Received Date : 02-Jul-2015

Revised Date : 02-Oct-2015

Accepted Date : 09-Nov-2015

Article type : Original Article

Impact of neuraminidase inhibitors on influenza A(H1N1)pdm09-related pneumonia: an IPD meta-analysis

Stella G Muthuri, Sudhir Venkatesan, Puja R Myles, Jo Leonardi-Bee, Wei Shen Lim, Abdullah Al Mamun, Ashish P Anovadiya, Wildo N Araújo, Eduardo Azziz-Baumgartner, Clarisa Báez, Carlos Bantar, Mazen M Barhoush, Matteo Bassetti, Bojana Beovic, Roland Bingisser, Isabelle Bonmarin , Victor H Borja-Aburto, Bin Cao, Jordi Carratala, María R Cuezzo, Justin T Denholm, Samuel R Dominguez, Pericles AD Duarte, Gal Dubnov-Raz, Marcela Echavarria, Sergio Fanella, James Fraser, Zhancheng Gao, Patrick Gérardin, Maddalena Giannella, Sophie Gubbels, Jethro Herberg, Anjarath L Higuera Iglesias, Peter H Hoeger, Matthias Hoffmann, Xiaoyun Hu, Quazi T Islam, Mirela F Jiménez, Amr Kandeel, Gerben Keijzers, Hossein Khalili, Gulam Khandaker, Marian Knight, Gabriela Kusznierz, Ilija Kuzman, Arthur MC Kwan, Idriss Lahlou Amine, Eduard Langenegger, Kamran B Lankarani, Yee-Sin Leo, Rita Linko, Pei Liu, Faris Madanat, Toshie Manabe, Elga Mayo-Montero, Allison McGeer, Ziad A Memish, Gokhan Metan, Dragan Mikić, Kristin GI Mohn, Ahmadreza Moradi, Pagbajabyn Nymadawa, Bulent Ozbay, Mehpare Ozkan, Dhruv Parekh, Mical Paul, Wolfgang Poeppl, Fernando P Polack, Barbara A Rath, Alejandro H Rodríguez, Marilda M Siqueira, Joanna Skręt-Magierło, Ewa Talarek, Julian W Tang, Antoni Torres, Selda H Törün, Dat Tran, Timothy M Uyeki, Annelies van Zwol, Wendy Vaudry, Daiva Velyvyte, Tjasa Vidmar, Paul Zarogoulidis, PRIDE Consortium Investigators†, Jonathan S Nguyen-Van-Tam

Author affiliations can be found on pages 26-30

†List of PRIDE Consortium Investigators' can be found on pages 20. For affiliations, please see Table E1 of the online supplement data

Corresponding Author: Jonathan Nguyen-Van-Tam, DM, Room A28b, Clinical Sciences Building, University of Nottingham, City Hospital, Nottingham NG5 1PB, United Kingdom (jvt@nottingham.ac.uk).

Title page items:

1. The title of the paper

Full title: Impact of neuraminidase inhibitors on influenza A(H1N1)pdm09-related pneumonia: an IPD meta-analysis

Running head: NAIs for Influenza related pneumonia

2. Name and address of each author

For names and affiliations of named authors please see pages 26-30.

The list of PRIDE Consortium Investigators' can be found on pages 20. For affiliations, please see Table E1 of the online supplement data.

3. Name and full postal address (with phone/fax numbers and e-mail) of the corresponding author

Corresponding author: Jonathan Nguyen-Van-Tam, DM, Room A28b, Clinical Sciences Building, University of Nottingham, City Hospital, Nottingham NG5 1PB, United Kingdom.

Email: jvt@nottingham.ac.uk; Phone: 0115 823 0276

Background

The impact of neuraminidase inhibitors (NAIs) on Influenza-related pneumonia (IRP) is not established. Our objective was to investigate the association between NAI treatment and IRP incidence and outcomes in patients hospitalised with A(H1N1)pdm09 virus infection.

Methods

A worldwide meta-analysis of individual participant data (IPD) from 20,634 hospitalised patients with laboratory confirmed A(H1N1)pdm09 (n=20,021) or clinically diagnosed (n=613) 'pandemic influenza'. The primary outcome was radiologically confirmed influenza-related pneumonia (IRP). Odds ratios (OR) were estimated using generalized linear mixed modelling, adjusting for NAI treatment propensity, antibiotics and corticosteroids.

Results

Among 20,634 included participants, 5,978 (29.0%) had IRP; conversely, 3,349 (16.2%) had confirmed absence of radiographic pneumonia (the comparator). Early NAI treatment (within 2 days of symptom onset) versus no NAI was not significantly associated with IRP [adj. OR 0.83 (95%CI 0.64 – 1.06; p=0.136)]. Among the 5,978 patients with IRP, early NAI treatment versus none did not impact on mortality [adj. OR=0.72 (0.44-1.17; p=0.180)] or likelihood of requiring ventilatory support [adj. OR=1.17 (0.71-1.92; p=0.537)]; but early treatment versus later significantly reduced mortality [adj. OR=0.70 (0.55-0.88; p=0.003)] and likelihood of requiring ventilatory support [adj. OR=0.68 (0.54-0.85; p=0.001)].

Conclusions

Early NAI treatment of patients hospitalised with A(H1N1)pdm09 virus infection versus no treatment did not reduce the likelihood of IRP. However, in patients who developed IRP early NAI treatment versus later reduced the likelihood of mortality and needing ventilatory support.

Key words: Influenza-related pneumonia; neuraminidase inhibitors; individual participant data meta-analyses; hospitalisation

Introduction

Influenza-related pneumonia was a common and severe complication during the 2009-10 influenza pandemic (1-5). Neuraminidase inhibitors (NAIs), primarily oseltamivir and zanamivir, were widely recommended for patients with suspected or confirmed influenza A (H1N1)pdm09 virus infection (6, 7). However, prior to the 2009-10 pandemic, evidence of their effectiveness in seasonal influenza, whilst strong for modest symptom alleviation, was less robust for reductions in pneumonia incidence or improvements in pneumonia outcome (8-10). The findings from meta-analyses have been inconsistent. One study, based on observational data from 150,660 patients with mainly seasonal influenza suggested no statistically significant reduced likelihood of pneumonia (9). Another used clinical trials data from 4,452 community adult patients with uncomplicated seasonal influenza and concluded that oseltamivir significantly reduced "self-reported, investigator-mediated,

unverified pneumonia" by 45%, compared with placebo; but data on radiologically confirmed pneumonia were not available (11).

A recent IPD analysis of clinical trial data investigating the efficacy of oseltamivir when compared to placebo in patients with seasonal influenza reported a reduction in risk of pneumonia by 60% (12). Individual observational studies during the 2009-10 pandemic suggest a possible benefit of NAIs in reducing pneumonia incidence, but are limited by small sample sizes (13-16). A meta-analysis of 2009-10 pandemic data from patients hospitalised with influenza A(H1N1)pdm09 virus infection reported that early treatment with NAIs reduced the likelihood of influenza-related pneumonia compared to late treatment by 65%(17). But this work encountered high degrees of heterogeneity and inconsistent or incomplete adjustment for potential confounders.

We present a global meta-analysis based on individual participant data (IPD), controlling for potential confounders and treatment propensity. We investigate the association between NAI treatment and radiologically confirmed influenza-related pneumonia (IRP) in patients hospitalised with A(H1N1)pdm09 virus infection; and outcomes including admission to intensive care units (ICUs), ventilatory support, Acute Respiratory Distress Syndrome (ARDS), and mortality in patients with IRP.

Some of these results have been previously reported in the form of an abstract (18).

Methodology

The PRIDE research consortium

Details of the Post-pandemic Review of anti-Influenza Drug Effectiveness (PRIDE) study have been published previously (19). Briefly, participating research centres were identified during the conduct of a systematic review of published studies on the same topic (17). Additional centres were recruited through this network of global collaborators, publicity at conferences, and by word-of-mouth. Centres that fulfilled the minimum dataset requirements (Table E2) were eligible for inclusion in the consortium. In total, 79 research groups from 38 countries and 6 World Health Organization (WHO) regions contributed data on 143786 patients with laboratory or clinically diagnosed influenza A(H1N1)pdm09 virus infection (Figure 1). No data were provided or funded for collection by pharmaceutical companies. The protocol was registered with the PROSPERO register of systematic reviews, number CRD42011001273 (20).

Data standardisation, exposure and outcome variables

Data were standardised using a common data dictionary (19) before pooling for analysis. For this analysis, the primary outcome was influenza-related pneumonia (IRP) defined as laboratory-confirmed or clinically diagnosed influenza A(H1N1)pdm09 virus infection plus pneumonia confirmed by chest radiography, occurring at any time after the onset of influenza like illness. For radiographic evidence of pneumonia we accepted:

1. A formal chest radiograph or computerised tomograph report documenting "pneumonia"

2. Datasets reporting pneumonia and chest radiograph as discrete variables, in which both items were marked positive or "yes".

3. Formal chest radiograph reports of one or more abnormalities consistent with pneumonia: pulmonary infiltrates; lobar consolidation; homogeneous segmental consolidation with or without cavitation; diffuse bilateral interstitial and/or interstitial-alveolar (mixed) infiltrates; segmental consolidation; lobar consolidation; rounded pneumonia; bronchopneumonia; interstitial pneumonia; pneumatoceles; acute pulmonary infiltrates, as previously validated by Bewick et al. and Franquet (21, 22), unless a formal radiograph report also stated "no pneumonia".

4. Chest radiograph report not provided, but specific mention in the clinical case notes that a radiograph had been formally reported as showing pneumonia.

The absence of IRP ('no IRP') was defined as laboratory-confirmed or clinically diagnosed influenza A(H1N1)pdm09 infection plus a radiographic report that did not identify abnormalities consistent with pneumonia, or which stated that pneumonia was "not present" (irrespective of any specific features reported).

Comparative exposure to neuraminidase inhibitor (NAI) treatment was defined as follows: early NAI treatment (≤2 days after symptom onset) versus no NAI treatment; early NAI treatment versus later NAI treatment (treatment commenced

>2 days after symptom onset); later NAI treatment versus no NAI treatment; and NAI treatment (irrespective of timing) versus no NAI treatment.

Propensity scoring

Propensity scores for likelihood of NAI treatment were calculated for each patient within individual datasets using multivariable logistic regression for each of the three NAI exposure measures, using covariates as described by Muthuri et al. (19) (Table E3). Subsequently, propensity scores were categorized into quintiles for each individual dataset.

Statistical analysis

To investigate the association between use of NAI treatment and IRP we compared patients with IRP against those with no IRP. We used generalised linear mixed modelling to conduct separate analyses for each NAI exposure comparison using the xtmelogit command in Stata (version 13). Individual studies were included in the model as a random intercept in order to account for differences in baseline outcome. Adjustment was performed for propensity of NAI treatment, antibiotics administered during hospitalisation and corticosteroids administered during hospitalisation. Missing data in the covariates were included as a separate dummy category to allow for comparisons across the crude and adjusted analyses. We excluded datasets in which all patients (n=1,352 from 14 datasets) were diagnosed with IRP. Stratified analyses were conducted for adults (≥16 years), children (<16

years; including <5 and 5-15 years subgroups), pregnant women, laboratory confirmed A(H1N1)pdm09 cases, and patients admitted to critical care units. We did not include patients with unknown pneumonia status (n=3,615 across 21 datasets) in this analysis.

In the subgroup of patients with IRP, we further examined the effect of NAI treatment on secondary clinical outcomes: admission to intensive care units (ICUs), ventilatory support, ARDS, and mortality. At this juncture we re-included the 14 datasets in which all patients were diagnosed with IRP.

Sensitivity analysis

In some clinical settings, chest radiography is not routinely performed for hospitalised patients with influenza unless a pulmonary complication is also suspected; therefore reliance on radiographic abnormalities is likely to give a conservative estimate of pneumonia incidence. Accordingly, we also performed a sensitivity analysis, which considered a diagnosis of 'any pneumonia' by combining IRP with physician diagnosed pneumonia (PDP), the latter defined as laboratory confirmed or clinically diagnosed influenza A(H1N1)pdm09 plus a physician diagnosis of pneumonia, but where no chest radiograph report was available. For this analysis, patients categorised as 'no pneumonia' had laboratory confirmed or clinically diagnosed influenza A(H1N1)pdm09 with no evidence of IRP on chest radiography; unknown pneumonia status or, in the absence of a chest radiograph

report, no documented clinical record of PDP, recognising that clinicians record positive findings in the case record but not all negative findings.

Results are presented as unadjusted and adjusted odds ratios (OR) with 95 percent confidence intervals (95% CI) and two-sided P values less than 0.05 were considered statistically significant. Statistical analyses were conducted using Stata (version 13).

Results

Overall, data were obtained on 35,169 individuals hospitalised with A(H1N1)pdm09 virus infection (Figure 1) . Of these, 29,512 (84%) patients were admitted from January 2009 through March 2011 (Figure E1) with information available on NAI treatment. A further 8 datasets comprising 8,878 hospitalised patients that did not provide data on pneumonia status were excluded from the analysis (Figure 1; Table E4).

Of the 20,634 patients included, 9,327 (45%) had a positive or negative diagnosis of IRP confirmed by chest radiography while 7,692 (37%) did not have chest radiography but had a positive or negative diagnosis of PDP documented. The remaining 3,615 (18%) hospitalised patients had neither radiological nor clinical documentation of pneumonia status; they were included in the sensitivity analysis (only) as having 'no pneumonia'. The characteristics of hospitalised patients with and without pneumonia included in the pooled dataset are shown in Table 1.

Baseline characteristics of each constituent dataset included in the analysis are presented in Table E5.

Overall, patients with IRP were more likely than patients with no IRP to be adult (p<0.001), non-pregnant (p<0.001), free of underlying medical conditions (p=0.038), be from outside the WHO European region (p<0.001) and have laboratory confirmed influenza A(H1N1)pdm09 infection (p<0.001). They were more likely to receive NAI treatment (p<0.001), antibiotics (p<0.001), and corticosteroids (p<0.001), be admitted to critical care facilities (p<0.001) and require ventilatory support (<0.001) or die (p<0.001) (Table 1).

Association between NAI treatment and influenza-related pneumonia (IRP)

Overall, 63 datasets provided data on 9,327 hospitalised patients with a positive or negative diagnosis of pneumonia confirmed by chest radiography. After exclusion of 14 datasets in which all patients had IRP (n= 1352, Table E5), 7,975 patients remained in the analysis.

a) Early NAI (≤2 days) vs. No NAI treatment

Early NAI use compared with no NAI use was not significantly associated with IRP in our overall sample (adjusted OR 0.83 [95%CI 0.64 – 1.06]), nor when we considered laboratory confirmed cases, adults, pregnant women, or children (Table 2). However, point estimates for subgroups tended to suggest an OR below unity,

except in ICU patients. When considering 'any pneumonia' we found a borderline significant reduced OR associated with early NAI use in all patients (adjusted OR 0.83 [95% CI 0.70 - 0.98]), with further borderline significant risk reductions also noted among laboratory confirmed cases; these findings lost statistical significance when further stratified by patient subgroups but the point estimates remained consistent (Table 2).

For this exposure, we also looked at the impact of corticosteroids on the association between NAI treatment and IRP. A test for interaction between NAI treatment and corticosteroids did not show any significant interaction (p-value: 0.275). Stratified analysis (by corticosteroid use) did not show any significant association between NAI use and IRP (Table E9).

b) Early NAI (≤2 days) vs. Later NAI (>2 days) treatment

Early NAI treatment compared with later was associated with significantly lower odds of IRP [adjusted OR, 0.43 (95% CI, 0.37 – 0.51)], (Table 2). The odds ratios did not change substantially when only cases of laboratory confirmed influenza were considered (Table 2). Similarly, statistically significant lower odds of IRP were observed in adults aged 16 years or older, children aged 0-15 years, pregnant women and among adult patients admitted to critical care. However, there was no statistically significant association with IRP among children admitted to critical care (Table 2). The pattern of these findings in terms of direction and significance was similar when considering 'any pneumonia' (Table 2).

c) Later NAI (>2 days) vs. No NAI treatment

NAI treatment beyond two days of symptom onset compared with no NAI was associated with statistically significant higher odds of IRP [adjusted OR, 1.70 (95% CI, 1.34 – 2.17)]. Similar statistically significant associations were observed among cases of laboratory-confirmed influenza, adults, and critically ill children but not among all children, pregnant women and critically ill adults. Likewise, with 'any pneumonia', the direction and statistical significance of these findings did not change (Table 2).

d) NAI anytime vs. No NAI treatment

After adjustment, the likelihood of IRP in patients treated with NAI (administered at any point after illness onset) was 1.32 (95% CI 1.10 – 1.59), compared with no NAI treatment (Table 2). This OR did not change substantially when only patients with laboratory confirmed A(H1N1)pdm09 were included (adjusted OR 1.29 [95% CI 1.06 – 1.57]). Similarly, we observed significantly higher odds of IRP associated with NAI antiviral use in adults and borderline significantly increased odds of IRP in adults admitted to an ICU. However, there was no significant association between NAI treatment and IRP in children aged 0–15 years, pregnant women and critically ill children. The pattern of these findings was not changed by considering 'any pneumonia', except in children admitted to critical care where we observed statistically significant higher odds of IRP for patients treated with an NAI (at any time).

Post-hoc analyses on non-ICU patients (all ages) are shown in Table E6; childrens' subgroups aged <5 years and 5-15 are shown in Tables E7 (all severities) and E8 (critically ill).

Impact of NAI treatment on clinical outcomes among patients with pneumonia

We performed a further analysis, restricted to patients with IRP (n=5,978) (Table 3) and a sensitivity analysis by including 'any pneumonia' patients (n=7,054). Datasets in which all patients had IRP (n=1,352 patients, 14 datasets) were re-added at this juncture.

In the IRP cohort, we did not observe any statistically significant associations with clinical outcomes when early NAI treatment was compared with no NAI treatment; but for 'any pneumonia' we observed that early NAI treatment versus no NAI was associated with an increased likelihood of admission to an ICU [adjusted OR, 1.81 (95% CI, 1.27 – 2.58); p=0.001], but a reduced likelihood of mortality [adj. OR, 0.62 (95% CI, 0.40 - 0.96); p=0.032].

In patients with IRP, early NAI treatment compared to later NAI was associated with significantly lower odds of ventilatory support [adjusted OR, 0.68 (95% CI, 0.54 - 0.85); p=0.001 and mortality [adjusted OR, 0.70 (95% CI, 0.55 - 0.88); p=0.003]. These effects were similar and remained statistically significant for 'any pneumonia'.

Later NAI treatment versus no NAI was significantly associated with increased likelihood of ICU admission and ventilatory support. The pattern of these findings in terms of direction and significance was unchanged when considering 'any pneumonia'. Likewise, patients with IRP who received NAI at any time versus no NAI treatment were more likely to be admitted to an ICU [adj. OR, 1.59 (95% CI, 1.21 – 2.09), p=0.001], and receive ventilatory support [adj. OR, 1.67 (95% CI, 1.22 – 2.29), p=0.001].

Discussion

The strengths of this study include having data on a large number of patients of all ages hospitalised with influenza A(H1N1)pdm09 virus infection (mainly laboratory confirmed) from different geographical regions worldwide. Given the practical and ethical constraints likely to be involved in conducting placebo controlled trials during pandemic periods, use of large-scale pooled observational data offers the best chance of producing meaningful results on the effect of NAIs on severe outcomes such as pneumonia.

Our definition of IRP, which required radiographic evidence of pneumonia, represents a conservative estimate of all cases of pneumonia as radiography was not routinely performed for every patient in all participating centres. We therefore also performed separate analyses, which included patients with physician-diagnosed pneumonia (PDP). Some patients with PDP would not have had pneumonia (false

positives) and thus we expect that the true effect estimates of the association of NAI with pneumonia and clinical outcomes probably fall somewhere between the values obtained in the analyses for IRP and 'any pneumonia'.

However, there are inevitable limitations, based on the use of retrospective observational data. Since we found an increase in IRP in several comparisons where we might have expected NAIs to have a protective effect, this suggests that our propensity scoring was not able to fully adjust for the tendency to use NAIs in more severe disease. We were unable to fully adjust for severity of illness within each propensity score because the different severity measures used across individual datasets were disparate. Furthermore, we included a broad spectrum of pneumonia severity and the available data did not permit stratification according pneumonia severity (for example, using CURB65 or the Pneumonia Severity Index).

NAI treatment and occurrence of pneumonia

Our findings that early initiation of NAI treatment (≤48h after illness onset) compared with later was associated with a significant reduction in IRP and 'any pneumonia' corroborate those previously reported from observational data on hospitalised influenza patients (9, 17, 19). These trends were consistently observed across multiple subgroups: laboratory-confirmed influenza, adults, children, pregnant women and adults requiring critical care (but not children). For early treatment versus none, highly consistent, protective point estimates were also

generated for most comparisons in adults and children, but failed to reach statistical significance for IRP (possibly due to Type II errors (sample size) although they reached borderline significance for 'any pneumonia' (all cases)). As such the results are somewhat incongruent with our previous work, which showed a 50% reduction in mortality associated with early treatment versus none (18). It is possibly a combination of residual confounding and misclassification of pneumonia that has led to our current results, and it remains plausible that these weak signals still suggest a reduction in the occurrence of influenza-related pneumonia.

Our other findings that NAI treatment at any time versus no NAI, and later NAI treatment compared with no NAI, universally increased the risks of IRP, contrast sharply with previous observational data on hospitalised influenza patients which found that NAI treatment (irrespective of timing) and later antiviral therapy (initiated >48 h after illness onset) may improve a range of clinical outcomes (19, 23-28). Essentially similar observations were made for 'any pneumonia'.

Thus, in terms of the occurrence of pneumonia, our data suggest differential effects depending on the timing and use of NAIs; apparent harm associated with any or later NAI use versus no NAI; but potential benefit from early NAI use versus late NAI use or none. Based upon what is known about the mechanism of action of NAIs (29, 30), it is theoretically possible that treatment might be ineffective (tending to produce an Odds Ratio (OR) close to 1) but rather implausible that it would be

genuinely harmful, producing an OR >1 as we measured. Instead, we surmise that NAIs were often prescribed after development of pneumonia or clinical deterioration; furthermore, patients with IRP were admitted to hospital a median of 4 days from symptom onset, compared to 2 days for those with no pneumonia. A process of reverse causation is more likely to be responsible for the elevated risk of IRP associated with any or late NAI treatment versus none. Indeed, from our dataset we were able to record the timing of initiation of NAI treatment in relation to illness onset, but we lacked the ability to record the timing of treatment in relation to the development of pneumonia, which precluded us conducting a survival analysis. With regard to the severity of illness at time of initiating NAI therapy, one functional measure would have been to consider site of NAI treatment initiation (outpatient, Emergency Department, hospital ward, ICU); unfortunately we were not able to do this because overall there were too many missing data.

NAI treatment and clinical outcomes in pneumonia

Our other main finding relates to the effect of NAI treatment on clinical outcomes in patients with IRP. Our data reveal that patients with IRP, who were treated early with an NAI versus later experienced a roughly one-third lower likelihood of dying or requiring ventilatory support. A mortality reduction of similar magnitude was noted when comparing early NAI versus no NAI, which was statistically significant for the analysis of 'any pneumonia' but not for IRP. Although we advise caution in the interpretation of these subgroup analyses, essentially the same finding has been

made about ventilatory support in a very large cohort of children hospitalised with seasonal and pandemic influenza (31).

We also found that among patients with 'any pneumonia', those who received NAIs were more likely to be managed in an ICU or require ventilatory support compared to those not treated with NAIs, regardless of the timing of treatment. Confounding by indication is an important consideration in relation to these data; that is, patients with severe pneumonia or ARDS who were escalated to ICU-based care would be more likely to be preferentially treated with NAIs compared to those not requiring ICU; indeed, in the PRIDE dataset overall (n=29,259) we noted that 82% of ICU patients received an NAI compared with 61% in non-ICU patients ($p<0.001$). The alternative explanation that NAI treatment results in clinical deterioration with resultant increased requirements for ICU admission or ventilatory support, but no increase in mortality is unlikely and our results should not be used to justify the avoidance of early empirical use of NAIs for patients who are severely unwell with suspected influenza.

Technical limitations

Insufficient data on influenza vaccination, limited our ability to assess its potential effect on the clinical course of influenza A(H1N1)pdm09 virus infection, albeit that 9,890 of 20,634 patients (48.5%) were admitted prior to November 2009 and could not have benefitted from H1N1pdm09 vaccine as it would not have been available by this point.

There were wide variations across included study centres in terms of individual study period, health care systems, clinical practice, treatment policies and resource availability. Although we attempted to control for these study-level biases using generalised linear mixed models, residual confounding is possible. Likewise, we cannot completely eliminate misclassification of exposure, covariate or outcome variables. Notwithstanding, we attempted to account for misclassification bias by conservatively restricting our main analysis to IRP based on chest radiograph reports. But, we were unable to discriminate between viral pneumonia, bacterial pneumonia, and concurrent viral and bacterial pneumonia; nor differentiate between community and hospital acquired pneumonia.

Despite requesting a minimum set of data variables (Table E2), the nature of the surveillance datasets provided, which were set up for monitoring during a public health emergency, meant that there were missing data on some variables of interest (e.g. admission diagnosis, comorbidities, interval from the onset of symptoms to NAI treatment, severity of disease at presentation, influenza vaccination, concomitant therapies, complications, information on follow up etc.).

Finally, this study does not reflect the full spectrum of disease caused by influenza A(H1N1)pdm09 virus infection in the community as it only examined hospitalised patients.

Implications and Conclusions

Early NAI treatment probably reduces the likelihood of IRP. We observed highly consistent protective point estimates for early initiation of NAI treatment versus late and early treatment versus no NAI, but only the former was statistically significant; therefore the evidence is strongest for an effect of early versus later NAI treatment. Overall, NAI treatment compared with no NAI treatment was associated with an increased likelihood of IRP; we surmise this is because NAIs are sometimes started later in response to the development of pneumonia.

In patients with IRP, early NAI treatment versus later reduced the need for ventilatory support and subsequent mortality. Since randomised controlled trials of NAI treatment versus no NAI or placebo, or early NAI treatment versus late are unlikely to be ethically or practically feasible, further evidence is needed from well-designed, prospective cohort studies in which disease severity, and the dates of symptom onset, hospital admission, NAI treatment initiation and pneumonia onset are all accurately and consistently described.

PRIDE CONSORTIUM INVESTIGATORS

Maria de Lourdes Aguiar-Oliveira, Tarig SA Al Khuwaitir, Malakita Al Masri, Robed Amin, Elena Ballester-Orcal, Jing Bao, Ariful Basher , Edgar Bautista, Barbara Bertisch, Julie Bettinger, Robert Booy, Emilio Bouza, Ilkay Bozkurt, Heinz Burgmann, Elvira Čeljuska-Tošev, Kenny KC Chan, Yusheng Chen, Tserendorj Chinbayar, Catia Cilloniz, Rebecca J Cox, Elena B Sarrouf, Wei Cui, Simin Dashti-Khavidaki, Bin Du, Hicham El Rhaffouli, Hernan Escobar, Agnieszka Florek-Michalska, John Gerrard, Stuart Gormley, Sandra Götberg, Behnam Honarvar,

Jianming Hu, Christoph Kemen, Evelyn SC Koay, Miroslav Kojic, Koichiro Kudo, Win M Kyaw, Leonard Leibovici, Xiao-li Li, Hongru Li, Romina Libster, Tze P Loh, Deborough Macbeth, Efstratios Maltezos, Débora N Marcone, Magdalena Marczynska, Fabiane P Mastalir, Auksė Mickiene, Mohsen Moghadami, Lilian Moriconi, Maria E Oliva, Blaž Pečavar, Philippe G Poliquin, Mahmudur Rahman, Alberto Rascon-Pacheco, Samir Refaey, Brunhilde Schweiger, Anna C Seale, Bunyamin Sertogullarindan, Fang G Smith, Ayper Somer, Thiago ML Souza, Frank Stephan, Payam Tabarsi, C B Tripathi, Diego Viasus, Qin Yu, Wei Zhang, Wei Zuo

Addendum

Author contributions: JSN-V-T, PRM, WSL, JL-B, SGM, and SV conceived and designed the study. All authors, apart from SGM, SV, JL-B and WSL contributed to the acquisition and local preparation of constituent datasets. SGM, SV, PRM, and JL-B contributed to dataset amalgamation and standardisation, design of statistical analyses, and data analysis. JSN-V-T, PRM, JL-B, WSL, SGM 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 centre; JSN-V-T and PRM act as overall guarantors for the pooled analysis and the report.

Acknowledgments

We thank the many medical personnel and other individuals who helped in collating and maintaining the clinical data used in our analyses. We thank all participating hospitals, institutions, and research networks (listed in Table E1) that supplied anonymised patient data.

References

1. Lee N, Chan PKS, Lui GCY, Wong BCK, Sin WWY, Choi K-W, Wong RYK, Lee ELY, Yeung ACM, Ngai KLK, Chan MCW, Lai RWM, Yu AWY, Hui DSC. Complications and outcomes of pandemic 2009 influenza a (h1n1) virus infection in hospitalized adults: How do they differ from those in seasonal influenza? *J Infect Dis* 2011;203:1739-1747.
2. Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S, Hernandez M, Quinones-Falconi F, Bautista E, Ramirez-Venegas A, Rojas-Serrano J, Ormsby CE, Corrales A, Higuera A, Mondragon E, Cordova-Villalobos JA, Influenza IWGo. Pneumonia and respiratory failure from swine-origin influenza a (h1n1) in mexico. *N Engl J Med* 2009;361:680-689.
3. Reyes S, Montull B, Martinez R, Cordoba J, Molina JM, Marti V, Martinez A, Ramirez P, Menendez R. Risk factors of a/h1n1 etiology in pneumonia and its impact on mortality. *Respiratory Medicine* 2011;105:1404-1411.
4. Louie JK, Acosta M, Winter K, Jean C, Gavali S, Schechter R, Vugia D, Harriman K, Matyas B, Glaser CA, Samuel MC, Rosenberg J, Talarico J, Hatch D, California Pandemic Working G. Factors associated with death or hospitalization due to pandemic 2009 influenza a(h1n1) infection in california. *Jama* 2009;302:1896-1902.
5. Nguyen-Van-Tam JS, Openshaw PJM, Hashim A, Gadd EM, Lim WS, Semple MG, Read RC, Taylor BL, Brett SJ, McMenamin J, Enstone JE, Armstrong C, Nicholson KG, Influenza Clinical Information N. Risk factors for hospitalisation and poor outcome with pandemic a/h1n1 influenza: United kingdom first wave (may-september 2009). *Thorax* 2010;65:645-651.
6. Centers for Disease Control and Prevention. Influenza antiviral medications: Summary for clinicians. [cited (accessed March 14, 2014). Available from: http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm#summary.
7. World Health Organization WHO. Clinical management of human infection with pandemic (h1n1) 2009: Revised guidance. 2009 [cited 2014 18 November 2009]. Available from: http://www.who.int/csr/resources/publications/swineflu/clinical_management_h1n1.pdf.
8. Kaiser L, Wat C, Mills T, Mahoney P, Ward P, Hayden F. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. *Arch Intern Med* 2003;163:1667-1672.
9. Hsu J, Santesso N, Mustafa R, Brozek J, Chen YL, Hopkins JP, Cheung A, Hovhannisyan G, Ivanova L, Flottorp SA, Saeterdal I, Wong AD, Tian J, Uyeki TM, Akl EA, Alonso-Coello P, Smaill F, Schunemann HJ. Antivirals for treatment of influenza: A systematic review and meta-analysis of observational studies. *Ann Intern Med* 2012;156:512-524.

10. Jefferson T, Jones MA, Doshi P, Del Mar CB, Heneghan CJ, Hama R, Thompson MJ. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev* 2012;1:CD008965.
11. Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ, Spencer EA, Onakpoya I, Mahtani KR, Nunan D, Howick J, Heneghan CJ. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev* 2014;4:CD008965.
12. Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: A meta-analysis of randomised controlled trials. *The Lancet*;385:1729-1737.
13. Hiba V, Chowers M, Levi-Vinograd I, Rubinovitch B, Leibovici L, Paul M. Benefit of early treatment with oseltamivir in hospitalized patients with documented 2009 influenza a (h1n1): Retrospective cohort study. *Journal of Antimicrobial Chemotherapy* 2011;66 1150-1155.
14. Nakai A, Minakami H, Unno N, Saito S, Morikawa M, Yoshimura Y, Terao T. Characteristics of pregnant japanese women who required hospitalization for treatment of pandemic (h1n1) 2009--low mortality rate may be due to early antiviral use. *J Infect* 2011;62:232-233.
15. Viasus D, Pano-Pardo JR, Pachon J, Riera M, Lopez-Medrano F, Payeras A, Farinas MC, Moreno A, Rodriguez-Bano J, Oteo JA, Martinez-Montauti J, Torre-Cisneros J, Segura F, Gudiol F, Carratala J. Pneumonia complicating pandemic (h1n1) 2009: Risk factors, clinical features, and outcomes. *Medicine* 2011;90:328-336.
16. Higuera Iglesias AL, Kudo K, Manabe T, Corcho Berdugo AE, Corrales Baeza A, Alfaro Ramos L, Guevara Gutierrez R, Manjarrez Zavala ME, Takasaki J, Izumi S, Bautista E, Perez Padilla JR. Reducing occurrence and severity of pneumonia due to pandemic h1n1 2009 by early oseltamivir administration: A retrospective study in mexico. *PloS one* 2011;6:e21838.
17. Muthuri SG, Myles PR, Venkatesan S, Leonardi-Bee J, Nguyen-Van-Tam JS. Impact of neuraminidase inhibitor treatment on outcomes of public health importance during the 2009-2010 influenza a(h1n1) pandemic: A systematic review and meta-analysis in hospitalized patients. *J Infect Dis* 2013;207:553-563.
18. Muthuri S, Myles P, Leonardi-Bee J, Venkatesan S, Nguyen-Van-Tam JS, on behalf of the PRIDE Research Collaboration. Post-pandemic review of anti-influenza drug effectiveness (pride study): An investigation of the impact of neuraminidase inhibitor antiviral use on pneumonia and length of hospital stay in hospitalized influenza a(h1n1)pdm09 patients [abstract]. The European Scientific Workshop on Influenza (ESWI). Riga; 2014.
19. Muthuri SG, Venkatesan S, Myles PR, Leonardi-Bee J, Al Khuwaitir TS, Al Mamun A, Anovadiya AP, Azziz-Baumgartner E, Baez C, Bassetti M, Beovic B, Bertisch B, Bonmarin I, Booy R, Borja-Aburto VH, Burgmann H, Cao B, Carratala J, Denholm JT, Dominguez SR, Duarte PA, Dubnov-Raz G, Echavarria M, Fanella S, Gao Z, Gerardin P, Giannella M, Gubbels S, Herberg J, Iglesias AL, Hoger PH, Hu X, Islam QT, Jimenez MF, Kandeel A, Keijzers G, Khalili H, Knight M, Kudo K, Kusznierz G, Kuzman I, Kwan AM, Amine IL, Langenegger E, Lankarani KB, Leo YS, Linko R, Liu P, Madanat F, Mayo-Montero E, McGeer A, Memish Z, Metan G, Mickiene A, Mikic D, Mohn KG, Moradi A, Nymadawa P, Oliva ME, Ozkan M, Parekh D, Paul M, Polack FP, Rath BA, Rodriguez AH, Sarrouf EB, Seale AC, Sertogullarindan B, Siqueira MM, Skret-Magierlo J, Stephan F, Talarek E, Tang JW, To KK, Torres A, Torun SH, Tran D, Uyeki TM, Van Zwol A, Vaudry W, Vidmar T, Yokota RT, Zarogoulidis P, Investigators PC, Nguyen-Van-Tam JS. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza a h1n1pdm09 virus infection: A meta-analysis of individual participant data. *The Lancet Respiratory medicine* 2014;2:395-404.
20. Myles P, Leonardi-Bee J, Van-Tam J, Muthuri S, Venkatesan S. A systematic review of the impact of neuraminidase inhibitor antiviral use on outcomes of public health importance during the 2009/10 (swine) influenza a/h1n1v pandemic. [cited accessed Feb 4, 2014. Available from: http://www.crd.york.ac.uk/IHR_PROSPERO/display_record.asp?ID=CRD42011001273#.UvDWqFFNKW8.
21. Franquet T. Imaging of pneumonia: Trends and algorithms. *Eur Respir J* 2001;18:196-208.

22. Bewick T, Myles P, Greenwood S, Nguyen-Van-Tam JS, Brett SJ, Semple MG, Openshaw PJ, Bannister B, Read RC, Taylor BL, McMenamin J, Enstone JE, Nicholson KG, Lim WS, Influenza Clinical Information N. Clinical and laboratory features distinguishing pandemic h1n1 influenza-related pneumonia from interpandemic community-acquired pneumonia in adults. *Thorax* 2011;66:247-252.
23. Lee N, Choi KW, Chan PKS, Hui DSC, Lui GCY, Wong BCK, Wong RYK, Sin WY, Hui WM, Ngai KLK, Cockram CS, Lai RWM, Sung JJY. Outcomes of adults hospitalised with severe influenza. *Thorax* 2010;65:510-515.
24. Louie JK, Yang S, Acosta M, Yen C, Samuel MC, Schechter R, Guevara H, Uyeki TM. Treatment with neuraminidase inhibitors for critically ill patients with influenza a (h1n1)pdm09. *Clin Infect Dis* 2012;55:1198-1204.
25. McGeer A, Green KA, Plevneshi A, Shigayeva A, Siddiqi N, Raboud J, Low DE, Toronto Invasive Bacterial Diseases N. Antiviral therapy and outcomes of influenza requiring hospitalization in ontario, canada. *Clin Infect Dis* 2007;45:1568-1575.
26. Adisasmito W, Chan PKS, Lee N, Oner AF, Gasimov V, Aghayev F, Zaman M, Bamgboye E, Dogan N, Coker R, Starzyk K, Dreyer NA, Toovey S. Effectiveness of antiviral treatment in human influenza a(h5n1) infections: Analysis of a global patient registry. *J Infect Dis* 2010;202:1154-1160.
27. Lee N, Cockram CS, Chan PKS, Hui DSC, Choi KW, Sung JJY. Antiviral treatment for patients hospitalized with severe influenza infection may affect clinical outcomes. *Clin Infect Dis* 2008;46:1323-1324.
28. Lee N, Chan PKS, Hui DSC, Rainer TH, Wong E, Choi K-W, Lui GCY, Wong BCK, Wong RYK, Lam W-Y, Chu IMT, Lai RWM, Cockram CS, Sung JJY. Viral loads and duration of viral shedding in adult patients hospitalized with influenza. *J Infect Dis* 2009;200:492-500.
29. Kim CU, Lew W, Williams MA, Liu H, Zhang L, Swaminathan S, Bischofberger N, Chen MS, Mendel DB, Tai CY, Laver WG, Stevens RC. Influenza neuraminidase inhibitors possessing a novel hydrophobic interaction in the enzyme active site: Design, synthesis, and structural analysis of carbocyclic sialic acid analogues with potent anti-influenza activity. *J Am Chem Soc* 1997;119:681-690.
30. Meindl P, Bodo G, Palese P, Schulman J, Tuppy H. Inhibition of neuraminidase activity by derivatives of 2-deoxy-2,3-dehydro-n-acetylneuraminic acid. *Virology* 1974;58:457-463.
31. Eriksson CO, Graham DA, Uyeki TM, Randolph AG. Risk factors for mechanical ventilation in u.S. Children hospitalized with seasonal influenza and 2009 pandemic influenza a*. *Pediatr Crit Care Med* 2012;13:625-631.

Figure Legends

Figure 1: Study flow diagram

Figure 2: Summary of main findings for IRP in laboratory and clinical diagnosed influenza patients, all ages

\

Front page author Affiliation

First name	Surname	Affiliation
Stella G	Muthuri	Division of Epidemiology and Public Health, University of Nottingham, Nottingham, UK
Sudhir	Venkatesan	Division of Epidemiology and Public Health, University of Nottingham, Nottingham, UK
Puja R	Myles	Division of Epidemiology and Public Health, University of Nottingham, Nottingham, UK
Jo	Leonardi-Bee	Division of Epidemiology and Public Health, University of Nottingham, Nottingham, UK
Wei Shen	Lim	Respiratory Medicine, Nottingham University Hospitals NHS Trust, City Hospital Campus, Nottingham, UK
Abdullah	Al Mamun	International Centre for Diarrhoeal Diseases, Research Bangladesh (ICDDRB), Dhaka, Bangladesh
Ashish P	Anovadiya	Department of Pharmacology, Government Medical College and Sir Takhtsinhji General Hospital, Bhavnagar, Gujarat, India
Wildo N	Araújo	University of Brasília, Brasília DF, Brazil
Eduardo	Azziz-Baumgartner	Centers for Disease Control and Prevention, Atlanta, Georgia, USA
Clarisa	Báez	Ministerio de Salud de la Provincia de Buenos Aires, Argentina
Carlos	Bantar	Dept. of Infection Control, Hospital San Martín de Paraná, Entre Ríos, Argentina
Mazen M	Barhoush	Department of Medicine, King Saud Medical City, Riyadh, Kingdom of Saudi Arabia
Matteo	Bassetti	Santa Maria Misericordia Hospital, Udine Italy
Bojana	Beovic	Department of Infectious Diseases, University Medical Centre, Ljubljana, Slovenia
Roland	Bingisser	Department of Emergency Medicine, University Hospital Basel, Switzerland
Isabelle	Bonmarin	Institut de Veille Sanitaire, France
Gulam	Khandaker	National Centre for Immunisation Research and Surveillance (NCIRS), The Children's Hospital at Westmead, University of Sydney, New South Wales, Australia
Victor H	Borja-Aburto	Instituto Mexicano del Seguro Social (IMSS), Mexico
Maddalena	Giannella	Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Madrid, Spain
Bin	Cao	Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China

First name	Surname	Affiliation
Jordi	Carratala	Department of Infectious Diseases, Hospital Universitari de Bellvitge, Bellvitge Institute for Biomedical Research, L'Hospitalet de Llobregat, Red Española de Investigación en Patología Infecciosa, University of Barcelona, Barcelona, Spain
María R	Cuezzo	Ministerio de Salud de Tucumán, Argentina
Justin T	Denholm	Victorian Infectious Diseases Service and Department of Microbiology and Immunology, at the Peter Doherty Institute for Infection and Immunity, Parkville, Australia.
Samuel R	Dominguez	Department of Pediatric Infectious Diseases, Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, Colorado, USA
Pericles AD	Duarte	Universidade Estadual do Oeste do Paraná - UNIOESTE - Cascavel (PR), Brazil
Gal	Dubnov-Raz	The Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Israel
Marcela	Echavarria	Clinical Virology Laboratory, CEMIC University Hospital, Galvan 4102, (1431) Buenos Aires, Argentina
Sergio	Fanella	Section of Pediatric Infectious Diseases, University of Manitoba, Winnipeg, Manitoba, Canada
James	Fraser	Paediatric Intensive Care Unit, Bristol Children's Hospital, UK
Zhancheng	Gao	Department of Respiratory & Critical Care Medicine, Peking University People's Hospital, Beijing, China
Patrick	Gérardin	[1] NICU/PICU, PFME, CHU Saint Pierre – [2] CIC 1410 (CHU/Inserm/ University of La Réunion/URML-OI), CHU Saint Pierre – [3] UMR PIMIT (CHU/Inserm/University of La Réunion/IRD/ CNRS), CYROI, Saint Denis - Reunion island, FranceNICU/PICU CHU of La Réunion -Groupe Hospitalier Sud Réunion
Sophie	Gubbels	Department of Infectious Disease Epidemiology, Sector for National Health Documentation and Research, Statens Serum Institut, Copenhagen, Denmark
Jethro	Herberg	Section of Paediatrics, Division of Infectious Disease, Imperial College, London, UK
Anjarath L	Higuera Iglesias	Epidemiology Research Unit, Instituto Nacional de Enfermedades Respiratorias, Ismael Cosío Villegas, Mexico City, Mexico
Matthias	Hoffmann	Division of Infectious Diseases and Hospital Epidemiology, Kantonsspital St. Gallen, Switzerland
Peter H	Hoeger	Cath. Children´s Hospital Wilhelmstift, Liliencronstr, Hamburg, Germany
Xiaoyun	Hu	Peking Union Medical College Hospital, Beijing, China
Quazi T	Islam	Dhaka Medical College Hospital, Bangladesh

First name	Surname	Affiliation
Mirela F	Jiménez	Departamento de Ginecologia e Obstetrícia - UFCSPA, Preceptora da Residência Médica do Hospital Fêmina, Brazil
Amr	Kandeel	Ministry of Health in Egypt, Cairo, Egypt
Gerben	Keijzers	Gold Coast Hospital, Gold Coast, Australia
Hossein	Khalili	Department of Clinical Pharmacy, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
Marian	Knight	National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, UK
Gabriela	Kusznierz	National Institute of Respiratory Diseases "Emilio Coni" ANLIS "C. Malbran, Argentina
Ilija	Kuzman	University Hospital for Infectious Diseases, University of Zagreb, School of Medicine, Zagreb, Croatia
Arthur MC	Kwan	Department of Intensive Care, Pamela Youde Nethersole Eastern Hospital, Chai Wan, Hong Kong
Idriss	Lahlou Amine	University Mohammed V-Souissi, Faculty of Medicine and Pharmacy, Mohammed V Military Teaching Hospital, Biosafety Level 3 and Research Laboratory, Rabat, Morocco
Eduard	Langenegger	Department of Obstetrics and Gynaecology, Stellenbosch University and Tygerberg, South Africa
Kamran B	Lankarani	Health Policy Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
Yee-Sin	Leo	Department of Infectious Diseases, Tan Tock Seng Hospital, Singapore
Rita	Linko	Helsinki University Hospital, Helsinki, Finland
Pei	Liu	Department of Infectious Diseases, the First Affiliated Hospital, China Medical University, Shenyang, China
Faris	Madanat	King Hussein Cancer Center, Department of Pediatrics, Amman, Jordan
Toshie	Manabe	Graduate School of Comprehensive Human Sciences, University of Tsukuba, Tsukuba, Ibaraki, Japan
Elga	Mayo-Montero	Instituto de Medicina Preventiva de la Defensa, Capitan Medico Ramon y Cajal (IMPDEF). Ministerio de Defensa, Madrid, Spain
Allison	McGeer	Toronto Invasive Bacterial Diseases Network, University of Torontol, Toronto, Canada
Ziad A	Memish	Ministry of Health, Riyadh, Kingdom of Saudi Arabia & College of Medicine, Alfaisal University, Riyadh, KSA
Gokhan	Metan	Department of Infectious diseases and clinical microbiology, Erciyes University Faculty of Medicine, Kayseri, Turkey

First name	Surname	Affiliation
Dragan	Mikić	Military Medical Academy, Clinic for Infectious and Tropical Diseases, Serbia.
Kristin GI	Mohn	[1] Section for Infectious Diseases, Medical Department, and Department of Research and Development, Haukeland University Hospital [2] The Influenza Centre, Department of Clinical Science, University of Bergen, Norway
Ahmadreza	Moradi	[1] The Division of Ocular Immunology, Department of Ophthalmology, Johns Hopkins University School of Medicine, Baltimore, Maryland, United States. [2] National Research Institute for Tuberculosis and Lung Disease, Massih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Pagbajabyn	Nymadawa	National Influenza Center, National Center of Communicable Diseases, Ministry of Health, Ulaanbaatar, Mongolia
Bulent	Ozbay	Yuzuncu Yil University Medical Faculty, Department of Pulmonary and Critical Care, Van, Turkey
Mehpare	Ozkan	Dr. Sami Ulus Research and Training Hospital of Women's and Children's Health and Diseases, Clinic of Pediatric Neurology, Ankara, Turkey
Dhruv	Parekh	Critical Care and Pain Perioperative, Critical Care and Trauma Trials Group, School of Clinical and Experimental Medicine, University of Birmingham, UK
Mical	Paul	Division of Infectious Diseases, Rambam Health Care Campus, Haifa, Israel
Wolfgang	Poeppl	Medical University of Vienna, Austria
Fernando P	Polack	[1] Vanderbilt Vaccine Center, Department of Pediatrics, Vanderbilt University, Nashville, TN, USA [2] Fundacion INFANT, Buenos Aires, Argentina
Barbara A	Rath	Department of Pediatrics, Division of Pneumonology-Immunology, Charité University Medical Center, Berlin, Germany
Alejandro H	Rodríguez	Hospital Joan XXIII, Critical Care Department - IISPV - URV - CIBERES, Tarragona, Spain
Marilda M	Siqueira	Laboratory of Respiratory Viruses, Oswaldo Cruz Institute/Fiocruz, Rio de Janeiro, Brazil
Joanna	Skręt-Magierło	Uniwersytet Rzeszowski, Poland
Ewa	Talarek	Department of Children`s Infectious Diseases, Medical University of Warsaw, Poland

First name	Surname	Affiliation
Julian W	Tang	[1] Division of Microbiology/ Molecular Diagnostic Centre, Department of Laboratory Medicine National University Hospital, Singapore [2] Alberta Provincial Laboratory for Public Health, University of Alberta Hospital, Canada [3] Department of Medical Microbiology and Immunology, University of Alberta, Edmonton, Alberta, Canada
Antoni	Torres	Hospital Clinic, University of Barcelona IDIBAPS, CIBERES, Spain
Selda H	Törün	Department of Pediatric Infectious Diseases, Instabul Medical Faculty, Instabul, Turkey
Dat	Tran	Division of Infectious Diseases, Department of Paediatrics, The Hospital for Sick Children, University of Toronto, Canada
Timothy M	Uyeki	Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia, USA
Annelies	van Zwol	Department of Pediatric Intensive Care, VU University Medical Center, Amsterdam, Netherlands
Wendy	Vaudry	Division of Infectious Diseases, Department of Pediatrics, University of Alberta, Stollery Children's Hospital, Edmonton, Alberta, Canada
Daiva	Velyvyte	Lithuanian University of Health Sciences, Kaunas, Lithuania
Tjasa	Vidmar	General Hospital Slovenj Gradec, Slovenia
Paul	Zarogoulidis	Unit of Infectious Diseases, University General Hospital of Alexandroupolis, Democritus University Thrace, Dragana, Greece
Jonathan S	Nguyen-Van-Tam	Division of Epidemiology and Public Health, University of Nottingham, Nottingham, UK

Table 1: Characteristics of pooled dataset of 20,634 patients admitted to hospital with influenza A(H1N1)pdm09 virus infection with and without pneumonia

Characteristic	Radiology diagnosed pneumonia status		Radiology or physician diagnosed pneumonia status	
	IRP	No IRP	Any pneumonia*	No pneumonia†
Number of patients ‡	5978 (100.0)	3349 (100.0)	7054 (100.0)	13580 (100.0)
Number of male cases	3266(54.6)	1879 (56.0)	3811 (54.0)	6645 (48.9)
Age: median (IQR) in years	36 (17 – 52)	26 (14 – 46)	35 (14- 51)	22 (8 - 38)
Adults (≥16 years)	4560 (76.3)	2436 (72.7)	5208 (73.8)	8482 (62.5)
Children (<16 years)	1411 (23.6)	912 (27.2)	1821 (25.8)	4966 (36.6)
Obese §	952 (15.9)	229 (6.8)	1072 (15.2)	744 (5.5)
Smoking	914 (15.3)	481 (14.4)	958 (13.6)	867 (6.4)
Pregnant women ‖	219 (13.1)	150 (16.0)	279/1967 (14.2)	1153/4397 (26.2)
WHO Regions				
African region	28 (0.5)	1 (0.03)	31 (0.4)	10 (0.1)
Region of the Americas	2314 (38.7)	550 (16.4)	2703 (38.3)	4948 (36.4)
Eastern Mediterranean Region	178 (3.0)	206 (6.2)	549 (7.8)	3086 (22.7)
European Region	2635 (44.1)	2032 (60.7)	2932 (41.6)	4080 (30.0)
South-East Asia Region	45 (0.8)	86 (2.6)	45 (0.6)	157 (1.2)
Western Pacific Region	778 (13.0)	474 (14.2)	794 (11.3)	1299 (9.6)
A(H1N1)pdm09 diagnosis				
Laboratory confirmed	5755 (96.3)	3146 (93.9)	6827 (96.8)	13194 (97.2)
Clinically diagnosed	223 (3.7)	203 (6.1)	227 (3.2)	386 (2.8)
Comorbidities **				
Any comorbidity	3021(50.5)	1795 (53.6)	3531 (50.1)	5449 (40.1)
Asthma	856 (14.3)	777 (22.7)	968 (13.7)	1430 (10.5)
COPD	432 (7.2)	249 (7.4)	454 (6.4)	345 (2.5)
Other chronic lung disease	492 (8.2)	525 (15.7)	648 (9.2)	1668 (12.3)
Heart disease	650 (10.9)	341 (10.2)	713 (10.1)	786 (5.8)

Characteristic	Radiology diagnosed pneumonia status		Radiology or physician diagnosed pneumonia status	
	IRP	No IRP	Any pneumonia*	No pneumonia†
Renal disease	278 (4.7)	113 (3.4)	328 (4.7)	349 (2.6)
Liver disease	122 (2.0)	73 (2.2)	127 (1.8)	121 (0.9)
Cerebrovascular disease	121 (2.0)	122 (3.6)	133 (1.9)	170 (1.3)
Neurological disease	436 (7.3)	237 (7.1)	492 (7.0)	508 (3.7)
Diabetes	634 (10.6)	280 (8.4)	725 (10.3)	690 (5.1)
Immunosuppression	525 (8.8)	242 (7.2)	610 (8.7)	852 (6.3)
H1N1pdm09 vaccination ††	121/2917 (4.2)	48/1701 (2.8)	163/3738 (4.4)	176/6237 (2.8)
Time from symptom onset to hospital admission, days, median (IQR)	4 (2 - 6)	2 (1 - 4)	3 (2 - 6)	2 (1 – 4)
Time from symptom onset to antiviral treatment, days, median (IQR)	4 (2 - 7)	2 (1 - 4)	4 (2 - 7)	2 (1 - 4)
Antiviral agents used				
No NAI treatment	582 (9.7)	540 (16.1)	724 (10.3)	4336 (31.9)
Any NAI	5396 (90.3)	2809 (83.9)	6330 (89.7)	9244 (68.1)
Oral oseltamivir ‡‡	5356 (99.3)	2782 (99.0)	6263 (98.9)	9068 (98.1)
Intravenous/inhaled zanamivir ‡‡	134 (2.5)	40 (1.4)	155 (2.5)	158 (1.7)
Intravenous peramivir ‡‡	42 (0.8)	5 (0.2)	42 (0.7)	7 (0.1)
NAI (regimen unknown) ‡‡	1 (0.02)	5 (0.2)	17 (0.3)	82 (0.9)
NAI and Non-NAI ‡‡	75 (1.4)	15 (0.5)	76 (1.2)	18 (0.2)
NAI combination therapy ‡‡	134 (2.5)	23 (0.8)	144 (2.3)	71 (0.8)
Early NAI (≤2 days of symptom onset) ‡‡	1067 (19.8)	1057 (37.6)	1353 (21.4)	3459 (37.4)
Later NAI (>2 days after symptom onset) ‡‡	2843 (52.7)	998 (35.5)	3362 (53.1)	3221 (34.8)
Other in-hospital treatment				
Antibiotics	3604 (60.3)	1731 (51.7)	4265 (60.5)	5521 (40.7)
Corticosteroids	1658 (27.7)	626 (18.7)	1709 (24.2)	1024 (7.5)
Hospital length of stay, days, median (IQR)	9 (5 - 17)	5 (3 - 7)	8 (4 - 17)	4 (2 – 7)
Other patient outcomes				
Acute respiratory distress syndrome (ARDS)	265 (4.4)	10 (0.3)	341 (4.8)	43 (0.3)

Characteristic	Radiology diagnosed pneumonia status		Radiology or physician diagnosed pneumonia status	
	IRP	No IRP	Any pneumonia*	No pneumonia†
Ventilation support	2372 (39.7)	450 (13.4)	2619 (37.1)	1059 (7.8)
Admission to critical care	3335 (55.8)	764 (22.8)	3859 (54.7)	1989 (14.7)
Mortality	903 (15.1)	90 (2.7)	1014 (14.4)	496 (3.7)

* Any pneumonia includes IRP (n=5978) and PDP (n=1076)

† No pneumonia includes no IRP (n=3349) , no PDP (n=6616) and unknown pneumonia status (n=3615)

‡ All percentages have been calculated using these denominators unless otherwise specified.

§ Reported as clinically obese or using WHO definition for obesity (BMI ≥30 kg/m² in adults aged ≥20 years).

|| 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.

** For definition of comorbidity, see Table E3

†† Denominators for pandemic vaccine based on patients admitted after Oct 1, 2009 (when vaccine potentially became available).

‡‡ Percentages calculated as a proportion of the total patients in that category who received NAI therapy.

Table 2: Association between NAI treatment and pneumonia

Subgroups	Influenza-related pneumonia (IRP)		Any Pneumonia†	
	Crude OR (95% CI)	**Adjusted‡ OR (95% CI)**	**Crude OR (95% CI)**	**Adjusted‡ OR (95% CI)**
1. Early NAI (≤2 days) vs. No NAI treatment				
Lab and clinically confirmed (all ages) ; *(n1=2605 ; n2=6710)*	0.97 (0.77 – 1.23)	0.83 (0.64 – 1.06)	1.02 (0.87 – 1.19)	**0.83 (0.70 – 0.98)***
Lab confirmed cases (all ages) ; *(n1=2462 ; n2=6541)*	0.97 (0.76 – 1.24)	0.83 (0.64 – 1.08)	1.02 (0.87 – 1.19)	**0.84 (0.70 – 0.99)***
Adults (≥16 years) ; *(n1=1934 ; n2=3897)*	0.90 (0.68 – 1.17)	0.80 (0.60 – 1.06)	1.00 (0.82 – 1.23)	0.82 (0.66 – 1.02)
Children (< 16 years) ; *(n1=670 ; n2=2765)*	1.04 (0.61 – 1.77)	0.76 (0.42 – 1.36)	0.89 (0.69 – 1.14)	0.78 (0.59 – 1.03)
Pregnant (13 - 54 years) ; *(n1=130 ; n2=424)*	0.88 (0.27 – 2.93)	0.96 (0.29 – 3.20)	0.94 (0.41 – 2.18)	0.67 (0.26 – 1.76)
ICU patients (all ages)				
Adults (≥16 years) ; (*n1=583 ; n2=1015)*	1.19 (0.67 – 2.13**)**	1.09 (0.59 – 2.02)	1.13 (0.76 – 1.67**)**	1.04 (0.69 – 1.56)
Children (< 16 years) ; *(n1=197 ; n2=447)*	1.51 (0.58 – 3.97)	1.33 (0.46 – 3.78)	1.75 (0.99 – 3.12)	1.44 (0.79 – 2.62)
2. *Early NAI (≤2 days) vs. Later NAI (>2 days)*				
Lab and clinically confirmed (all ages) ; *(n1=5058 ; n2=10925)*	**0.34 (0.30 – 0.39)*** **	**0.43 (0.37 – 0.51)*** **	**0.40 (0.37 – 0.45)*** **	**0.51 (0.46 – 0.57)*** **
Lab confirmed cases (all ages) ; *(n1=4834 ; n2=10667)*	**0.35 (0.30 – 0.40)*** **	**0.44 (0.38 – 0.52)*** **	**0.41 (0.37 – 0.45)*** **	**0.52 (0.47 – 0.58)*** **
Adults (≥16 years) ; *(n1=4189 ; n2=7549)*	**0.34 (0.29 – 0.39)*** **	**0.43 (0.36 – 0.51)*** **	**0.41 (0.36 – 0.46)*** **	**0.51 (0.45 – 0.58)*** **
Children (<16 years) ; *(n1=864 ; n2=3295)*	**0.43 (0.29 – 0.62)*** **	**0.47 (0.32 – 0.71)*** **	**0.43 (0.35 – 0.53)*** **	**0.53 (0.43 – 0.66)*** **
Pregnant (13 - 54 years) ; *(n1=256 ; n2=649)*	**0.26 (0.13 – 0.53)*** **	**0.32 (0.13 – 0.75)** **	**0.27 (0.17 – 0.44)*** **	**0.34 (0.20 – 0.58)*** **
ICU patients (all ages)				
Adults (≥16 years) ; *(n1=1846 ; n2=2850)*	**0.38 (0.29 – 0.51)*** **	**0.47 (0.34 – 0.63)*** **	**0.55 (0.45 – 0.68)*** **	**0.62 (0.50 – 0.77)*** **
Children (<16 years) ; *(n1=251 ; n2=655)*	**0.46 (0.22 – 0.94)***	0.45 (0.20 – 1.01)	**0.61 (0.42 – 0.89)** **	0.71 (0.47 – 1.05)
3. Later (>2 days) vs No NAI treatment:				
Lab and clinically confirmed (all ages) ; *(n1=3991 ; n2=8251)*	**2.53 (2.02 – 3.16)*** **	**1.70 (1.34 – 2.17)*** **	**2.41 (2.09 – 2.79)*** **	**1.57 (1.34 – 1.84)*** **
Lab confirmed cases (all ages) ; *(n1=3822 ; n2=8048)*	**2.51 (1.98 – 3.16)*** **	**1.68 (1.30 – 2.16)*** **	**2.38 (2.06 – 2.76)*** **	**1.55 (1.32 – 1.82)*** **
Adults (≥16 years) ; *(n1=3263 ; n2=5572)*	**2.29 (1.78 – 2.95)*** **	**1.64 (1.25 – 2.16)*** **	**2.30 (1.91 – 2.77)*** **	**1.58 (1.29 – 1.92)*** **
Children (<16 years); *(n1=724 ; n2=2598)*	**2.26 (1.28 – 3.99)** **	1.68 (0.89 – 3.16)	**1.99 (1.55 – 2.57)*** **	**1.42 (1.08 – 1.87)** **
Pregnant (13 - 54 years) ; *(n1=186 ; n2=383)*	2.21 (0.76 – 6.45)	1.60 (0.40 – 6.49)	**2.86 (1.30 – 6.25)** **	1.58 (0.61 – 4.09)
ICU patients				
Adults (≥16 years) ; *(n1=1511 ; n2=2249)*	**2.35 (1.31 – 4.23)** **	1.55 (0.83 – 2.89)	**1.68 (1.15 – 2.46)** **	**1.47 (1.00 – 2.17)***
Children (<16 years) ; *(n1=236 ;*	**5.84 (1.50 –**	**4.25 (1.07 –**	**3.50 (1.90 –**	**2.63 (1.39 –**

Subgroups	Influenza-related pneumonia (IRP)		Any Pneumonia†	
	Crude OR (95% CI)	Adjusted‡ OR (95% CI)	Crude OR (95% CI)	Adjusted‡ OR (95% CI)
n2=518)	**22.75)***	**16.88)***	**6.46)*****	**4.96)****
4. NAI anytime vs. No NAI treatment:				
Lab and clinically confirmed (all ages); *(n1=7975 ; n2=20164)*	**1.57 (1.32 – 1.86)*****	**1.32 (1.10 – 1.59)****	**1.62 (1.45 – 1.81)*****	**1.22 (1.08 – 1.38)****
Lab confirmed cases (all ages); *(n1=7620 ; n2=19553)*	**1.55 (1.29 – 1.86)*****	**1.29 (1.06 – 1.57)***	**1.58 (1.41 – 1.78)*****	**1.19 (1.05 – 1.35)****
Adults (≥16 years); *(n1= 5964 ; n2=13247)*	**1.53 (1.24 – 1.91)*****	**1.30 (1.03 – 1.63)***	**1.63 (1.40 – 1.89)*****	**1.24 (1.06 – 1.46)****
Children (< 16 years); *(n1=2005 ; n2=6760)*	**1.38 (1.00 – 1.90)***	1.30 (0.92 – 1.82)	**1.41 (1.18 – 1.69)*****	1.18 (0.97 – 1.43)
Pregnant (13 - 54 years) ; *(n1=348 ; n2=1430)*	1.48 (0.58 – 3.74)	1.03 (0.32 – 3.29)	1.74 (0.93 – 3.23)	1.08 (0.52 – 2.22)
ICU patients (all ages) Adults (≥16 years) ; *(n1=2721 ; n2=4071)* Children (<16 years) ; *(n1= 970 ; n2=1579)*	**2.02 (1.30 – 3.14)**** 1.45 (0.89 – 2.38)	**1.57 (1.00 – 2.48)*** 1.39 (0.85 – 2.29)	**1.58 (1.14 – 2.18)**** **1.76 (1.22 – 2.53)****	**1.38 (1.00 – 1.92)*** **1.59 (1.10 – 2.30)***

† Influenza related pneumonia (IRP) and physician diagnosed pneumonia (PDP)

‡adjusted for treatment propensity quintiles, corticosteroid use and antibiotic use

n1= total number of patients included in IRP analysis; n2= total number of patients included in 'any pneumonia' analysis

* P < 0.05, ** P < 0.01, *** P < 0.001

Table 3: Association between NAI treatment and clinical outcomes among patients with pneumonia

	Influenza-related pneumonia (IRP)		Any Pneumonia†	
Clinical outcomes/ exposures studied	**Crude OR (95% CI)**	**Adjusted‡ OR (95% CI)**	**Crude OR (95% CI)**	**Adjusted‡ OR (95% CI)**
5. Admission to an ICU				
Early vs No NAI *(n1=1480 ; n2=1855)*	**1.51 (1.01 – 2.25)***	1.44 (0.94 – 2.18)	**2.02 (1.44 – 2.83)*****	**1.81 (1.27 – 2.58)****
Early vs Later NAI *(n1=3905 ; n2=4709)*	1.15 (0.94 – 1.39)	0.89 (0.71 – 1.11)	1.09 (0.92 – 1.29)	0.95 (0.79 – 1.14)
Later vs No NAI *(n1= 3255 ; n2=3864)*	**2.59 (1.85 – 3.61)*****	**2.43 (1.71 – 3.45)*****	**2.91 (2.16 – 3.91)*****	**2.66 (1.95 – 3.62)*****
NAI vs No NAI *(n1=5962 ; n2=6976)*	**1.69 (1.30 – 2.19)*****	**1.59 (1.21 – 2.09)****	**1.96 (1.55 – 2.50)*****	**1.78 (1.38 – 2.28)*****
6. Ventilation support				
Early vs No NAI *(n1=1131 ; n2=1287)*	1.12 (0.70 – 1.79)	1.17 (0.71 – 1.92)	1.24 (0.82 – 1.87)	1.13 (0.73 – 1.75)
Early vs Later NAI *(n1=3084 ; n2=3459)*	**0.69 (0.56 – 0.86)****	**0.68 (0.54 – 0.85)****	**0.74 (0.60 – 0.90)****	**0.75 (0.61 – 0.93)****
Later vs No NAI *(n1=2489 ; n2=2760)*	**2.31 (1.50 – 3.55)*****	**2.48 (1.57 – 3.92)*****	**2.18 (1.48 – 3.21)*****	**2.21 (1.47 – 3.32)*****
NAI vs No NAI *(n1=4739 ; n2=5182)*	**1.70 (1.25 – 2.30)****	**1.67 (1.22 – 2.29)****	**1.69 (1.27 – 2.25)*****	**1.59 (1.19 – 2.13)****
7. ARDS				
Early vs No NAI *(n1=454 ; n2=546)*	1.14 (0.32 – 4.07)	1.98 (0.46 – 8.54)	2.26 (0.76 – 6.67)	2.98 (0.77 – 11.60)
Early vs Later NAI *(n1=1234; n2=1434)*	**0.54 (0.33 – 0.90)***	0.65 (0.38 – 1.11)	**0.55 (0.37 – 0.83)****	**0.61 (0.40 – 0.94)***
Later vs No NAI *(n1=1032 ; n2=1178)*	2.34 (0.98 – 5.55)	2.23 (0.90 – 5.54)	**3.42 (1.50 – 7.82)****	**3.21 (1.36 – 7.58)****
NAI vs No NAI *(n1=1549 ; n2=1836)*	1.99 (0.84 – 4.70)	2.13 (0.87 – 5.21)	**3.06 (1.35 – 6.94)****	**3.14 (1.37 – 7.29)****
8. Mortality				
Early vs No NAI *(n1=1490 ; n2=1866)*	**0.61 (0.38 – 0.96)***	0.72 (0.44 – 1.17)	**0.59 (0.39 – 0.89)***	**0.62 (0.40 – 0.96)***
Early vs Later NAI *(n1=3906 ; n2=4711)*	0.84 (0.67 – 1.04)	**0.70 (0.55 – 0.88)****	**0.77 (0.63 – 0.95)***	**0.69 (0.56 – 0.86)****
Later vs No NAI *(n1=3266 ; n2=3875)*	1.05 (0.73 – 1.52)	1.18 (0.81 – 1.74)	1.06 (0.76 – 1.49)	1.13 (0.80 – 1.61)
NAI vs No NAI *(n1=5974 ; n2=7050)*	0.88 (0.66 – 1.18)	0.90 (0.67 – 1.22)	0.89 (0.69 – 1.17)	0.89 (0.67 – 1.17)

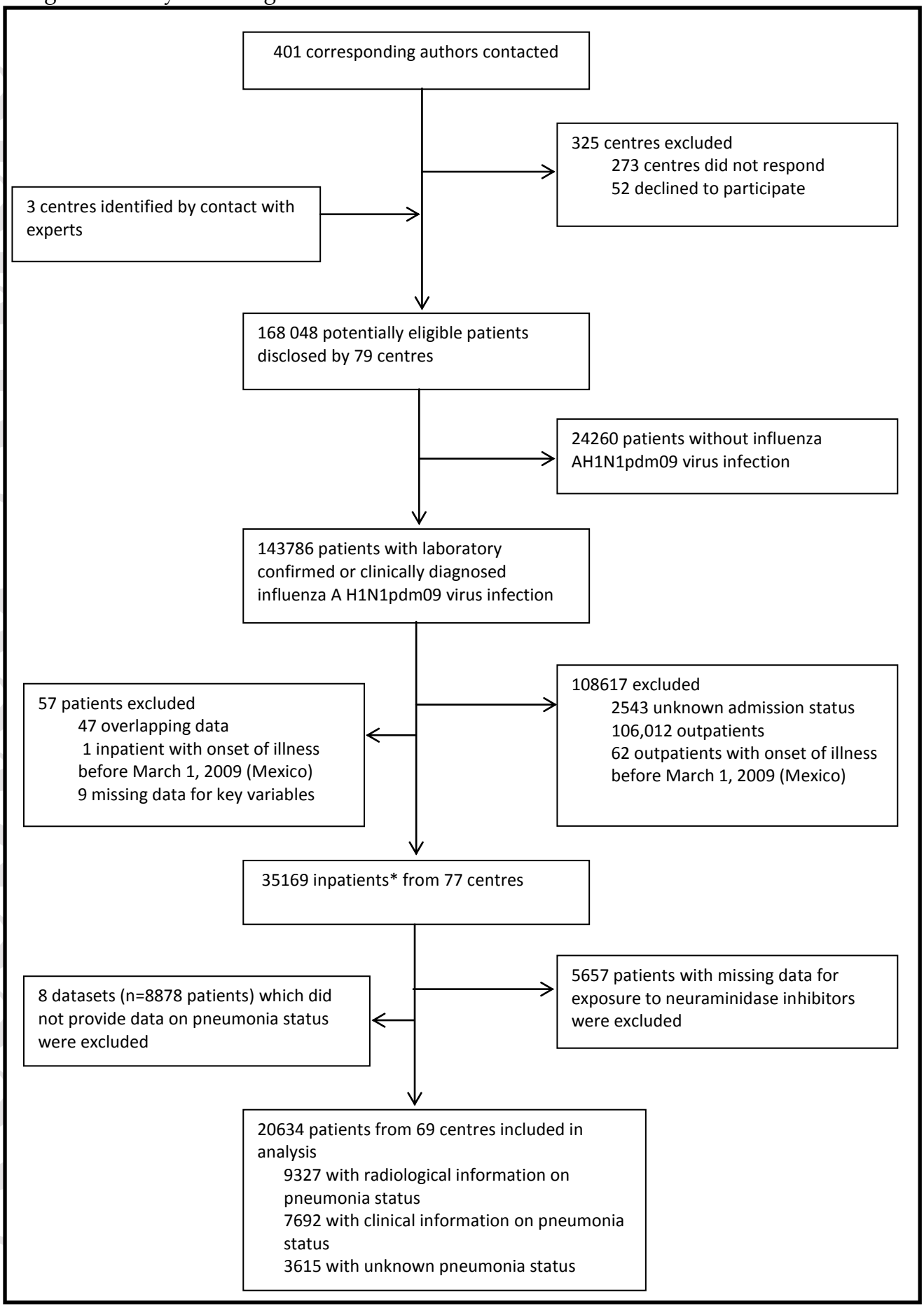
† Influenza related pneumonia (IRP) and physician diagnosed pneumonia (PDP)

‡adjusted for treatment propensity quintiles, corticosteroid use and antibiotic use

n1= total number of patients included in IRP analysis; n2= total number of patients included in any pneumonia analysis

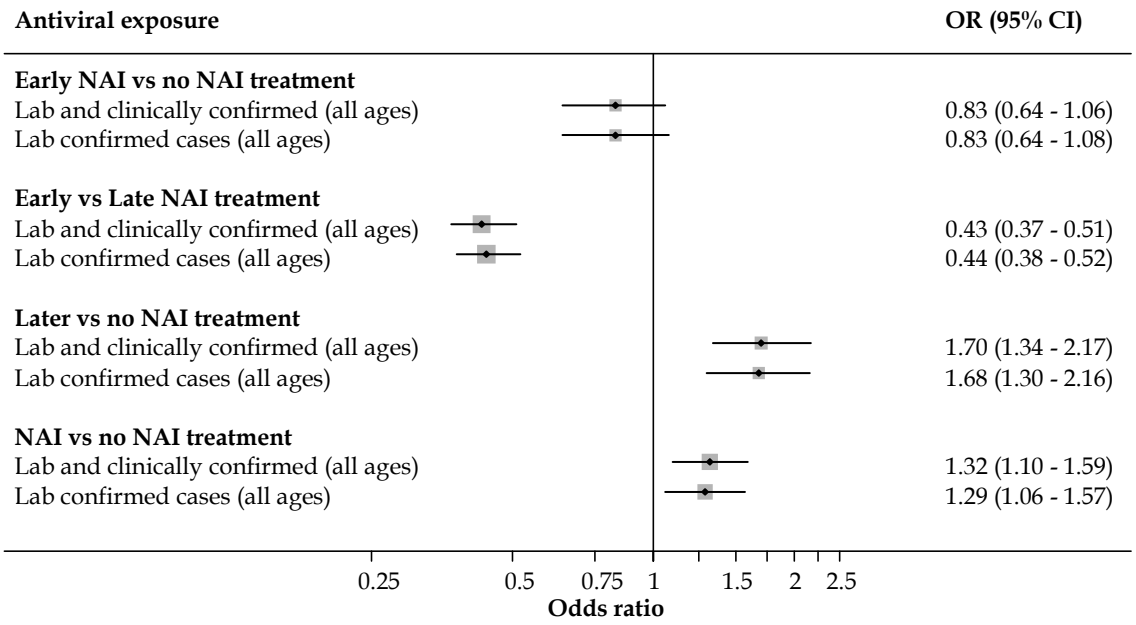
* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$

Figure 1: Study flow diagram



*260 patients added since publication of Muthuri et al (17) following clarification of inpatient status from data collaborator

Figure 2: Summary of main findings for IRP in laboratory and clinical diagnosed influenza patients, all ages



Funding statement:

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

Conflict of interest statement:

Puja R Myles and Jo Leonardi–Bee are recipients of grants from F. Hoffmann-La Roche, during the conduct of the study.

Wei Shen Lim reports unrestricted investigator initiated research funding from Pfizer to his department for research into pneumonia, a research grant from the National Institute for Health Research, and consultancy fees paid to his department from the Wellcome Trust, outside the submitted work.

Roland Bingisser has received consultancy fees from Philips and Alere.

Jordi Carratala reports grants from Instituto de Salud Carlos III, personal fees from F. Hoffmann-La Roche, outside the submitted work.

Allison McGeer reports grants from Hoffman LaRoche, during the conduct of the study; grants from GlaxoSmithKline, grants from Crucell (Johnson & Johnson), other from Cepheid, grants from Merck, grants from Sanofi-Pasteur, outside the submitted work.

Barbara Rath reports grants from Hofmann LA Roche Inc. to her Insitution (Charité Universitätsmedizin Berlin), outside the submitted work.

Dat Tran 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.

Wendy Vaudry reports grants from Candian Pediatric Society, grants from Public Health Agency of Canada, during the conduct of the study.

Jonathan S Nguyen-Van-Tam reports that a grant from F. Hoffmann-La Roche funded the current study; grants from GlaxoSmith Kline in the area of influenza, and non-financial support from ESWI (European Scientific Working Group on Influenza) to lecture on influenza, outside the submitted work; his brother is a current employee of GlaxoSmithKline

JSN-V-T is Editor-in-Chief of Influenza and Other Respiratory Viruses; however he played no role whatsoever in the editorial process for this paper, including decisions to send the manuscript for independent peer-review or about final acceptance of a revised version. All of the above functions were handled independently by Dr Alan Hampson, Senior Editor (formerly Editor-in-Chief).

All other named authors declare no conflicts of interest.