



衛生防護中心
Centre for Health Protection

Scientific Committee on Emerging and Zoonotic Diseases

General Guide to Doctors: Antiviral Use for Novel Influenza Treatment and Prophylaxis

Introduction

Influenza pandemic may cause high morbidity, excess mortality, and social and economic disruption. Novel influenza viruses, including avian and non-avian strains, may cause a pandemic. The government and the medical sector are currently taking the lead in preparing for the pandemic so as to reduce its impact when it strikes. The Government's preparedness plan for influenza pandemic includes a three-level response system. These levels pitch at different degrees of public health risks to the community and each of them depicts certain scenarios and prescribes a given set of public health actions.

1. Alert Response Level

- (a) Confirmation of highly pathogenic avian influenza (HPAI) outbreaks in poultry populations outside Hong Kong, or
- (b) Confirmation of HPAI in Hong Kong in imported birds in quarantine, in wild birds, in recreational parks, in pet bird shops or in the natural environment, or
- (c) Confirmation of human case(s) of avian influenza outside Hong Kong.



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The Centre for Health

Protection is a

professional arm of the

Department of Health for

disease prevention and

control

The aims of public health actions are to attain timely and accurate information from other territories in order to prevent disease importation into Hong Kong, and to facilitate prompt surveillance for any local cases.

2. Serious Response Level

- (a) Confirmation of HPAI outbreaks in the environment of or among poultry population in Hong Kong due to a strain with known human health impact, or
- (b) Confirmation of human case(s) of avian influenza in Hong Kong without evidence of efficient human-to-human transmission.

The aims of public health actions are to control the spread of the diseases, identify the source of infection and contain the spread of the virus in and out of Hong Kong at the early stage of infection.

3. Emergency Response Level

- (a) Confirmation of efficient human-to-human transmission of novel influenza occurring overseas or in Hong Kong, or

The aims of public health actions are to identify the strain of virus and determine its sensitivity to available antiviral agents, so as to slow down the progression of the epidemic and minimize loss of human lives, before an effective vaccine against the pandemic influenza strain can be produced.

Use of Antivirals

With respect to drug use, the Serious and Emergency Response Levels are most relevant to medical practitioners directly involved in patient management.

Antiviral drugs are useful to reduce morbidity and mortality during a pandemic. Since effective vaccines are unlikely to be available in the early phase of a pandemic, antiviral drug will be the only virus-specific intervention available. There are two classes of antiviral drugs specific for influenza, namely M2 blockers (amantadine and rimantadine) and neuraminidase inhibitors (oseltamivir and zanamivir).

Studies have demonstrated that some, but not all, strains of H5N1 are resistant to M2 blockers. The susceptibility of pandemic strains should be taken into consideration when choosing antiviral agents. Both oseltamivir and zanamivir are active for the treatment of influenza. Though the latter is not yet approved for influenza prophylaxis in some countries, both oseltamivir and zanamivir are licensed in Hong Kong for treatment and prophylaxis against influenza.

Since infection due to highly pathogenic influenza strains is a

multi-organ disease, an antiviral drug with a high systemic level is preferred for treatment purpose. Oseltamivir is readily absorbed from the gut and thus has high bioavailability (at least 75%). In contrast, zanamivir has low systemic bioavailability (10 - 20%). There are no data on the serum levels of inhaled zanamivir in patients suffering from pneumonic consolidations. When a pandemic is caused by a highly pathogenic influenza virus which readily invades extrapulmonary tissues, effective antiviral agents with high systemic bioavailability will be more useful for treatment purpose.

The recommended regimens described below are based on experience of treating influenza infections due to the usual human strains. Assuming that the efficacy of the treatment for the novel influenza strain in a pandemic situation is not too different, the Scientific Committee on Emerging and Zoonotic Diseases of the Centre for Health Protection recommends the following for doctors' reference.

1. For Patient Treatment

At Serious and/or Emergency Response Levels, when there are confirmed or strongly suspected local cases of human avian influenza, antiviral agents would be useful for treatment.

Oseltamivir should be administered as soon as possible, preferably within 48 hours after the onset of symptoms, to achieve maximum efficacy. In contrast to uncomplicated seasonal influenza, evidence showed that influenza A (H5N1) continues to replicate for a prolonged period. Therefore, Oseltamivir treatment is also warranted for patients with influenza A (H5N1) virus infection presenting to clinical care at a later stage of illness.

It should be taken with meals to reduce gastrointestinal side effects. It is available in 75 mg capsule and 12 mg/ml oral suspension. The recommended dosage for the treatment of seasonal influenza in adults and adolescents aged 13 years and above is 150 mg per day (given as 75 mg bd) for 5 days. According to WHO guidelines published in August 2007, modified regimens of Oseltamivir treatment, including a two-fold higher dosage, longer duration and possibly combination therapy with amantadine or rimantadine (in countries where A (H5N1) viruses are likely to be susceptible to adamantanes) may be considered on a case by case basis, especially in patients with pneumonia or progressive disease. Continued fever and clinical deterioration may suggest ongoing viral replication. If no clinical improvement has been observed after a standard 5-day course, the Oseltamivir therapy may be extended for a further 5 days.

Adults & adolescents 13 years of age or above **75 mg BD x 5 days (standard regimen)**

Children between 1 and 12 years of age

The following unit dosing is recommended to minimize the emergence of resistance due to under dosing.

<=15 kg	30 mg BD x 5 days
>15 - 23 kg	45 mg BD x 5 days
>23 - 40kg	60 mg BD x 5 days
> 40kg	75 mg BD x 5 days

The dispensing syringe for oral suspension is calibrated with graduations of 30, 45 and 60 mg. If a patient cannot tolerate 75 mg capsules, the dosage may be dispensed as oral suspension using a 30 + 45 mg combination.

Infants

The safety and efficacy of oseltamivir as a therapeutic agent for infants (<12 months of age) have not been established. However, the drug may still be considered for treatment (off label use) in this age group when the benefits are expected to outweigh the risks. Dosages should be adjusted according to the patients' body weight. (Recommendation: 2 mg/kg BD)

Zanamivir might be considered as an alternative treatment agent for patients who are able to use the diskhaler device according to the WHO rapid advice guidelines on treatment but the recommendation is classified as weak by the WHO and based on very low quality evidence. Limited information is available about the utility of other antivirals in the treatment of A (H5N1) disease. Topically applied (inhaled) Zanamivir has not been studied in human A (H5N1) illness. Adequacy of orally inhaled Zanamivir delivery in patients with serious lower respiratory tract or extra-pulmonary disease is a major concern.

Amantadine or **rimantadine** alone should not be used as a first-line treatment for patients with confirmed or strongly suspected H5N1 infection (WHO strong recommendation) except when neuraminidase inhibitors are not available for treatment and local data show that the H5N1 virus is known or likely to be susceptible (WHO weak recommendation).

2. For Post-exposure Prophylaxis of Contacts

The WHO has recently stratified exposure risk to facilitate decisions to initiate antiviral chemoprophylaxis:

- (a) High risk exposure - Household or close family contact (oseltamivir should be administered).
- (b) Moderate risk exposure - Involved in e.g. intubation, nebulization, tracheal suction (oseltamivir might be administered).
- (c) Low risk exposure - Healthcare workers not in close contact (unprotected distance > 1 meter or having no direct contact), oseltamivir should probably not be administered).

At the Serious and/or Emergency Response Levels, individuals will present with histories of contact with or exposure to confirmed human cases. Post-exposure prophylaxis of these contacts, which may include healthcare workers and community contacts, will be provided by the public health authority to achieve as far as is feasible containment of the spread of the infection.

In practice, **Oseltamivir** 75 mg is to be taken **once daily** with meals as prophylaxis to high risk (WHO strong recommendation) and moderate risk contacts (WHO weak recommendation) as soon as possible after exposure status is known, if the last contact with the patients falls within 7 days. Oseltamivir should be used continuously for 7-10 days after the last known exposure.

Adults & adolescents 13 years of age or above 75mg QD x 7-10 days after last known exposure

Children 1-13 years old

Oseltamivir has been licensed for use as prophylaxis for this age group in Hong Kong. The dosage should be adjusted according to body weight.

<u>Body weight</u>	<u>Duration after last known exposure</u>
<=15 kg	30 mg QD x 7-10 days
>15 - 23 kg	45 mg QD x 7-10 days
>23 - 40kg	60 mg QD x 7-10 days
> 40kg	75 mg QD x 7-10 days

Note: Administration of chemoprophylaxis should begin as soon as possible after exposure. The duration of post-exposure prophylaxis may be extended to 14 days if continuous spread in the source environment occurs.

3. For Pre-exposure Prophylaxis

(a) **Healthcare Workers with at least Moderate Risk Exposure** (i.e. in close contact with strongly suspected or confirmed H5N1 patients)

At the Serious/Emergency Response Levels, health care providers and workers must enhance infection control measures including the appropriate use of personal protective equipment (PPE), so that they can provide essential medical treatment to patients towards containment of the disease. At the Emergency Response Level, pre-exposure prophylaxis for healthcare workers is an important consideration. In case availability of antiviral agents is limited, priority for antiviral use among healthcare workers is recommended in the following order: (i) early treatment, (ii) unprotected post-exposure (without adequate personal protective equipment) prophylaxis, and (iii) pre-exposure prophylaxis among healthcare workers directly involved in management of patients suffering from pandemic influenza.

Oseltamivir 75 mg is to be taken **once daily** with meals as prophylaxis to this moderate risk exposure group during the Emergency Response phase of pandemic influenza and be used continuously for 7-10 days after the last known exposure (WHO weak recommendation). The duration of prophylaxis will be determined by the intensity and duration of exposure. Safety and efficacy of prophylactic oseltamivir administration have been demonstrated for up to 8 weeks of continued use.

Zanamivir might be considered as an alternative prophylactic anti-viral for healthcare workers without pre-existing airway diseases, and be used continuously for 7-10 days after the last known exposure (WHO weak recommendation). It is administered using a diskhaler by oral inhalation and age-related adjustment is not required. Two inhalations (2 inhalations of 5 mg zanamivir in each inhalation) should be given **once daily**. The duration of prophylaxis will be determined by the intensity and duration of exposure. Safety and efficacy of prophylactic zanamivir administration have been demonstrated for up to 4 weeks of continued use.

Caution: Because of the risk of bronchospasm, persons with asthma and COPD are advised to have a fast-acting inhaled bronchodilator available. Stop zanamivir if difficulty in breathing occurs.

(b) **Essential Service Providers**

Pre-exposure prophylaxis for essential service providers may be considered at the Emergency Response Level subject to the overall availability of antiviral agents. If antiviral agents are sufficiently available, **Oseltamivir** 75 mg should be given **once daily** with meals during the Emergency Response phase of pandemic influenza, the duration of prophylaxis having regard to the

safety and efficacy of prophylactic oseltamivir administration which have been demonstrated for up to 8 weeks of continued use.

(c) Workers involved in Culling Operation

Culling operations would only be called for in the Serious Response Level or above. The operation will be centrally coordinated by the Government and prophylaxis will be given to the workers by the public health authority.

Oseltamivir 75mg will be given **once daily** with meals to cullers throughout the operation and continued for 7-10 days after the last day of exposure.

Role of M2 Blockers (Amantadine / Rimantadine)

In the event that the pandemic strain of influenza virus is sensitive to M2 blockers such as amantadine, there may be a potential role for these drugs in high or moderate risk exposure groups if neuraminidase inhibitors are not available (WHO weak recommendation) as (i) post exposure prophylaxis for community-contacts, and (ii) pre-exposure prophylaxis for essential service providers. Administration of chemoprophylaxis should begin as soon as possible after exposure status is known and continue for 7-10 days after the last known exposure. The recommended dosages are as follows:

Amantadine	Age				
	1-6 yrs	7-9 yrs	10-12	13-64 yrs	>=65 yrs
Prophylaxis for influenza A	5mg/kg body wt/ day up to 150 mg in two divided doses	5mg/kg body wt/ day up to 150 mg in two divided doses	100 mg bd	100 mg bd	<=100 mg/day

Amantadine has been used safely in seasonal influenza A as chemoprophylaxis for as long as 6 weeks. The duration of post-exposure prophylaxis may be extended to 14 days if continuous spread in the source environment occurs.

Caution: Amantadine should be avoided in patients with seizure disorders or receiving neuropsychiatric treatment unless benefits outweigh potential risks.

It is important to note in all situations requiring administration of amantadine that the dosage should be adjusted according to recipients' age,

body weight and pre-existing medical illness (e.g. renal impairment). Drug information provided by the manufacturer should always be referred to.

The current recommendations are based on best available information and are subject to updating in the light of scientific evidence. The updated versions will be available at <http://www.chp.gov.hk/>

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