Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: an individual participant data meta-analysis

Stella G. Muthuri, Sudhir Venkatesan, Puja R. Myles, Jo Leonardi-Bee, Tarig S. A. Al Khuwaitir, Adbullah Al Mamun, Ashish P. Anovadiya, Eduardo Azziz-Baumgartner, Clarisa Báez, Matteo Bassetti, et al.

EFFECTIVENESS OF NEURAMINIDASE INHIBITORS IN REDUCING MORTALITY IN HOSPITALISED INFLUENZA A(H1N1)pdm09 PATIENTS: AN INDIVIDUAL PARTICIPANT DATA META-ANALYSIS

STELLA G MUTHURI*, SUDHIR VENKATESAN*, PUJA R MYLES, JO LEONARDI-BEE, TARIG S A AL KHUWAITIR, ADBULLAH AL MAMUN, ASHISH P ANOVADIYA, EDUARDO AZZIZ-BAUMGARTNER, CLARISA BÁEZ, MATTEO BASSETTI, BOJANA BEOVIC, BARBARA BERTISCH, ISABELLE BONMARIN, ROBERT BOOY, VICTOR H BORJA-ABURTO, HEINZ BURGMANN, BIN CAO, JORDI CARRATALA, JUSTIN T DENHOLM, SAMUEL R DOMINGUEZ, PERICLES A D DUARTE, GAL DUBNOV-RAZ, MARCELA ECHAVARRIA, SERGIO FANELLA, ZHANCHENG GAO, PATRICK GÉRARDIN, MADDALENA GIANNELLA, SOPHIE GUBBELS, JETHRO HERBERG, ANJARATH L HIGUERA IGLESIAS, PETER H HOGER, XIAOYUN HU, QUAZI T ISLAM, MIRELA F JIMÉNEZ, AMR KANDEEL, GERBEN KEIJZERS, HOSSEIN KHALILI, MARIAN KNIGHT, KOICHIRO KUDO, GABRIELA KUSZNIERZ, ILIJA KUZMAN, ARTHUR M C KWAN, IDRISS LAHLOU AMINE, EDUARD LANGENEGGER, KAMRAN B LANKARANI, YEE-SIN LEO, RITA LINKO, PEI LIU, FARIS MADANAT, ELGA MAYO-MONTERO, ALLISON MCGEER, ZIAD MEMISH, GOKHAN METAN, AUKSĖ MICKIENE, DRAGAN MIKIĆ, KRISTIN G I MOHN, AHMADREZA MORADI, PAGBAJABYN NYMADAWA, MARIA E OLIVA, MEHPARE OZKAN, DHRUV PAREKH, MICAL PAUL, FERNANDO P POLACK, BARBARA A RATH, ALEJANDRO H RODRÍGUEZ, ELENA B SARROUF, ANNA C SEALE, BUNYAMIN SERTOGULLARINDAN, MARILDA M SIQUEIRA, JOANNA SKRĘT-MAGIERŁO, FRANK STEPHAN, EWA TALAREK, JULIAN W TANG, KELVIN K W TO, ANTONI TORRES, SELDA H TÖRÜN, DAT TRAN, TIMOTHY M UYEKI, ANNELIES VAN ZWOL, WENDY VAUDRY, TJASA VIDMAR, RENATA T C YOKOTA, PAUL ZAROGOULIDIS, PRIDE CONSORTIUM INVESTIGATORS†, JONATHAN S NGUYEN-VAN-TAM

*SGM and SV are joint first-authors

Front author affiliations can be found on pp 25-29
†List of PRIDE Consortium Investigators' can be found on pages 20, and affiliations listed in appendix pp 1-6

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

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SUMMARY

BACKGROUND

Neuraminidase inhibitors were widely used during the 2009–10 influenza A H1N1 pandemic, but evidence for their effectiveness in reducing mortality is uncertain. We did a meta-analysis of individual participant data to investigate the association between use of neuraminidase inhibitors and mortality in patients admitted to hospital with pandemic influenza A H1N1pdm09 virus infection.

METHODS

We assembled data for patients (all ages) admitted to hospital worldwide with laboratory confirmed or clinically diagnosed pandemic influenza A H1N1pdm09 virus infection. We identified potential data contributors from an earlier systematic review of reported studies addressing the same research question. In our systematic review, eligible studies were done between March 1, 2009 (Mexico), or April 1, 2009 (rest of the world), until the WHO declaration of the end of the pandemic (Aug 10, 2010); however, we continued to receive data up to March 14, 2011, from ongoing studies. We did a meta-analysis of individual participant data to assess the association between neuraminidase inhibitor treatment and mortality (primary outcome), adjusting for both treatment propensity and potential confounders, using generalized linear mixed modelling. We assessed the association with time to treatment using time-dependent Cox regression shared frailty modelling.

FINDINGS

We included data for 29 234 patients from 78 studies of patients admitted to hospital between Jan 2, 2009, and March 14, 2011. Compared with no treatment, neuraminidase inhibitor treatment (irrespective of timing) was associated with a reduction in mortality risk (adjusted odds ratio [OR] 0·81; 95% CI 0·70–0·93; p=0·0024). Compared with later treatment, early treatment (within 2 days of symptom onset) was associated with a reduction in mortality risk (adjusted OR 0·48; 95% CI 0·41–0·56; p<0·0001). Early treatment versus no treatment was also associated with a reduction in mortality (adjusted OR 0·50; 95% CI 0·37–0·67; p<0·0001). These associations with reduced mortality risk were less pronounced and not significant in children. There was an increase in the mortality hazard rate with each day's delay in initiation of treatment up to day 5 as compared with treatment initiated within 2 days of symptom onset (adjusted HR 1·23 [95% CI 1·18–1·28]; p<0·0001 for the increasing HR with each day's delay).

INTERPRETATION

We advocate early instigation of neuraminidase inhibitor treatment in adults admitted to hospital with suspected or proven influenza infection.

FUNDING

F. Hoffmann-La Roche.

INTRODUCTION

The neuraminidase inhibitors, oral oseltamivir and inhaled zanamivir, were the predominant medical countermeasure available from emergence of the influenza A H1N1pdm09 virus in early 2009, until the first release of monovalent H1N1 vaccines in October, 2009. Prescribing data from seven countries (Australia, Canada, France, Germany, Japan, UK, USA) suggest at least 18·3 million individuals received oseltamivir between May 1, 2009, and Dec 31, 2009.[1] Country-specific policies for use of neuraminidase inhibitors during the 2009–10 pandemic varied from no use, to targeted use in at-risk patients (most countries), to treatment of all patients with clinical illness (UK). Most use of neuraminidase inhibitors worldwide was in the form of oseltamivir—eg, 97·5% of neuraminidase inhibitors used in the USA.[2]

There is little prepandemic evidence pertaining to the effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza; most evidence comes from observational studies of treatment of seasonal influenza, often in highly specific groups of patients.[3-9] Thus, in 2009–10, neuraminidase inhibitors were used on the basis of rational deduction that they would reduce mortality due to influenza A H1N1pdm09 virus infection rather than on strong pre-existing evidence, although data from treatment of human influenza A H5N1 cases suggested this reduction in mortality might be possible.[10, 11] Japanese clinicians used neuraminidase inhibitors widely to treat all people presenting with clinical influenza in 2009–10 and recorded the lowest pandemic mortality rate of any developed country.[12-14] Although a similar treat-all policy existed in the UK in 2009, uptake of neuraminidase inhibitors in patients admitted to hospital with influenza A H1N1pdm09 was low.[15]

Two systematic reviews and meta-analyses have examined the effectiveness of neuraminidase inhibitors in reducing mortality due to influenza. Both suggest substantial reductions in mortality by two-thirds to three-quarters compared with no treatment.[16, 17] However, limitations are apparent, such as the heterogeneity of studies included and inadequate adjustment for potential confounding. Importantly, neither was able to adjust for the likelihood of a patient receiving antiviral treatment (propensity)—a crucial consideration when antiviral drugs might have been prioritised towards the sickest patients—and neither was able to use a pooled analysis approach with individual participant data.[18]

METHODS

Study design and identification of datasets

The Post-pandemic Review of anti-Influenza Drug Effectiveness (PRIDE) research consortium was set up in October, 2011, and is coordinated by the Health Protection and Influenza Research Group at the University of Nottingham, Nottingham, UK. The aim of the collaboration is to do individual participant data meta-analyses of the effectiveness of antiviral use on outcomes of public health importance during the 2009–10 influenza pandemic.Members of the PRIDE research consortium are listed in appendix pp 1–6.

The initial identification of potential data contributors was done on the basis of a systematic search of 11 databases (date of last search April 19, 2012) for observational studies (case series, case-control, and cohort studies) and randomised controlled trials done between March 1, 2009 (Mexico), or April 1, 2009 (rest of the world), until the WHO declaration of the end of the pandemic (Aug 10, 2010), assessing the association between neuraminidase inhibitor treatment and clinical outcomes (mortality, influenza-related pneumonia, admission to critical care, length of stay in hospital and admission to hospital). We searched Ovid Medline (reports from 1996 onwards) and Embase (1980 onwards) using a comprehensive search strategy. We also searched CINAHL, CAB Abstracts, ISI Web of Science, PubMed, UK PubMed Central, Scopus, WHO regional indexes, LILAC, and J-STAGE databases using Boolean logic and core search terms relating to pandemic influenza (including influenza A virus OR H1N1 subtype OR swine origin influenza AH1N1 virus) AND exposure of interest—ie, antiviral drugs (including neuraminidase inhibitors OR oseltamivir OR zanamivir OR peramivir) AND clinical outcome measures (including pneumonia, or critical care/intensive care, or mortality). We identified further studies from reference lists of relevant articles and through contact with subject area experts (via JSN-V-T). All search results were limited to human beings with no language restrictions. Our detailed search strategy is reported elsewhere.[17]

On the basis of this search, we contacted 401 potential data contributors, identified during the conduct of our previously reported systematic review;[17] these potential contributors included several corresponding authors from different papers but potentially related to the same source dataset, as an all-inclusive approach. We recruited additional centres through our network of global collaborators, publicity at conferences attended, and by word-of-mouth. Centres fulfilling the minimum dataset requirement (appendix pp 7–8) were eligible for inclusion. We requested data for both laboratory

confirmed and clinically diagnosed pandemic influenza A H1N1pdm09 cases, but allowed centres to provide individual patient data extending to March 14, 2011 (third pandemic wave cases). Clinically diagnosed cases that could not be confirmed by virology were diagnosed on the basis of clinical signs and symptoms that, in the opinion of the attending physician, were judged to be representative of influenza-like illness, in the absence of any other more likely diagnosis. We deliberately accepted diagnoses made on clinical judgment rather than specifying a set of clinical criteria, since case definitions of influenza-like illness vary within and between countries. This study was granted exemption from full ethical review by the University of Nottingham Medical School Research Ethics Committee, provided that each contributing centre held its own institutional review board approval for data collection and sharing.

Data standardisation, exposures, outcomes, and covariates

A common data dictionary was developed and individual datasets standardised according to these definitions (appendix pp 9–15) before pooling for analysis.

The primary outcome variable was mortality, defined as death occurring during admission to hospital or individual study follow-up period for the generalised linear mixed regression models and as death occurring within 30 days of illness onset in the Cox regression models. Use of neuraminidase inhibitors (exposure) was defined and compared as follows: neuraminidase inhibitor treatment (irrespective of timing) versus none; early neuraminidase inhibitor treatment (starting treatment ≤2 days after symptom onset) versus later (initiation >2 days after symptom onset); early neuraminidase inhibitor treatment versus none; and later neuraminidase inhibitor treatment versus none. Additionally, we created a continuous exposure variable, representing time (in days) between symptom onset and treatment initiation (0 meaning treatment commenced on day of symptom onset). Covariates in the final multivariable models were "inpatient treatment with oral or intravenous antibiotics" and "inpatient treatment with systemic corticosteroids" prescribed during the admission to hospital for influenza along with treatment propensity scores. We were unable to adjust for dose or duration of such treatments because of the scarce availability of these data across the individual datasets.

Propensity scoring

We calculated propensity scores for the likelihood of neuraminidase inhibitor treatment for each patient within individual datasets using multivariable logistic regression for binary treatment variables and generalised propensity score estimation for the continuous time to treatment variable as described by Hirano and Imbens.[19] For each separate study dataset we calculated propensity scores (likelihood of treatment) for each of the four main exposure measures: neuraminidase inhibitor at any time (yes or no), early versus late neuraminidase inhibitor, early versus no neuraminidase inhibitor, and later (>2 days) versus no neuraminidase inhibitor. Covariates were then included as follows, irrespective of significance: age, sex, comorbidity (yes or no), a proxy indicator of severe disease (yes or no), which were, in order of preference, severe respiratory distress; shortness of breath; unweighted symptom score; or, if none of these indicators were available, we used one of the following measures of severity: AVPU (alert, voice, pain, unresponsive) mental status examination score, Glasgow Coma Scale score, Sequential Organ Failure Assessment score, or CURB-65 (confusion, urea, respiratory rate, blood pressure, age ≥65 years) pneumonia severity scores, if these were available, entered as a continuous variable. We added the following variables when available to create an extended model, using a parsimonious approach that retained only significant covariates in the final model: obesity, smoking, pregnancy, asthma, chronic obstructive pulmonary disease, lung disease, heart disease, immunosuppression, neurological disease, renal disease, and diabetes. We rejected variables with more than 25% missing data. Some variables used for the propensity score calculation, such as comorbidity (binary) and illness severity at presentation (binary), were derived at individual study level only and were not appropriate for inclusion in the pooled dataset analysis because of the heterogeneity in definition of these variables between studies.

The appropriateness of the propensity derivation models was assessed graphically by comparing the distribution of estimated propensity scores across treatment groups for each individual dataset.[20] Propensity scores were then categorised into quintiles for each individual dataset.

Statistical analysis

We used a generalised linear mixed model to account for clustering of effects by study using the xtmelogit command in Stata (version 12). We included "study" as a random intercept to account for differences in baseline crude mortality rate at each site. We adjusted the model for treatment

propensity, inpatient antibiotics, and systemic corticosteroids. We included missing data in covariates as a separate dummy category. The overall analysis included patients of all ages with laboratory or clinically diagnosed influenza A H1N1pdm09. We did prespecified stratified analyses for adults and children (<16 years), pregnant women (irrespective of age), laboratory confirmed influenza A H1N1pdm09 cases, and patients admitted to critical care units. Additionally, for a subset of our sample for whom exact onset and treatment initiation times were available, we investigated the association between time to initiation of antiviral treatment and mortality within 30 days of illness onset using a time-dependent Cox regression shared frailty model (to account for clustering by study) adjusted for propensity score and inpatient treatment with antibiotics or systemic corticosteroids. Antiviral treatment was modelled as a time-dependent covariate to overcome immortal time bias (ie, survivor bias). Results from the generalised linear mixed model are expressed as relative risks of mortality using odds ratios (ORs) and hazard ratios (HRs) for the Cox regression analysis with 95% CIs. We used Stata (version 12) for all analyses.

The protocol[21] for this study was registered with the PROSPERO register of systematic reviews, number CRD42011001273.

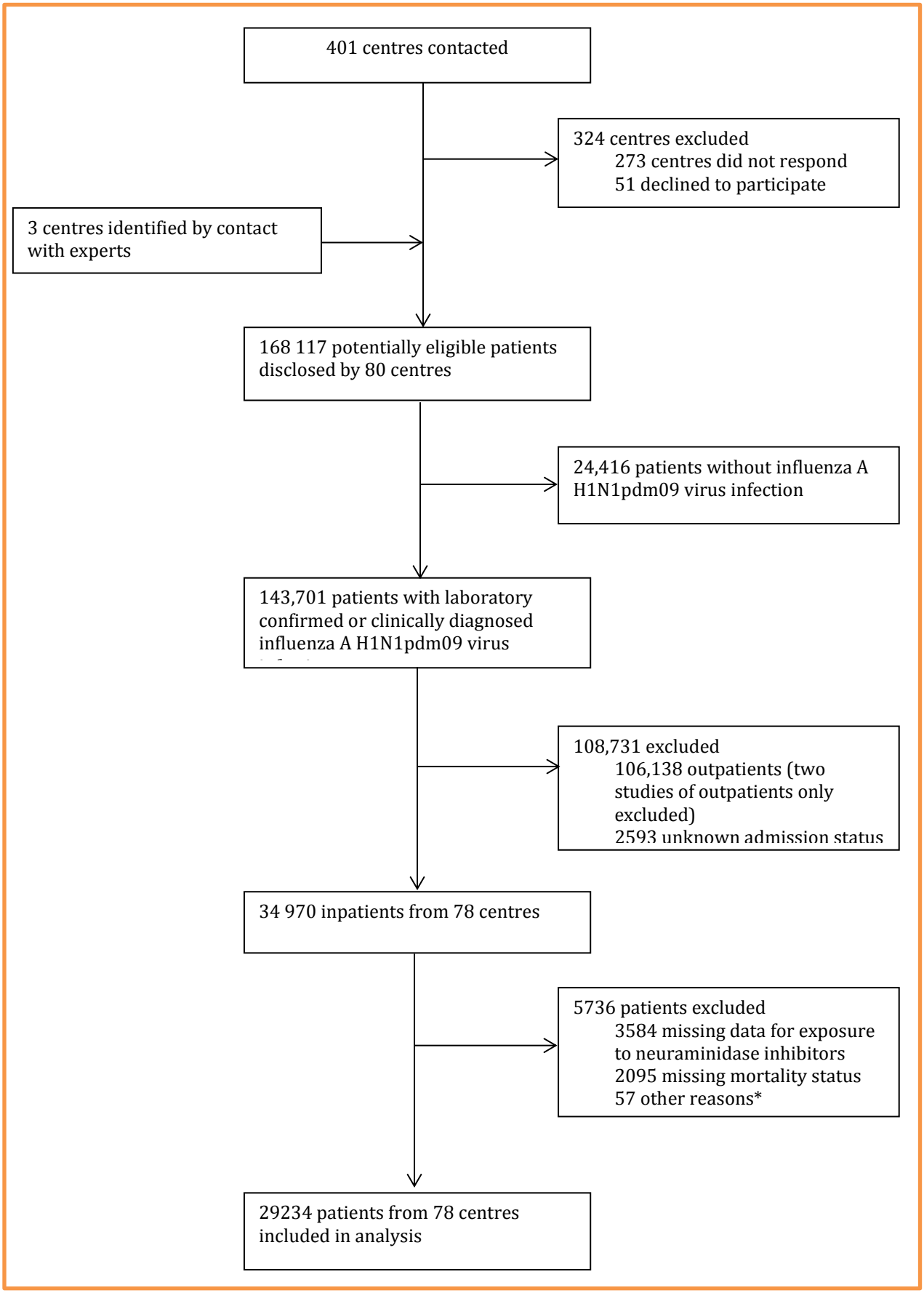
Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report. The funder has not and will never have access to the data. Each collaborator had access to the raw data from his or her centre. SGM, SV, PRM, JL-B, and JSN-V-T had access to the pooled dataset. The corresponding author (JSN-V-T) had full access to all the data in the study and the final responsibility for the decision to submit for publication.

RESULTS

We received replies from 128 (32%) of 401 centres contacted; of these 77 (60%) confirmed willingness to participate and the remainder declined (36 [28%] had no data; three [2%] agreed initially but later withdrew because of lack of capacity for data extraction, institutional review board restrictions preventing sharing of individual participant data, or failure to obtain government approval for data sharing; 12 [9%] had agreed in principle, but were unable to share data within project timescales). No data were requested from nor provided by pharmaceutical companies. After exclusion of duplicate responses (same source dataset), and addition of three further datasets provided through informal contact with domain experts, 80 research groups from 38 countries in six WHO regions contributed anonymised data for 168 117 patients, of whom 24 416 had laboratory results indicative of noninfluenza A H1N1 disease. Among the remaining 143 701 laboratory confirmed or clinically diagnosed (without standard study-wide case definition) influenza A H1N1pdm09 cases, 106 138 were outpatients and 2593 had missing information for hospital admission. The remaining 34 970 inpatients were eligible for inclusion (figure 1).

Figure 1: Study flow diagram



*47 overlapping data; one onset of illness before March 1, 2009 (Mexico); nine missing data for key variables.

Of the 34 970 inpatients eligible for inclusion, 2095 (6%) had missing information for mortality status, and 3584 (10%) for exposure to neuraminidase inhibitors; 57 (<1%) were unsuitable for inclusion for other reasons (figure 1). Ultimately, we included 29 234 records from 78 studies (two studies provided only outpatient data and were excluded from analysis) of patients admitted to hospital between Jan 2, 2009, and March 14, 2011: 25 001 (86%) laboratory confirmed; 9218 (32%) children; and 1600 (5%) aged 65 years or older. Appendix p 16 show the incidence of cases by month. Full characteristics of the pooled dataset are listed in table 1with absolute risks of mortality for various exposure categories and subgroups summarised in appendix p 16. Baseline characteristics of each constituent dataset are presented in appendix pp 17–21.

Patients without neuraminidase inhibitor treatment data and therefore excluded from analysis were more likely to be older, to have presented to hospital later, less likely to have a laboratory confirmed diagnosis, and more likely to be treated with antibiotics than were patients included in the analysis (appendix pp 26–27). However, they were less likely to be smokers, obese, or to have an underlying comorbidity. Additionally, their hospital stay was shorter, and they were less likely to have severe outcomes (admission to critical care unit or death), or influenza-related pneumonia (appendix pp 26–27).

After adjustment for propensity score and corticosteroid and antibiotic treatment, the likelihood of mortality in patients treated with a neuraminidase inhibitor was 0·81 (95% CI 0·70–0·93), compared with no treatment (table 2). The OR did not change substantially when only laboratory confirmed cases were included (adjusted OR 0·82 [95% CI 0·70–0·95]). Similarly, we identified significant associations with a reduced mortality risk in adults, pregnant women, and critically ill adult patients (table 2). However, there was no significant association between neuraminidase inhibitor treatment and mortality in children aged 0–15 years (table 2). Post-hoc analyses restricted to children up to 1 year of age and up to 5 years of age did not change this finding (appendix p 27).

Early neuraminidase inhibitor treatment compared with later treatment initiation was associated with an overall significant reduction in mortality risk (adjusted OR 0·48 [95% CI 0·41–0·56]; table 3). The ORs remained essentially unchanged when only laboratory confirmed cases were considered, but risk reduction was higher in pregnant women (table 3). Notably, there was again no significant association between early treatment and mortality in children after adjustment (table 3).

Table 1: Characteristics of pooled dataset of 29,234 patients hospitalised with A(H1N1)pdm09 virus infection included in mortality analysis

Characteristic (denominator)	All hospitalised patients n (%)	Deceased n (%)	Survived n (%)
Number of patients†	29,234 (100·0)	2,784 (9·5)	26,450 (90·5)
Number of male cases (n=29,226)†	14,431 (49·4)	1,433 (51·5)	12,998 (49·1)
Age: median (IQR) in years (n=29,034)†	26 (11 - 44)	40 (26 - 54)	25 (10 - 42)
Adults (≥16 years)	19,816 (67·8)	2,450 (88·0)	17,366 (65·7)
Children (<16 years)	9,218 (31·5)	325 (11·7)	8,893 (33·6)
Obese‡ (n=22,527)†	2,607 (8·9)	517 (18·6)	2,090 (7·9)
Smoking (n=19,066)†	2,406 (8·2)	285 (10·2)	2,121 (8·0)
Pregnant women§ (n=9,513)†	2,166 (22·8)	177 (18·6)	1,989 (23·2)
WHO Regions (n=29,234)†			
African region	41(0·1)	14 (0·5)	27 (0·1)
Region of the Americas	14,186 (48·5)	1,477 (53·1)	12,709 (48·1)
Eastern Mediterranean Region	5,262 (18·0)	518 (18·6)	4,744 (17·9)
European Region	7,272 (24·9)	680 (24·4)	6,592 (24·9)
South-East Asia Region	210 (0·7)	14 (0·5)	196 (0·7)
Western Pacific Region	2,263 (7·7)	81 (2·9)	2,182 (8·3)
A(H1N1)pdm09 diagnosis (n=29,234)†			
Laboratory confirmed	25,001 (85·5)	2,486 (89·3)	22,515 (85·1)
Clinically diagnosed	4,233 (14·5)	298 (10·7)	3,935 (14·9)
Comorbidities† ¶			
Any comorbidity (n=28,672)	11,011 (37·7)	1,471 (52·8)	9,540(36·1)
Asthma (n=20,518)	2,820 (9·7)	134 (4·8)	2,686 (10·2)
COPD (n=17,081)	1,012 (3·5)	171 (6·1)	841 (3·2)
Other chronic lung disease (n=17,853)	2,479 (8·5)	272 (9·8)	2,207 (8·3)
Heart disease (n=18,419)	1,624 (5·6)	317 (11·4)	1,307 (4·9)
Renal disease (n=19,860)	710 (2·4)	151 (5·4)	559 (2·1)
Liver disease (n=12,264)	295 (1·0)	81 (2·9)	214 (0·8)
Cerebrovascular disease (n=9,803)	304 (1·0)	34 (1·2)	270 (1·0)
Neurological disease (n=13,598)	1,013 (3·5)	136 (4·9)	877 (3·3)
Diabetes (n=24,764)	2,087 (7·1)	418 (15·0)	1,669 (6·3)
Immunosuppression (n=25,268)	1,803 (6·2)	346 (12·4)	1,457 (5·5)
Pandemic H1N1 vaccination (n=4,382) †‖	347 (2.3)	27 (1.7)	320 (2.3)
Time from symptom onset to hospital admission, days, median (IQR) (n=23,769)†	2 (1 – 5)	4 (2 - 6)	2 (1 - 4)
Antiviral agents used			
No NAI treatment	10,431 (35·7)	959 (34·5)	9,472 (35·8)
Any NAI	18,803 (64·3)	1,825 (65·6)	16,978 (64·2)
Oral oseltamivir (n=18,803)**	17,309 (92·1)	1,675 (91·8)	15,634 (92·1)
Intravenous/inhaled zanamivir (n=18,803)**	435 (2·3)	52 (2·9)	383 (2·3)
Intravenous peramivir (n=18,803)**	49 (0·3)	28 (1·5)	21 (0·1)
NAI (regimen unknown) (n= 18,803)**	1,251 (6·7)	140 (7·7)	1,111 (6·5)
NAI and Non-NAI (n=18,803)**	94 (0·5)	18 (1·0)	76 (0·5)
NAI combination therapy (n= 18,803)**	238 (1·3)	69 (3·8)	169 (1·0)
Early NAI (≤2 days of symptom onset) (n=13,254)†**	5,995 (31·9)	358 (19·6)	5,637 (33·2)
Later NAI (>2 days after symptom onset) (n=13,254)†**	7,259 (38·6)	942 (51·6)	6,317 (37·2)
Time from symptom onset to antiviral treatment, days, median (IQR) (n=12,284)†	3 (1 – 5)	4 (2 - 7)	3 (1 - 5)
Other in-hospital treatment †			
Antibiotics (n=20,362)	13,230 (45·3)	1,096 (39·4)	12,134 (45·9)
Corticosteroids (n= 9,982)	2,745 (9·4)	453 (16·3)	2,292 (8·7)
Hospital length of stay, days, median (IQR) (n=22,366)†	5 (2 – 9)	7 (2 - 15)	5 (2 - 8)
Other patient outcomes †			
Influenza-related pneumonia†† (n=16,551)	7,225 (24·7)	1,035 (37·2)	6,190 (23·4)
Admission to critical care (n=24,435)	6,848 (23·4)	1,957 (70·3)	4,891 (18·5)

Data are n (%) or median (IQR). COPD=chronic obstructive pulmonary disease. NAI=neuraminidase inhibitor.
*All percentages have been calculated using these denominators unless otherwise specified.
†Missing data; n shows number of cases with data.
‡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 appendix pp 9–11.
‖Denominators for pandemic vaccine based on patients admitted after Oct 1, 2009 (when vaccine potentially available).
**Percentages calculated as a proportion of the sample receiving NAI therapy.
††Clinically or radiologically diagnosed pneumonia.

Table 2: NAI TREATMENT (AT ANY TIME) VS. NONE

Subgroups	Crude analysis		Adjusted† analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Laboratory confirmed or clinically diagnosed (all ages); n=29,234	0·92 (0·81 to 1·05)	0·21	0·81 (0·70 to 0·93)	0·0024
Laboratory confirmed cases (all ages) ; n=25,001	0·94 (0·81 to 1·09)	0·42	0·82 (0·70 to 0·95)	0·0104
Adults (16 years and above) ; n=19,816	0·82 (0·70 to 0·95)	0·0071	0·75 (0·64 to 0·87)	0·0002
Children (below 16 years); n=9,218	1·02 (0·73 to 1·42)	0·90	0·82 (0·58 to 1·17)	0·28
Pregnant women; n=2,166	0·47 (0·24 to 0·90)	0·0228	0·46 (0·23 to 0·89)	0·0215
ICU patients				
Adults (≥16 years); n=5,103	0·74 (0·57 to 0·95)	0·0187	0·72 (0·56 to 0·94)	0·0155
Children (<16 years); n=1,725	0·84 (0·52 to 1·37)	0·49	0·70 (0·42 to 1·16)	0·17

†adjusted for treatment propensity (by quintile), corticosteroid use and antibiotic use

Neuraminidase inhibitor treatment within 2 days of symptom onset compared with none was also associated with a significant reduction in mortality in all patients (adjusted OR 0·50 [95% CI 0·37–0·67]; table 3), with significant risk reductions also noted among laboratory confirmed cases, adults, pregnant women, and adult patients admitted to critical care (table 3). However, there was no significant association with a lower mortality risk in children aged 0–15 years (table 3).

With regard to neuraminidase inhibitor treatment started more than 2 days after symptom onset compared with none, we identified no significant association with mortality in all patients (adjusted OR 1·20 [95% CI 0·93–1·54]), nor in laboratory confirmed cases, adults, pregnant women, or children (table 4). However, we noted an associated mortality risk reduction of about a third (adjusted OR 0·65 [95% CI 0·46–0·93]) in adult patients admitted to critical care.

Table 3: EARLY NAI TREATMENT (≤2 DAYS AFTER ONSET) VS. LATER (>2 DAYS) OR NONE

Early treatment vs. Later treatment:				
Subgroups	**Crude analysis**		**Adjusted† analysis**	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Laboratory confirmed or clinically diagnosed (all ages); n=13,254	0·36 (0·31 to 0·41)	<0·0001	0·48 (0·41 to 0·56)	<0·0001
Laboratory confirmed cases (all ages) ; n=12,992	0·36 (0·31 to 0·41)	<0·0001	0·48 (0·41 to 0·56)	<0·0001
Adults (16 years and above); n=9,270	0·37 (0·32 to 0·44)	<0·0001	0·45 (0·38 to 0·54)	<0·0001
Children (below 16 years); n=3,899	0·53 (0·35 to 0·80)	0·0026	0·67 (0·44 to 1·03)	0·07
Pregnant women ; n= 917	0·20 (0·09 to 0·46)	0·0002	0·27 (0·11 to 0·63)	0·0026
ICU patients Adults (≥16 years); n=3,385 Children (<16 years); n=683	 0·64 (0·51 – 0·79) 1·12 (0·63 to 1·99)	 <0·0001 0·69	 0·62 (0·49 to 0·77) 1·15 (0·64 to 2·06)	 <0·0001 0·64
Early treatment vs. none:				
Laboratory confirmed or clinically diagnosed (all ages); n=16,425	0·54 (0·40 to 0·72)	<0·0001	0·50 (0·37 to 0·67)	<0·0001
Laboratory confirmed cases (all ages); n= 13,200	0·53 (0·39 to 0·71)	<0·0001	0·48 (0·36 to 0·66)	<0·0001
Adults (16 years and above) ; n=10,607	0·39 (0·28 to 0·55)	<0·0001	0·38 (0·27 to 0·54)	<0·0001
Children (below 16 years); n=5,696	1·08 (0·61 to 1·93)	0·79	0·85 (0·47 to 1·53)	0·59
Pregnant women, n=1,303	0·16 (0·04 to 0·64)	0·0099	0·16 (0·04 to 0·67)	0·0118
ICU patients Adults (≥16 years); n=1,608 Children (<16 years); n=572	 0·30 (0·19 to 0·45) 0·88 (0·40 to 1·91)	 <0·001 0·74	 0·31 (0·20 to 0·47) 0·76 (0·34 to 1·67)	 <0·001 0·49

†adjusted for treatment propensity (by quintile), corticosteroid use and antibiotic use

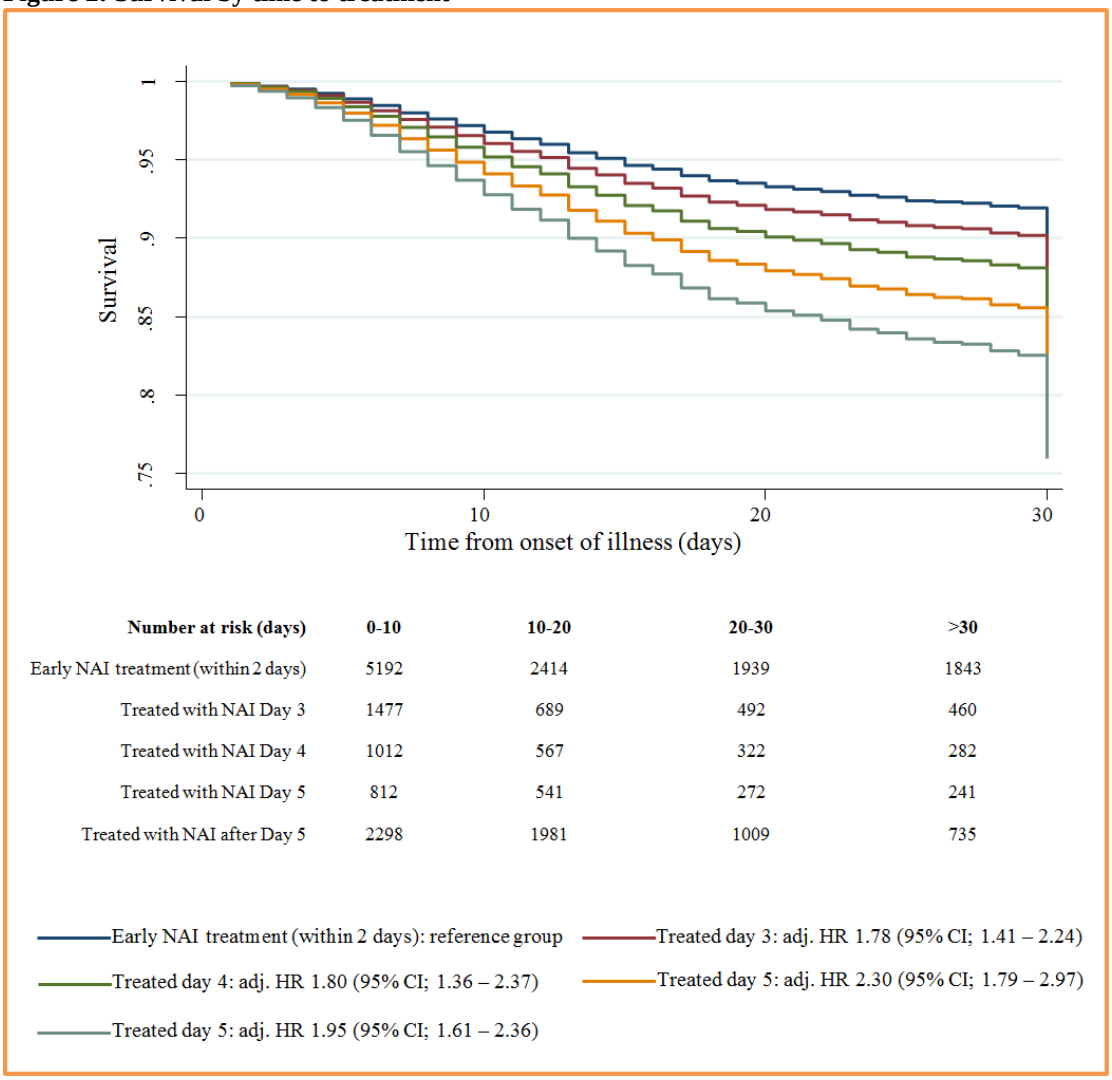
Information about exact timing of neuraminidase inhibitor treatment from symptom onset was available for 65% (12284 of 18803) of those receiving such treatment. After taking into account clustering by study, propensity score quintiles, and inhospital treatment with antibiotics or systemic corticosteroids, when antiviral use was modelled as a time-dependent covariate to overcome potential immortal time bias (ie, survivor bias), neuraminidase inhibitor treatment was significantly associated with decreased hazard rate of mortality over a 30-day follow-up period (adjusted HR 0·51 [95% CI 0·45–0·58], p<0·0001) as compared with no antiviral treatment. When only treated cases were included, there was an increase in the hazard with each day's delay in initiation of treatment up to day 5 as compared with treatment initiated within 2 days of symptom onset (adjusted HR 1·23 [95% CI 1·18–1·28], p<0·0001 for the increasing HR with each day's delay). The unadjusted and adjusted survival curves comparing survival by time to treatment initiation are shown in figure 2 and appendix pp 28–29.

Table 4: LATER NAI TREATMENT (>2 DAYS) VS. NONE

Population Subgroups	Crude analysis		Adjusted† analysis	
	OR (95% CI)	**P value**	**OR (95% CI)**	**P value**
Laboratory confirmed or clinically diagnosed (all ages); n=17,670	1·27 (1·00 to 1·61)	0·0497	1·20 (0·93 to 1·54)	0·15
Laboratory confirmed cases (all ages); n=14,409	1·25 (0·98 to 1·59)	0·07	1·17 (0·92 to 1·51)	0·21
Adults (16 years and above); n=12,269	1·01 (0·77 to 1·32)	0·94	1·01 (0·76 to 1·33)	0·96
Children (below 16 years); n=5,282	1·34 (0·78 to 2·31)	0·29	1·29 (0·75 to 2·21)	0·36
Pregnant women, n=1,302	0·72 (0·26 to 2·01)	0·53	0·70 (0·24 to 2·06)	0·51
ICU patients Adults (≥16 years); n=2,977 Children (<16 years); n=644	 0·61 (0·43 to 0·86) 0·65 (0·32 to 1·36)	 0·0045 0·25	 0·65 (0·46 to 0·93) 0·75 (0·35 to 1·57)	 0·0183 0·44

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

Figure 2: Survival by time to treatment



HR=hazard ratio. NAI=neuraminidase inhibitor.
*Cox regression shared frailty model (adjusted for treatment propensity and in hospital steroid or antibiotic use)

Panel: Research in context

Systematic reviews

Two systematic reviews and meta-analyses have examined the effectiveness of neuraminidase inhibitors in reducing mortality due to influenza. Hsu and colleagues[16] considered reported observational data, mainly for seasonal influenza, and concluded that oral oseltamivir might reduce mortality (odds ratio [OR] 0·23 [95% CI 0·13–0·43). In our own systematic review, we included only reported data from the 2009–10 influenza A H1N1pandemic (all observational) and showed that early neuraminidase inhibitor treatment versus none reduced mortality by two thirds (OR 0·35 [95% CI 0·18–0·71]).[17] We applied search terms relating to pandemic influenza (including "Influenza A Virus" OR "H1N1Subtype" OR "swine origin influenza AH1N1 virus"), AND exposure of interest—ie, antiviral drugs (including "neuraminidase inhibitors" OR "oseltamivir" OR "zanamivir" OR "peramivir") AND clinical outcome measures (including "pneumonia", "critical or intensive care", "mortality") to 11 databases (search range from Jan 1, 2009, to Aug 10, 2010; last search on April 19, 2012) without imposing language restrictions. Importantly, both studies acknowledged limitations such as the heterogeneity of studies included and inadequate adjustment for potential confounding. Moreover, neither was able to adjust for the likelihood of a patient receiving antiviral treatment (propensity)—a crucial consideration when antiviral drugs might have been prioritised towards the sickest patients.

Interpretation

By using a meta-analysis of individual patient data, which permits a uniform approach to potential confounding and adjustment for treatment propensity, and through the assembly of a very large international dataset, our study adds substantially to the evidence that neuraminidase inhibitors administered to adults admitted to hospital with influenza A H1N1pdm09 reduced mortality, especially when started promptly. Since placebo-controlled randomised controlled trials of neuraminidase inhibitors are not ethically feasible during a pandemic, the evidence we have assembled is likely to be the best that will be available. The US Centers for Disease Control and Prevention recommend neuraminidase inhibitor treatment as early as possible for any patient with confirmed or suspected influenza who is hospitalised; has severe, complicated or progressive illness; or is at higher risk for influenza complications. [22] Neuraminidase inhibitors are also widely prescribed in Japan, but elsewhere their use is far less common. Although a similar treat-all policy existed in the UK in 2009, uptake of neuraminidase inhibitors inpatients admitted to hospital with influenza A H1N1pdm09 virus was low.[15] We advocate early instigation of neuraminidase inhibitor treatment in adults admitted to hospital with suspected or proven influenza infection.

DISCUSSION

Our results show that neuraminidase inhibitor treatment was associated with reduced mortality in adult patients admitted to hospital with influenza A H1N1pdm09 virus infection. Neuraminidase inhibitor treatment of influenza A H1N1pdm09 at any stage of illness compared with none revealed an associated reduction in the likelihood of mortality (table 2). We identified an associated likelihood of lower mortality when comparing early versus later initiation of treatment and when comparing early treatment with none (table 3, panel). Although we included 4233 patients (14%) without laboratory confirmed influenza A H1N1pdm09, restriction to laboratory-confirmed cases produced near identical estimates, suggesting that the data are not confounded by misclassification bias attributable to other causes (tables 2, 3). Additionally, we noted much the same findings in adults, pregnant women, and adult patients needing admission to critical care. The finding regarding critical care suggests that neuraminidase inhibitors were associated with mortality reduction across the spectrum of severity in adult patients admitted to hospital with influenza A H1N1pdm09. These findings accord closely with previous studies[16, 17] but have increased precision and reduced estimates of effectiveness consistent with more complete adjustment for confounders and treatment propensity. They are also consistent with ecological data. [23-25]

We were consistently unable to show any association of neuraminidase inhibitor treatment with mortality reduction in children. Possible explanations include lower case fatality proportion in paediatric patients (thus reduced statistical power),[26, 27] higher influenza A H1N1pdm09 viral load in children[28] than adults leading to reduced drug effectiveness, suboptimum dosing in very young children,[29] secondary bacterial infections (eg, methicillin-resistant *Staphylococcus aureus*), confounding by indication[30] (children might have been more likely to have had antivirals prescribed if they had more severe disease or if they failed to respond to other treatments), or a combination of these factors. Since it has been suggested that younger children might be admitted with milder disease compared with older children and adults (precautionary physician behaviour), that the pharmacokinetics and pharmacology of oseltamivir might be different in very young children,[29] and that influenza pathogenesis might differ by age,[31] we did post-hoc sensitivity analyses separately in children up to 1 year of age and up to 5 years of age, but our findings did not change (appendix p 27). However, we note that these results contrast with those of Louie and colleagues,[32] who recently showed

a two-thirds reduction in mortality among children treated with neuraminidase inhibitors admitted to hospital with influenza (OR 0·36 [95% CI 0·16–0·83]).

The finding that no treatment was better than late treatment is probably explained by confounding due to illness severity at the point of treatment initiation (ie, confounding by indication). Untreated patients probably had milder disease and patients treated later in the course of their illness might have had delays in hospital admission, delays in diagnosis after admission, or delays in being considered for neuraminidase inhibitor treatment (treatment only started once their condition deteriorated), or combinations of these factors. We advocate early consideration of a diagnosis of influenza in patients admitted to hospital with respiratory infection during periods of known influenza activity, and early instigation of neuraminidase inhibitor treatment based on rapid laboratory confirmation or clinical suspicion.

Our analyses examining the effect of later treatment versus none are especially relevant to the continued clinical debate about the value of delayed therapy. Combining all subgroups of patients, we did not identify any protective association with treatment delayed more than 2 days after symptom onset (table 4). This finding could be explained by confounding by indication. However, we noted that in adult patients admitted to critical care, delayed treatment was associated with reduced likelihood of mortality compared with no treatment (table 4), suggesting that delayed therapy might still be worthwhile in severely ill patients; this finding is plausible since, within this subgroup, treated and untreated patients (who all needed admission to critical care) are likely to have been more balanced in terms of illness severity thereby overcoming confounding by this factor to some extent. Additionally, some patients admitted to critical care might have had prolonged influenza A H1N1pdm09 virus replication in the lower respiratory tract, which might benefit from later initiation of neuraminidase inhibitor treatment. To gain further understanding about overall timing-dependent benefit, we modelled time to start of antiviral treatment using a time-dependent Cox regression model, which showed a significant detrimental survival benefit associated with delay in treatment beyond 2 days after symptom onset ($p<0·0001$), albeit with overlapping 95% CIs when time to treatment was modelled as a categorical variable; the latter finding suggests that potential differences in treatment benefit between starting on day 3 after symptom onset through to more than 5 days after symptom onset cannot be further clarified through our data. This finding could seem to conflict with the findings in table 4

comparing later neuraminidase inhibitor treatment to no neuraminidase inhibitor treatment but is not surprising, because by comparing only treated patients in figure 2, we possibly eliminated some of the confounding due to indication, which allowed us to identify the potential survival benefits conferred by later treatment, albeit detrimental in proportion to treatment delay.

One of the strengths of this study is the very large number of patients from geographically diverse clinical centres and source populations. We made exhaustive efforts to identify suitable datasets from around the world, but nevertheless cannot comment on the extent to which bias might have been introduced by failing to include centres that did not respond (we cannot say if they had suitable data or not), or that declined to share data; in a worst case scenario, it is possible that less than 20% of potential sites contributed to this analysis. Furthermore, comparatively few cases were from the WHO African (0·1%) and South-East Asia (0·7%) regions, which might limit the extent to which our findings can be generalised.

A clear limitation of our study is that we were unable to adjust specifically for disease severity in our multilevel models because of the heterogeneity of severity measures used across individual datasets. However, we made every effort to include relevant data including severity measures, within each propensity score, but there is still likely to be some residual confounding, particularly due to illness severity at presentation. Likewise, we attempted to control for study-level biases, such as treatment policies, and healthcare seeking behaviour, using multilevel models but there might be residual confounding. A further limitation of our dataset is that 10% of the patients had missing data for exposure to neuraminidase inhibitors and were excluded from the analysis; the characteristics of these patients are compared with those with data for neuraminidase inhibitor exposure in appendix pp 26–27; these patients were more likely to be older, to have presented to hospital later, less likely to have a laboratory confirmed diagnosis, and more likely to be treated with antibiotics.

The decision to adjust for treatment with antibiotics and corticosteroids was taken after consultation with clinical colleagues within the PRIDE study collaboration. This decision results from widespread clinical practice to treat patients admitted to hospital with respiratory illness with corticosteroids and antibiotics. There is particular uncertainty about the possible effect of corticosteroids on the course of severe influenza infection.[33, 34] Therefore, it was necessary to separate out the possible effects of antivirals from these other commonly used treatments. We did not do specific analyses to establish the

potential effect of antibiotic or corticosteroid use on mortality, but recognise that these factors both warrant further research. Although we were able to adjust for inpatient antibiotics and systemic corticosteroid use, we were unable to adjust for pandemic H1N1 vaccination since 35% (8284 of 23633) of our case series were admitted to hospital before the first availability of vaccine in October, 2009, and 71% (10 967 of 15 349) of data for vaccination status were missing among those admitted after that juncture; however, the available data suggest uptake was no higher than 8% during the study period.

This meta-analysis of individual patient data offers the most rigorous assessment of mortality benefits of neuraminidase inhibitor treatment during the 2009–10 pandemic that is likely to be possible using retrospective observational data. The greatest likelihood of reduced mortality seems to be attributable to treatment started within 2 days of symptom onset. These data offer evidence of the effectiveness of neuraminidase inhibitors during the 2009–10 pandemic and are superior to extrapolations from earlier data on seasonal influenza; they could retrospectively vindicate prepandemic neuraminidase inhibitor antiviral stockpiling decisions made by governments worldwide. Treatment guidance policies should increase emphasis on early empirical neuraminidase inhibitor treatment of adult patients admitted to hospital after presenting with proven or clinically suspected influenza A H1N1pdm09 virus infection. However, most adult patients with suspected or confirmed influenza are not admitted to hospital within 48 h of illness onset. Therefore, the implications of these findings, although based on patients admitted to hospital with influenza A H1N1pdm09, encourage early initiation of neuraminidase inhibitor treatment in outpatients who are appreciably unwell with suspected or confirmed influenza, or at increased risk of complications, including those with influenza A H3N2 or influenza B. Further studies are needed in children to confirm the adequacy of present dose regimens and duration of therapy in terms of clinical efficacy.

Contributors

JSN-V-T, PRM, SGM, SV, and JL-B conceived and designed the study. All authors, apart from SGM, SV, and JL-B, contributed to 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, SGM, SV, and JL-B 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.

PRIDE CONSORTIUM INVESTIGATORS

Maria De Lourdes Aguiar-Oliveira, Malakita Al Masri, Robed Amin, Wildo N Araújo, Elena Ballester-Orcal, Carlos Bantar, Jing Bao, Mazen M Barhoush, Ariful Basher, Edgar Bautista, Julie Bettinger, Roland Bingisser, Emilio Bouza, Ilkay Bozkurt, Elvira Čeljuska-Tošev, Kenny K C Chan, Yusheng Chen, Tserendorj Chinbayar, Catia Cilloniz, Rebecca J Cox, María R Cuezzo, Wei Cui, Simin Dashti-Khavidaki, Bin Du, Hicham El Rhaffouli, Hernan Escobar, Agnieszka Florek-Michalska, James Fraser, John Gerrard, Stuart Gormley, Sandra Götberg, Matthias Hoffmann, Behnam Honarvar, Jianmin Hu, Christoph Kemen, Gulam Khandaker, Evelyn S C Koay, Miroslav Kojic, Win M Kyaw, Leonard Leibovici, Hongru Li, Xiao-Li Li, Romina Libster, Tze P Loh, Deborough Macbeth, Efstratios Maltezos, Toshie Manabe, Débora N Marcone, Magdalena Marczynska, Fabiane P Mastalir, Mohsen Moghadami, Lilian Moriconi, Bulent Ozbay, Blaž Pečavar, Wolfgang Poeppl, Philippe G Poliquin, Mahmudur Rahman, Alberto Rascon-Pacheco, Samir Refaey, Brunhilde Schweiger, Fang G Smith, Ayper Somer, Thiago M L Souza, Payam Tabarsi, Chandrabhanu B Tripathi, Daiva Velyvyte, Diego Viasus, Qin Yu, Kwok-Yung Yuen, Wei Zhang, Wei Zuo. Affiliations listed in appendix pp 1–6.

Declaration of interest

Between October 2007 and September 2010, Jonathan S Nguyen-Van-Tam (JSN-V-T) undertook ad hoc paid consultancy and lecturing for several influenza vaccine manufacturers (Sanofi-Pasteur MSD, Sanofi-Pasteur, GlaxoSmithKline plc (GSK), Baxter AG, Solvay, Novartis) and manufacturers of neuraminidase inhibitors (F. Hoffmann-La Roche: oseltamivir (Tamiflu®) and GSK: zanamivir (Relenza®)). He is a former employee of both SmithKline Beecham plc (now part of GSK), Roche Products Ltd. (UK), and Sanofi-Pasteur MSD, all prior to 2005). He has no outstanding interests related to shares, share options or accrued pension rights in any of these companies. He is in receipt of current or recent research funding, related to influenza vaccination from GSK and Astra-Zeneca and non-financial support (travel) from Baxter AG. His brother became an employee of GSK in January 2014. JL-B is Statistical Editor of the Cochrane Skin Group. PRM is the recipient of the unrestricted educational grant for research in the area of pandemic influenza from F. Hoffman La-Roche, used to fund this work. She has also received travel grants from F. Hoffman La Roche and its subsidiaries to

attend clinical seminars to present this work. Professor Robert Booy (RB) has received financial support from CSL, Sanofi, GlaxoSmithKline, Novartis, Roche and Wyeth to conduct research and present at scientific meetings. Any funding received is directed to an NCIRS research account at The Children's Hospital at Westmead, New South Wales, Australia, and is not personally accepted by RB. All other named authors declare no conflicts of interest.

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Front page author affiliations:

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
Tarig SA	Al Khuwaitir	Department of Medicine, King Saud Medical City, Riyadh, Kingdom of Saudi Arabia
Adbullah	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
Eduardo	Azziz-Baumgartner	Centers for Disease Control and Prevention, Atlanta, Georgia, USA
Clarisa	Báez	Ministerio de Salud de la Provincia de Buenos Aires, Argentina
Matteo	Bassetti	Santa Maria Misericordia Hospital, Udine Italy
Bojana	Beovic	Department of Infectious Diseases, University Medical Centre, Ljubljana, Slovenia
Barbara	Bertisch	Division of Infectious Diseases and Hospital Epidemiology, Kantonsspital St. Gallen, Switzerland
Isabelle	Bonmarin	Institut de Veille Sanitaire, France
Robert	Booy	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
Heinz	Burgmann	Medical University of Vienna, Austria
Bin	Cao	Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China
Jordi	Carratala	Department of Infectious Diseases, Hospital Universitari de Bellvitge-IDIBELL, L'Hospitalet de Llobregat, REIPI, University of Barcelona, Barcelona, Spain
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,

First name	Surname	Affiliation
		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
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
Maddalena	Giannella	Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón, Madrid, Spain
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
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
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

First name	Surname	Affiliation
Koichiro	Kudo	National Center for Global Health and Medicine, Tokyo Japan
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
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 Toronto, 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
Auksė	Mickiene	Lithuanian University of Health Sciences, Kaunas, Lithuania
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

First name	Surname	Affiliation
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
Maria E	Oliva	Dept. of Infection Control, Hospital San Martín de Paraná, Entre Ríos, Argentina
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
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
Elena B	Sarrouf	Ministerio de Salud de Tucumán, Argentina
Anna C	Seale	[1] Paediatric Intensive Care Unit, Bristol Children's Hospital, UK [2] Bristol Children's Vaccine Centre, School of Clinical Sciences, University of Bristol, Bristol, UK
Bunyamin	Sertogullarindan	Yuzuncu Yil University Medical Faculty, Department of Pulmonary Medicine Van, Turkey
Marilda M	Siqueira	Laboratory of Respiratory Viruses, Oswaldo Cruz Institute/Fiocruz, Rio de Janeiro, Brazil
Joanna	Skręt-Magierło	Uniwersytet Rzeszowski, Poland
Frank	Stephan	Department of Emergency Medicine, University Hospital Basel, Switzerland
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
Kelvin KW	To	Carol Yu Centre for Infection and Div of Infectious Diseases, Dept of Microbiology, The University of Hong Kong, Queen Mary Hospital, Hong Kong
Antoni	Torres	Hospital Clinic, University of Barcelona IDIBAPS, CIBERES, Spain
Selda H	Törün	Department of Pediatric Infectious Diseases, Istanbul Medical Faculty, Istanbul, 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
Tjasa	Vidmar	General Hospital Slovenj Gradec, Slovenia
Renata TC	Yokota	Departamento de Vigilância Epidemiológica, Secretaria de Vigilância em Saúde, Ministério da Saúde, Brasília DF, Brazil
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