# E Planning Recommendations for the Use of Antivirals (Anti-Influenza Drugs) in Canada During a Pandemic

## Background

### General Considerations

Antivirals (anti-influenza drugs) are effective for both treatment and prophylaxis and could have a role as an adjunctive strategy to vaccination for the management of pandemic influenza. Antivirals will likely be the only virus-specific intervention during the initial pandemic response, given that vaccine is unlikely to be available for the early months of a pandemic. Protection afforded by antivirals is virtually immediate and does not interfere with the response to inactivated influenza vaccines.

Current supplies of antivirals, both within and outside of Canada, are very limited. At this time there is limited "routine" use of these drugs in Canada during annual influenza seasons; therefore providing little incentive for manufacturers to store significant amounts of these products in Canada. The issue of security of supply for a pandemic situation needs to be addressed during planning activities.

Prior to the 1997 Hong Kong avian influenza incident, antivirals were not considered as a component of the Canadian pandemic response, in light of costs and other factors. During the Hong Kong outbreak, several countries rapidly depleted global supplies of anti-influenza drugs. In light of the lessons learnt since 1997, and the licensure of new antivirals, the neuraminidase inhibitors, the Antivirals Working Group of the Pandemic Influenza Committee was formed to develop options, recommendations and guidelines for the use of antivirals.

The first "Pandemic Influenza Antiviral Drugs Supply Options" paper was developed in January 1999. This current document contains recommendations that were developed by the Antivirals Working Group in June 2000 and were updated in March 2002 and January 2003.

### Classes of Antivirals (Anti-Influenza Drugs)

Two classes of antivirals are currently available in Canada and have a role in the prevention and treatment of influenza infection: M2 ion channel inhibitors (cyclic amines) and neuraminidase inhibitors. There are important differences in pharmacokinetics, side effects and drug resistance between these two classes of antivirals. Such performance characteristics and costs should be considered in selecting the specific drugs to be used for prophylaxis or treatment.

1. **M2 Ion Channel Inhibitors (Cyclic Amines or Adamantanes)**

   M2 ion channel inhibitors interfere with the replication cycle of influenza A but are not effective against influenza B. Amantadine and rimantadine are examples of M2 ion channel inhibitors. Currently, only amantadine is licensed in Canada. Amantadine is approved in Canada for both prophylaxis and treatment of infection due to influenza A. Amantadine is approximately 70-90% effective in preventing illness from influenza A infection.

   When administered within 2 days of illness onset, it can reduce the duration of uncomplicated influenza A illness by approximately one day but it has not been shown to reduce the complications of influenza. Resistance to amantadine has been shown to develop rapidly when this drug is used for treatment purposes.

The Antivirals Working Group will be investigating the potential role of rimantadine for both prophylaxis and treatment during a pandemic, including whether special permission could be obtained to use this drug if it is not licensed in Canada at the time of the pandemic.

2. **Neuraminidase Inhibitors**

   Zanamivir and oseltamivir are examples of neuraminidase inhibitors. These drugs interfere with replication of both influenza A and B viruses in three ways: (1) they interfere with the release of virus from infected cells, (2) they cause the aggregation of virus, and (3) they may improve the inactivation of virus by respiratory mucous secretions. The drugs are well tolerated and have been used effectively for the prophylaxis and treatment of influenza A and B infections. When administered within 2 days of illness onset, zanamivir and oseltamivir can reduce the duration of uncomplicated influenza A and B illness by approximately 1 day. Further evidence is needed on their effectiveness in reducing complications of influenza. Recent community studies suggest that both drugs are similarly effective in preventing febrile laboratory-confirmed influenza illness (efficacy: zanamivir 84%; oseltamivir 82%). Both drugs were licensed in Canada in 1999 for the treatment of infection due to either influenza A or B virus. Since December 2003, oseltamivir has been approved for influenza prophylaxis in Canada. Zanamivr is not licensed for prophylaxis. Current evidence suggests that the development of resistance during treatment of influenza is less likely with neuraminidase inhibitors than with amantadine. Neuraminidase inhibitors are much more expensive than amantadine at this time.

## Recommendations of the Antivirals Working Group

The following is a list of recommendations that may assist with planning of the antivirals component of a pandemic influenza response plan.

1. Endorse the goal of influenza pandemic planning as follows:

   *First, to minimize serious illness and overall deaths, and second to minimize societal disruption among Canadians as a result of an influenza pandemic*

2. Vaccines, if and when available, should be considered the first line for prevention of pandemic influenza.
3. Security of supply for antiviral drugs should be considered as part of planning in the pre-pandemic period.
4. The F/P/T governments should control the supply and distribution of available anti-influenza drugs, to the end user, during a pandemic.
5. Antivirals should only be used in a community when the pandemic influenza virus is detected in the community. The trigger for starting the use of antivirals in the community will be decided at the local level in conjunction with the province/territory and will be dependent on availability.
6. During a pandemic, the amount of amantadine required by persons with Parkinson's disease should be reserved for this indication.

7. During a pandemic, the antivirals strategy should utilize all anti-influenza drugs available to Canadians. Either M2 ion channel inhibitors (e.g., amantadine) or neuraminidase inhibitors (e.g., oseltamivir) can be used for prophylaxis but only neuraminidase inhibitors should be used for treatment.
8. The following priority groups for the use of anti-influenza drugs in times of short supply should be used for planning purposes during the inter-pandemic period.

> The following groups, in descending order of priority, are offered as planning guidance but will need to be re-examined at the time of a pandemic alert when epidemiologic data about the pandemic virus is available.
>
> 1. Treatment of persons hospitalized for influenza
> 2. Treatment of ill health care and emergency services workers
> 3. Treatment of ill high-risk persons* in the community
> 4. Prophylaxis of health care workers
> 5. Control outbreaks in high-risk residents of institutions (nursing homes and other chronic care facilities)
> 6. Prophylaxis of essential service workers
> 7. Prophylaxis of high-risk persons* hospitalized for illnesses other than influenza
> 8. Prophylaxis of high-risk persons* in the community
>
> **Note: during a pandemic the definition of high-risk persons may change based on epidemiologic evidence.*
>
> The mass prophylaxis of children to control a pandemic is currently not recommended.

9. The susceptibility of circulating influenza strains to available antivirals should be monitored.
10. Given the rapidly changing scientific evidence, recommendations and options for treatment and prophylaxis with antivirals should be regularly reviewed.

## Rationales for Specific Recommendations

### Rationale for addressing supply issues (recommendation #3)

Vaccination with an effective vaccine is the primary public health intervention during a pandemic. However, vaccine production requires the acquisition of the seed virus and therefore cannot be initiated until the pandemic virus is already infecting humans. Once a suitable vaccine seed strain is available to manufacturers, it is anticipated that vaccine production will require at least 3 to 4 months and even then the availability of doses will be staggered and limited. Furthermore each individual may need to receive two doses of vaccine to be protected.

At this time antiviral drugs are the only specific medical intervention targeting influenza that will potentially be available during the initial pandemic response. Antiviral drugs can be used to prevent influenza and, unlike vaccines, can also be used to treat cases that are identified early in their illness. The strategic use of these drugs in identified priority groups, therefore, will

be critical to achieving the goal of minimizing serious illness and overall deaths, and secondly minimizing societal disruption among Canadians as a result of an influenza pandemic.

Current supplies of antivirals in Canada (and outside of Canada) are very limited and surge capacity is negligible. In 1997 when a strain of influenza that was believed to have pandemic potential was identified in Hong Kong, antiviral drugs rapidly became virtually unavailable for purchase world-wide.

### Rationale for governmental control of anti-influenza drugs during a pandemic (recommendation #4)

During a pandemic, governmental control of anti-influenza drugs will be essential to ensure equitable distribution and appropriate use of these drugs in limited supply. Without strict control over the use of these drugs, it is possible that amantadine will be used for treatment purposes, further increasing the risk of drug resistance. In addition, governmental control may reduce wastage including the use of these drugs on cases presenting more than 48 hours after onset of illness.

### Rationale for the roles of amantadine and neuraminidase inhibitors (recommendation #7)

Neuraminidase inhibitors are preferred for the treatment of pandemic influenza since the emergence of drug resistance during treatment is less likely to occur as opposed to amantadine where emergence of resistance occurs rapidly. In addition, neuraminidase inhibitors are associated with fewer side effects than amantadine. Neuraminidase inhibitors have been shown to be effective at preventing influenza and oseltamivir is now licensed for prophylaxis. These drugs will likely be better tolerated than amantadine, facilitating compliance, and will need to be available for this purpose should the circulating virus become resistant to amantadine.

### Rationale for priority groups (recommendation #8)

Priority groups have to be in keeping with the overall goal of reducing morbidity, mortality and secondly to reduce societal disruption. Since it will not be possible to determine a "risk level" for individuals until the pandemic virus has started causing illness in a population, these groups were identified based on past experience with severe influenza seasons and historic accounts of past pandemics. It is important to recognize that during a pandemic the definition of "high-risk persons" will be based on the epidemiologic data available at that time.

What is known is that in order to ensure an optimal pandemic response it will be imperative to provide as much protection as possible against influenza to health care workers and other essential emergency service workers. Since onset of the pandemic in Canada is expected to precede the availability of an effective vaccine, antiviral drugs represent one method of preventing infection until these workers can achieve protection through immunization. Typically immunity is assumed to have been conferred 2 weeks after influenza immunization; however, this may differ for the pandemic vaccine and it may be necessary to give two doses of vaccine to each individual before immunity is assured.

- ***Priority group 1***: To be consistent with the goal of reducing morbidity and mortality and considering the optimal use of these drugs in relation to onset of illness, those who are hospitalized within the first 48 hours of onset of illness should be highest priority for treatment.

- ***Priority group 2***: Considering the essential role that health care providers and emergency service workers will have in the pandemic response, influenza cases in these groups that are identified within the first 48 hours of onset of illness should be high priority for treatment.
- ***Priority group 3***: Persons with underlying heart and lung conditions or those who are immunocompromised, who present to ambulatory settings within 48 hours of onset of symptoms (before they get sick enough to be hospitalized) will also be considered high priority for treatment since they are at high risk for complications.
- ***Priority group 4***: Until an effective vaccine becomes available or during the interval between administration of an effective vaccine (or vaccine series) and induction of immunity, antivirals should be provided for HCWs, including public health staff, since their continuing functions are essential to the pandemic response plan and to the care of patients with other conditions.
- ***Priority group 5***: Reducing the impact of influenza outbreaks in institutions where the most vulnerable persons reside will contribute to the objectives of reducing morbidity and mortality and reduce health care demands.
- ***Priority group 6***: Emergency service workers (ESWs) will be important for maintaining the pandemic response, key community services and national defence. Prophylaxis of this group will minimise societal disruption. Each P/T should consider the list below as the "main" list and make additions as necessary based on their own unique needs and priorities for ESWs.
  - police, fire, correctional services
  - armed forces
  - key emergency response decision makers (e.g., elected officials, essential government workers and disaster services personnel)
  - funeral services
  - utilities (water, gas, electricity)
  - telecommunications
  - public transport and transportation of essential goods (e.g., food)
- ***Priority group 7***: High-risk persons hospitalized for conditions other than influenza related complications will be at risk for acquiring influenza while in hospital, given the large numbers of patients and hospital staff who may be infected during a pandemic. Influenza may result in influenza-related complications in such patients, an increase in severity of their underlying illness, prolonged hospital stay and death. Prophylaxis of this group will contribute to the objectives of reducing morbidity and mortality and reduce health care demands.
- ***Priority group 8***: Prophylaxis of high-risk persons who have not received influenza vaccine or for whom the effectiveness of the vaccine may be reduced is a current recommendation of NACI. This group is likely to experience severe illness during a pandemic and prophylaxis with anti-influenza drugs should be considered if an effective vaccine is not available. Prophylaxis of this group will contribute to the objectives of reducing morbidity and mortality and reduce health care demands.

## Outstanding Issues

The Antivirals working group has identified several outstanding issues. Some of these issues will be addressed through consultation with the other pandemic working groups, while others require research and consultation with the drug manufacturers.

There are several antiviral supply issues including:

- security of supply;
- bulk purchasing;
- control of inventory;
- possibility of domestic production (explore possibility for manufacturing of amantadine raw products in Canada);
- sequestering available supply for public health use and Parkinson's disease patients (need to know the amount of drug used by Parkinson's disease patients);
- buying more drugs at time of pandemic (likely availability and should this be pursued if drugs available)

These supply issues will be further examined by a sub-committee of the Antivirals working group.

All antivirals guidelines should be validated during the pre-pandemic period. The recommendations regarding the use of antivirals in short supply for targeted groups requires further consultation including ethics and public opinion. More specific definition of high-risk groups is also necessary.

Further data on neuraminidase inhibitors efficacy as prophylactic agents and evidence that they have a greater efficacy than amantadine for prophylaxis are required. As well, the reduction in cost of these drugs before they can be considered for prophylaxis.

While there has been no experience with the use of any of the antiviral drugs for pandemic influenza control, research during the inter-pandemic period is providing reasonable robust evidence upon which the pandemic antiviral drug strategy can be developed.

Communication with health care professionals and the public on the appropriate use of antivirals is needed during the pre-pandemic and pandemic periods. Clinical guidelines on the use of antivirals in the hospital and the community will be developed as part of the clinical care guidelines. Guidelines for delivery/administration of antivirals, the monitoring of drug distribution, uptake, and wastage, including antiviral security still needs to be addressed.

Communication materials for health care providers and the public on the appropriate use of antiviral drugs should be developed and circulated during the pre-pandemic period

Research during the pre-pandemic period and protocols for studies at the time of a pandemic are required to further evaluate the outcomes of specific antiviral prophylaxis and treatment strategies.

Research issues include:

- The outcomes of specific interventions and the value of antiviral prophylaxis versus treatment.
- The benefit of antivirals in reducing complications of influenza and death, especially in high-risk persons and in those with severe influenza illness (e.g., severe viral pneumonitis).

- The efficacy and safety of antivirals for the treatment and prophylaxis of children and select high-risk groups such as infants, pregnant women, immunocompromised persons, elderly with underlying disease.
- The minimum effective dose and duration for prophylaxis or treatment of complicated and uncomplicated influenza.
- The use of combination therapy in different populations.
- The mechanism for resistance to both classes of antivirals and assessment of the biological consequences (infectiousness, virulence) of resistance.
- The use of laboratory testing including rapid diagnostics to assist in decision making for use of antivirals.
- The effect of antiviral administration on the response to live attenuated influenza vaccines.
- The shelf life of antivirals and raw materials, beyond those estimated by manufacturer.