients who received NAI treatment in the community on the day of hospital admission, on the grounds that treatment would have not had sufficient opportunity to work in these patients; this exclusion also accounts for any physician decisions to prescribe NAIs taken *after* a decision to admit the patient to hospital – amounting to confounding by indication. Covariates adjusted for in the final multivariable model were outpatient or community-based antibiotic treatment (yes/no) and propensity score (by quintile) for receiving NAI treatment in the community.

Propensity scoring

We computed propensity scores for the likelihood of community-based NAI treatment for individual patients within each contributing dataset using the method described by Hirano and Imbens [8]. Multivariable logistic regression models developed to calculate propensity scores included the following covariates: age, sex, presence of a comorbid condition (yes/no) and an indicator of disease

severity (in order of preference: documented severe respiratory distress or shortness of breath). The resulting propensity scores were then categorized into quintiles for use in subsequent analyses.

Statistical analysis

In the primary analysis, we used a mixed-effects logistic regression model to investigate the association between community-based NAI treatment and subsequent hospital admission using the xtmelogit command in Stata (Version 14). To account for differences in baseline outcome between individual datasets, we included individual study centers as a random intercept. We ran both unadjusted and adjusted models, the latter containing covariates for community-based antibiotic treatment and propensity scores. To allow for comparisons between the unadjusted and the adjusted models, we included missing data as a dummy variable category. The C-statistic (area under the receiver operating characteristic (ROC) curve) was used to assess model fit. Where data were available, we explored the potential impact of timing of NAI administration (early NAI treatment versus later NAI treatment) on hospitalization. We also performed stratified analysis in patients with laboratory-confirmed A(H1N1)pdm09 influenza and adults (≥16 years) and children.

Furthermore, we carried out an additional analysis restricted to patients with high-risk conditions. Patients were classified as having a high-risk condition if they had at least one chronic illnesses recorded that would trigger seasonal influenza vaccination [9], or were aged ≥65 years.

Results from our mixed-effects logistic regression models are presented as odds ratios (OR) with 95% confidence intervals (95% CI).

RESULTS

We received outpatient data on 130,077 patients with clinically or laboratory-confirmed influenza from 25 centers. However, 16 centers (n=125,049 patients) offered surveillance data that did not contain clinical data on either NAI use or subsequent hospitalization status. Therefore, the final study population comprised 3,376 patients from nine study centers (Figure 1). Data from seven of

the nine included study centers (n=1,183 patients) came from outpatient (ambulatory care) clinics attached to hospitals. Of the remaining two study centers, one provided community surveillance data collected by the Ministry of Health (n=1,762) and the other provided data from primary care (n=431). Three of the nine included centers (Canada, Germany and Israel; total n=535) were from pediatric outpatient clinics and comprised entirely of patients under the age of 18 years. Patients from the German study center were particularly young with a median age of 1.4 years (Supplementary table 3).

Of 3,376 patients in our pooled dataset: 3,085 (91.4%) had laboratory confirmed A(H1N1)pdm09 infection; 1,747 (51.8%) were children (<16 years); 67 (2.0%) were over 64 years old. Overall, 1,705 (50.1%) were admitted to hospital and 928 (928/2,395; 38.7%) had clinically observed shortness of breath or respiratory distress as a marker of severity. Where data were available (n=473), the median interval between date of symptom onset and date of NAI treatment initiation was 1 day (interquartile range (IQR): 0 to 3) for the whole study population, 1 day (IQR: 0 to 2) for non-hospitalized patients, and 1 day (IQR: 0 to 4) for hospitalized patients. Of the hospitalized patients, where calculable (n=1,363), the median interval between date of symptom onset and date of hospital admission was 2 days (IQR: 1 to 3). General characteristics of the study population are presented in Table 1. About one half (50.1%) of the cohort was eventually admitted to hospital and 38.8% had one or more indications of severe respiratory illness as denoted by observed shortness of breath or respiratory distress. In addition, under 2% of the cohort were elderly and about 72% had no recorded comorbid conditions suggesting patients were mainly young and previously healthy; indeed 51.8% were children and 37.1% of women aged 15 to 44 years were pregnant, reflecting the inclusion of one obstetric clinic (n=81) within the data.

Of the 1,705 patients who were hospitalized, we had data on the subsequent course in 1,433 patients. Of these 1,433 hospitalized patients, 1,155 (80.6%) were treated with NAIs in-hospital, 147 patients (10.3%) were subsequently admitted to critical care facilities (of which 119 (80.9%) treated,

28 (19.1%) untreated) and 14 patients (1%) died (13 (92.9%) treated, 1 (7.1%) untreated). In a smaller subgroup of 1,392 patients on whom we had data relating to pneumonia, 215 (15.5%) were found to have clinical signs of pneumonia, with radiographic confirmation of pneumonia in 101 (7.3%) patients (64 (63.4%) treated, 37 (36.6%) untreated). Further, we had data on length of subsequent hospital stay in a smaller subgroup of 522 patients where the median length of stay was 3 days (IQR: 2 to 5 days) (median: 3 days (IQR: 2 to 5 days) in treated, median: 2 days (IQR: 1.5 to 5 days) untreated). Of the 1,647 patients who were excluded from the analyses because they were hospitalized on the same day of NAI treatment initiation, 116 (7%) were admitted to critical care facilities and 23 (1.4%) died. In 1,595 of these patients on whom we had pneumonia data, 154 (9.7%) were found to have had clinical signs of pneumonia in 31 (1.9%) of whom pneumonia was radiologically confirmed. The median length of hospital stay in an even smaller sub-group (n=186 where data were available) was found to be 3 days (IQR: 2 to 5).

In patients with laboratory-confirmed or clinically diagnosed A(H1N1)pdm09 influenza, after adjustment for community-based antibiotic treatment and propensity score, the likelihood of hospital admission in patients with outpatient or community-based NAI treatment was 0.24 (95% CI: 0.20 to 0.30) when compared to no NAI treatment in the community (Table 2). A C-statistic of 0.813 (95% CI: 0.799 to 0.827) suggested that the predictive performance of our model was acceptable.

When restricted to laboratory-confirmed A(H1N1)pdm09 patients, the estimate was very similar to the estimate for the overall study population (Table 2). NAI treatment, when compared to no treatment, was associated with reduced odds of hospitalization in both children (adjusted OR: 0.25; 95% CI 0.18 to 0.34) and adults (adjusted OR: 0.26; 95% CI: 0.19 to 0.35). In the sub-group of 473 patients in whom data on the interval between symptom onset and start of NAI treatment were available, early NAI treatment was associated with an adjusted OR of 0.44 (95% CI: 0.23 to 0.86) when compared to later NAI treatment.

In the pooled dataset, 1,019 patients (30.1%) were recorded to have at least one high-risk condition. In this sub-population of higher-risk patients, we also observed a reduction in the odds of hospital admission (OR: 0.27; 95% CI: 0.19 to 0.38) in those treated with NAIs in the community compared with no NAI treatment.

Full results of the sensitivity and stratified analyses are summarized in Table 2.

Hospital admission rate varied widely between each of the 9 included study centers ranging from 3.94% to 69.3%. To separate any effects that hospital admission rates between centers may have had on the association between NAIs and hospitalization, we did a post-hoc stratified analysis by median hospitalization rate (50.6%). After adjusting for community-based antibiotic treatment and propensity score, the pooled OR for the association between NAI treatment and subsequent hospitalization in study centers with a hospital admission rate <50.6% (n=991) was 1.00 (95% CI: 0.61 to 1.64), whereas in centers where the admission rate was >50.6% (n=2,385), the OR was 0.17 (95%: CI: 0.14 to 0.22).

DISCUSSION

In this study, we assembled data from a large cohort of community based patients, who had pandemic influenza in 2009-10, of whom 91% had laboratory confirmation of influenza A(H1N1)pdm09 infection. The demographic and clinical findings (Table 1) reveal that the patients studied were mainly young, mostly previously healthy, yet with relatively severe influenza (indicated by the presence of either documented severe respiratory distress or shortness of breath at presentation). As such, we recognize that our results are not generalizable to a wider range of community-based patients with mild pandemic influenza, and may not be generalizable to the elderly.

Our main findings (Table 2) suggest that NAI treatment in the community for patients with severe pandemic influenza substantially reduced the likelihood of hospital admission due to influenza

A(H1N1)pdm09. In a pandemic context, individuals generally have little or no pre-existing cross-reactive immunity to the infecting virus; therefore effect size might be lower for seasonal (interpandemic) influenza, and our findings should be interpreted with more caution in that context. In a sensitivity analysis restricted to patients with laboratory-confirmed A(H1N1)pdm09 this finding was unaltered; and in patients with underlying at-risk conditions, the risk reduction was greater. A limitation of our analysis is that we did not have data on body mass index (BMI), therefore, we could not include obesity as a high-risk condition.

We also explored potential differences in effect size between adults and children and found that the effect of NAIs in reducing the likelihood of hospital admission was maintained and broadly consistent in both age groups. These findings contrast with our previous analysis of mortality data, in which we failed to demonstrate significantly reduced mortality in hospitalized children treated with NAIs[5]. This discrepancy is potentially explained by the relatively high attack [10], and hospitalization rates in children with A(H1N1)pdm09 [11], compared with a relatively low case fatality rate [12], but could also relate to statistical under-powering in the mortality study [5].

A question of considerable clinical relevance relates to the timing of antiviral treatment in relation to the magnitude of benefit obtained, especially since data already exist suggesting that symptom alleviation and mortality reduction are both diminished by delayed treatment [5],[13]. We were able to perform a sensitivity analysis on 473 NAI treated patients in whom we had specific data on the timing of symptom onset and antiviral treatment. This revealed that earlier treatment (within 48h of symptom onset) was significantly more beneficial than later treatment.

Because the dataset contained so few elderly patients, perhaps reflecting the low incidence of A(H1N1)pdm09 infection in the elderly [14, 15], we were unable to cast any further light on the effectiveness of NAIs in this particular subgroup of patients.

Although smaller than our previous IPD analysis focused on mortality reduction in hospitalized patients [5], one of the strengths of this study is still the relatively large number of patients included from nine geographically diverse clinical centers. Although we were unable to adjust specifically for disease severity in our multilevel models because of the heterogeneity of severity measures used across individual datasets, we nevertheless included physician recorded breathlessness and severe respiratory distress when deriving propensity scores. However, we acknowledge that confounding by indication [16] may still be present. If it is, we surmise that physicians may have been more likely to treat severe cases than milder ones or putative at-risk groups like pregnant women with NAIs; therefore the treated group would have a higher underlying likelihood of being admitted to hospital, which in turn would produce a bias in the analysis tending towards underestimation of any treatment effect. Likewise, we recognize that some NAI treatment may have been given immediately prior to hospital admission when there was no practical window in which an antiviral drug could have had time to work; or perhaps even when the physician had already decided that the patient needed to be admitted. Therefore we think there is sound clinical rationale for excluding patients in whom NAI treatment was initiated on the day of hospital admission.

Another potential limitation of our propensity scoring approach is that we lacked data on vaccination, albeit knowledge of vaccination status might be associated with physicians' decisions to prescribe NAIs and hospitalize. To explore this further, we determined that patients whose illness onset was on or before 15th October 2009 could not have been vaccinated due to non-availability prior to this date; and even vaccinated, they would not have had time to seroconvert. We subsequently performed a stratified analysis around this date by dividing the overall pooled dataset into 'early pandemic' and 'later pandemic'. We had onset dates in 2,175 patients of whom 903 were on or before 15th October 2009. The adjusted ORs (95% CI) in both groups were very similar [Early pandemic group: 0.12 (0.06 to 0.24) & Late pandemic group: 0.11 (0.07 to 0.18)]. On this basis, we

believe that vaccination is unlikely to have been a major confounder in our study. Other residual confounding is nevertheless possible as these are observational data.

Two obvious drawbacks in our data, are the overall high rate of hospitalization in the cohort studied, which limits generalizability to patients at high risk of hospitalization; and the substantial variability between hospitalization rates across individual centers, ranging from 4% to 70%. The dataset with the lowest hospitalization rate was from a surveillance system in the UK where a national policy operated in 2009-10 to offer NAI treatment to all patients with clinically apparent influenza, irrespective of severity. Stratifying the analysis around median hospitalization rate revealed no effect of NAIs in centers below the median, but a strong positive effect in centers above the median. We surmise that these data confirm the beneficial effect of NAIs (beyond symptom relief) in patients who are severely unwell and at high risk of hospitalization, versus those with milder illness.

To our knowledge, this is the first individual participant data meta-analysis investigating the association between pre-admission NAI antiviral use and hospitalization relating to the 2009-10 influenza pandemic. As such, these data have potential importance for future pandemic stockpiling and treatment policies; but may possibly be of relevance to seasonal epidemics, especially for community patients with relatively severe influenza and those with underlying comorbidities. We note that our point estimates of treatment effectiveness are somewhat higher than the 25% reduction in hospitalization for the treatment of seasonal influenza previously reported by Hsu and colleagues [6]. However the disparity in effect size might be explained by the fact that the four studies [17] meta-analyzed by Hsu contained patients with generally milder influenza than in the present study; in addition three of these four studies were based on diagnoses of influenza-like illness (ILI) without laboratory confirmation, therefore highly vulnerable to misclassification bias. An earlier pooled analysis of clinical trial data from patients with laboratory-confirmed seasonal influenza also observed a 59% reduction in hospitalization [18]. This was confirmed in recent IPD analysis of seasonal influenza patients which reported a risk reduction of 63% in treated patients

(intention-to-treat infected population) [19], which is somewhat similar to our own data. A further paper not included in Hsu's meta-analysis also suggested a 29% reduction in hospitalization associated with oseltamivir but was again based on diagnoses of ILI without laboratory confirmation [20]. A recent study from British Columbia, based on clinically diagnosed cases of pandemic influenza A(H1N1)pdm09, also noted 16% effectiveness of NAIs in reducing hospitalization [21]; however the hospitalization rate is this cohort was 0.6% suggesting cases were comparatively very mild. We therefore recognize that our findings reflect the experience of NAI use in a cohort of community patients at high risk of hospitalization. In addition we noted higher effectiveness in patients with one or more comorbidities that would have placed them in a target group for annual seasonal influenza vaccination.

Placed in the context of the limited previous work on this subject, our findings suggest that greatest benefit from community use of NAIs is likely to be achieved by targeting individuals for treatment who have clinically suspected or proven influenza, and who are also in a recognized at risk-group, or clinically assessed to have severe influenza (irrespective of comorbid status). In these two groups of patients, substantial reductions in the likelihood of hospitalization can be achieved, especially if treatment is commenced within 48 hours of symptom onset. Our data support current advice on NAI treatment given by major public health agencies [22],[23] and the findings of a recent independent report from the UK Academy of Medical Sciences and the Wellcome Trust, which recommend against using NAIs in the community for the treatment of mild influenza, but advise that patients with severe influenza should be treated as soon as possible [24].

NOTES

Author contributions: JSN-V-T, PRM, JL-B, SV and SGM conceived and designed the study. All authors, apart from SV, JL-B and SGM, contributed to the acquisition and local preparation of constituent data sets. SV, PRM, JL-B and SGM, contributed to data set amalgamation and standardization, design of statistical analyses and data analysis. JSN-V-T, PRM, JL-B and SV interpreted the data and wrote the paper. All authors contributed to critical examination of the paper for important intellectual content and approval of the final report. Each author acts as the guarantor of data from their individual study center. 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.

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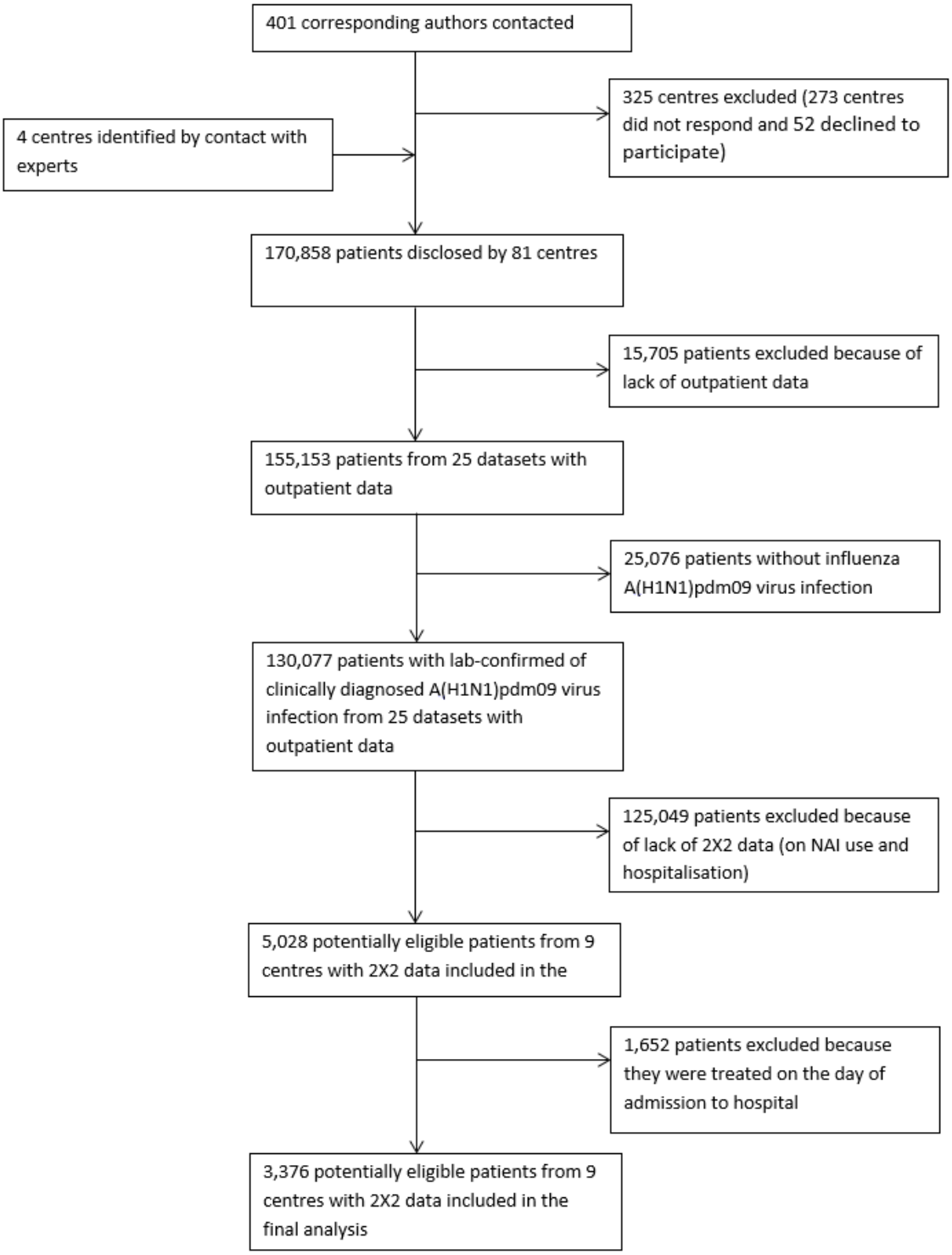
Figure Legends: Figure 1: Study flow diagram



Tables

Table 1: General characteristics of study population (n=3,376)

Variable	All patients (n=3,376)	Non-hospitalized (n=1,671)	Hospitalized (n=1,705)
Number of male cases	1,712 (50.71)	859 (51.41)	853 (50.03)
Age: median (IQR) in years (n=3,253)	14 (4.95 to 27.88)	14 (6.24 to 27)	15 (3.85 to 28.47)
Population groups (no. of persons)			
Adults (≥16 years)	1,506 (44.61)	730 (43.69)	776 (45.51)
Children (<16 years)	1,747 (51.75)	879 (52.60)	868 (50.91)
Aged≥ 65 years	67 (1.98)	22 (1.32)	45 (2.63)
Pregnant women† (n=741)	237/639 (37.09)	121/278 (43.53)	116/361 (32.13)
Countries			
Argentina	17 (0.50)	13 (0.78)	4 (0.23)
Canada	148 (4.34)	113 (6.76)	35 (2.05)
France	81 (2.40)	55 (3.29)	26 (1.52)
Germany	314 (9.29)	161 (9.63)	153 (8.95)
Israel	73 (2.16)	36 (2.15)	37 (2.16)
Saudi Arabia	1,762 (52.11)	613 (36.68)	1,149 (67.19)
Singapore	490 (14.49)	242 (14.48)	248 (14.50)
Slovenia	60 (1.77)	24 (1.44)	36 (2.11)
UK	431 (12.77)	414 (24.78)	17 (1.00)
A(H1N1)pdm09 diagnosis			
Laboratory confirmed	3,085 (91.38)	1,522 (91.08)	1,563 (91.67)
Clinically diagnosed	291 (8.61)	149 (8.92)	142 (8.33)
Severe disease (n=2,395) (Severe respiratory distress or shortness of breath at presentation)	928/2,395 (38.75)	321/991 (32.39)	607/1,404 (43.23)
Comorbidities			
Any comorbidity (n=2,945)	824/2,945 (27.98)	302/1,257 (24.03)	522/1,688 (30.92)
Asthma (n=1,172)	214/1,172 (18.26)	91/634 (14.35)	123/538 (22.86)
COPD (n= 902)	120/902 (13.30)	38/471 (8.07)	82/431 (19.03)
Other chronic lung disease (n= 2,257)	290/2,257 (12.85)	98/871 (11.25)	192/1,386 (13.85)
Heart disease (n=614)	20/614 (3.26)	4/294 (1.36)	16/320 (5.00)
Renal disease (n= 2,299)	92/2,299 (4.00)	40/879 (4.55)	52/1,420 (3.66)
Liver disease (n=541)	11/541 (2.03)	5/258 (1.94)	6/283 (2.12)
Cerebrovascular disease (n=490)	7/490 (1.43)	1/242 (0.41)	6/248 (2.42)
Neurological disease (n= 2,448)	57/2,488 (2.33)	9/963 (0.93)	48/1,485 (3.23)
Diabetes (n= 2,449)	135/2,449 (5.51)	47/964 (4.88)	88/1,485 (5.93)
Immunosuppression (n= 2,390)	97/2,390 (4.06)	36/918 (3.92)	61/1,472 (4.14)
Community/outpatient NAI treatment			
Any NAI treatment	873 (25.82)	653 (39.08)	220 (12.90)
Oseltamivir* (n=2,945)	590 /2,94 (20.03)	385/1,257 (30.63)	205/1,688 (12.14)

Percentages presented in this table are column percentages unless other denominators are specified

† Proportions were calculated as a percentage of pregnant patients among female patients of reproductive age; 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 includes data from an

obstetric outpatients clinic (n=81).

* Where it was explicitly stated that the NAI administered was oseltamivir.

Tabl 2: Association between NAI administration and hospital admission

Population	**Unadjusted analysis**		**Adjusted analysis †**	
	Unadjusted OR (95% CI)	**p-value**	**Adjusted OR (95% CI)**	**p-value**
Patients with laboratory-confirmed or clinically diagnosed A(H1N1)pdm09 influenza (n=3,376)	0.23 (0.19 to 0.28)	<0.001	0.24 (0.20 to 0.30)	<0.001
Patients with laboratory-confirmed A(H1N1)pdm09 influenza (n=3,085)	0.23 (0.19 to 0.28)	<0.001	0.24 (0.19 to 0.29)	<0.001
Adults (16 years and above) (n=1,506)	0.26 (0.19 to 0.35)	<0.001	0.26 (0.19 to 0.35)	<0.001
Children (below 16 years) (n=1,747)	0.22 (0.17 to 0.30)	<0.001	0.25 (0.18 to 0.34)	<0.001
Patients with at least 1 high-risk condition (n=1,019)	0.26 (0.19 to 0.37)	<0.001	0.27 (0.19 to 0.38)	<0.001
Early NAI Treatment (≤2 days after onset) VS. Later (>2 days) in patients with laboratory-confirmed or clinically diagnosed A(H1N1)pdm09 influenza (n=473)	0.51 (0.28 to 0.93)	0.031	0.44 (0.23 to 0.86)	0.016

†adjusted for treatment propensity (by quintile) and community-based antibiotic use