Department of Health

The Use of antivirals in an Influenza Pandemic

Scientific Evidence Base Review

May 2014

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***Conflicts of interest:** *J.S. Nguyen-Van-Tam has served on speaker bureaus for, served as a consultant to, and received grants and support for travel from F.Hoffmann-La Roche and GSK, but all personal remuneration ceased in September 2010. He now provides limited free advice to both companies on an ad-hoc basis, claiming reimbursement of travel in accordance with ABPI guidelines when appropriate. No other authors declare personal specific conflicts. The work performed for this review builds upon research work initially funded by F. Hoffman-La Roche; for that initial work the funder was: not allowed to formulate, contribute to, see or approve the protocol; not allowed to access any data; not allowed to analyse data; not allowed to see or comment on the results in advance of peer-review publication; not allowed to see, contribute to or approve manuscripts and reports arising. For the work of this review, funding from F.Hoffmann-La Roche was not used to support any aspect of the work or the salaries of research staff so involved.*

Acknowledgements

This report is an update to and supplement to the original review completed in March 2011 and which appears at

http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_125328.pdf (last accessed 05 March 2013).

This update was peer reviewed by the Scientific Pandemic Influenza Advisory Committee, March 2013

Executive summary

This review updates and supplements the previous review of NAI effectiveness completed in March 2013 and considers published evidence from the influenza A(H1N1)pdm09 pandemic period, which was indexed to PubMed and other databases on or before 17th March 2013.

Data availability is limited to patients hospitalised with A(H1N1)pdm09 and almost all data relate to patients with laboratory confirmed A(H1N1)pdm09 infection. 107 published studies were meta-analysed, involving over 46,000 patients treated with NAIs.

New data emanate from observational studies, which are of weaker quality than randomised trials.

Early treatment with NAIs compared with late treatment significantly reduced mortality in hospitalised patients by 62%. This result is likely confounded (overestimated) by treatment propensity.

Early treatment versus none significantly reduced mortality in hospitalised patients by 65%. Confounding by treatment propensity is most likely to have resulted in an underestimate of protective effect.

Early treatment versus late significantly reduced the likelihood of severe outcome in hospitalised patients by 53% but overall NAI treatment versus none almost doubled the risk of severe outcome. These apparently conflicting findings are most likely explained by the use of NAI treatment late on in unsalvageable, severely ill patients. A similar finding was made for pneumonia.

Overall the data suggest that early treatment with NAIs produced public benefits in mortality and severe outcome in hospitalised patients

The findings offer retrospective endorsement of the UK's use of NAIs during the 2009-10 pandemic and increase the weight of evidence in favour of stockpiling for a future pandemic.

Background

Neuraminidase inhibitors (NAIs) are widely regarded as the only class of influenza-specific antiviral drugs that are suitable for potential deployment during an influenza pandemic. Two drugs, oseltamivir (Tamiflu®; F. Hoffmann-La Roche) and zanamivir (Relenza®; GlaxoSmithKline plc.) were first licensed in 1999 and at present remain the only two licensed products available in the United Kingdom (UK), although newer compounds from the same drug class (peramivir; BioCryst Pharmaceuticals Inc., and laninamivir; Daiichi Sankyo Co. Ltd.) have very recently been licensed in parts of the Far East. The initial licensure of both zanamivir then oseltamivir was based on proof of a reduction in symptom duration and/or severity in healthy patients.

Subsequently, the worldwide use of NAIs for seasonal influenza has been generally low and geographically patchy, partially explained by scepticism about the value of modest symptom reduction (especially in countries where healthcare is government-funded), partially by uncertainty over the effect on more meaningful public health outcomes such as complications, hospitalisations, and mortality; and partly related to controversies about the robustness of the evidence base in general. A notable exception is Japan, where NAIs have been widely prescribed since launch, especially to treat symptomatic children. In the UK use of NAIs for seasonal influenza in the National Health Service has been tightly constrained by guidance from the National Institute for Clinical Excellence (NICE) which effectively limits treatment usage to at-risk patients and post-exposure prophylaxis (PEP) to those at-risk but unvaccinated. Further problems in primary care in the UK relate to consistent messaging of patients over several years to avoid seeking help for respiratory virus infections (thus the message is well established and precludes access to antiviral drugs), and troublesome although generally mild adverse effects of oseltamivir (nausea) in some patients.

The evidence base leading to licensure of NAIs was derived entirely from the study of seasonal influenza, which importantly may not always be generalisable to a novel pandemic virus, for example a future severe pandemic arising from influenza A(H5N1). However, with hindsight, it has been recognised that the 2009 A(H1N1) pandemic virus was of similar lethality to seasonal influenza, albeit in younger age groups; thus the generalisability argument is not entirely defunct. Pandemic policy makers view NAIs in terms of their deployment to reduce the public health impact of a future pandemic and therefore need evidence most about the effects of NAIs on public health outcomes, where paradoxically this has always been weakest. We conduct an initial rapid review for the Department of Health England in March 2011, concluding broadly that:

- NAIs used to treat clinically suspected influenza reduced symptom duration and return to normal activity by modest amounts, typically 0.5 to 1.5 days.
- That the magnitude of this effect was strongly dependent on both diagnostic certainty (accuracy of clinical diagnosis) and time between symptom onset and initiation of therapy.
- NAIs used to treat clinically suspected influenza reduce subsequent antibiotics prescribing (for secondary complications) by 25-45%.
- Data on the effectiveness of NAIs in reducing other complications were based entirely on weaker observational data but nevertheless showed consistently protective, but highly heterogeneous effects in reducing complications such as otitis media (in children), pneumonia, hospitalization and death. These data did not allow robust conclusions to be drawn but did not provide evidence of 'no effect' either.
- NAIs were highly effective when used for long-term (seasonal prophylaxis) and for post-exposure prophylaxis in household settings.

At the time of our initial review, we noted that most of our data emanated from studies of seasonal influenza prior to 2009. Due to the timing of the first review, very limited quantities of data were yet available from the 2009-10 pandemic period; but, so far, these suggested

advantages of early versus late treatment albeit based on weaker observational data. We predicted that the quantity of data available would increase very substantially in the next 1-2 years but that its quality was unlikely to improve as randomized studies would not have been possible during the pandemic.

Prescribing data from seven countries: Australia, Canada, France, Germany, Japan, UK, and USA estimate that 18.3 million individuals worldwide received oseltamivir between 1 May 2009 and 31 December 2009 [1]. International policies for NAI use during the pandemic varied from no use, through targeted use in at-risk patients (most countries), to treatment of all with clinical illness (UK). The vast majority of NAI use worldwide was in the form of oseltamivir, for example comprising 97.5% of NAIs used in the USA [2].

Accordingly we have conducted a systematic review and meta-analysis of NAI effectiveness during the 2009-10 pandemic, drawing on all publicly available global medical literature. We have targeted outcomes of public health importance (mortality; ICU admission; pneumonia) and patients hospitalized with pandemic influenza A(H1N1)pdm09 simply because insufficient published data are available on community patients. However our search revealed some data on pre-hospital use of NAIs in patients subsequently hospitalised; these were analysed separately and are included in the results. An earlier version of this work appeared in the Journal of Infectious Diseases in 2012 (http://jid.oxfordjournals.org/content/207/4/553.full.pdf+html); however the work has been further updated for the Department of Health, England with the incorporation of additional published data and complete re-analysis.

Methods

Eligibility criteria and assessment

Types of studies: We included all comparative epidemiological studies (case series, case-control and cohort studies) and randomized controlled trials conducted during the time period between 1st March 2009 (Mexico), or 1st April 2009 (rest of the world) until the WHO declaration of the end of the pandemic (10th August, 2010); assessing the association between NAI treatment and clinical outcomes. Studies with fewer than 10 participants were excluded.

Types of participants: Subjects of all ages hospitalized with a clinical or laboratory diagnosis of A(H1N1)pdm09.

Types of interventions: Treatment with a neuraminidase inhibitor (oseltamivir, zanamivir and peramivir [3]) administered via any route for A(H1N1)pdm09. Articles reporting combined results with other influenza virus types, subtypes and strains were excluded.

Types of outcome measures: Mortality, admission to critical care, and A(H1N1)pdm09 influenza- related pneumonia.

Search strategy

We searched Medline, EmBase, CINAHL, CAB Abstracts, ISI Web of Science, PubMed UK, PubMed central, Scopus, WHO regional indexes, LILAC and J-STAGE (**to 17 Jan 2013**), imposing no language restrictions. Further studies were also identified from scanning reference lists of identified studies and through contact with content experts (via JVT).

We used 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 i.e. antiviral drugs (including “neuraminidase inhibitors” OR “oseltamivir” OR “zanamivir” OR “peramivir”) AND clinical outcome measures (including “pneumonia”, “critical or intensive care”, “mortality”). Our detailed search strategy is included in Supplementary Table 1.

Screening, data extraction and quality assessment

Titles, abstracts and full texts of identified studies were screened independently by two reviewers (SM, SV) with differences being resolved through discussion with a third review (PM). Data of the included studies were independently extracted by two investigators (SM and SV) using a previously piloted data extraction form, and scored for methodological quality using the Newcastle-Ottawa Quality Assessment Scale (NOS)[4]. This scale awards a maximum score of 9 points to each included study based on representativeness of the cohort, adjustment for confounders and assessment of the outcome/ exposure. Where necessary, further data were sought from corresponding authors of included studies. Differences in quality assessment were resolved by referral to a third investigator (PM).

Data analysis

Results from individual studies were either extracted directly as odds ratios, with 95% CI or standard errors, or as tabulated data, from which odds ratios were estimated based on adjustment for the greatest number of covariates possible in each analysis. The data were pooled using random effect meta-analysis. Separate analyses were performed for the following three treatment exposures: NAI treatment *versus* none; early NAI treatment (within 2 days of symptom onset) *versus* late; and early NAI treatment *versus* none. Heterogeneity between studies was assessed using the I^2 statistic[5], and where moderate (I^2>50%), subgroup analyses were conducted to explore the effects of age; ascertainment of A(H1N1)pdm09 diagnosis; special health states, e.g. pregnancy, ICU cases, pneumonia; and study quality (NOS >6 *vs.* ≤6). Publication bias was determined using funnel plots and the Egger's test [6], and analyses conducted using Stata™ v11.2 (Statacorp Inc.).

Protocol and registration

We adhered to the recommendations for Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [7], and the protocol is published in the National Institute for Health Research international prospective register of systematic reviews (PROSPERO), registration number: CRD42011001273) [8].

Results

Study selection and characteristics

9625 records were identified from the electronic searches, of which 1847 titles were potentially relevant and their abstracts screened for relevance. After an assessment of 302 full text records, 134 articles, (supplementary table S2) were eligible. Of the 134 articles, 64 assessed mortality, 73 assessed severe outcome (defined as critical care admission or death) and 16 assessed pneumonia associated with A(H1N1)pdm09 infection (supplementary table 2). 27 of these articles could not be included in the meta-analyses (specific reasons for exclusions are provided in Supplementary Table 3). These include 15 studies which were likely to have been included as part of a national surveillance dataset or larger study within the overall meta-analysis.

Characteristics of the 107 studies eligible for meta-analyses are summarised in Table 1. Overall, 91% of studies (n=97) reported exclusively laboratory confirmed H1N1 diagnoses (i.e. defined as positive by specific PCR for pandemic 2009 influenza A[H1N1]) and/ or cases classified as probable (defined as positive by PCR for influenza A but non typeable for human subtypes seasonal H1 or H3)) whereas 7% articles (n=8) studied hospitalized patients with confirmed, probable, or suspected A(H1N1)pdm09 infection.

A total of 52 of 107 studies (49%) included in the meta-analyses reported treatment with oseltamivir only whereas 27(25%) reported treatment with NAI only. Overall, 46,086 patients were treated with any NAI, 73 of whom were treated with peramivir either alone or as dual therapy with oseltamivir. 11 of the 90 included studies also reported combined use of NAI and non-NAI therapies in some patients (n=147).

Figure 1: Summary of study selection process

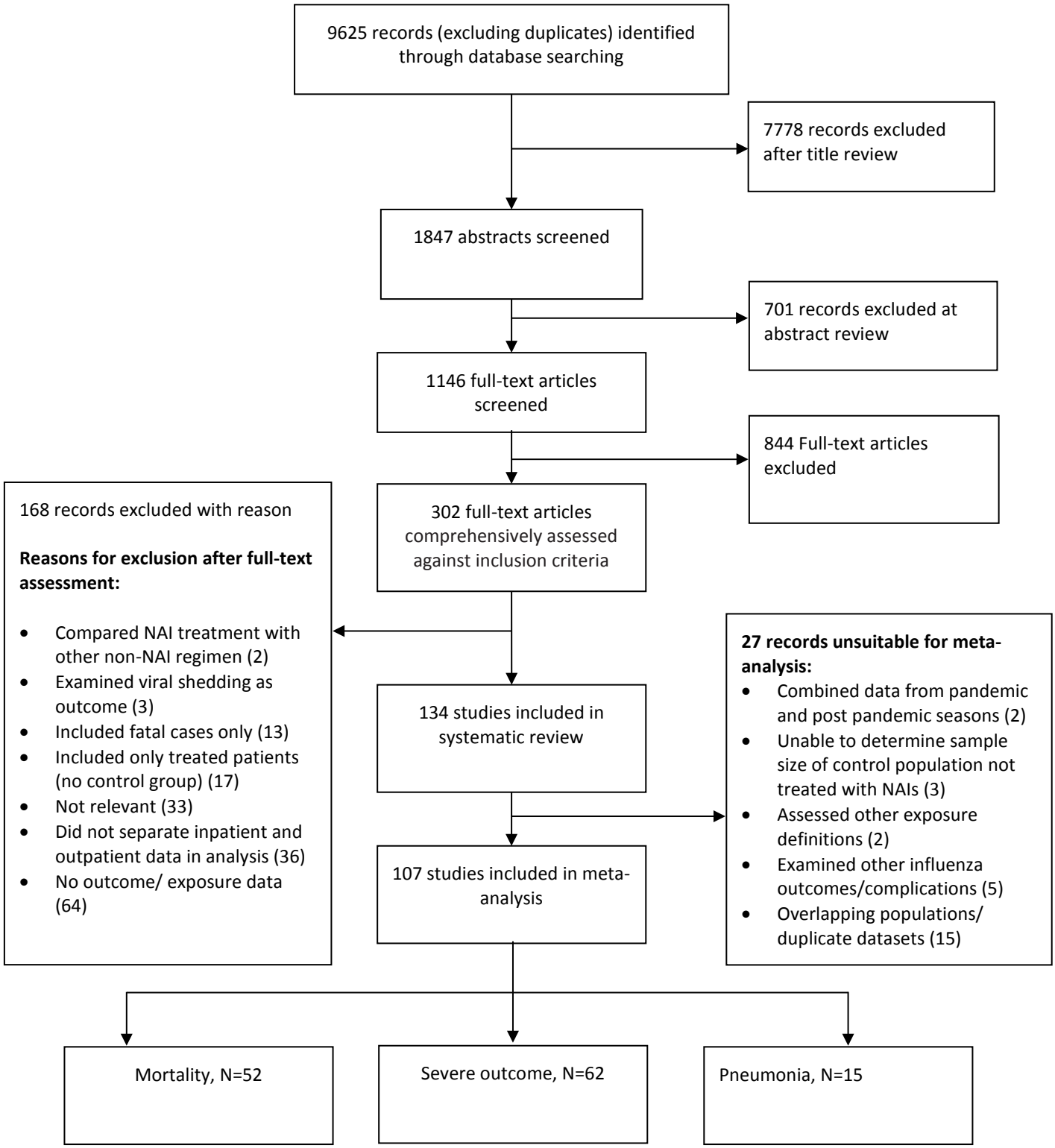


Table 1: Summary of 107 studies included in the meta-analysis by outcome measure†

Outcome measure:[a]	Mortality	Severe outcome[b]	Pneumonia
Number of studies	52	62	16
Total sample size (persons)	23,161	43,218	4,050
Number of male cases[c]	11,177	22,040	1,983
Age range (years)	<1 - 93	<1-91	<1 - 93
Population groups (no. of studies)			
Mixed age groups	24	21	7
Adults	9	7	3
Children	7	17	3
Pregnant women	5	7	3
Other	7	10	-
Regions (no. of studies)			
North America	13	20	3
Latin America	10	4	2
Europe and Australia/ New Zealand	13	23	4
Asia - Pacific	14	15	7
Others	2	-	-
A(H1N1)pdm09 diagnosis (no of studies)			
Laboratory confirmed	46	58	14
Laboratory confirmed or clinically diagnosed cases	5	4	1
Confirmed cases but method of confirmation not stated	1	-	1
Number of patients treated with any NAI	17,830	33,619	3,370
Antiviral agents used (no. of studies)[d]			
Oseltamivir only	25	30	10
NAIs only	9	12	14
NAI and non-NAI antiviral[e]	7	6	-
NAI drug name not specified	11	14	1
Exposure comparison (no. of studies)[f]			
NAI *vs.* none	30	37	8
NAI within ≤2 days (early) *vs*. > 2 days after symptom onset (late)	32	36	12
NAI within ≤2 days of symptom onset *vs.* none	13	17	5
NAI within ≤2 days (early) *vs*. > 2 days after symptom onset (late)/ no treatment	-	2	-
NAI before admission vs. no pre-admission NAI	2	3	-
Number of studies adjusting for potential confounders (%)	9 (17)	14 (23)	2 (13)
Median NOS score (range)	6 (4-9)	6 (4-9)	6 (3-8)

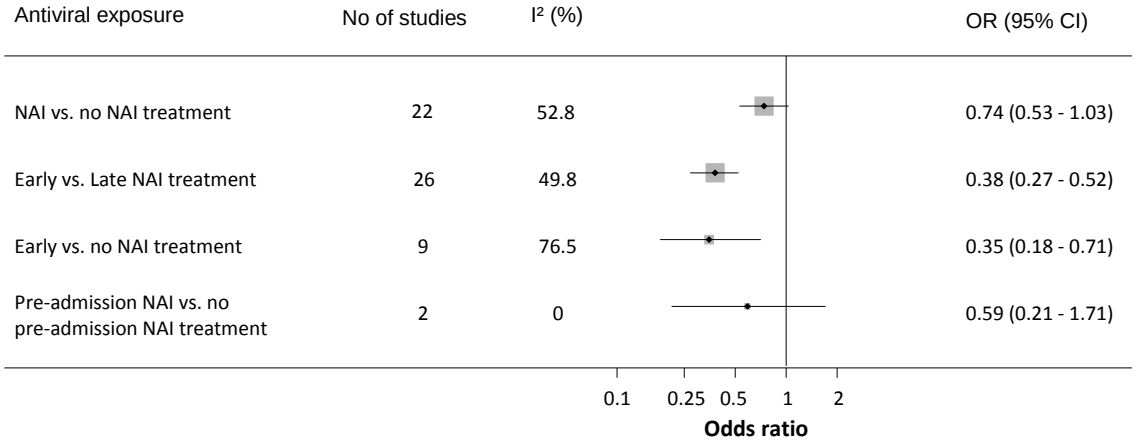
[a] Some articles examined multiple outcomes
[b] Critical care admission or death
[c] Gender split unknown in a small number of studies: mortality, n=3; severe outcome, n=2; pneumonia, n=0
[d] Overall, 9 studies provided information on combined oseltamivir and peramivir use in 73 patients (see supplementary Table S2)
[e] Overall, 11 studies reported combined use of NAI and non-NAI (rimantadine, amantadine or ribavirin) therapy, n= 147 patients (see supplementary Table S2)
[f] Some articles examined multiple exposure comparisons

Meta-analysis findings

1. Mortality

Sixty-four studies presented data on the association between NAI treatment and mortality. Twelve studies were unsuitable for meta-analyses and were excluded (Tables S2 and S3). Analyses of the remaining 52 are summarised in Figure 2 and Table 2. The pooled analysis of 22 studies comparing NAI treatment (at any time) versus none revealed a non-significant reduction in risk of mortality (OR, 0.74 [95% CI, 0.53 – 1.03]), with moderate statistical heterogeneity (I^2, 53%) and no evidence of publication bias (Egger's test, P = 0.877). Additionally, separate meta-analysis of two studies examining pre-admission NAI treatment versus no pre-admission NAI in subsequently hospitalised patients did not find a statistically significant reduction in mortality (OR, 0.59 [95% CI, 0.21 – 1.71]) (Table 2).

Figure 2: Summary of pooled analyses from studies examining mortality



Separate meta-analyses showed that early NAI treatment versus late (26 studies) was associated with a significant reduction in mortality (OR, 0.38 [95% CI, 0.27 – 0.52]; I^2, 50%), although there was evidence of asymmetry in tests for publication bias (Egger's test, P = 0.004). Pooled analyses for early NAI therapy compared with no treatment (9 studies) also found a significant reduction in mortality (OR=0.35, 95% CI: 0.18 – 0.71, I^2 = 77%; Egger's test, P = 0.142). The high level of heterogeneity in this meta-analysis was partly attributable to the heterogeneous populations. Our sub-group analysis based on sub-populations found no evidence of heterogeneity for studies in children or pregnant women, but high heterogeneity in ICU-based studies (Table 2).

Table 2: Summary of results (random effects model) including subgroup analyses for mortality

Hospitalised patients (died vs. survived)	No of studies included in analysis	Pooled OR (95%CIs)	I^2, %	References
a) NAI vs. no NAI treatment (overall)	22	0.74 (0.53 - 1.03)	52.8	[9-30]
NAI vs. no NAI treatment (unadjusted studies)	19	0.78 (0.56 - 1.10)	49.5	[10-17, 19-27, 29, 30]
NAI vs. no NAI treatment (adjusted studies)	3	0.62 (0.1 - 3.9)	69.7	[9, 18, 28]
A(H1N1)pdm09 diagnosis				
Laboratory confirmed cases	19	0.76 (0.55 - 1.06)	51.6	[10, 11, 13-17, 19-30]

	Laboratory confirmed or clinically diagnosed	3	0.67 (0.08 - 5.96)	69.4	[9, 12, 18]
	Mixed age groups	13	0.81 (0.54 - 1.19)	63.9	[9, 11, 14-16, 18, 22, 25, 27, 28, 30, 31]
	Adults	8	0.49 (0.24 - 1.03)	60.7	[11, 12, 17, 20, 24, 30, 32, 33]
	Children	7	0.71 (0.39 - 1.31)	0	[11, 13, 19, 26, 30, 34, 35]
	Pregnant women	2	0.25 (0.05 - 1.10)	21.3	[10, 29]
	Pneumonia patients	6	0.96 (0.22 - 4.19)	77.2	[17, 19, 23, 30, 31, 36]
	ICU patients	10	0.73 (0.41 - 1.29)	72.3	[9, 12, 13, 15, 21, 24, 26, 34, 37, 38]
	Others				[24]
b)	**Pre-admission NAI treatment vs. no pre-admission NAI treatment**	2	0.59 (0.21 -1.71)	0	[14, 39]
c)	**Early Treatment (ET) vs. Late Treatment (LT) (overall)**	26	0.38 (0.27 - 0.52)	49.8	[11, 14, 15, 21, 25, 30, 32, 40-58]
	ET vs. LT (unadjusted studies)	24	0.35 (0.25 - 0.50)	51	[11, 14, 15, 21, 25, 30, 32, 40-47, 49-54, 56-58]
	ET vs. LT (adjusted studies)	2	0.61 (0.31 - 1.19)	26.1	[55, 58]
	A(H1N1)pdm09 diagnosis				
	Laboratory confirmed cases	24	0.37 (0.26 - 0.52)	51	[11, 14, 15, 21, 25, 30, 32, 40-46, 48-55, 57, 58]
	Laboratory confirmed or clinically diagnosed cases	2	0.33 (0.03 - 3.73)	60.7	[47, 56]
	Mixed age groups	14	0.51 (0.36 - 0.72)	49.6	[11, 14, 15, 25, 30, 32, 41, 42, 44, 46-48, 55, 58]
	Adults	10	0.41 (0.28 - 0.59)	0	[11, 30, 32, 40, 43, 49, 50, 53, 54, 59]
	Children	6	0.41 (0.24 - 0.72)	0	[11, 30, 35, 51, 52, 57]
	Pregnant women	4	0.09 (0.04 - 0.21)	0	[21, 45, 56, 60]
	ICU patients	11	0.33 (0.2 - 0.53)	60.2	[15, 21, 37, 38, 40, 43, 47, 49, 52, 58, 60]
	Pneumonia patients	2	0.33 (0.12 - 0.91)	37.6	[30, 36]
	Others				[46, 61]
d)	**ET vs. No treatment (overall)**	9	0.35 (0.18 - 0.71)	76.5	[11, 14, 15, 21, 25, 30, 32, 45, 55]
	Mixed age groups	6	0.43 (0.23 - 0.80)	69.1	[11, 14, 15, 25, 30, 55]
	Adults	5	0.22 (0.07 - 0.66)	72.6	[11, 21, 30, 32, 45]
	Children	3	0.25 (0.06 - 1.09)	0	[11, 30, 35]
	Pregnant women	2	0.07 (0.02 - 0.20)	0	[21, 45]
	ICU patients	4	0.23 (0.07 - 0.76)	91.6	[15, 21, 37, 38]

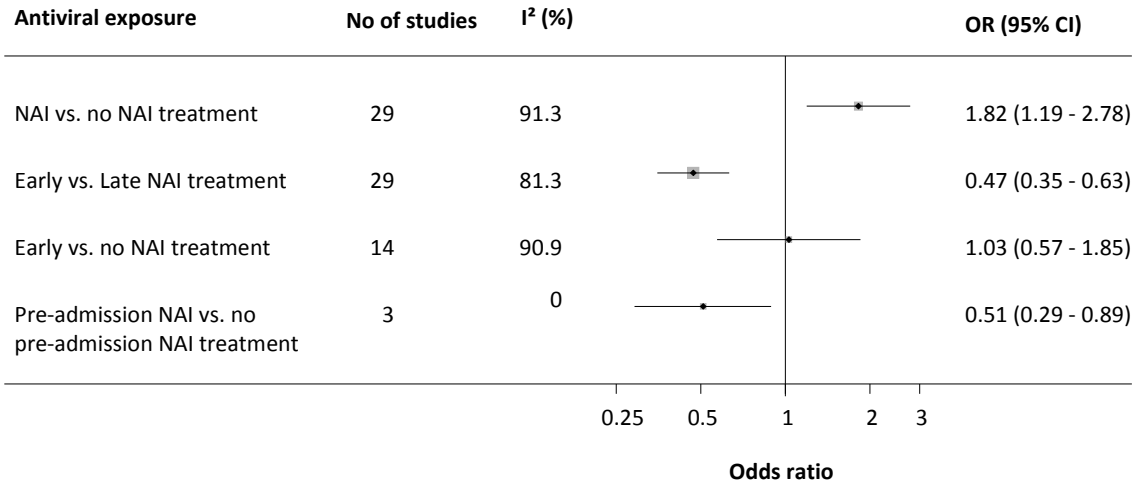
2. Severe outcome (critical care admission or death)

Using a composite variable for 'severe outcome' based on receiving critical care or death, 73 studies reported this outcome of which 62 were suitable for inclusion in meta-analyses; these are summarised in Figure 3 and Table 3.

For NAI treatment versus none (29 studies), a statistically significant association was observed between severe outcome and NAI therapy (OR, 1.82 [95% CI, 1.19 – 2.78]; I^2, 91%; Egger's test, P = 0.146). We pooled three studies providing data on pre-admission NAI use in hospitalised patients and found a statistically significant reduction in severe outcomes compared with no pre-admission NAI (OR, 0.51 [95% CI, 0.29 – 0.89]; I^2, 0%; Egger's test, P = 0.46).

Early NAI treatment compared with late (29 studies) also significantly reduced the likelihood of severe outcome (OR, 0.47 [95% CI, 0.35 – 0.63]; I^2, 81%; Egger's test, P = 0.071); however, early NAI treatment versus none (14 studies) revealed no obvious association with the likelihood of severe outcome (OR, 1.03 [95% CI, 0.57 – 1.85]; I^2, 91%; Egger's test, P = 0.047).

Figure 3: Summary of pooled analyses from studies examining severe outcome



Two studies which assessed early NAI treatment versus late or none (combined), also revealed no significant association with severe outcomes (OR, 0.27 [95% CI, 0.04 – 2.00]; I^2, 23%; Egger's test, not calculable), (Table 3). Findings from all these analyses were subject to high levels of heterogeneity (I^2>75%), which were neither explained by subgroup analyses (Table 3) nor attributable to methodological quality (data not shown).

Table 3: Summary of results (random effects model) including subgroup analyses for severe outcome

ICU and/ died vs. hospitalised and survived	No of studies included in analysis	Pooled OR (95%CIs)	I^2, %	References
a) NAI vs. no NAI treatment (overall)	29	1.82 (1.19 - 2.78)	91.3	[10, 14, 22, 62-87]
NAI vs. no NAI treatment (unadjusted studies)	28	1.97 (1.39 - 2.78)	83.3	[10, 14, 22, 62-84, 86, 87]
Mixed age groups	14	1.77 (1.14 - 2.76)	88.3	[10, 14, 22, 30, 62, 63, 65, 66, 70, 76, 78, 81, 82, 88]
Adults	5	1.26 (0.64 - 2.46)	59.5	[30, 74, 79, 88, 89]
Children	17	2.96 (1.29 - 6.77)	87.7	[30, 64, 67-69, 71, 73, 75, 77, 83, 85-88, 90-92]
Pregnant women	5	2.04 (1.07 - 3.91)	25.2	[74, 80, 82, 93, 94]
Other				[77, 84]
b) Pre-admission NAI treatment (before hospital admission)	3	0.51 (0.29 - 0.89)	0	[14, 39, 95]
c) Early Treatment vs. Late Treatment (overall)	29	0.47 (0.35 - 0.63)	81.3	[10, 14, 40, 41, 45, 46, 48, 50, 53, 55-57, 66, 67, 70, 79-83, 87, 96-103]
ET vs. LT (unadjusted studies)	23	0.52 (0.36 - 0.74)	81.1	[10, 14, 40, 41, 45, 46, 50, 53, 56, 57, 66, 67, 79, 80, 82, 83, 87, 97-102]
ET vs. LT (adjusted	6	0.35 (0.21 - 0.59)	72.9	[48, 55, 70, 81, 96, 103]

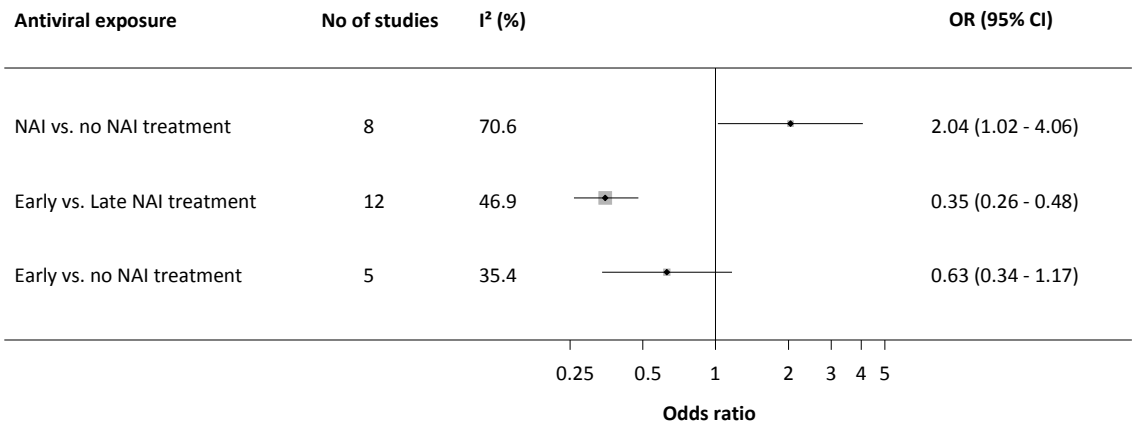
	studies)				
	Mixed age groups	11	0.44 (0.31 - 0.62)	85.6	[10, 14, 41, 48, 55, 66, 70, 81, 82, 96, 101]
	Adults	10	0.62 (0.38 - 1.03)	65.4	[30, 40, 50, 53, 79, 99, 100, 104-106]
	Children	10	1.06 (0.66 - 1.71)	57.2	[30, 57, 67, 83, 87, 92, 98, 102, 103, 107]
	Pregnant women	6	0.29 (0.09 - 0.94)	85.5	[45, 56, 80, 82, 94, 97]
	Pneumonia patients	3	0.51 (0.11 - 2.36)	83	[30, 89, 96]
	Other (ARDs, diabetics, cancer, HIV)				[46, 84, 99, 105]
d)	**ET vs. No treatment (overall)**	14	1.03 (0.57 - 1.85)	90.9	[10, 14, 45, 55, 66, 68, 70, 79-83, 87, 102]
	Mixed age groups	5	1.58 (0.7 - 3.58)	95.6	[14, 30, 66, 70, 82]
	Adults	2	1.01 (0.18 - 5.74)	82.9	[30, 79]
	Children	5	3.68 (1.03 - 13.15)	59.9	[30, 68, 83, 87, 92]
	Pregnant women	4	1.09 (0.21 - 5.64)	85.5	[45, 80, 82, 94]
	Pneumonia patients	1	3.77 (1.78 - 7.97)	-	[30]
	Diabetics				[84]
e)	**ET vs. Late ET/ no NAI**	2	0.27 (0.04 - 2.00)	23	[16, 108]

3. Pneumonia associated with A(H1N1)pdm09 infection

Sixteen studies reported data on hospitalised patients with A(H1N1)pdm09 infection and documented the presence or absence of pneumonia . Most reported radiographic pneumonia, whereas three did not provide information on ascertainment; the latter were still included in the meta-analysis, but apportioned lower scores during quality assessment (Table 4).

The meta-analysis based on 15 articles is summarised in Figure 4. The pooled analysis comparing NAI treatment versus none (8 studies) revealed a significantly increased likelihood of pneumonia associated with NAI treatment (OR, 2.04 [95% CI, 1.02 – 4.06]; I^2, 71%; Egger's test, P = 0.686).

Figure 4: Summary of pooled analyses from studies examining A(H1N1)pdm09-associated pneumonia



However, early versus late treatment (12 studies) significantly reduced the likelihood of pneumonia (OR, 0.35 [95% CI, 0.26 – 0.48]; I^2, 47%; Egger's test, P = 0.719). A comparison between early treatment and none (5 studies) revealed no clear association with the likelihood of pneumonia (OR, 0.63 [95% CI, 0.34 – 1.17]; I^2, 35%; Egger's test, P = 0.626). One pneumonia study (92) was unsuitable for inclusion in any of the pooled analyses because treatment exposure was measured as early versus late or none (combined). This

study showed early oseltamivir treatment to be associated with a significantly increased likelihood of pneumonia (unadjusted OR, 6.67 [95% CI, 2.61–17.06]; P< 0.001).

Table 4: Summary of results (random effects model) including subgroup analyses for pneumonia associated with A(H1N1)pdm09 infection

Hospitalised with pneumonia vs. hospitalized without pneumonia	No of studies included in analysis	Pooled OR (95%CIs)	I^2, %	References
a) NAI treatment vs. none (overall)	8	2.04 (1.02 - 4.06)	70.6	[36, 63, 71, 73, 109-112]
NAI vs. no NAI treatment (unadjusted studies)	8	2.04 (1.02 - 4.06)	70.6	[36, 63, 71, 73, 109-112]
A(H1N1)pdm09 diagnosis				
Laboratory confirmation	7	2.31 (1.15 - 4.63)	72	[36, 63, 71, 73, 109, 110, 112]
Not specified	1	0.26 (0.02 - 4.06)	-	[111]
Pneumonia confirmation				
Chest radiographs	6	2.19 (1.05 - 4.57)	75.9	[36, 63, 71, 73, 109, 112]
Not specified	2	1.17 (0.07 - 20.09)	70.6	[110, 111]
Mixed age groups	4	1.22 (0.58 - 2.56)	24.5	[36, 63, 109, 110]
Adults	2	1.1 (0.12 - 10.16)	66.2	[111, 112]
Children	2	3.99 (2.41 - 6.60)	0	[71, 73]
Pregnant women	1	0.26 (0.02 - 3.04)	-	[111]
b) Early Treatment vs. Late Treatment (overall)	11	0.36 (0.26 - 0.49)	49.4	[36, 50, 56, 109-116]
ET vs. LT (unadjusted studies)	10	0.37 (0.26 - 0.55)	53.3	[36, 50, 56, 109-111, 113-116]
ET vs. LT (adjusted studies)	1	0.29 (0.19 - 0.45)	-	[112]
A(H1N1)pdm09 diagnosis				
Laboratory confirmation	9	0.38 (0.27 - 0.52)	55.8	[36, 50, 109, 110, 112-116]
Laboratory and/or clinical confirmation	1	0.19 (0.02 - 1.78)	-	[56]
Not specified	1	0.12 (0.02 - 0.66)	-	[111]
Pneumonia confirmation				
Chest radiographs	9	0.36 (0.26 - 0.50)	53.9	[36, 50, 56, 109, 112-116]
Not specified	2	0.24 (0.06 - 1.05)	38.3	[110, 111]
Mixed age groups	4	0.34 (0.17 - 0.70)	72.7	[36, 109, 110, 113]
Adults	7	0.35 (0.25 - 0.47)	14.4	[50, 56, 111, 112, 114, 116, 117]
Children	1	0.81 (0.25 - 2.63)	-	[115]
Pregnant women	3	0.13 (0.04 - 0.45)	0	[56, 111, 117]
ICU patients	1	0.06 (0.00 - 1.85)	-	[117]
c) ET vs. No treatment (overall)	5	0.63 (0.34 - 1.17)	35.4	[36, 109-112]
Mixed age groups	3	0.58 (0.28 - 1.20)	38.4	[36, 109, 110]
Adults	2	0.62 (0.11 - 3.69)	53.9	[111, 112]
Children	0	-	-	-
Pregnant women	1	0.18 (0.02 - 1.81)	-	[111]
d) ET vs. Late ET/ no NAI	1	6.67 (2.61–17.06)		[100]

Discussion

Mortality

Overall, our meta-analyses suggest that NAI treatment of A(H1N1)pdm09 in hospitalised cases reduced mortality. Although comparing treatment (at any time) with none, revealed a 26% non-significant reduction in mortality, when comparing early versus late treatment we observed a significant 62% reduction in mortality albeit with significant publication bias. Finally, we noted a significant 65% reduction in mortality when comparing early treatment with none, along with high levels of heterogeneity. This suggests that early initiation of treatment following symptom onset is key for reducing mortality. Of note, we did not detect a significant reduction in mortality associated with pre-admission NAI treatment in subsequently hospitalised patients; very few studies were available to address this question and the absence of data from cases which remained in the community does not allow us to draw conclusions about whether community NAI treatment prevented hospital admission.

Severe outcome

Alongside mortality, critical care admission due to influenza is an undesirable outcome of public health importance, worth preventing, not least because ICU beds are in short supply in most healthcare systems including the NHS and especially prone to pandemic 'surge pressure' as seen in 2009-10. Many studies described 'severe outcome' using a common definition of critical care admission or mortality, reflecting the occurrence of severe but sometimes survivable A(H1N1)pdm09 infection. It should however be appreciated that some patients with severe disease might have failed to access critical care due limited availability, which may have introduced bias. Notwithstanding we observed that NAI treatment (at any time) was associated with a 82% significant **increase** in the likelihood of severe outcome compared with none. In contrast, a 53% significant reduction in the likelihood of severe outcome was seen comparing early versus late NAI treatment, but no significant reduction with early NAI treatment versus none. But, importantly, our data also suggest that pre-admission NAIs in patients subsequently hospitalised significantly reduced the likelihood of severe outcome by 49% albeit based on only three studies.

Pneumonia

Our findings on pneumonia may have been influenced by differential ascertainment and classification of pneumonia. We therefore gave a lower quality score to studies in which information pneumonia ascertainment was not available and performed a sub-group analysis to take this into account (Table 2). We found the likelihood of pneumonia to be significantly **increased** (doubled) comparing NAI treatment with none, whereas early versus late NAI treatment significantly reduced the likelihood of pneumonia by 65%; and we did not find a statistically significant reduction when comparing early treatment versus none.

Interpretation

Our findings are consistent with earlier data on seasonal influenza, showing that the magnitude of symptomatic benefit due to oseltamivir treatment is increased by early instigation of therapy [118, 119]. We believe the three different comparisons in our analyses: treatment at any time versus none; early versus late; and early versus none) help reveal confounding related to treatment propensity but at the same time offer important clinical coherency. We hypothesise that patients with mild disease, more likely to survive and less likely to develop pneumonia were also less likely to be offered antiviral treatment in most settings during the 2009 pandemic either due to physician preference or patient care-seeking behaviour. Furthermore, we surmise that access to rapid diagnostic testing was variable across international settings and that A(H1N1)pdm09 was either not suspected and/or not confirmed in many patients until late in their illness (or late in their admission), by which time they were either recovering or had deteriorated. This may explain the apparent increase in severe outcomes associated with NAI use at any time. It is most likely that those with mild illness who were recovering were left untreated with NAIs, and that cases initially mild but later severe were treated late as a final attempt at disease reversal. Indeed,

unpublished data from the UK FLU-CIN study [120] reveal that among patients with a length of stay ≤4 days (as a proxy for mild to moderate disease) the proportions of patients receiving early, late or no NAI treatment were 36%, 27% and 37% respectively, compared with 22% 41% and 36% respectively in patients with length of stay >4 days (Chi^2-trend, P = 0.008; data available on request) [121]. Thus, comparisons of early treatment versus late may have overestimated treatment effectiveness, whereas comparisons of treatment versus none and early treatment versus none may have underestimated effectiveness. In that context, our findings on mortality (early treatment versus none and any treatment versus none), suggest potentially important public health effects because untreated patients were likely to have had milder disease; and our finding of an association between NAI treatment and increased severe outcome appears explainable.

Limitations

We observed a high degree of heterogeneity among studies examining severe outcome, and although we performed subgroup analyses and stratified by methodological quality, this remained largely unexplained. For some of the outcomes we found evidence of publication bias which may have overestimated the observed pooled effect. All the studies included in the systematic review were observational designs. This is, in itself, a limitation that cannot be overcome; but it can be argued that such observational data provide a more realistic estimate of the field effectiveness of NAIs in a pandemic situation. Most studies did not provide adjusted risk estimates; but even when these were available there were differences in the extent to which adjustment had been made for potential confounding. One major limitation of the current review is the inability to adjust for propensity to treatment. In the absence of random allocation to antivirals, one of the inherent biases in observational studies is the likelihood of receiving treatment. Some of the studies included in the meta-analysis are from low-resource countries and it is likely that treatment was given preferentially to the more severely ill patients, thereby underestimating the effectiveness of antiviral therapy in reducing severe outcomes. Without access to comprehensive patient-level data from every included study, we cannot adjust for treatment propensity. Lastly, a very small proportion of patients received intravenous peramivir (alone or as dual therapy) or dual therapy with oseltamivir and zanamivir. Such patients were widely dispersed between studies and excluding these would have sacrificed too much data. However, since they account for such a small proportion of cases overall, we do not believe they have introduced meaningful bias into the results.

The question of whether NAI treatment has an impact on patient outcomes in a pandemic situation can only ever be answered using observational data because of the ethical implications around randomisation to treatment during a public health emergency. The logical next step is to conduct an individual patient level meta-analysis based on obtaining raw data from observational studies around the world and re-analyzing pooled data [122]. This approach (currently underway) will allow more complete adjustment for confounders such as comorbidities, disease severity, concomitant therapies, propensity for NAI treatment and the assessment of different NAI treatment regimens.

Conclusion and implications

This systematic review and meta-analysis is, to our knowledge, the first to examine the effectiveness of NAI treatment solely during the 2009-10 pandemic, measured against clinical outcomes of likely importance to public health policy makers. It should be read in conjunction with and as a supplement to our earlier review for the Department of Health, which focused mainly on pre-pandemic data. The findings suggest that mortality was reduced among hospitalised patients through early NAI treatment, although the magnitude of benefit offered by early versus late treatment may have been overestimated by treatment propensity. Nevertheless our finding of a 65% mortality reduction in early treated versus untreated patients suggests a meaningful public health benefit, of relevance to pandemic policy makers, because it is more likely that untreated cases were less severe than vice-

versa and the true effect may therefore have been underestimated. If this is so, pandemic preparedness policies need to emphasise not only the issue of appropriate NAI stockpiling, but also practical mechanisms for ensuring easy and early access to treatment during a pandemic.

Our findings add to the evidence presented in our previous review, and offer greater confidence about the likelihood that early intervention with NAIs reduces mortality compared with late treatment or no treatment; similarly that early treatment reduces severe outcomes compared with late treatment and that pre-admission NAI treatment my be beneficial in reducing severe outcomes. The new findings offer retrospective endorsement of the UK Government's pandemic policies for stockpiling and early access to treatment. They strongly suggest that early use after admission to hospital (if not before) is critical for the maximisation of public health benefits. However they do not provide guidance on the targeting of specific patient groups versus 'treat all' policies.

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Appendices/Supplementary material
Supplementary Table S1: Search strategy using Ovid Medline
Medline (OVID) – 1996 to present

	Search terms
1.	exp Influenza A Virus, H1N1 Subtype/
2.	swine flu.mp.
3.	swine influenza.mp.
4.	(H1N1 pandemic influenza or H1N1v or pandemic influenza 2009).mp.
5.	novel influenza.mp.
6.	H1N1pdm.mp.
7.	(swine-origin influenza or swine-origin type A).tw.
8.	(nH1N1 or pH1N1 or H1N1 or AH1N1).hw.
9.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10.	oseltamivir.mp. or exp Oseltamivir/
11.	zanamivir.mp. or exp Zanamivir/
12.	exp Neuraminidase/ or neuraminidase inhibitors.mp.
13.	tamiflu.mp.
14.	relenza.mp.
15.	peramivir.mp.
16.	antiviral$.mp.
17.	treatment.mp.
18.	therapy.mp.
19.	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18
20.	9 and 19
21.	epidemi$.ti.
22.	pneumonia.mp.
23.	hospital$.mp.
24.	risk factor$.mp.
25.	incidence.mp.
26.	intensive care$.mp.
27.	critical$.mp.
28.	21 or 22 or 23 or 24 or 25 or 26 or 27
29.	9 and 28
30.	20 or 29
31.	remove duplicates from 30
32.	limit 31 to human
33.	limit 32 to yr="2009 -Current"

Supplementary Table S2: Summary of 134 studies included in systematic review (SR) and meta-analysis (MA), by outcome measure

Author, year (ref)	Outcome						Studies excluded from MA[a]
	Mortality		Severe outcome		Pneumonia		
	SR, n=64	MA, n=52	SR, n=73	MA, n=62	SR, n=16	MA, n=15	N =27
Cao et al 2009 [109]					√	√	
Louie et al 2009 [63]			√	√	√	√	
Dominguez-Cherit et al 2009 [9] [d]	√	√					
Echevarria-Zuno et al 2009 [123]	√						√
Jain et al 2009 [10] [d]	√	√	√	√			
Kwan-Gett et al 2009 [62]			√	√			
Rello et al 2009 [124]	√						√
Aquino-Esperanza et al 2010 [40]	√	√	√	√			
Bagdure et al 2010 [64][c]			√	√			
Boehringe, 2010 [65]			√	√			
CDC 2010 [117] [c]					√	√	
Chien et al 2010 [96]			√	√			
Chitnis et al 2010 [41]	√	√	√	√			
Creanga et al 2010 [125]			√				√
Dubar et al 2010 [97]			√	√			
Estenssoro et al 2010 [12]	√	√					
Farias et al 2010 [13]	√	√					
Fuhrman et al 2010 [66]			√	√			
Hernandez-Garcia et al 2010 [88]			√	√			
Jean et al 2010 [61]	√						√
Koegelenberg et al 2010 [43]	√	√					
Libster et al 2010 [67]			√	√			
Louie et al 2010 [98]			√				√
Louie et al 2010 [68]			√	√			
Mady et al 2010 [126]	√						√
Nguyen-Van-Tam et al 2010 [14][b]	√	√	√	√			
O'Riordan et al 2010 [69]			√	√			
Riquelme et al 2010 [95]			√	√			
Rodriguez et al 2010 [127]	√						√
Santa-Olalla Peralta et al 2010 [70]			√	√			
Siston et al 2010 [45][d]	√	√	√	√			
Souza et al 2010 [46]	√	√	√	√			
Stein et al 2010 [71]			√	√	√	√	
To et al 2010 [128]							√
Vasoo et al 2010 [72]			√	√			
Wada et al 2010 [47]	√	√					
Xi et al 2010 [32]	√	√					
Yang et al 2010 [16]	√	√	√	√			
Yates et al 2010 [108]			√	√			
Akinci et al 2011 [100]			√	√	√		

Author, year (ref)	Outcome						Studies excluded from MA[a]
	Mortality		Severe outcome		Pneumonia		
	SR, n=64	MA, n=52	SR, n=73	MA, n=62	SR, n=16	MA, n=15	N =27
Altmann et al 2011 [34]	√	√					
Choi et al 2011 [49] [c d]	√	√					
Choi W.I et al 2011 [17] [c d]	√	√					
Chudasama et al 2011 [101]			√	√			
Creanga et al 2011 [74]			√	√			
Ellington et al 2011 [129]	√						√
Fuhrman et al 2011 [104]			√	√			
Hasegawa et al 2011 [130]							√
Hiba et al 2011 [50]	√	√	√	√	√	√	
Ismail et al 2011 [51]	√	√					
Jeon et al 2011 [114]					√	√	
Kendirli et al 2011 [52]	√	√					
Launes et al 2011 [91]			√	√			
Louie et al 2011 [131]	√						√
Lucker et al 2011 [78]			√	√			
Maravi-Poma et al 2011 [132]							√
Meschi et al 2011 [110]					√	√	
Mickiene et al 2011 [53]	√	√	√	√			
Moral et al 2011 [107]			√	√			
Nakai et al 2011 [111]					√	√	
Oh et al 2011 [79] [c d]			√	√			
Poeppl et al 2011 [22]	√	√	√	√			
Schellongowski et al 2011 [24]	√	√					
Skarbinski et al 2011 [81] [c d]			√	√			
Thompson et al 2011 [55]	√	√	√	√			
Viasus et al 2011 [106]			√	√			
Viasus et al 2011 [89]			√	√			
Viasus et al 2011 [133]	√		√				√
Yokota et al 2011 [25]	√	√					
Yu et al 2011 [82]			√	√			
Zheng et al 2011 [92]			√	√			
Campbell et al 2011 [48]	√	√	√	√			
Custodio et al 2011 [102] [d]			√	√			
Del Rosal et al 2011 [90]			√	√			
Gonzalez-Velez et al 2011 [134]			√				√
Higuera Iglesias et al 2011 [113]					√	√	
Hsann et al 2011 [76]			√	√			
Newsome et al 2011 [21]	√	√					
Rhim et al 2011 [115]					√	√	
Louie et al 2011 [135]			√				√
Viasus et al 2011 [112]					√	√	
Rodriguez et al 2011 [59]	√	√					

Author, year (ref)	Outcome						Studies excluded from MA[a]
	Mortality		Severe outcome		Pneumonia		
	SR, n=64	MA, n=52	SR, n=73	MA, n=62	SR, n=16	MA, n=15	N =27
Riquelme et al 2011 [23]	√	√					
Riquelme et al 2011 [136]	√						√
Lee et al 2010 [44]	√	√					
Louie et al 2009 [11]	√	√					
Da Dalt et al 2011 [75]			√	√			
Randolph et al 2011 [137]			√				√
Perez-Padilla et al 2009 [31]	√	√					
Chudasama et al 2010 [138]			√				√
Chudasama et al 2010 [42]	√	√					
Chudasama et al 2010 [139]			√				√
Santa-Olalla Peralta et al 2010 [15]	√	√					
Gilca et al 2011 [39]	√	√	√	√			
Javadi et al 2011 [18]	√	√					
Kedia et al 2011 [77] [c d]			√	√			
Martin-Loeches et al 2011 [33]	√	√					
Miranda-Choque et al 2011 [19]	√	√					
Qiao et al 2011 [60]	√	√					
Yung et al 2011 [26]	√	√					
Cortes Garcia et al 2012 [84]			√	√			
Figueiro-Filho et al 2012 [56]	√	√	√	√	√	√	
Mady et al 2012 [140]	√	√					
Rhim et al 2012 [116]					√	√	
Yang et al 2012 [30]	√	√	√	√			
Low et al 2010 [99][b]			√	√			
Peters et al 2011 [105]			√	√			
Tabarsi et al 2011 [54][b]	√	√					
Blumental, S., et al., 2011 [73]			√	√	√	√	
Ozyer, S., et al., 2011 [80]			√	√			
Adlhoch et al 2012 [27]	√	√					
Bramley et al 2012 [37]	√	√					
Chen et al 2012 [83]			√	√			
Chowell et al 2012 [141]	√						√
Delgado-Rodriguez et al 2012 [142]			√				√
Dolan et al 2012 [93]			√	√			
Jain et al 2012 [36]	√	√			√	√	
Kinikar et al 2012 [57]	√	√	√	√			
Kobayashi et al 2012 [103]			√	√			
Li et al 2012 [143]	√						√
Pano-Pardo et al 2012 [94]			√	√			
Soydinc et al 2012 [29]	√	√					
Eriksson et al 2012 [d] [85]			√	√			
Gastanaduy et al 2012 [86]			√	√			

Author, year (ref)	Outcome						Studies excluded from MA[a]
	Mortality		Severe outcome		Pneumonia		
	SR, n=64	MA, n=52	SR, n=73	MA, n=62	SR, n=16	MA, n=15	N =27
Louie et al 2012 [c d] [38]	√	√					
Ko et al 2012 [87]			√	√			
Chowell et al 2012 [28]	√	√					
Moretti et al 2011 [144]	√	√					
Yen et al 2012 [c d] [35]	√	√					
Altmann et al 2012 [145]	√						√
Lee et al 2012 [146]			√				√
Lopez-Aldeguer et al 2012 [147]							√
Morris et al 2012 [148]			√				√
Takeuchi et al 2012 [149]							√

SR, systematic review; MA, meta-analysis

[a] Reasons for exclusions are outlined in supplementary Table S3

[b] authors provided additional data on NAI use

[c] provided information on combined oseltamivir and peramivir use

[d] reported combined use of NAI and non-NAI (rimantadine, amantadine or ribavirin) therapy

Supplementary Table S3: Reasons for rejection of 27 articles unsuitable for meta-analysis

1. Includes pandemic 2009-10 and post-pandemic seasons 2010-11 Altmann et al [145]	
2. Data based on post-pandemic seasons 2010-11 Rodriquez et al [136]	
3. Unable to determine sample size of control population not treated with antivirals Randolph et al 2011 [137], Morris et al 2012 [148] and Lee et al [146]	
4. Assessed other exposure definitions	
Author (year)	***Exposure assessed :***
Viasus et al 2011 [133]	Oseltamivir administration (+ 1-d increase). This study also overlaps with references [89, 106] used in the meta-analysis
Li et al [143]	Assessed early antiviral treatment as 0 to ≤3 days from onset of symptoms
5. Examined other influenza outcomes/complications	
Author (year)	***Outcome assessed:***
Hasegawa et al 2011[130]	Complications following pandemic (H1N1) 2009–associated pneumonia
To et al 2010 [128]	ARDS and/ died vs. survived without ARDS
Maravi-Poma et al 2011 [132]	Compares pregnant and non-pregnant women affected by influenza A/H1N1v and admitted to ICU. This study also overlaps with reference [59] used in meta-analysis
Lopez- Aldeguer et al 2012 [147]	Definition of severe outcomes includes: two lobules or bilateral pneumonia, oxygen saturation <90% or po2 <60mmHg, respiratory distress, sepsis, intensive care admission or death
Takeuchi et al 2012 [149]	Assessed complications: neurologic, respiratory (pneumonia, bronchiolitis/ asthma, croup, and respiratory apnoea), other (e.g. cardiac complications), or as concomitant severe bacterial infections)
6. Duplicate/ overlapping population	
Rejected article: Author (year)	***Alternate article used in meta-analysis: Author (year)***
Echevarria-Zuno et al 2009 [123]	Chowell et al 2012 [28]
Rello et al 2009 [124]	Rodriguez et al 2011 [59]
Chudasama et al 2010 [138]	Chudasama et al 2011 [101]
Chudasama et al 2010 [139]	Chudasama et al 2011 [101]
Creanga et al 2010 [125]	Siston et al 2010 [45]
Jean et al 2010 [61]	Louie et al 2009 [11]
Louie et al 2010 [98]	Siston et al 2010 [45]
Mady et al 2010 [126]	Mady et al 2012 [58]
Rodriguez et al 2010 [127]	Rodriguez et al 2011 [59]
Ellington et al 2011 [129]	Newsome et al 2011 [21]
Gonzalez-Velez et al 2011 [134]	Santa-Olalla Peralta et al 2010 [70]
Louie et al 2011 [131]	Louie et al 2009 [11]
Louie et al 2011[135]	Siston et al 2010 [45]
Delgado-Rodriguez et al [142]	Santa-Olalla Peralta et al 2010 [70]
Chowell et al 2012 [141]	Chowell et al 2012 [28]