

## The Use of Antivirals in Interior Health

### Executive Summary

In the event of an influenza pandemic, measures available to mitigate the spread of the virus and treat those who are infected will be limited. Because the severity of the next pandemic will not be known until the virus emerges and is capable of human-to-human transmission, traditional influenza response measures, including vaccination, will not be available until much later in the course of the pandemic. This lag in vaccine availability remains to be the case, even as health experts around the world argue that the currently-circulating avian influenza H5N1 has the greatest potential to become the next pandemic influenza strain.

However, given the effectiveness of neuraminidase inhibitor antivirals such as oseltamivir (Tamiflu) to treat patients infected H5N1, the World Health Organization (WHO) continues to recommend that governments stockpile these drugs for the purposes of treating their infected populations during the outset of a pandemic. Countries around the world have heeded this call, in addition to many private sector organizations, which are now creating their own stockpiles for both treatment and prophylaxis purposes.

A key element to Interior Health's PIPP is a draft framework for antiviral receipt and distribution, which follows from a clear set of guiding principles, planning assumptions, and the current plans in place at the provincial and federal levels. While this draft planning document will likely be updated both prior to and during an influenza pandemic, current planning considerations for antiviral use within Interior Health include the following elements:

- Following current federal recommendations (as of December 2006), Interior Health is planning for the use of antivirals during an influenza pandemic **for treatment purposes only.**
- Interior Health is not planning on creating a health authority-specific stockpile of antivirals. Instead, the IH planning framework will rely on the national and provincial stockpile, which will be distributed to Interior Health as per its receiving requirements.
- As outlined in the current federal recommendations (as of December 2006), Interior Health recognizes the fact that specific references to “priority groups” have been removed since they no longer are consistent with the decisions made to date regarding the use of Canada's stockpile.
- On the basis of these updated federal guidelines, and the proposed receiving strategy from the provincial government, Interior Health will plan for three distribution stages during an influenza pandemic:
  - **Stage A**, which will consider dispensing antivirals to those patients and critical service personnel, who meet the clinical criteria, and who are admitted to receive some level of site-based care (traditional or alternative) during the pandemic;
  - **Stage B**, which will consider dispensing antivirals to those patients, who meet the clinical criteria, and who are admitted to receive some level of site-based care (traditional or alternative) during the pandemic OR to those patients, who meet the clinical criteria, and who visit an assessment centre to be screened for infection; and,

- **Stage C**, which will consider the mass distribution of antivirals to treat all individuals, who meet the clinical criteria, and who are clinically ill (35% of the total population).

**Please note that Stage C** will only be considered from a theoretical perspective in this draft of the PIPP, due to the uncertainty regarding provincial planning assumptions, the size of the provincial stockpile, Interior Health's allocation of the stockpile, its own internal resources available at the time, and related federal/provincial/territorial planning considerations (e.g., current F/P/T discussions as to the national strategy for prophylaxis).

## General Planning Assumptions for the Interior Health Antiviral Distribution Framework

Interior Health's planning assumes a severe pandemic event based on a 35% cumulative attack rate over the course of the first pandemic wave. As a result, Interior Health's estimated impacts exceed provincial and federal projections for several reasons, including:

- The Canadian Pandemic Influenza Plan for the Health Sector (2006) states that, "During 'normal' influenza epidemics, which occur almost every winter, an average of 5 to 20 per cent of the population becomes ill, but as high as 30 to 50 per cent of the population may become ill during severe influenza A epidemics." As a result, Interior Health is planning for an influenza pandemic that causes high rates of infection and illness in the first pandemic wave to prepare our staff and facilities for a much higher patient-load.
- Interior Health is also keenly aware of the impacts caused by the Spanish Flu pandemic of 1918-19. If similar rates of illness and mortality occur during the next influenza pandemic, **local impacts will exceed the planning projections provided by federal and provincial governments**. Therefore, Interior Health is planning for a more severe pandemic event to ensure heightened levels of preparedness are in place.
- Regarding federal planning assumptions, the CPIP 2006 states, "...**These estimates may over or under-estimate the potential impact in Canada.**" Therefore, Interior Health has determined it is prudent to plan for the worst and be prepared to respond to either a moderate or severe pandemic scenario.
- Therefore, the numbers estimated for both Stages 1 and 2 reflect this assumption.
- As of 31 March 2008, the size and composition of the antiviral stockpile in British Columbia is not known.
- As a result, Interior Health is not aware of the size of this stockpile to be allocated to the Health Authority following the declaration of a pandemic.

### Human Impact:

- The global death toll could range between 20 to over 100 million. The federal government conservatively estimates that Canada will face between 11,000 and 58,000 deaths.
- Interior Health estimates that during a severe pandemic:
  - More than 130,000 residents will seek some form of outpatient care.
  - Over 3,000 will require hospitalization (either traditional or alternative).
  - Approximately 800 people could die within the first 6-8 weeks.

### Timeframe of a Pandemic:

- Global public health officials contend that a severe influenza pandemic could last anywhere between 12 to 18 months.

- A pandemic usually spreads in two or more waves, either in the same year or in successive influenza seasons. A second wave may occur within three to nine months of the initial outbreak wave, and may cause more serious illnesses and deaths than the first.
- In any locality, the length of each wave is likely to be six to 12 weeks. However, Interior Health is planning for each pandemic wave to last approximately **eight weeks**.
- As Interior Health is planning for a “worst-case” scenario, the above-mentioned estimates are considered occurring entirely in the **first wave**.

**Groups to be Affected:**

- All ages will be affected, but children and otherwise fit adults could be at relatively greater risk, particularly should elderly people have some residual immunity from exposure to a similar virus earlier in their lifetime.

## General Antiviral Distribution Guidelines within Interior Health

### Receiving Antiviral Stockpile from BCCDC

Interior Health is currently in the process of ascertaining the status and system for the delivery of antivirals from the provincial stockpile to the health authority. It is anticipated that receipt of the Interior Health allocation of antivirals from the Ministry of Health will take place via the distribution from the BC Centre for Disease Control (BCCDC). Moreover, distribution will take place after a declaration of a pandemic (i.e., WHO, PHAC, BC Ministry of Health). A formal agreement between BCCDC and Interior Health's Logistics and Support Services will be required to confirm the central location of receipt of the antivirals within Interior Health, and the shipping requirements from BCCDC storage facilities.

Once received, Interior Health's Pharmacy Department will be responsible for the management and oversight of the stockpile. Any and all additional supplies received from the province during a pandemic would be stored at the same location. However, as the dispensing of antivirals may take place in both acute care and community program facilities, Health Services and Public Health leaders will also work closely with Pharmacy regarding the formalization and operational elements of this strategy.

### Distribution of Antivirals throughout Interior Health

From this central point of distribution, and through the use of its system of Emergency Operations Centres, Interior Health will be responsible for the distribution of the antivirals to its various facilities and communities. Again, the focus of this strategy will be on the treatment of patients and critical resource personnel who meet the clinical criteria during an influenza pandemic.

Should **Stage A** be activated, Interior Health will distribute the necessary stockpiles to each acute care site in the respective communities for the dispensing of antivirals to patients requiring site-based care. Acute care facilities and their Health Services Emergency Operations Centres will then be responsible for ensuring adequate portions of the site-based supplies are distributed to all activated alternative care sites (as applicable). Specific distribution plans between the central storage facility within IH and acute care sites will follow current processes and practices, as feasible, during the pandemic. However, antiviral-specific operating procedures will have to be developed following the confirmation of distribution processes from BCCDC to Interior Health. These plans will be developed in collaboration between the Interior Health EOC Security Officer and site-specific Health Services EOC leaders (e.g., Incident Commander, Pharmacy Manager, Security Officer, etc.).

Should **Stage B** be activated, and antiviral stockpiles allow, Interior Health will distribute the necessary stockpiles to each acute care site in the respective communities for dispensing to patients requiring site-based care, in addition to assessment centres located within the various communities (as applicable). Acute care facilities and their Health Services Emergency Operations Centres will then be responsible for ensuring adequate portions of the site-based supplies are distributed to all activated alternative care sites and assessment centres. However, novel distribution strategies, and collaborative engagements with municipal stakeholders (e.g., Emergency Planners, Police Departments), will be required to ensure the safe, secure, and efficient distribution of antivirals to assessment centres in the community.

Should **Stage C** be activated (when completed, and as stockpiles allow), Interior Health will utilize multiple points of distribution across the health authority to ensure the mass treatment of all clinically ill people (who meet the clinical criteria) can take place in an efficient and organized fashion. Formal protocols and guidelines for **Stage C** will be developed in the near future, pending additional information and guidance on the part of the Ministry of Health's planning considerations and F/P/T discussions regarding the updated national antiviral strategy.

## Proposed Patient Flow and Antiviral Dispensing Process

During an influenza pandemic, Interior Health will activate one of two stages for the distribution of antivirals to patients in the community who meet the clinical criteria and who present at either an acute care facility or assessment centre.

**Stage A** involves a fairly straightforward process of the following steps:

- Receipt of antiviral stockpile from the province, via BCCDC, and to a central storage location within IH (TBD).
- Based on the community planning estimates, the stockpile will then be divided and distributed internally within Interior Health to all acute care facilities for dispensing to patients receiving site-based care.
- Upon receipt at the acute care site, and under the HSEOC structure, the Pharmacy Unit Leader will be the site representative responsible for the stockpile and internal distribution at the facility.
- Site-based and current dispensing protocols will likely be followed when **Stage A** is activated, with pandemic-specific revisions as required.

Option-specific storage and security considerations are outlined in the next section.

**Stage B**, however, will require additional logistical and human resources support, as antivirals may be distributed both at acute care facilities and at assessment centres established within Interior Health communities (i.e., likely off-site of acute care facilities). Upon distribution to acute care facilities and assessment centres (option-specific storage and security considerations are outlined in the next section), antiviral distribution will become part of the alternative care site model through the use of assessment centres and frontline screening.

Antiviral distribution under **Stage B** will include the following elements:

- Suspected cases of pandemic influenza will be encouraged through public education and communications campaigns prior to the declaration of a pandemic to self-screen and visit local assessment centres if they feel unwell and have symptoms of an influenza-like illness.
- Suspected cases will arrive at assessment centres and be greeted by a staff member who will provide them with information regarding the site and screening process, along with personal protective equipment.
- The site screener will then take a basic fever test of the suspected case to complete an initial assessment and discern whether or not the patient requires basic self-care materials and can be discharged, or if they require registration and a secondary assessment.
- Patients requiring registration will proceed into the facility's designated registration area where they will wait for an on-site triage nurse to provide them with the secondary assessment. Once this has been completed, and if the patient meets the clinical criteria, they could be provided with a treatment course of antivirals. At this point, the patient will then be:
  - Discharged home with their antivirals, instructions for taking their antivirals, and self-care materials; or,
  - Triage to an alternative care site for further observation.

*NOTE: In some cases, a severe case of pandemic influenza will immediately be triaged to the transport/resuscitation area of the assessment centre for transfer to the community's acute care facility. Antiviral distribution will likely occur on-site for these cases. However, length of time must be considered as rapid transport of the patient will be of the essence.*

The distribution elements of **Stage C** will be developed over the course of future planning phases within Interior Health.

## General Storage and Security Considerations

Storage and security considerations related to the antiviral stockpile in Interior Health will be extremely important, both prior to and during the next influenza pandemic. Interior Health recommends that the provincial Ministry of Health ensure its allocation of antivirals is distributed from the BC Centre for Disease Control to a centralized location within IH, so the Health Authority can be responsible for the centralized distribution of the antivirals to its various facilities and communities. Discussions are required between IH and the Ministry to formalize this process of distribution.

It is anticipated that the pandemic virus will originate outside of Interior Health, and Canada for that matter, allowing planners time to respond, activate, and mobilize resources prior to pandemic cases being identified in the local communities. During this period of time, Emergency Operations Centres, both at the Corporate and Health Services levels, will be activated and Incident Command positions delegated. For the purposes of this antiviral distribution strategy, the following actions will have particular significance in the lead-up to formal distribution of antivirals across Interior Health and security resource availability will need to be discussed well in advance of a pandemic to ensure said actions can take place. For example, resources will be required to:

- Complete a formal security assessment of all facilities designated within Interior Health to act as storage and/or points of distribution of antivirals during the pandemic.
- Work with the Logistics Officer to discern the most efficient, safe, and secure way to transport the antiviral supplies to the various distribution points in the communities (e.g., using internal resources, contracted couriers, etc.), and develop a formal transport plan. Additional considerations for such plans will include route selection, route variations, use of secure vehicles, etc.
- Work with Security Officers (or similar resources), the Pharmacy Unit Leaders, and Incident Commanders of all acute care sites to ensure internal plans are formalized and in place for the distribution of antivirals to patients on-site, and also to ensure oversight of antivirals to be distributed at assessment centres in the community. Site/facility assessments will also be required for such facilities, and will likely involve support/input from the necessary municipal stakeholders.
- Make linkages with local law enforcement agencies for both information purposes (i.e., letting them know of the antiviral distribution plan) and capacity considerations (i.e., ability of police departments having resources available to supplement internal security staff at Interior Health facilities) should antivirals be dispensed in facilities other than acute care sites.
- Consider the ramifications of having to expand the process to include “mass distribution” methods, should the impact of the virus be extreme and the stockpiles of antivirals allocated for Interior Health be large enough to cover a higher percentage of the population, or should the policy move to one focusing on prophylaxis.

**Recommended Next Steps**

- Develop planning estimates for the required number of doses of oseltamivir (Tamiflu) and zanamivir (Relenza®) within Interior Health, on the basis of estimated numbers of individuals in Interior Health likely to require the drugs according to the three stages, and the supply to be received from the provincial stockpile.
- Liaise with other health authorities and ask the provincial Ministry of Health provide all health authorities with the anticipated number of doses, and types of antivirals, that will be made available via both provincial and federal stockpiles.
- Work with the Ministry of Health and BCCDC to plan for its allocation of antivirals to be distributed from the BC Centre for Disease Control to a centralized location within IH, so the health authority can be responsible for the centralized distribution of the antivirals to its various facilities and communities.
- Complete operational planning for all stages outlined in this proposed antiviral distribution framework.

## Annex 1 for the Use of Antivirals in IH: PHAC CPIP Overview of Antiviral (Anti-Influenza) Drugs in Canada

Two classes of antiviral drugs are currently approved in Canada for prevention and/or treatment of influenza infection: M2 ion channel inhibitors and neuraminidase inhibitors. There are important differences in pharmacokinetics, side effects, and drug resistance between these two classes of antivirals. Summary information on these drugs is presented in the table at the end of this section.

### Neuraminidase Inhibitors

Oseltamivir (Tamiflu) and zanamivir (Relenza) are the two neuraminidase inhibitors that are currently approved for use in Canada. They are currently the only neuraminidase inhibitors in the global market; however, other agents such as peramivir are under development. Oseltamivir and zanamivir interfere with replication of both influenza A and B viruses in three ways:

- They interfere with the release of virus from infected cells,
- They cause the aggregation of virus, and
- They may improve the inactivation of virus by respiratory mucous secretions.

These drugs are well tolerated and have been used effectively for the treatment and prophylaxis of influenza A and B infections. They are expected to be effective against pandemic viruses including H5N1 avian influenza. H5N1 viruses are susceptible to neuraminidase inhibitors in vitro and oseltamivir has been shown to protect mice against lethal experimental H5N1 influenza pneumonia, although at higher than usual doses.

Neuraminidase inhibitors are effective when administered within 2 days of onset of illness. When used in this way, current estimates of the benefits of oseltamivir therapy include a 25-30% reduction in symptom duration plus a reduction in illness severity, a 59% reduction in hospitalizations (range: 30% to 70%), a 63% reduction in antimicrobial drug use (range: 40% to 80%) and a 1-day reduction in lost work days under treatment (range: 0.5 to 1.5 days). No data on reductions in mortality caused by influenza due to oseltamivir treatment are currently available.

Evidence is limited on the effects of neuraminidase inhibitors in reducing the complications of influenza in individuals with co-morbid conditions that increase their risk of these complications. The available evidence supporting such a beneficial effect derives from analyses of pooled data from multiple independent studies. Both oseltamivir and zanamivir have similar effectiveness of 70-90% in preventing laboratory-confirmed influenza illness.

Both oseltamivir and zanamivir were approved for use in Canada in 1999 for the treatment of infection due to influenza A or B. Since December 2003, oseltamivir has also been approved for influenza prophylaxis in Canada. Zanamivir was recently approved for prophylaxis in Canada and guidelines are currently forthcoming. Current evidence suggests that the development of resistance during treatment of influenza is less likely with neuraminidase inhibitors than with amantadine and any resistant viruses that develop are less likely to be transmissible. That being said, neuraminidase inhibitors are more expensive than amantadine at this time.

M2 Ion Channel Inhibitors (Cyclic Amines or Adamantanes)

M2 ion channel inhibitors (amantadine and rimantadine) interfere with the replication cycle of influenza A, but are not effective against influenza B. Rimantadine is not currently approved for use in Canada.

Amantadine is approximately 70% to 90% effective in preventing illness from influenza A infection. When administered within 2 days of onset of illness, it can reduce the duration of uncomplicated influenza A illness by approximately 1 day, but it has not been studied as to its ability to reduce the complications of influenza. Resistance to amantadine has been shown to develop rapidly (in up to 30% of recipients) when this drug is used for treatment purposes and these resistant viruses are readily transmissible.

The federal Antivirals Working Group has considered a potential role for amantadine or rimantadine. Their role in treatment is not supported. They could be used for prophylaxis during a domestic outbreak of avian influenza or during a pandemic if the novel virus is susceptible. However, in order to use rimantadine, which has fewer side effects than amantadine, special permission would need to be sought as it is not currently approved for use in Canada. Most of the H5N1 avian influenza viruses have been found to be resistant to these drugs.

**Table – Overview of Antivirals Drugs Approved for Use in Canada**

Drug	Trade name and Manufacturer	Class	Indications	Formulation(s)	Shelf Life/Stability	Expected use(s) during a pandemic
Oseltamivir	Tamiflu®, Hoffmann-La Roche Inc.	Neuraminidase Inhibitor	Treatment of influenza A and B in persons 1 year and older who have been symptomatic for no more than 2 days	Capsules (75 mg/capsule): 10 capsules per blister pack or bottles of 10 and 100 capsules	Shelf life: 5 years	Capsules for those presenting and requiring early treatment.
			Prevention of influenza A and B in persons 1 year of age and older following close contact with an infected individual	Powder for oral suspension (12 mg/ml when reconstituted): 900 mg per bottle (volume of 75 ml in a 100-ml glass bottle)	Shelf life: 2 years Stability: Once reconstituted, 10 days in refrigerator (at 2 to 8 degrees Celsius)	Oral suspension for treatment of children weighing less than 40 kg and/or those who cannot swallow the capsules.  No decision has been made at this time to use the drugs in the national stockpile for prophylaxis indications. It is recognized that outside of the national

						stockpile, stockpiling with the intent to use this drug for prophylaxis may have occurred
Zanamivir	Relenza®, GlaxoSmithKline	Neuraminidase Inhibitor	Treatment of influenza A and B in persons 7 years of age and older who have been symptomatic for no more than 2 days	ROTADISK® consisting of a circular foil disk with four blisters each containing 5mg of zanamivir. ADISKHALER® inhalation device is provided to administer the medication (through inhalation). One box contains 5 disks, which is equivalent to one treatment course.	Shelf life: currently 3 years (expected to be extended to 5 years on new product)	Treatment for those presenting and requiring early treatment with specific focus on pregnant and nursing women.
Amantadine	Symmetrel® and Endantadine® -Bristol Myers Squibb, Generic amantadine manufacturers: Dominion Pharmacal, GenPharm, Medican Pharma, Pharmel, Pharmascience	M2 Ion Channel Inhibitors (Cyclic Amines or Adamantanes)	Treatment of influenza A in persons 1 year of age and older	Capsules (100 mg/capsule): bottles of 100 capsules	Shelf life: 3 years*	This drug has not been included in the national stockpile. It is recognized that it may be available at the time of a pandemic but should be used for prophylaxis only and only if the strain is known to be susceptible to amantadine.
			Prevention of influenza A in persons 1 year of age and older	Syrup (10 mg/ml): bottles of 500 ml	Shelf life: 2 years	

\* Note: In one study, amantadine was found to be stable after 25 years of uncontrolled storage on the shelf. Stability of other antiviral drugs may also extend beyond the currently stated expiry date. If the currently stockpiled antivirals are not used by their respective expiry dates, stability testing will likely be implemented to determine whether the drugs are still expected to be effective and should be retained in the stockpile.

## Annex 2 for the Use of Antivirals in IH: Antiviral Priority Groups – British Columbia (2005)

Antivirals will likely be the only virus-specific intervention during the initial pandemic response, given that vaccine is unlikely to be unavailable in the early months of a pandemic.

As per the recommendations of the British Columbia Ministry of Health, and the BCCDC Pandemic Influenza Preparedness Plan, the following priority groups for the use of antiviral medications in times of short supply were developed for the provincial PIPP in 2005. These groups are provided in this supplemental section of the IH plan **purely for information purposes**, as the federal CPIP (2006) has removed all reference to priority groups and is anticipated to release updated antiviral distribution guidelines for treatment and prophylaxis purposes in 2008.

<b>Antiviral Priority Groups – BC PIPP (2005)</b>	
<b>1. Persons hospitalized for influenza.</b>	<i>Rationale: Those who are hospitalized within the first 48 hours of onset of illness should be highest priority for treatment.</i>
<b>2. Ill health care and emergency services workers.</b>	<i>Rationale: 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 receive a high priority for treatment.</i>
<b>3. Ill high-risk persons in the community.</b>	<i>Rationale: Persons with underlying heart and lung conditions or those who are immunocompromised, who present to ambulatory settings within 48 hours of onset of symptoms should receive a high priority for treatment.</i>
<b>4. Health care workers (prophylaxis)</b>	<i>Rationale: As HCW's are essential to the pandemic response plan and for the care of patients, they are a priority group.</i>
<b>5. High-risk residents of institutions (e.g. nursing homes)</b>	<i>Rationale: To control outbreaks/reduce health care demands.</i>
<b>6. Emergency and essential service workers (prophylaxis)</b>	<i>Rationale: To minimize societal disruption by maintaining key community services.</i>
<b>7. High risk persons hospitalized for illnesses other than influenza (prophylaxis)</b>	<i>Rationale: These individuals will be at higher risk.</i>
<b>8. High-risk persons in the community.(prophylaxis)</b>	<i>Rationale: A group likely to experience severe illness.</i>
<b><i>The mass prophylaxis of children is currently not recommended.</i></b>	

Annex 3 for the Use of Antivirals in IH: Size of the Federal Antiviral Stockpile (*Federal CPIP for the Health Sector*)

Creation of a national stockpile helps ensure equitable access across Canada to a secure supply of antivirals for pandemic influenza, along with equitable access to these drugs through governmental control. The national antiviral stockpile was created in the fall of 2004 as a result of a joint federal and provincial and territorial (P/T) purchase of oseltamivir capsules. The initial quantity in the stockpile was 16 million doses, which was originally estimated to be sufficient to cover:

- the early treatment of hospitalized patients, health care workers, public health and pandemic societal responders, key health decision makers, high-risk individuals in the community and residents of long-term care facilities experiencing outbreaks; and
- 6 weeks of prophylaxis of one-third of all health care professionals in Canada (to cover front-line workers).

In the fall of 2005, the PIC Antivirals Working Group reviewed the assumptions used to derive the initial estimates and recommended changes to these assumptions\*. The "modified scenario" that resulted from these adjusted assumptions (including a clinical attack rate of 25%, more severe impact in terms of morbidity, higher uptake of the drugs, and 50% for the proportion of "front-line" health care workers), would require substantially more drug to cover the groups previously expected to be covered by the 16M dose stockpile. These estimates led the working group to recommend to the Pandemic Influenza Committee (PIC) that the size of the stockpile be substantially increased. The working group also recommended expansion of treatment to everyone ill enough to need care, in line with the approach being taken in many other developed countries.

At a joint meeting of the Council of Chief Medical Officers of Health (CCMOH) and the Public Health Network in February 2006, recommendations for the size, composition and use of the National Antiviral Stockpile were formalized. It was determined that the size (and diversity) of the stockpile should be increased to 55 million doses or 5.5 million treatment courses of neuraminidase inhibitors. Based on past pandemics, and reflected in the Flu-aid model developed in the U.S. by Meltzer et al, during mild-moderate pandemics approximately half of those who develop a clinical illness present for medical attention. With a clinical attack rate of 35% over the course of the pandemic, and half of the clinically ill seeking medical care, 55 million doses would be required (based on the current standard treatment course), assuming that all persons presenting for care require antivirals.

The national stockpile was distributed on a per capita basis to each of the P/Ts. Some P/Ts have chosen to purchase additional quantities of antivirals. At the time of publication, it is estimated that approximately 39 million doses (including the 16 million in the national stockpile) of oseltamivir have been stockpiled by the federal and P/T governments in Canada. If the government stockpiles that currently exist outside of the national stockpile are incorporated into the national stockpile, the target of 55 million doses could be achieved as early as spring 2007. The content of the stockpile (i.e. number of doses and drugs) will be assessed on an ongoing basis as planning activities continue and additional science and resources (including drug supply) become available to further inform the antiviral strategy. The latest set of recommendations, specifically regarding the size of the National Antiviral Stockpile, are intended to assist planning and should not be interpreted as establishing the absolute requirements for an influenza pandemic.

*NOTE: Original assumptions used for antivirals needs estimate: Mild-moderate severity, 20% clinical attack rate, 6 weeks pandemic wave, 33% of health care workers are "front-line".*

## **Use of the Federal Antiviral Stockpile**

Use of the initial 16 million dose national stockpile was originally anticipated to be a combination of treatment and prophylaxis indications which would have covered a limited number of the nationally agreed upon priority groups. With the expansion of the stockpile to 55 million doses, the strategy has been revised and is described below.

### Early Treatment (i.e., treatment within 48 hours of symptom onset)

The National Antiviral Stockpile should be used at the time of a pandemic for early treatment of all persons with influenza-like illness (presumed pandemic influenza) who are ill enough to need care, and who are assessed within 48 hours of the onset of symptoms. At the time of implementation of the antiviral strategy prioritization may still be necessary, for example if treatment is found to require more than 10 doses or the stockpile is not yet completely built up. If prioritization for treatment is recommended at that time then the doses from the national stockpile would be used for those with ILI who are deemed to be most at risk of serious morbidity and mortality based on the available data.

There has been an accumulation of literature and modeling studies, particularly in the past year, to support a focus on early treatment (in contrast to prophylaxis) as the most efficient way to prevent hospitalizations and death in both high risk individuals and the general public. Based on the estimated impact of a pandemic, treatment with antivirals is expected to be cost-saving to the economy under several treatment strategies. One recent international study has shown therapeutic treatment and post-exposure prophylaxis both to be cost-saving. Canadian modeling is underway and early indications are that a treatment-focused strategy is the most cost-effective strategy.

There are ethical obligations to provide effective treatment to persons who can benefit, through the timely administration of a safe and effective treatment that keeps harm (in this situation, the risk of complications of influenza), if not fully avoidable, at the lowest possible level. The principle challenge of a treatment-focused strategy is ability to deliver drugs in a timely manner to ill individuals. To be effective, neuraminidase inhibitors must be administered as early as possible, ideally within 12 hours after the start of illness but definitely within 48 hours. Delivery of the drugs is primarily the responsibility of the respective P/T and local governments. Since the current antiviral supplies have been allocated on a per capita basis, treatment courses should be provided through the local distribution point regardless of whether the individual has any ties to the federal system (e.g., lives on a First Nations reserve or is a federal government employee).

### Prophylaxis

Both the Antivirals Working Group and PIC recognize that prophylaxis of health care workers, key decision makers and public health and societal responders (see Glossary for definitions) could contribute to the Canadian pandemic goals of minimizing serious illness and death, and societal disruption. Prophylaxis of health care workers could help keep the health care work force in place at a time of greatly increased need and help maintain an effective early treatment strategy for the general public.

Unlike the situation during SARS, it is unclear whether health care workers will be at increased risk in the health care setting because of their use of infection control precautions and personal protective equipment. Health care workers are as likely as anyone else to be exposed in the community. Should their onset of illness occur while at work in the health care setting, they could expose vulnerable patients and residents in closed units, which could in turn lead to outbreaks.

Control of influenza outbreaks in health care facilities is usually (during the annual influenza season) swiftly accomplished by antiviral prophylaxis of all residents and unvaccinated staff. During a pandemic similar availability of antivirals for outbreak control in these facilities would also be of value, likely providing significant benefits in terms of hospitalizations averted and lives saved.

It also must be recognized that beyond the goal of the Plan, there is also the goal of business continuity and optimal personal protection. Coupled with the efforts of governments and the private sector to build appropriate business continuity plans, the issue of supplying antivirals for prophylaxis has also been raised in this context.

Antiviral prophylaxis requires considerably more drug than early treatment. Four to five individuals could be treated with the amount of drug required to provide prophylaxis for one individual for a 6 week period. Implementation of a prophylaxis strategy has several challenges, including identification of eligible personnel, the need to adjust timing to local epidemiology, compliance, potential for drug diversion (e.g., to family members), and the requirement for off-label use of the drug (in the case of zanamivir).

**At this time the recommended use of the National Antiviral Stockpile is for treatment only.** However, a national process, including citizen and stakeholder dialogue, is underway in order to inform future policy decisions regarding whether antivirals provided through the National Antiviral Stockpile should be used for prophylaxis and to whom, during the pandemic period. There are health care system, scientific, economic, societal/ethical, legal, and policy considerations that must be explored. Any decision to include prophylaxis indications would require F/P/T consensus on whether the existing stockpile should be expanded for this purpose.

### Containment

The role and impact of antivirals in preventing transmission and slowing down the spread of a novel influenza virus is unknown. The use of antivirals for this purpose is under discussion as part of containment measures during the Pandemic Alert Period.

### **Composition of the Federal Stockpile**

It is expected that when the 55 million dose stockpile is completed, it will be composed of approximately:

- 90% oseltamivir (2 million doses as oseltamivir solution)
- 10% zanamivir

Adding zanamivir to the stockpile provides an option against oseltamivir-resistant strains, allows for a more optimal treatment option for pregnant and nursing women and enhances security against supply disruptions by supporting two manufacturers. Oral oseltamivir suspension would

be used for the treatment of children and adults or intubated patients that cannot swallow capsules.

Although oral oseltamivir suspension has a relatively limited shelf-life (2 years from date of manufacture), at this time data are lacking on the effectiveness of oseltamivir capsules that have been opened and mixed with another substance (e.g., applesauce) to facilitate administration to children or adults that cannot swallow capsules. The decision to stock oral oseltamivir suspension on an ongoing basis will be reviewed pending the availability of data on alternative antiviral treatment options for children or individuals that cannot swallow capsules.

At this time there are no plans to include adamantanes in the national stockpile. Compared to the neuraminidase inhibitors, there is an increased likelihood of resistance to adamantanes from the outset. Ongoing monitoring of antiviral drug resistance suggests that there is no role for M2 inhibitors in the stockpile but that diversification within the NAI drug class would be beneficial.