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

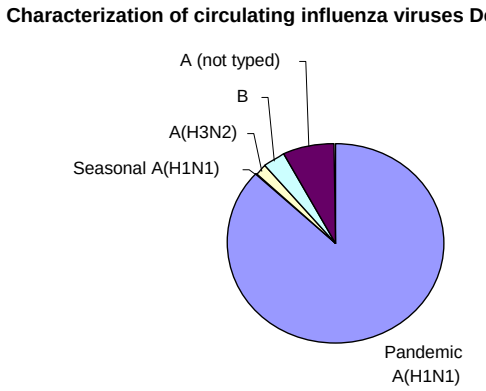
Certain patients with seasonal influenza virus infection or pandemic influenza (H1N1) 2009 virus infection are recognized to be at **higher risk** of developing severe or complicated illness. The Guidelines Panel did not review the evidence for the definition of these higher risk groups, but adopted, 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 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.