WHO Guidelines for Pharmacological Management of Pandemic Influenza A(H1N1) 2009 and other Influenza Viruses

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Part II
Review of evidence

World Health Organization

Contents

Summary of Evidence for Benefits and Harms[1]

1. Treatment of Seasonal or Pandemic Influenza

1.1 Use of oseltamivir – treatment

Oseltamivir, a neuraminidase inhibitor, is available for oral administration as hard capsules (75mg, 45mg, and 30mg) or as a powder for reconstitution (12mg/ml suspension). Extemporaneous preparation for nasogastric administration has been described and enteric absorption appears to be comparable between critically ill and ambulatory influenza patients (Ariano et al., In press; Taylor et al., 2008). Treatment is now indicated for infants <1 year when treating pandemic influenza; dosage and administration are described elsewhere (see Annexes 7 and 8).

There are no systematic reviews or randomized controlled trials assessing the efficacy and safety of antivirals for pandemic influenza A (H1N1) 2009 infection. There are, however, a number of recent observational studies addressing a range of outcomes for antiviral use, with oseltamivir the most commonly used antiviral (see 'Observational data – pandemic influenza' below for a summary of these studies). Given the lack of clinical trial evidence specifically addressing pandemic influenza, a description of evidence for seasonal influenza is provided below.

<u>Systematic review/clinical trial evidence – seasonal influenza</u>
A recent systematic review of neuraminidase inhibitors (Jefferson et al., 2009) provides an updated assessment of the efficacy and safety of oseltamivir for the treatment of influenza in adults and a second systematic review (Shun-Shin et al., 2009) provides an assessment of the use of neuraminidase inhibitors in children (see Section 2.1 for prophylactic evidence and Sections 1.2 and 2.2 for zanamivir evidence).

The Jefferson et al. (2009) review included five trials of oseltamivir used for treatment of influenza in otherwise healthy adults. The results of these trials indicated a statistically significant advantage for oseltamivir compared to placebo in the alleviation of symptoms (HR=1.20; 95% CI: 1.06, 1.35; see Table A5.1, Annex 5). However the reduction in duration of illness is less than a day, which suggests a modest treatment benefit (Jefferson et al., 2009). The evidence presented by Jefferson (2009), although limited to healthy adults instead of the additional at-risk, children, and elderly populations assessed by Burch et al. (2008), concurs with the results reported by Burch (2008), which formed the basis of the evidence used in the formulation of the WHO Pharmacological Guidelines (August 2009).

The Jefferson (2009) review excludes some of the evidence used in the previous review by Kaiser et al. (2003). Eight of the 10 trials included in the Kaiser (2003) meta-analysis remain unpublished, resulting in inaccessibility of data for re-evaluation of outcomes presented in the Kaiser (2003) paper. The remaining available evidence addressing safety of oseltamivir

[1] Updated January 2010.

indicates that oseltamivir induced nausea (OR=1.79; 95% CI: 1.10, 2.93; see Table A5.1, Annex 5) and did not significantly reduce influenza-related lower respiratory tract infections (RR=0.55; 95% CI: 0.22, 1.35; see Table A5.1, Annex 5). This evidence is based on a relatively small number of trials (three for lower respiratory tract complications and two for nausea). Jefferson (2009) states that it is possible there is publication bias, however a funnel plot was not undertaken given that there are only three trials.

There are no new reviews of the efficacy and safety of oseltamivir in at-risk patients and, as such, the evidence provided in the August 2009 Guidelines, which indicated a reduction of slightly less than a day in duration of illness (-22.75 hours), remains current (Burch et al., 2008).

The Shun-Shin (2009) review included two trials assessing the efficacy of oseltamivir for the treatment of seasonal influenza in children. The authors did not pool efficacy results from these trials due to inadequate reporting and heterogeneity of trial data. The results of the two oseltamivir trials indicated a median reduction of 0.4 to 1.5 days in time to illness resolution. The trials were pooled for some adverse event outcomes, which showed that oseltamivir significantly increased vomiting (RD=0.05; 95% CI: 0.02, 0.09; p=0.007; see Table A5.2, Annex 5), however there was no difference in occurrence of nausea and diarrhoea. There were also no data available on serious complications such as pneumonia or hospitalizations.

The Jefferson (2009) review and available randomized comparative trials do not provide any information regarding the outcomes of mortality, progression to severe disease, or hospitalization. There are, however, several observational studies of fatal outcomes and hospitalization as discussed below (see seasonal observational data and Annex 6).

<u>Observational data – seasonal influenza</u>

A summary of observational data for the use of antivirals in seasonal influenza is provided in Table A6.1 in Annex 6. The studies vary in terms of design, patient population, outcomes assessed, and analyses conducted. Most assessed the use of oseltamivir, with a few assessing zanamivir use and one study assessing the use of amantadine.

Some studies indicated advantages associated with the use of oseltamivir, however some conflicting results were observed. For example, Kawai et al. (2009), in a retrospective review of Japanese influenza patients receiving a neuraminidase inhibitor, reported that the mean duration of fever was longer for oseltamivir-treated patients than those treated with zanamivir ($p<0.001$). However, these results are based on a small population of 164 patients and were specifically for infection with 2008-09 H1N1 influenza, which is a predominantly oseltamivir-resistant (H275Y) strain. The impact of oseltamivir versus zanamivir on time to afebrile state may depend upon the influenza strain in question. A further report demonstrated no significant difference in fever duration for seasonal H1N1, but a shorter fever when treating H3N2 with oseltamivir and when treating influenza B with zanamivir (Kawai et al., 2009). Earlier data also demonstrated this lower clinical effectiveness of oseltamivir against influenza B compared to influenza A infection (Sugaya et al., 2007).

In an analysis of observational data for oseltamivir use, Freemantle and Calvert (2009) reviewed nine post-marketing studies of oseltamivir. The authors concluded that although the studies were of variable quality, they generally supported the conclusion that oseltamivir may reduce the incidence of pneumonia and other complications of influenza in healthy adults. Freemantle and Calvert (2009) highlight that these events are rare; therefore, treatment of influenza with oseltamivir is not likely to be clinically important for otherwise healthy adults. The authors also discuss the potential biases in the studies, in particular the studies' selection criteria, which excluded those who received oseltamivir later than the recommended time frame, so may not represent real world use. Differences in baseline comorbidity or geographical distribution were present in several studies and the direction of bias from confounding by indication was uncertain. These factors, or similar factors, may impact upon all observational studies; therefore, the results of the observational data provided should be critically assessed to consider potential sources of bias.

Several observational studies address the impact of oseltamivir on outcomes such as hospitalization and death in seasonal influenza. It was reported in August that oseltamivir may be associated with significant reductions in pneumonia, otitis media, and hospitalization compared to unmatched controls (Blumenthals et al., 2007; Gums et al., 2008). Two observational studies, McGeer et al (2007) and Lee et al. (2008), indicate a reduction in mortality in seasonal influenza, with odds ratios of 0.21 and 0.26, respectively, for impact of antiviral treatment on mortality. There is also a new observational study (Hanshaoworakul et al., 2009) which assessed the impact of oseltamivir treatment on fatal outcomes in hospitalized patients with severe influenza in Thailand. The study found that when cardiovascular disease and hypertension were controlled, oseltamivir was associated with increased survival (OR=0.13; 95% CI: 0.04, 0.38 for cardiovascular disease and OR=0.14; 95% CI: 0.04, 0.44 for hypertension, see Table A5.3, Annex 5). This study was a retrospective review of medical charts and, as such, may be open to bias and does not allow for the establishment of causal relationships.

Following are descriptions of recent observational studies of oseltamivir.

Piedra et al. (2009) assessed influenza-related complications in children with chronic medical conditions. This retrospective review of a medical database in the US covering six influenza seasons found that oseltamivir was associated with a statistically significant reduction in the risk of respiratory illnesses other than pneumonia (OR=0.74; 95%CI, 0.63–0.87), otitis media (OR=0.69; 95%CI, 0.48–0.99), and all-cause hospitalization (OR=0.33; 95%CI, 0.13–0.83) at 14 and 30 days following influenza diagnosis in children with chronic medical conditions (see Table A5.4, Annex 5). This study is based on the same database reported by Blumentals et al. (2007) previously reviewed by the Guidelines Panel, which noted that the observational data are derived from cohorts in the US; therefore, they may not be representative of the occurrence of these events in other populations or locations. In addition, the authors of the current study acknowledge a number of limitations of the study, including the fact that the database is limited primarily to patients covered by employer-sponsored health insurance; the use of diagnostic coding for influenza was assigned on basis of physicians' clinical diagnoses alone; it was impossible to confirm if patients began antiviral treatment within the recommended timeframe; and patients were not assigned randomly nor matched with respect to propensity to be given oseltamivir. Although there were few clinically significant differences between the two cohorts and multivariate analyses were used to adjust for differences, the results of this study should still be interpreted with caution.

Another observational study assessing safety (Casscells et al., 2009) was a retrospective review of administrative data for members of the US Department of Defense, which assessed occurrence of cardiovascular events in patients with a history of vascular disease (see Table A5.3, Annex 5). This study found that oseltamivir provided a statistically significant protective effect against recurrent cardiovascular events in patients with a history of vascular disease (OR=0.417; 95% CI: 0.349, 0.498). Given the study design, the authors acknowledge that the study is susceptible to a number of sources of confounding, including omission of potentially important variables such as severity and prior duration of patient's symptoms, presence of specific comorbidities, prior prophylactic treatment, subject compliance with critical medications, or death due to causes unrelated to influenza. As such, the results, which are only relevant to patients with vascular disease, should also be interpreted with caution.

There are no new data available regarding the use of oseltamivir in pregnant women in seasonal influenza. Evidence previously presented showed that the use of oseltamivir in pregnant women (Tanaka et al., 2009) has not indicated any additional dangers. The Tanaka study reported on a population of 90 pregnant Japanese women who received oseltamivir and found that the incidence of malformation (1.1%) was within the incidence of major malformations in the general population. Oseltamivir does not appear to have a negative impact on breastfeeding, although the only data available are based on the report of one lactating woman (Wentges-van Holthe et al., 2008).

There are no published randomized controlled trials assessing the efficacy and safety of oseltamivir in children aged <1 year. However a recent retrospective chart review (Kimberlin et al., 2009) assessed the comparative safety of oseltamivir, rimantadine, and amantadine in 180 infants treated with antivirals. This review found that children <1 year of age treated with oseltamivir were significantly less likely to develop abnormalities in the head/eyes/ears/nose/throat system, such as otitis media, compared to children treated with rimantadine or amantadine (1.7% versus 15.4%; $p<0.01$; see Table A5.5, Annex 5). However, there were no statistically significant differences in the occurrence of neurologic, pulmonary, gastrointestinal, cardiovascular, dermatologic, systemic response, genitourinary, musculoskeletal, hematologic/lymphatic, hepatobillary/pancreatic, and endocrine/metabolic abnormalities in children treated with oseltamivir or one of the adamantanes. A second retrospective chart review (Siedler et al., 2009) investigated the frequency of side-effects and duration of fever by time to oseltamivir treatment in infants <1 year (n=157). All except one infant completed the 5-day course. Seventy-eight infants experienced mild additional symptoms, of which vomiting (39%) and diarrhoea (22%) were the most common. These reviews are based on small numbers of subjects (n=180 and 157) and are open to bias given the lack of randomization, control group, or blinding of outcome assessment.

<u>Observational data – pandemic influenza</u>

Table 1.1 below provides a summary of the available observational data addressing the use of neuraminidase inhibitors for pandemic (H1N1) 2009 infection. All of these studies included ill or severely ill patients. Most of the studies did not specify which neuraminidase inhibitor was used; however, the only drug mentioned is oseltamivir and it is likely it was the most commonly used antiviral.

Some studies showed advantages associated with neuraminidase treatment (e.g. Dominguez-Cherit et al., 2009), such as indicating that neuraminidase treatment compared to no treatment was associated with improved survival (OR=7.4; 95% CI: 1.8, 31.0). However, all studies, except Echevarria-Zuno et al. (2009), had relatively small sample sizes and were likely to be open to a number of sources of bias.

In vitro and animal studies have demonstrated the efficacy of oseltamivir against pandemic (H1N1) 2009 virus (Itoh et al., 2009; MMWR, 1 May 2009).

Several observational studies have demonstrated the impact of time to treatment on disease progression and outcome for pandemic (H1N1) 2009 infection. Cao et al. (2009) identified treatment delays of greater than 48 hours as an independent risk factor for prolonged viral replication. Several retrospective studies reported fatal cases as rarely receiving treatment within 48 hours (Echevarria-Zuno et al., 2009; Jain et al., 2009; Jamieson et al, 2009; Libster et al., 2010), though no statistical comparison was made to other outcome groups. One case control study demonstrated that time to antiviral therapy was the strongest correlate of disease severity, with an odds ratio for ICU versus community cases of 12.0 (4.65–30.7) for an interval from symptom onset to antiviral treatment of more than 48 hours as compared to less than 48 hours (Zarachynski et al. 2010). In addition, a chart review has indicated that patients treated within 48 hours of symptom onset experience shorter median hospitalization. Much of the data presented is uncontrolled, retrospective clinical data; therefore, results should be interpreted with caution.

One observational study has been conducted with regard to the use of oseltamivir in pregnancy for pandemic influenza (Louie et al., 2009b). This study indicated that treatment initiation more than 48 hours after illness onset was associated with ICU admission or death. No data on adverse events from antiviral use were reported.

The WHO's *Weekly Epidemiological Record* (WER 2009) reported 39 cases of oseltamivir-resistant pandemic (H1N1) 2009 virus up to October 2009; a subsequent WER reported cumulative cases of 190 up to January 2010. WHO concluded that the relatively small number of oseltamivir-resistant pandemic viruses does not constitute a public health threat at this point and there is no evidence that such viruses are circulating at a community level, although transmission has occurred in local settings. Further discussion on antiviral sensitivity of circulating strains of influenza virus is in Part I, Section 5. Of relevance is the recent publication by Kawai et al. (2009) demonstrating that oseltamivir is clinically less effective in treatment of infection by oseltamivir-resistant viruses carrying the H275Y mutation. Lack of oseltamivir efficacy for oseltamivir-resistant seasonal H1N1 containing the same H275Y mutation was also noted in animal models (Itoh et al., 2009) and observational clinical studies (Gooskens et al., 2009; van der Vries et al., 2008).

With the exception of the two studies looking at adherence and adverse effects associated with prophylactic oseltamivir in UK school children (Kitching et al., 2009; Wallensten et al., 2009; see Section 4.1), as well as the observational data described here, there is a relative absence of data based directly on the use of oseltamivir in pandemic (H1N1) 2009. While the seasonal influenza data may be applicable to pandemic influenza infection, the similarities and differences between the two types of influenza should be considered when applying treatment recommendations.

Initial recommendations for dose and duration of oseltamivir treatment for pandemic (H1N1) 2009 influenza were based upon data from seasonal, uncomplicated influenza. However, the extent to which this is applicable to the pandemic strain is uncertain, given the high incidence of severe disease and longer viral replication experienced in pandemic influenza (Lee et al., 2009; Li et al., 2010; Witkop et al., 2009 ; de Serres et al., 2009; Lye et al., 2009).

Table 1.1: Available observational data for pandemic influenza A (H1N1) 2009

Studies	Design	N	Population characteristics	Key results
Cao 2009	Observational study	426	Quarantined patients in Chinese hospitals	– Delay of >48 hours from symptom onset to oseltamivir treatment is an independent risk factor for prolonged real-time RT-PCR positivity (OR=4.46; 95% CI: 2.58, 7.72; P<0.001).
Denholm 2010	Prospective case series	112	Hospitalized patients with laboratory-confirmed pandemic (H1N1) 2009	– 93 patients, or 83%, received oseltamivir treatment – Antiviral treatment was initiated at a median time of 3 days, with fever persisting for a median of 1 day after treatment. – 30 patients required admission to an intensive care unit and 3 patients died. The paper does not indicate if any of these patients were treated. – A quarter (n=15) of female patients were pregnant.
Dominguez-Cherit 2009	Retrospective review Description of critically ill patients	58	Critically ill hospitalized patients with confirmed, probable or suspected H1N1 (2009) in Mexico	– By 60 days, 24 patients had died (41.4%; 95% CI: 28.9, 55.0). – Fatal cases have a reduced time frame/opportunity to receive treatment. After adjustment for this bias, neuraminidase inhibitor treatment versus no treatment was associated with improved survival (OR=7.4; 95% CI: 1.8, 31.0).
Echevarria-Zuno 2009	Retrospective review Protective and risk factors for infection, severe disease, and death	6945 confirmed cases of pandemic (H1N1) 2009	Mexican patients with influenza-like illness seeking treatment at clinics of the Mexican social security network	– Confirmed pandemic (H1N1) 2009 mortality rate of 0.9%. – Of those reporting whether antivirals were used, 75% (488/650), or 7.1% of the total confirmed population, used antivirals. – Of 61 deaths, 40 (66%) used antivirals. – 4 pregnant patient fatalities, all received oseltamivir within 5-9 days of symptom onset.
Jain 2009	Medical chart review Description of clinical characteristics	272	Hospitalized patients with confirmed pandemic (H1N1) 2009 influenza	– Antiviral therapy was used in 200 of 268 patients (75%) at a median of 3 days following illness onset. – In a multivariable model, the only variable significantly associated with a positive outcome was antiviral treatment within 2 days after illness onset. – 7% mortality rate, or 19 cases. 90% of fatal cases received antivirals, but the median time from symptoms to initiation was 8 days and none received treatment within 48 hours.
Jamieson 2009	Summary of infection and death in pregnant women	34	Pregnant women	– 17 patients (50%) received oseltamivir. – 6 deaths were reported, none of which were treated within 48 hours; authors recommend early antiviral treatment.

Studies	Design	N	Population characteristics	Key results
Libster 2010	Retrospective case series	251 pandemic (H1N1) 2009 cases and an equal number of age-matched 2007-8 seasonal influenza cases	Children hospitalized with confirmed pandemic (H1N1) 2009 (6 hospitals) in Buenos Aires May-July 2009. Age-matched children with 2007-8 seasonal influenza	– The use of antiviral therapy did not significantly affect the risk of admission to an ICU (OR=0.88; 95% CI, 0.20-2.95; p = 0.83). – 12% of children in the ICU and 13% of those in the wards received oseltamivir within 48hours of symptom onset. – Of 13 fatal cases, none received oseltamivir within 48 hours of symptom onset.
Louie 2009	Public health surveillance	1088	Hospitalized or fatal cases with laboratory evidence of pandemic (H1N1) 2009	– 1088 cases of hospitalization or death. – 884 with treatment data; 21% did not receive antiviral treatment and 49% received treatment more than 48 hours after symptom onset.
Louie 2010	Surveillance of hospitalization and death from pandemic (H1N1) 2009 influenza	Pregnant (94), postpartum (8), non-pregnant (137)	Women of reproductive age hospitalized with pandemic (H1N1) 2009 influenza	– In pregnancy, treatment >48hours after illness onset was associated with admission to an ICU or death (relative risk = 4.3, 95% CI: 1.4, 13.7).
Slopen (MMWR) 2010	Medical chart review	99	Patients hospitalized with confirmed pandemic (H1N1) 2009 influenza	– Those treated within 2 days (47%) had a shorter median hospitalization than those treated later (median hospitalization of 2 vs. 3 days, P=0.02).
Zarychans-ki 2010	Nested case control study	795 ICU (45), hospitalized (181), community (569)	Confirmed pandemic (H1N1) 2009 cases for whom final treatment location known	– Antiviral therapy prescribed to 34% of community, 54% of hospitalized and 95% of ICU patients ($p<0.001$). – Of those treated, approximately 97% were given oseltamivir. – Symptom onset median delay to antiviral treatment was 2 days (IQR1-3) for community, 4 days (IQR2-6) for hospitalized, and 6 days (IQR4-9) for ICU patients ($p\leq0.001$). – Community vs. ICU: Time to antiviral therapy OR=8.24 (95%CI: 2.82, 24.1). – Time to antiviral therapy was the strongest correlate of disease severity.

1.2 Use of zanamivir - treatment

Zanamivir, also a neuraminidase inhibitor, is administered as an inhaled powder (10mg twice daily). It is licensed for adults and children aged 5 years and above.

As for oseltamivir, there are no systematic reviews or randomized controlled trials assessing the efficacy of zanamivir for pandemic (H1N1) 2009 infection. However, there are individual case reports of intravenous zanamivir use in the treatment of the severely ill, often immunocompromised patients with proven or suspected oseltamivir-resistant pandemic (H1N1) 2009 illness. As a result, seasonal clinical trial evidence and observational data are presented, alongside case studies of intravenous zanamivir.

Systematic review/clinical trial evidence – seasonal influenza
Jefferson et al.'s (2009) recent systematic review of neuraminidase inhibitors includes an assessment of zanamivir treatment in otherwise healthy adults with naturally occurring influenza (see Section 2.2 for prophylactic evidence and Sections 1.1 and 2.1 for oseltamivir evidence). A second systematic review (Shun-Shin et al., 2009) provides an assessment of the use of zanamivir in children.

The Jefferson et al. (2009) review includes a total of 8 treatment trials, 2 of which were linked to the others, leaving 6 separate trials. There was a statistically significant advantage of zanamivir compared to placebo for the alleviation of symptoms (HR=1.24; 95% CI: 1.13, 1.36; see Table A5.6, Annex 5). However, as with oseltamivir, the reduction of illness was less than a day. The Shun-Shin et al. (2009) review included two trials of zanamivir treatment in children. As for oseltamivir, the authors did not pool these trials for efficacy outcomes due to inadequate reporting and heterogeneity of data. The NA130009 trial (published as Hedrick et al., 2000) showed a median reduction of 1.25 days (95%CI: 0.5, 2.0; $p<0.001$) to resolution or alleviation of symptoms when comparing zanamivir to placebo for treatment of confirmed influenza. For the treatment of clinical influenza a significant reduction remained associated with zanamivir, but it decreased to 0.5 days (95% CI: 0.0, 1.5; $p=0.011$). The second zanamivir trial included in the Shun-Shin review is unpublished and it showed a similar reduction of 0.5 days in median time to resolution of symptoms, but did not report confidence intervals or a p-value. The Hedrick et al. (2000) trial also showed that children with confirmed or clinical influenza returned to school or normal activity one day sooner than those treated with placebo (p=0.019 and p=0.022, respectively). Overall, the data summarized by Jefferson et al. (2009) and Shun-Shin (2009) indicates the same as had been previously reported for zanamivir (Burch et al., 2008): a reduction of less than a day for alleviation of symptoms.

The trials included in the Jefferson (2009) review showed there was no occurrence of statistically significant adverse events associated with zanamivir. Similar results were reported for the zanamivir treatment trials in children in the Shun-Shin (2009) review, with no significant difference in the number of withdrawals due to adverse events between zanamivir and placebo. In addition, the Hedrick (2000) trial reported no significant difference in asthma exacerbations between zanamivir and placebo (difference=-0.01; 95% CI: -0.03, 0.01; p=0.30).

<u>Observational data – seasonal influenza</u>
There are no new data available addressing the outcomes of mortality, progression to severe disease or hospitalization. As reported in the August 2009 Guidelines, an observational study conducted in the US indicated that the occurrence of complications is similar between those treated with zanamivir and untreated controls (Cole et al., 2002). A retrospective analysis of published trials assessing the impact of zanamivir on the occurrence of respiratory events leading to the use of antibiotics found that zanamivir reduced the number of antibiotic prescriptions (Kaiser et al., 2000). However the number of patients with respiratory events was small and the post-hoc nature of the study indicates the results should be interpreted with caution.

There remains no publicly available data describing the use of zanamivir in children aged <1 year. There is no additional data regarding the use of zanamivir in pregnant women beyond the Tanaka (2009) report described in the August Guidelines, which illustrated the outcomes of four pregnant women who were exposed to zanamivir (one spontaneous miscarriage, one termination, and two healthy births). The Tanaka (2009) paper also concluded that the amount of zanamivir that would be ingested by a 5kg infant is much lower than the recommended dose for children.

<u>Observational data – pandemic influenza</u>
The body of clinical trials and reviews addressing the use of zanamivir are all for seasonal influenza. However, there are several published case reports summarizing the use of intravenous zanamivir in severely ill patients with confirmed pandemic (H1N1) 2009 infection (Kidd et al., 2009; Englund et al., 2009; Gaur et al., 2009). The patient reported by Kidd was neutropenic following chemotherapy for Hodgkin's disease and was not responding to oseltamivir or nebulized zanamivir. Intravenous zanamivir (600mg twice daily) was started in conjunction with methylprednisolone and the patient's condition improved within 48 hours. The authors concluded that although the data presented was a single case report and direct cause and effect cannot be confirmed, the improvement associated with intravenous zanamivir treatment warrants further investigation, both alone and in combination with methylprednisolone. The Englund case report detailed the treatment of a leukemia patient on immunosuppressive therapy. After identification of oseltamivir-resistant pandemic H1N1 2009, and poor tolerance to inhaled ribavirin and zanamivir, the patient received IV zanamivir and oral ribavirin. This case, however, was ongoing at time of print, so the impact of IV zanamivir was unknown. The Gaur correspondence reports a case of prolonged oseltamivir-resistant infection in a 10 year old with leukemia. The patient was given 600mg IV zanamivir every 12 hours for 15 days, during which viral load substantially decreased and, after 10 days, the patient was weaned off ventilation. No zanamivir-related adverse effects were observed.

As discussed for oseltamivir, dosing and duration recommendations for zanamivir are based on data from seasonal, uncomplicated influenza. However, due to the different experiences of clinical severity and duration of viral shedding in pandemic influenza, different treatment regimens may also be considered for zanamivir (Li et al., 2009; Lee et al., 2009).

1.3 Use of amantadine - treatment

Systematic review/clinical trial evidence – seasonal influenza

The reviews by Jefferson (2006) and Alves Galvao et al. (2008) are the most current source of information regarding the efficacy of amantadine. These reviews demonstrated that amantadine is superior to placebo in terms of a reduction in duration of fever for both adults and children, with a decrease in fever duration of a day for adults (MD=-0.99; 95% CI: -1.26, -0.71) and fewer cases of fever for children (see Table A5.7, Annex 5). There was no statistically significant difference demonstrated between amantadine and placebo in the occurrence of adverse events in the randomized trials.

Observational data – seasonal influenza

A retrospective chart review by Kimberlin et al. (2009) assessed the comparative safety of oseltamivir and the adamantanes rimantadine and amantadine in 180 infants treated with antivirals. As reported above for oseltamivir (see Section 1.1), the review found that children <1 year of age treated with oseltamivir were significantly less likely to develop abnormalities in the head/eyes/ears/nose/throat system, such as otitis media, compared to children treated with rimantadine or amantadine (1.7% versus 15.4%; p<0.01; see Table A5.5, Annex 5). However, there were no statistically significant differences in the occurrence of body system abnormalities in infants treated with oseltamivir or one of the adamantanes. This review is based on a small number of subjects (n=180) and is open to bias given the lack of randomization and lack of blinding of outcome assessment. A comparison of M2 inhibitors for prophylaxis in elderly patients concluded that amantadine was much less well-tolerated than rimantadine (Keyser et al., 2000). There remains no new published comparison of the safety of amantadine in adults.

There are also no published data assessing the outcomes of mortality, progression to severe disease or hospitalization, or the use of amantadine in pregnant women. Nor are there any published data assessing the use of amantadine in pandemic (H1N1) 2009 infection.

1.4 Use of rimantadine - treatment

Systematic review/clinical trial evidence – seasonal influenza

As for amantadine, the reviews by Jefferson (2006) and Alves Galvao et al. (2008) are the most current source of information regarding the efficacy of rimantadine. The reviews demonstrated that rimantadine is superior to placebo in terms of a reduction in duration of fever for adults of greater than a day (MD=-1.24; 95% CI: -1.71, -0.76) and fewer cases of fever for children (see Table A5.8, Annex 5). There was no statistically significant difference demonstrated between rimantadine and placebo in the occurrence of adverse events in the randomized trials.

Observational data – seasonal influenza

As noted above in Sections 1.1 and 1.3, the Kimberlin (2009) review found that children <1 year of age who were treated with oseltamivir were significantly less likely to develop abnormalities in the head/eyes/ears/nose/throat system, such as otitis media, compared to children treated with rimantadine or amantadine (1.7% versus 15.4%; p<0.01; see Table A5.5, Annex 5). However there were no statistically significant differences in the occurrence of body system abnormalities in children treated with oseltamivir or one of the adamantanes. In addition, the Keyser (2000) study indicates that rimantadine is better tolerated than amantadine.

There have been no further publications assessing the safety of rimantadine nor is there any information available regarding the outcomes of mortality, progression to severe disease, or hospitalization. Rimantadine is not recommended for use in pregnant women.

1.5 Use of peramivir - treatment

Peramivir, an investigational neuraminidase inhibitor, has received an Emergency Use Authorization (EUA) in the US and market authorization in Japan. The US authorization was based on a review by the Food and Drug Administration (FDA) of four trials assessing intravenous peramivir. These trials have not yet been published and there are no current publications assessing the use of intravenous peramivir in humans. A discussion of the EUA for peramivir (Birnkrant and Cox, 2009) provides some information regarding the peramivir data.

A total of 1891 patients have received peramivir in a variety of doses, formulations (intravenous or intramuscular), and/or durations. The usual adult dose is 600mg/day administered intravenously for 5 to 10 days. Birnkrant and Cox (2009) report one trial demonstrating that alleviation of symptoms was approximately one day sooner with peramivir than with placebo in otherwise healthy adults with uncomplicated seasonal influenza, similar to the effects observed with oseltamivir and zanamivir. Two trials were conducted using oseltamivir as the comparator, however the results did not indicate that peramivir was superior and, since a clinically meaningful non-inferiority margin has not been established, no conclusions can be drawn about the trial results. The fourth trial demonstrated no statistically significant distinctions between two different doses or single and multiple doses of peramivir.

The most commonly reported adverse events in the clinical trials were diarrhoea, nausea, vomiting, and neutropenia. The Birnkrant and Cox (2009) report does not provide any further details on adverse events.

No paediatric patients have received peramivir in clinical trials, although the Birnkrant and Cox (2009) report states that a limited number of paediatric patients have received peramivir under the earlier FDA Emergency Investigational New Drug procedures. The report does not provide any information regarding the use of peramivir in these paediatric patients.

There have been no trials of peramivir in patients with pandemic (H1N1) 2009 virus. The Birnkrant and Cox (2009) report indicates that peramivir was granted EUA as it is reasonable to believe that it may be effective in patients with pandemic influenza given the available evidence in seasonal influenza, the serious nature of the disease, and the lack of alternative treatment options.

1.6 Use of arbidol

Arbidol is a Russian-made antiviral that is widely used in Russia and China. A review by Boriskin et al. (2008) provides a summary of the studies of arbidol, although little detailed information is provided regarding the trials.

According to Boriskin (2008), arbidol taken at a dose of 200mg/day for 5 to 10 days was reported to reduce the duration of influenza by about 1.7 to 2.65 days. This is a greater increase than that observed for the neuraminidase inhibitors; however, no information is available regarding the size or design of the trials from which this result was derived. Boriskin (2008) also states that arbidol has been shown to prevent the development of post-influenza complications and lower the frequency of re-infection. The table below provides a summary of the trials reported by Boriskin (2008).

Table 1.6: Summary of arbidol data, as reported by Boriskin (2008)

Trial	Design/setting	Results summary
Guskova 1999	– Prophylaxis during epidemic outbreak of influenza B – Russia	– Number of diseased reduced by 86.3%.
Guskova 1999	– Community outbreaks caused by influenza A H3N2 or seasonal H1N1 viruses – Russia	– Efficacy index (EI)[a] highest in non-vaccinated (2.5) compared to vaccinated subjects (1.3) – Protective effect of arbidol lasted beyond its prophylactic course and was superior to that of rimantadine in terms of duration of effect.
Kubar 1997	– Randomized placebo-controlled trial of arbidol for prophylaxis – Russia	– Arbidol prophylaxis reduced duration of illness by 1.8 to 3.5 days and overall morbidity was reduced by 1.2 to 4-fold.
Kramerev 2003	– Study comparing children receiving two doses of arbidol prophylaxis – Ukraine	– Arbidol prophylaxis prevented the development of severe forms of respiratory disease and/or complications.
Uchaikin 2004	– Children with chronic respiratory infections taking arbidol – Russia	– Number of sick subjects was 3.7-fold lower in the arbidol group compared to the untreated group and number of cases of acute bronchitis, pneumonia, or otitis was 4-fold lower.
Gagarinov 1993	NR	– Arbidol prophylaxis shown to be 80% effective during influenza outbreaks in 1988-1989.
Belyaev 1996	– Prophylactic use of arbidol in 335 children aged 6-15 years – Arbidol treatment – Russia	– EI=2.05 to 2.22 – Acute respiratory disease in arbidol-treated children was milder and 2-3 days shorter than that in placebo-treated patients. Incidence of recurrent illness was 4.6 to 5 times higher in the placebo group.
Drinevsky 1998	– Arbidol treatment in 158 pre-school and school-aged children – Russia	– Treatment efficiency coefficient was 84.8% with statistically significant reductions of fever period, larynxotracheitis symptoms and virus nasal shedding. Efficacy was most pronounced when the drug was administered early in the infection, although the review does not define “early”.

Trial	Design/setting	Results summary
Yi 2004	– Randomized, double-blind comparison of arbidol and placebo in 125 patients presenting with fever within 36 hours of onset of disease during a community acquired-influenza outbreak. – China	– Proportion of patients with alleviated symptoms significantly higher with arbidol compared to placebo. Similar frequency of adverse events in both groups.

[a] Efficacy Index refers to the ratio of the number of diseased per hundred of subjects taking placebo compared to that taking the drug.
NR = not reported; EI = efficacy index.

While the results described by Boriskin (2008) report some efficacy and safety of arbidol, the lack of information regarding trial design, trial numbers, and comparative analyses indicates the results should be interpreted with caution.

The use of prophylactic arbidol to prevent acute viral respiratory infections and complications in over 4000 Russian servicemen (Shuster 2004) demonstrated a lower infection rate (14.1%) compared to placebo (30.8%). Arbidol also lowered the rate of viro-bacterial pneumonia. The authors conclude the results demonstrate that the use of arbidol allows for lowering the rate of infection of influenza and also lowering the rate of viro-bacterial pneumonia.

Kolobukhina et al. (2009) reports on a comparison of ingavirin and arbidol in adult patients with influenza. This trial included 105 patients with confirmed uncomplicated influenza. The results indicated that duration of fever with ingavirin (34.5 hours) was significantly lower compared to duration of fever with arbidol (48.4 hours). There were no side effects observed and no complications reported in patients treated with ingavirin.

1.7 Use of ribavirin

Ribavirin is a broad-spectrum antiviral agent, active *in vitro* against various RNA and DNA viruses. Ribavirin treatment of hepatitis C and respiratory syncytial virus infections has been approved in many countries, but no wide-scale authorizations have been made for its use against influenza.

The table below provides a summary of the available ribavirin data for influenza. The available randomized placebo-controlled trials provide inconsistent results. Symptomatic improvement was significant in studies by Knight (Knight et al., 1981; MEDA 2009), Stein (1987) and Rodriguez (1994), whereas Schiff (MEDA 2009) and Bernstein (1988) reported no statistical difference between ribavirin and placebo. Impact on viral load is uncertain, as case reports of intravenous (Hayden et al., 1996) and one trial of aerosolized ribavirin (Knight et al., 1981) suggest an antiviral-induced reduction, whereas two RCTs of oral ribavirin and one of aerosolized ribavirin report no impact on viral load (Smith et al., 1980; Stein et al., 1987; Berstein et al., 1988).

All of the ribavirin efficacy trials had small sample sizes, with most trials having less than 35 patients and only the Rodriguez trial having more than 50 patients (n=62). Data for the clinical efficacy of ribavirin against influenza virus are limited, particularly due to small sample sizes, incomplete trial information and incompatible protocols for meta-analysis.

Pharmacokinetic trials in rats and monkeys have been conducted using oral, inhaled, and intravenous administration routes. Bioavailability of 45-65% has been reported upon oral administration (eMC 2009). High lung and plasma concentrations have been reported for inhaled and intravenous administration, respectively (MEDA 2009).

Adverse effects recorded in humans include mild to moderate haemolytic anaemia, reversible upon cessation of therapy. Animal data also indicate possible genotoxicity, carcinogenicity, and teratogenicity (MEDA 2009).

Table 1.7: Summary of Ribavirin studies and reviews for influenza

Studies	Design	N	Population characteristics	Key results
Bell 1988	Case report Aerosolized ribavirin	1	Ventilated immunocompromised adult with influenza B viral pneumonia	– Initial reduction of fever upon treatment, followed by deterioration on day 2. By day 7, normal temperature restored and on day 8 managed short periods of spontaneous breathing, but began developing ARDS. – 4 days after stopping ribavirin (day 11), fever reappeared. Died on day 30 of hypoxic cardiac arrest. – Noted disadvantage of cost of ribavirin.
Bernstein 1988	Randomized double-blind placebo-controlled trial Aerosolized ribavirin	20	10 treatment and 10 placebo adults with confirmed influenza B	– No significant difference observed in clinical scores or viral titres.
Chan-Tack 2009	Letter	n/a	Influenza patients (naturally and artificially infected)	– Ribavirin studies are limited by small sample sizes, differences in subjects enrolled, dose and duration of ribavirin, timing between infection and treatment, and reporting of outcomes, microbiologic data and adverse events (AEs). – Reported AEs consistent with labelling. Substantial safety issues (e.g. haemolytic anaemia). – The studies are inconclusive as to the clinical benefit for influenza treatment.
Hayden 1997	Review of clinical data	7	Immunocompromised transplant patients	– IV ribavirin: Bone marrow transplant patients, n=2, 1 survivor (50%). – Aerosolized ribavirin: Solid organ transplant n=2 with 2 survivors, bone marrow transplant n=4 with 3 survivors. Overall 71% survival. – Lower survival rate than other treatment options, but limitation of low number and tendency of use for severe cases. – Combination therapy with adamantanes gave enhanced in vitro activity. Clinical case in a bone marrow transplant patient was associated with survival.
Hayden 1996	Case reports IV ribavirin	3	Patients with serious influenza and parainfluenza infection	– IV ribavirin was generally well tolerated (anaemia in one patient). – Viral shedding diminished in 1 patient and ceased in 2 patients in temporal association with ribavirin administration.

Studies	Design	N	Population characteristics	Key results
Knight 1981	Randomized, controlled clinical trial Aerosolized ribavirin	32	College students with influenza Treated: 14 seasonal H1N1 and 1 H3N2 Untreated controls: 17	– In seasonal H1N1 patients, a significant reduction in height and duration of fever, reduction in systemic illness, and disappearance of influenza virus from respiratory secretions. – H3N2 patient recovered. – Suggests inhaled ribavirin may be more effective than oral, but there is no directly comparable data.
MEDA 2009	Company summary of information on aerosolized ribavirin formulation Virazole	n/a	PK data in rats/monkeys	– 70% of aerosolized ribavirin reached bronchial tree, with high concentrations in lung tissue. Bioavailability from oral dosing is 45-65%. IV ribavirin rapidly reaches high plasma concentrations.
			Effectiveness studies in animal models	– Animal studies give differing conclusions: effective, not significant, or only effective in combination. Suggest teratogenicity as possible adverse event.
			Clinical data	– Knight: 6 double-blind, placebo-controlled trials. N=157 (74 treated, 83 controls). Pooled p-value for illness severity significant, but not for temperature or viral titres reduction. – Schiff: 4 double-blind placebo-controlled trials. No statistical difference found. – IV and inhaled: well-tolerated. Side effect: haemolytic anaemia. – Suggest ribavirin should be reserved for the severely ill.
Riner 2009	Retrospective review of FDA's EIND database Literature review	n/a	Patients granted EIND[1] use of ribavirin between Feb 1997-Dec 2008	– EIND: Only outcome measure with sufficient data was disease - 18 requests for ribavirin for influenza. – Literature: 2 IV ribavirin influenza patients identified, both patients died. – No adverse events were reported when treating influenza. – Limitation of sample size, poor reporting and bias.
Rodriguez 1994	Double blind multicentre, placebo-controlled trial Aerosolized ribavirin	62	Children hospitalized with confirmed influenza ≤48 hours of symptom onset Placebo = 35 Ribavirin = 27	– Aerosolized ribavirin shortened fever duration by an average of 14 hours (p=0.04) and reduced convalescent antibody titres (p=0.04). – Did not significantly affect other illness measures compared to placebo.

Studies	Design	N	Population characteristics	Key results
Smith 1980	Randomized, blinded, placebo-controlled trial Oral ribavirin	97	Young adult males naturally infected with seasonal H1N1	– Mean antibody titres lower in treated group, but not significantly different to placebo. – No significant difference between mean total symptom scores. Nor was a difference observed when frequency of moderate to severe symptoms was compared. – Same number of febrile patient-days in the two groups. – No clinical effect of ribavirin. – Adverse effect was a transient increase in serum bilirubin.
Stein 1987	Randomized, blinded, placebo-controlled trial Oral ribavirin	25	Adults with uncomplicated influenza A or B 15 patients treated, 10 given placebo	– Oral ribavirin significantly improved symptoms and signs of influenza (A or B). – Rate of decline of mean symptom score was 2.5 times faster in treatment arm than placebo (not significant). – Within 48 hours, Influenza A treated patients had 42% decrease in symptom load (as opposed to 23% in placebo; p=0.01). – Antiviral effect not significant (no difference in virus-positive status). – No adverse effects.

[1] Emergency Investigational New Drug.
n/a = Not available.

1.8 Other products

Intranasal interferons

In vitro data indicate no major cytokine dysregulation due to pandemic (H1N1) 2009 virus. Therefore, whether immunomodulators such as interferons are useful as an adjunctive therapy is uncertain, with the possible exception of individual severe cases (Woo et al., 2010). However, Osterlund et al. (2009) demonstrated the sensitivity of pandemic (H1N1) 2009 virus to the antiviral effects of interferons. Other influenza viruses vary in their *in vitro* interferon sensitivity. Thus, uncertainty remains regarding the potential value of interferons for treatment of influenza. Animal data show constraint of viral replication and prevention of transmission by intranasal interferons (Steel et al., 2009).

There are no published clinical randomized controlled trials or observational studies of current intranasal interferon preparations for the treatment of influenza. Other routes of administration, such as suppositories and sublingual tablets, were not considered in this review.

Immunoglobulins

Although monoclonal antibodies have been tested in pre-clinical models, there are no published, randomized controlled trials or observational data for the use of immunoglobulins in the treatment or prophylaxis for influenza.

1.9 Anti-inflammatory products

Aspirin

The association between Reye's syndrome and salicylates in children and adolescents (<18 years) is well established. A series of five key case control studies informed recognition of this association in 1980, which has been followed by extensive published epidemiological and observational data over the last thirty years (Starko et al., 1980; Halpin et al., 1982; Waldman et al., 1982; CDC MMWR, 1980). U.S. surveillance data demonstrate the likely impact on incidence of Reye's syndrome due to the reduction in aspirin use since the association was first identified. Reported cases rapidly descended from a peak of 555 cases in 1980, to less than 36 per annum since 1987 (Belay et al., 2009).

Corticosteroids

Corticosteroids, such as methylprednisolone and hydrocortisone, are occasionally used as an adjunctive therapy for the treatment of ARDS in severe influenza due to their immunomodulatory properties. The influenza virus mechanisms of cytokine dysregulation, and the action of corticosteroids to potentially correct this, are incompletely understood (Carter et al., 2008). A summary of key corticosteroid literature for influenza is provided in the table below (Table 1.9).

Recently published retrospective observational studies suggest that corticosteroid treatment of influenza is associated with a higher likelihood of ICU admission and mortality as clinical outcomes (Jain et al., 2009; Liem et al., 2009). In addition, two observational studies demonstrate that corticosteroid use is associated with slower viral clearance, significantly increased odds of persistent viral replication 7 days after symptom onset (Lee et al., 2009), and a longer duration of viral shedding with increased corticosteroid dose (Nichols et al., 2004).

Dosage recommendations have changed as new data have emerged, but consensus on whether corticosteroids should be used for the treatment of influenza and, if so, at what dosage, has still not been attained. High dose methylprednisolone has been demonstrated as ineffective in ARDS (Bernard et al. 1987), though results from several studies and reviews suggest a positive impact on ARDS by long duration low-dose corticosteroids (Sessler et al., 2008; Quispe-Laime et al., 2009). However, there are no placebo-controlled clinical trials specifically assessing the impact of low-dose corticosteroids in patients with serious influenza. Therefore, the evidence base for the treatment of influenza with corticosteroids is largely extrapolated from trials conducted for ARDS resulting from different aetiologies (Annane et al., 2004; Tang et al., 2009). One such trial for late-stage ARDS demonstrated the impact of treatment timing on clinical outcome. Corticosteroids 7-13 days after ARDS onset reduced mortality, whereas after 13 days is associated with increased mortality (Steinberg et al., 2006), indicating possible harms from the use of corticosteroids.

In addition to the scarcity of influenza-specific trial data, many existing studies are limited by low participant numbers, lack of a control group, and confounding.

Table 1.9: Clinical data for corticosteroids in influenza

Studies	Design	Population characteristics	Key results
Abdel-Ghafar 2008	H5N1 review	H5N1 cases	– Prolonged or high-dose corticosteroid therapy can result in serious adverse events, including opportunistic infections (e.g. CNS toxoplasmosis). – In a Vietnamese study, mortality was 59% among 29 recipients of corticosteroids, as compared with 24% among 38 persons who did not receive corticosteroids (*P*=0.004). – Recommends against routine use of corticosteroids.
Carter 2007	Literature review	Clinical and laboratory literature for H5N1	– Adrenal insufficiency can be overcome with prolonged (7-10 days or more) of supraphysiological steroid treatment at a high enough dose to reduce activation of NF-κB, but low enough not to cause immune suppression. – Annane (2004) sepsis review suggests a long course of low dose steroids is more protective against mortality than high dose short courses. – Few animal studies for influenza, plus it is difficult to extrapolate dosage thresholds. – Human H5N1 data are limited as there are few cases (28) and confounding complicates analysis. – Steroids should not be used as monotherapy. – Conclusion: there is weak evidence suggesting steroids have an adjunctive role in influenza.
Jain 2009	Medical chart review N= 272	Hospitalized patients with confirmed pandemic H1N1 influenza	– Fatal cases and patients admitted to an ICU were more likely to have received corticosteroids than those hospitalized on wards (52% vs. 31%, significant $p<0.05$).
Lee 2009	1-year, prospective observational study N=147	Adult patients hospitalized with influenza 37 (25.2%) using corticosteroids	– Systemic corticosteroid use for asthma or COPD was associated with slower viral clearance. – Viral RNA detected at symptom day 7: 53.8% in those using corticosteroids and 25% in those not (p=0.007). – Virus isolated at symptom day ≥4: 24.1% and 14.9% (corticosteroids vs. none) (p=0.256). – Corticosteroid use is associated with persistent viral replication at 1 week after illness onset (OR=5.44, 95% CI:1.86, 15.89, p=0.002).
Liem 2009	Retrospective review	Laboratory confirmed cases of H5N1 in	– Stratified analysis of the effect of steroid treatment on outcome, after controlling for possible confounding by the presence or absence of neutropenia at admission (as a marker of severity),

Studies	Design	Population characteristics	Key results
	N=67	Vietnam	still found evidence of an increased risk of death (Mantel-Haenszel summary OR=4.11; 95% CI: 1.14, 14.83; P=0.027)
Nichols 2004	Reviewed records of 12 seasons from 1 transplant centre N= 62	Influenza after haemopoietic stem cell transplantation	– Duration of influenza virus shedding was longer in patients treated with steroid doses of >1mg/kg than among those treated with doses of <1mg/kg (mean, 15 vs. 9 days).
Quispe-Laime 2009	Prospective evaluation Uncontrolled study N=13	Suspected pandemic H1N1 acute lung injury–ARDS patients in ICU. 8 H1N1 patients, 1 Influenza A (not H1N1), and 4 influenza A negative.	– All received oseltamivir. Severe ARDS patients received methylprednidone (1mg/kg/day), others received hydrocortisone (300mg/day). – By treatment day 7: significant improvement in lung injury and multiple organ dysfunction scores (p<0.001). Results were similar for pandemic H1N1 positive and negative patients. – Similar impact of both corticosteroids. – Prolonged low-to-moderate dose was well-tolerated and associated with significant improvement in lung injury and organ dysfunction score.
Sessler 2008	Review	Influenza patients with ARDS	– High dose methylprednisolone (MP) (120mg/kg/day) administered early in ARDS is ineffective. – Extended course (≤28 days) of low dose (1mg/kg/day) corticosteroids are associated with reduced systemic inflammation, shorter duration of ventilation and lower mortality. – Timing is important. MP administered >13 days after ARDS onset was associated with higher mortality. Administering MP on day 7-13 was associated with lower mortality.

2. Chemoprophylaxis of Influenza

2.1 Use of oseltamivir - chemoprophylaxis

Systematic review/clinical trial evidence – seasonal influenza

There are no new trials available addressing the chemoprophylactic use of oseltamivir. The updated Jefferson (2009) review reported that the two trials of prophylactic use of oseltamivir in adults demonstrated that oseltamivir reduced the chance of symptomatic, laboratory-confirmed influenza (RR=0.39; 95% CI: 0.18, 0.85; see Table A5.1x, Annex 5). The trials did not support or refute the impact of oseltamivir on ILI (RR=1.28; 95% CI: 0.45, 3.66; see Table A5.1, Annex 5). Two trials assessing post-exposure prophylaxis demonstrated significant protection for households.

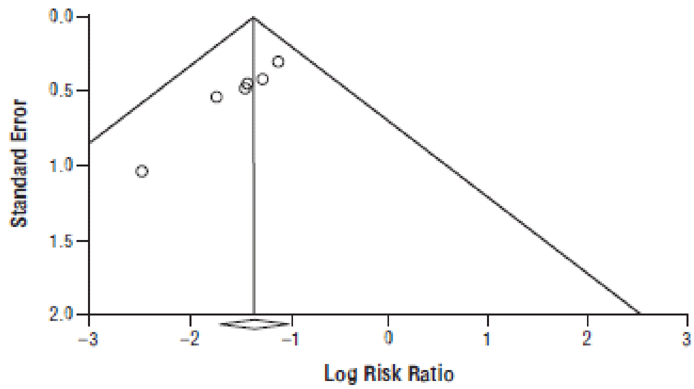
The Shun-Shin (2009) review of the use of neuraminidase inhibitors in children reported on one post-exposure prophylactic trial of oseltamivir. This trial demonstrated a reduction in the risk of developing confirmed symptomatic influenza after introduction of an index case into the household (RD=-0.12; 95% CI: -0.21, -0.03).

A systematic review by Khazeni et al. (2009) assessed the safety and efficacy of extended duration (>4 weeks) of chemoprophylaxis with neuraminidase inhibitors. Pooled results of the four oseltamivir trials demonstrated a decreased incidence of symptomatic influenza (RR=0.236; 95% CI: 0.144, 0.387; see Table A5.9, Annex 5). The Khazeni (2009) review also provides results for oseltamivir and zanamivir combined – these results follow the same pattern as those observed for the individual drugs (see Table A5.10, Annex 5). There was no statistically significant difference between the efficacy of oseltamivir and zanamivir (p=0.64). However, the review provides no information regarding the methodology used to indirectly compare the two drugs to obtain this result.

Based on the same four trials, there was no statistically significant advantage for oseltamivir compared to placebo for asymptomatic influenza (RR=0.781; 95% CI: 0.563, 1.082, see Table A5.9, Annex 5). There were no serious adverse events reported with oseltamivir in prophylactic treatment, although this is based on only one trial in the Khazeni (2009) review. Oseltamivir was associated with an increased risk for nausea and vomiting based on the results of four trials, compared with placebo (RR=1.48; 95% CI: 1.86, 2.33). There was no statistically significant difference between oseltamivir and zanamivir in the occurrence of adverse events (p=0.32).

The results presented by Khazeni (2009) should be interpreted with caution, given the risk of publication bias. The authors noted that although assessments for publication bias were limited by the small sample size, a funnel-plot analysis was asymmetric and the Begg method suggested bias (*p*=0.009). Figure 2.1 below provides the funnel plot assessing publication bias in the Khazeni (2009) review.

Figure 2.1: Funnel plot for symptomatic influenza



The results described above for the Khazeni (2009) review are consistent with the evidence provided by the Tappenden et al. (2009) review summarized in the August 2009 Guidelines, which found that in adults there were statistically significantly fewer cases of laboratory confirmed infection in patients receiving oseltamivir compared to placebo (RR=0.27, 95% CI: 0.09, 0.83; see Table A5.11, Annex 5). In mixed households, including adults and children, post-exposure prophylaxis resulted in fewer cases of infection (RR=0.19; 95% CI: 0.08, 0.45). The Tappenden et al., (2009) review also reported that for elderly individuals there were statistically significantly fewer cases of infection (RR=0.08; 95% CI: 0.01, 0.63) with oseltamivir use.

Khazeni (2009) reported that antiviral therapy is contraindicated for only two weeks after live attenuated vaccination (LAIV) due to the possibility of limiting viral replication, therefore interfering with the response to vaccination. They also reported that, if the use of LAIV increases, it will be unclear whether individuals receiving LAIV could safely receive neuraminidase prophylaxis during a pandemic. The authors encouraged randomized controlled trials to study the efficacy and safety of neuraminidase inhibitors administered two weeks after LAIV.

<u>Observational data – pandemic influenza</u>

Two studies (Kitching et al., 2009; Wallensten et al., 2009) report on surveys of treatment adherence and adverse events associated with the prophylactic use of oseltamivir for H1N1 influenza in the UK. Wallensten et al. (2009) reported on 248 students (11-12 year olds) who received prophylaxis with oseltamivir. Over three-quarters of children (77.2%) reported that they took the full 10-day course of prophylaxis, while 91.9% reported they took the medication for at least 7 days. Half of the children (50.8%) reported they felt unwell while taking oseltamivir and 50.6% reported at least one symptom compatible with side effects of oseltamivir. Headaches were reported by 24.3% and stomach ache by 21.1%. The report states that although some children were ill with flu-like symptoms, none of the children tested had pandemic H1N1 infection. The proportion of subjects reporting adverse events was considerably higher than that reported in clinical trials (Tappenden et al., 2009), where less than 10% of patients reported adverse events with prophylactic use of oseltamivir.

The survey reported by Kitching et al. (2009) was sent to 256 schoolchildren and 103 (40%) responded. Of the responders, 95 were offered oseltamivir prophylaxis, of which 85 (89%)

took any of the drug. Less than half of the primary school children (48%) took a full course, while 76% of secondary school children completed a full course. More than half of all children (53%) reported side effects, with gastrointestinal symptoms reported by 40% of children, nausea by 29%, and mild neuropsychiatric side effects reported by 18%.

Unlike Wallensten (2009), Kitching (2009) found low adherence with prophylaxis. This may be related to the fact that the Wallensten (2009) review was the first school affected by the pandemic (H1N1) 2009 outbreak in the UK and media attention was high at the time. The results of both surveys should be interpreted with caution given that the numbers are relatively small and responses may have been influenced by a number of sources. Both surveys indicated a relatively high proportion of adverse events; however, the severity of these events does not appear to be high.

2.2 Use of zanamivir - chemoprophylaxis

Systematic review/clinical trial evidence – seasonal influenza
There are no new trials available addressing the prophylactic use of zanamivir. The updated Jefferson (2009) review reported that the two trials of prophylactic use of zanamivir in adults demonstrated a reduction in the likelihood of symptomatic laboratory-confirmed influenza (RR=0.38; 95% CI: 0.17, 0.85; see Table A5.6, Annex 5). The trials did not support or refute the impact of zanamivir on ILI (RR=1.51; 95% CI: 0.77, 2.95; see Table A5.6, Annex 5). Two trials assessing post-exposure prophylaxis demonstrated significant protection for households.

The Shun-Shin (2009) review in children reported that two trials of post-exposure prophylactic zanamivir were associated with a reduction in the risk of developing confirmed symptomatic influenza following introduction of an index case in the household (RD=-0.07; 95% CI: -0.12, -0.02; RD=-0.08; 95% CI: -0.14, -0.03). When the zanamivir and oseltamivir trials were pooled, the absolute risk reduction was 8% (RD=-0.08; 95% CI: -0.12, -0.05).

The systematic review by Khazeni (2009) (described in Section 2.1 above) reported a decreased risk of the incidence of symptomatic influenza with zanamivir prophylaxis (RR=0.256; 95% CI: 0.179, 0.367; see Table A5.9, Annex 5), with no significant advantage for zanamivir for asymptomatic influenza (RR=1.402; 95% CI: 0.900, 1.983). There was no statistically significant difference between zanamivir and placebo in the occurrence of serious adverse events (RR=0.952; 95% CI: 0.525, 1.728).

The results of the recent reviews concur with those in the Tappenden review (2009) presented in the August 2009 Guidelines, which demonstrated a statistically significant benefit for zanamivir prophylaxis compared to placebo in all populations (except for the elderly), with protective efficacy ranging from 70% to just over 80% (see Tables A5.12-A5.13, Annex 5).

2.3 Use of amantadine - chemoprophylaxis

Systematic review/clinical trial evidence – seasonal influenza

There are no new trials or reviews addressing chemoprophylactic use of amantadine for influenza. The Tappenden review (2009) assessed the use of amantadine for chemoprophylaxis of influenza A, only reporting individual trial results, given the between-trial heterogeneity. Amantadine demonstrated advantages in post-exposure chemoprophylaxis; however, the authors state that the results should be interpreted with caution given the age and quality of the amantadine trials. The occurrence of adverse events was usually similar between amantadine and placebo, however two trials demonstrated a greater occurrence of adverse events in amantadine-treated patients, with severe adverse effects more frequent for those given amantadine chemoprophylaxis compared to placebo.

2.4 Use of rimantadine - chemoprophylaxis

Systematic review/clinical trial evidence – seasonal influenza

As for amantadine, there are no new trials or reviews addressing chemoprophylactic use of rimantadine. The data provided in the Jefferson (2006) review and the Alves Galvao (2008) review directionally favour rimantidine compared to placebo, with protective efficacy of 70% in adults and 50% in children. However, the results were not statistically significant. Assessment of the occurrence of adverse events in the Jefferson (2006) review revealed a statistically significant increase with rimantadine compared to placebo.

Annexes

Annex 4: Methods used to prepare guidelines

The WHO Guidelines on the pharmacological management of humans infected by influenza were prepared as a "rapid advice guideline", as defined in the WHO Handbook for Guideline Development.[2] The scope of the guidelines on pharmacological management was defined by a working group of WHO staff and circulated to the Guidelines Panel for comment. A consultant was contracted to update evidence summaries from secondary sources, according to the GRADE methodology (GRADE Working Group 2008). Search strategies used for identifying relevant systematic reviews, clinical study reports and other observational data are described below.

The evidence was assessed according to the methodology described in GRADE. In this system, evidence is classified as high, moderate, low, or very low and the definition of each is listed below.

- High: Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low: Any estimate of effect is very uncertain.

Factors that are considered in classifying evidence are: the study design and rigor of its execution, the consistency of results and how well the evidence can be directly applied to patients, interventions, outcomes, and comparator. Other important factors are whether the data are sparse or imprecise and whether there is potential for reporting bias. The randomized, controlled trials of antivirals are generally of a high quality in terms of study design, interventions, comparators, outcomes, and consistency of results. However, there are currently no clinical trials of available antivirals used in a pandemic situation. Consequently, there is some uncertainty about the applicability of the available evidence to a pandemic situation. While a group of trials can produce "high quality" evidence for one question, because of uncertainty about their applicability or directness, the same trials can produce "very low" quality evidence for a different question.

The recommendations were drafted according to the GRADE method for assessing quality of evidence and strength of recommendations. A Guidelines Panel comprising international scientists and experts in clinical treatment of influenza, guideline methodology, basic research, policy making, pharmacology and virology was convened in June 2009. The Guidelines Panel was asked to identify critical clinical outcomes for the purposes of making

[2] WHO Handbook for Guideline Development. Guidelines Review Committee, World Health Organization, 2007, 7.

the recommendations. Mortality, duration of hospitalization, incidence of lower respiratory tract complications, antiviral resistance, and serious adverse effects were rated as critical outcomes in the assessment of treatment interventions for human influenza infection. For chemoprophylaxis, influenza cases, outbreak control, drug resistance, and serious adverse effects were rated as critical outcomes. The impact of chemoprophylaxis on these outcomes was the basis of the deliberations used in making judgments. All outcomes reported in the clinical trials are summarized in the evidence profiles, Annex 2.

The Panel reviewed the evidence summaries and the draft guidelines and made recommendations. All recommendations were based on consensus.

Formulating the recommendations included explicit consideration of the quality of evidence, benefits, harms, burdens, costs, and values and preferences, described in the 'Remarks' for each recommendation. "Values" are the desirability or preference that individuals exhibit for a particular health state. Individuals usually assign less value to and have less preference for more impaired health states (e.g. death or dependency after a stroke) compared to other health states (e.g. full health or having a very mild stroke without serious secondary effects). In this document, the term "values" refers to the relative worth or importance of a health state or consequences (benefits, harms, and costs) of a decision.

For this guideline, the main cost consideration was the acquisition cost of the antivirals.

Recommendations are classified as "strong" or "weak" recommendations, as suggested in the GRADE methodology. "Strong" recommendations can be interpreted as:

- Most individuals should receive the intervention.
- Most well-informed individuals would want the recommended course of action and only a small proportion would not.
- Could unequivocally be used for policy making

"Weak" recommendations can be interpreted as:

- The majority of well-informed individuals would want the suggested course of action, but an appreciable proportion would not.
- Widely varying values and preferences.
- Policy making will require extensive debates and the involvement of many stakeholders.

After the meeting, the guideline was revised by the WHO Secretariat, according to the recommendations from the Panel, and circulated to the panel members for review. Comments were reviewed by the WHO Secretariat and were incorporated into the final version. A record of comments not included, with reason for the rejections, was kept and is available on request.

Updating of the Guidelines

A WHO Rapid Advice Guidelines Group on Influenza met in January 2010 to review revised background documentation produced based on new evidence.

The panel agreed on the same ranking of outcomes as used in formulation of the Guidelines of August 2009. A value of 7-9 indicated an outcome was considered critical for a decision, 4-6 indicated it was important, and 1-3 indicated it was not important.

Outcomes were included roughly in order of their relative importance in evidence tables and outcomes that were considered not important (a score of 3 or less) were not included. The table below provides the rankings given to the treatment and prophylaxis outcomes by the panel members for the Guidelines of August 2009.

Table A4.1: Ranking of outcomes for antiviral treatment

Treatment outcome	Mean	Median
Mortality	8.3	9.0
Hospitalization	7.2	8.0
Duration of hospitalization	6.1	6.5
Time to alleviation of symptoms	5.8	6.0
Time to return to normal activity	5.4	5.5
Complications (LRTI, otitis media)	6.9	7.0
Serious adverse events	7.7	8.0
Mild adverse events	4.2	4.5
Drug-related adverse events	6.4	6.5
Viral shedding	5.8	6.0
Resistance	7.6	8.0
Cost of drugs	5.6	6.0

Table A4.2: Ranking of outcomes for antiviral prophylaxis

Treatment outcome	Mean	Median
Influenza cases prevented	8.0	8.0
Influenza-like illness cases	5.7	6.0
Mortality	7.6	8.5
Hospitalization	6.8	7.5
Complications (LRTI, otitis media)	6.2	6.5
Serious adverse events	8.1	9.0
Mild adverse events	5.4	6.0
Drug-related adverse events	6.9	7.5
Viral shedding	5.1	5.0
Resistance	6.9	7.5
Cost of drugs	6.7	7.0

Search strategy

Relevant systematic reviews, study and trial reports, and observational data were identified through searches of MEDLINE (Pubmed), Embase, BMJ clinical evidence and the Cochrane Library. Search terms comprised generic and trade names of individual antivirals (e.g. oseltamivir), drug classes (e.g. neuraminidase), and common names for other therapeutic classes (e.g. corticosteroids). In addition, information was collated from principal regulatory authorities and regular monitoring of published medical literature.

In reviewing and updating the evidence base in January 2010, further searches were conducted, following the process described above with the addition of new antivirals, such as arbidol. These subsequent searches were limited to 2009-2010.

Selection criteria, data collection, and judgments

The update used systematic reviews to summarize evidence from randomized trials. The systematic reviews were supplemented with individual randomized trials and observational studies when necessary.

Evidence profiles based on the systematic reviews were created using the GRADE approach and GRADE profiler software (version 3.2.2). Using this approach, assessments of the quality of evidence for each important outcome take into account the study design, limitations of the studies, consistency of the evidence across studies, the directness of the evidence, and the precision of the estimate. Three main criteria were used for assessing trial limitations: concealment of allocation, blinding, and follow-up. If most of the evidence for an outcome (based on the weight given to each study in the meta-analysis) came from trials that did not have serious limitations, the overall assessment for that outcome was that there were no important limitations. GRADE quality assessments were given for evidence based on randomized controlled trials.

Because all of the evidence in the reviews was based on seasonal influenza and thus indirect for pandemic influenza, this aspect of the GRADE profile was scored accordingly, resulting in "moderate" or "low" classification of evidence. This does not mean that the trials were of a moderate or low quality, but rather that there is some uncertainty about applying the evidence, based on seasonal influenza, to a pandemic situation.

Summary of findings tables

The key findings for each question were summarized in GRADE tables using the most important findings from the systematic reviews.

Annex 5: Summaries of findings tables

Following are the GRADE evidence tables for the data described in the Guidelines.

Author(s): P Whyte
Date: 2009-12-20
Question: Should oseltamivir be used for influenza?
Settings: Adults and children
Bibliography: Jefferson (2009), as well as articles by Hanshaoworakul (2009), Casscells (2009), and Piedra (2009).

Table A5.1

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Oseltamivir	Control	Relative (95% CI)	Absolute		
oseltamivir 75mg - prophylaxis against influenza-like illness												
2[1]	randomized trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	34/675 (5%)[5]	19/413 (4.6%)	RR 1.28 (0.45 to 3.66)	13 more per 1000 (from 25 fewer to 122 more)	⊕OOO VERY LOW	IMPORTANT
oseltamivir 150mg - prophylaxis for influenza-like illness												
1[6]	randomized trials	serious[7]	no serious inconsistency	no serious indirectness	serious[8]	reporting bias[4]	6/520 (1.2%)	3/259 (1.2%)	RR 1.00 (0.25 to 3.95)	0 fewer per 1000 (from 9 fewer to 34 more)	⊕OOO VERY LOW	IMPORTANT
oseltamivir 75mg - prophylaxis against laboratory-confirmed influenza												
2[1]	randomized trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	15/675 (2.2%)[5]	28/412 (6.8%)	RR 0.39 (0.18 to 0.85)	41 fewer per 1000 (from 10 fewer to 56 fewer)	⊕OOO VERY LOW	CRITICAL
oseltamivir 150mg - prophylaxis for laboratory-confirmed influenza												
1[6]	randomized trials	serious[7]	no serious inconsistency	no serious indirectness	serious[8]	reporting bias[4]	7/520 (1.3%)	13/260 (5%)	RR 0.27 (0.11 to 0.67)	36 fewer per 1000 (from 16 fewer to 45 fewer)	⊕OOO VERY LOW	CRITICAL
alleviation of symptoms												
3[9]	randomized trials	no serious limitations[10]	no serious inconsistency	no serious indirectness	serious[11]	reporting bias[4]	1118	679	-	1.20 higher (1.06 to 1.35 higher)[12]	⊕⊕OO LOW	IMPORTANT
oseltamivir 75mg - nausea												
2[1]	randomized trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	reporting bias[4]	71/675 (10.5%)[5]	23/413 (5.6%)	OR 1.79 (1.1 to 2.93)	40 more per 1000 (from 5 more to 92 more)	⊕OOO VERY LOW	IMPORTANT
oseltamivir 150mg - nausea												
1[6]	randomized trials	serious[7]	no serious inconsistency	no serious indirectness	serious[8]	reporting bias[4]	76/520 (14.6%)	18/259 (6.9%)	OR 2.29 (1.34 to 3.92)	77 more per 1000 (from 21 more to 157 more)	⊕OOO VERY LOW	IMPORTANT
complications												
3[13]	randomized trials	no serious limitations[10]	no serious inconsistency	no serious indirectness	serious[11]	none	14/402 (3.5%)	27/402 (6.7%)	RR 0.55 (0.22 to 1.35)	30 fewer per 1000 (from 52 fewer to 24 more)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Hayden (1999) and Kashiwagi (2000).
[2] The Jefferson (2009) review indicates that the Hayden (1999) and Kashiwagi (2000) trials would not be judged adequate by the Cochrane criteria and that the trials were at risk of bias, given poor

descriptions of methods. Although the Jefferson review does not identify which authors of the oseltamivir papers were contacted, those who were indicated that they did not have original data. Consequently, the results of these trials should be interpreted with caution.
[3] All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.
[4] Although the Jefferson (2009) review does not indicate which authors of the included-oseltamivir trials were contacted, those who were indicated that they did not have original data. Roche was not able to provide the data to the review authors in time to update the review. As such, there is the potential for reporting bias.
[5] Oral oseltamivir 75mg.
[6] Hayden 1999.
[7] The Jefferson (2009) review indicates that the Hayden (1999) trial would not be judged adequate using the Cochrane methods and is at risk of bias due to poor description of methods.
[8] The trial is for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.
[9] Li (2003), Nicholson (2000), and Treanor (2000).
[10] The Jefferson (2009) review indicates that the Nicholson (2000) and Treanor (2000) trials would be considered adequate using the Cochrane criteria, while the Li (2003) trial would not.
[11] All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.
[12] The Jefferson (2009) review states that the results from meta-analyses using hazard ratios should be interpreted with caution because of the methods used. As hazard ratios were seldom reported directly, the authors used the ratio of the observed median duration of symptoms in each group as an approximation to the hazard ratio.
[13] Nicholson (2000), Treanor (2000), and Li (2003). Complications include pneumonia, bronchitis, otitis media, and sinusitis.

Author(s): P. Whyte
Date: 2009-12-28
Question: Should oseltamivir in children be used for influenza?
Settings: children
Bibliography: Shun-Shin (2009)

Table A5.2

Quality assessment							Summary of findings					Importance
							No. of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Oseltamivir in children	Control	Relative (95% CI)	Absolute		
vomiting												
1[1]	randomized trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	0/0 (0%)[4]	0/0 (0%)	RD 0.05 (0.02 to 0.09)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕OO LOW	IMPORTANT

[1] Whitley (2000) (WV15758) from the Shun-Shin review (2009).
[2] Shun-Shin (2009) indicates that this trial did not report sufficient details to determine whether allocation concealment and blinding were adequate.
[3] All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.
[4] Number with event not provided in review.

Author(s): P Whyte
Date: 2009-12-20
Question: Should oseltamivir be used for influenza?
Settings: adults and children
Bibliography: Jefferson (2009), as well as articles by Hanshaoworakul (2009), Casscells (2009), and Piedra (2009).

Table A5.3

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oseltamivir	control	Relative (95% CI)	Absolute		
death												
1[14]	observational studies[15]	serious[16]	no serious inconsistency	no serious indirectness	serious[3]	none	5/318 (1.6%)	17/131 (13%)	OR 0.11 (0.04 to 0.3)[17]	114 fewer per 1000 (from 87 fewer to 124 fewer)		CRITICAL
recurrent cardiovascular events												
1[18]	observational studies[19]	serious[20]	no serious inconsistency	no serious indirectness	serious[21]	none	575/6771 (8.5%)	6508/30711 (21.2%)	OR 0.417 (0.349 to 0.498)[22]	111 fewer per 1000 (from 94 fewer to 126 fewer)		IMPORTANT

[3] All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.
[14] Hanshaoworakul 2009.
[15] Retrospective medical chart review
[16] This study is a retrospective review of medical charts and as such may be open to bias and does not allow for establishment of causal relationships.
[17] When cardiovascular disease and hypertension were controlled for, oseltamivir was associated with survival (OR=0.13; 95% CI: 0.04, 0.38 for cardiovascular disease and OR=0.14; 95% CI: 0.04, 0.44 for hypertension).
[18] Casscells 2009.
[19] Casscells 2009 was a retrospective review which uses a propensity-scored logistic regression model to control for demographic differences.
[20] Casscells 2009 was a retrospective review of administrative data of members of the US Department of Defense. The authors acknowledge that the study is susceptible to a number of sources of confounding, including omission of potentially important variables such as severity and prior duration of patient's symptoms, presence of specific comorbidities, prior prophylactic treatment, subject compliance with critical medications or death due to causes unrelated to influenza may have influenced attempts to balance the groups and confounded findings.
[21] Only seasonal influenza was considered and therefore the generalizability of the results to pandemic influenza is unknown. In addition, the potential for confounding due to study design (patient comorbidities, compliance with medication, previous symptoms) limit the confidence with which results can be generalized to other situations.
[22] The odds ratio was based on a propensity-scored logistic regression model which controlled for demographic differences in the population. Authors conclude the results indicate that oseltamivir provided a statistically significant protective effect against recurrent cardiovascular events in patients with a history of vascular disease.

Author(s): P Whyte
Date: 2009-12-20
Question: Should oseltamivir be used for influenza?
Settings: adults and children
Bibliography: Jefferson (2009), as well as articles by Hanshaoworakul (2009), Casscells (2009), and Piedra (2009)

Table A5.4

Quality assessment							Summary of findings						Importance
							No of patients		Effect		Quality		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oseltamivir	control	Relative (95% CI)	Absolute			
pneumonia in 14 days after influenza diagnosis													
1[23]	observational studies	serious[24]	no serious inconsistency	no serious indirectness	serious[8]	none	17/1634 (1%)	71/3721 (1.9%)	HR 0.55 (0.29 to 1.03)[25]	9 fewer per 1000 (from 14 fewer to 1 more)			IMPORTANT
respiratory illnesses other than pneumonia in 14 days after influenza diagnosis													
1[23]	observational studies	serious[24]	no serious inconsistency	no serious indirectness	serious[8]	none	324/1634 (19.8%)	885/3721 (23.8%)	HR 0.74 (0.63 to 0.87)[25]	56 fewer per 1000 (from 27 fewer to 81 fewer)			IMPORTANT
otitis media complications in 14 days after influenza diagnosis													
1[23]	observational studies	serious[24]	no serious inconsistency	no serious indirectness	serious[8]	none	46/1634 (2.8%)	184/3721 (4.9%)	HR 0.69 (0.48 to 0.99)[25]	15 fewer per 1000 (from 0 fewer to 25 fewer)			IMPORTANT
all-cause hospitalizations in 14 days after influenza diagnosis													
1[23]	observational studies	serious[24]	no serious inconsistency	no serious indirectness	serious[8]	none	10/1634 (0.6%)	48/3721 (1.3%)	HR 0.33 (0.13 to 0.83)[25]	9 fewer per 1000 (from 2 fewer to 11 fewer)			CRITICAL
pneumonia-related hospitalizations in 14 days after influenza diagnosis													
1[23]	observational studies	serious[24]	no serious inconsistency	no serious indirectness	serious[8]	none	2/1634 (0.1%)	13/3721 (0.3%)	HR 0.49 (0.09 to 2.49)[25]	2 fewer per 1000 (from 3 fewer to 5 more)			CRITICAL
hospitalizations respiratory illness other than pneumonia in 14 days after influenza diagnosis													
1[23]	observational studies	serious[24]	no serious inconsistency	no serious indirectness	serious[8]	none	1/1634 (0.1%)	9/3721 (0.2%)	HR 0.23 (0.03 to 2.09)[25]	2 fewer per 1000 (from 2 fewer to 3 more)			CRITICAL
pneumonia in 30 days after influenza diagnosis													
1[23]	observational studies	serious[24]	no serious inconsistency	no serious indirectness	serious[8]	none	26/1634 (1.6%)	91/3721 (2.4%)	HR 0.67 (0.42 to 1.07)[25]	8 fewer per 1000 (from 14 fewer to 2 more)			IMPORTANT
respiratory illnesses other than pneumonia in 30 days after influenza diagnosis													
1[23]	observational studies	serious[24]	no serious inconsistency	no serious indirectness	serious[8]	none	498/1634 (30.5%)	1201/3721 (32.3%)	HR 0.87 (0.77 to 0.97)[25]	35 fewer per 1000 (from 8 fewer to 64 fewer)			IMPORTANT
otitis media complications in 30 days after influenza diagnosis													
1[23]	observational studies	serious[24]	no serious inconsistency	no serious indirectness	serious[8]	none	75/1634 (4.6%)	276/3721 (7.4%)	HR 0.70 (0.53 to 0.92)[25]	22 fewer per 1000 (from 6 fewer to 34 fewer)			IMPORTANT
all-cause hospitalizations in 30 days after influenza diagnosis													
1[23]	observational studies	serious[24]	no serious inconsistency	no serious indirectness	serious[8]	none	15/1634 (0.9%)	61/3721 (1.6%)	HR 0.49 (0.27 to 0.89)[25]	8 fewer per 1000 (from 2 fewer to 12 fewer)			CRITICAL

pneumonia-related hospitalizations in 30 days after influenza diagnosis												
1[23]	observational studies	serious[24]	no serious inconsistency	no serious indirectness	serious[8]	none	4/1634 (0.2%)	6/3721 (0.2%)	HR 0.56 (0.17 to 1.83)[25]	1 fewer per 1000 (from 1 fewer to 1 more)		CRITICAL
hospitalizations respiratory illness other than pneumonia in 30 days after influenza diagnosis												
1[23]	observational studies	serious[24]	no serious inconsistency	no serious indirectness	serious[8]	none	3/1634 (0.2%)	14/3721 (0.4%)	HR 0.34 (0.09 to 1.2)[25]	2 fewer per 1000 (from 3 fewer to 1 more)		CRITICAL
adverse events infants under one year of age												
1[26]	observational studies	serious[27]	no serious inconsistency	no serious indirectness	serious[8]	none	1/47 (2.1%)	41/486 (8.4%)	RR 0 (0 to 0)[28]	84 fewer per 1000 (from 84 fewer to 84 fewer)		CRITICAL

[8] The trial is for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.
[23] Piedra 2009. This study compared children and adolescents aged 1 to 17 years who were defined as being at high risk of influenza complications (chronic medical conditions or neurologic or neuromuscular disease) who received oseltamivir or did not receive antiviral therapy.
[24] The Piedra 2009 study was a retrospective review of medical databases covering six seasons of influenza. The authors acknowledge a number of limitations, including the fact the databases are limited primarily to patients covered by employer-sponsored health insurance; the use of diagnostic coding for influenza was assigned on basis of physicians' clinical diagnoses alone; impossible to confirm if patients began antiviral treatment within recommended timeframe; patients were not assigned randomly nor matched with respect to propensity to be given oseltamivir. In regard to the last two points the authors note that there were few potentially clinically significant differences between the two patient cohorts and multivariate analyses were used to adjust for differences.
[25] Adjusted for demographic and medical history variables.
[26] Tamura 2005
[27] The Tamura (2005) study was non-randomized and little information was provided regarding the study design except to say that infants under one year of age were treated with oseltamivir and a control group of children aged 1 to 15 years was also treated with oseltamivir and a third control group of children received no treatment. The treatment groups also varied considerably in size, with n=47 for children less than one year, n=486 for children aged 1 to 15 and n=95 for the children who received no treatment.
[28] No comparative results were provided in the publication.

Author(s): P Whyte
Date: 2009-12-24
Question: Should oseltamivir vs rimantadine or amantadine be used in children <1 year old?[1]
Settings: USA
Bibliography: Kimberlin (2009)

Table A5.5

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oseltamivir	rimantadine or amantadine	Relative (95% CI)	Absolute		
neurologic abnormalities												
1[2]	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	serious	none	19/115 (16.5%)	17/65 (26.2%)	RR 0 (0 to 0)[5]	262 fewer per 1000 (from 262 fewer to 262 fewer)[5]		IMPORTANT
pulmonary abnormalities												
1[2]	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	serious	none	59/115 (51.3%)	30/65 (46.2%)	RR 0 (0 to 0)[5]	462 fewer per 1000 (from 462 fewer to 462 fewer)[5]		IMPORTANT

gastrointestinal abnormalities												
1[2]	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	serious	none	26/115 (22.6%)	14/65 (21.5%)	RR 0 (0 to 0)[5]	215 fewer per 1000 (from 215 fewer to 215 fewer)[5]		IMPORTANT
cardiovascular abnormalities												
1[2]	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	serious	none	4/115 (3.5%)	4/65 (6.2%)	RR 0 (0 to 0)[5]	62 fewer per 1000 (from 62 fewer to 62 fewer)[5]		IMPORTANT
otologic, ocular abnormalities												
1[2]	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	serious	none	2/115 (1.7%)	10/65 (15.4%)	RR 0 (0 to 0)[5,6]	154 fewer per 1000 (from 154 fewer to 154 fewer)[5]		IMPORTANT
dermatologic abnormalities												
1[2]	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	serious	none	5/115 (4.3%)	4/65 (6.2%)	RR 0 (0 to 0)[5]	62 fewer per 1000 (from 62 fewer to 62 fewer)[5]		IMPORTANT
systemic response abnormalities												
1[2]	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	serious	none	6/115 (5.2%)	4/65 (6.2%)	RR 0 (0 to 0)[5]	62 fewer per 1000 (from 62 fewer to 62 fewer)[5]		IMPORTANT
genitourinary abnormalities												
1[2]	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	serious	none	4/115 (3.5%)	2/65 (3.1%)	RR 0 (0 to 0)[5]	31 fewer per 1000 (from 31 fewer to 31 fewer)[5]		IMPORTANT
musculoskeletal abnormalities												
1[2]	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	serious	none	2/115 (1.7%)	0/65 (0%)	RR 0 (0 to 0)[5]	0 fewer per 1000 (from 0 fewer to 0 fewer)[5]		IMPORTANT
hematologic/lymphatic abnormalities												
1[2]	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	serious	none	6/115 (5.2%)	2/65 (3.1%)	RR 0 (0 to 0)[5]	31 fewer per 1000 (from 31 fewer to 31 fewer)[5]		IMPORTANT
hepatobillary/pancreatic abnormalities												
1[2]	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	serious	none	5/115 (4.3%)	0/65 (0%)	RR 0 (0 to 0)[5]	0 fewer per 1000 (from 0 fewer to 0 fewer)[5]		IMPORTANT
endocrine/metabolic abnormalities												
1[2]	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	serious	none	0/115 (0%)	1/65 (1.5%)	RR 0 (0 to 0)[5]	15 fewer per 1000 (from 15 fewer to 15 fewer)[5]		IMPORTANT

[1] Median dose of oseltamivir ranged from 2mg/kg to 2.21mg/kg and subjects were treated for a median of 5 days.
[2] Kimberlin (2009).
[3] Retrospective chart review focusing on comparative safety of oseltamivir and adamantanes in children less than a year old.
[4] This study is a retrospective chart review and as such may be open to bias due to lack of randomization, lack of blinding of outcome assessment.
[5] Only p values based on chi-square tests were provided by the paper. No statistically significant difference between the groups.
[6] Only p values based on chi-square tests were provided by the paper. There were statistically significantly more events in the rimantadine or amantadine group ($p<0.01$).

Author(s): P Whyte
Date: 2009-12-21
Question: Should zanamivir be used for influenza?
Settings: adults
Bibliography: Jefferson (2009)

Table A5.6

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	zanamivir	control	Relative (95% CI)	Absolute		
inhaled zanamivir 10mg - prophylaxis for influenza-like illness												
2[1]	randomized trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	37/697 (5.3%)	21/602 (3.5%)	RR 1.51 (0.77 to 2.95)	18 more per 1000 (from 8 fewer to 68 more)	⊕⊕OO LOW	IMPORTANT
inhaled zanamivir 10mg - prophylaxis against laboratory confirmed influenza												
2[1]	randomized trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	30/697 (4.3%)	62/602 (10.3%)	RR 0.38 (0.17 to 0.85)	64 fewer per 1000 (from 15 fewer to 85 fewer)	⊕⊕OO LOW	CRITICAL
intranasal zanamivir 6.4mg - prophylaxis for influenza-like illness												
1[4]	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	7/141 (5%)	3/48 (6.3%)	RR 0.79 (0.21 to 2.95)	13 fewer per 1000 (from 49 fewer to 122 more)	⊕⊕OO LOW	IMPORTANT
intranasal zanamivir 6.4mg - prophylaxis against laboratory confirmed influenza												
1[4]	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	26/141 (18.4%)	9/48 (18.8%)	RR 1.06 (0.54 to 2.08)	11 more per 1000 (from 86 fewer to 202 more)	⊕⊕OO LOW	CRITICAL
inhaled and intranasal zanamivir- prophylaxis for influenza-like illness												
1[4]	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	3/146 (2.1%)	3/48 (6.3%)	RR 0.33 (0.07 to 1.58)	42 fewer per 1000 (from 58 fewer to 36 more)	⊕⊕OO LOW	IMPORTANT
inhaled and intranasal zanamivir- prophylaxis against laboratory confirmed influenza												
1[4]	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	6/146 (4.1%)	9/48 (18.8%)	RR 0.22 (0.08 to 0.58)	146 fewer per 1000 (from 79 fewer to 172 fewer)	⊕⊕OO LOW	CRITICAL
alleviation of symptoms												
6[7]	randomized trials	serious[8]	no serious inconsistency	no serious indirectness	serious[3]	none	1878	1310	-	1.24 higher (1.13 to 1.36 higher)[9]	⊕⊕OO LOW	IMPORTANT

[1] Kaiser (2000) and Monto (1999).
[2] The Jefferson (2009) review indicates that the Monto (1999) trial would be judged adequate using Cochrane criteria but the Kaiser (2000) trial is not and is at risk of bias due to poor description of methods.
[3] The trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.
[4] Kaiser (2000).
[5] The Jefferson (2009) review indicates that this trial would not be judged adequate according to the Cochrane criteria and is at risk of bias due to poor reporting of methods.
[6] The trial is for seasonal influenza thus the generalizability of the results to pandemic influenza is unknown.
[7] Hayden (1997), Makela (2000), Matsumoto (1999), MIST (1998), Monto (1999), and Puhakka (2003).
[8] The Jefferson (2009) review indicates that of the 6 trials only two -- Makela (2000) and MIST (1998) -- would meet the Cochrane criteria for adequate, with the remaining trials open to bias due to poor description of methods.

[9] The Jefferson (2009) review states that the results from meta-analyses using hazard ratios should be interpreted with caution because of the methods used - as hazard ratios were seldom reported directly the authors used the ratio of the observed median duration of symptoms in each group as an approximation to the hazard ratio.

Author(s): P. Whyte
Date: 2009-06-05
Question: Should amantadine be used for influenza - adults?
Settings: adults
Bibliography: Jefferson (2006)

Table A5.7

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	amantadine	control	Relative (95% CI)	Absolute		
duration fever (days) (Better indicated by lower values)												
10	randomized trials	no serious limitations	no serious inconsistency	serious[1]	serious	none	250	292	-	MD 0.99 lower (1.26 to 0.71 lower)	⊕⊕OO LOW	
duration of hospitalization (Better indicated by lower values)												
1	randomized trials	no serious limitations	no serious inconsistency	serious[2]	serious[3]	none	20	16	-	MD 0.90 lower (2.2 lower to 0.4 higher)	⊕⊕OO LOW	6.5
viral nasal shedding												
3	randomized trials	no serious limitations	no serious inconsistency	serious[2]	serious[4]	none	62/75 (82.7%)	87/95 (91.6%)	RR 0.97 (0.76 to 1.24)	27 fewer per 1000 (from 220 fewer to 220 more)	⊕⊕OO LOW	6

[1] All trials are were conducted in the 1960s and early 1970s; in addition the trials were relatively small, with N's ranging from less than 20 to 150.
[2] All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.
[3] Eelatively old trial (1970) with small n (36 total subjects).
[4] Two trials from the 1960s and one from the early 1980s, all with small N.

Author(s): P Whyte
Date: 2009-06-05
Question: Should rimantadine be used for influenza - adults?
Settings: adults
Bibliography: Jefferson (2006)

Table A5.8

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	rimantadine	control	Relative (95% CI)	Absolute		
duration of fever (Better indicated by lower values)												
3	randomized trials	no serious limitations	no serious inconsistency	serious[1]	serious[2]	none	36	46	-	MD 1.24 lower (1.71 to 0.76 lower)	⊕⊕OO LOW	
viral nasal shedding												
3	randomized trials	no serious limitations	no serious inconsistency	serious[1]	serious[2]	none	46/69 (66.7%)	77/83 (92.8%)	RR 0.68 (0.3 to 1.53)	297 fewer per 1000 (from 649 fewer to 492 more)	⊕⊕OO LOW	6

[1] All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.
[2] All trials had small N's, ranging from less than 15 to 50, two trials were conduct in the 1960s and one in the 1980s.

Author(s): P.Whyte
Date: 2009-12-21
Question: Should neuraminidase inhibitors - oseltamivir and zanamivir be used for influenza?
Settings: adults
Bibliography: Jefferson (2009) and Khazeni (2009).

Table A5.9

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	neuraminidase inhibitors - oseltamivir and zanamivir	control	Relative (95% CI)	Absolute		
oseltamivir only - extended prophylaxis against laboratory confirmed symptomatic influenza												
3[8]	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	serious[3]	none	19/1471 (1.3%)	87/1463 (5.9%)	RR 0.236 (0.144 to 0.387)	45 fewer per 1000 (from 36 fewer to 51 fewer)	⊕⊕OO LOW	CRITICAL
zanamivir only - extended prophylaxis against laboratory confirmed symptomatic influenza												
2[9]	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	serious[3]	none	18/2321 (0.8%)	66/2239 (2.9%)	RR 0.280 (0.166 to 0.474)	21 fewer per 1000 (from 16 fewer to 25 fewer)	⊕⊕OO LOW	CRITICAL

oseltamivir only - extended prophylaxis against laboratory confirmed asymptomatic influenza												
3[8]	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	serious[3]	none	62/1471 (4.2%)	79/1463 (5.4%)	RR 0.781 (0.563 to 1.082)	12 fewer per 1000 (from 24 fewer to 4 more)	⊕⊕OO LOW	CRITICAL
zanamivir only - extended prophylaxis against laboratory confirmed asymptomatic influenza												
2[9]	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	serious[3]	none	74/2321 (3.2%)	53/2239 (2.4%)	RR 1.402 (0.900 to 1.983)	10 more per 1000 (from 2 fewer to 23 more)	⊕⊕OO LOW	CRITICAL

[2] According to the Jefferson (2009) review, only the Monto (1999) trial is adequate according to the Cochrane criteria.
[3] All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.
[4] Hayden 1999 (both 75mg/day and 150mg/day), Kashiwagi (2000), Peters (2001), Monto (1999), and LaForce (2007). All trials had a minimum of 4 weeks prophylactic treatment.
[5] The Khazeni (2009) review indicated that recruitment methods were not specified in most studies, and this concurs with Jefferson (2009) who indicated that all trials except Monto (1999) were not adequate according to Cochrane criteria.
[6] Kashiwagi (2000), (Monto 1999), (LaForce 2007), and (Webster 1999).
[7] Results indicate no difference between neuraminidase inhibitors and placebo in the occurrence of adverse events.
[8] Hayden (1999) (both 75mg/day and 150mg/day), Kashiwagi (2000), and Peters (2001). All trials had a minimum of 4 weeks prophylactic treatment.
[9] Monto (1999) and LaForce (2007). All trials had a minimum of 4 weeks prophylactic treatment.

Author(s): P Whyte
Date: 2009-12-21
Question: Should neuraminidase inhibitors - oseltamivir and zanamivir be used for influenza?
Settings: adults
Bibliography: Jefferson (2009) and Khazeni (2009).

Table A5.10

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	neuraminidase inhibitors - oseltamivir and zanamivir	control	Relative (95% CI)	Absolute		
prophylaxis for influenza-like illness												
4[1]	randomized trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	87/2179 (4%)	49/1370 (3.6%)	RR 1.20 (0.77 to 1.87)	7 more per 1000 (from 8 fewer to 31 more)	⊕⊕OO LOW	IMPORTANT
prophylaxis against laboratory confirmed influenza												
4[1]	randomized trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	86/2179 (3.9%)	121/1370 (8.8%)	RR 0.41 (0.25 to 0.65)	52 fewer per 1000 (from 31 fewer to 66 fewer)	⊕⊕OO LOW	CRITICAL
extended prophylaxis against laboratory confirmed symptomatic influenza												
6[4]	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	serious[3]	none	37/3792 (1%)	153/3702 (4.1%)	RR 0.256 (0.179 to 0.367)	31 fewer per 1000 (from 26 fewer to 34 fewer)	⊕⊕OO LOW	CRITICAL

extended prophylaxis against laboratory confirmed asymptomatic influenza												
6[4]	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	serious[3]	none	136/3709 (3.7%)	132/3702 (3.6%)	RR 1.028 (0.81 to 1.304)	1 more per 1000 (from 7 fewer to 11 more)	⊕⊕OO LOW	CRITICAL
serious adverse events												
4[6]	randomized trials	serious[5]	no serious inconsistency	no serious indirectness	serious[3]	none	21/2456 (0.9%)	23/2460 (0.9%)	RR 0.919 (0.511 to 1.651)[7]	1 fewer per 1000 (from 5 fewer to 6 more)	⊕⊕OO LOW	CRITICAL

[1] Hayden (1999), Kashiwagi (2000), Kaiser (2000), and Monto (1999).
[2] According to the Jefferson (2009) review, only the Monto (1999) trial is adequate according to the Cochrane criteria.
[3] All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.
[4] Hayden (1999) (both 75mg/day and 150mg/day), Kashiwagi (2000), Peters (2001), Monto (1999), and LaForce (2007). All trials had a minimum of 4 weeks prophylactic treatment.
[5] The Khazeni (2009) review indicated that recruitment methods were not specified in most studies, and this concurs with Jefferson (2009) who indicated that all trials except Monto (1999) were not adequate according to Cochrane criteria.
[6] Kashiwagi (2000), Monto (1999), LaForce (2007), and Webster (1999).
[7] Results indicate no difference between neuraminidase inhibitors and placebo in the occurrence of adverse events.

Author(s): P.Whyte
Date: 2009-06-05
Question: Should oseltamivir be used for prophylaxis in adults?
Settings: adults
Bibliography: Tappenden 2009

Table A5.11

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**oseltamivir**	**control**	**Relative (95% CI)**	**Absolute**		
symptomatic laboratory confirmed infection												
2	randomized trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	6/520 (1.2%)	25/519 (4.8%)	RR 0.27 (0.09 to 0.83)	35 fewer per 1000 (from 8 fewer to 44 fewer)	⊕⊕⊕O MODERATE	8

[1] All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.

Author(s): P Whyte
Date: 2009-06-05
Question: Should zanamivir be used for prophylaxis for adults?
Settings: adults
Bibliography: Tappenden (2009)

Table A5.12

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	zanamivir	control	Relative (95% CI)	Absolute		
symptomatic laboratory confirmed influenza												
1	randomized trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	11/553 (2%)	34/554 (6.1%)	RR 0.32 (0.17 to 0.63)	42 fewer per 1000 (from 23 fewer to 51 fewer)	⊕⊕⊕O MODERATE	8

[1] All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.

Author(s): P Whyte
Date: 2009-06-05
Question: Should zanamivir be used for prophylaxis for at-risk adults and adolescents?
Settings: at-risk adults and adolescents
Bibliography: Tappenden (2009)

Table A5.13

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	zanamivir	control	Relative (95% CI)	Absolute		
symptomatic laboratory confirmed infection												
1	randomized trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	4/1678 (0.2%)	23/1685 (1.4%)	RR 0.17 (0.07 to 0.44)	11 fewer per 1000 (from 8 fewer to 13 fewer)	⊕⊕⊕O MODERATE	8

[1] All trials are for seasonal influenza and while this does not provide direct evidence for a pandemic situation, the data is the best evidence available. It is recommended that similarities and differences between the characteristics of seasonal influenza and pandemic influenza be considered when applying the recommendations based on the available evidence.

Annex 6: Summary of observational data

The following table includes observational studies addressing the use of antivirals. All studies except one (Kawai 2009) assess outcomes other than efficacy outcomes.

Table A6.1: Summary of observational studies assessing the use of antivirals

Studies	Design	N	Population characteristics	Key results
Barr 2007	Retrospective cohort study	4,447 received oseltamivir prescription 20,407 did not receive prescription	Children aged 1 to 12 with clinically diagnosed influenza	– Patients prescribed oseltamivir were less likely to develop pneumonia, 0.7% versus 1.4% (RR=0.483; 95% CI: 0.326, 0.717).
Bowles 2002	Retrospective review	178	Nursing home residents	– Use of oseltamivir within 48 hours of symptom onset resulted in significantly less antibiotic use, fewer hospitalizations and fewer deaths compared to residents receiving no therapy or using amantadine.
Blumentals 2007	Retrospective cohort analysis Propensity score matching	36,751 treated with oseltamivir Equal number of matched sample controls	Adolescents ≥13 years and adults diagnosed with seasonal influenza	– Reduction in risk of otitis media of 23% (HR+0.77; 95% CI: 0.65, 0.93). – Reduction in any respiratory disease by 18% (HR=0.82; 95% CI: 0.79, 0.86). – Reduction in hospitalization for any reason of 22% (HR=0.78; 95% CI: 0.67, 0.91).
Casscells 2009	Retrospective review	37,482	Coded history of cardiovascular disease and influenza diagnosis	– Recurrence of CV outcomes within 30 days after influenza diagnosis was significantly lower in treated group (p=0.005). – Statistically significant protective effect associated with oseltamivir treatment (OR=0.417; 95% CI: 0.349, 0.498).
Cole 2002	Retrospective review of medical /pharmacy health insurance data	2341 treated with zanamivir 2337 untreated comparator group	US patients with diagnosis of seasonal influenza	– Fewer zanamivir-treated patients were hospitalized for complications (RR=0.58; 95% CI: 0.30, 1.12). – More outpatient visits for zanamivir-treated patients (16.9% versus 14.5% for untreated patients), RR=1.16; 95% CI: 1.02, 1.33.

Studies	Design	N	Population characteristics	Key results
Dutkowski 2009	Safety and tolerability study	391	Healthy adults 75mg, 225mg, or 450mg for 5days	– Dose-related increases in nausea, vomiting, dizziness and hot flushes, but overall high-doses were well tolerated.
French 2007	Post-marketing surveillance	13,137	Patients prescribed amantadine	– 36 (0.27%) prescribed amantadine were diagnosed with corneal oedema (RR=1.7; 95% CI: 1.1, 2.8).
Gums 2008	Retrospective review of health care claims	45,751 treated with oseltamivir and 45,751 matched untreated controls	Patients diagnosed with influenza during 5 influenza seasons in the US	– Statistically significant reductions in risk of pneumonia (OR= 0.89, 95% CI: 0.80, 1.00), otitis media (OR=0.84, 95% CI: 0.77, 0.91) and hospitalization (OR=0.71, 95% CI: 0.62, 0.83). – Risk of pneumonia and otitis media were also lower in children and adolescents (≤ 17 years) prescribed oseltamivir (OR=0.4, 95% CI: 0.60, 0.91 and OR: 0.77, 95% CI: 0.69, 0.85, respectively).
Hanshaow-orakul 2009	Retrospective medical record review	2075	Thai individuals with influenza infection	– Treatment with oseltamivir statistically associated with survival (crude OR=0.11; 95% CI: 0.04, 0.30, controlled for age OR=0.13; 95% CI: 0.04, 0.40). – 1.5% (5/318) mortality in those oseltamivir treated, in comparison to 5% (17/131) of those untreated.
Kawai 2009	Retrospective review	291	164 H1N1 patients and 59 H3N2 patients (2008-09 influenza season); 68 H1N1 patients (2007-08 season).	– Mean duration of fever after commencing oseltamivir therapy was significantly longer in H1N1 2008-09 (49.1±30.2h) than in H3N2 (33.7±20.1h, p<0.01) or H1N1 2007-08 (32.0±18.9h, p<0.001). – Mean duration of fever was longer for oseltamivir than zanamivir for 2008-09 H1N1 (*P*<0.001).
Kimberlin 2009	Retrospective chart review	180	Infants treated with oseltamivir, amantadine or rimantadine	– Children less than one year of age treated with oseltamivir were significantly less likely to develop abnormalities in the head/eyes/ears/ nose/throat system, such as otitis media, compared to children treated with rimantadine or amantadine (1.7% versus 15.4%; p<0.01).
Lee 2007	Retrospective cohort study	356	Patients hospitalized with laboratory confirmed seasonal influenza	– Oseltamivir initiated within 2 days of illness was associated with shorter total length of stay (Kaplan-Meier estimated median 4 versus 6 days; adjusted HR=1.54; 95% CI: 1.23, 1.92; p<0.0001).

Studies	Design	N	Population characteristics	Key results
Lee 2009	1-year prospective observational study	147	Adults hospitalized from influenza (H3N2)	– Antiviral treatment initiated on presentation was an independent factor affecting viral concentration. – Treatment started on symptom days 1–4 was significantly associated with shortened viral RNA detection. – Oseltamivir started on symptom day 1–2 was also significantly associated with shortened viral RNA detection, OR=0.10 (95%CI: 0.03, 0.35; $p<0.001$). – Antiviral treatment started on symptom day 1 or days 2–3 was associated with accelerated viral concentration decrease, compared with no treatment.
Liem 2009	Retrospective review	67	Laboratory confirmed cases of H5N1 in Vietnam	– Risk of death was higher in patients not receiving oseltamivir treatment (p=0.048). – Benefit of oseltamivir was observed even after controlling for age (OR=0.24; 95% CI: 0.065, 0.916) or neutropenia as a marker of severity (Mantel-Haenszel summary OR=0.15; 95% CI: 0.026-0.893; p=0.034).
Madjid 2009	Retrospective cohort study Propensity score adjusted	49,238 treated with oseltamivir 102,692 no antiviral treatment	Adults with clinical influenza diagnosis	– Treated with oseltamivir within 1 day before or 2 days after diagnosis. – HR for stroke or transient ischaemic attack at 6 months was 0.717 (95% CI: 0.624, 0.823).
McGeer 2007	Prospective cohort study	327	Adult patients hospitalized for influenza	– 106 of 327 (32%) prescribed antivirals. – Antiviral treatment was associated with significant reduction in mortality (OR=0.21; 95% CI: 0.06, 0.80).
Nordstrom 2004	Post-marketing safety study	32,459	Physician diagnosis of influenza and/or prescription for oseltamivir	– Adjusted rate ratio for skin reactions for oseltamivir users versus non-users was 1.05 (95% CI: 0.88, 1.24) for incident cases and 0.98 (95% CI: 0.77, 1.24) for patients with history of skin reactions. – Oseltamivir not associated with increased risk of skin reactions.
Nordstrom 2005	Retrospective cohort study	11,632 taking oseltamivir 60,427 not taking oseltamivir	Individuals aged >1 year prescribed oseltamivir within 1 day of influenza diagnosis	– Pneumonia influenza-like illness: HR=0.72 (95% CI: 0.60, 0.86). – Hospital admission with oseltamivir: HR=0.74 (95% CI: 0.61, 0.90).

Studies	Design	N	Population characteristics	Key results
Orzeck 2007	Retrospective cohort study	2919 treated with oseltamivir 6171 not prescribed treatment	Patients with diabetes treated with oseltamivir	– Patients treated with oseltamivir had 17% risk reduction for respiratory illness (RR=0.83; 95% CI: 0.73, 0.93). – A 30% risk reduction for hospitalization for any cause (RR=0.70; 95% CI: 0.52, 0.94). – No significant differences between groups for risk of pneumonia, otitis media or hospitalizations for pneumonia.
Peters 2008	Case control study	31,674 taking oseltamivir 31,674 matched controls	Children and adults taking oseltamivir within 1 day of onset of influenza symptoms	– Oseltamivir reduced risk of pneumonia by 15% (RR=0.85; 95% CI: 0.73, 0.98). – Risk reduction 20% for other respiratory illnesses (RR=0.80; 95% CI: 0.76, 0.83). – Risk reduction 30% for otitis media and other complications (RR=0.69; 95% CI: 0.61, 0.79). – Risk reduction 38% for overall hospital admission (RR=0.62; 95% CI: 0.52, 0.74).
Piedra 2009	Retrospective review	1634 received oseltamivir 3721 received no antiviral therapy	Paediatric patients receiving oseltamivir	– Oseltamivir was significantly associated with a reduction in respiratory illness other than pneumonia (OR=0.74; 95%CI: 0.63, 0.87), otitis media (OR=0.69; 95%CI: 0.48, 0.99), and all-cause hospitalizations (OR=0.33; 95%CI: 0.13, 0.83) within 14 and 30 days after diagnosis.
Tanaka 2009	Literature review	90 using oseltamivir 4 using zanamivir	Pregnant women using oseltamivir or zanamivir	– 1 malformation in 90 pregnancies with women using oseltamivir. – For 4 women using zanamivir, one spontaneous miscarriage, one termination and 2 healthy births.

Author(s): Holger J Schunemann
Date: 2009-06-24
Question: Should oseltamivir be used for influenza-infected at-risk populations?
Settings: Outpatient
Bibliography: Blumenthals and Schulman (2007), Orzeck et al. (2007), and Gums et al. (2008).

Table A6.2

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Oseltamivir	Control	Relative (95% CI)	Absolute		
Hospitalization (follow-up mean 14 days)												
3[1]	observational studies	no serious limitations[2]	no serious inconsistency	no serious indirectness[3]	no serious imprecision	none	625/69929 (0.9%)	979/73080 (1.3%)	OR 0.73 (0.63 to 0.83)[4]	4 fewer per 1000 (from 2 fewer to 5 fewer)	⊕⊕OO LOW	CRITICAL
								10%		25 fewer per 1000 (from 16 fewer to 35 fewer)		
								20%		46 fewer per 1000 (from 28 fewer to 64 fewer)		

1. Although 5 observational studies were identified, only three included the outcome hospitalization.
2. All of these studies were case-control studies. Although we did not downgrade for selection bias, this always is a concern with this study design.
3. The studies were performed in patients with seasonal influenza. We did not downgrade for indirectness in relation to Influenza H1N1 infection.
4. We used the adjusted OR or RR from each study and calculated a pooled OR. The study by Gums et al. used propensity score matching and the unadjusted OR was used.

Annex 7: Independent evaluation of oseltamivir dosing in children

The literature review and independent evaluation of the validity of recently recommended oseltamivir doses in children by Greg Kearns and Susan Abdel-Rahman is an unpublished report, but is available upon request from the WHO secretariat (see contact information in Part I).

Summary

This report examines available data on oseltamivir's disposition profile in infants and the pathologic and physiologic characteristics that may form the basis for differences between infant and adult populations. Evidence indicates that the standard peroral doses are well tolerated and premature neonates are capable of effectively metabolising oseltamivir and attaining sufficient blood oseltamivir carboxylate levels for antiviral activity. Paediatric pharmokinetic data indicate substantial variability in the dose-plasma concentration relationship, possibly due to oral bioavailability associated with feeding composition and frequency and the maturation of renal function. Dose recommendations for treatment are 2.5-3.0 mg/kg/day for the first 14 days postnatal, 3.0 mg/kg twice daily 0.5 to 12 months of age, and 3-3.5 mg/kg twice daily from 12-24 months. Recommendations are also given for paediatric patients with renal impairment.

Annex 8: Review of extemporaneous preparations of oseltamivir

The review of extemporaneous preparations of oseltamivir for home-based use and also for hospital or local production by Tony Nunn is an unpublished report, but is available upon request from the WHO secretariat (see contact information in Part I).

Summary

The report reviews published literature on extemporaneous liquid preparations of oseltamivir and considers feasibility and alternatives in resource-poor settings. It concludes that recommendations for emergency compounding of oseltamivir oral liquid preparations can be made, but that the vehicles required may not be available in many countries. However, a pragmatic approach to preparation using locally-available ingredients may be appropriate, depending on the risk-benefit for oseltamivir treatment. Dispersion of capsule contents in water should allow measurement of smaller doses for infants, but measuring device availability will be important for success.

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