



TITLE: Antivirals for Pandemic and Human Avian Influenzas: A Review of the Clinical Effectiveness – An Update

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CONTEXT AND POLICY ISSUES

Pandemic influenza is defined as a new strain of influenza that spreads quickly globally.¹ In Canada, among patients diagnosed with pandemic influenza (H1N1) from April 2009 to January 2010, 17% were admitted to intensive care unit (ICU), 10% needed mechanical ventilation, and 5% died in hospital.² Antiviral agents are recommended for the treatment and chemoprophylaxis of pandemic influenza A(H1N1) and human avian influenza A(H5N1) by the Advisory Committee on Immunization Practices (ACIP) (January 2011).³ Amantadine and the neuraminidase inhibitors oseltamivir (Tamiflu, Roche) and zanamivir (Relenza, GlaxoSmithKline) are available in Canada for use as prophylaxis for and treatment of influenza. Oseltamivir is not approved for use in very young children (less than one year of age), and zanamivir is not approved for use in children under the age of seven years.⁴⁻⁶ Evaluation of the SDI (Surveillance Data, Inc.) electronic database in the US showed that the proportion of hospitalized patients who received antiviral treatment, comprising almost entirely neuraminidase inhibitors, increased from 34% in the 2006-2007 season to 70% during the 2009 H1N1 pandemic.⁷

A review of the evidence on the clinical benefits and harms of antivirals for the treatment and prevention of pandemic influenza A (H1N1) and human avian influenza A (H5N1) will be conducted. This report is an update of a previous CADTH report published in 2010 entitled “Antivirals for Pandemic and Human Avian Influenzas: A Review of the Clinical Effectiveness.”⁸

RESEARCH QUESTIONS

1. What are the clinical benefits and harms of the use of antivirals to treat pandemic influenza A(H1N1) and human avian influenza A(H5N1), including early initiation of therapy?
2. What are the clinical benefits and harms of the use of antivirals as prophylaxis for pandemic influenza A(H1N1) and human avian influenza A(H5N1)?

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3. What is the evidence to show clinically important benefits obtained by early initiation of antiviral treatment compared to initiation at 36 to 48 hours for pandemic influenza A(H1N1) and human avian influenza A(H5N1)?

KEY MESSAGE

There is limited evidence that oseltamivir is clinically effective for the treatment of pandemic influenza A(H1N1) and limited evidence that it is especially effective with treatment within 48 hours of symptom onset. There is insufficient evidence to make a definitive conclusion regarding the clinical effectiveness of antivirals for prophylaxis or treatment of pandemic influenza A(H1N1), and no evidence was identified regarding antiviral treatment for human avian influenza A(H5N1).

METHODS

Literature search

A limited literature search was conducted on key resources including PubMed In Process, Ovid MEDLINE, EMBASE, The Cochrane Library (2011, Issue 12), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and non-randomized studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between November 11, 2010 and January 6, 2012.

Article selection

One reviewer screened the titles and abstracts of the retrieved publications and examined the full-text publications for the final article selection. Selection criteria are outlined in Table 1.

Table 1: Selection Criteria

Population	Patients of all ages, with or exposed to H1N1 or H5N1 influenza type A
Intervention	Antivirals, including amantadine, rimantadine, and neuraminidase inhibitors (for example, zanamivir, oseltamivir, and peramivir)
Comparator	Placebo, standard treatment, or none
Outcomes	Clinical benefits and harms for treatment and prophylaxis
Study design	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and observational studies

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1, if they were published prior to November 2010, if they were duplicate publications of the same study, or if they were referenced in at least one of the selected systematic reviews. This report excluded the studies in which the benefit outcomes of antiviral drugs were reported without a control group. For outcomes on harms where the drug-related adverse effects can be seen without a comparator group, studies without a control group were included.

Critical Appraisal of Individual Studies

To assess the quality of the included studies, the Downs and Black checklist was used.⁹ No health technology assessments or systematic reviews were identified for critical appraisal.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 498 citations, and 28 additional studies were identified by searching the grey literature. After screening of abstracts, 35 potentially relevant studies were selected for full-text review.

Nine observational studies on the benefits and harms of antiviral treatment,¹⁰⁻¹⁸ one observational study on efficacy and harms of prophylactic antiviral treatment,¹⁹ and seven observational studies on early initiation of antiviral treatment^{13,14,20-24} were included in this report. No studies on human avian influenza A(H5N1) were found. No health technology assessments or systematic reviews that assessed the clinical benefits and harms of the use of antivirals as prophylaxis or treatment for pandemic influenza A(H1N1) and human avian influenza A(H5N1) were identified. The PRISMA flowchart in Appendix 1 details the process of the study selection.

Summary of Study Characteristics

Study design

There are 15 included studies on the clinical benefits and harms of antiviral agents in the treatment and prophylaxis of pandemic H1N1 influenza, and the effect of early antiviral administration.¹⁰⁻²⁴ No study on human avian influenza A(H5N1) was found. All included studies were observational in design; eight prospective cohort studies,^{12,15,17-19,21,23,25} six retrospective cohort studies,^{10,11,13,14,22,24} and one case series.¹⁶ Length of follow-up was indicated in three studies,^{11,16,18} as was compliance with the intervention.^{16,26,27}

Interventions and comparators

Oseltamivir was the intervention treatment in 13 studies,^{10-14,17-24} zanamivir was the intervention treatment in the case series¹⁶ and was a comparator to oseltamivir in another study,¹¹ and peramivir was the intervention treatment in one study.¹⁵ Comparators varied: other antiviral treatment,¹¹ no other antiviral treatment,^{10-12,14,18,19,22,28} or no comparator.¹⁵⁻¹⁷ Seven studies compared times of initiation of oseltamivir treatment from symptom onset, with no other comparators.^{13,14,20-24}

Outcomes

For studies on benefits and harms of antiviral agents, main study outcomes were length of hospital stay, duration of fever, viral load, complication rates, and adverse drug reactions. For studies on prophylactic treatment, main outcomes included secondary attack rate in households in contact with the index cases. For studies on the impact of early administration of antiviral agents, main outcomes were comparison of influenza severity between different treatment initiation times from the onset of the disease. Detailed characteristics on the included studies are summarized in Appendix 2.

Summary of Critical Appraisal

All studies explicitly stated their objectives and described the interventions of interest. However, due to their observational nature, there was no blinding of the study subjects, and it was not indicated in any of the studies if those individuals measuring the outcomes were blinded. Length of follow-up was indicated in only three studies,^{11,16,18} as was compliance with the intervention.^{16,26,27} Lack of randomization and blinding, as well as inadequate reporting on loss to follow up and compliance with the intervention may have compromised the internal validity of the studies. Strengths and limitations of the studies are presented in Appendix 3.

Summary of Findings

What are the clinical benefits and harms of the use of antivirals to treat pandemic influenza A(H1N1) and human avian influenza A(H5N1), including early initiation of therapy?

Benefits

A retrospective study was performed using the nationwide inpatient Diagnosis Procedure Combination Database in Japan for 1,023 H1N1 influenza-hospitalized infants (< 12 months old).¹⁰ Oseltamivir was prescribed to 535 (53.3%) of the infants, 96% of whom received antiviral treatment within one day of admission. There was no statistically significant difference in mean length of stay between patients treated with or without oseltamivir (4.26 versus 4.30 days; $P = 0.68$). The rate of complications was similar between the two groups (18.8% versus 15.8%; $P = 0.21$).

A prospective surveillance study was conducted on 56 infants with H1N1 influenza, of whom 35 were confirmed to have pandemic influenza, and 20 were treated with oseltamivir.¹² The median length of hospital stay was the same (2.5 days) in the oseltamivir-treated and the control group. Among the subgroup with pandemic influenza, the median length of hospital stay was non-significantly shorter (2.5 days) in the treatment group ($n = 14$) compared with the control group ($n = 31$; 3.0 days). The difference in complications during hospital stay was not significant between the two groups.

An retrospective study examined viral load and length of hospital stay in 39 hospitalized patients with pandemic H1N1 influenza, of whom 29 received oseltamivir.¹³ The mean value of viral load was significantly lower in the treated patients compared with the untreated patients (3.6 ± 1.6 versus 4.2 ± 1.7 Log 10 copies/mL; $P = 0.038$). Mean duration of hospital stay was shorter in the treated group, but the difference was not statistically significant (7.7 ± 1.8 versus 10.2 ± 7.2 days; $P = 0.378$).

An prospective surveillance study was conducted on 308 pandemic H1N1 influenza patients,¹⁴ of whom 178 were given oseltamivir and 130 were given no antiviral treatment. Oseltamivir treatment did not shorten the duration of fever as compared to no antiviral treatment (70.37 ± 36.17 h versus 68.33 ± 34.05 h; $P = 0.624$).

A proportional mortality study was conducted on 198 death cases from confirmed pandemic H1N1 influenza.¹¹ Of the 119 deaths after Tamiflu (oseltamivir) was prescribed, 38 patients (32%) deteriorated within 12 hours, while none deteriorated within 12 hours among the 15

deaths after initiation of Relenza (zanamivir). Odds for deterioration leading to death after Tamiflu versus after Relenza use was significantly higher in Tamiflu (OR: 5.78; 95% CI: 1.28 to 26.1; P = 0.015). Odds of early death, within two days, from antiviral use was also significantly higher in Tamiflu users than in Relenza users (OR: 3.45; 95% CI: 1.11 to 14.82; P = 0.02).

Harms

A prospective study examined adverse events in children treated with oseltamivir for pandemic H1N1 influenza.¹⁷ Among 42 oseltamivir-treated children from newborn to 18 years old, 36% displayed neuropsychiatric adverse events such as nightmare, agitation, irritability, sleeping disorder, and seizure.

In a prospective study of adverse drug reactions in suspected or confirmed cases of pandemic H1N1 influenza,¹⁸ oseltamivir was administered 75mg once daily for 10 days in the prophylactic group (n = 257), and 75mg twice daily for five days in the therapeutic group (n = 37). One hundred and seven patients (41.63%) in the prophylactic group and 23 (62.16%) in therapeutic group reported adverse drug reactions. The incidence of adverse drug reactions was significantly higher in the therapeutic group (P = 0.029). Severity of adverse reactions was also higher in the therapeutic group (P = 0.04). In both groups, gastrointestinal symptoms such as gastritis, nausea, vomiting, diarrhea, and abdominal pain were the most common adverse reactions.

An observational study examined the adverse events and adverse drug reactions of intravenous peramivir in children with pandemic H1N1 influenza.¹⁵ A total of 116 adverse events were reported in 73 (62.4%) of the 117 hospitalized children; 45 events in 34 patients (29.1%) were considered to be adverse drug reactions.

Adverse effects of intravenous zanamivir were examined in a case series of five patients with severe pandemic H1N1 influenza who were not responsive to oral oseltamivir.¹⁶ Data showed there were no side effects attributable to the use of intravenous zanamivir.

In summary, findings from observational studies on pandemic H1N1 influenza included in the review showed that, despite viral shedding being significantly lower in the oseltamivir-treated patients as compared with the untreated ones, there were no statistically significant differences in length of hospital stay, duration of fever, and complication rates between the oseltamivir-treated and no oseltamivir-treated groups. Most frequent adverse drug reactions of oseltamivir were gastrointestinal symptoms; the majority of them were mild. A summary of outcomes is presented in Appendix 4 (Table A5).

What are the clinical benefits and harms of the use of antivirals as prophylaxis for pandemic influenza A(H1N1) and human avian influenza A(H5N1)?

An observational epidemiological study examined the protective role of oseltamivir in 205 household contacts of 65 pandemic H1N1 influenza student patients in a secondary school.¹⁹ The protective role of oseltamivir was examined by comparing the secondary household attack rate of household contacts who had received oseltamivir prophylaxis to those who had not. Of 511 students, 65 cases of H1N1 influenza were identified (attack rate 12.7%). The secondary household attack rate was 0% in the 64 household contacts who had received oseltamivir

prophylaxis, while it was 8.5% (12/141) in those who did not receive prophylactic oseltamivir (Odds ratio [OR]: 0; 95% confidence interval [CI]: 0 to 0.9).

The protective role of oseltamivir prophylaxis on pandemic H1N1 influenza was proven by reducing the odds of secondary infection cases in household contacts of primary cases. A summary of outcomes is presented in Appendix 4 (Table A6).

What is the evidence to show clinically important benefits obtained by early initiation of antiviral treatment compared to initiation at 36 to 48 hours for pandemic influenza A(H1N1) and human avian influenza A(H5N1)?

An observational study of a prospective cohort of 538 adults hospitalized with pandemic H1N1 influenza was conducted to examine the effects of timing of oseltamivir administration.²⁰ Patients were divided into four groups, according to the time from onset of symptoms to antiviral administration: ≤ 2 days, 3-4 days, 5-6 days and ≥ 7 days. Data showed that duration of fever (median two days), length of hospital stay (median five days), need for mechanical ventilation, and mortality increased with time to oseltamivir administration (chi-squared test for trend $P = 0.001$, $P \leq 0.001$, $P = 0.008$, and $P \leq 0.001$, respectively). Compared to patients who received oseltamivir within the first 24 hours, patients to whom oseltamivir administration was delayed more than 24 hours had prolonged duration of fever (OR: 1.67; 95% CI: 1.03 to 2.72), prolonged length of hospital stay (OR: 1.67, 95% CI: 1.06 to 2.63), more often need mechanical ventilation (OR: 3.13; 95% CI: 1.56 to 6.27), and had a higher mortality rate (OR: 4.29, 95% CI: 1.25 to 14.63).

A prospective study looked at the impact of early oseltamivir treatment on outcomes in 385 critically ill patients with pandemic H1N1 influenza.²¹ Seventy-nine patients received early treatment within two days of the onset of symptoms, and 306 received late treatment after two days. The late treatment group had longer length of stay in the intensive care unit (ICU) (22.7 ± 16.7 versus 18.4 ± 14.2 days, $P = 0.03$), longer hospital length of stay (34.0 ± 20.3 versus 27.2 ± 18.2 days, $P = 0.001$), more days on mechanical ventilation (17.4 ± 15.2 versus 14.0 ± 12.4 ; $P = 0.04$), and higher ICU mortality rate (34.3% versus 21.5%; OR: 1.9; 95% CI: 1.06 to 3.41) than the early treatment group. The number-needed-to treat (NNT) to save one life was eight (NNT = 8), indicating that, in this population, one additional life would be saved for every eight patients treated with oseltamivir within the first two days of the onset of influenza symptoms.

An retrospective study examined viral shedding and length of hospital stay in 39 hospitalized patients with pandemic H1N1 influenza, of whom 29 received oseltamivir.¹³ The study found that duration of viral shedding in patients with pandemic H1N1 influenza who started oseltamivir treatment within 2 days of therapy initiation was significantly shorter than those who started therapy at later times (6.6 ± 2.7 versus 13.0 ± 8.5 ; $P = 0.042$).

A retrospective surveillance study was conducted on 308 pandemic H1N1 influenza patients,¹⁴ of whom 178 were given oseltamivir and 130 were given no antiviral treatment. The duration of virus shedding was shorter in patients with treatment, either oseltamivir treatment or conventional supportive treatment, within 24 hours after illness onset than in those who received treatment more than 24 hours after illness onset. There was also no significant difference in the duration of virus shedding between the groups who received early oseltamivir treatment and the group who received early conventional supportive treatment.

A retrospective study examined the effect of the timing of oseltamivir treatment in index cases of pandemic H1N1 influenza to reduce the spread of influenza to contacts in 362 households.²² Treatment with oseltamivir in index cases on the onset day or the following day (early treatment) was associated with a 42% reduction (OR: 0.58; 95% CI: 0.19 to 1.73) in the odds of a secondary case in a household, and a 50% reduction (OR: 0.5; 95% CI: 0.17 to 1.46) in the odds of a secondary case in individual contacts, as compared to use on day three or later, or never.

In an observational study on 67 patients with pandemic H1N1 influenza who received oseltamivir treatment, 29 patients received oseltamivir in the first 48 hours from the onset of the symptoms, and 38 patients received oseltamivir after 48 hours.²³ Among the early-treated patients, one (3.4%) developed acute respiratory distress syndrome (ARDS), while four (10.5%) from the late-treated group developed ARDS.

A retrospective study looked at the impact of early oseltamivir administration on the occurrence and severity of pneumonia due to pandemic H1N1 influenza in 442 patients.²⁴ Patients were divided into four groups based on the timing of oseltamivir administration: ≤ 2 days, 3-7 days, 8-14 days and > 7 days (groups 1 to 4, respectively). The proportions of patients with severe pneumonia or mild to moderate pneumonia increased as time to start of medication increased ($p < 0.001$). The odds ratios for severity of pneumonia for groups 2 to 4 were 5.17 (95% CI: 2.86 to 9.37), 15.02 (95% CI: 7.55 to 29.89), and 29.40 (95% CI: 8.48 to 49.10) times higher than that of group 1. Patients with a shorter time to oseltamivir administration were discharged earlier from the hospital ($P < 0.001$).

In summary, early administration of oseltamivir within the first two days from onset of symptoms of pandemic H1N1 influenza significantly reduced the length of hospital stay, duration of fever, duration of viral shedding, and mortality rate. A summary of outcomes is presented in Appendix 4 (Table A7).

Limitations

The identified evidence was limited to observational studies, comparing the efficacy of antiviral agents to no antiviral treatment. These study designs are considered to be lower quality evidence due to methodological limitations and increased risk of bias. There was no evidence found regarding human avian influenza (H5N1). Randomized studies with large populations and long-term follow-up are needed. Lack of randomization and blinding, as well as inadequate reporting on loss to follow up and compliance with the intervention may have compromised the internal validity of the studies. The external validity of the studies may allow the study results to be generalized to the general population. The level of evidence is limited, leaving uncertainty with regards to the reliability of the evidence on the effectiveness and harms of antiviral agents in the treatment and prevention of pandemic influenza. No Canadian studies were identified regarding use of antivirals to treat pandemic influenza A(H1N1), which may limit the generalizability of findings to the Canadian healthcare context.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

There is not enough evidence to firmly conclude on the clinical effectiveness of antivirals in the treatment and prophylaxis of pandemic influenza A(H1N1) and human avian influenza A(H5N1). The systematic reviews included in the 2010 CADTH report on the effects of neuraminidase

inhibitors on patients with pandemic H1N1 influenza^{29,30} provided inconclusive evidence that antiviral treatments are clinically effective in terms of reduction in mortality rates, the number and length of hospitalizations, and secondary attack rates. Findings from recent observational studies on efficacy of antiviral treatment showed that early administration of antiviral agents reduces the severity of some clinical outcomes of pandemic influenza A. Antiviral therapy should be started as soon as possible.²⁷ The effectiveness of antiviral treatment on pandemic H5N1 influenza is not known due to the rarity of published evidence

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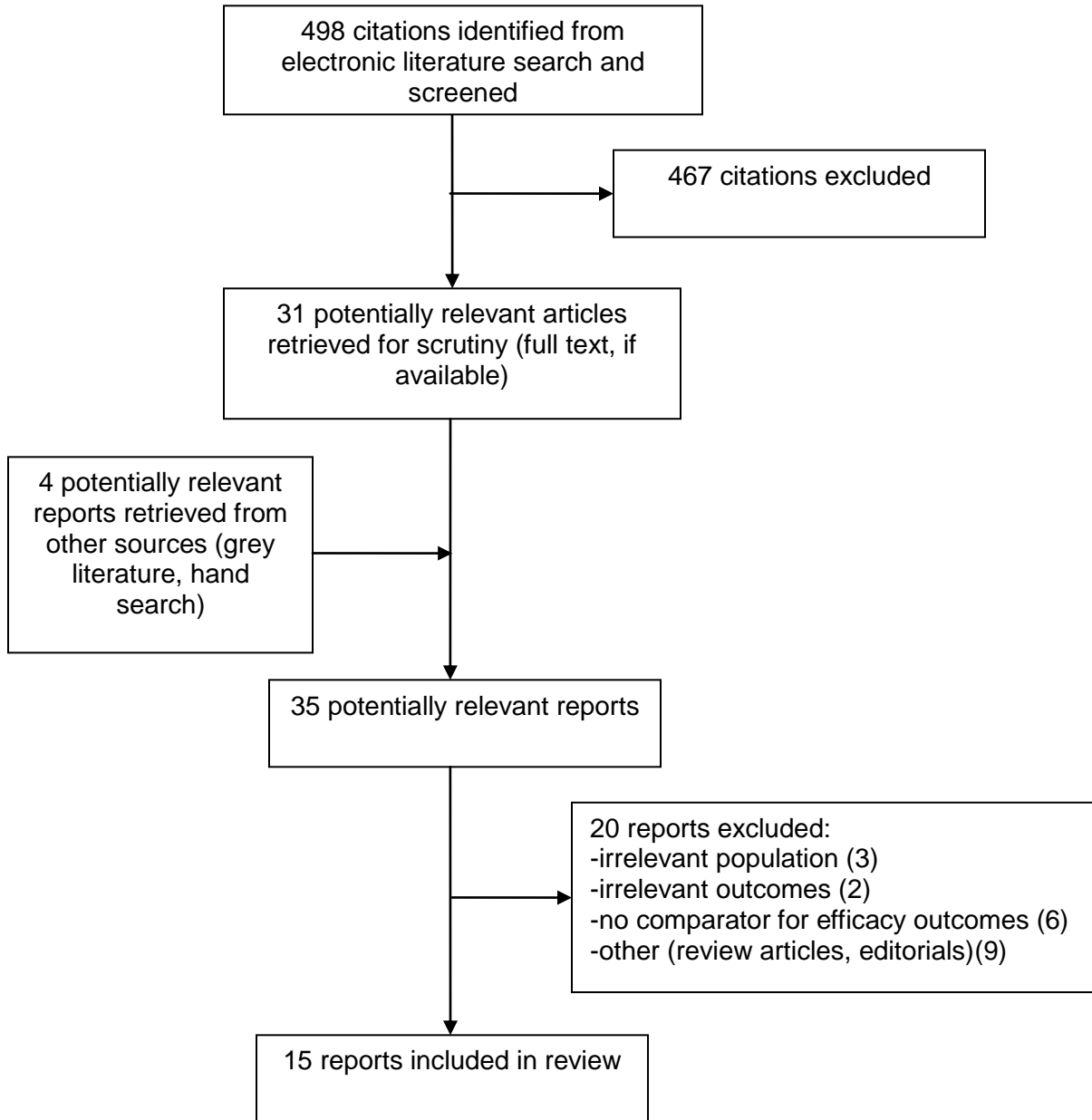
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Appendix 1: Selection of Publications



Appendix 2: Characteristics of Included Trials

Table A1: Trials included for research question 1: benefits and harms of influenza therapy

First author, Publication year; Country	Study design; Length of follow-up	Intervention	Comparator(s)	Patient characteristics	Main study outcomes
Anovadiya, 2011; India ¹⁸	Prospective study; 15 days	Oseltamivir Prophylactic group: 75 mg/ day for 10 days Therapeutic group: 75 mg twice/day for 5 days	No comparator	Total: 294 patients (ages not reported) 257 prophylactic (close contacts of cases with H1N1 influenza A) 37 therapeutic (suspected or confirmed cases of H1N1 influenza A)	Adverse drug reactions
Hama, 2011; Japan ¹¹	Retrospective (proportional mortality) study; Length of follow-up not applicable	Oseltamivir (Tamiflu) Dose not reported	Zanamivir (Relenza) or no antiviral medication	162 death cases (all ages) of ordinarily consulted patients with H1N1 influenza A, with no deterioration before prescription	Early (within 12 hours) deterioration and overall death
Khandaker, 2011; Australia ¹²	Prospective study; 6 weeks	Oseltamivir Dose (for 5 days): ages 0 to 1 month, 2 mg/kg twice/ day; ages >1 month to 3 months, 2.5 mg/kg twice/ day; >3 months to 12 months, 3 mg/kg twice/ day	No antiviral medication	Total: 56 children (age <12 months) with confirmed influenza 20 received oseltamivir (14 with confirmed H1N1 influenza) 36 received no antiviral medication (21 with confirmed H1N1 influenza)	Length of hospital stay
L'Huillier, 2011; Switzerland ¹⁷	Prospective cohort study; 30 days	Oseltamivir (Tamiflu) Oseltamivir doses (for 5 days): ages <12 months, 2 to 3 mg/kg twice/ day; ages >12 months, 30 to 75 mg, twice/ day	No comparator	Total: 54 children (ages newborn to 18 years) with confirmed H1N1 influenza	Adverse events, with a focus on neuropsychiatric adverse events
Meschi, 2011; Italy ¹³	Retrospective study; Length of follow-up not reported	Oseltamivir Dose: 75 mg twice/day or 150 mg twice/day	No antiviral medication	Total: 39 adult patients 11 patients with pneumonia	Viral load and extent, duration of viral shedding, and length of hospital stay

Table A1: Trials included for research question 1: benefits and harms of influenza therapy					
First author, Publication year; Country	Study design; Length of follow-up	Intervention	Comparator(s)	Patient characteristics	Main study outcomes
Sugaya, 2011; Japan ¹⁵	Prospective study; Length of follow-up not reported	Peramivir with Dose: intravenous infusion of 10 mg/kg (up to 600 mg) over 15-60 min., once/day for up to 5 days	No comparator	115 children up to 15 years of age with confirmed H1N1 infection	Time to alleviation of influenza symptoms, influenza virus titers, adverse events, and adverse drug reactions
Takeuchi, 2011; Japan ¹⁰	Retrospective study; Length of follow-up not reported	Oseltamivir Dose not reported	No antiviral treatment	1,023 infants <12 months of age	Length of hospital stay, complications, and severe adverse events
Wijaya, 2011; Singapore ¹⁶	Case series; Length of follow-up not reported	Zanamivir Dose 600mg/12 hours	No comparator	5 adult patients with severe pneumonia caused by 2009 H1N1, who had received oral oseltamivir prior to zanamivir	Complications
Zhang, 2011; China ¹⁴	Retrospective study; Length of follow-up not reported	Oseltamivir started at various times following symptom onset Dose not reported	No antiviral treatment	Total: 308 patients (ages 7 months to 79 years) 159 patients received oseltamivir; 12 patients received both oseltamivir and zanamivir 130 patients received no antiviral medication	Duration of fever

Table A2: Trial included for research question 2: benefits and harms of influenza prophylaxis					
First author, Publication date; Country	Study design; Length of follow-up	Intervention	Comparator	Patient characteristics	Main study outcomes
Leung, 2011; Hong Kong ¹⁹	Prospective epidemiological study; Length of follow-up not reported	Oseltamivir Dose not reported	No oseltamivir	205 household contacts (ages not reported) of secondary school students (aged 12 to 18 years)	Secondary household attack rate

Table A3: Trials included for research question 3: effects of early antiviral administration

First author, Publication date; Country	Study design; Length of follow-up	Intervention	Comparator(s)	Patient characteristics	Main study outcomes
Goldstein, 2010; US ²²	Retrospective study; Length of follow-up not reported	Oseltamivir started at day 0 to day 3+ Dose not reported	No oseltamivir	Total: 135 households (children and adults) 91 households started oseltamivir 44 households did not start oseltamivir	Secondary attack rates in households
Iglesias, 2011; Mexico ²⁴	Retrospective study; Length of follow-up not reported	Oseltamivir started at various times following symptom onset Dose: 150 mg/day for 5 days or longer	No comparator	Total: 442 patients (ages 4 months to 85 years) Oseltamivir administration initiation: ≤2 days: n=92 3-7days: n=213 8-14 days: n=101 >14 days: n=36	Clinical symptoms and duration of hospitalization
Meschi, 2011; Italy ¹³	Retrospective study; Length of follow-up not reported	Oseltamivir started at various times following symptom onset Dose: 75 mg twice/day or 150 mg twice/day	No antiviral medication	Total: 39 adult patients 11 patients had pneumonia 29 patients received oseltamivir	Viral load shedding
Mikic, 2011; Serbia ²³	Prospective study; Length of follow-up not reported	Oseltamivir started at various times following symptom onset Dose: 150 mg/day	Oseltamivir in combination with azithromycin, and oseltamivir with azithromycin plus ceftriaxone	Total: 98 patients (ages 14 to 88 years) 67 patients received antiviral therapy: 3 patients received only oseltamivir; 31 patients received oseltamivir + azithromycin; 33 patients received oseltamivir, azithromycin and ceftriaxone	Development of acute respiratory distress syndrome, mortality, and risk factors for severe forms of influenza

Table A3: Trials included for research question 3: effects of early antiviral administration

First author, Publication date; Country	Study design; Length of follow-up	Intervention	Comparator(s)	Patient characteristics	Main study outcomes
Rodriguez, 2011; Spain ²¹	Prospective, study; Length of follow-up not reported	Oseltamivir started early (≤ 2 days) or late Dose: 150 mg/24 hours or 300 mg/24 hours	No comparator	Total: 657 patients (age ≥ 15 years) 452 patients received high dose oseltamivir 147 received early (≤ 2 days) oseltamivir	Mortality, length of stay in ICU and hospital, time on mechanical ventilation
Viasus, 2011; Spain ²⁰	Prospective study; Length of follow-up not reported	Oseltamivir started at various times following symptom onset Dose not specified for all patients (35 patients received a dose of 150 mg twice/day)	No comparator	Total: 538 patients (age > 15 years) Oseltamivir administration initiation: ≤ 2 days: n= 202 3-4 days: n= 160 5-6 days: n= 87 ≥ 7 days: n=89	Mortality, length of fever, length of hospital stay, need for mechanical ventilation
Zhang, 2011; China ¹⁴	Retrospective study; Length of follow-up not reported	Oseltamivir started at various times following symptom onset Dose not reported	No antiviral treatment	Total: 308 patients (ages 7 months to 79 years) 159 patients received oseltamivir; 12 patients received both oseltamivir and zanamivir 130 patients received no antiviral medication	Virus shedding

Appendix 3: Critical appraisal of included studies

Table A4: Critical appraisal of included studies		
First author, Publication year	Strengths	Limitations
Anovadiya, 2011 ¹⁸	<ul style="list-style-type: none"> Prospective study Length of follow-up stated 	<ul style="list-style-type: none"> No comparator Unable to determine compliance with intervention Unable to determine if subjects in study were representative of the entire population from which they were recruited No blinding indicated
Goldstein, 2010 ²²	<ul style="list-style-type: none"> Study subjects representative of the entire population from which they were recruited Confounders considered 	<ul style="list-style-type: none"> Retrospective study Patient characteristics not clearly described No blinding indicated Unable to determine compliance with intervention
Hama, 2011 ¹¹	<ul style="list-style-type: none"> Study and patient characteristics clearly described Confounders considered 	<ul style="list-style-type: none"> Retrospective study No comparator Unable to determine compliance with intervention No blinding indicated
Iglesias, 2011 ²⁴	<ul style="list-style-type: none"> Study subjects representative of the entire population from which they were recruited Confounders considered 	<ul style="list-style-type: none"> Retrospective study No comparator No blinding indicated
Khandaker, 2011 ¹²	<ul style="list-style-type: none"> Prospective study Study subjects representative of the entire population from which they were recruited Length of follow-up stated 	<ul style="list-style-type: none"> Small sample size No blinding indicated
Leung, 2011 ¹⁹	<ul style="list-style-type: none"> Prospective study 	<ul style="list-style-type: none"> Unable to determine compliance with intervention No blinding indicated Confounders not considered
L'Huillier, 2011 ¹⁷	<ul style="list-style-type: none"> Prospective study Confounders considered Reporting of study and patient characteristics clearly described Study subjects representative of the entire population from which they were recruited Length of follow-up stated 	<ul style="list-style-type: none"> Small sample size No comparator No blinding indicated
Meschi, 2011 ¹³	<ul style="list-style-type: none"> Patient characteristics clearly described Study subjects representative of the entire population from which they were recruited 	<ul style="list-style-type: none"> Retrospective study Small sample size Unable to determine compliance with intervention No blinding indicated
Mikic, 2011 ²³	<ul style="list-style-type: none"> Prospective study Confounders considered 	<ul style="list-style-type: none"> No blinding indicated Unable to determine if study subjects were representative of the entire population from which they were recruited

First author, Publication year	Strengths	Limitations
Rodriguez, 2011 ²¹	<ul style="list-style-type: none"> • Prospective study • Study subjects representative of the entire population from which they were recruited • Confounders considered 	<ul style="list-style-type: none"> • No comparator • No blinding indicated
Sugaya, 2011 ¹⁵	<ul style="list-style-type: none"> • Prospective study • Study and patient characteristics clearly described • Study subjects representative of the entire population from which they were recruited 	<ul style="list-style-type: none"> • Unable to determine compliance with intervention • No blinding indicated
Takeuchi, 2011 ¹⁰	<ul style="list-style-type: none"> • Study and patient characteristics clearly described • Study subjects representative of the entire population from which they were recruited • Confounders considered 	<ul style="list-style-type: none"> • Retrospective study • No blinding indicated
Viasus, 2011 ²⁰	<ul style="list-style-type: none"> • Prospective study • Study subjects representative of the entire population from which they were recruited • Confounders considered 	<ul style="list-style-type: none"> • No comparator • No blinding indicated • Unable to determine compliance with intervention
Wijaya, 2011 ¹⁶	<ul style="list-style-type: none"> • Patient characteristics clearly described 	<ul style="list-style-type: none"> • Case series • Small sample size
Zhang, 2011 ¹⁴	<ul style="list-style-type: none"> • Prospective study 	<ul style="list-style-type: none"> • Retrospective study • No blinding indicated • Unable to determine compliance with intervention

Appendix 4: Main study findings and authors' conclusions

Table A5: Benefits and harms of influenza therapy		
First author; Publication year	Main study findings	Authors' conclusions
Anovadiya, 2011; ¹⁸	<p>Greater number of patients with adverse drug reactions in the therapeutic group than the prophylactic group (62.16% patients versus 41.63% patients)</p> <p>Higher incidence of adverse drug reactions in the therapeutic group than the prophylactic group (p = 0.029)</p> <p>Increased severity of adverse drug reactions in the therapeutic group versus in the prophylactic group: 76% mild and 24% moderate versus 89% mild and 11% moderate (p = 0.04)</p>	Oseltamivir is well tolerated in this population.
Hama, 2011; ¹¹	<p>Greater number with early (within 12 hours) deterioration after oseltamivir use than after zanamivir (32% patients versus 0% patients)</p> <p>Higher odds for deterioration leading to death after oseltamivir versus after zanamivir (OR: 5.78; 95% CI: 1.28 - 26.1; p = 0.015)</p> <p>Higher odds of early death, within two days, after oseltamivir versus after zanamivir (OR: 3.45; 95% CI: 1.11 - 14.82; p = 0.02)</p>	Tamiflu use could cause sudden deterioration leading to death. The potential harm of oseltamivir should be considered.
Khandaker, 2011; ¹²	Same median length of hospital stay in oseltamivir group and no treatment group (2.5 days)	The length of hospital stay was the same in the oseltamivir-treated and the control group.
L'Huillier, 2011; ¹⁷	Neuropsychiatric adverse events with oseltamivir use: 36% displayed neuropsychiatric adverse events such as nightmare, agitation, irritability, sleeping disorder, and seizure.	36% displayed neuropsychiatric adverse events.
Meschi, 2011; ¹³	<p>Smaller mean viral load in oseltamivir group than no treatment group (3.6 ± 1.6 versus 4.2 ± 1.7 Log 10 copies/mL; p = 0.038)</p> <p>Shorter mean length of hospital stay in oseltamivir group than no treatment group (7.7 ± 1.8 versus 10.2 ± 7.2 days; p = 0.378)</p>	Oseltamivir was associated with an early reduction in viral load but delayed the duration of shedding only marginally. The difference in duration of hospital stay was not statistically significant between the treated and non-treated groups.
Sugaya, 2011; ¹⁵	Adverse events, and adverse drug reactions of peramivir: 116 adverse events in 62.4% of the hospitalized children; 45 events in 34 patients (29.1%) were considered to be adverse drug reactions.	Peramivir is clinically safe in children with pandemic H1N1 infection.
Takeuchi, 2011; ¹⁰	<p>Similar mean length of hospital stay in oseltamivir group than no treatment group (4.26 versus 4.30 days; p = 0.68)</p> <p>Similar mean rate of complications in oseltamivir group than no treatment group (18.8% versus 15.8%; p = 0.21)</p>	<p>There was no statistically significant difference in length of stay between patients treated with or without oseltamivir.</p> <p>The rate of complications was similar between the two groups.</p>

Table A5: Benefits and harms of influenza therapy

First author; Publication year	Main study findings	Authors' conclusions
Wijaya, 2011; ¹⁶	Side effects of zanamivir in 5 cases: no side effects reported	There were no side effects associated with the use of intravenous zanamivir.
Zhang, 2011; ¹⁴	Similar mean duration of fever oseltamivir versus no treatment (70.37 ± 36.17h versus 68.33 ± 34.05h; p = 0.624)	Oseltamivir treatment did not shorten the duration of fever as compared to no antiviral treatment.

Table A6: Benefits and harms of influenza prophylaxis

First author, Publication date	Main study findings	Authors' conclusions
Leung, 2011; ¹⁹	Smaller secondary household attack rate with oseltamivir use than no treatment (0% versus 8.5%; OR: 0; 95% CI: 0 – 0.9)	Oseltamivir prophylaxis seemed to prevent secondary infection in household settings.

Table A7: Effects of early antiviral administration

First author	Main study findings	Authors' conclusions
Goldstein, 2010; ²²	Reduced in the odds of a secondary case infection in a household when oseltamivir was administered to index cases on the onset day or the following day (42% reduction; OR: 0.58; 95% CI: 0.19 - 1.73) Reduced in the odds of a secondary case infection in individual contact when oseltamivir was administered to index cases on the onset day or the following day (50% reduction; OR: 0.5; 95% CI: 0.17 - 1.46)	Early administration of oseltamivir may help to prevent H1N1 influenza transmission.
Iglesias, 2011; ²⁴	The odds ratios for severity of pneumonia for late-treated groups were 5.17 (95% CI: 2.86 – 9.37), 15.02 (95% CI: 7.55 – 29.89), and 29.40 (95% CI: 8.48 – 49.10) times higher than that of early-treated group (≤2 days) Patients with a shorter time to oseltamivir administration were discharged earlier from the hospital (p < 0.001)	Early administration of oseltamivir reduced rate and severity of pneumonia, and shortened the duration of hospital stay.
Meschi, 2011; ¹³	Shorter duration of viral shedding in patients who started oseltamivir treatment within 2 days of therapy initiation than those who started therapy at later times (6.6 ± 2.7 versus 13.0 ± 8.5; p = 0.042).	Early administration of oseltamivir reduced duration of viral shedding.
Mikic, 2011; ²³	Smaller number of patients who received oseltamivir in the first two days developed acute respiratory distress syndrome (ARDS) than the late-treated group (3.4% versus 10.5%)	Early antiviral administration seems to improve clinical outcomes.

Table A7: Effects of early antiviral administration

First author	Main study findings	Authors' conclusions
Rodriguez, 2011; ²¹	<p>Longer median length of stay in the intensive care unit (ICU) in patients receiving oseltamivir within the first 2 days, as compared to those whom oseltamivir administration was delayed (22.7 ± 16.7 versus 18.4 ± 14.2 days, $p = 0.03$)</p> <p>Longer length of stay in the hospital (34.0 ± 20.3 versus 27.2 ± 18.2 days, $p = 0.001$)</p> <p>More days on mechanical ventilation (17.4 ± 15.2 versus 14.0 ± 12.4; $p = 0.04$),</p> <p>Higher ICU mortality rate (34.3% versus 21.5%; OR: 1.9; 95% CI: 1.06 – 3.41)</p>	Early oseltamivir administration seemed to improve clinical outcomes.
Viasus, 2011; ²⁰	<p>Shorter duration of fever in patients receiving oseltamivir within the first 24 hours, as compared to those whom oseltamivir administration was delayed more than 24 hours (OR: 1.67; 95% CI: 1.03 - 2.72)</p> <p>Shorter length of hospital stay in early oseltamivir administration group (OR: 1.67; 95% CI: 1.06-2.63)</p> <p>Less need for mechanical ventilation in early oseltamivir administration group (OR: 3.13; 95% CI: 1.56 - 6.27)</p> <p>Decrease in mortality rate in early oseltamivir administration group (OR: 4.29, 95% CI: 1.25 -14.63)</p>	Early administration of oseltamivir seemed to provide clinical benefits.
Zhang, 2011; ¹⁴	The duration of virus shedding was shorter in patients with treatment, either oseltamivir treatment or conventional supportive treatment, within 24 hours after illness onset than in those who received treatment more than 24 hours after illness onset	Early administration of oseltamivir helped to reduce the duration of viral shedding.