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

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Executive summary

The purpose of this document is to provide a basis for advice to clinicians on the use of the currently available antivirals for patients presenting with illness due to influenza virus infection as well the potential use of the medicines for chemoprophylaxis. The document addresses specifically the two neuraminidase inhibitors oseltamivir and zanamivir, and the two M2 inhibitors amantadine and rimantadine. It includes recommendations on the use of some other potential pharmacological treatments. While the focus of the document is on management of patients with pandemic influenza (H1N1) 2009 virus infection, the document includes guidance on the use of the antivirals for other seasonal influenza virus strains, and for infections due to novel influenza A virus strains. WHO recommends that country and local public health authorities issue local guidance for clinicians from time to time that places these recommendations in the context of epidemiological and antiviral susceptibility data on the locally circulating influenza strains.

This guidance expands on the recommendations published in May 2009 titled "Clinical management of human infection with new influenza A (H1N1) virus: Initial guidance". The recommendations are based on a review of data obtained with previously circulating strains, and treatment of human H5N1 influenza virus infections. It is anticipated that as the prevalence and severity of the current epidemic changes, further information will become available that may warrant revision of the recommendations .

The table below summarizes the treatment recommendations that are described in full in sections 3.5 (Pandemic H1N1) 2009) and 3.6 (other influenza strains and co-circulating seasonal strains) and in WHO Rapid Advice Guidelines on pharmacological management of humans infected with avian influenza A(H5N1) virus (sporadic zoonotic viruses). Numbers refer to the specific recommendations within this document:

Table R1: Use of antivirals for treatment of influenza

Population	Pandemic (H1N1) influenza virus 2009	Multiple co-circulating influenza A sub-types or viruses with different antiviral susceptibilities	Sporadic zoonotic influenza A viruses including H5N1
Mild to moderate uncomplicated clinical presentation			
At-risk[a] population	oseltamivir or zanamivir (04)	Zanamivir, or oseltamivir plus M2 inhibitor[b] (10)	oseltamivir or zanamivir
Otherwise healthy[c]	Need not treat (03)	Need not treat (09)	oseltamivir
a Infants and children aged less than 5, the elderly (>65 years), nursing home residents, pregnant women, patients with chronic co-morbid conditions such as cardiovascular, respiratory or liver disease, diabetes, and those with immunosuppression related to malignancy, HIV infection or other diseases. b Amantadine should not be used in pregnant women (recommendation 12). c All those not covered by the at-risk definition above.			
Severe or progressive clinical presentation[d]			
At-risk[a] population	Oseltamivir (01) (zanamivir should be used where virus is known to be resistant to oseltamivir, or if oseltamivir unavailable) (02)	oseltamivir plus M2 inhibitor[b], or zanamivir (05,06, 07)	oseltamivir plus M2 inhibitor
Otherwise healthy[c]			
d See section 2 Case Description. Would include all patients requiring hospitalization.			

Recommendations - use of antivirals for treatment of pandemic (H1N1) 2009 influenza virus infection (for full details see Section 3.5)

Context: Treatment of patients with confirmed or strongly suspected infection with influenza pandemic (H1N1) 2009, where clinical presentation is severe or progressive and antiviral medications for influenza are available.

Rec 01: Patients who have severe or progressive clinical illness should be treated with oseltamivir. (Strong recommendation, low quality evidence). Treatment should be initiated as soon as possible. Consideration may be given to the use of higher doses up to 150 mg bid, and longer duration of treatment depending on clinical response.

This recommendation applies to all patient groups, including pregnant women, and young children <5 years, including neonates.

Rec 02: In situations where (1) oseltamivir is not available or not possible to use, or (2) if the virus is resistant to oseltamivir but known or likely to be susceptible to zanamivir, patients who have severe or progressive clinical illness should be treated with zanamivir. (Strong recommendation, very low quality evidence).

Context: Treatment of patients with confirmed or strongly suspected but uncomplicated illness due to pandemic influenza virus infection, and antiviral medications for influenza are available.

Rec 03: Patients not in 'at risk' groups (defined below Table 1) who have uncomplicated illness due to confirmed or strongly suspected influenza virus infection need not be treated with antivirals. (Weak recommendation, low quality evidence).

Rec 04: Patients in 'at-risk' groups, with uncomplicated illness due to influenza virus infection, should be treated with oseltamivir or zanamivir. Treatment should be initiated as soon as possible following onset of illness. (Strong recommendation, very low quality evidence).

Recommendations - use of antivirals for chemoprophylaxis of pandemic (H1N1) 2009 influenza virus infection

(for full details see Section 4.5)

Context: Use of antivirals as chemoprophylaxis of pandemic (H1N1) 2009 influenza.

Rec 14: Where the risk of human-to-human transmission of influenza is high or low and the likelihood of complications of infection is high (either due to the strain or baseline risk of the exposed group) oseltamivir or zanamivir might be used as post exposure chemoprophylaxis for the affected community or group, individuals in 'at risk' groups or health care workers. (Weak recommendation, moderate quality evidence).

Rec 15: If the likelihood of complications of infection is low, antiviral chemoprophylaxis need not be offered to individuals in 'at risk' groups or health care workers. This recommendation applies independent of risk of human to human transmission. (Weak recommendation, low quality evidence).

Other recommendations

Additional recommendations, including the use of antivirals where strains other than pandemic (H1N1) 2009 are circulating, are covered in detail in sections 3.6, 4.5 and section 5. Of these additional recommendations, the following are also applicable to pandemic (H1N1) 2009 influenza:

Rec 08: In situations where the circulating influenza A virus has probable or known M2 inhibitor resistance (e.g., pandemic H1N1), patients who have severe or progressive clinical presentation should not be treated with amantadine or rimantadine (alone or in combination with other medicines). (Strong recommendation, low quality evidence).

Rec 12: Pregnant women and children aged less than 1 year with uncomplicated illness due to influenza virus infection should not be treated with amantadine or rimantadine. (Strong recommendation, very low quality evidence).

Rec 16: In patients with confirmed or strongly suspected influenza virus infection, ribavirin should not be administered as monotherapy. If ribavirin is to be used in combination with other therapies, this should be done only in the context of prospective clinical and virological data collection.

Rec 17: In pregnant women with confirmed or strongly suspected influenza virus infection, ribavirin should not be administered as treatment or chemoprophylaxis.

Rec 18: In patients with confirmed or strongly suspected influenza virus infection, immunoglobulins or interferons or other unapproved therapies should not be administered unless in the context of prospective clinical and virological data collection.

1. Introduction

In April 2009, the World Health Organization (WHO) received reports of sustained person to person infections with a novel influenza A (H1N1) virus in Mexico and the United States. Subsequent international spread led WHO to declare on 11 June 2009that the first influenza pandemic in 41 years had occurred . This 2009 pandemic H1N1 influenza virus has now spread worldwide, with confirmed cases of pandemic H1N1 virus infection reported in more than 100 countries in all 6 WHO regions. This pandemic has led to the need to add to the existing guidance on the use of antivirals (WHO Rapid advice guidelines on pharmacological management of humans infected with highly pathogenic avian influenza A(H5N1) virus) to include antiviral use for infections caused by new strains of pandemic (A)H1N1 virus as well as use in the context of seasonal influenza or of infections due to other novel influenza A viruses. The WHO rapid advice guidelines on pharmacological management of humans infected with highly pathogenic avian influenza A(H5N1) virus remain unchanged by these new guidelines.

The purpose of this document is to provide a basis for advice to clinicians on the use of the currently available antivirals for patients presenting with illness due to influenza virus infection as well the potential use of the medicines for chemoprophylaxis. It is expected that the document will also be used by health care managers and policy makers. The document addresses specifically the two neuraminidase inhibitors oseltamivir and zanamivir, and the two M2 inhibitors amantadine and rimantadine. It includes recommendations on the use of some other potential pharmacological treatments, specifically ribavirin, interferons, immunoglobulins and corticosteroids. While the focus of the document is on management of patients with pandemic (H1N1) 2009 virus infection, the document includes guidance on the use of the antivirals for seasonal influenza virus strains, and for infections due to novel zoonotic influenza A virus strains, including circumstances encompassing high and low transmission of disease, high and low risks of adverse outcomes and severity of illness, and emergence of drug resistance.

The guidance has been prepared as a WHO 'Rapid Advice guideline' and expands on the recommendations published in May 2009 titled "Clinical management of human infection with new influenza A (H1N1) virus: Initial guidance". Full details of the process used are in Annex 1. The evidence used as the basis for the guideline is provided in Annex 4. It is anticipated that as the prevalence and severity of the current epidemic changes, further information will become available that may warrant revision of the recommendations . It is therefore planned to review the guidance no later than September 2009, to determine whether modifications to the recommendations are needed.

2. Case description

Presentation of influenza virus infection can vary from asymptomatic infection through to serious complicated illness that may include exacerbation of other underlying conditions and severe viral pneumonia with multi-organ failure. Since a wide range of pathogens can cause influenza-like illness, a clinical diagnosis of influenza will be guided by epidemiologic data and confirmed by laboratory tests. However, on an individual patient basis, initial treatment decisions should be based on clinical presentation and epidemiological data and should not be delayed pending laboratory confirmation. In developing these guidelines, the Panel considered three broad scenarios, set out below.

Uncomplicated influenza

- Influenza-like illness symptoms: fever, cough, sore throat, rhinorrhea, headache, muscle pain, malaise, but no shortness of breath, no dyspnoea. Patients may present with some or all of these symptoms.
- Gastrointestinal illness may also be present, such as diarrhoea and/or vomiting, especially in children, but without evidence of dehydration.

Complicated or severe influenza

- Presenting clinical (shortness of breath, dyspnoea, tachypnea, hypoxia) and/or radiological signs of lower respiratory tract disease (e.g. pneumonia), CNS findings (e.g. encephalopathy), severe dehydration or presenting secondary complications, renal failure, multi-organ failure, and septic shock. Other complications can include musculoskeletal (rhabdomyolysis) and cardiac (myocarditis).
- Exacerbation of underlying chronic disease, including asthma, chronic obstructive pulmonary disease, chronic hepatic or renal failure, diabetes or other cardiovascular conditions.
- Any other condition or clinical presentation requiring hospital admission for clinical management.
- Any of the signs of disease progression listed below.

Signs and symptoms of progressive disease

Patients who present initially with uncomplicated influenza may progress to more severe disease. Progression can be rapid. The following are some of the indicators of progression, which would necessitate an urgent review of patient management:

- Symptoms and signs suggesting oxygen impairment or cardiopulmonary insufficiency:

- shortness of breath (with activity or at rest), difficulty in breathing, turning blue, bloody or coloured sputum, chest pain, low blood pressure;
- in children, fast or laboured breathing.
- Hypoxia as indicated by pulse oximetry

– Symptoms and signs suggesting CNS complications:

- altered mental status, unconscious, drowsiness, or difficult to awaken; recurring or persistent convulsions (seizures), confusion, severe weakness or paralysis.

– Evidence of sustained virus replication or invasive secondary bacterial infection:

- based on laboratory testing or clinical signs (e.g. persistent high fever and other symptoms beyond three days).

– Severe dehydration:

- decreased activity, dizziness, decreased urine output, lethargy.

3. Treatment of seasonal or pandemic influenza: recommendations for use of antivirals

The Guideline Panel identified the following treatment outcomes as critical for developing recommendations:

- mortality;
- hospitalization;
- complications;
- serious adverse events (not drug-related);
- drug resistance.

All outcomes rated by the Panel are listed in Annex 1.

There are no adequate data from head-to-head randomized controlled trials directly comparing the effects of different antiviral medicines. All treatment recommendations are based on trials that compare active treatment to placebo and therefore comparisons between treatments are indirect.

All the recommendations are strongly influenced by patterns of antiviral resistance. Resistance prevalence in circulating influenza strains is collated and reported by WHO[1]. Recommendations herein therefore may need to be modified in the light of current or local knowledge of the antiviral susceptibility of circulating viruses.

As of June 2009, the antiviral susceptibilities of circulating viruses are:

	Oseltamivir	Zanamivir	M2 inhibitors
Pandemic A(H1N1) 2009	Susceptible[a]	Susceptible	Resistant
Seasonal A (H1N1)	Mostly resistant	Susceptible	Mostly susceptible
Seasonal A (H3N2)	Susceptible	Susceptible	Resistant
Influenza B	Susceptible	Susceptible	Resistant
Avian influenza (H5N1)	Susceptible	Susceptible	Variable resistant

a A small number of isolated cases of resistance to oseltamivir have been reported

The recommendations have therefore been guided by three key principles with respect to resistance:

- An antiviral should not be used where the virus is known or highly likely to be resistant to that antiviral.
- Where more than one virus strain is circulating, and the viruses have different antiviral susceptibilities, more than one antiviral may be used to increase the probability of providing coverage with at least one effective agent. There will be continual monitoring for drug susceptibility, so that appropriate local and timely information is available to guide treatment choices.

1 http://www.who.int/csr/disease/influenza/2008-9nhemisummaryreport/en/index.html

The cost of all antivirals for treatment will vary across countries and the cost to the health system will depend on prevalence and how each drug is procured. Recommended doses for each antiviral (based on marketing authorizations in most countries) are provided in Table 3.1.

Table 3.1: Dosage recommendations - treatment

Agent	Age Groups (yrs)					
	Duration	**1-4**	**5-9**	**10-12**	**13-64**	**≥ 65**
Amantadine[a]						
	5 days	5 mg/kg/day up to 150 mg in 2 divided doses	5 mg/kg/day up to 150 mg in 2 divided doses	100 mg twice daily	100 mg twice daily	≤ 100 mg/day
Rimantadine[b]						
	5 days	Not licensed for use	Not licensed for use	Not licensed for use	100 mg twice daily	100 mg/day
Oseltamivir						
	5 days	Weight-adjusted doses[c]: - 30 mg twice daily for ≤ 15 kg - 45 mg twice daily for >15 to 23 kg - 60 mg twice daily for >23 to 40 kg - 75 mg twice daily for >40 kg			75 mg twice daily[c]	75 mg twice daily[c]
Zanamivir						
	5 days	Not licensed for use	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily

a Amantadine package insert should be consulted for dosage recommendations for persons with creatinine clearance ≤50 ml/min/1.73m^2.

b Reduction in rimantadine dosage to 100 mg/day is recommended for persons who have severe hepatic dysfunction or those with creatinine clearance <10 ml/min. Other persons with less severe hepatic or renal dysfunctions taking 100 mg/day should be observed closely and dosage should be reduced or drug discontinued if necessary.

c Reduction in dose of oseltamivir is recommended for persons with creatinine clearance <30 ml/min.

Source: http://www.cdc.gov/flu/professionals/antivirals/dosagetable.htm#table

3.1 Use of oseltamivir - treatment

Summary of findings- evidence for benefits and harms

The evidence for use of oseltamivir for the treatment of uncomplicated seasonal influenza is summarized in a recent systematic review[1]. This review included six placebo controlled trials of oseltamivir in 'healthy' adults; six trials in 'at-risk' patients; two trials in children and three trials in the elderly. The 'at-risk' patients included those with co-morbidities, the elderly and children (aged 6 to 12 years). The following outcomes were reported based on analyses of intention-to-treat (ITT) populations as well as intention-to-treat 'infected' populations:

- time (in hours) to alleviation of symptoms; time to return to normal activity (in hours); overall complications; complications requiring hospitalization; bronchitis; pneumonia; antibiotic use; overall adverse events; serious adverse events; and drug-related adverse events.

The results reported in the review showed that oseltamivir is associated with a reduction of slightly less than one day in duration of symptoms (-16.28 hours) for an ITT population and slightly longer for an infected population (-22.75 hours). The time to resume normal activity was slightly greater than a day (34.8 hours for the ITT population and 36.3 hours for an infected population). There was no significant difference between oseltamivir and placebo in the occurrence of complications or adverse events.

The available systematic reviews and controlled trials do not provide any information regarding the outcomes of mortality, progression to severe disease or hospitalization. Individual observational studies reviewed by the Panel showed that oseltamivir may be associated with statistically significant reductions in risk of pneumonia, otitis media and hospitalization compared to matched untreated controls[2 3] (detailed observational results are provided in Annex 4). The pooled estimate of effect (as odds ratio) from three case-control studies including data from over 140,000 patients and controls was 0.73 (0.63 to 0.83) for the outcome of any hospitalization. However, these results are based on cohorts in the United States and therefore may not be representative of the occurrence of these events in other populations or locations.

The use of oseltamivir in pregnant women[5] has not indicated any additional risks for adverse events. Reports of malformation (1.1%) in a population of 90 pregnant Japanese women who received oseltamivir were within the incidence of major malformations in the general population. Oseltamivir was not assocaiated with any adverse effect in neonates while on breast-feeding, although the only data available are based on the report of one lactating woman[6].

Use of oseltamivir in children aged less than one year has been described in retrospective reports or those that have been provided to regulatory authorities but are currently unpublished; to date, no additional safety concerns have been identified.

Evidence on the efficacy and safety of oseltamivir for use in influenza other than seasonal influenza is based on case reports of its use in humans infected with avian H5N1 and emerging reports of its use in H1N1. Information on the use of oseltamivir for the treatment of avian H5N1 has been summarized by the Writing Committee of the Second World Health Organization Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus[4], and no safety concerns have been raised.

3.2 Use of zanamivir - treatment

Summary of findings -evidence for benefits and harms

The evidence for use of zanamivir for the treatment of influenza is based on a recent systematic review[1], which included seven placebo controlled trials of zanamivir in 'healthy' adults; nine trials in 'at-risk' patients; two trials in children and five trials in the elderly. The 'at-risk' patients included those with co-morbidities, the elderly and children. As for oseltamivir, the review assessed the following outcomes in healthy adults, at-risk patients, the elderly and children as analyses of intention-to-treat populations as well as intention-to-treat 'infected' populations:

- time (in hours) to duration of symptoms; time to return to normal activity (in hours); overall complications; complications requiring hospitalization; bronchitis; pneumonia; antibiotic use; overall adverse events; serious adverse events; and drug-related adverse events.

The results reported in the review showed that zanamivir is associated with a reduction of less than one day in alleviation of symptoms (-0.71 days) for an ITT population and slightly longer than one day for an infected population (-1.07 days). The time to resume normal activity showed no statistically significant advantage for zanamivir compared to placebo. There was no significant difference between zanamivir and placebo in the occurrence of complications or adverse events.

The available systematic reviews and controlled trials do not provide any information regarding the outcomes of mortality, progression to severe disease or hospitalization. An observational study conducted in the United States indicated that the occurrence of complications is similar between those treated with zanamivir and untreated controls[7]. A retrospective analysis of published trials[8] assessed the impact of zanamivir on the occurrence of respiratory events leading to use of antibiotics and concluded that zanamivir reduced the number of antibiotic prescriptions; however, the number of patients with respiratory events in the trials was small and therefore results should be interpreted with caution.

There is very little published information describing the use of zanamivir in pregnant women. Tanaka et al.[5] describe the outcomes of four pregnant women who were exposed to zanamivir, with one pregnancy spontaneously miscarried, one terminated and two healthy babies delivered. Although no studies assessing use of zanamivir during lactation are available, this study concludes that the amount of zanamivir that would be ingested by a 5 kg infant is much lower than the recommended dose for children. There are no publicly available data describing the use of zanamivir in children aged less than one year.

There is no evidence on the efficacy and safety of zanamivir for use in influenza other than uncomplicated seasonal influenza.

3.3 Use of amantadine - treatment

Summary of findings-evidence for benefits and harms

The use of amantadine for the treatment of influenza is based on the Jefferson et al.[9] and the Alves Galvao et al.[10] systematic reviews. The Jefferson et al.[9] review included ten placebo controlled trials of amantadine in adults and the Alves Galvao et al.[10] review included two placebo controlled trials of amantadine in children. The outcomes assessed in the Jefferson et al.[9] review included duration of fever in days, adverse effects and viral shedding. The Alves Galvao et al.[10] review assessed proportion of patients with fever at 3 days, cough at day 7, malaise at day 6, conjunctivitis at day 5 and eye symptoms on day 5 as well as adverse effects. Key results from the amantadine trials are in Annex 4.

As for oseltamivir and zanamivir, the available systematic reviews do not provide any information regarding the outcomes of mortality, progression to severe disease or hospitalization. The reviews show 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 one day for adults (MD=-0.99; 95% CI: -1.26, -0.71) and fewer cases of fever for children. No statistically significant difference was demonstrated between amantadine and placebo in the occurrence of adverse events in the randomized trials.

It is generally assumed that there is a greater occurrence of adverse events with amantadine, compared to the neuraminidase inhibitors. However, these conclusions have been drawn on the basis of prospective comparisons of amantadine and rimantadine for tolerability in infected and uninfected persons and on observational studies assessing the use of M2 inhibitors in prophylaxis in elderly patients, in which amantadine was much less well tolerated than rimantadine[11].

There are very limited published data available assessing the use of amantadine in children under the age of one year, and very little data available assessing use in children aged less than five.

3.4 Use of rimantadine - treatment

Summary of findings -evidence for benefits and harms

The use of rimantadine for the treatment of influenza is based on two systematic reviews. The Jefferson et al.[9] review included three placebo controlled trials of rimantadine in adults and the Alves Galvao et al.[10] review included one placebo controlled trial of rimantadine in children. The outcomes assessed in the Jefferson et al.[9] review included duration of fever in days, adverse effects and viral shedding while the Alves Galvao et al.[10] review assessed proportion of patients with fever at 3 days, cough at day 7, malaise at day 6, conjunctivitis at day 5 and eye symptoms on day 5 as well as adverse effects. Key results are in Annex 4.

The available systematic reviews do not provide any information regarding the outcomes of mortality, progression to severe disease or hospitalization for rimantadine. Based on the Jefferson et al.[9] review and the Alves Galvao et al.[10] review, rimantadine is superior to

placebo, with a reduction in duration of fever for adults of greater than one day (MD=-1.24; 95% CI: -1.71, -0.76) and fewer cases of fever in children. No statistically significant difference was demonstrated between rimantadine and placebo in the occurrence of adverse events.

There are limited observational studies of rimantadine assessing other outcomes and adverse events. One chemoprophylaxis study[11] indicated that the occurrence of adverse events was less with rimantadine than that observed with amantadine in elderly nursing home patients.

There are no published data describing the use of rimantadine in children under the age of one year. Rimantadine is not recommended for use in pregnant women.

The recommendations below were developed by the Panel for the contexts as described, taking account of the different main scenarios for circulating virus strains and also taking account of the absence of trials directly comparing the different antivirals.

3.5 Treatment recommendations: Influenza pandemic (H1N1) 2009 influenza virus infection

Context:	Treatment of patients with confirmed or strongly suspected infection with influenza pandemic (H1N1) 2009 virus, , where clinical presentation is severe or progressive and antiviral medications for influenza are available.

Rec 01: Patients who have severe or progressive clinical illness should be treated with oseltamivir. (Strong recommendation, low quality evidence). Treatment should be initiated as soon as possible. Consideration may be given to the use of higher doses up to 150 mg bid, and longer duration of treatment depending on clinical response.

This recommendation applies to all patient groups, including pregnant women, and young children <5 years, including neonates.

Treatment should be started as soon as possible (laboratory confirmation of influenza virus infection is not necessary for the initiation of treatment). The evidence from clinical trials suggest most patients benefit from treatment commencing within 48 hours of symptoms, but experience from use in patients with H5N1 virus infection and severe lower respiratory tract disease suggests that later initiation of treatment may also be effective, whenever viral replication is present or strongly suspected.

In patients with severe or progressive illness not responding to normal treatment regimens, higher doses of oseltamivir and longer duration of treatment may be appropriate, although there is no clinical trial evidence to show benefit. An adult dose of 150 mg bid is being used in some situations.

Remarks:

This recommendation takes account of:

- The concern about the increased risk of severe complications or death from influenza in this context.
- The evidence from randomized controlled trials that shows a reduction of approximately one day in symptoms in outpatients, and evidence from observational studies in all patients that demonstrates a reduction in progression to severe disease and hospitalization in patients treated with antivirals.
- The ease of use and suitability of oseltamivir compared to other currently available neuraminidase inhibitors, i.e. oral administration versus inhaled.
- The opportunity cost of providing antivirals to these patients is considered low.

Rec 02: In situations where (1) oseltamivir is not available or not possible to use, or (2) if the virus is resistant to oseltamivir but known or likely to be susceptible to zanamivir, patients who have severe or progressive clinical illness could be treated with zanamivir. (Strong recommendation, very low quality evidence).

Remarks:

This recommendation takes account of:

- The need to offer alternative treatment to patients with severe or progressive illness in the absence of oseltamivir or if the virus is known to be resistant to oseltamivir.
- The practical difficulties in administering zanamivir to severely ill patients in its current dosage form.

Context: Treatment of patients with confirmed or strongly suspected but uncomplicated illness due to pandemic influenza virus infection, and antiviral medications for influenza are available.

Rec 03: Patients not in 'at risk' groups (defined below) who have uncomplicated illness due to confirmed or strongly suspected influenza virus infection need not be treated with antivirals. (Weak recommendation, low quality evidence).

Risk groups are defined as: infants and children aged less than 5, the elderly (>65 years), nursing home residents, pregnant women, patients with chronic co-morbid conditions such as cardiovascular, respiratory or liver disease, diabetes, and those with immunosuppression related to malignancy, HIV infection or other diseases.

Remarks:

This recommendation takes account of:

- The consideration of the potential opportunity cost of providing antivirals on a large scale to the community compared with taking public health measures to manage an outbreak.

– The concern about the potential development of resistant viruses that might transmit from person to person.

Rec 04: Patients in 'at-risk' groups, with uncomplicated illness due to influenza virus infection, should be treated with oseltamivir or zanamivir. Treatment should be initiated as soon as possible following onset of illness. (Strong recommendation, very low quality evidence).

Remarks:

This recommendation takes account of:

– The concern about the increased risk of severe complications or death from influenza in this patient group.

– The consideration of the potential opportunity cost of providing antivirals to this limited group, compared with taking public health measures to manage a pandemic.

– The evidence from randomized trials that shows a reduction of approximately one day in symptoms in outpatients, and evidence from observational studies that demonstrates a reduction in progression to severe disease and hospitalization in patients treated with antivirals.

3.6 Treatment recommendations: Other influenza virus strains

Context: Treatment of patients with confirmed or strongly suspected infection with seasonal influenza virus, where antiviral susceptibility is known, and where clinical presentation is severe or progressive and antiviral medications for influenza are available.

Rec 05: Patients who have severe or progressive clinical illness due to oseltamivir-susceptible and M2 inhibitor-susceptible virus might be treated with both oseltamivir and either amantadine or rimantadine. (Weak recommendation, very low quality evidence).

Remarks:

This recommendation takes account of:

– In vitro and animal model studies showing synergistic antiviral effects with the combination for dually susceptible strains compared to individual treatments. However, if clinicians choose to use combination treatment, whenever possible this should be done in the context of prospective clinical and virological data collection.

Rec 06: Patients who have severe or progressive clinical illness due to oseltamivir-resistant and M2 inhibitor-resistant virus should be treated with zanamivir. (Strong recommendation, very low quality evidence).

Remarks:

This recommendation takes account of:

– The severity of the illness, and that zanamivir is the only alternative licensed antiviral drug.

Rec 07: In situations where there are co-circulating influenza A virus subtypes (even if there is probable or known oseltamivir resistance) patients who have severe or progressive clinical presentation should be treated with oseltamivir and either amantadine or rimantadine. (Strong recommendation, very low quality evidence).

This recommendation applies to all patients including pregnant women, in whom the risks of severe illness are likely to outweigh the risk of adverse events during treatment. However there is a lack of evidence supporting use of amantadine or rimantadine in neonates.

Remarks:

This recommendation takes account of:

– The concern about the increased risk of severe complications or death from influenza in this context.

– The need to commence treatment with at least one active agent.

– The probability that the virus will be resistant to one or other classes of antivirals. If laboratory data confirm drug resistance in the infecting strain, then the inactive drug should be stopped.

– The evidence from pharmacokinetic studies and animal studies that show combination therapy is safe.

Rec 08: In situations where the circulating influenza A virus has probable or known M2 inhibitor resistance (including pandemic (H1N1) 2009), patients who have severe or progressive clinical presentation should not be treated with amantadine or rimantadine (alone or in combination with other medicines). (Strong recommendation, low quality evidence).

Remarks:

This recommendation takes account of:

– The concern about adverse effects of a treatment likely to be ineffective.

Context: Treatment of patients with confirmed or strongly suspected but uncomplicated illness due to seasonal or pandemic influenza virus infection, where antiviral sensitivity is known, and antiviral medications for influenza are available.

Rec 09: Patients not in 'at risk' groups (defined below Table 1) who have uncomplicated illness due to confirmed or strongly suspected influenza virus infection need not be treated with antivirals. (Weak recommendation, low quality evidence).

Remarks:

– As for recommendation 3 above

Rec 10: In situations where there are co-circulating influenza A virus subtypes (even when these include probable or known oseltamivir resistance), patients in 'at-risk groups' with uncomplicated illness due to confirmed or strongly suspected seasonal influenza virus

infection should be treated with zanamivir, or with oseltamivir plus amantadine or rimantadine. (Weak recommendation, very low quality evidence). This recommendation does not apply to pregnant women - see Recommendation12.

Remarks:

This recommendation takes account of:

- The need to provide potentially effective treatment to vulnerable patients.
- The consideration of the potential opportunity cost of providing antivirals to this limited group, compared with taking public health measures to manage a pandemic.

Rec 11: Where the most prevalent virus is probably or known to be oseltamivir-resistant, pregnant women with uncomplicated illness due to seasonal influenza virus infection might be treated with zanamivir. (Weak recommendation, very low quality evidence).

Rec 12: Pregnant women and children aged less than 1 year with uncomplicated illness due to influenza virus infection should not be treated with amantadine or rimantadine. (Strong recommendation, very low quality evidence).

Remarks:

This recommendation takes account of:

- The concern about the increased risk of adverse events due to amantadine in pregnant women and lack of evidence supporting use in young children

Rec 13: Where the most prevalent virus is probably or known to be oseltamivir-resistant, immunosuppressed patients with seasonal influenza virus infection should be treated with zanamivir plus rimantadine (Weak recommendation, low quality evidence).

Remarks:

This recommendation takes account of:

- The need to provide potentially effective treatment to vulnerable patients.

4. Chemoprophylaxis of influenza: recommendations for use of antivirals

The Guideline Panel identified the following treatment outcomes as critical for developing recommendations:

- mortality;
- hospitalization;
- influenza cases prevented;
- serious adverse events (not drug related);
- drug related adverse events;
- drug resistance.

All outcomes rated by the Panel are listed in Annex 1.

There are few head-to-head randomized controlled trials directly comparing antivirals. There are very limited clinical data comparing rimantadine and zanamivir and no published trials comparing oseltamivir and zanamivir directly for chemoprophyalxis. As such no firm conclusions can be drawn regarding comparative efficacy for the neuraminidase inhibitors. Several studies have compared amantadine and rimantadine for prophylaxis. These have generally found comparable clinical efficacy but better tolerability of rimantadine with respect to central nervous system side effects.

All chemoprophylaxis recommendations are principally based on trials that compare active treatment to placebo and therefore comparisons between treatments are indirect.

The cost of all antivirals for chemoprophylaxis will vary with duration of chemoprophylaxis, and across countries, and the cost to the health system will depend on prevalence and how each drug is procured. Table 4.1 provides dosage recommendations for chemoprophylaxis.

Table 4.1: Dosage recommendations - chemoprophylaxis

Agent	Age Groups (yrs)					
	Duration	**1-6**	**7-9**	**10-12**	**13-64**	**≥ 65**
Amantadine[a]						
	Begin as soon as exposure identified and continue for 5-7 days after last known exposure[b]	5 mg/kg/day up to 150 mg in two divided doses	5 mg/kg/day up to 150 mg in two divided doses	100 mg twice daily	100 mg twice daily	≤100 mg/day
Rimantadine[c]						
	Begin as soon as exposure identified and continue for 5-7 days after last known exposure[b]	5 mg/kg/day up to 150 mg in two divided doses	5 mg/kg/day up to 150 mg in two divided doses	100 mg twice daily	100 mg twice daily	100 mg/day
Oseltamivir						
	Begin as soon as exposure identified and continue for 5-7 days after last known exposure[b]	Weight adjusted doses[d]: - 30 mg/day for ≤ 15 kg - 45 mg/day for >15 to 23 kg - 60 mg/day for >23 to 40 kg - 75 mg/day for >40 kg			75 mg/day	75 mg/day
Zanamivir						
	Begin as soon as exposure identified and continue for 5-7 days after last known exposure[b]	**1-4 yrs:** NA	**5-6 yrs:** 10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily

a Amantadine package insert should be consulted for dosage recommendations for persons with creatinine clearance ≤50 ml/min/1.73m^2.

b For control of outbreaks in long-term care facilities and hospitals, CDC recommends chemoprophylaxis for a minimum of two weeks, and up to one week after the last known case was identified.

c Reduction in rimantadine dosage to 100 mg/day is recommended for persons who have severe hepatic dysfunction or those with creatinine clearance <10 ml/min. Other persons with less severe hepatic or renal dysfunctions taking 100 mg/day should be observed closely and dosage should be reduced or drug discontinued if necessary.

d Reduction in dose of oseltamivir is recommended for persons with creatinine clearance <30 ml/min.

Source: http://www.cdc.gov/flu/professionals/antivirals/dosagetable.htm#table

4.1 Use of oseltamivir - chemoprophylaxis

Summary of findings- evidence for benefits and harms

The use of oseltamivir for chemoprophylaxis of influenza is based on a recent systematic review,[12] which included six trials, two in adults, two in the elderly and two assessing post-exposure chemoprophylaxis in mixed households. The key outcome assessed in the review was the occurrence of symptomatic laboratory-confirmed infection.

The review found that in adults there were statistically significantly fewer cases of laboratory-confirmed symptomatic infection in patients receiving oseltamivir compared to placebo, with RR=0.27 (95% CI: 0.09, 0.83). There were also statistically significantly fewer cases of infection in elderly individuals(RR=0.08; 95% CI: 0.01, 0.63) and in mixed households including adults and children post-exposure prophylaxis resulted in RR=0.19 (95% CI: 0.08, 0.45). Adverse events occurred in a similar proportion of oseltamivir and placebo-treated patients, generally less than 10%.

The Tappenden review[12] and the available trials of chemoprophylaxis did not report mortality as an outcome. Observational studies considering other outcomes such as complications have focused on oseltamivir treatment and have not assessed chemoprophylaxis.

4.2 Use of zanamivir - chemoprophylaxis

Summary of findings-evidence for benefits and harms

The use of zanamivir for chemoprophylaxis of influenza was also assessed by the Tappenden et al.[12] review. Nine zanamivir trials were included, with two in adults, one in adults and adolescents above 12 years of age, one in the elderly, three post-exposure trials and two trials in long-term care settings.

The analyses presented in the Tappenden et al.[12] review demonstrated a statistically significant benefit for zanamivir compared to placebo in all populations except the elderly, with protective efficacy ranging from 70% to just over 80%. The occurrence of adverse events was similar for zanamivir and placebo groups and generally occurred in less than 10% of patients.

As for oseltamivir, the Tappenden review[12] and available trials did not consider mortality or other outcomes such as occurrence of complications. The zanamivir observational studies focus on treatment and do not address chemoprophylaxis.

4.3 Use of amantadine - chemoprophylaxis

Summary of findings -evidence for benefits and harms

The use of amantadine for chemoprophylaxis of influenza A was assessed by the Tappenden et al.[12] review. A total of eight amantadine chemoprophylaxis trials were included, with two in adults, one in the elderly, two in residential settings including adults and adolescents, and three trials in which normal subjects were challenged experimentally with influenza virus. As there was a large degree of hetereogeneity and the trials differed in their primary outcomes, the Tappenden et al.[12] review did not provide meta-analyses and instead reported results of the individual trials.

Amantadine demonstrated advantages in post-exposure chemoprophylaxis; however, Tappenden et al.[12] state that the results should be interpreted with caution given the age and quality of the amantadine trials. The occurrence of adverse events was generally similar

between amantadine and placebo; however, two trials demonstrated a greater occurrence of adverse events in amantadine-treated patients, with severe adverse effects higher for those given amantadine chemoprophylaxis compared to placebo.

4.4 Use of rimantadine - chemoprophylaxis

Summary of findings- evidence for benefits and harms

The use of rimantadine for chemoprophylaxis of influenza A was assessed in the 2006 systematic review by Jefferson et al.[9] and the 2008 systematic review assessing use in children and the elderly by Alves Galvao et al.[10]. The Alves Galvao et al.[10] review included three rimantadine trials in children and nine trials in the elderly and assessed occurrence of infection in children and proven clinical infection in the elderly. The Jefferson et al.[9] review included three rimantadine trials in adults and assessed the occurrence of influenza cases.
The analyses presented in the reviews did not show statistically significant advantages for rimantadine compared to placebo, with protective efficacy of 70% in adults and 50% in children; however, the direction of the results favoured rimantadine. Assessment of the occurrence of adverse events in the Jefferson et al.[9] review revealed statistically significantly greater occurrence of adverse events with rimantadine compared to placebo.

4.5 Chemoprophylaxis recommendations

Antiviral chemoprophylaxis of influenza should generally be considered with regard to the benefit of providing short-term protection from illness and possibly infection, and the cost (medicine, healthcare resource utilization and monetary). Chemoprophylaxis is generally not recommended, as the opportunity cost and utilization of antiviral drugs that may be needed for treatment is not warranted. Before examining the evidence, the Guidelines Panel undertook an exercise to estimate the threshold number of individuals who would need to be treated (number needed to treat or NNT) to prevent a single case of influenza to balance the trade-off between use of resources and benefits. It was determined that an NNT of 20 or less may be reasonable in certain situations associated with more serious consequences from infection. Different users of the guidelines might adjust this in accord with national pandemic plans, and to accommodate differences in values in their own specific countries and settings, and develop local guidelines accordingly.

The use of chemoprophylaxis assumes that:

- Other control measures (i.e. infection control) are in place.
- Vaccination is planned.
- Mechanisms for delivery of drugs and costs are acceptable.

Antiviral chemoprophylaxis may have particular benefits in the higher risk situations set out below. These are based on an assessment of the likely impact of an influenza outbreak in certain settings, or the benefits of preventing infection in certain key vulnerable groups together with high quality data from studies of seasonal influenza.

High risk settings

- Settings where a high proportion of the community falls within one or more at-risk groups, and the morbidity and mortality of influenza may be higher than the population average. Such settings may include residential healthcare institutions such as nursing homes, certain hospital wards and hospices.
- Discrete closed or semi-closed settings with a high level person-to-person contact and finite healthcare resources, where a high attack rate over a short time span may be expected. The impact of an outbreak in these circumstances may overload healthcare resources, resulting in high morbidity and mortality.
- Combination of the above two settings, such as refugee camps or disaster zones where a high proportion of the community may fall within one or more risk groups, with a consequent higher morbidity and mortality, and the setting has a high level of person-to-person contact leading to a high attack rate.

The aim in these settings is to reduce morbidity and mortality.

High gain groups

- Groups with high exposure to infection but whose function is crucial to mitigation of the epidemic, and where a high attack rate over a short period of time would severely compromise health service provision. This group is principally health care workers, who may if infected also serve to transmit infection to their high risk patients.
- Other groups that are critical to maintaining core functions, with a high level person-to-person contact, where a high attack rate over a short time span would likely compromise service function.

The aim in these settings is to reduce the impact of illness so that services can be maintained.

Higher risk individuals

- Individuals whose circumstances lead to a particular high risk of complications from influenza, and with high risk of exposure. Examples include stem cell transplantation or solid organ transplant surgery at a time of high local prevalence of infection.

The aim in this setting is to reduce the probability of infection at a time of exceptional vulnerability, and particularly to be able to provide protective cover until vaccination can be introduced or can become effective.

Based on the context set out above, the recommendations below are separated into situations of high and low risk of transmission. For each, the recommendations are further divided into high and low risk of adverse outcomes if infected. The recommendations are contingent on the availability of antivirals and estimated susceptibility of the influenza virus strain.

If the risk of transmission is high, and the risk of adverse consequences of influenza infection is also high, and if the drug is available and thought to be active against the circulating strain of virus, then chemoprophylaxis might be used for individual patients and healthcare workers or in an outbreak involving a high-risk setting(with weak evidence to support the

recommendations). However, if the risk of adverse consequences of influenza infection is low, then there is no need to use chemoprophylaxis for any of these populations.

If the risk of transmission is low, the risk of complications of influenza virus infection is high, and the drug is available, then chemoprophylaxis might be used for individual patients (and healthcare workers with high risk of exposure), but not for communities (with low quality evidence to support the recommendations). And if the risk of adverse consequences of influenza virus infection is low, then there is no need to use chemoprophylaxis for any of these populations.

Context: Use of antivirals as chemoprophylaxis of pandemic (H1N1) 2009 influenza.

Rec 14: Where the risk of human-to-human transmission of influenza is high or low and the likelihood of complications of infection is high (either due to the strain or baseline risk of the exposed group) oseltamivir or zanamivir might be used as post exposure chemoprophylaxis for the affected community or group, individuals in 'at risk' groups or health care workers. (Weak recommendation, moderate quality evidence).

Remarks:

This recommendation takes account of:

- Low or high risk of transmission and higher risk of poor outcomes of infection.

Rec 15: If the likelihood of complications of infection is low, antiviral chemoprophylaxis need not be offered to individuals in 'at risk' groups or health care workers. This recommendation applies independent of risk of human to human transmission. (Weak recommendation, low quality evidence).

Remarks:

This recommendation takes account of:

- Low risk of transmission andlow risk of poor outcomes of infection.

4.6 Summary table for antiviral chemoprophylaxis recommendations.

Table 4.6.1: Use of antivirals - chemoprophylaxis

Risk		Recommendation	Population	Strength of recommendation
Transmission	**Complications**			
High	**High**	If drug available and virus susceptible, use either neuraminidase inhibitor or M2 inhibitor	Defined target population Individual patients Healthcare workers	weak weak weak
High	**Low**	chemoprophylaxis not recommended	Individual patients Healthcare workers	weak weak
Low	**High**	If drug available and virus susceptible, use either neuraminidase inhibitor or M2 inhibitor	Individual patients Healthcare workers	weak weak
Low	**Low**	chemoprophylaxis not recommended	Individual patients Healthcare workers	strong strong

5. Other interventions for management of patients with influenza

A number of other products, including ribavirin, immunoglobulin and interferons, are not licensed for the treatment of influenza in most countries but have been used for treatment of individual patients. The Guidelines Panel did not consider the evidence for the use of these drugs for the treatment of influenza as none of these medicines are registered or licensed for use in influenza.

Rec 16: In patients with confirmed or strongly suspected influenza virus infection, ribavirin should not be administered as monotherapy. If ribavirin is to be used in combination with other therapies, this should be done only in the context of prospective clinical and virological data collection.

Rec 17: In pregnant women with confirmed or strongly suspected influenza virus infection, ribavirin should not be administered as treatment or chemoprophylaxis.

Rec 18: In patients with confirmed or strongly suspected influenza virus infection, immunoglobulins or interferons or other unapproved therapies should not be administered unless in the context of prospective clinical and virological data collection.

The Guidelines Panel is aware of other investigational products and routes of administration, (e.g. peramivir, intravenous zanamivir); however, these products, as well as products licensed for indications other than influenza, should be used only in the context of prospective data collection.

The use of antibiotics, oxygen and ventilator therapy, and other modalities for the treatment of pneumonia, acute lung injury, ARDS, septic shock, multi-organ failure, and other severe complications requiring critical care intensive care management is beyond the scope of the current antiviral guidelines document. It is recommended that clinicians consult national guidelines for recommendations regarding the use of these therapies.

6. Product supply

Table 6.1: Summary of product supply

Product	Manufacturer(s) examples	Generics available?	Approved indications	Drug regulatory authority	Average wholesale prices (US dollars)
Amantadine hydrochloride 100 mg capsules 50 mg/5 ml syrup	Endo Laboratories, Alliance	yes	Chemoprophylaxis and treatment of signs and symptoms of infection caused by various strains of influenza A viruses	UK, US FDA, national authorities in Europe, Japan MHLW	$0.73 per 100 mg capsule $72.75 for 50 mg/5 ml 16oz
Oseltamivir 75 mg capsules; 30 mg capsules; 45 mg capsules; powder for reconstitution as 12 mg/ml suspension	Roche (innovator) Cipla	Limited; licensing agreements in India	Treatment of uncomplicated acute illness due to influenza A virus infection in patients 1 year and older; and chemoprophylaxis of influenza A in patients 1 year and older	US FDA, EMEA, Japan MHLW	$10.17 per 75 mg capsule $10.17 per 30 mg capsule $10.17 per 45 mg capsule $50.85 12 mg/ml (25 ml)
Rimantadine 100 mg tablets 50 mg/5 ml syrup	Forest	yes	Chemoprophylaxis and treatment of signs and symptoms of infection caused by various strains of influenza A viruses	US FDA, national authorities in Europe	$1.73 per 100 mg tablet $55.79 for 50 mg/5 ml 8oz
Zanamivir diskhaler (dry powder for inhalation disks, 5 mg per disk)	GlaxoWellcome	no	Treatment of uncomplicated influenza A in patients over 7 years (over 5 years in Japan); for prevention of influenza A in adults and children 5 years of age and older	US FDA, EMEA, Japan MHLW	$16.80 per disk

7. Priorities for update

Plans for updating this guideline

An update to this guideline will be needed if any of the following events occur:

- major new research is published (particularly randomized controlled trials of any of the antivirals or observational studies);
- new antiviral drugs becoming available;
- there is a change in the severity of illness associated with the current pandemic (H1N1), or in its susceptibility to antiviral drugs.

Updating or adapting recommendations locally

The methods used to develop the guidelines are transparent. Therefore it will be possible to update the information contained in them by simply re-running the search described in the Methods Annex. The recommendations have been developed to be as specific and detailed as possible without loosing sight of the user-friendliness of this document and the individual recommendations. The Panel encourages feedback on all aspects of these guidelines, including their applicability in individual countries. Then it may be possible to decide whether the recommendations should be amended to accommodate the changes in information. The Guidelines have also been designed in such a way to facilitate this process, in case users need to update or adapt the recommendations before the WHO has itself updated them globally.

8. Priorities for research

In developing the recommendations, the panel highlighted the following topics where further research is needed:

- Studies to assess the efficacy of existing and investigational antiviral treatment for severe or complicated influenza illness.
- Comparative clinical studies of neuraminidase inhibitors, used for treatment of influenza in all populations, assessing comparative efficacy and safety.
- Standardization of outcomes for these studies.
- Comparative studies of combination treatment, including combinations of neuraminidase inhibitors and M2 inhibitors, in all populations.
- Studies in children under one year to define dose, safety and efficacy of all antivirals, particularly in neonates.
- Development of alternative formulations, including different routes of administration, of zanamivir and oseltamivir, particularly for use in severely ill patients.
- Studies of higher doses (oseltamivir particularly).
- Urgent further evaluation of the safety of use of oseltamivir, particularly in the children, given recent widespread use in the UK, Australia and the USA.
- Definition of prognostic factors for developing severe disease.

Annexes

Annex 1:
Methods used to prepare guidelines

The WHO Guidelines on the clinical management of humans infected by influenza were prepared as a 'rapid advice guideline', according to the WHO Handbook for Guideline Development. The scope was defined by a group of WHO staff and circulated to the guideline panel for comment. A consultant was contracted to update evidence summaries from secondary sources according to the GRADE methodology. The approach used is described below in 'Preparation of Background Documentation'. Search strategies used for identifying relevant systematic reviews and health technology assessments are described below.

The evidence was assessed according to the methodology described in GRADE (GRADE Working Group 2008). 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 the 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 be 'high quality' evidence for one question, because of uncertainty about their applicability or directness, the same trials can be '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 guideline 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 (see Annex 2 for list of members; conflict of interest declarations in Annex 3). The panel was asked to identify critical clinical outcomes for the purposes of making 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 4.

The panel reviewed the evidence summaries and the draft guideline and made recommendations. All recommendations were based on consensus. Declarations of interests were reviewed at the guideline panel meeting and are listed in Annex 3. A number of panel members declared potential interests relevant to the discussion and recommendations, both personal or institutional. It was therefore agreed that if there were contentious recommendations, these panels members would withdraw from the discussion and recommendations would be finalized by panel members with no declared interests. However, the recommendations were formulated by consensus without contention.

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 sequelae). 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. Estimates of current acquisition costs are in Section 6 on drug supply.

Recommendations are classified as 'strong' or 'weak', as recommended 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 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.

Preparation of the background documentation

Background documentation was prepared in order to assist the WHO Rapid Advice Guidelines Group on Influenza revise earlier guidance on the treatment and prophylaxis of avian influenza (H5N1) infection in humans.

Summaries of the best available evidence were prepared to inform questions regarding the use of antivirals for treatment and prophylaxis in a range of populations (adults, elderly, children, 'at-risk'). The sensitivity of the virus and case fatality of the illness were taken into consideration.

Identification of important outcomes

A list of potential outcomes to be considered by the panel was initially developed for the rapid guidelines for avian H5N1 influenza. These outcomes were ranked by the Guidelines group, who were also requested to identify any relevant critical outcomes not included in the list. The group members were asked to identify which outcome they felt were critical, important but not critical and not important. The Group members when then asked to score the outcomes, using numbers corresponding to the GRADE importance of outcomes, where 7-9 indicated the outcome was critical for a decision, 4-6 indicated it was important, and 1-3 indicated it was not important. The individual scores were discussed and disagreements were resolved by consensus. 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.

Table A1.1: Ranking of outcomes for antiviral treatment

Treatment outcome	Mean	Median
Mortality	8.3	9
Hospitalization	7.2	8
Duration of hospitalization	6.1	6.5
Time to alleviation of symptoms	5.8	6
Time to return to normal activity	5.4	5.5
Complications (LRTI, otitis media)	6.9	7
Serious adverse events	7.7	8
Mild adverse events	4.2	4.5
Drug-related adverse events	6.4	6.5
Viral shedding	5.8	6
Resistance	7.6	8
Cost of drugs	5.6	6

Table A1.2: Ranking of outcomes for antiviral prophylaxis

Treatment outcome	Mean	Median
Influenza cases prevented	8.0	8
Influenza-like illness cases	5.7	6
Mortality	7.6	8.5
Hospitalization	6.8	7.5
Complications (LRTI, otitis media)	6.2	6.5
Serious adverse events	8.1	9
Mild adverse events	5.4	6
Drug-related adverse events	6.9	7.5
Viral shedding	5.1	5
Resistance	6.9	7.5
Cost of drugs	6.7	7

LRTI: Lower respiratory tract infection.

Search strategy

The search strategy sought to identify relevant systematic reviews assessing the use of oseltamivir, zanamivir, amantadine and rimantadine in the treatment and prophylaxis of influenza. Once systematic reviews were identified, searches were also conducted for randomized controlled trials in order to identify any additional trials not included in the reviews. These searches were limited to the years 2006 to 2009.

In addition to randomized controlled trials, a search was also conducted for observational studies, in particular those assessing outcomes not included in the systematic reviews, such as influenza complications, adverse events and mortality. Case reports and studies including fewer than 10 subjects were excluded from further consideration on the basis of title and abstract review. Summaries of all identified systematic reviews, individual trials and observational studies were sent to members of the Guidelines group before the June 2009 meeting, and they were asked to identify any important evidence that had not been included.

Searches were also conducted for any papers discussing modeled evaluation of influenza, including assessment of cost-effectiveness of the drugs and impact of interventions to control pandemic spread.

All searches were conducted in May 2009.

Selection criteria, data collection and judgments

Systematic reviews were used to summarize the evidence from randomized trials. The most recent reviews of good quality were focused upon and were supplemented with additional data from other reviews when necessary.

Evidence profiles based on the systematic reviews were created using the GRADE approach using 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. A liberal approach to assessment of study limitations was taken and the quality of evidence was not lowered because of reporting limitations, such as not clearly reporting whether there was concealment of allocation in trials. 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.

Because all of the evidence in the reviews was based on seasonal influenza and was thus indirect for pandemic influenza, this aspect of the GRADE profile was scored accordingly, resulting in 'moderate' of 'low' classification of evidence.

Annex 2: List of participants

Dr Edgar Bautista
Médico Neumólogo Intensivista
Jefe de UCI- INER
Calzada de Tlalpan no. 4502
Colonia sección XVI
C.P. 14080 México, D.F.
Tel: +52 55 5487 1716
drbautista40@yahoo.com.mx

Associate Professor Tawee Chotpitayasunondh
Senior Medical Officer
Queen Sirikit National Institute of Child Health
Department of Medical Services, Ministry of Public Health
Tel.and Fax: +662-354-8400
ctawee@health.moph.go.th

Dr Claudia Torres Codeço
Theoretical Epidemiology Group, Instituto Gulbenkian de Ciência
Rua da Quinta Grande, 6 Oeiras
Portugal 2780-156
Tel.: +351 21 446 4626
codeco@fiocruz.br

Professor Chris B Del Mar
Dean, Faculty of Health Sciences and Medicine, Bond University
Gold Coast, Queensland, 4229, Australia
Tel: +61 (0)7 5595 5499
Fax: +61 (0) 75595 4122
cdelmar@bond.edu.au

Dr Alan Hay
Director, WHO Collaborating Centre for Reference and Research on Influenza
National Institute for Medical Research
The Ridgeway, Mill Hill
NW7 1AA – London, Royaume-Uni
Tel.: +44 208 816 2141
Fax: +44 2089064477
ahay@nimr.mrc.ac.uk

Professor Frederick G. Hayden
Professor of Internal Medicine & Pathology
Health Sciences Center, University of Virginia
22908 - Charlottesville, VA
USA
Tel: +1 (434) 924 5059
Fax: +1 (434) 804 924 9065
FGH@virginia.edu

Professor Yoshihiro Kawaoka
Dept of Pathobiological Sciences
University of Wisconsin - Madison
2015 Linden Drive West
WI 53706 - Madison
United States of America
Tel: +813 5449 5310
Tel: + 1 608 265 4925
kawaokay@svm.vetmed.wisc.edu

Dr Simon Mardel
Clinician/Consultant/Consultant for WHO Emergency Medicine
Leicester Royal Infirmary
Parkhouse Farmhouse, Yarlside,
Barrow in Furness, Cumbria LA13 0PL
United Kingdom
Tel.: +447770 277321; +41 79 221 78 59 (WHO)
simon.mardel@uhl-tr.nhs.uk;
simonmardel@doctors.org.uk; mardels@who.int

Professor Arnold Monto
Director
The Michigan Bioterrorism and Health Preparedness, Department of Epidemiology
University of Michigan School of Public Health
109 Observatory street
48109-2029 - Ann Arbor, MI
USA
Tel. : + 1 734 764 5453
Fax : + 1 734 764 3192
asmonto@umich.edu

Dr Pilar Ramon Pardo
Advisor on antimicrobial resistance
and infection control - Communicable
Diseases
Pan American Health Organization
World Health Organization
525, 23rd Street, NW.
Washington, DC 20037
Tel:+ 1 202 974 3901
Fax:+ 1 202 974 3331
ramonpap@paho.org

Professor Holger Schünemann
Michael Gent Chair in Healthcare Research
Professor of Clinical Epidemiology,
Biostatistics and Medicine
Department of Clinical Epidemiology &
Biostatistics
McMaster University Health Sciences Centre,
Room 2C10B
1200 Main Street West
Hamilton, ON L8N 3Z5, Canada
Tel: +1 905 525 9140 ext 24931
schuneh@mcmaster.ca

Dr Norio Sugaya
Director
Department of Pediatrics,
Keiyu Hospital,
3-7-3 Minatomirai, Nishi-ku,
Yokohama, 220-0012 Kanagawa,
Japon
Tel.: +81 (45) 221 8181
Fax: +81 (45) 681 9665
sugaya-n@za2.so-net.ne.jp

Dr John Siu Lun Tam
Consultant for WHO HSE/GIP
tams@who.int

Dr Timothy M. Uyeki
Deputy Chief, Epidemiology and Prevention
Branch, Influenza Division
National Center for Immunization and
Respiratory Diseases
Coordinating Center for Infectious Diseases
MS A-20
Centers for Disease Control and Prevention
1600 Clifton Road, N.E.
Atlanta, Georgia 30333
USA
Tel.: +1404-639-0277
Mobile: +1404-384-9040
tuyeki@cdc.gov; tmu0@cdc.gov

Dr Sylvie Van der Werf
Head of Unit of Molecular Genetics of RNA
Viruses
Unité de Génétique Moléculaire des virus
ARN
Institut Pasteur
25 rue du Docteur Roux
75724 - Paris Cedex 15
France
Tel.: +33 1 45 68 87 22
Fax: +33 1 40 61 32 41
Mobile: +33 (6) 8776 1442
svdwerf@pasteur.fr

WHO Staff:

Dr Sylvie Briand, HSE/GIP
Dr Suzanne Hill, HSS/PSM/PAR
Dr Nahoko Shindo, HSE/EPR/GIP
Dr Matthew Lim, HSE/EPR/BDP
Dr Carmen Pessoa da Silva, HSE/EPR/BDP
Dr Cathy Roth, HSE/EPR/BDP
Dr Charles R Penn, HSE/EPR/GIP
Ms Patti Whyte, HSE/EPR/GIP
Dr Nicolas Collin, HSE/EPR/GIP
Koh Shinohara, HSE/EPR/GIP

Annex 3:
Declarations of interests

The following participants declared financial interests related to commercial organizations as listed below:

Del Mar:	Technical adviser to GSK <$1000, institutional.
Hay:	Technical adviser to GSK <$3000, personal.
Kawaoka:	Consulting and research support from Cricell Holland BV, Theraclone Scoiences, Chagai Pharmacuetcials, Daiichi Sankyo Pharmaceuticals, Toyama chemical, personal, >$10000; speakers honoraria from Chugai Pharmaceutcials, Novartis, Sankyo, Toyama chemical, Wyeth, GSK, personal.
Monto:	Consultant for GSK and Roche, (<$10000), personal.
Tam:	Holds shares in Wyeth (>$10000), personal.
Suagya:	Technical adviser to Daiicji-Sankyo (>$10000), travel support from Denka Seiken, personal.
Van der Werf:	Consultancy and research support from Danone, GSK, Roche to research unit, not personal.

The following participants declared non-financial academic interests related to commercial organizations:

Hayden:	Unpaid advisor (with access to confidential information) for Nexbio, Biocryst, GSK, Roche, Toyama, Respirvert, 3V biosciences, Inhibikase, as well as advisor to US government authorities on antivirals.

The following participants declared no interests:

Bautista, Codeco, Chotpitayasunondh, Mardel, Schünemann, Uyeki.

Participants noted that, given their roles as advisers to a number of professional and government bodies in the current pandemic situation, many had made public statements regarding use of antivirals. These were not considered to be conflicts for the purposes of the meeting.

Annex 4: Evidence summaries and summaries of findings tables

Following are the GRADE evidence tables as well as tables providing a summary of results across the different populations assessed for each drug.

Table A4.1: Summary of oseltamivir treatment results[1]

Outcome/population	Oseltamivir N	Placebo N	Pooled results (WMD, hrs)
Time to alleviation of symptoms for ITT population			
Healthy adults	700	710	-13.59 (-25.15, -3.43)
Children (>1 year)	514	515	-21.05 (-33.81, -8.29)
Elderly	360	376	-10.00 (-45.05, 25.05)
At-risk	729	743	-17.84 (-36.20, 0.52)
Overall	2746	2290	-16.28 (-22.70, -9.86)
Conclusion	• statistically significant advantage for oseltamivir compared to placebo in healthy adults and children • advantage in overall population of time to alleviation of symptoms of less than a day (16.28 hours).		
Time to alleviation of symptoms for ITT infected population			
Healthy adults (WMD, hours)	579	603	-22.19 (-37.32, -7.07)
Children (>1 year) (WMD, hours)	301	330	-28.88 (-43.77, -14.0)
Elderly (median diff, hours)	223	254	-24.9 (-68.77, 18.97)
At-risk (WMD, hours)	425	482	-14.04 (-36.34, 8.26)
Overall	1221	1320	-22.75 (-33.39, -12.11)
Conclusion	• statistically significant advantage for oseltamivir compared to placebo in healthy adults and children • advantage in overall population of time to alleviation of symptoms of less than a day (22.75 hours).		
Time to resume normal activity for ITT population			
Healthy adults	481	480	-31.94 (-46.95, -16.93)
Children (>1 year)	331	338	-30.08 (-43.35, -16.81)
Elderly	359	375	-98.07 (-170.98, -25.16)
At-risk	558	576	-58.84 (-116.58, -1.11)
Overall	1370	1384	-34.80 (-45.73, -23.87)
Conclusion	• statistically significant advantage for oseltamivir compared to placebo in time to return to normal activity for all populations • reduction in time to return to normal activity of greater than 1 day (34.8 hours) for oseltamivir compared to placebo for overall population.		

Outcome/population	Oseltamivir N	Placebo N	Pooled results (WMD, hrs)
Time to resume normal activity for ITT infected population			
Healthy adults	301	309	-63.17 (-99.08, -27.27)
Children (>1 year)	293	320	-31.85 (-46.73, -16.96)
At-risk	425	482	-19.20 (-41.42, 3.01)
Overall	1637	1376	-36.31 (-48.44, -24.17)
Conclusion	• statistically significant advantage for oseltamivir compared to placebo in time to return to normal activity for healthy adults and children • reduction in time to return to normal activity of greater than 1 day (36.3 hours) for oseltamivir compared to placebo for overall population.		
Occurrence of complications requiring hospitalization for ITT population			
	Oseltamivir N	**Placebo N**	**Pooled results (OR)**
Healthy adults	6/1050 (0.6%)	6/1021 (0.6%)	0.97 (0.33, 2.90)
Children (>1 year)	0/344 (0%)	2/351 (0.6%)	0.20 (0.01, 4.24)
Elderly	3/223 (1.3%)	8/254 (3.1%)	0.42 (0.11, 1.6)
At-risk	0/165 (0%)	1/164 (1.6%)	0.33 (0.01, 8.84)
Conclusion	• small number of events, no advantage for oseltamivir compared to placebo.		
Occurrence of adverse events for ITT population			
Healthy adults	35/247 (14.2%)	26/262 (9.9%)	1.45 (0.83, 2.53)
Conclusion	• no statistically significant difference between oseltamivir and placebo in occurrence of drug-related adverse events in healthy adult population; results not available for other populations.		

Author(s): P Whyte
Date: 2009-06-03
Question: Should oseltamivir be used for influenza - adult population?
Settings: adult population
Bibliography: Burch 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oseltamivir	control	Relative (95% CI)	Absolute	Quality	
Alleviation of symptoms (measured with: hours until alleviation of symptoms; Better indicated by lower values)												
4	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	700	710	-	13.29 lower (25.15 to 3.43 lower)	+++ MODERATE	6
Time to resume normal activity (measured with: hours until resumption of normal activity; Better indicated by lower values)												
3	randomised trials	no serious limitations	no serious inconsistency	serious	no serious imprecision	none	481	480	-	31.94 lower (46.95 to 16.93 lower)	+++ MODERATE	5.5
Rate of overall complications												
1	randomised trials	no serious limitations	no serious inconsistency	serious	no serious imprecision	none	18/210 (8.6%)	28/209 (13.4%)	OR 0.61 (0.32 to 1.13)	48 fewer per 1000 (from 87 fewer to 15 more)	+++ MODERATE	7
Complications requiring hospitalization												
3	randomised trials	no serious limitations	no serious inconsistency	serious	no serious imprecision	none	6/1050 (0.6%)	6/1021 (0.6%)	OR 0.97 (0.33 to 2.9)	0 fewer per 1000 (from 4 fewer to 11 more)	+++ MODERATE	7
Drug-related adverse events												
2	randomised trials	no serious limitations	no serious inconsistency	serious	no serious imprecision	none	35/247 (14.2%)	26/262 (9.9%)	OR 1.45 (0.83 to 2.53)	39 more per 1000 (from 15 fewer to 119 more)	+++ MODERATE	6.5
Serious adverse events												
3	randomised trials	no serious limitations	no serious inconsistency	serious	no serious imprecision	none	1/488 (0.2%)	3/497 (0.6%)	OR 0.32 (0.03 to 1.17)	4 fewer per 1000 (from 6 fewer to 1 more)	+++ 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: 2009-06-04
Question: Should oseltamivir be used for influenza - at-risk population?[1]
Settings: at-risk population
Bibliography: Burch 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oseltamivir	control	Relative (95% CI)	Absolute	Quality	
Alleviation of symptoms (Better indicated by lower values)												
3	randomised trials	no serious limitations	no serious inconsistency	serious[2]	no serious imprecision	none	729	743	-	17.84 lower (36.2 lower to 0.52 higher)	+++ MODERATE	6
Time to resume normal activity (Better indicated by lower values)												
5	randomised trials	no serious limitations	no serious inconsistency	serious		none	558	576	-	58.84 lower (116.58 to 1.11 lower)		5.5
Complications requiring hospitalization												
1	randomised trials	no serious limitations	no serious inconsistency	serious	no serious imprecision	none	0/165 (0%)	1/164 (0.6%)	OR 0.33 (0.01 to 8.14)	4 fewer per 1000 (from 6 fewer to 41 more)	+++ MODERATE	7
Overall adverse events												
2	randomised trials	no serious limitations	no serious inconsistency	serious	no serious imprecision	none	85/228 (37.3%)	84/224 (37.5%)	OR 0.96 (0.63 to 1.46)	10 fewer per 1000 (from 101 fewer to 92 more)	+++ MODERATE	

1. 'At-risk' population defined in Burch et al.1 as patients, including adults and children with co-morbid conditions, as well as elderly patients.
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.

Author(s): P Whyte
Date: 2009-06-04
Question: Should oseltamivir be used for influenza - children?
Settings: children
Bibliography: Burch 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oseltamivir	control	Relative (95% CI)	Absolute	Quality	
Alleviation of symptoms (Better indicated by lower values)												
2[1]	randomised trials	no serious limitations	no serious inconsistency	serious[2]	no serious imprecision	none	514	515	-	21.05 lower (33.81 to 8.29 lower)	+++ MODERATE	6
Time to resume normal activity (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[2]	no serious imprecision	none	331	338	-	30.08 lower (43.35 to 16.81 lower)	+++ MODERATE	5.5
Complications requiring hospitalization												
1	randomised trials	no serious limitations	no serious inconsistency	serious[2]	no serious imprecision	none	0/344 (0%)	2/351 (0.6%)	OR 0.20 (0.01 to 4.24)	5 fewer per 1000 (from 6 fewer to 18 more)	+++ MODERATE	7
Overall adverse events												
1	randomised trials	no serious limitations	no serious inconsistency	serious[2]	no serious imprecision	none	83/170 (48.8%)	84/164 (51.2%)	OR 0.91 (0.59 to 40)	24 fewer per 1000 (from 130 fewer to 465 more)	+++ MODERATE	

1. Includes one trial with 'at-risk' children (i.e. those with co-morbidities). This trial was also included in the 'at-risk' population.
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.

Author(s): P Whyte
Date: 2009-06-04
Question: Should oseltamivir be used for influenza - elderly?
Settings: elderly
Bibliography: Burch 2008

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		
Alleviation of symptoms (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	360	376	-	10.00 lower (45.05 lower to 25.05 higher)	+++ MODERATE	6
Time to resume normal activity (Better indicated by lower values)												
3	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	359	375	-	98.07 lower (170.98 to 25.16 lower)	+++ MODERATE	5.5
Complications requiring hospitalization												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	3/223 (1.3%)	8/254 (3.1%)	OR 0.42 (0.11 to 1.6)	18 fewer per 1000 (from 28 fewer to 18 more)	+++ MODERATE	7

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: 2009-06-04
Question: Should oseltamivir be used for influenza - all populations combined?
Settings: all populations
Bibliography: Burch 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oseltamivir	control	Relative (95% CI)	Absolute	Quality	
Alleviation of symptoms (Better indicated by lower values)												
9	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	2746	2290	-	16.28 lower (22.7 to 9.86 lower)	+++ MODERATE	6
Time to resume normal activity (Better indicated by lower values)												
9	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	1370	1384	-	34.80 lower (45.73 to 23.87 lower)	+++ MODERATE	5.5

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.

Table A4.2: Summary of zanamivir treatment results[1]

Outcome/population	Zanamivir N	Placebo N	Pooled results (WMD, days)
Time to alleviation of symptoms for ITT population			
Healthy adults	1368	1333	-0.57 (-1.07, -0.08)
Children (>1 year)	400	337	-0.94 (-1.43, -0.46)
Elderly	249	226	-1.13 (-2.90, 0.63)
At-risk	622	630	-0.98 (-1.84, -0.11)
Overall	2320	2218	-0.71 (-1.04, -0.41)
Conclusion	statistically significant advantage for zanamivir compared to placebo for healthy adults, children, at-risk and overall populations with time to alleviation of symptoms less than a day (0.71 days).		
Time to alleviation of symptoms for ITT infected population			
Healthy adults (WMD, days)	948	878	-0.96 (-1.38, -0.54)
Children (>1 year) (median diff, days)	164	182	-1.00 (-1.60, -0.40)
Elderly (WMD, days)	165	158	-1.85 (-4.77, 1.07)
At-risk (WMD, days)	364	366	-1.83 (-2.81, -0.86)
Overall (WMD, days)	1455	1410	-1.07 (-1.39, -0.74)
Conclusion	• statistically significant advantage for zanamivir compared to placebo for healthy adults, children, at-risk and overall populations with time to alleviation of symptoms greater than a day (1.07 days).		

Outcome/population	Zanamivir N	Placebo N	Pooled results (WMD, days)
Time to resume normal activity for ITT population			
Healthy adults	1533	1492	-0.37 (-0.84, 0.09)
Children (>1 year)	224	247	-0.50 (-1.25, 0.25)
At-risk	304	309	-0.96 (-2.32, 0.41)
Conclusion	• no statistically significant advantage for zanamivir compared to placebo for time to resume normal activity in healthy adults, children or at-risk population.		
Time to resume normal activity for ITT infected population			
Healthy adults (WMD, days)	1044	979	-0.39 (-0.84, 0.06)
Children (>1 year) (median diff, days)	164	182	-0.50 (-1.35, 0.35)
At-risk (WMD, days)	381	383	-1.89 (-3.95, 0.17)
Conclusion	• no statistically significant advantage for zanamivir compared to placebo for time to resume normal activity in healthy adults, children or at-risk population.		
Occurrence of complications requiring hospitalization for ITT population			
	Zanamivir N	**Placebo N**	**Pooled results (OR)**
Healthy adults	48/293 (16.4%)	37/295 (12.5%)	1.37 (0.86, 2.17)
Children (>1 year)	1/176 (0.6%)	0/90 (0%)	1.55 (0.06, 38.36)
At-risk	3/261 (1.1%)	6/263 (2.3%)	0.50 (0.12, 2.01)
Overall	52/730 (7.1%)	43/648 (6.6%)	1.24 (0.8, 1.92)
Conclusion	• all results based on single trial for each population; no advantage for zanamivir compared to placebo.		
Occurrence of adverse events for ITT population			
Healthy adults	62/691 (9.0%)	60/715 (8.4%)	1.11 (0.76, 1.62)
Children (>1 year)	18/400 (4.5%)	10/337 (3.3%)	1.32 (0.59, 2.92)
At-risk	23/261 (8.8%)	23/263 (8.7%)	1.01 (0.55, 1.85)
Overall	149/1771 (8.4%)	152/1737 (8.8%)	0.97 (0.76, 1.24)
Conclusion	• no statistically significant difference between zanamivir and placebo in occurrence of drug-related adverse events across all populations.		

Author(s): P Whyte
Date: 2009-06-04
Question: Should zanamivir be used for influenza - adult population?
Settings: adult population
Bibliography: Burch 2008

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		
Alleviation of symptoms (Better indicated by lower values)												
6	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	1368	1333	-	0.57 lower (1.07 to 0.08 lower)	+++ MODERATE	6
Time to resume normal activity (Better indicated by lower values)												
7	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	1533	1492	-	0.37 lower (0.84 lower to 0.09 higher)	+++ MODERATE	5.5
Complications requiring hospitalization												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	48/293 (16.4%)	37/295 (12.5%)	OR 1.37 (0.86 to 2.17)	39 more per 1000 (from 16 fewer to 112 more)	+++ MODERATE	7
Drug-related adverse events												
4	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	62/691 (9%)	60/715 (8.4%)	OR 1.11 (0.76 to 1.62)	8 more per 1000 (from 19 fewer to 45 more)	+++ MODERATE	6.5
Serious adverse events												
3	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	3/559 (0.5%)	2/571 (0.4%)	OR 1.44 (0.28 to 7.35)	2 more per 1000 (from 3 fewer to 22 more)	+++ 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: 2009-06-04
Question: Should zanamivir be used for influenza - at-risk population?[1]
Settings: at-risk population
Bibliography:

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		
Alleviation of symptoms (Better indicated by lower values)												
7	randomised trials	no serious limitations	no serious inconsistency	serious[2]	no serious imprecision	none	622	630	-	0.98 lower (1.84 to 0.11 lower)[3]	+++ MODERATE	6
Time to resume normal activity (Better indicated by lower values)												
6	randomised trials	no serious limitations	no serious inconsistency	serious[2]	no serious imprecision	none	304	309	-	0.96 lower (2.32 lower to 0.41 higher)[4]	+++ MODERATE	5.5
Rate of overall complications												
4	randomised trials	no serious limitations	no serious inconsistency	serious[2]	no serious imprecision	none	83/290 (28.6%)	102/285 (35.8%)	OR 0.73 (0.51 to 1.04)	69 fewer per 1000 (from 137 fewer to 9 more)	+++ MODERATE	7
Complications requiring hospitalization												
1	randomised trials	no serious limitations	no serious inconsistency	serious[2]	no serious imprecision	none	3/261 (1.1%)	6/263 (2.3%)	OR 0.50 (0.12 to 2.01)	11 fewer per 1000 (from 20 fewer to 22 more)	+++ MODERATE	7
Drug-related adverse events												
1	randomised trials	no serious limitations	no serious inconsistency	serious[2]	no serious imprecision	none	23/261 (8.8%)	23/263 (8.7%)	OR 1.01 (0.55 to 1.85)	1 more per 1000 (from 37 fewer to 63 more)	+++ MODERATE	6.5
Serious adverse events												
3	randomised trials	no serious limitations	no serious inconsistency	serious[2]	no serious imprecision	none	10/675 (1.5%)	17/535 (3.2%)	OR 0.72 (0.32 to 1.62)	9 fewer per 1000 (from 21 fewer to 19 more)	+++ MODERATE	8

1. Including children and adults with co-morbidities and elderly patients.
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. When trial with children as subjects was removed, leaving only adult subjects, results were similar, with WMD= -0.95 (95% CI: -1.83, -0.07).
4. When trial with children was removed, leaving only adult subjects, results were similar and remained non-significant with WMD= -1.07 (95% CI: -2.81, 0.68).

Author(s): P Whyte
Date: 2009-06-05
Question: Should zanamivir be used for influenza - children?
Settings: children
Bibliography: Burch 2008

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		
Alleviation of symptoms (Better indicated by lower values)												
2	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	400	337	-	0.94 lower (1.43 to 0.46 lower)[2]	+++ MODERATE	6
Time to resume normal activity (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	224	247	-	0.50 lower (1.25 lower to 0.25 higher)	+++ MODERATE	5.5
Overall complications												
2	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	96/396 (24.2%)	81/336 (24.1%)	OR 0.88 (0.62 to 1.24)	23 fewer per 1000 (from 77 fewer to 42 more)	+++ MODERATE	7
Complications requiring hospitalization												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	1/176 (0.6%)	0/90 (0%)	OR 1.55 (0.06 to 38.36)	0 more per 1000 (from 0 fewer to 0 more)	+++ MODERATE	7
drug-related adverse events												
2	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	18/400 (4.5%)	10/337 (3%)	OR 1.32 (0.59 to 2.92)	9 more per 1000 (from 12 fewer to 52 more)	+++ MODERATE	6.5
Serious adverse events												
2	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	2/400 (0.5%)	0/337 (0%)	OR 2.29 (0.24 to 22.09)	0 more per 1000 (from 0 fewer to 0 more)	+++ 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.
2. When the population from one of the included trials was spilt into healthy and at-risk children, the statistically significant advantage for zanamivir remained for healthy children although there was no difference between zanamivir and placebo in at-risk children. However the at-risk population was small, including 22 patients treated with zanamivir and 14 with placebo.

Author(s): P Whyte
Date: 2009-06-05
Question: Should zanamivir be used for influenza - elderly?
Settings: elderly
Bibliography: Burch 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	zanamivir	control	Relative (95% CI)	Absolute	Quality	
Alleviation of symptoms (Better indicated by lower values)												
5	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	249	226	-	1.13 lower (2.9 lower to 0.63 higher)	+++ MODERATE	6
Overall complications												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	57/191 (29.8%)	56/167 (33.5%)	OR 0.84 (0.54 to 1.32)	38 fewer per 1000 (from 121 fewer to 64 more)	+++ MODERATE	7

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 influenza - all populations combined?
Settings: all populations
Bibliography:

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	zanamivir	control	Relative (95% CI)	Absolute	Quality	
Alleviation of symptoms (Better indicated by lower values)												
11	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	2320	2218	-	0.71 lower (1.01 to 0.41 lower)	+++ MODERATE	6
Overall complications												
6	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	316/1400 (22.6%)	348/1278 (27.2%)	OR 0.75 (0.63 to 0.9)	53 fewer per 1000 (from 20 fewer to 82 fewer)	+++ MODERATE	7
Complications requiring hospitalization												
3	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	52/730 (7.1%)	43/648 (6.6%)	OR 1.24 (0.8 to 1.92)	15 more per 1000 (from 13 fewer to 54 more)	+++ MODERATE	7
Drug-related adverse events												
8	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	149/1771 (8.4%)	152/1737 (8.8%)	OR 0.97 (0.76 to 1.24)	2 fewer per 1000 (from 20 fewer to 19 more)	+++ MODERATE	6.5
Serious adverse events												
11	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	23/2447 (0.9%)	26/2218 (1.2%)	OR 0.78 (0.44 to 1.4)	3 fewer per 1000 (from 7 fewer to 5 more)	+++ 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.

Table A4.3: Summary of results for amantadine

Outcome/population	Amantadine N or n/N	Placebo N or n/N	Pooled results
Adults (duration fever)	250	292	MD=-0.99 (-1.26, -0.71)
Children (>1 year; cases on day 3)	4/51 (7.8%)	12/53(22.6%)	RR=0.37 (0.08, 1.75)
Conclusion	• advantage for amantadine compared to placebo in adults (one day less of fever) and children, however trials are small.		

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

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	amantadine	control	Relative (95% CI)	Absolute	Quality	
Duration fever (days) (Better indicated by lower values)												
10	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious	none	250	292	-	MD 0.99 lower (1.26 to 0.71 lower)	++ LOW	
Duration of hospitalization (Better indicated by lower values)												
1	randomised 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)	++ LOW	6.5
Viral nasal shedding												
3	randomised 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)	++ LOW	6

1. All trials are were conducted in the 1960's and early 1970's; 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. Relatively old trial (1970) with small n (36 total subjects).
4. Two trials from the 1960's and one from the early 1980's, 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

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	rimantadine	control	Relative (95% CI)	Absolute	Quality	
Duration of fever (Better indicated by lower values)												
3	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[2]	none	36	46	-	MD 1.24 lower (1.71 to 0.76 lower)	++ LOW	
Viral nasal shedding												
3	randomised 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)	++ 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 1960's and one in the 1980's.

Author(s):
Date: 2009-06-05
Question: Should amantadine be used for influenza - children?
Settings: children
Bibliography: Alves Galvao 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	amantadine	control	Relative (95% CI)	Absolute	Quality	
Response to treatment (cases of fever on day 3)												
2	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[2]	none	4/51 (7.8%)	12/53 (22.6%)	RR 0.37 (0.08 to 1.75)	143 fewer per 1000 (from 208 fewer to 170 more)	++ LOW	

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. Both trials are small (n of approximately 50) and date from the 1960's.

Table A4.4: Summary of results for rimantadine

Rimantadine	Rimantadine N or n/N	Placebo N or n/N	Pooled results
Healthy adults (duration fever)	36	46	MD=-1.24 (-1.71, -0.76)
Children (> 1 year; cases on day 3)	5/37 (13.5%)	12/32(37.5%)	RR=0.36 (0.14, 0.91)
Conclusion	• advantage for rimantadine compared to placebo in adults (>one day reduction of fever) and children, however trials are small.		

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

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		
Response to treatment (cases of fever on day 3)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	5/37 (13.5%)	12/32 (37.5%)	RR 0.36 (0.14 to 0.91)	240 fewer per 1000 (from 34 fewer to 322 fewer)[2]	+++ MODERATE	

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. No explanation was provided.

Author(s): P Whyte
Date: 2009-06-09
Question: Should oseltamivir be used for influenza - infected adults?
Settings: adults with confirmed infection
Bibliography: Burch 2008

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		
Alleviation of symptoms (Better indicated by lower values)												
6	randomised trials	no serious limitations	no serious inconsistency	serious	no serious imprecision	none	579	603	-	22.19 lower (37.32 to 7.07 lower)	+++ MODERATE	6
Time to resume normal activity (Better indicated by lower values)												
3	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	301	309	-	63.17 lower (99.08 to 27.27 lower)	+++ MODERATE	5.5
Overall complications												
3	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	20/277 (7.2%)	27/287 (9.4%)	OR 0.75 (0.41 to 1.37)	22 fewer per 1000 (from 53 fewer to 30 more)	+++ MODERATE	7

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: 2009-06-09
Question: Should oseltamivir be used for influenza - infected at-risk population?
Settings:
Bibliography: Burch 2008

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		
Alleviation of symptoms (Better indicated by lower values)												
3	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	425	482	-	14.04 lower (36.34 lower to 8.26 higher)	+++ MODERATE	6
Time to resume normal activity (Better indicated by lower values)												
6	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	425	482	-	19.20 lower (41.42 lower to 3.01 higher)	+++ MODERATE	5.5
Overall complications												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[2]	none	1/43 (2.3%)	8/51 (15.7%)	OR 0.13 (0.02 to 1.07)	133 fewer per 1000 (from 153 fewer to 9 more)	++ LOW	7
Complications requiring hospitalization												
3	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	7/334 (2.1%)	14/378 (3.7%)	OR 0.54 (0.21 to 1.37)	17 fewer per 1000 (from 29 fewer to 13 more)	+++ MODERATE	7
Serious adverse events												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[2]	none	1/43 (2.3%)	1/51 (2%)	OR 1.19 (0.07 to 19.62)	4 more per 1000 (from 18 fewer to 262 more)	++ LOW	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.
2. Only one small trial (n=94 total).

Author(s): P Whyte
Date: 2009-06-09
Question: Should oseltamivir be used for influenza - infected children?
Settings: infected children
Bibliography: Burch 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oseltamivir	control	Relative (95% CI)	Absolute	Quality	
Alleviation of symptoms (Better indicated by lower values)												
2	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	301	330	-	28.88 lower (43.77 to 14 lower)	+++ MODERATE	6
Time to resume normal activity (Better indicated by lower values)												
2	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	293	320	-	31.85 lower (46.73 to 16.96 lower)	+++ MODERATE	5.5
Complications requiring hospitalization												
2	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	2/301 (0.7%)	3/335 (0.9%)	OR 0.79 (0.16 to 4.02)	2 fewer per 1000 (from 8 fewer to 26 more)	+++ MODERATE	7

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: 2009-06-09
Question: Should oseltamivir be used for influenza - infected elderly population?
Settings: infected elderly
Bibliography: Burch 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oseltamivir	control	Relative (95% CI)	Absolute	Quality	
Alleviation of symptoms (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	223	254	-	median 24.9 lower (68.77 lower to 18.97 higher)	+++ MODERATE	6
Time to resume normal activity (Better indicated by lower values)												
3	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	223	254	-	73.68 lower (151.2 lower to 3.84 higher)	+++ MODERATE	5.5
Complications requiring hospitalization												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	3/223 (1.3%)	8/254 (3.1%)	OR 0.42 (0.11 to 1.6)	18 fewer per 1000 (from 28 fewer to 18 more)	+++ MODERATE	7

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: 2009-06-09
Question: Should oseltamivir be used for influenza - infected overall population?
Settings: infected overall population
Bibliography: Burch 2008

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		
Alleviation of symptoms (Better indicated by lower values)												
10	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	1221	1320	-	22.75 lower (33.39 to 12.11 lower)	+++ MODERATE	6
Time to resume normal activity (Better indicated by lower values)												
11	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	1637	1376	-	36.31 lower (48.44 to 24.17 lower)	+++ MODERATE	5.5
Overall complications												
4	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	33/320 (10.3%)	41/338 (12.1%)	OR 0.88 (0.28 to 2.76)	13 fewer per 1000 (from 84 fewer to 155 more)	+++ MODERATE	7
Complications requiring hospitalization												
4	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	9/351 (2.6%)	21/402 (5.2%)	OR 0.47 (0.2 to 1.11)	27 fewer per 1000 (from 41 fewer to 5 more)	+++ MODERATE	7

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: 2009-06-09
Question: Should zanamivir be used for influenza - infected adults?
Settings: infected adults
Bibliography: Burch 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	zanamivir	control	Relative (95% CI)	Absolute	Quality	
Alleviation of symptoms (Better indicated by lower values)												
6	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	948	878	-	0.96 lower (1.38 to 0.54 lower)	+++ MODERATE	6
Time to resume normal activity (Better indicated by lower values)												
7	randomised trials	no serious limitations	no serious inconsistency	serious[1]		none	1044	979	-	0.39 lower (0.84 lower to 0.06 higher)		5.5
Overall complications												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[2]	none	115/222 (51.8%)	108/213 (50.7%)	OR 1.04 (0.72 to 1.52)	10 more per 1000 (from 82 fewer to 103 more)	++ LOW	7

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. Only one trial.

Author(s): P Whyte
Date: 2009-06-09
Question: Should zanamivir be used for influenza - infected at-risk population?
Settings: infected at-risk population
Bibliography: Burch 2008

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		
Alleviation of symptoms (Better indicated by lower values)												
6	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	364	366	-	1.83 lower (2.81 to 0.86 lower)	+++ MODERATE	6
Time to resume normal activity (Better indicated by lower values)												
7	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	381	383	-	1.89 lower (3.95 lower to 0.17 higher)[2]	+++ MODERATE	5.5
Overall complications												
4	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	107/328 (32.6%)	121/328 (36.9%)	OR 0.82 (0.59 to 1.13)	45 fewer per 1000 (from 112 fewer to 29 more)	+++ MODERATE	7
Complications requiring hospitalization												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	5/120 (4.2%)	4/114 (3.5%)	OR 1.20 (0.31 to 4.57)	7 more per 1000 (from 24 fewer to 107 more)	+++ MODERATE	7

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. For at-risk chikdren only, difference is statistically singificantly different, with WMD=-2.50 (95% CI: -4.37, -0.63).

Author(s): P Whyte
Date: 2009-06-09
Question: Should zanamivir be used for influenza - infected children?
Settings: infected children
Bibliography: Burch 2008

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		
Alleviation of symptoms (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[2]	none	164	182	-	median 1.00 lower (1.6 to 0.4 lower)	++ LOW	6
Time to resume normal activity (Better indicated by lower values)												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[2]	none	164	182	-	median 0.50 lower (1.36 lower to 0.35 higher)	++ LOW	5.5
Overall complications												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[2]	none	26/164 (15.9%)	41/182 (22.5%)	OR 0.65 (0.38 to 1.12)	66 fewer per 1000 (from 126 fewer to 20 more)	++ LOW	7

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. Only one trial.

Author(s): P Whyte
Date: 2009-06-09
Question: Should zanamivir be used for influenza - infected elderly population?
Settings: infected elderly population
Bibliography: Burch 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	zanamivir	control	Relative (95% CI)	Absolute	Quality	
Alleviation of symptoms (Better indicated by lower values)												
5	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	165	158	-	1.85 lower (4.77 lower to 7 higher)	+++ MODERATE	6
Overall complications												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[2]	none	39/120 (32.5%)	46/114 (40.4%)	OR 0.71 (0.42 to 1.21)	79 fewer per 1000 (from 182 fewer to 47 more)	++ LOW	7
Complications requiring hospitalization												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[2]	none	5/120 (4.2%)	4/114 (3.5%)	OR 1.20 (0.31 to 4.57)	7 more per 1000 (from 24 fewer to 107 more)	++ LOW	7

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. Only one trial.

Author(s): P Whyte
Date: 2009-06-09
Question: Should zanamivir be used for influenza - infected overall population?
Settings: infected overall population
Bibliography: Burch 2008

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		
Alleviation of symptoms (Better indicated by lower values)												
13	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	1455	1410	-	1.07 lower (1.39 to 0.74 lower)	+++ MODERATE	6
Overall complications												
7	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	352/1341 (26.2%)	403/1288 (31.3%)	OR 0.77 (0.65 to 0.92)	53 fewer per 1000 (from 18 fewer to 84 fewer)	+++ MODERATE	7
Complications requiring hospitalization												
2	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	39/342 (11.4%)	24/327 (7.3%)	OR 1.64 (0.96 to 2.81)	42 more per 1000 (from 3 fewer to 109 more)	+++ MODERATE	7

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.

Table A4.5: Prophylaxis - occurrence of infection

Drug/population			
Oseltamivir (symptomatic laboratory confirmed infection)	**Oseltamivir n/N**	**Placebo n/N**	**Pooled results (RR)**
Healthy adults	6/520 (1.2%)	25/519 (4.8%)	0.27 (0.09, 0.83)
Elderly	1/276 (0.4%)	12/272 (4.4%)	0.08 (0.01, 0.63)
Post-exposure (mixed households)			0.19 (0.08, 0.45)
Conclusion	• statistically significantly fewer cases of infection associated with oseltamivir prophylaxis in adult and elderly populations.		
Zanamivir (symptomatic laboratory confirmed infection)	**Zanamivir n/N**	**Placebo n/N**	**Pooled results (RR)**
Healthy adults	11/553 (2.0%)	34/554 (6.1%)	0.32 (0.17, 0.63)
At-risk	4/1678 (0.2%)	23/1685 (1.4%)	0.17 (0.07, 0.44)
Conclusion	• statistically significantly fewer cases of infection associated with zanamivir prophylaxis in adults and at-risk populations.		
Amantadine (influenza infection)	**Amantadine n/N**	**Placebo n/N**	**Individual trial results (RR)**
Healthy adults	2/159 (1.3%)	5/159 (3.1%)	0.40 (0.08, 2.03)
Children (>1 year)	4/371 (1.1%)	40/402 (10%)	0.11 (0.04, 0.30)
Conclusion	• no advantage for amantadine prophylaxis in adults, however this is based on a small number of subjects; • statistically significant advantage in children.		
Rimantadine (influenza infection)	**Rimantadine N or n/N**	**Placebo N or n/N**	**Pooled results (RR)**
Healthy adults	20/347 (5.8%)	54/341 (15.8%)	0.28 (0.08, 1.28)
Children (> 1 year)	8/84 (9.5%)	22/94 (23.4%)	0.49 (0.21, 1.15)
Conclusion	• no statistically significant advantage for rimantadine compared to placebo for prophylaxis in adults or children, however direction of results favours rimantadine.		

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

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		
Influenza infection												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	2/159 (1.3%)	5/159 (3.1%)	RR 0.40 (0.08 to 2.03)	19 fewer per 1000 (from 29 fewer to 32 more)	+++ MODERATE	8
Total adverse events												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	47/159 (29.6%)	49/159 (30.8%)	RR 0 (0 to 0)[2]	308 fewer per 1000 (from 308 fewer to 308 fewer)	+++ MODERATE	
Influenza infection Jefferson 2006												
11	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	146/2396 (6.1%)	280/2249 (12.4%)	RR 0.39 (0.24 to 0.65)	76 fewer per 1000 (from 44 fewer to 95 fewer)	+++ MODERATE	8
Total adverse events Jefferson 2006												
6	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	386/2624 (14.7%)	172/1650 (10.4%)	RR 1.70 (0.99 to 2.93)	73 more per 1000 (from 1 fewer to 201 more)	+++ MODERATE	
Viral nasal shedding												
1	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[3]	none	36/59 (61%)	18/20 (90%)	RR 0.68 (0.53 to 0.87)	288 fewer per 1000 (from 117 fewer to 423 fewer)	++ LOW	7.5

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. Only proportion reporting AEs was provided, no comparison was provided.
3 . Small trial with 59 subjects in the amantadine arm and 20 in the control arm.

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

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oseltamivir	control	Relative (95% CI)	Absolute	Quality	
Symptomatic laboratory confirmed infection												
2	randomised 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)	+++ 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 oseltamivir be used for prophylaxis in the elderly?
Settings: elderly
Bibliography: Tappenden 2009

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	oseltamivir	control	Relative (95% CI)	Absolute	Quality	
Symptomatic laboratory confirmed infection												
2	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	1/276 (0.4%)	12/272 (4.4%)	RR 0.08 (0.01 to 0.63)	41 fewer per 1000 (from 16 fewer to 44 fewer)	+++ 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

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	zanamivir	control	Relative (95% CI)	Absolute	Quality	
Symptomatic laboratory confirmed influenza												
1	randomised 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)	+++ 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

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	zanamivir	control	Relative (95% CI)	Absolute	Quality	
Symptomatic laboratory confirmed infection												
1	randomised 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)	+++ 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: 2009-06-08
Question: Should amantadine be used for prophylaxis in children?
Settings: children
Bibliography: Alves Galvao 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	amantadine	control	Relative (95% CI)	Absolute	Quality	
Cases of infection												
2	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	4/371 (1.1%)	40/402 (10%)	RR 0.11 (0.04 to 0.3)	89 fewer per 1000 (from 70 fewer to 96 fewer)	+++ 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: 2009-06-08
Question: Should rimantadine be used for prophylaxis in children?
Settings: children
Bibliography: Alves Galvao 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	rimantadine	control	Relative (95% CI)	Absolute	Quality	
Cases of infection												
3	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[2]	none	8/84 (9.5%)	22/94 (23.4%)	RR 0.49 (0.21 to 1.15)	119 fewer per 1000 (from 185 fewer to 35 more)	++ LOW	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.
2. Three relatively small trials, with the total numbers across all trials less than 100 in each arm.

Author(s): P Whyte
Date: 2009-06-08
Question: Should rimantadine be used for prophylaxis in children and elderly?
Settings: both children and elderly
Bibliography: Alves Galvao 2008

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		
Cases of infection												
5	randomised trials	no serious limitations	no serious inconsistency	serious[1]	serious[2]	none	14/156 (9%)	27/125 (21.6%)	RR 0.49 (0.27 to 0.92)	110 fewer per 1000 (from 17 fewer to 158 fewer)	++ LOW	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.
2. The authors caution there may be differences across the trials in addition to age that could impact results. In addition, follow-up ranged from 3 to 11 weeks across the trials and all trials had relatively small N's with most less than 50 subjects total.

Author(s): P Whyte
Date: 2009-06-08
Question: Should rimantadine be used for prophylaxis in adults?
Settings: adults
Bibliography: Jefferson 2006

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		
Influenza infection												
3	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	20/347 (5.8%)	54/341 (15.8%)	RR 0.28 (0.08 to 1.08)	114 fewer per 1000 (from 146 fewer to 13 more)	+++ MODERATE	8
Total adverse events												
3	randomised trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	none	52/279 (18.6%)	30/279 (10.8%)	RR 1.96 (1.19 to 3.22)	103 more per 1000 (from 20 more to 239 more)	+++ MODERATE	

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 5:
Summary of observational data

The following table includes observational studies which the Panel members used to obtain information regarding outcomes that were not included in the systematic reviews, for example complications. Observational studies assessing efficacy outcomes are not included here.

Table A5.1: Other outcomes observational data

Other outcomes	Design/results
Complications	
Bowles 2002[13]	• Assessment of use of oseltamivir in nursing home residents (n=178) found that compared to residents receiving no therapy or who became ill using amantadine, the use of oseltamivir within 48 hours of symptom onset resulted in significantly less use of antibiotics, fewer hospitalizations and fewer deaths
Blumentals 2007[14]	• Retrospective cohort analysis of 36,751 US patients treated with oseltamivir compared to matched sample receiving no antiviral showed reduction in risk of otitis media of 23% (HR=0.77; 95% CI: 0.65, 0.93); any respiratory disease by 18% (HR=0.82; 95% CI: 0.79, 0.86); and hospitalization for any reason by 22% (HR=0.78; 95% CI: 0.67, 0.91).
Cole 2002[7]	• Retrospective comparison of patients treated with zanamivir (n=2341) and those untreated (n=2337) showed occurrence of complications were similar between the two groups
Gums 2008[3]	• Retrospective review of health care claims for 45,751 patients treated with oseltamivir and matched untreated controls found 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). Risks of pneumonia and otitis media also lower in those aged ≤17 years. Healthcare use and costs also less for those using oseltamivir compared to those untreated.
Lee 2007[15]	• Retrospective cohort study of patients hospitalized for influenza (n=356) found significantly shorter length of stay for those treated with oseltamivir within 2 days of illness compared to those receiving no treatment or treatment on days 3-4.
Kaiser 2003[16]	• Analysis of data from 10 trials of oseltamivir versus placebo in influenza, assessing occurrence of lower respiratory tract complications leading to antibiotic use and hospitalizations. Analysis found that oseltamivir reduced overall antibiotic use for any reason by 26.7% (14.0% versus 19.1% with placebo: $p<0.001$) and reduced incidence of influenza-related lower respiratory tract infections leading to antibiotic use by 55% (4.6% compared to 10.3% with placebo: $p<0.001$) for patients with confirmed illness. Also statistically significantly fewer oseltamivir-treated at-risk patients required antibiotic use 34.0% reduction: $p=0.02$).

Other outcomes	Design/results
Orzeck 2007[17]	• Retrospective cohort study of patients with diabetes treated with oseltamivir (n=2919) compared to those who were not prescribed treatment (n=6171) found that patients receiving oseltamivir had 17% reduction in risk of Respiratory illness (RR=0.83; 95 % CI: 0.73, 0.93); and 30% reduction in risk of hospitalization for any reason (RR=0.70; 95% CI: 0.52, 0.94). No significant differences between groups for risk of pneumonia, otitis media or hospitalizations for pneumonia.
Mortality	
McGeer 2007[18]	• Prospective cohort study of patients hospitalized for influenza found that 106 of 327 adult patients were prescribed antivirals and antiviral treatment was associated with a significant reduction in mortality (OR=0.21; 95% CI: 0.06, 0.80).
Neonates	
Kiso 2004[19]	• 6 children aged less than 1 year were treated with oseltamivir, however no efficacy results provided, only assessment of development of mutations
Pregnant and breastfeeding women	
Tanaka 2009[5]	• Assessment of use of oseltamivir and zanamivir in pregnant and breastfeeding women • Post-marketing surveillance of oseltamivir in 61 women with pregnancies found 10 abortions; another Japanese study which followed 90 pregnant women found there was 1 malformation (which paper states is within the incidence of major malformations in the general population). • 3 pregnant women were accidentally exposed to zanamivir, with 1 pregnancy spontaneously miscarried, one terminated and 1 delivered a healthy baby; Japanese Drug Information Institute in Pregnancy has info about 1 woman who took zanamivir at 4 weeks of gestation and delivered a healthy baby.
Wentges-van Holthe 2007[6]	• Assessment of oseltamivir concentration in breast milk of one individual showed that oseltamivir exposure via breast milk is not expected to cause clinically significant concentrations of oseltamivir in an infant.
Adverse events	
French 2007[20]	• Post-marketing surveillance study to assess concurrent diagnosis of corneal oedema or Fuchs dystrophy and new prescription for amantadine found that 0.27% of patients prescribed amantadine were diagnosed with corneal oedema (RR=1.7; 95% CI: 1.1, 2.8)
Loughlin 2002[21]	• Retrospective review of patients treated with zanamivir (n=5450) showed low risk of respiratory events associated with treatment
Toovey 2008[22]	• Risk of neuropsychiatric events with oseltamivir - two Japanese studies reported neuropyshiatric events, however a review assessing clinical trials, post-marketing data an observational data found no relationship between oseltamivir treatment and neuropsychiatric events.
Blumentals 2007[2]	• Retrospective review of oseltamivir use and CNS-related and neuropsychiatric events (n=40,704) found no relationship between such outcomes and use of oseltamivir.
Nordstrom 2004[23]	• Retrospective review of use of oseltamivir in 32,459 patients found no evidence of increased skin reactions with oseltamivir
Keyser 2000[11]	• Retrospective review of use of amantadine and rimantadine as prophylaxis in nursing home patients found a significantly greater occurrence of CNS adverse events with amantadine compared to rimantadine.

Author(s): Holger J Schunemann
Date: 2009-06-24
Question: Oseltamivir for new influenza
Settings: Outpatient
Bibliography: Blumenthals and Schulman, 2007 Orzeck et al., 2007 Gums et al., 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Oseltamivir	Control	Relative (95% CI)	Absolute	Quality	
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)	++ 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 6:
Table of recommended dosages

Adapted from CDC Table: Recommended daily dosage of seasonal influenza antiviral medications for treatment and chemoprophylaxis for the 2008-09 season, United States. Available at:

http://www.cdc.gov/flu/professionals/antivirals/dosagetable.htm#table
(accessed June 28 2009)

Table 6.1: Dosage recommendations

Agent	Age Groups (yrs)					
	Duration	1-6	7-9	10-12	13-64	≥ 65
Amantadine[d]						
Treatment	5 days	5 mg/kg/day up to 150 mg in 2 divided doses	5 mg/kg/day up to 150 mg in 2 divided doses	100 mg twice daily for	100 mg twice daily	≤ 100 mg/day
Prophylaxis	Begin as soon as exposure identified and continue for 5-7 days after last known exposure[a]	5 mg/kg/day up to 150 mg in two divided doses †	5 mg/kg/day up to 150 mg in two divided doses	100 mg twice daily	100 mg twice daily	≤ 100 mg/day
Rimantadine[b]						
Treatment	5 days	Not licensed for use	Not licensed for use	Not licensed for use	100 mg twice daily	100 mg/day
Prophylaxis	Begin as soon as exposure identified and continue for 5-7 days after last known exposure[a]	5 mg/kg/day up to 150 mg in two divided doses	5 mg/kg/day up to 150 mg in two divided doses	100 mg twice daily	100 mg twice daily	100 mg/day
Oseltamivir						
Treatment	5 days	Weight adjusted doses[c]: - 30 mg twice daily for ≤ 15 kg - 45 mg twice daily for >15 to 23 kg - 60 mg twice daily for >23 to 40kg - 75 mg twice daily for >40kg			75 mg twice daily[c]	75 mg twice daily[c]
Prophylaxis	Begin as soon as exposure identified and continue for 5-7 days after last known exposure[a]	Weight adjusted doses[c]: - 30 mg/day for ≤ 15 kg - 45 mg/day for >15 to 23 kg - 60 mg/day for >23 to 40 kg - 75 mg/day for >40 kg			75 mg/day	75 mg/day
Zanamivir						
Treatment	5 days	Not licensed for use	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily	10 mg (2 inhalations) twice daily
Prophylaxis	Begin as soon as exposure identified and continue for 5-7 days after last known exposure[a]	**1-4 yrs:** NA / **5-6 yrs:** 10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily	10 mg (2 inhalations) once daily

a For control of outbreaks in long-term care facilities and hospitals, CDC recommends chemoprophylaxis for a minimum of two weeks, and up to one week after the last known case was identified.

b Reduction in rimantadine dosage to 100 mg/day is recommended for persons who have severe hepatic dysfunction or those with creatinine clearance <10 ml/min. Other persons with less severe hepatic or renal dysfunctions taking 100 mg/day should be observed closely and dosage should be reduced or drug discontinued if necessary.

c Reduction in dose of oseltamivir is recommended for persons with creatinine clearance <30 ml/min.

d Amantadine package insert should be consulted for dosage recommendations for persons with creatinine clearance ≤50 ml/min/1.73 m2.

References

1. Burch J PM, Conti S et al. for the CRD/CHE Technology Assessment Group (Centre for Reviews and Dissemination/Centre for Health Economics), University of York. Influenza - zanamivir, amantadine and oseltamivir (review): assessment report. *http://www.nice.org.uk/Guidance/TA168* 2008.

2. Blumentals WA SX. The safety of oseltamivir in patients with influenza: analysis of healthcare claims data from six influenza seasons. *Medscape General Medicine* 2007;9(4):23.

3. Gums JG PE, Blumentals WA. . Oseltamivir and influenza-related complications, hospitalization and healthcare expenditure in healthy adults and children. *Expert Opinion on Pharmacotherapy* 2008;9(2):151-61.

4. C W. Update on Avian Influenza A (H5N1) Virus Infection in Humans. . *NEJM* 2008;358:261-73.

5. Tanaka T NK, Murashima A et al. Safety of neuraminidase inhibitors against novel influenza A (H1N1) in pregnant and breastfeeding women. *CMAJ* 2009;181:55-58.

6. Wentges-van Holthe N vEM, van der Laan JW. Oseltamivir and breastfeeding. *Int J Infect Dis* 2008;12(4):451.

7. Cole JA LJ, Ajene AN et al. The effect of zanamivir treatment on influenza complications: a retrospective cohort study. *Clin Ther* 2002;24(11):1824-39.

8. Kaiser L KO, Hammond JMJ. Impact of zanamivir on antibiotic use for respiratory events following acute influenza in adolescents and adults. *Arch Intern Med* 2000;160:3234-40.

9. Jefferson T DV, Pietrantoni C et al. Amantadine and rimantadine for influenza A in adults. . *Cochrane Database of Systematic Reviews 2006, Issue 2* 2006.

10. Alves Galvao MG RCSM, Alves da Cunha AJL. Amantadine and rimantadine for influenza A in children and the elderly. *Cochrane Database of Systematic Reviews 2008; Issue 1* 2008.

11. Keyser LA KM, Nafziger AN et al. .Comparison of central nervous system adverse effects of amantadine and rimantadine used as sequential prophylaxis of Influenza A in elderly nursing home patients. *Arch Int Med* 2000;160:1485-88.

12. Tappenden P JR, Cooper K et al. Amantadine, oseltamivir and zanamivir for the prophylaxis of influenza (including a review of existing guidance no. 67): systematic review and economic evaluation. .*Health Tech Assessment* 2009;13(11):1-268.

13. Bowles SK LW, Simor AE et al. Use of oseltamivir during influenza outbreaks in Ontario nursing homes, 1999-2000. *J Amer Geriatr Soc* 2002;50(4):608-16.

14. Blumentals WA SK. Impact of oseltamivir on the incidence of secondary complications of influenza in adolescent and adult patients: results from a retrospective population-based study. *Current Medical Research & Opinion* 2007;23(12):2961-70.

15. Lee C LM, Phillips A et al. Zanamivir use during transmission of amantadine-resistant influenza A in a nursing home. *Infect Control Hosp Epidemiol* 2000;21(11):700-04.

16. Kaiser L WC, Mills T et al. Impact of oseltamivir treatment on influenza-related lower respiratory tract complications and hospitalizations. *Arch Int Med* 2003;163:1667-72.

17. Orzeck EA SN, Blumentals WA. . Oseltamivir and the risk of influenza-related complications and hospitalizations in patients with diabetes. *Clin Ther* 2007;29(10):2246-55.

18. McGeer A GK, Pievneshi A et al. Antiviral therapy and outcomes of influenza requiring hospitalisation in Ontario, Canada. *Clin Infect Dis* 2007;45:1568-75.

19. Kiso M MK, Sakai-Tagawa Y et al. Resistant influenza A viruses in children treated with oseltamivir: descriptive study. *Lancet* 2004;364:733-34.

20. French DD MC. Postmarketing Surveillance of Corneal Edema, Fuchs Dystrophy, and Amantadine Use in the Veterans Health Administration. *Cornea* 2007;26:1087-89.

21. Loughlin JE AT, Ajene AN et al. Risk for respiratory events in a cohort of patients receiving inhaled zanamivir: a retrospective study. *Clin Ther* 2002;24(11):1786-99.

22. Toovey S RC, Prinssen E et al. Assessment of neuropsychiatric adverse events in influenza patients treated with oseltamivir: a comprehensive review. *Drug Safety* 2008;31(12):1097-114.

23. Nordstrom BL OK, Sacks ST et al. Skin reactions in patients with influenza treated with oseltamivir: a retrospective cohort study. *Antiviral Therapy* 2004;9:187-95.