

The use of antiviral drugs for influenza: Recommended guidelines for practitioners

***A joint statement with the Association of Medical Microbiology
and Infectious Disease Canada***



SUMMARY

Each year, there is a significant burden of illness due to influenza A viruses, and occasionally strains of influenza B. While acknowledging the importance of immunization against influenza, it was thought appropriate to develop contemporary guidelines on the use of antiviral drugs for chemoprophylaxis and therapy of influenza illness, which are appropriate for the management of influenza in interpandemic periods. The present article is an abbreviated version of a full statement outlining recommendations that are the result of a joint effort supported by the Canadian Paediatric Society (CPS) and the Association of Medical Microbiology and Infectious Disease (AMMI) Canada. The guidelines reflect the current state of knowledge regarding the use of influenza antiviral drugs, and will be modified as additional research data become available. Additional information on strategies to prevent influenza illness in the interpandemic period may be obtained from the annual statement by the National Advisory Committee on Immunization.

RECOMMENDATIONS

With respect to the role of antiviral drugs for the treatment or prevention of influenza infection, the CPS and AMMI Canada recommend the following:

I. Drugs for the prevention and treatment of influenza

- A. Amantadine is approved and recommended for the prevention (evidence grade IB) and treatment (evidence grade IB) of influenza A virus infection in individuals one year of age or older, but only if the strain in circulation is susceptible to amantadine.
- B. Zanamivir is approved and recommended for the treatment of influenza A and B virus infection in individuals older than seven years of age (evidence grade IA). It may be used off-label for the prevention of influenza A and B virus infection in individuals five years of age or older (evidence grade IA).
- C. Oseltamivir is approved for the prevention of influenza A and B virus infection in individuals 13 years of age or older (evidence grade IA). The drug is also approved for the treatment of influenza A and B virus infection in individuals one year of age or older (evidence grade IA). It may be used off-label for the prevention of influenza A and B virus infection in individuals one year of age or older (evidence grade IA). Based on current evidence, it should not be used in infants younger than one year of age (evidence grade IIID).
- D. Because there are no antivirals currently approved for use in infants younger than one year of age, the CPS and AMMI Canada strongly encourage research on this issue.

II. Prevention of influenza

Antiviral drugs are recommended as a substitute for immunization to prevent influenza in the situations outlined below. These strategies should be accompanied by awareness and the appropriate education to enable early access to antivirals.

- A. When a vaccine is not available that is effective against a strain(s) of influenza circulating in the community, and exposure and the risk of illness is considered to persist throughout the outbreak, amantadine, zanamivir or oseltamivir may be administered until a vaccine becomes available or the outbreak has subsided (applies to 'seasonal prophylaxis') (evidence grade IB). Current data indicate that the effect of these three drugs for seasonal prophylaxis is not uniform across all age groups. Because no comparative trials have been conducted to support the selection of one agent from among the group, the choice of drug to administer will depend on other factors, such as virus susceptibility (eg, influenza A H5N1 is susceptible to neuraminidase inhibitors but not M2 inhibitors), ease of dosing (zanamivir = oseltamivir >> amantadine), tolerance (zanamivir > oseltamivir >> amantadine) and cost (amantadine << zanamivir = oseltamivir). Zanamivir is not easy to administer in young children or adults who are incapable of operating the inhalation device. Prophylaxis may be continued until the outbreak has subsided (usually six to eight weeks). Alternatively, it may be discontinued if a vaccine has become available or if it is suspected that the individual has experienced (mild) influenza attenuated by chemoprophylaxis or has been shown to have been infected, based on laboratory results demonstrating the occurrence of subclinical influenza as demonstrated by culture, rapid antigen testing, or polymerase chain reaction of respiratory secretions.
- B. When the vaccine is contraindicated, seasonal chemoprophylaxis as discussed in section IIA may be considered (evidence grade IIIC). For example, when a high-risk individual has immediate-type hypersensitivity to egg protein, traces of which may be present in vaccines prepared in embryonated chicken eggs, or to some other substance in the vaccine formulation, chemoprophylaxis is recommended. The choice of drug will require consideration, at least, of the factors listed in section IIA. The duration of prophylaxis may be as described in section IIA.
- C. When an immediate protective effect is required, chemoprophylaxis has been shown to be effective and

well tolerated. Such a need may exist in the following situations:

- i) An outbreak is diagnosed in a closed institutional setting; or
- ii) In the family setting; or
- iii) When influenza is causing illness in the community even as vaccine is being administered.

An outbreak is diagnosed in a closed institutional setting:

Prophylaxis in a closed institutional setting may be initiated when an outbreak is diagnosed (evidence grade IIB). An outbreak may be diagnosed if at least two residents develop acute influenza-like illness within 72 h of each other and have laboratory-proven influenza illness confirming the transmission of influenza. Amantadine, zanamivir and oseltamivir have all been used for outbreak control in nursing homes. Zanamivir and oseltamivir may be preferable to amantadine (evidence grade IB).

Usually, chemoprophylaxis for outbreak control in an institution is administered for at least 10 days. Prophylaxis may be discontinued if eight or more days have elapsed since the onset of the last case of influenza in the unit. If new cases continue to appear, then prophylaxis will, by corollary, need to be continued so that this strategy could become, in effect, seasonal prophylaxis.

In the family setting: When influenza occurs in the family setting, postexposure chemoprophylaxis in unaffected members should be considered to reduce illness in the family (evidence grade IA).

Unaffected family members should be started on chemoprophylaxis as soon as possible after recognition of influenza-like illness in the index case. Amantadine, zanamivir and oseltamivir are all recommended for postexposure prophylaxis when the virus is susceptible. The duration of prophylaxis is usually seven to 10 days.

The index case may be treated with the recommended five-day course of zanamivir or oseltamivir, but not amantadine. Treatment of the index case with amantadine has resulted in failure of amantadine prophylaxis in other family members due to the rapid development of amantadine-resistant mutants in the treated index case. If amantadine is the only option available for the index case in a household, do not use it for prophylaxis for other family members.

When influenza is causing illness in the community even as vaccine is being administered: Chemoprophylaxis may be used to protect individuals until vaccine-induced immunity develops (evidence grade IIIB). Chemoprophylaxis should be continued for two weeks after appropriate vaccination (one or two doses). When vaccine is coadministered, which is expected to protect against a circulating strain causing illness in the community, chemoprophylaxis should be continued until vaccine-induced immunity is likely to have developed. The time for vaccine-induced immunity to develop may be seven to 10 days if the virus strains in the vaccine are drift variants of strains that have been causing the illness in one or more previous years, such that some heterologous immunity is likely to exist that can be boosted by the current vaccine.

Where the vaccine contains a virus arising as a result of antigenic shift (ie, a pandemic strain), vaccine-induced immunity may require two or more doses of the vaccine. Chemoprophylaxis will need to be continued until it is probable that immunity has

developed, as demonstrated by clinical trials. This duration is most likely to be two to three weeks.

- D. When high-risk individuals have been immunized, but the vaccine strain(s) poorly matches one or both of the hemagglutinin and/or neuraminidase antigens of the circulating strain, seasonal chemoprophylaxis is recommended (evidence grade IIIB). The duration of prophylaxis is as described in section IIA.
- E. When individuals are not likely to respond to the vaccine due to an immunocompromised state due to drugs or disease, seasonal chemoprophylaxis is recommended (evidence grade IIIB). The duration of prophylaxis is as described in section IIA.

III. Treatment of influenza illness

In general, antiviral chemotherapy is recommended for individuals with severe illness and those most likely to develop complications of influenza or to die prematurely as a result. The duration of therapy is five days (longer therapy may be indicated in patients with severe immunodeficiency who remain symptomatic and virus-positive).

- A. When antiviral drugs are administered for the treatment of influenza A or B infection, it is recommended that amantadine not be prescribed because of the high probability of the emergence of resistance (evidence grade IA), with possible treatment failure (evidence grade IB) and spread to others receiving amantadine for prophylaxis (evidence grade IA).

Because there have been no studies directly comparing the relative efficacies and safety of zanamivir and oseltamivir, the selection of one drug from among these agents needs to be based on considerations such as the ability to orally inhale zanamivir or to tolerate its uncommon irritant effect on the tracheobronchial tree with resulting bronchospasm.

- B. When zanamivir or oseltamivir are administered for the treatment of influenza, they should be started as soon as possible after the onset of symptoms (evidence grade IA) and within 48 h of symptoms (see point C below).
- C. When the patient has been symptomatic for longer than 48 h, it is recommended that antiviral therapy not be prescribed unless the patient is immunocompromised and has progressive respiratory infection (evidence grade IIIC).
- D. For seriously ill patients, combination therapy with amantadine and a neuraminidase inhibitor may be considered (evidence grade IIIC).
- E. For the treatment of pregnant women ill with influenza, it is noted that none of the drugs listed above can be recommended because none have been evaluated for efficacy or safety in pregnant women or approved for administration to them (evidence grade IIIC). However, zanamivir is minimally bioavailable after oral administration. Thus, zanamivir administered by inhalation to pregnant women is unlikely to cause much fetal exposure. Hence, from the point of view of safety, it may be the drug of choice for administration to pregnant women (evidence grade IIIC).

APPENDIX
Levels of evidence and strength of recommendations*

Level of evidence	Description
I	Evidence obtained from at least one properly randomized controlled trial.
II-1	Evidence obtained from well-designed controlled trial without randomization.
II-2	Evidence obtained from well-designed cohort or case-controlled analytical studies, preferably from more than one centre or research group.
II-3	Evidence obtained from comparisons between times and places, with or without the intervention. Dramatic results in uncontrolled experiments could also be included in this category.
III	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.
Grade	Description
A	There is good evidence to recommend the clinical preventive action.
B	There is fair evidence to recommend the clinical preventive action.
C	The existing evidence is conflicting and does not allow a recommendation to be made for or against use of the clinical preventive action; however, other factors may influence decision-making.
D	There is fair evidence to recommend against the clinical preventive action.
E	There is good evidence to recommend against the clinical preventive action.
I	There is insufficient evidence to make a recommendation; however, other factors may influence decision-making.

*Data from reference 12

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For more information, please refer to the full influenza guidelines statement, which can be found in *The Canadian Journal of Infectious Diseases & Medical Microbiology* [Can J Infect Dis Med Microbiol Vol 17 No 5 September/October 2006] or online at <http://www.pulsus.com/Infdis/17_05/Pdf/Allen.pdf>

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Principal authors: Drs Upton D Allen, University of Toronto, Toronto, Ontario; Fred Y Aoki, University of Manitoba, Winnipeg, Manitoba; H Grant Stiver, University of British Columbia, Vancouver, British Columbia

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The recommendations in this statement do not indicate an exclusive course of treatment or procedure to be followed. Variations, taking into account individual circumstances, may be appropriate.