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# Antiviral Therapy for Pandemic Influenza A (H1N1) Infection: a Meta-Analysis

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## Abstract

The influenza A (H1N1) pandemic has generated a large volume of cohort data with respect to antiviral therapy, but to date this has not been systematically reviewed. We performed a meta-analysis of all studies of laboratory-confirmed pH1N1 influenza infection in adults and children which correlated antiviral therapy with hospitalization, ICU admission or death. Early antiviral therapy (<48 hours from symptom onset) was associated with a statistically significant decrease in ICU admission and death. There was no improvement in clinical outcomes when antiviral therapy in general was compared to no antiviral therapy. The literature on therapy for pandemic H1N1 (pH1N1) consists largely of observational studies and is insufficient to draw strong conclusions about the effectiveness of antiviral therapy.

## Introduction

Currently available antiviral agents against influenza infection include inhibitors of the matrix 2 protein (adamantanes: amantadine and rimantadine) and neuraminidase inhibitors (oseltamivir and zanamivir). Neuraminidase inhibitors have emerged as the treatment of choice for a number of reasons. Adamantanes lack activity against all strains of influenza B, the 2009 pandemic influenza A (H1N1) (pH1N1), and current seasonal H3N2 influenza strains, whereas neuraminidase inhibitors are active against the great majority of currently circulating strains (1). Several randomized controlled trials have documented reduction in duration of illness, in the severity of illness and in viral shedding associated with early therapy with a neuraminidase inhibitor in healthy outpatients with seasonal influenza (2-6). A recent systematic review concluded that when patients initiate treatment within 48 hours of the onset of symptoms, the duration of illness is decreased by one day (7).

The question of whether neuraminidase inhibitors reduce complications associated with influenza (lower respiratory tract infection [LRTI], hospitalization, ICU admission, and death) is much more controversial. Data in this regard come largely from one meta-analysis of a combination of ten published and unpublished studies, which demonstrated a reduction of 26% in antibiotic use, a reduction of 55% in LRTI, and a reduction of 59% in hospitalization (8). Restriction of the analysis to published studies failed to demonstrate a benefit (7). The in vitro data, evidence of effectiveness in symptomatic relief in mild to moderate influenza, evidence of effect on viral shedding, and low rates of adverse events have resulted in a reluctance among experts to randomize seriously ill patients to placebo in putative clinical trials, creating a significant barrier to improving the understanding of the utility of these drugs in more seriously ill patients.

The 2009 H1N1 pandemic was associated with a dramatic rise in antiviral use and posed a number of challenging questions. Although guidelines support the use of

neuraminidase inhibitors in most circumstances (1, 9) there remains a lack of evidence with regards to their efficacy in pH1N1 infection and in influenza associated with hospitalization and ICU admission. The data supporting effectiveness when used early in illness have also raised important questions about the utility of late initiation of therapy in hospitalized patients. Other important and unanswered questions concern the effect of antiviral therapy in certain populations, including the critically ill, children, and the immunocompromised. The objective of this study is to systematically review the data on antiviral therapy in pH1N1 infection.

## Materials and Methods

We followed the meta-analyses of observational studies in epidemiology (MOOSE) guidelines for reporting our results (10).

### *Search strategy*

We identified all relevant studies, searching OVID MEDLINE and EMBASE (from January 1st 2009 to January 26th 2011) with the help of an experienced librarian (detailed search strategy provided in Supplemental Data A). We also searched reference lists of included studies. Conference proceedings and abstracts were included in the search. We did not include theses, dissertations, or national or local vital statistics data not published as peer reviewed articles.

### *Study selection*

#### Inclusion criteria

Observational studies (cohort and case-control studies) or randomized trials that reported on rates of hospitalization, ICU admission or death in pediatric or adults patients with laboratory-confirmed pH1N1 infection were included. Laboratory confirmed influenza infection was defined as a positive result for influenza by PCR, viral culture or rapid antigen test.

#### Exclusion criteria

The following types of studies were excluded: case reports and case series where the denominator population could not be determined; studies that reported outcomes other than hospitalization, death or ICU admission; studies in which outcomes could not be correlated with whether or not the patient received effective antiviral therapy; and studies in which influenza strains other than pH1N1 were (or might have been) included.

#### Selection

One review author (MD) inspected the abstract of each reference identified by the search and selected the studies for full review, and inspected all possibly relevant articles for inclusion.

### *Data extraction*

Data from included studies were independently extracted by two review authors (MD and PL). Data from studies included year of publication, country of origin, characteristics of study population (adults, children, outpatient, hospitalized, ICU, immunocompromised), number of subjects included, and the specific antiviral used. Where possible, if cohorts included both children and adults, data from these groups were extracted separately. For the therapy analysis, patients were categorized based on whether or not they received effective antiviral therapy (a neuraminidase inhibitor), and whether or not therapy was started within 48 hours of the onset of symptoms. When abstracted data differed between reviewers, studies were reviewed again until a consensus was reached.

### *Outcome*

The outcome measures of interest were death, ICU admission, or (for cohorts of patients who were initially outpatients) hospitalization.

### *Assessment of risk of bias*

Risk of bias among included studies was assessed by MD using the Newcastle-Ottawa Scale (11).

### *Data synthesis and analysis*

A priori, we planned a stratified

meta-analysis because of anticipated clinical heterogeneity among included studies. Subgroup categories were: adults versus pediatrics, and outpatients versus hospitalized patients. Strata with at least two eligible studies were synthesized by conducting a meta-analysis of incidence rates. Variances around estimates of incidence rates from various studies were calculated. The meta-analysis was performed using Review Manager software (RevMan version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). Because we anticipated heterogeneity between studies, a random-effects model was used for all analyses. Statistical heterogeneity was initially inspected graphically (forest plot) and assessed by calculating tests of heterogeneity using the Cochran Q test (Chi-square test).

## Results

### *Search Results*

The initial search identified 4329 articles. After reviewing titles and abstracts, 335 articles were deemed to be potentially relevant and were reviewed in full. Thirty-eight publications were not accessible and 23 publications were not written in English. An additional 47 articles were added based on a review of references. Fifty-seven studies met all inclusion criteria and were used for the systematic review.

### *Characteristics of studies and patients*

The publications consisted of 52 cohort studies, 3 case-control studies, and 2 conference abstracts. There were no randomized controlled trials or meta-analyses that met the inclusion criteria. There were 18 studies which included outpatient data, 34 studies limited to hospitalized patients, and 10 studies limited to ICU cohorts. As for patient demographics, 20 studies included adult cohorts, 13 studies used pediatric cohorts, and 22 studies did not differentiate children from adults in their analysis. Twelve studies consisted of immunocompromised patients (malignancy, immunosuppression or HIV).

The quality of the studies was assessed using the Newcastle Ottawa method. The selection bias was low in 25 studies, whereas it was moderate or high in the remaining 32 studies. No study attempted a multivariate analysis in order to control for confounders during their analysis of therapeutic effect. Forty of the studies documented adequate follow-up of their patients and included data at least regarding mortality.

### *Antiviral Therapy versus No Antiviral Therapy*

The studies included in the meta-analysis are summarized in Table 1. There were 23 studies which included outpatient data. Of the 3459 patients in these studies, 2488 received antiviral therapy. The hospitalization rates were 39.3% in the treatment group and 17.3% in the non-treatment group. For the 47 studies that reported mortality data (4481 patients), the mortality rate was 16.3% in the treatment group and 15.5% in the non-treatment group. Figure 1 summarizes these studies and demonstrates no difference in mortality in all studies (OR 1.03 [0.73, 1.44]). Thirty-nine studies correlated antiviral therapy with ICU admission, and rates were 30.7% in the treatment group versus 11.8% in the non-treatment group.

For adults, 18 studies reported a cumulative mortality rate of 18.9% in 1280 patients receiving antiviral therapy versus 10.4% in 125 patients not receiving therapy (Figure 2). Restricting this to inpatient studies, the rates were 30.0% with treatment and 24.2% without treatment. Eighteen studies reported cumulative ICU admission rate of 43.0% in 942 patients receiving therapy versus 19.5% in patients who did not receive therapy. There was only one study included in our analysis that was able to compare hospitalization rates in adult patients (12). This was a cohort of 788 pregnant women where the hospitalization rate in 541 patients who were treated was 68%, versus 61% in 74 patients who were not treated.

For children, 12 studies reported a cumulative mortality of 16.3% in 472 patients who received antiviral therapy versus 12.8% in 195 patients not receiving therapy (Figure 2). Restricting this to inpatients, the rates were 13.6% with treatment and 4.9% without treatment. Again, there was only one study that was able to compare hospitalization rates for pediatrics patients. This was a small cohort of 15 HIV-infected patients, where none of the 5 patients who received antiviral therapy (all within 48 hours) were hospitalized, compared to one of the 10 patients who did not receive therapy.

### *Early versus late initiation of antiviral therapy*

We defined early initiation of therapy as within 48 hours of the onset of symptoms. Twenty-six studies used this criterion in differentiating outcomes based on timing of therapy. Figures 3 and 4 summarize their results. In the 18 studies that reported mortality, there was a statistically significant reduction in mortality in patients who were treated within 48 hours of onset of symptoms (11.6% versus 20.5%, OR 0.19 [0.05, 0.69]). Similarly there was also a significant reduction in ICU admission associated with early therapy (27.7% versus 36.8%, OR 0.23 [0.12, 0.45]). A subset analysis

of the studies involving only adult patients showed a similar trend in mortality (1.7% versus 18.9%, OR 0.07 [0.0, 1.14]) and ICU admissions (7.2% versus 29.9%, OR 0.19 [0.08, 0.44]). Only one pediatric study was able to compare early versus late therapy in terms of mortality, with a mortality rate of 3.7% in the early treatment group versus 12.6% in the late treatment group.

We also compared the high quality studies to the low- and moderate-quality studies to determine if part of this effect was due to bias (Figure 5). Eight of the publications were considered to be high quality cohort studies (unbiased selection process, all important outcomes determined, and adequate follow-up). The mortality rates were much higher in the low- and moderate-quality group, owing primarily to one large cohort that had a very high mortality rate (13). However, the magnitude of treatment effects was similar in the two groups (OR 0.22 [0.03, 1.58] in high quality studies and 0.12 [0.01, 1.61] in low- and moderate- quality studies).

## Discussion

To our knowledge this is the first meta-analysis aimed at summarizing the cohort data with regards to antiviral use during the 2009 pandemic. Our main findings are that early antiviral therapy (less than 48 hours after the onset of symptoms) was associated with a significantly decreased rate of ICU admission and death, compared with late therapy. This association was evident in the population in general as well as in the adult-only population, however there was insufficient data to draw conclusions about the pediatrics population. In contrast, patients who received antiviral therapy in general did not show improved rates of mortality or ICU admission compared to patients who did not receive antiviral therapy.

A meta-analysis of observational data with regard to therapy for influenza in general was recently published (14). Similar to our study, they noted that there are no randomized controlled trials of influenza treatment with data on mortality or other complications. Four studies were included in their subgroup analysis looking at mortality in pH1N1 studies, and they were unable to demonstrate a benefit of oseltamivir over no therapy. When comparing early to late therapy (for pH1N1 and seasonal influenza), they showed a non-statistically significant improvement in mortality (OR 0.39 [0.12, 1.30], and a statistically significant improvement in ICU admission (OR 0.22 [0.15, 0.33]). However many of these studies were not included in the final analysis due to a lack of adjustment for confounders.

Our main findings are that early antiviral therapy (less than 48 hours after the onset of symptoms) was associated with a significantly decreased rate of ICU admission and death, compared with late therapy.

Meta-analyses of observational studies are problematic in that they are subject to the same bias as original studies. The fact that patients who did not receive antiviral therapy had better or equivalent outcomes likely illustrates that they had less severe infections and therefore did not warrant treatment. On the other hand, patients who were treated late in the course of the disease may have had a delay in diagnosis and therefore more severe disease prior to initiating therapy. Unfortunately none of the studies captured in this review undertook a multivariate analysis to adjust for confounders. We did control for selection bias using a standardized quality assessment instrument, which strengthens the validity of this study's results.

Another useful role for meta-analyses of observational studies would be to comment on the overall quality of the literature and areas for future work. There were no randomized controlled trials found in our search, and there are unlikely to be such studies given the mounting evidence that neuraminidase inhibitors are useful in pH1N1 infection. To date, studies have mostly focused on symptom improvement and viral shedding as outcomes. Our main objective was to determine whether treatment affected clinical outcomes such as hospitalization, ICU admission and death. To ultimately answer this question there will likely need to be a well-designed case-control study or a large multi-site cohort study with careful multivariate analysis.

Another question of interest relates to the point at which delayed antiviral therapy is no longer effective, in particular with respect to hospitalized and critically ill patients. We used a cutoff of 48 hours from symptom onset based on current guidelines, but several of the studies used different time points to characterize their patients. Certainly

individual practices vary with respect to this, and a further analysis looking at multiple time points may provide more insight.

In summary, early initiation of effective antiviral therapy was associated with both a reduction in mortality and in ICU admissions in pH1N1 infection. We were unable to demonstrate a beneficial effect associated with antiviral therapy in general. There was an immense body of literature generated during the H1N1 pandemic, however almost all studies demonstrated association rather than causality with respect to antiviral therapy. This meta-analysis serves to summarize the growing body of evidence supporting antiviral use in pH1N1. However more rigorous studies are still needed to help guide clinical practice.

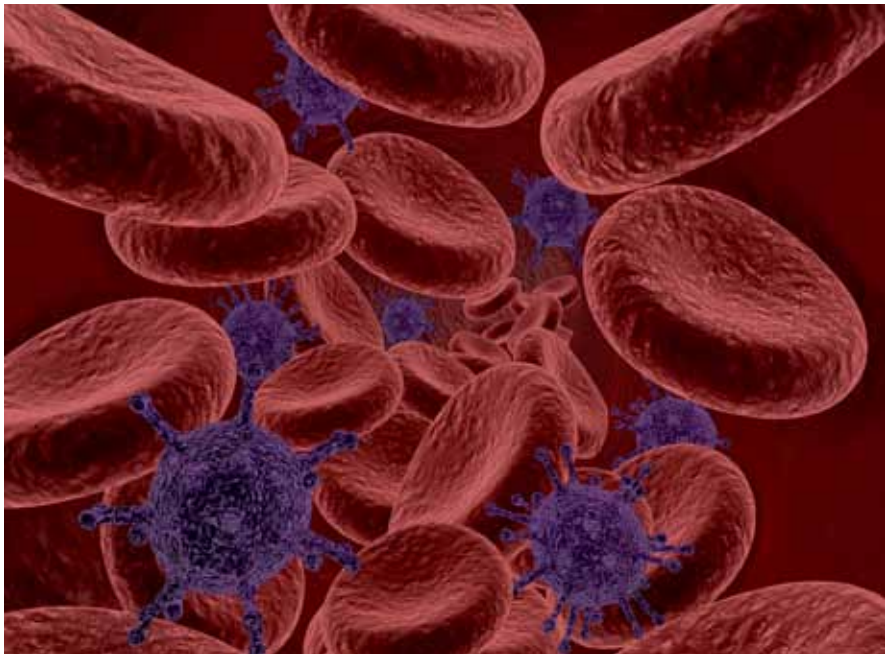


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**Table 1. Summary of studies used in the meta-analysis with respect to mortality, hospitalization and ICU admission.**

| | | | Treated with Antivirals | | | | No treatment | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Author, year | Timing of antiviral therapy specified | No. of patients | No. of patients | Deaths | Hospitalized | ICU admission | No. of patients | Deaths | Hospitalized | ICU admission |
| Cheng 2010 | Yes | 16 | 16 | 0 | 16 | 0 | 0 | 0 | 0 | 0 |
| Li 2010 | Yes | 146 | 118 | 0 | 118 | 0 | 27 | 0 | 27 | 0 |
| Feiterna-Sperling 2010 | Yes | 15 | 5 | 0 | 0 | 0 | 10 | 0 | 1 | 10 |
| Rubin 2010 | No | 4 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 |
| Isais 2010 | No | 11 | 10 | 0 | | 0 | 1 | 0 | | 0 |
| Liang 2009 | Yes | 10 | 10 | 0 | 10 | 0 | 0 | 0 | 0 | 0 |
| Ridao-Cano 2010 | No | 13 | 13 | 0 | 7 | 0 | 0 | 0 | 0 | 0 |
| Inusa 2010 | No | 21 | 21 | 0 | 19 | 1 | 0 | 0 | 0 | 0 |
| Launes 2010 | No | 10 | 10 | 0 | 6 | 1 | 0 | 0 | 0 | 0 |
| Jardim 2010 | No | 4 | 1 | 0 | 1 | 1 | 3 | 0 | 3 | 3 |
| Yun 2010 | No | 18 | 18 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| Shinde 2009 | No | 11 | 4 | 0 | 2 | 2 | 6 | 0 | 2 | 0 |
| Seville 2010 | No | 6 | 6 | 1 | 6 | 2 | 0 | 0 | 0 | 0 |
| Couturier 2010 | Yes | 4 | 4 | 2 | 3 | 2 | 0 | 0 | 0 | 0 |
| Low 2010 | No | 22 | 22 | 1 | 22 | 3 | 0 | 0 | 0 | 0 |
| Lalayanni 2010 | No | 8 | 8 | 3 | 8 | 3 | 0 | 0 | 0 | 0 |
| McLean 2010 | Yes | 365 | 335 | | 14 | 3 | 30 | | 0 | 0 |
| Nishiyama 2010 | Yes | 21 | 21 | 0 | 21 | 4 | 0 | 0 | | |
| Bertisch 2010 | Yes | 15 | 15 | 0 | 14 | 6 | 0 | 0 | 0 | 0 |
| Bantar 2009 | No | 30 | 30 | 1 | 30 | 7 | 0 | 0 | 0 | 0 |
| O'Riordan 2010 | Yes | 61 | 12 | 0 | 12 | 8 | 49 | 0 | 49 | 4 |
| Langenegger | Yes | 13 | 13 | 3 | 13 | 8 | 0 | 0 | 0 | 0 |
| Hajjar 2010 | Yes | 8 | 8 | 5 | 8 | 8 | 0 | 0 | 0 | 0 |
| CDC July2009 | No | 10 | 10 | 3 | 10 | 10 | 0 | 0 | 0 | 0 |
| Lockman 2010 | Yes | 13 | 11 | 0 | 11 | 11 | 2 | 0 | 2 | 2 |
| Gaüzère 2011 | No | 13 | 13 | 4 | 13 | 13 | 0 | 0 | 0 | 0 |
| Kwan-Gett 2009 | Yes | 528 | 297 | | 54 | 14 | 231 | | 16 | 3 |
| Vasoo 2010 | Yes | 32 | 22 | | 22 | 15 | 10 | | 10 | 1 |
| Chudasama 2010 | Yes | 274 | 274 | 71 | 274 | 16 | 0 | 0 | 0 | 0 |
| CDC Mar2009 | Yes | 17 | 17 | | | 17 | 0 | 0 | 0 | 0 |
| Louie Jan2010 | Yes | 239 | 168 | | 168 | 21 | 40 | | 40 | 1 |
| Cui 2010 | Yes | 68 | 68 | 10 | 68 | 30 | 0 | 0 | 0 | 0 |
| Gooskens 2009 | Yes | 96 | 96 | 10 | 96 | 35 | 0 | 0 | 0 | 0 |
| Kumar 2010 | Yes | 237 | 223 | 10 | 167 | 37 | 14 | 0 | 0 | 0 |
| Zarychanski 2010 | Yes | 667 | 256 | | 125 | 42 | 411 | | 73 | 2 |
| Jain 2009 | No | 272 | 200 | 17 | 200 | 56 | 68 | 2 | 68 | 9 |
| Siston 2010 | Yes | 588 | 509 | 25 | 354 | 82 | 74 | 5 | 45 | 15 |
| Farias 2010 | Yes | 147 | 135 | 52 | 135 | 135 | 12 | 5 | 12 | 12 |
| Nukiwa 2010 | Yes | 254 | 200 | 158 | 158 | 158 | 54 | 40 | 54 | 54 |
| Estenssoro 2010 | No | 337 | 328 | 150 | 328 | 328 | 8 | 5 | 8 | 8 |
| Chan 2010 | No | 50 | 50 | 0 | 50 | | 0 | 0 | 0 | |
| Ou 2009 | No | 150 | 140 | 0 | | | 10 | 0 | | |
| Zhou 2010 | Yes | 72 | 72 | 0 | 72 | | 0 | 0 | 0 | 0 |
| Ling 2010 | Yes | 70 | 70 | 0 | 70 | | 0 | 0 | 0 | 0 |
| Schreuder 2010 | No | 3 | 3 | 0 | | | 0 | 0 | 0 | 0 |
| Morgan 2010 | No | 74 | 57 | 0 | | | 17 | 0 | | |
| Shen 2010 | Yes | 237 | 236 | 0 | | | 1 | 0 | | |
| Jamieson 2009 | Yes | 34 | 17 | 1 | | | 17 | 0 | | |
| Louie Nov2010 | Yes | 319 | 221 | 6 | 221 | | 98 | 3 | 98 | |
| CDC Sept2009 | Yes | 36 | 19 | 19 | | | 17 | 17 | | |
| Xi 2010 | Yes | 155 | 125 | 24 | | | 25 | 3 | | |
| Lee2010 | Yes | 47 | 32 | 32 | 32 | | | | | |
| Davies 2009 | No | 505 | 409 | 54 | 409 | | 96 | 15 | 96 | |
| D'Ortenzio 2010 | Yes | 171 | 92 | | | | 79 | | | |
| Fuhrman 2010 | Yes | 459 | 449 | | | | | | | |
| Libster 2010 | Yes | 251 | 208 | | | | 43 | | | |
| Chitnis 2010 | Yes | 250 | 215 | | 215 | | 35 | | 35 | |

**Figure 1. Forest plot of studies comparing treatment to no treatment of patients with H1N1 infection with regards to mortality.**

| Study or Subgroup | Treatment Events | Treatment Total | No Treatment Events | No Treatment Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| CDC Sept2009 | 19 | 19 | 17 | 17 | | Not estimable |
| Davies 2009 | 54 | 409 | 15 | 96 | 30.1% | 0.82 [0.44, 1.53] |
| Estenssoro 2010 | 150 | 328 | 5 | 8 | 5.5% | 0.51 [0.12, 2.15] |
| Farias 2010 | 52 | 135 | 5 | 12 | 8.1% | 0.88 [0.26, 2.91] |
| Feiterna-Sperling 2010 | 0 | 5 | 0 | 10 | | Not estimable |
| Isais 2010 | 0 | 10 | 0 | 1 | | Not estimable |
| Jain 2009 | 17 | 200 | 2 | 68 | 5.2% | 3.07 [0.69, 13.63] |
| Jamieson 2009 | 1 | 17 | 0 | 17 | 1.1% | 3.18 [0.12, 83.76] |
| Jardim 2010 | 0 | 1 | 0 | 3 | | Not estimable |
| Kumar 2010 | 10 | 223 | 0 | 14 | 1.4% | 1.43 [0.08, 25.57] |
| Li 2010 | 0 | 118 | 0 | 27 | | Not estimable |
| Lockman 2010 | 0 | 11 | 0 | 2 | | Not estimable |
| Louie Nov2010 | 6 | 221 | 3 | 98 | 5.9% | 0.88 [0.22, 3.61] |
| Morgan 2010 | 0 | 57 | 0 | 17 | | Not estimable |
| Nukiwa 2010 | 158 | 200 | 40 | 54 | 23.9% | 1.32 [0.66, 2.64] |
| O'Riordan 2010 | 0 | 12 | 0 | 49 | | Not estimable |
| Ou 2009 | 0 | 140 | 0 | 10 | | Not estimable |
| Shen 2010 | 0 | 236 | 0 | 1 | | Not estimable |
| Shinde 2009 | 0 | 4 | 0 | 6 | | Not estimable |
| Siston 2010 | 25 | 509 | 5 | 74 | 11.8% | 0.71 [0.26, 1.92] |
| Xi 2010 | 24 | 125 | 3 | 25 | 7.0% | 1.74 [0.48, 6.30] |
| **Total (95% CI)** | | **2980** | | **609** | **100.0%** | **1.03 [0.73, 1.44]** |
| Total events | 516 | | 95 | | | |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.80$, df = 9 (P = 0.76); $I^2 = 0\%$

Test for overall effect: Z = 0.15 (P = 0.88)

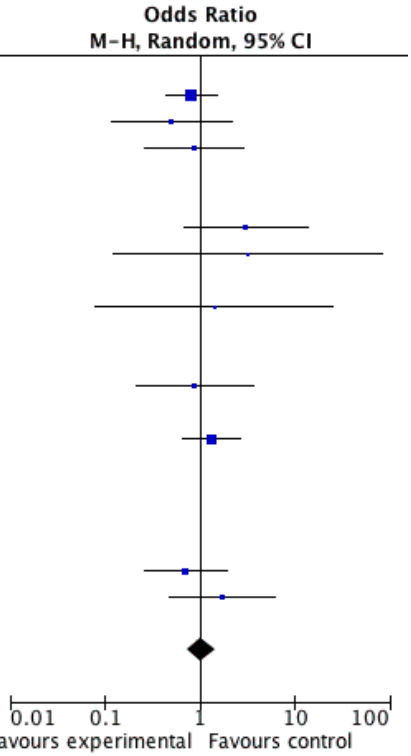
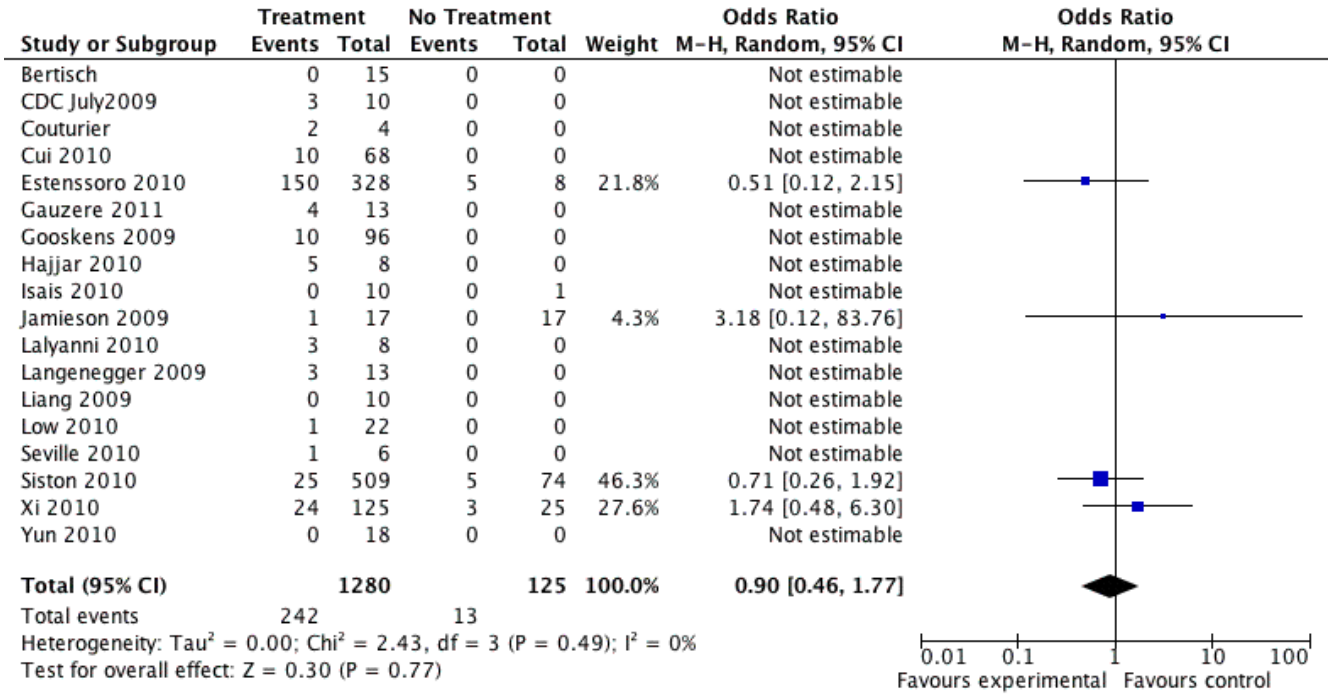


**Figure 2. Subgroup analysis of studies comparing treatment to treatment of patients with H1N1 infection with regards to mortality in. A: Adult patients. B: Pediatric patients.**

A

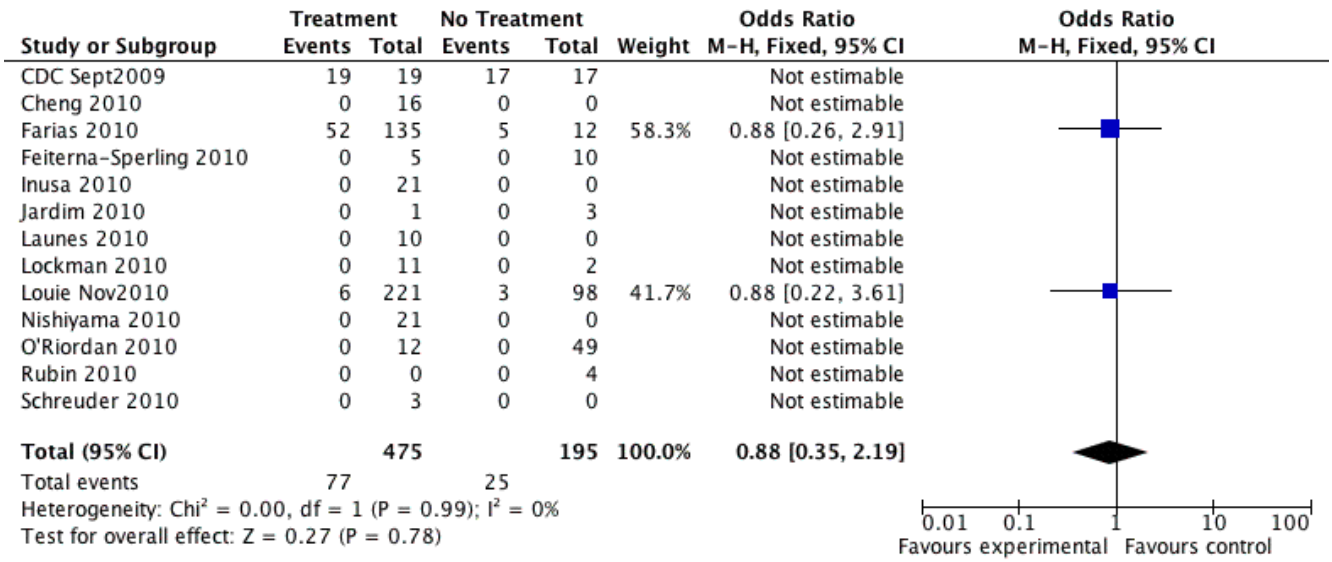


| Study or Subgroup | Treatment Events | Total | No Treatment Events | Total | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Bertisch | 0 | 15 | 0 | 0 | | Not estimable |
| CDC July2009 | 3 | 10 | 0 | 0 | | Not estimable |
| Couturier | 2 | 4 | 0 | 0 | | Not estimable |
| Cui 2010 | 10 | 68 | 0 | 0 | | Not estimable |
| Estenssoro 2010 | 150 | 328 | 5 | 8 | 21.8% | 0.51 [0.12, 2.15] |
| Gauzere 2011 | 4 | 13 | 0 | 0 | | Not estimable |
| Gooskens 2009 | 10 | 96 | 0 | 0 | | Not estimable |
| Hajjar 2010 | 5 | 8 | 0 | 0 | | Not estimable |
| Isais 2010 | 0 | 10 | 0 | 1 | | Not estimable |
| Jamieson 2009 | 1 | 17 | 0 | 17 | 4.3% | 3.18 [0.12, 83.76] |
| Lalyanni 2010 | 3 | 8 | 0 | 0 | | Not estimable |
| Langenegger 2009 | 3 | 13 | 0 | 0 | | Not estimable |
| Liang 2009 | 0 | 10 | 0 | 0 | | Not estimable |
| Low 2010 | 1 | 22 | 0 | 0 | | Not estimable |
| Seville 2010 | 1 | 6 | 0 | 0 | | Not estimable |
| Siston 2010 | 25 | 509 | 5 | 74 | 46.3% | 0.71 [0.26, 1.92] |
| Xi 2010 | 24 | 125 | 3 | 25 | 27.6% | 1.74 [0.48, 6.30] |
| Yun 2010 | 0 | 18 | 0 | 0 | | Not estimable |
| **Total (95% CI)** | | **1280** | | **125** | **100.0%** | **0.90 [0.46, 1.77]** |
| Total events | 242 | | 13 | | | |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.43$, df = 3 (P = 0.49); $I^2 = 0\%$
Test for overall effect: Z = 0.30 (P = 0.77)



B

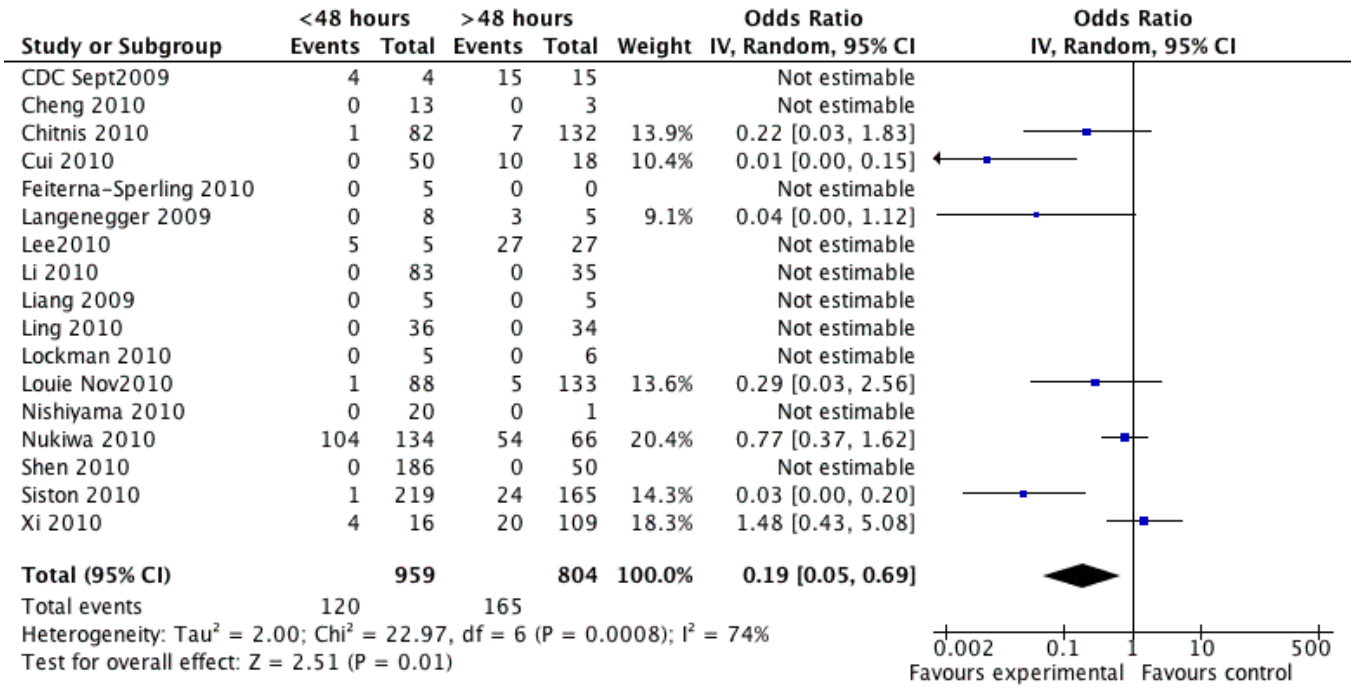


| Study or Subgroup | Treatment Events | Total | No Treatment Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| CDC Sept2009 | 19 | 19 | 17 | 17 | | Not estimable |
| Cheng 2010 | 0 | 16 | 0 | 0 | | Not estimable |
| Farias 2010 | 52 | 135 | 5 | 12 | 58.3% | 0.88 [0.26, 2.91] |
| Feiterna-Sperling 2010 | 0 | 5 | 0 | 10 | | Not estimable |
| Inusa 2010 | 0 | 21 | 0 | 0 | | Not estimable |
| Jardim 2010 | 0 | 1 | 0 | 3 | | Not estimable |
| Launes 2010 | 0 | 10 | 0 | 0 | | Not estimable |
| Lockman 2010 | 0 | 11 | 0 | 2 | | Not estimable |
| Louie Nov2010 | 6 | 221 | 3 | 98 | 41.7% | 0.88 [0.22, 3.61] |
| Nishiyama 2010 | 0 | 21 | 0 | 0 | | Not estimable |
| O'Riordan 2010 | 0 | 12 | 0 | 49 | | Not estimable |
| Rubin 2010 | 0 | 0 | 0 | 4 | | Not estimable |
| Schreuder 2010 | 0 | 3 | 0 | 0 | | Not estimable |
| **Total (95% CI)** | | **475** | | **195** | **100.0%** | **0.88 [0.35, 2.19]** |
| Total events | 77 | | 25 | | | |

Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 0.99); $I^2 = 0\%$
Test for overall effect: Z = 0.27 (P = 0.78)

**Figure 3. Forest plots of studies comparing patients treated within 48 hours of symptom onset with patients treated after 48 hours. A: Studies with mortality data. B: Studies with ICU admission data.**

A




B

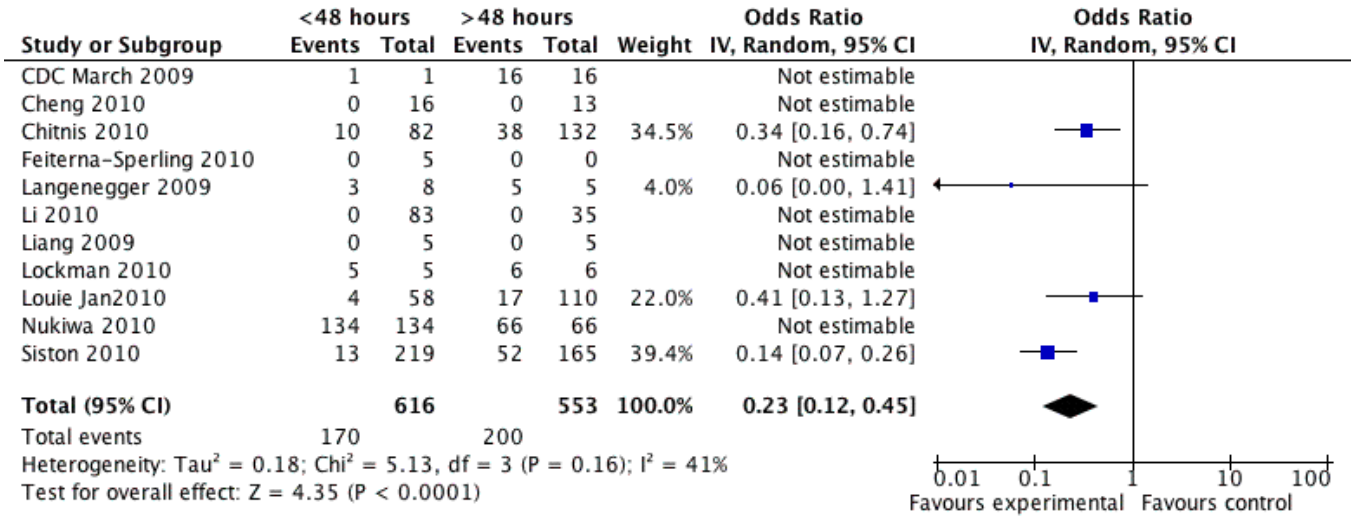
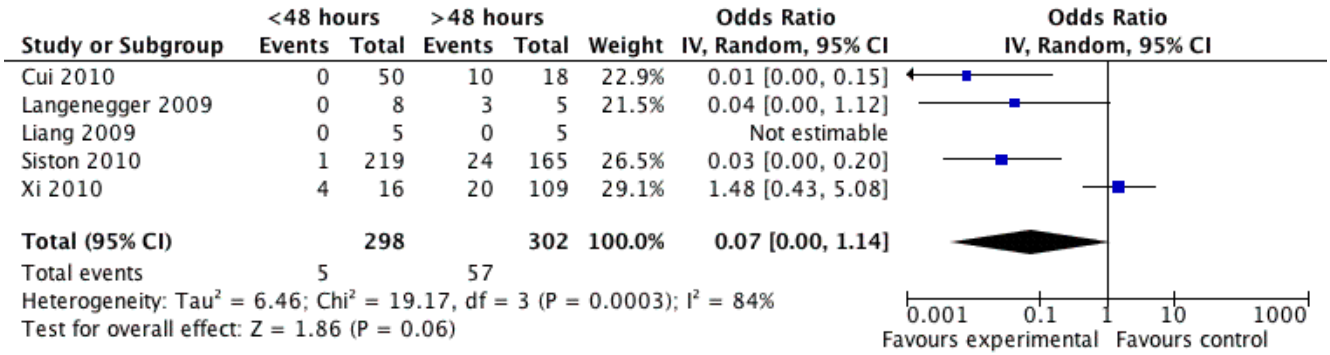


**Figure 4. Forest plots of adult studies comparing patients treated within 48 hours of symptom onset with patients treated after 48 hours. A: Studies with mortality data. B: Studies with ICU admission data.**

A




B

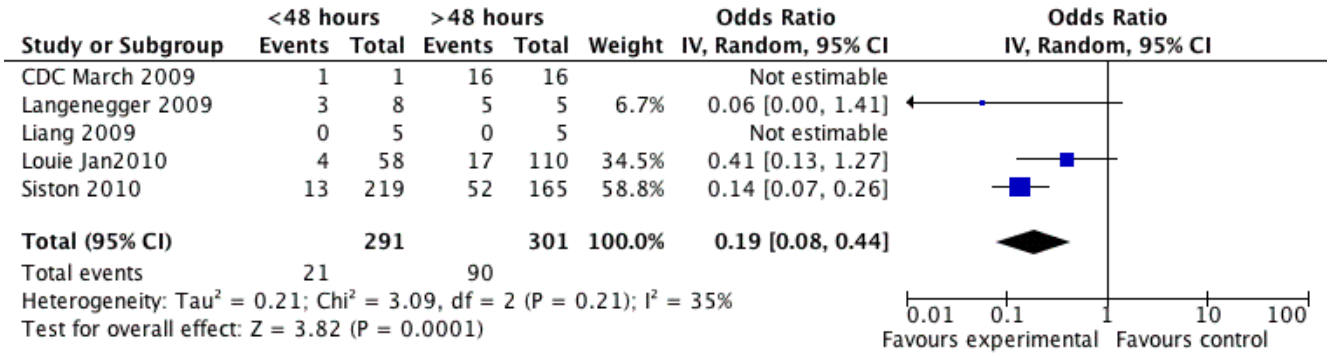
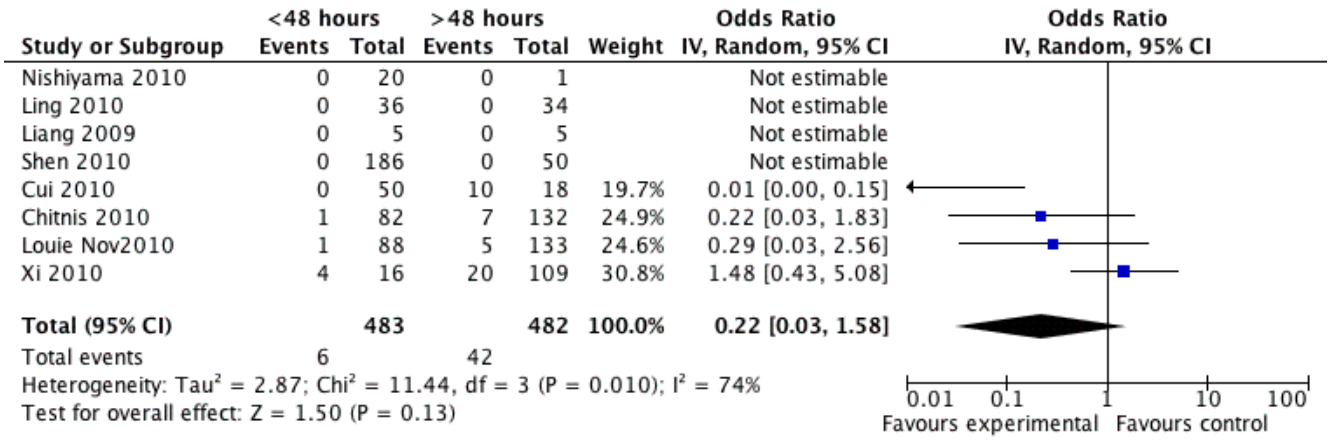
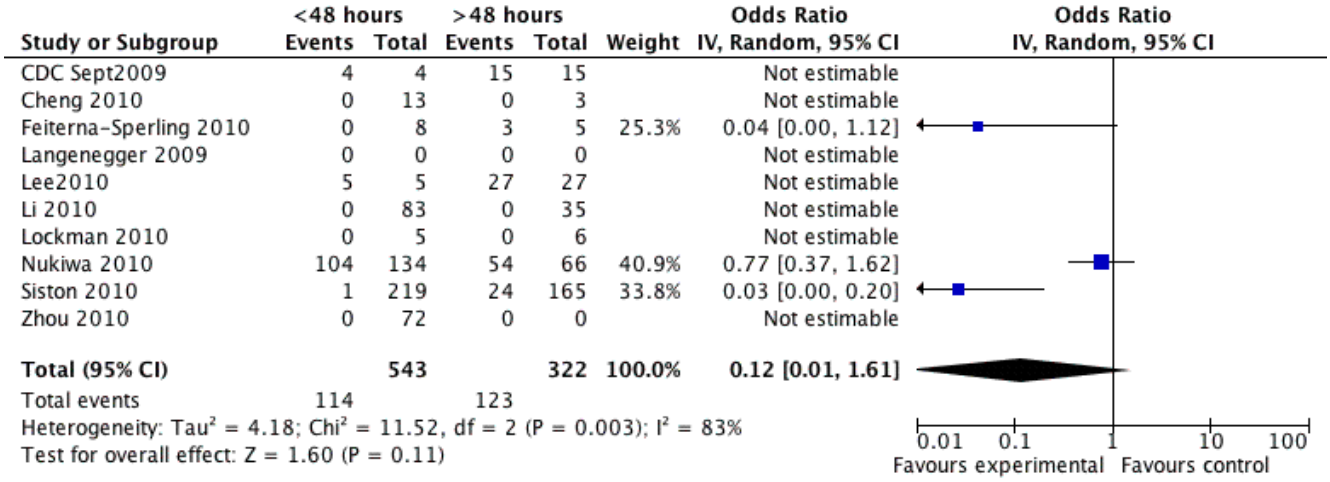


**Figure 5. Forest plots of high quality studies versus low-moderate quality studies comparing mortality in patients treated within 48 hours of symptom onset with patients treated after 48 hours. A: High quality studies. B: Low Quality studies.**

A




B



## Supplemental Data A: Detailed Search strategy

Medline/Ovid and Embase were searched using the following search strategy:

1. influenza a virus/ or influenza a virus, h1n1 subtype/
2. (h1n1 or (swine adj2 (flu or flus or influenza*))).mp.
3. 1 or 2
4. exp Antiviral Agents/ or (tamiflu or "gs-4071" or "gs 4071" or gs4071 or oseltamivir or zanamivir or relenza or "gg 167" or "gg-167" or gg167 or amantadin* or amantadinneuraxpharm or aman or amantahciazu or mantadix or cerebramed or tregor or midantan or pmsamantadine or "infecto-flu" or "infectoflu" or infectoflu or wiregyt or aminoadamantane or symmetrel or amantasulfateazu or adamantylamine or endantadine or symadine or genamantadine or amixx or adekin or viregyt or infex or RIMANTADINE or rimantadine or roflual or flumadine).mp.
5. 3 and 4
6. cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/
7. case-control studies/ or retrospective studies/
8. prognosis/ or disease-free survival/ or treatment outcome/ or treatment failure/
9. prognosis/ or disease-free survival/ or medical futility/ or pregnancy outcome/ or treatment outcome/ or treatment failure/
10. disease progression/
11. morbidity/ or incidence/ or prevalence/ or mortality/ or "cause of death"/ or child mortality/ or fatal outcome/ or fetal mortality/ or hospital mortality/ or infant mortality/ or maternal mortality/ or perinatal mortality/ or survival rate/
12. survival analysis/ or disease-free survival/
13. natural history.mp.
14. or/6-13
15. 5 and 14
16. ("clinical trial, all" or clinical trial).pt. or clinical trials as topic/
17. clinical trial, phase i.pt. or clinical trials, phase i as topic/
18. clinical trial, phase ii.pt. or clinical trials, phase ii as topic/
19. clinical trial, phase iii.pt. or clinical trials, phase iii as topic/
20. clinical trial, phase iv.pt. or clinical trials, phase iv as topic/
21. controlled clinical trial.pt. or controlled clinical trials as topic/
22. meta-analysis.pt. or meta-analysis as topic/
23. multicenter study.pt. or multicenter studies as topic/
24. randomized controlled trial.pt. or randomized controlled trials as topic/
25. control groups/ or double-blind method/ or random allocation/ or single-blind method/
26. or/16-25
27. 5 and 26
28. 15 or 27
29. limit 5 to (case reports or guideline or letter or practice guideline or "review" or government publications)
30. 29 not 28
31. limit 30 to yr="2009 -Current"
32. limit 28 to yr="2009 -Current"

***Revised with:***

1. influenza a virus/ or influenza a virus, h1n1 subtype/
2. (h1n1 or (swine adj2 (flu or flus or influenza*))).mp.
3. 1 or 2
4. exp Antiviral Agents/ or (tamiflu or "gs-4071" or "gs 4071" or gs4071 or oseltamivir or zanamivir or relenza or "gg 167" or "gg-167" or gg167 or amantadin* or amantadinneuraxpharm or aman or amantahciazu or mantadix or cerebramed or tregor or midantan or pmsamantadine or "infecto-flu" or "infectoflu" or infectoflu or wiregyt or aminoadamantane or symmetrel or amantasulfateazu or adamantylamine or endantadine or symadine or genamantadine or amixx or adekin or viregyt or infex or RIMANTADINE or rimantadine or roflual or flumadine).mp. or disease outbreaks/ or disease transmission/ or hospitalization/
5. 3 and 4
6. limit 5 to yr="2009 -Current"
7. prophyla*.mp.
8. 6 and 7
9. 6 not 8

## Supplemental Data B: Studies included in the meta-analysis.

| Author, Year | Citation | Study Design | Adult versus Pediatrics | Outpatient/ Inpatient/ ICU | Immunoc-ompromised | Number of patients |
|---|---|---|---|---|---|---|
| Estenssoro 2010 | American Journal of Respiratory & Critical Care Medicine 182(1): 41-48. | Cohort | Adult | ICU | No | 337 |
| Hajjar 2010 | Annals of Oncology 21(12): 2333-2341. | Cohort | Adult | Inpatient | Yes | 8 |
| Louie Nov2010 | Arch Pediatr Adolesc Med. 2010 Nov;164(11):1023-31. | Cohort | Peds | Inpatient | No | 319 |
| Ou 2009 | Biosci Trends. 2009 Aug;3(4):127-30. | Cohort | Did not separate adults/peds | Outpatient | No | 150 |
| Inusa 2010 | Blood. 2010 Mar 18;115(11):2329-30. | Cohort | Peds | Outpatient | Yes | 21 |
| Xi 2010 | BMC Infect Dis. 2010 Aug 27;10:256. | Cohort | Adult | Inpatient | No | 155 |
| Cui 2010 | BMC Infect Dis. 2010 May 31;10:145. | Cohort | Adult | Inpatient | No | 68 |
| Launes 2010 | Br J Haematol. 2010 Jun;149(6):874-8. Epub 2010 Mar 21. | Cohort | Peds | Inpatient | Yes | 10 |
| Cheng 2010 | Br J Haematol. 2010 Oct;151(2):202-6. doi: 10.1111/j.1365-2141.2010.08351.x. Epub 2010 Aug 25. | Cohort | Peds | Inpatient | Yes | 16 |
| Li 2010 | Chest. 2010 Apr;137(4):759-68. Epub 2010 Jan 8. | Case-Control | Did not separate adults/peds | Outpatient | No | 146 |
| Zhou 2010 | Chinese Medical Journal 123(19): 2651-2654. | Cohort | Did not separate adults/peds | Outpatient | No | 72 |
| Ling 2010 | Clin Infect Dis. 2010 Apr 1;50(7):963-9. | Cohort | Did not separate adults/peds | Inpatient | No | 70 |
| Lee2010 | Clin Infect Dis. 2010 Jun 1;50(11):1498-504. | Cohort | Did not separate adults/peds | Outpatient | No | 47 |
| Schreuder 2010 | Clin Infect Dis. 2010 May 15;50(10):1427-8. | Cohort | Peds | Inpatient | No | 3 |
| Vasoo 2010 | Clin Infect Dis. 2010 May 15;50(10):1428-9. | Cohort | Did not separate adults/peds | Inpatient | No | 32 |
| Nukiwa 2010 | Clin Infect Dis. 2010 Oct 15;51(8):993-4. | Case-Control | Did not separate adults/peds | ICU | No | 254 |
| Bantar 2009 | Clinical Infectious Diseases 49(9): 1458-1460. | Cohort | Did not separate adults/peds | ICU | No | 30 |
| Feiterna-Sperling 2010 | Clinical Infectious Diseases 51(11): e90-e94. | Cohort | Peds | Outpatient | Yes | 15 |
| D'Ortenzio 2010 | Clinical Microbiology & Infection 16(4): 309-316. | Cohort | Did not separate adults/peds | Outpatient | No | 171 |
| Zarychanski 2010 | CMAJ. 2010 Feb 23;182(3):257-64. Epub 2010 Jan 21. | Case-Control | Did not separate adults/peds | Outpatient | No | 667 |
| O'Riordan 2010 | CMAJ. 2010 Jan 12;182(1):39-44. Epub 2009 Nov 19. | Cohort | Peds | Inpatient | No | 61 |
| Kwan-Gett 2009 | Disaster Med Public Health Prep. 2009 Dec;3 Suppl 2:S109-16. | Cohort | Did not separate adults/peds | Outpatient | No | 528 |
| Jardim 2010 | Early Human Development 86: S75-S76. | Abstract | Peds | Inpatient | No | 4 |
| Morgan 2010 | Emerg Infect Dis. 2010 Apr;16(4):631-7. | Cohort | Did not separate adults/peds | Outpatient | No | 74 |
| Shen 2010 | Emerg Infect Dis. 2010 Jun;16(6):1011-3. | Cohort | Did not separate adults/peds | Outpatient | No | 237 |
| Gaüzère 2011 | Emerging Infectious Diseases 17(1): 140-141. | Cohort | Adult | ICU | No | 13 |
| McLean 2010 | Epidemiol Infect. 2010 Nov;138(11):1531-41. Epub 2010 Jul 1. | Cohort | Did not separate adults/peds | Outpatient | No | 365 |
| Rubin 2010 | Eur J Pediatr. 2010 Sep;169(9):1159-61. Epub 2010 Mar 7. | Cohort | Peds | Outpatient | No | 4 |
| Nishiyama 2010 | Euro Surveill. 2010 Sep 9;15(36). pii: 19659. | Cohort | Peds | Inpatient | No | 21 |
| Fuhrman 2010 | Euro Surveillance: Bulletin Europeen sur les Maladies Transmissibles = European Communicable Disease Bulletin 15(2): 14. | Cohort | Did not separate adults/peds | Inpatient | No | 459 |
| Chudasama 2010 | Indian Journal of Critical Care Medicine 14(3): 113-120. | Cohort | Did not separate adults/peds | Inpatient | No | 274 |
| Couturier 2010 | Influenza Other Respi Viruses. 2010 Jul;4(4):199-204. | Cohort | Adult | Outpatient | Yes | 4 |

## Supplemental Data B: Studies included in the meta-analysis Continued

| Author, Year | Citation | Study Design | Adult versus Pediatrics | Outpatient/ Inpatient/ ICU | Immunoc-ompromised | Number of patients |
|---|---|---|---|---|---|---|
| Farias 2010 | Intensive Care Med. 2010 Jun;36(6):1015-22. Epub 2010 Mar 18. | Cohort | Peds | ICU | No | 147 |
| Matos 2010 | Intensive Care Medicine 36: S319. | Conference Abstract | Adult | ICU | No | 429 |
| Gooskens 2009 | JAMA - Journal of the American Medical Association 301(10): 1042-1046. | Cohort | Adult | Inpatient | No | 96 |
| Davies 2009 | JAMA - Journal of the American Medical Association 302(17): 1888-1895. | Cohort | Did not separate adults/peds | ICU | No | 505 |
| Siston 2010 | JAMA - Journal of the American Medical Association 303(15): 1517-1525. | Cohort | Adult | Outpatient | No (pregnant) | 588 |
| Lalayanni 2010 | Journal of Infection 61(3): 270-272. | Cohort | Adult | Inpatient | Yes | 8 |
| Isais 2010 | Journal of Infection 61(5): 437-440. | Case-Control | Adult | Outpatient | Yes | 11 |
| Yun 2010 | Korean J Radiol. 2010 Jul-Aug;11(4):417-24. Epub 2010 Jun 21. | Cohort | Adult | Outpatient | No | 18 |
| Kumar 2010 | Lancet Infect Dis. 2010 Aug;10(8):521-6. Epub 2010 Jul 9. | Cohort | Did not separate adults/peds | Outpatient | Yes | 237 |
| Jamieson 2009 | Lancet. 2009 Aug 8;374(9688):451-8. Epub 2009 Jul 28. | Cohort | Adult | Outpatient | No (pregnant) | 34 |
| CDC July2009 | MMWR Morb Mortal Wkly Rep. 2009 Jul 17;58(27):749-52. | Cohort | Adult | ICU | No | 10 |
| CDC Sept2009 | MMWR Morb Mortal Wkly Rep. 2009 Sep 4;58(34):941-7. | Cohort | Peds | Outpatient | No | 36 |
| CDC Mar2009 | MMWR Morb Mortal Wkly Rep. 2010 Mar 26;59(11):321-6. | Cohort | Adult | ICU | No (pregnant) | 17 |
| Shinde 2009 | N Engl J Med. 2009 Jun 18;360(25):2616-25. Epub 2009 May 7. | Cohort | Did not separate adults/peds | Outpatient | No | 11 |
| Jain 2009 | N Engl J Med. 2009 Nov 12;361(20):1935-44. Epub 2009 Oct 8. | Cohort | Did not separate adults/peds | Inpatient | No | 272 |
| Louie Jan2010 | N Engl J Med. 2010 Jan 7;362(1):27-35. Epub 2009 Dec 23. | Cohort | Adult | Inpatient | No | 239 |
| Libster 2010 | New England Journal of Medicine 362(1): 45-55. | Cohort | Peds | Inpatient | No | 251 |
| Lockman 2010 | Pediatr Crit Care Med. 2010 Mar;11(2):173-8. | Cohort | Peds | ICU | No | 13 |
| Liang 2009 | Singapore Med J. 2009 Jun;50(6):581-3. | Cohort | Adult | Outpatient | No | 10 |
| Bertisch 2010 | Swiss Med Wkly. 2010 Jul 15;140:w13069. doi: 10.4414/ smw.2010.13069. | Cohort | Adult | Inpatient | No | 15 |
| Ridao-Cano 2010 | Transplantation. 2010 Jul 27;90(2):224-5. | Cohort | Did not separate adults/peds | Outpatient | Yes | 13 |
| Low 2010 | Transplantation. 2010 Nov 15;90(9):1016-21. | Cohort | Adult | Inpatient | Yes | 22 |
| Seville 2010 | Transplantation. 2010 Sep 15;90(5):571-4. | Cohort | Adult | Inpatient | Yes | 6 |
| Chitnis 2010 | WMJ. 2010 Aug;109(4):201-8. | Cohort | Did not separate adults/peds | Inpatient | No | 250 |

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