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Post-pandemic Review of anti-Influenza Drug Effectiveness (PRIDE Study):

An individual patient data (IPD) meta-analysis investigating the impact of antiviral use on patient outcomes during the 2009-10 influenza A(H1N1)pdm09 pandemic

PRIDE Research Consortium

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Conflict of interest

- The IPD meta-analysis study has been made possible through an unrestricted educational grant funding from F.Hoffmann-La Roche to the University of Nottingham
- The study is being undertaken fully independently of the company, which has had/will have:
  - no input to the project design;
  - no access to any of the data;
  - no role in analysis or data interpretation;
  - no preview of the study results;
  - no opportunity to preview or comment on this presentation or any manuscripts arising from the work.

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Background

- Neuraminidase inhibitors (NAIs) are widely used as influenza-specific antiviral drugs
- During the 2009 pandemic two licensed antiviral drugs: oseltamivir (Tamiflu®) and zanamivir (Relenza ®)*
- Prior to the 2009 pandemic, evidence base that NAIs reduced severe outcomes of public health importance limited, inconclusive and hotly debated
- Many studies supported the potential benefit of NAIs during 2009-10 but lacked statistical power to be conclusive
- Should countries stockpile again or replenish?

*peramivir (Rapiacta®) used under special license or for compassionate use in some territories

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MAJOR ARTICLE

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

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Journal of Infectious Diseases, 2013: 207 (15 February)

Outcomes studied:

- Mortality
- Severe outcomes: admission to HDU/ICU or death
- (Based on published manuscripts not raw data)

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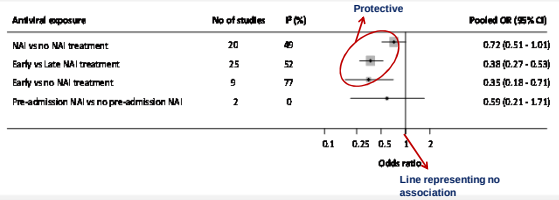
Summary of pooled analysis from studies examining mortality, 44 studies, n=23,723

Antiviral exposure	No of studies	I² (%)	Pooled OR (95% CI)
NAI vs no NAI treatment	20	49	0.72 (0.51 - 1.01)
Early vs Late NAI treatment	25	52	0.38 (0.27 - 0.53)
Early vs no NAI treatment	9	77	0.35 (0.18 - 0.71)
Pre-admission NAI vs no pre-admission NAI	2	0	0.59 (0.21 - 1.71)



- NAI treatment (at any time) vs none: ↓28%, NS
- Early vs late: ↓62%, publication bias
- Early vs none: ↓65% , high levels of heterogeneity

Muthuri et al. (2013).

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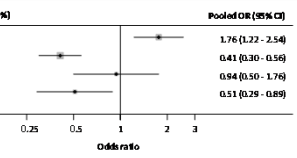
Summary of pooled analysis from studies examining severe outcome, 52 studies, n= 31,428

Antiviral exposure	No of studies	I² (%)	Pooled OR (95% CI)
NAI vs no NAI treatment	23	86	1.76 (1.22 - 2.54)
Early vs Late NAI treatment	24	82	0.41 (0.30 - 0.56)
Early vs no NAI treatment	11	93	0.94 (0.50 - 1.76)
Pre-admission NAI vs no pre-admission NAI	3	0	0.51 (0.29 - 0.89)



- NAI treatment (at any time) vs none: ↑ 76%
- Early vs late: ↓59%
- Early vs none: ↓6%, NS
- Overall, high degree of heterogeneity

Muthuri et al. (2013).

Key findings

During the 2009-10 influenza A(H1N1) pandemic, early initiation of NAI treatment reduced the likelihood of severe outcomes compared with late or no treatment

Limitations of meta-analysis

- High degree of heterogeneity between studies
- Most studies did not provide adjusted risk estimates
- Where adjusted risk estimates were available there were differences in the extent of adjustment or confounders included in final models
- Inability to adjust for propensity to receive treatment

PRIDE Study

Aim: To carry out an individual patient data (IPD) meta-analysis to investigate the impact of NAI use on public health outcomes for influenza A(H1N1)pdm09

❑ Outcome measures include:

1) Mortality
2) Admission to intensive care units
3) Influenza-related pneumonia
4) Hospitalisation (community data)

Prospero Registration: CRD42011001273

Establishing a Research Consortium

- 80 Research groups* from 38 countries and 6 WHO regions
- Total sample size of 168,117. Of these 29,234 were hospitalised (with known mortality status and NAI antiviral use data).
- Practical considerations: data sharing agreements, Institutional Review Board approval, standardisation of datasets.

* Two research groups provided exclusively outpatient data.

Methodology

Standardisation of datasets

- Exposure defined as:
  - NAI treatment (at any time) vs no NAI treatment
  - Early NAI (≤2 days of symptom onset) treatment vs late NAI (>2 days after symptom onset) treatment
  - Early NAI (≤2 days of symptom onset) treatment vs no NAI treatment
  - Later NAI >2 days after symptom onset) treatment vs no NAI treatment
- Standardised definitions created for confounder variables such as 'comorbidity', 'disease severity'
- Propensity scores were calculated by including the following covariates in a regression model with 'treatment' as the outcome variable (minimum model): age, sex, comorbidity (yes/no), disease severity at admission (yes/no)

Methodology

Statistical analysis

- Multilevel regression modelling with each individual study centre included in the hierarchical model as a random intercept
- Adjustment carried out for: propensity score quintile, steroid use in hospital, antibiotic treatment
- Additional analyses: by age group (adults, children), pregnant women, intensive care unit (ICU) cases, laboratory confirmed A(H1N1)
- For sub-group of patients with time to treatment initiation data, survival analysis using time-dependent Cox regression shared frailty model.
- Analyses conducted using Stata™ V.12

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Results

Characteristics of pooled sample of hospitalised patients (N= 29,234)

Characteristics	All (%)* N= 29,234	Died (%)† n=2,784 (10%)
Population groups		
Adults (ages ≥16 years)	19,816 (68%)	2,450 (12%)
Children (ages <16 years)	9,218 (32%)	325 (4%)
Pregnant women (ages:13-54 years)	2,166 (7%)	177 (8%)
ICU admission (Critical care)	6,848 (23%)	1,957 (29%)
Laboratory confirmed A(H1N1)pdm09	25,001 (86%)	2,486 (10%)
Males	14,431 (49%)	1,433 (10%)
Median Age (IQR)	26y (11-44)	40y (26-54)

* All percentages calculated as a proportion of N
† Percentage died in each sub-group (row percentages)

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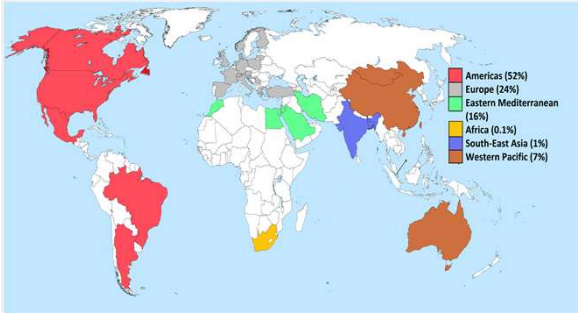
Distribution of patients by WHO Regions



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Distribution of patients by WHO Regions

WHO Regions	No of centres N=78	All (%) N= 32,815
AMRO (Americas)	19	17,080 (52%)
EURO (Europe)	32	7,855 (24%)
EMRO (Eastern Mediterranean)	9	5,279 (16%)
AFRO (Africa)	1	42 (0.1%)
SEARO (South-East Asia)	3	216 (1%)
WPRO (Western Pacific)	14	2,343 (75%)

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Treatment Characteristics of pooled sample of hospitalised patients (n= 29,234)

Exposure definition	All (%) N= 29,234	Died (%)‡ n=2,784
NAI (at any time)	18,803 (64%)	1,825 (10%)
Oseltamivir (at any time)	17,309 (92%)†	1,675 (10%)
Zanamivir (at any time)	435 (2%)†	52 (12%)
Peramavir (at any time)	49 (<1%)†	28 (57%)
No NAI treatment	10,431 (36%)	959 (9%)
Time of treatment after symptom onset		
Early NAI (≤2 days)	5,995 (32%)*	358 (6%)
Late NAI (>2 days)	7,259 (39%)*	942 (13%)

† Expressed as a percentage of all NAIs (n=18,803); * missing data
‡ Percentage deaths in each exposure group (row percentages)

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Time to antiviral administration and hospitalisation in PRIDE dataset

- The median time in days from symptom onset to antiviral treatment could be calculated for 55% of our subjects and was 3 days (IQR: 1-5).
- The median time from symptom onset to hospital admission could be calculated for 83% of our subjects and was 2 days (IQR: 1-5).

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Outcome: Mortality

Exposure: NAI treatment at anytime vs No NAI treatment

Population Subgroups	Crude OR (95% CI)	Adjusted† OR (95% CI)
Lab confirmed cases (all ages)	0.94 (0.81 - 1.09)	**0.82 (0.70 – 0.95)**
Lab confirmed and clinical diagnoses (all ages)	0.92 (0.81 - 1.05)	**0.81 (0.70 – 0.93)**
Adults (16 years and above)	**0.82 (0.70 - 0.95)**	**0.75 (0.64 – 0.87)**
Children (<16 years)	1.02 (0.73 - 1.42)	0.82 (0.58 - 1.17)
Pregnant (13 - 54 years)	**0.47 (0.24 - 0.90)**	**0.46 (0.23 - 0.89)**
ICU patients (adults ≥16 years)	**0.74 (0.57 – 0.95)**	**0.72 (0.56 - 0.94)**

Statistically significant results in bold

Outcome : Mortality

Exposure: Early NAI (≤2 days) vs. no NAI treatment

Population Subgroups	Crude OR (95% CI)	Adjusted† OR (95% CI)
Lab confirmed cases (all ages)	**0.53 (0.39 - 0.71)**	**0.48 (0.36 - 0.66)**
Lab and clinically confirmed (all ages)	**0.54 (0.40 - 0.72)**	**0.50 (0.37 - 0.67)**
Adults (16 years and above)	**0.39 (0.28 - 0.55)**	**0.38 (0.27 - 0.54)**
Children (<16 years)	1.08 (0.61 - 1.93)	0.85 (0.47 - 1.53)
Pregnant (13 - 54 years)	**0.16 (0.04 - 0.64)**	**0.16 (0.04 - 0.67)**
ICU patients (adults ≥ 16 years)	**0.30 (0.19 - 0.45)**	**0.31 (0.20 - 0.47)**

†Adjusted for propensity score quintile, steroid use in hospital, antibiotic treatment in hospital

Outcome : Mortality

Exposure: 'early' NAI (≤2 days) vs. 'late' (>2 days)

Population Subgroups	Crude OR (95% CI)	Adjusted† OR (95% CI)
Lab confirmed cases (all ages)	**0.36 (0.31 - 0.41)**	**0.48 (0.41 - 0.56)**
Lab and clinically confirmed (all ages)	**0.36 (0.31 - 0.41)**	**0.48 (0.41 - 0.56)**
Adults (16 years and above)	**0.37 (0.32 - 0.44)**	**0.45 (0.38 - 0.54)**
Children	**0.53 (0.35 - 0.80)**	0.67 (0.44 - 1.03)
Pregnant (13 - 54 years)	**0.20 (0.09 - 0.46)**	**0.27 (0.11 - 0.63)**
ICU patients (adults ≥ 16 years)	**0.64 (0.51 - 0.79)**	**0.62 (0.49 - 0.77)**

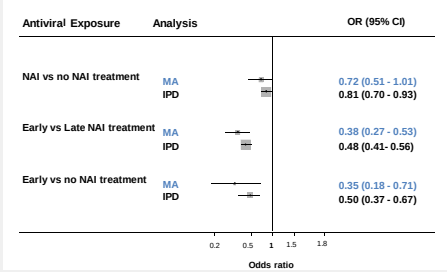
†Adjusted for propensity score quintile, steroid use in hospital, antibiotic treatment
Statistically significant results in bold

Summary of key findings (lab confirmed, all ages)

Outcome	Treatment	Adjusted† Odds ratio (95%CI)	Percentage risk reduction/increase
Mortality	Antiviral treatment vs. none	**0.82 (0.70 - 0.95)**	**↓18%**
	Early treatment (≤2 days) after illness onset vs. no treatment	**0.48 (0.36 - 0.66)**	**↓52%**
	Early treatment (≤2 days) after illness onset vs. Later treatment (> 2days)	**0.48 (0.41 - 0.56)**	**↓52%**

†Adjusted for propensity score quintile, steroid use in hospital, antibiotic treatment in hospital

Comparison of results: meta-analysis versus IPD meta-analysis [Lab confirmed and clinically confirmed (all ages)]



Does later treatment with NAIs offer any benefits in relation to mortality?

Exposure: Later NAI (>2 days) vs. no treatment

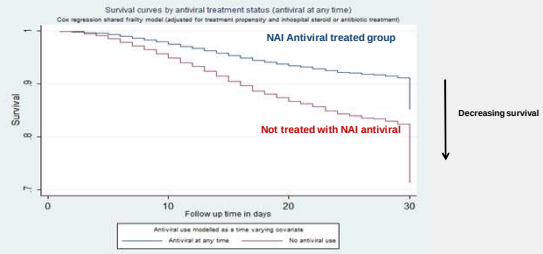
Population Subgroups	Crude OR (95% CI)	Adjusted† OR (95% CI)
Lab confirmed cases (all ages)	1.25 (0.98 - 1.59)	1.17 (0.92 - 1.51)
Lab and clinically confirmed (all ages)	**1.27 (1.00 - 1.61)**	1.20 (0.93 - 1.54)
Adults (16 years and above)	1.01 (0.77 - 1.32)	1.01 (0.76 - 1.33)
Children	1.34 (0.78 - 2.31)	1.29 (0.75 - 2.21)
Pregnant (13 - 54 years)	0.72 (0.26 - 2.01)	0.70 (0.24 - 2.06)
ICU patients (adults ≥16 years)	**0.61 (0.43 to 0.86)**	**0.65 (0.46 to 0.93)**

†Adjusted for propensity score quintile, steroid use in hospital, antibiotic treatment in hospital

Exploring treatment effects using survival analysis

- Cox regression shared frailty model to account for clustering
- NAI treatment compared to no NAI treatment
- Outcome: Mortality over a 30-day follow up period from illness onset

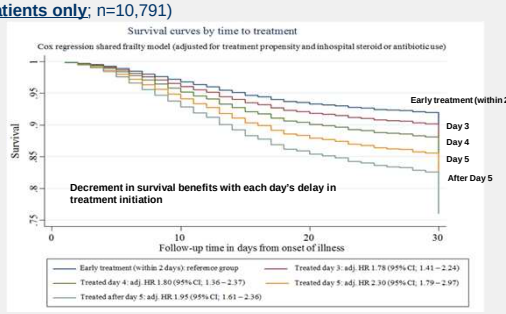
Adjusted survival curves in NAI treated and untreated patients



Decreasing survival

Adjusted Hazard Ratio: 0.51 (95% CI: 0.45- 0.58); P<0.0001

Adjusted survival curves by time to treatment initiation (**treated patients only**; n=10,791)

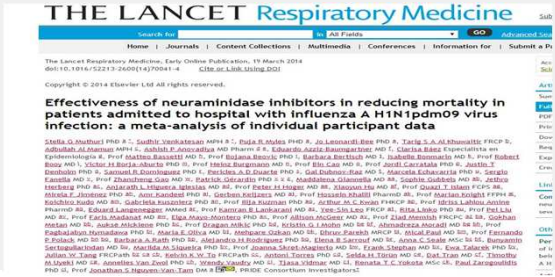


Conclusions

- IPD analysis has confirmed the findings of our initial meta-analysis but also increased the precision of measurement
- By adjusting for confounders and treatment propensity, offers greater confidence that NAI treatment reduced mortality during the 2009-10 pandemic in hospitalised patients.
- Confirms the importance of early treatment in maximising mortality reduction benefits.
- Some indication that treatment administered >2 days following symptom onset may confer some mortality reduction benefits in critically ill patients.
- Endorses policy decisions to stockpile and use NAIs in hospitalised patients during the 2009-10 pandemic.

Muthuri et al. (2014)

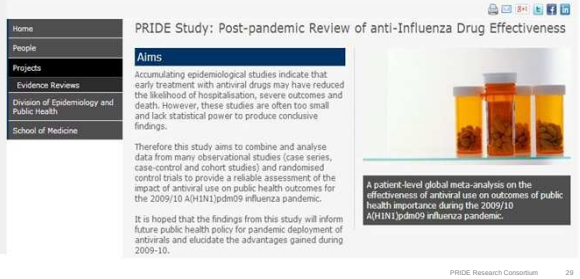
Read the published paper and commentary on: http://www.thelancet.com/journals/lanres/onlinefirst


THE LANCET Respiratory Medicine

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

For more information

Google Search: "Nottingham PRIDE study"



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