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

Revised February 2010

Part I
Recommendations

Contents

Summary

This guidance updates and replaces the recommendations published in August 2009. This document will again be reviewed in September 2010 and, if necessary, updated.

Key changes to the guidelines are:

- Simplification of recommendations as pandemic influenza A(H1N1) 2009 virus has become the predominant influenza virus worldwide.
- Specific guidance for the treatment of young children from birth, including guidance on dose and formulation (Recommendations 06-08).
- Additional guidance for treatment or chemoprophylaxis of patients with severe immunosuppression (Recommendations 03 and 04).
- Consideration of a wider range of investigational, regional[1] or adjunctive treatments (Recommendations 14 and 15).
- Specific contraindications for some medicines (Recommendations 16-18).

The table below summarizes the treatment recommendations that are described in full in the subsequent sections:

Use of antivirals for treatment of influenza

Population	Pandemic influenza A (H1N1) 2009 and other seasonal influenza viruses	Influenza viruses known or suspected to be oseltamivir resistant
Uncomplicated clinical presentation		
Patients in higher risk groups	Treat with oseltamivir or zanamivir as soon as possible (05)	Treat with zanamivir as soon as possible (05)
Severe or progressive clinical presentation		
All patients (including children and adolescents)	Treat with oseltamivir as soon as possible (01) (zanamivir should be used if oseltamivir unavailable) (02)	Treat with zanamivir as soon as possible (03)
Patients with severe immunosuppression	Treat with oseltamivir as soon as possible. Consider higher doses and longer duration of treatment (03)	Treat with zanamivir as soon as possible (03)

[1] Regional products are those that have market authorisations in only one or a few countries.

1. Introduction

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 their use for chemoprophylaxis. This document addresses the most widely available and licensed antiviral medicines, the two neuraminidase inhibitors oseltamivir and zanamivir, and the two M2 inhibitors amantadine and rimantadine. It also includes recommendations on the use of some other potential pharmacological treatments, including other investigational neuraminidase inhibitors, other agents such as arbidol, ribavirin, intranasal interferons, immunoglobulins, and corticosteroids. While the focus of the document is on management of patients with pandemic (H1N1) 2009 virus infection, it also includes guidance on the use of antivirals for seasonal influenza A and B virus strains, and for infections due to novel influenza A virus strains.

WHO recommends that national and regional authorities periodically issue local guidance that place these recommendations in the context of local epidemiological and antiviral susceptibility data on the circulating influenza virus strains. Such local guidance would also take into account local health priorities and resources.

This guidance updates and replaces the recommendations published in August 2009. These recommendations are based on a review of available data obtained on treatment of previously circulating influenza virus strains and treatment of human infection with highly pathogenic avian influenza A (H5N1) virus, as well as more recent observational data and experience in the clinical management of pandemic (H1N1) 2009 influenza. 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.

This revised guidance is published in two parts. Part I contains treatment recommendations. Part II documents the procedures followed in developing this guidance, together with a review of evidence and other new information on the pharmacological agents considered.

These guidelines should be read in conjunction with the World Health Organization's (WHO) revised guidance for clinical management of human infection with pandemic influenza A(H1N1) 2009 virus, published in November 2009.[2]

The WHO rapid advice guidelines on pharmacological management of humans infected with highly pathogenic avian influenza A(H5N1) virus[3] remain unchanged by these new guidelines.

[2] Clinical management of human infection with pandemic (H1N1) 2009: revised guidance. World Health Organization, November 2009. Available at: http://www.who.int/csr/resources/publications/swineflu/clinical_management/en/index.html. Last accessed on 10 February 2010.

[3] WHO Rapid Advice Guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus. World Health Organization, May 2006. Available at:

2. Case description

Human infection with influenza virus can vary from asymptomatic infection to uncomplicated upper respiratory tract disease 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 (ILI), a clinical diagnosis of influenza should be guided by clinical and epidemiologic data and can be 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 Guidelines Panel (the Panel) considered three broad scenarios, set out below.

Uncomplicated influenza

- Influenza-like illness (ILI) symptoms include: fever, cough, sore throat, nasal congestion or rhinorrhea, headache, muscle pain, and malaise, but not shortness of breath and not 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.
- Some patients with uncomplicated illness may experience atypical symptoms and may not have fever (e.g. elderly or immunosuppressed patients).

Complicated or severe influenza

- Presenting clinical (e.g. shortness of breath/dyspnoea, tachypnoea, hypoxia) and/or radiological signs of lower respiratory tract disease (e.g. pneumonia), central nervous system (CNS) involvement (e.g. encephalopathy, encephalitis), severe dehydration, or presenting secondary complications, such as renal failure, multiorgan failure, and septic shock. Other complications can include rhabdomyolysis and myocarditis.
- Exacerbation of underlying chronic disease, including asthma, chronic obstructive pulmonary disease (COPD), chronic hepatic or renal insufficiency, diabetes, or other cardiovascular conditions (e.g. congestive cardiac failure).
- Any other condition or clinical presentation requiring hospital admission for clinical management (including bacterial pneumonia with influenza).
- Any of the signs and symptoms of progressive disease 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 (i.e. within 24 hours). The following are some of the indicators of progression, which would necessitate an urgent review of patient management:

http://www.who.int/csr/disease/avian_influenza/guidelines/pharmamanagement/en/index.html Last accessed on 10 February 2010.

- Symptoms and signs suggesting oxygen impairment or cardiopulmonary insufficiency:
    - Shortness of breath (with activity or at rest), difficulty in breathing, tachypnoea, presence of cyanosis, bloody or coloured sputum, chest pain, and low blood pressure;
    - In children, fast or laboured breathing; and
    - Hypoxia, as indicated by pulse oximetry or arterial blood gases.

- Symptoms and signs suggesting CNS complications:
    - Altered mental status, unconsciousness, drowsiness, or difficult to awaken and 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 or recurrent high fever and other symptoms beyond 3 days without signs of resolution).
- Severe dehydration, manifested as decreased activity, dizziness, decreased urine output, and lethargy.

3. Risk groups

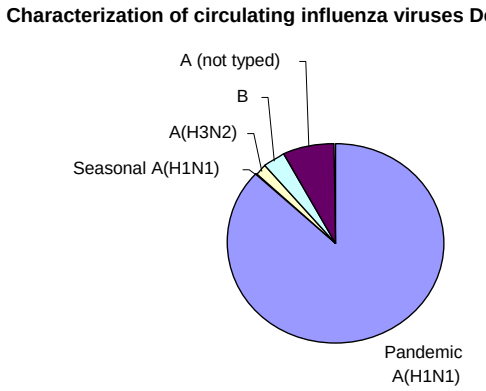
Certain patients with seasonal influenza virus infection or pandemic influenza (H1N1) 2009 virus infection are recognized to be at **higher risk** of developing severe or complicated illness. The Guidelines Panel did not review the evidence for the definition of these higher risk groups, but adopted, as the basis for treatment decisions in the context of these guidelines, the description developed through the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza[4] as listed in Part I, Annex 1.

However, an important consideration in the management of influenza virus infections is that influenza virus infection in any patient can result in severe or complicated illness. This is particularly true for pandemic (H1N1) 2009 virus infection, in which about 1/3 of severely ill patients admitted to intensive care units were previously healthy persons not belonging to any known higher risk group.

[4] Clinical management of human infection with pandemic (H1N1) 2009: revised guidance. World Health Organization, November 2009. Available at: http://www.who.int/csr/resources/publications/swineflu/clinical_management/en/index.html. Last accessed on 10 February 2010.

4. Epidemiology

Currently, WHO publishes weekly information from global influenza surveillance[5]. As of December 2009, the most prevalent circulating influenza virus was pandemic (H1N1) 2009. The following figure shows the breakdown of results of laboratory testing of 7380 influenza viral isolates from 27 countries (mostly in the Northern Hemisphere):



For the purpose of development of these revised guidelines, it is anticipated that the prevalent influenza viruses in the coming year are most likely to be pandemic (H1N1) 2009, H3N2 and influenza B virus strains, as is reflected in the vaccine composition recommendations for the Southern Hemisphere 2010 season.[6]

The impact of pandemic (H1N1) 2009 virus infection has been highest in the paediatric and younger adult populations, when measured by attack rates and hospitalization rates.

Influenza A (H5N1) virus (avian influenza) continues to cause sporadic human infections in some countries, with 72 cases (32 deaths) reported in 2009 in 5 countries.[7] Thus, although pandemic influenza A (H1N1) 2009 virus may displace other circulating influenza A virus strains, novel influenza A viruses, such as H5N1, remain a pandemic threat.

[5] Situation updates - Pandemic (H1N1) 2009. World Health Organization. Available at: http://www.who.int/csr/disease/swineflu/updates/en/index.html. Last accessed on 10 February 2010.

[6] Pandemic influenza a (H1N1) 2009 virus vaccine – conclusions and recommendations from the October 2009 meeting of the immunization Strategic Advisory Group of Experts. World Health Organization, *Weekly Epidemiological Record*, 4 December 2009, 8449:505-509. Available at: http://www.who.int/wer/2009/wer8449.pdf. Last accessed on 10 February 2010.

[7] Cumulative Number of Confirmed Human Cases of Avian Influenza A/(H5N1) Reported to WHO. World Health Organization, 30 December 2009. Available at: http://www.who.int/csr/disease/avian_influenza/country/cases_table_2009_12_30/en/index.html. Last accessed on 10 February 2010.

5. General Considerations

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

- mortality;
- hospitalization;
- complications;
- serious adverse events (drug-related); and
- antiviral drug resistance.

There are no adequate data from head-to-head randomized, controlled trials directly comparing the efficacy of one antiviral medicine against another for treatment of influenza. All treatment recommendations are based on trials that compare active antiviral treatment to placebo among patients with seasonal influenza and, therefore, comparisons between treatments are indirect.

All the recommendations herein are strongly influenced by patterns of antiviral resistance. Resistance prevalence in circulating influenza strains is collated and reported by WHO.[8] Therefore, these recommendations may need to be modified in light of current or local knowledge of the antiviral susceptibility of circulating viruses.

As of January 2010, the antiviral susceptibilities of circulating viruses are:

	Oseltamivir	**Zanamivir**	**M2 inhibitors[b]**
Pandemic (H1N1) 2009	Susceptible[a]	Susceptible	Resistant
Seasonal A (H1N1)[c]	Mostly resistant	Susceptible	Mostly susceptible
Seasonal A (H3N2)	Susceptible	Susceptible	Resistant
Influenza B	Susceptible	Susceptible	Resistant

a. See text below

b. Amantadine and rimantadine

c. Seasonal A (H1N1) refers to the human influenza A (H1N1) viruses that were circulating prior to the introduction of pandemic influenza A(H1N1) 2009 virus and which continued to circulate during 2009.

The Panel recommends that an antiviral should not be used for treatment where the virus is known or highly likely to be resistant to that antiviral. Since the current epidemiological data indicate an exceptionally low level of prevalence of seasonal H1N1 influenza viruses, amantadine and rimantadine are not currently recommended for use in the treatment of illness from circulating influenza virus strains, except when seasonal H1N1 virus infection is proven or strongly suspected, since all other circulating human influenza virus strains are resistant to these antivirals.

[8] Influenza A virus resistance to oseltamivir and other antiviral medicines. World Health Organization, 4 June 2009. Available at: http://www.who.int/csr/disease/influenza/2008-9nhemisummaryreport/en/index.html. Last accessed on 10 February 2010.

Infections with oseltamivir-resistant pandemic (H1N1) 2009 virus have been documented, comprising both sporadic cases and a limited number of clusters. While limited transmission of these viruses among contacts has been observed, there is no evidence of their wider community level or on-going circulation. WHO's assessment and conclusions on oseltamivir-resistant pandemic (H1N1) 2009 viruses, as set out in the *Weekly Epidemiological Record*[9,10] include:

- All oseltamivir-resistant isolates have the same H275Y mutation that confers resistance to oseltamivir, but not zanamivir.
- No evidence of reassortment between pandemic influenza A (H1N1) 2009 and other seasonal influenza A viruses.
- No association with an altered or unexpected severity of disease, although fatalities have occurred in some severely ill patients.

The largest proportion of cases of oseltamivir resistant pandemic (H1N1) 2009 virus infection has occurred in severely immunocompromised patients. Transplant patients (and especially bone marrow or haemopoetic stem cell transplant recipients) on immunosuppressive chemotherapy have emerged as a particularly vulnerable patient group. A number of cases have also been associated with failure of post-exposure oseltamivir chemoprophylaxis.

Chemoprophylaxis is not generally recommended for the established circulating human influenza viruses, including pandemic (H1N1) 2009, as the opportunity cost and utilization of antiviral drugs that may be needed for treatment is not warranted. With the availability of vaccines for both seasonal influenza and pandemic H1N1 2009 influenza, there should now be less reliance on antiviral chemoprophylaxis for prevention of illness in close community settings and in groups such as health-care workers. The association of post exposure chemoprophylaxis failures (described above) with oseltamivir resistance is an additional consideration in reducing chemoprophylactic use of antiviral medicines. Different considerations however apply to the avian (H5N1) and other zoonotic influenza viruses[11].

[9] Oseltamivir-resistant pandemic (H1N1) 2009 influenza virus, October 2009. World Health Organization, *Weekly Epidemiological Record*, 30 October 2009, 8444:453-458. Available at: http://www.who.int/wer/2009/wer8444/en/index.html. Last accessed on 10 February 2010.

[10] Update on oseltamivir resistant pandemic A (H1N1) 2009 influenza virus, January 2010. World Health Organization, Weekly Epidemiological Record, 5 February 2010, 8506:37-39. Available at: http://www.who.int/wer/2010/wer8506.pdf. Last accessed on 10 February 2010.

[11] WHO Rapid Advice Guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus. World Health Organization, May 2006. Available at: http://www.who.int/csr/disease/avian_influenza/guidelines/pharmamanagement/en/index.html Last accessed on 10 February 2010.

6. Recommendations

Formal recommendations are set out below as numbered, highlighted paragraphs (01-20). Most recommendations are accompanied by other treatment considerations, since the recommendations may not cover all situations, and, in most cases, are based on low or very low quality evidence.

For the purpose of these guidelines, reference to adults includes adolescents aged 13 to 18 years. Children are defined as persons up to and including the age of 12. Treatment recommendations for children are generally the same as for adults (see Recommendations 01-06), but with special considerations for dosing in younger children (see Recommendation 08).

6.1 Use of antivirals for treatment of pandemic influenza A (H1N1) 2009 virus infection in adults and adolescents

Context:	Treatment of adults and adolescents with confirmed or strongly suspected infection with pandemic influenza A(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 as soon as possible. (Strong recommendation, low quality evidence.)

This recommendation applies to all patient groups, including pregnant and postpartum women up to 2 weeks following delivery, and breastfeeding women.

Other Treatment Considerations:

Timing. Treatment should be started as soon as possible. Laboratory confirmation of influenza virus infection is not necessary for the initiation of treatment and a negative laboratory test for H1N1 does not exclude the diagnosis in all patients, therefore early, empiric treatment is strongly recommended. The evidence from clinical trials in uncomplicated seasonal influenza suggests most patients benefit from antiviral treatment commencing within 48 hours of onset 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.

Dose and duration. Higher doses of oseltamivir and longer duration of treatment may be appropriate, although there is no available clinical trial evidence to inform recommendations. An adult dose of 150 mg twice daily has been administered to some critically ill patients. When treating patients with renal impairment,

consideration needs to be given to the likely higher systemic exposure to oseltamivir (see Section 6.7 below).

Where the clinical course remains severe or progressive, despite 5 or more days of antiviral treatment, monitoring of virus replication and shedding, and antiviral drug susceptibility testing is desirable. Antiviral treatment should be maintained without a break until virus infection is resolved or there is satisfactory clinical improvement.

Antiviral resistance. Zanamivir is the treatment of choice for all patients where oseltamivir resistance is demonstrated or highly suspected. Intravenous zanamivir may be considered where available.

Drug delivery. Patients who have severe or progressive clinical illness, but who are unable to take oral medication may be treated with oseltamivir administered by nasogastric or orogastric tube (e.g. mechanically ventilated patients).

Remarks:

This recommendation takes account of:

- That the prescribing information (5 day treatment course) is based on clinical studies in outpatient settings, and with uncomplicated influenza virus infection.
- Evidence from case reports and case series of prolonged virus replication in the lower respiratory tract of severely ill patients.
- The concern about the increased risk of severe complications or death from influenza in this context.
- The evidence from observational studies that demonstrates a reduction in progression to severe disease and hospitalization in patients treated early (within 2 days of illness onset) with antivirals.
- The ease of use and suitability of oseltamivir compared to other currently available neuraminidase inhibitors, i.e. oral administration versus inhaled.
- Limited data from observational studies that indicate that oseltamivir delivered by nasogastric tube achieves adequate serum levels in critically ill patients.
- The opportunity cost of providing antivirals to these patients is considered low.

Rec 02: In situations where oseltamivir is not available, or not possible to use, patients who have severe or progressive clinical illness should be treated with inhaled zanamivir, where feasible. (Strong recommendation, very low quality evidence.)

Other Treatment Considerations:

Drug delivery. Zanamivir containing lactose (powder for inhalation) should not be administered by nebulizer (see Recommendation 18).

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 inhaled zanamivir to severely ill patients in its current commercially available dosage form, and the need for caution in use of inhaled zanamivir in patients with underlying respiratory disease.
- Intravenous zanamivir or peramivir may be considered if available (see Recommendation 17).

Context: Treatment of patients with confirmed or strongly suspected infection with pandemic influenza A(H1N1) 2009 virus, and who have severe immunosuppression expected to delay viral clearance.

Severe or complicated influenza virus infections attributable at least in part to severe immunosuppression have been most frequently described in transplant patients (including hematopoetic stem cell recipients, bone marrow transplant patients, and other transplant patients on immunosuppressive chemotherapy). Other patients with severe immonosuppression include those with graft versus host disease, or with haematological malignancies.

Other cancer patients undergoing chemotherapy and patients infected with HIV, who have developed severe immunodeficiency, may also need to be treated in accordance with the recommendations below.

Rec 03: Patients who have severe or progressive clinical illness should be treated with oseltamivir as soon as possible. Consideration should be given to the use of higher doses, such as 150 mg twice daily (for adults), and longer duration of treatment depending on clinical response. (Strong recommendation, low quality evidence.)

Other Treatment Considerations:

Prevention of infection in this patient group should be a prime objective. This is considered further in the recommendations for chemoprophylaxis below (Recommendation 04).

Duration. Regular monitoring of on-going viral replication and antiviral drug susceptibility is strongly recommended in this patient group. Antiviral treatment should be maintained without a break until virus infection is resolved (as indicated by clinical improvement or sequentially negative results for virus in the respiratory tract).

Antiviral resistance. Zanamivir is the treatment of choice for all patients where oseltamivir resistance has been demonstrated or is highly suspected (see pediatric section; inhaled zanamivir is not approved for use in children aged less than 5 years).

Alternative treatments. Intravenous zanamivir should be considered where available and is recommended for those with serious or progressive illness. If not available, intravenous peramivir may be considered, athough oseltamivir-resistant viruses are reported to have reduced susceptibility *in vitro* to peramivir.

Remarks:

These recommendations take account of:

- The impaired host immune response, such that standard antiviral regimens may not be as effective in clearing virus.
- The higher probability of emergence of oseltamivir-resistant virus in these patients.

Rec 04: When a person with influenza virus infection is present in the immediate setting, severely immunosuppressed patients may be offered chemoprophylaxis with oseltamivir or zanamivir. (Strong recommendation, very low quality evidence.)

Other Treatment Considerations:

Infection control procedures should be rigorously applied in this context, including vaccination against seasonal and pandemic influenza in all persons who have direct contact with these patients. Other infection control procedures include hand hygiene, gloves, gowns and masks the use of which is described in full in WHO interim guidance for infection prevention and control in health care for confirmed or suspected cases of pandemic (H1N1) 2009 and influenza-like illnesses[12].

Antiviral resistance. Zanamivir may be the preferred option for chemoprophylaxis for those patients able to take inhalation medicine, due to the known risk of development of oseltamivir resistance in this patient group.

Dose and duration. In severely immunosuppressed persons, there needs to be on-going weekly monitoring for evidence of prolonged viable viral replication, and chemoprophylaxis continued until there is no evidence of on-going viral replication in any patient in the same room or healthcare unit. Where exposure to infection may have occurred and the individual may be within the incubation period, consideration should be given to presumptive treatment (i.e. through the use of treatment doses).

Remarks:

[12] Infection prevention and control in health care for confirmed or suspected cases of pandemic (H1N1) 2009 and influenza-like illnesses. World Health Organization, December 2009. Available at: http://www.who.int/csr/resources/publications/swineflu/swineinfinfcont/en/index.html. Last accessed on 2 March 2010

This recommendation takes account of:

– The importance of preventing infection in this vulnerable patient group.

6.2 Use of antivirals for treatment of uncomplicated pandemic influenza A (H1N1) 2009 virus infection in adults and adolescents

Context:	Treatment of adult and adolescent patients with confirmed or strongly suspected, but uncomplicated illness, due to pandemic (H1N1) 2009 virus infection, and where antiviral medications for influenza are available.

The decision to treat patients in this context will depend on the availability of health-care resources (including antiviral medication), local priorities for health provision, and assessment of the risk that the patient will develop more serious disease. While some groups of patients are recognized as having a higher risk of developing more severe or complicated illness (see Part I, Annex 1), all patients are at some risk.

The recommendation below, therefore, needs to be applied in the context of clinical judgment and local or national guidance.

Rec 05: Patients who have uncomplicated illness due to confirmed or strongly suspected virus infection and **are** in a group known to be at higher risk of developing severe or complicated illness, should be treated with oseltamivir or zanamivir as soon as possible. (Strong recommendation, low quality evidence.)

This recommendation applies to all patient groups, including pregnant and postpartum women, up to 2 weeks following delivery, and breastfeeding women.

Patients who have uncomplicated illness, and are not in a group known to be at higher risk of developing severe or complicated illness, may not need to be treated with antivirals. A decision to treat will depend upon clinical judgment and availability of antivirals. Patients who present for medical attention, but do not receive antiviral treatment, should be counseled on signs of progression or deterioration of illness and advised to seek medical attention immediately, should their condition deteriorate or persist.

Other Treatment Considerations:

Antiviral resistance. Zanamivir, where available, is the treatment of choice for all patients where oseltamivir resistance is demonstrated or highly suspected.

Remarks:

This recommendation takes account of:

- The concern about the higher risk of severe complications or death from influenza in these patient groups.
- The evidence from observational studies that demonstrates a reduction in progression to severe disease and hospitalization in patients treated with antivirals.
- The importance of clinical judgment in deciding whether to initiate antiviral treatment for uncomplicated illness in persons not in a group known to be at higher risk for influenza complications.

6.3 Use of antivirals for treatment of pandemic influenza A (H1N1) 2009 virus infection in children

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

Rec 06: Children who have severe or progressive clinical illness should be treated with oseltamivir as soon as possible. (Strong recommendation, low quality evidence.)

This recommendation applies to all children, including neonates and young children (in particular those less than 2 years of age).

Other Treatment Considerations:

There are generally fewer data available on the safety and efficacy of antiviral medicines in very young children (especially from birth to 1 year). In particular, there are insufficient efficacy or safety data to support guidelines on the use of intravenous zanamivir or peramivir in children.

The validity of recently recommended oseltamivir doses in children has been independently evaluated for WHO (Abdel-Rahman and Kearns, Part II, Annex 7). This evaluation was based on an assessment of the available literature, including knowledge of the drug's disposition and knowledge of pathological and physiological characteristics of the target population. On the basis of this evaluation, the Guidelines Panel made the following recommendations with regard to oseltamivir doses for young children:

Rec 07: Oseltamivir treatment doses for children from 14 days up to 1 year of age should be 3 mg/kg/dose, twice daily. For children <14 days of age, the recommended oseltamivir dose is 3 mg/kg/dose once daily. Lower doses should be considered for infants who are not receiving regular oral feedings and/or those who have a concomitant medical condition which is expected to reduce significantly renal function.

Other Treatment Considerations:

Timing of treatment. Evidence indicates that the greatest benefit is derived from early oseltamivir treatment. Therefore, suitable preparations of oseltamivir need to be available at the point of care.

Drug delivery. Where capsules containing the appropriate oseltamivir dose are available but cannot be swallowed, the contents can be added to a sweet liquid or soft food immediately before administration to disguise bitter taste. Where different doses are required, the following methods may be used:

Powder for oseltamivir oral suspension, where available, is the preferred formulation for children unable to take the capsules, when capsules of appropriate strength are not available or where the smaller capsule of 30 mg is greater than the calculated dose. Where this is not available, an oseltamivir suspension or solution can be produced by extemporaneous preparation from the contents of capsules, or by preparation from bulk powder (also referred to as Active Pharmaceutical Ingredient, or API). WHO recommends that local guidance be developed that takes into account local availability of oseltamivir capsules or API, local facilities, and availability of suitable suspending agents or diluents.

The following points need to be considered in the development of such local guidance (see also Part II, Annex 8, report by A Nunn):

Extemporaneous preparation of oseltamivir treatment course. Preparation of a full oseltamivir treatment course is best done where commercially available suspending agents, containing antimicrobial preservatives, are available. Further information on available suspending agents, and proposed shelf life for suspensions, is provided in Part II Annex 8 (report by A Nunn).

Consideration also needs to be given to availability or provision of suitable measuring devices for individual dose measurement and administration, as well as provision of clear information for the caregiver.

Manipulation of oseltamivir capsules to prepare a solution for immediate use. Where suitable suspending agents or diluents containing preservative are not available and stability and sterility cannot, therefore, be assured, capsules can be opened and mixed with a measured volume of water immediately before administration. Any smaller dose volume required can be calculated and measured for administration.

Local guidance should take into account the availability of materials and measuring devices. User instructions for choice of substrate, dilution, calculation, and measurement of dose should be provided.

Some wastage of drug material is inevitable under these circumstances.

Magistral preparations from API. Preparation of a stable solution from oseltamivir phosphate powder (the API) has been used during the 2009/10 outbreak in the United Kingdom. Further information is provided in Part II, Annex 8 (report by A Nunn).

Remarks:

This recommendation takes account of:

- The need for a clear and simple dose schedule.
- The lack of clinical evidence for dosing in this age group and the lack of suitable, commercially available paediatric formulations of oseltamivir.

Context:	Treatment of children with confirmed or strongly suspected, but uncomplicated, illness due to pandemic (H1N1) 2009 virus infection and where antiviral medications for influenza are available.

Rec 08: Children who have uncomplicated illness due to confirmed or strongly suspected influenza virus infection and **are in a group known to be at higher risk** of developing severe or complicated illness should be treated with oseltamivir or zanamivir as soon as possible. (Strong recommendation, low quality evidence).

Recommendation 08 applies to all infants and young children (in particular those less than 2 years of age), since they are known to be at higher risk of developing severe or complicated illness.

Other Treatment Considerations:

Zanamivir (as inhaled powder) is only indicated for use in persons aged 5 years or above.
Oseltamivir dosing should be as described in Recommendation 07 above.

Other remarks and notes are as given for Recommendation 05 above. In particular, carers of children who do not receive antiviral treatment should be counseled on signs of progression or deterioration of illness and advised to seek medical attention immediately, should the condition deteriorate or persist.

6.4 Use of antivirals where antiviral resistance is known or suspected

The Guidelines Panel recommends that, in general, an antiviral medication should not be used where the virus is known or highly likely to be resistant to that antiviral. This is based on the principle that the drug is expected to be ineffective and, therefore, the potential cost or adverse events would not be justified. However, the evidence for lack of clinical efficacy in these settings is of low quality.

Continued use of an antiviral drug (to which resistance is known or suspected), the use of combination treatments, or alternative doses may be appropriate in the context of prospective clinical and virological data collection as part of an approved research protocol.

Of current concern is the mutation (H275Y) in the neuraminidase that confers resistance to oseltamivir, but not to zanamivir, since this had become prevalent in the seasonal H1N1

influenza virus, and sporadic cases have been reported in pandemic (H1N1) 2009 virus. The following recommendation addresses this particular context:

Rec 09: Patients who have severe or progressive clinical illness with virus resistant to oseltamivir but known or likely to be susceptible to zanamivir, should be treated with zanamivir. (Strong recommendation, very low quality evidence.)

Other Treatment Considerations:

Intravenous zanamivir is likely to be the preferred formulation in this setting, (where available and subject to the provisions of Recommendation 15).

Where intravenous zanamivir is not available, intravenous peramivir may be considered (subject to Recommendation 15), although oseltamivir-resistant viruses are reported to have reduced susceptibility *in vitro* to peramivir.

The panel noted an urgent need for alternative dosage form and products with data to support their use in this population.

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 inhaled zanamivir to severely ill patients in its current dosage form.
- The uncertain activity and clinical efficacy of intravenous peramivir against infection with oseltamivir-resistant pandemic (H1N1) 2009 virus that has the H275Y mutation.

6.5 Antiviral treatment recommendations: Other influenza virus strains

Antiviral treatment recommendations for infection with influenza virus strains other than pandemic (H1N1) 2009 virus, including when the virus type or influenza A virus subtype is not known, are generally the same as for pandemic (H1N1) 2009 virus infection. The following additional points should be considered:

For the treatment of those presenting with uncomplicated illness, the decision to treat should allow for the risk of development of severe or progressive disease, which may not be the same as observed with the pandemic (H1N1) 2009 virus, and should be based upon clinical judgment.

If illness is known or suspected to be due to a zoonotic (animal-derived) influenza A virus, such as swine influenza viruses (H1, H2, H3) or avian influenza viruses (H7, H9), oseltamivir or zanamivir are treatment options. For known or suspected infection with avian influenza H5N1 virus, antiviral treatment should follow the

WHO rapid advice guidelines on pharmacological management of humans infected with highly pathogenic avian influenza A (H5N1) virus.[13]

Where the infection is known or suspected to be due to seasonal influenza A (H1N1) virus, oseltamivir is unlikely to be effective, but either amantadine or rimantadine may be used when the virus is likely susceptible (subject to Recommendation 10 below). Zanamivir is also a treatment option if available.

Rec 10: Pregnant women and children aged less than 1 year with uncomplicated illness due to seasonal influenza A (H1N1) 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 or rimantadine in pregnant women and lack of evidence supporting use in young children aged <1 year.

6.6 Use of antivirals for chemoprophylaxis of pandemic influenza A (H1N1) 2009 virus infection

Antiviral chemoprophylaxis is generally not recommended,

Presumptive (post-exposure) antiviral treatment may have particular benefits in some higher risk situations. That is, the initiation of an antiviral treatment course (twice daily) on the presumption that influenza virus infection has happened, even if symptoms have not yet appeared. This is likely to be limited to health-care settings such as groups of patients at higher risk for complications from influenza virus infection (including, but not limited to, transplant units, other patients with severe immunosuppression, neonatal units) and other highly vulnerable patients in other settings. In these situations, when influenza virus infection is present in the institution or immediate community, the following recommendation applies:

Rec 11: If higher risk individuals have been exposed to a patient with influenza, consider presumptive treatment with oseltamivir or zanamivir. (Strong recommendation, very low quality evidence).

In other situations where risk of infection is a cause for concern, caregivers are advised to monitor exposed, high-risk patients closely for early signs and symptoms of acute respiratory infection and ILI (see Section 2: Case Description) and to initiate antiviral treatment promptly as described in Recommendations 05 and 08.

Remarks:

[13] WHO Rapid Advice Guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus. World Health Organization, May 2006. Available at: http://www.who.int/csr/disease/avian_influenza/guidelines/pharmamanagement/en/index.html. Last accessed on 10 February 2010.

This recommendation takes account of:

- Reports of oseltamivir resistance following post-exposure prophylaxis failure.
- Severely immunosuppressed persons who may not manifest fever with influenza virus infection or who might have atypical symptoms that do not meet a definition of ILI.

6.7 Other considerations

Additional treatment considerations concerning the use of antiviral medicines and which may modify recommendations 01-11 are as follows:

Renal Impairment
When treating patients with renal impairment, consideration needs to be given to the likely higher systemic exposure to oseltamivir. This is particularly important for those patient groups (pregnancy, pediatric populations) where there is less experience or data on the use of higher oseltamivir doses. Caution should be exercised in these patients, particularly over the use of higher doses of oseltamivir (information on dose adjustment based on creatinine clearance is given in the Summary of Product Characteristics[14]).

Obesity
The panel noted reports of severe illness in obese patients and a recent report indicating that oseltamivir volume of distribution in obese patients was similar to that in non-obese patients. However, there are currently insufficient data to determine whether dose adjustment (e.g. higher dosing) is needed in obese patients.

Pregnancy and breastfeeding
Treatment recommendations for pregnancy and breastfeeding are covered by recommendations 01-05 and 09-18 and there are no exclusions, except as covered by Recommendations 10 and 13. The following are some additional considerations for treatment of influenza virus infection in pregnancy:

- There are fewer data on safety and efficacy in this patient group for all antiviral medicines, though there is more reported experience with the use of oseltamivir.
- The dosing recommendations are as for other adult patient groups for each antiviral discussed.

7. Other interventions for management of patients with influenza

A number of other products are not licensed for the treatment of influenza in most countries but have been used for treatment of individual patients or are approved in a very limited

[14] Avaiable from http://www.ema.europa.eu/humandocs/PDFs/EPAR/tamiflu/emea-combined-h402en.pdf. Last accessed on 2 March 2010.

number of countries. The Panel considered the evidence for the use of the following drugs (see below) for the treatment of influenza, but concluded that there were insufficient data on either efficacy or safety or both and, therefore, there is inadequate evidence for treatment recommendations at this time for:

Immunoglobulins (including monoclonal antibodies, immune and convalescent sera/plasma and related products)
Intranasal interferons
Arbidol
Ribavirin
Favipiravir

The Panel made two recommendations with regard to the lack of efficacy data and known toxicity of ribavirin:

Rec 12: 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 as part of an approved research protocol.

Rec 13: In pregnant women with confirmed or strongly suspected influenza virus infection, ribavirin should not be administered as treatment or chemoprophylaxis. (Strong recommendation, regulatory contraindication.)

With regard to all investigational, regional,[15] and other unapproved therapies, including all antiviral medicines and their formulations as listed above, the Guidelines Panel had the following recommendation:

Rec 14: In patients with confirmed or strongly suspected influenza virus infection, investigational, regional, or other unapproved therapies should not be administered unless in the context of prospective clinical and virological data collection as part of an approved research protocol.

Recommendation 16 should also be applied to the use of combinations of antiviral drugs (including approved medicines), since there are few published clinical trial data on the safety or efficacy of such combinations.

With regard to the investigational and regional products listed below, the Guidelines Panel acknowledged the status of these products in clinical development and that they were of the same class or chemical entity as the existing, approved neuraminidase inhibitors. However, in light of the paucity of published data on efficacy and safety, the panel made the following recommendation:

[15] Regional products are those that have market authorisations in only one or a few countries.

Rec 15: In patients with confirmed or strongly suspected influenza virus infection, investigational neuraminidase inhibitors should only be used in the context of a clinical trial or in accordance with relevant emergency use provisions.

Remarks

This recommendation applies to the following investigational or regional products:

- Peramivir (parenteral formulation)
- Laninamivir
- Zanamivir (parenteral formulation)
- Oseltamivir (parenteral formulation)

Peramivir has received market authorization in Japan, but is investigational or unregistered elsewhere. There are few published clinical trial data for peramivir.

This recommendation takes account of:

- The limited availability of these products in most countries.
- Legal and ethical complexities, including import/export restrictions and consent requirements, on compassionate or emergency use of investigational or unregistered products.

Individual countries should develop local recommendations in the context of local market authorizations.

Rec 16: Zanamivir containing lactose (powder for inhalation) should not be administered by nebulizer. (Strong recommendation, regulatory warning.)

Exacerbated co-morbidities (underlying conditions) and co-infections should be managed in accordance with standard of care for such conditions, except as qualified below:

Rec 17: Patients who have severe or progressive clinical illness, including viral pneumonitis, respiratory failure, and ARDS due to influenza virus infection, should not be given systemic corticosteroids unless indicated for other reasons or as part of an approved research protocol. (Strong recommendation, low quality evidence).

Remarks:

This recommendation takes account of:

- A lack of evidence of benefit in these patients.
- Risk of harm, including opportunistic infection and prolongation of virus replication.
- The need for corticosteroid treatment for other conditions such as asthma, COPD, ongoing anti-inflammatory treatment, and adrenal insufficiency.

Rec 18: In children and adolescent (<18 year old) patients with confirmed or strongly suspected influenza virus infection, treatment with drugs containing salicylates (e.g. aspirin) should not be initiated. (Strong recommendation, regulatory warning.)

Remarks:

These recommendations take account of:

- The increased risk of Reye's syndrome with influenza and salicylate administration in younger patient populations.
- Patients who may already be taking such medicines for other indications.

8. Product supply

The list of influenza antiviral medicines that have been approved through the WHO prequalification programme is set out below. For an up-to-date list, consult the WHO website at www.who.int/prequal. The availability and price of these products will vary on a country-by-country basis.

WHO List of Prequalified Medicinal Products

Printed from WHO prequalification web site (http://www.who.int/prequal/) on 2010-Jan-05 13:56 GMT.

For information about the listing of prequalified products and the alternative approval procedure, please see "General information" at http://www.who.int/prequal/info_general/notes_registry.htm.

Legend:

"+" means combination product, both fixed-dose combination (co-formulated) and co-packaged product (i.e. co-blister)
[A+B] + C means A and B are in a fixed-dose formulation and C is co-packaged
"*" refers to products approved by both WHO Prequalification Programme and US FDA
USFDA1 - approved by USFDA; USFDA2 - tentatively approved by USFDA

Therapeutic area	INN	Formulation and strength	Applicant	Manufacturing site	Packaging	Reference	Date of PQ
IN	Oseltamivir (as phosphate)	Capsules 75mg	Cipla Ltd	Goa, India	HDPE bottle 30; PVC/PE/PVdC Aluminum blister 10	IN001	2009-May-13
IN	Oseltamivir (as phosphate)	Powder for oral suspension 12mg/ml	Roche Ltd, Switzerland	Grenzacherstr, Basel, Switzerland (Galenic bulk production); Wurmisweg, Kaiseraugst, Switzwerland (packaging); GP Grenzach Produktions GmbH, Wyhlen, Germany (packaging)	Amber glass bottle 30g	IN003	2009-Sep-21
IN	Oseltamivir (as phosphate)	Capsules 30mg	Roche Ltd, Switzerland	Grenzacherstr, Basel, Switzerland (Galenic bulk production); Wurmisweg, Kaiseraugst, Switzerland (packaging)	Blister (PVC/PE/PVDC, sealed with aluminium foil) 10	IN004	2009-Sep-21
IN	Oseltamivir (as phosphate)	Capsules 45mg	Roche Ltd, Switzerland	Grenzacherstr, Basel, Switzerland (Galenic bulk production); Wurmisweg, Kaiseraugst, Switzerland (packaging)	Blister (PVC/PE/PVDC, sealed with aluminium foil) 10	IN005	2009-Sep-21
IN	Oseltamivir (as phosphate)	Capsules 75mg	Roche Ltd, Switzerland	Grenzacherstr, Basel, Switzerland (Galenic bulk production); Catalent Germany Schorndorf GmbH, Schorndorf, Germany (Galenic bulk production); CENEXI SAS, Fontenay-sous-Bois, France (Galenic bulk production); Hoffmann-La Roche Inc., New Jersey, USA (Galenic bulk production); Patheon Inc., Cincinnati, OH, USA (Galenic bulk production); Catalent Germany Schorndorf GmbH, Schorndorf, Germany (packaging); GP Grenzach Produktions GmbH, Grenzach-Wyhlen, Germany (packaging); Wurmisweg, Kaiseraugst, Switzerland (packaging)	Blister (PVC/PE/PVDC, sealed with aluminium foil) 10	IN006	2009-Sep-21
IN	Zanamivir	Inhalation powder 5mg/dose	GlaxoSmithKline Ltd, United Kingdom	GlaxoSmithKline Australia Pty Ltd, Boronia, Australia; Glaxo Wellcome Production, Evreux, France	Alu/Alu blister, 4 blisters per disk (a pack contains 1 or 5 Alu foil disks)	IN007	2009-Sep-22
IN	Zanamivir	Inhalation powder 5mg/dose	GlaxoSmithKline Ltd - UK	GlaxoSmithKline Australia Pty Ltd, Boronia, Australia; Glaxo Operations UK Ltd, Hertfordshire, UK; SmithKline Beecham Corporation, Zebulon, USA; GlaxoSmithKline Inc., Ontario, Canada	HDPE bottle: a pack contains 1 bottle of 20 capsules and an inhaler device	IN008	2009-Nov-02

9. 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 or dosage forms become available; and/or
- there is a change in the severity of illness associated with the current pandemic (H1N1) 2009 or other circulating influenza viruses, or in their susceptibility to antiviral drugs, or the emergence of a novel influenza A virus of global public health importance.

WHO will review the validity of these guidelines every 6 months, with regard to the above criteria, unless these guidelines are superseded by new, consolidated or standard guidelines. The next such review will be September 2010.

Updating or adapting recommendations locally

The methods used to develop these guidelines are transparent. Therefore it will be possible to update the information contained in them by re-running the search described in Part II. The recommendations have been developed to be as specific and detailed as possible without losing 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. It may then 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.

10. Priorities for research

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

- Studies to assess the efficacy of existing and investigational antiviral and adjunctive treatments, including regional products, for severe or complicated influenza illness.
- Studies to assess efficacy of immunotherapy using either post-infection sera/plasma or monoclonal antibodies in complicated illness due to influenza virus infection.
- Comparative clinical studies of neuraminidase inhibitors, used for treatment of influenza in all populations but especially for parenteral neuraminidase inhibitors for critically ill patients, assessing comparative efficacy and safety.
- Standardization of clinical and laboratory virological endpoints used to assess outcomes for these studies.
- Comparative studies of combination treatments in all populations, but especially for severely or critically ill patients with influenza virus infection.
- Studies in children under one year to define dose, safety, and efficacy of all antivirals, particularly in neonates with influenza virus infection.
- Development of alternative formulations, including different routes of administration, of zanamivir and oseltamivir, particularly for use in severely ill patients and for infants with influenza virus infection.
- Studies of higher doses, loading doses, longer durations, and combinations.
- Definition of prognostic factors for developing severe influenza disease.
- Better pharmacokinetic and pharmacodynamic studies, with particular regard to correlations between dose, routes of administration and viral load in the (lower) respiratory tract with influenza virus infection.
- Data on treatment of influenza in particular higher risk groups, including pregnant women, obese patients, and immunosuppressed (including HIV) infected persons.
- Development of better definitions of patients with higher risk for severe or progressive influenza illness such as HIV-infected population (adults and children), obesity, pregnancy.
- Prospective studies on mechanisms and clinical conditions by which resistance to antiviral medications is likely to develop while influenza patients are under treatment.
- Development of a robust surveillance system for influenza antiviral resistance monitoring.

Annex 1: Risk factors for severe disease

Risk factors for severe disease from pandemic (H1N1) 2009 virus infection reported to date are considered similar to those risk factors identified for complications from seasonal influenza. These include the following groups:

- Infants and young children, in particular <2 years
- Pregnant women
- Persons of any age with chronic pulmonary disease (e.g. asthma, COPD)
- Persons of any age with chronic cardiac disease (e.g. congestive cardiac failure)
- Persons with metabolic disorders (e.g. diabetes)
- Persons with chronic renal disease, chronic hepatic disease, certain neurological conditions (including neuromuscular, neurocognitive and seizure disorders, but not including autism spectrum disorders),
- Hemoglobinopathies, or immunosuppression, whether due to primary immunosuppressive conditions, such as HIV infection, or secondary conditions, such as immunosuppressive medication or malignancy
- Children receiving chronic aspirin therapy
- Persons aged 65 years and older

A higher risk of severe complications from pandemic (H1N1) 2009 virus infection has also been observed in individuals who are obese (particularly in those who are morbidly obese) and among disadvantaged and indigenous populations.

The Guidelines panel had the following additional comments concerning persons at higher risk of developing complicated or severe influenza disease, which should be taken into account in applying these guidelines:

- The higher risk during pregnancy should be applied to a two-week post-partum period[16]
- There are limited data from the pandemic on the extent to which HIV-infected patients are at higher risk of complicated or severe illness, though there are some data from seasonal influenza indicating a higher risk and limited data relating to mortality from pandemic influenza[17]. The decision to administer influenza antiviral medicines to such patients will depend on local priorities and availability of such antivirals.

[16] Louie JK, Acosta M, Jamieson DJ, Honein MA. Severe 2009 H1N1 influenza in pregnant and postpartum women in California. *N Engl J Med* 2010;362(1):27-35.

[17] Archer B, Cohen C, Naidoo D, Thomas J, Makunga C, Blumberg L, et al. Interim report on pandemic H1N1 influenza virus infections in South Africa, April to October 2009: epidemiology and factors associated with fatal cases. *Euro Surveill* 2009;14(42).

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Professor Gregory Kearns and Professor Susan Abdel-Rahman (Pediatric dosing)
Professor Anthony Nunn (Extemporaneous preparations)

Annex 3:
Declarations of Interests

The Guidelines Panel participants completed the WHO standard form for declaration of interests prior to the meeting. At the start of the meeting, all participants were asked to confirm their interests, and to provide any additional information relevant to the subject matter of the meeting.

The following participants declared current or recent (<1 year) financial interests related to commercial organizations as listed below:

Del Mar:	Technical adviser to GSK <$1000, institutional.
Hay:	Technical adviser to GSK <$1000, personal.
Sugaya:	Technical adviser to Daiicji-Sankyo (>$10 000) institutional, adviser for Shionogi pharmaceutical, institutional.
van der Werf:	Consultancy and research support from Danone, GSK, Roche to research unit, not personal. Travel support from GSK, personal.
Blumberg:	Unconditional educational grant from Sanofi Pasteur for conference organization, institutional.

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

Hayden:	Unpaid adviser (sometimes with access to confidential information) for Alios, Adamas, Kirin, Abbott, Crucell, Nexbio, Biocryst, GSK, Roche, Toyama, Respirivert, 3V biosciences, Inhibikase, Vaxinnate.

The following participants declared non-commercial academic interests in the subject of the meeting, and have (co) authored publications that include reports on commercially funded clinical trials or opinions or recommendations on specific antiviral treatment of influenza virus infection:
Del Mar, Hay, Hayden, Sugaya

Several participants described academic interest in the subject matter of the meeting, including participation in non-commercially funded clinical studies. These were not regarded as conflicts of interest since they formed the basis of the expertise of the panel.

The following participants declared no interests in the subject matter of the meeting:
Bero, Blumberg, Chotpitayasunondh, Farrar, Gray, Hui, Kearns, Nunn, Uyeki, Zaidi.

On the basis of their declared interests in the subject of the meeting and with regard to the nature and extent of financial and/or academic interests, the following panel participants

took no part in the final session of the meeting during which the guidelines recommendations were confirmed, and took no part in finalization of the recommendations (Part I) subsequent to the panel meeting:
Del Mar, Hay, Hayden, Sugaya, Van der Werf.

Two experts, initially identified as potential participants, were asked not to participate in the meeting on the basis of declared personal and commercial interests.

Annex 4:
Table of standard dosages

The standard doses for oseltamivir and zanamivir are based on clinical studies in outpatient settings, and with uncomplicated influenza virus infection. Doses for management of severe or complicated illness are discussed within these recommendations. Specific recommendations have also been made for doses for young children, infants and neonates. Further information is also provided in the Prescribing Information and Summary of Product Characteristics for each product.

As a reference, the standard adults doses, as given in Summary of Product Characteristics, for each product are provided below:

Oseltamivir

Oseltamivir is indicated for treatment of patients one year of age and older.

For adolescents (13 to 17 years of age) and adults the recommended oral dose (based on data from studies in typical uncomplicated influenza) is 75 mg oseltamivir twice daily for 5 days.

Zanamivir

Zanamivir is indicated for treatment of influenza in adults and children (>5 years).

The recommended dose for treatment of adults and children from the age of 5 years (based on data from studies in typical uncomplicated influenza) is two inhalations (i.e. 2 x 5mg) twice daily for 5 days.

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

Revised February 2010

Part II
Review of evidence

Contents

Summary of Evidence for Benefits and Harms[1]

1. Treatment of Seasonal or Pandemic Influenza

1.1 Use of oseltamivir – treatment

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

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

Systematic review/clinical trial evidence – seasonal influenza

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

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

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

[1] Updated January 2010.

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

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

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

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

Observational data – seasonal influenza

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

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

In an analysis of observational data for oseltamivir use, Freemantle and Calvert (2009) reviewed nine post-marketing studies of oseltamivir. The authors concluded that although

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

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

Following are descriptions of recent observational studies of oseltamivir.

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

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

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

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

Observational data – pandemic influenza

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

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

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

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

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

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

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

and differences between the two types of influenza should be considered when applying treatment recommendations.

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

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

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

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

1.2 Use of zanamivir - treatment

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

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

Systematic review/clinical trial evidence – seasonal influenza

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

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

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

Observational data – seasonal influenza

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

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

Observational data – pandemic influenza

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

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

1.3 Use of amantadine - treatment

Systematic review/clinical trial evidence – seasonal influenza

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

Observational data – seasonal influenza

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

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

1.4 Use of rimantadine - treatment

Systematic review/clinical trial evidence – seasonal influenza

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

Observational data – seasonal influenza

As noted above in Sections 1.1 and 1.3, the Kimberlin (2009) review found that children <1 year of age who were treated with oseltamivir were significantly less likely to develop abnormalities in the head/eyes/ears/nose/throat system, such as otitis media, compared to children treated with rimantadine or amantadine (1.7% versus 15.4%; p<0.01; see Table A5.5,

Annex 5). However there were no statistically significant differences in the occurrence of body system abnormalities in children treated with oseltamivir or one of the adamantanes. In addition, the Keyser (2000) study indicates that rimantadine is better tolerated than amantadine.

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

1.5 Use of peramivir - treatment

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

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

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

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

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

1.6 Use of arbidol

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

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

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

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

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

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

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

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

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

1.7 Use of ribavirin

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

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

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

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

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

Table 1.7: Summary of Ribavirin studies and reviews for influenza

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

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

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

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

1.8 Other products

Intranasal interferons

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

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

Immunoglobulins

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

1.9 Anti-inflammatory products

Aspirin

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

Corticosteroids

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

Recently published retrospective observational studies suggest that corticosteroid treatment of influenza is associated with a higher likelihood of ICU admission and mortality as clinical

outcomes (Jain et al., 2009; Liem et al., 2009). In addition, two observational studies demonstrate that corticosteroid use is associated with slower viral clearance, significantly increased odds of persistent viral replication 7 days after symptom onset (Lee et al., 2009), and a longer duration of viral shedding with increased corticosteroid dose (Nichols et al., 2004).

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

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

Table 1.9: Clinical data for corticosteroids in influenza

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

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

2. Chemoprophylaxis of Influenza

2.1 Use of oseltamivir - chemoprophylaxis

Systematic review/clinical trial evidence – seasonal influenza

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

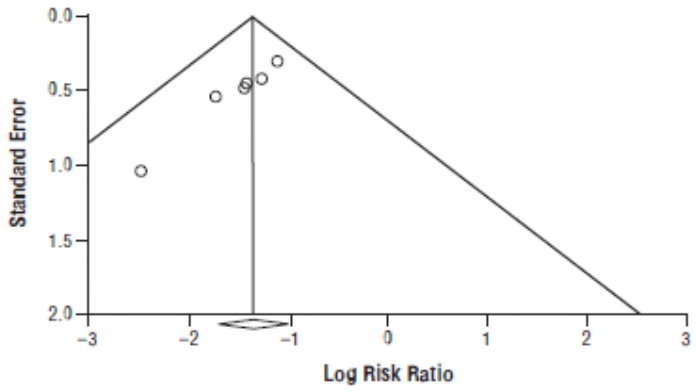
The Shun-Shin (2009) review of the use of neuraminidase inhibitors in children reported on one post-exposure prophylactic trial of oseltamivir. This trial demonstrated a reduction in the risk of developing confirmed symptomatic influenza after introduction of an index case into the household (RD=-0.12;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

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

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

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

Figure 2.1: Funnel plot for symptomatic influenza



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

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

Observational data – pandemic influenza

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

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

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

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

2.2 Use of zanamivir - chemoprophylaxis

Systematic review/clinical trial evidence – seasonal influenza

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

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

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

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

2.3 Use of amantadine - chemoprophylaxis

Systematic review/clinical trial evidence – seasonal influenza

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

2.4 Use of rimantadine - chemoprophylaxis

Systematic review/clinical trial evidence – seasonal influenza

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

Annexes

Annex 4: Methods used to prepare guidelines

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

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

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

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

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

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

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

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

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

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

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

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

"Weak" recommendations can be interpreted as:

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

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

Updating of the Guidelines

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

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

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

Table A4.1: Ranking of outcomes for antiviral treatment

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

Table A4.2: Ranking of outcomes for antiviral prophylaxis

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

Search strategy

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

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

Selection criteria, data collection, and judgments

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

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

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

Summary of findings tables

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

Annex 5: Summaries of findings tables

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

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

Table A5.1

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

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

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

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

Table A5.2

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

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

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

Table A5.3

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

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

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

Table A5.4

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

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

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

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

Table A5.5

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

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

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

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

Table A5.6

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

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

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

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

Table A5.7

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

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

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

Table A5.8

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

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

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

Table A5.9

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

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

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

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

Table A5.10

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

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

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

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

Table A5.11

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

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

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

Table A5.12

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

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

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

Table A5.13

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

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

Annex 6: Summary of observational data

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

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

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

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

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

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

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

Table A6.2

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

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

Annex 7: Independent evaluation of oseltamivir dosing in children

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

Summary

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

Annex 8: Review of extemporaneous preparations of oseltamivir

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

Summary

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

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