

Nova Scotia Health System Pandemic Influenza Plan

Chapter 5: Antiviral Drug Strategy

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Background

Antiviral medications are effective in both the treatment and prophylaxis of influenza. While limited in supply, they are likely to be the only virus-specific intervention available during the initial response to a pandemic.

Vaccination with an effective vaccine is the primary public health intervention during a pandemic. However, vaccine production requires the acquisition of a seed virus and, therefore, cannot be initiated until the pandemic virus has infected humans. Once a suitable vaccine seed strain is available, it is anticipated that vaccine production will require at least three to four months. 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 that targets influenza and that will 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.

Objectives

The national Pandemic Influenza Committee has developed a national antiviral strategy. The objectives of this strategy are to

- recommend a strategy for the use of antiviral drugs during an influenza pandemic
- address issues around the security of supply of antiviral drugs
- facilitate planning to ensure the distribution of available antiviral drugs to the appropriate groups of people during an influenza pandemic
- support monitoring of drug resistance during an influenza pandemic

Planning Assumptions

- A limited supply of antiviral medications will be available during an influenza pandemic.
- The use of antiviral medications across the province and country must be consistent.
- A quantity of antiviral drugs will be designated for containment during the pandemic alert period.
- The clinical attack rate could be up to 35 per cent over the course of the entire pandemic.
- Of those who are symptomatic, 50 per cent will present to a health-care setting for medical attention.
- Treatment doses will still be required in the second wave even if a vaccine is available.
- Antiviral drugs have a limited shelf life.
- Resistance to antiviral medications may develop.
- The efficacy of antiviral drugs for treatment and prophylaxis of the pandemic influenza strain will not be known until the pandemic begins and may differ from that of seasonal influenza; therefore, recommendations may change.
- The dose and duration of antiviral drugs needed for the treatment and prophylaxis of the pandemic influenza strain will not be known until the pandemic begins and may differ from that of seasonal influenza; therefore, recommendations may change.
- Communication with health-care providers and the public on the use of antiviral medications is necessary.

Key Recommendations

- The recommended use of antiviral drugs changes according to the pandemic period. During the pandemic alert period, the objective is containment, which includes treatment of cases and post-exposure prophylaxis of close contacts. During the pandemic period, the objective is early treatment.
- Neuraminidase inhibitors (oseltamivir and zanamivir) can be used for both treatment and prophylaxis. Amantadine should be used only for prophylaxis and only if the strain is known to be susceptible.

- Treatment with neuraminidase inhibitors should be initiated within 48 hours of symptom onset.
- The susceptibility of the pandemic influenza strain to antiviral drugs should be monitored.

Government Stockpiles

At the time of the next influenza pandemic, antiviral drugs will be in short supply and likely not available through normal commercial channels. Therefore, a national stockpile of antiviral drugs has been created. The current national stockpile of 16 million doses of oseltamivir has been distributed per capita across the country, with Nova Scotia having approximately 500,000 doses. This is sufficient to treat 50,000 people (5 per cent of the population) once. Outside of the stockpiled quantity, the supply of antiviral drugs in Canada is limited.

The national stockpile is being increased to 55 million doses, sufficient to treat 17.5 per cent of the population. This recommendation is based on the assumption that there will be a 35 per cent attack rate, with 50 per cent of patients presenting for medical care. Along with oseltamivir capsules, the stockpile will include oseltamivir solution (4 per cent of stockpile) and inhaled zanamivir (10 per cent of stockpile).

Classes of Antiviral Drugs

Two classes of antiviral drugs are currently available: M2 ion channel inhibitors and neuraminidase inhibitors.

M2 Ion Channel Inhibitors

M2 ion channel inhibitors include amantadine and rimantadine, of which only amantadine is licensed in Canada. Amantadine is effective only against influenza A. It is approximately 65 per cent effective in preventing influenza A cases (Jefferson et al. 2006). When administered within 48 hours of symptom onset, it shortens the duration of fever (Jefferson et al. 2006). Resistance to amantadine develops rapidly when the drug is used for treatment and these resistant strains are readily transmissible.

During a pandemic, amantadine should not be used for treatment. It can be used for prophylaxis if the virus is susceptible.

Neuraminidase Inhibitors

Oseltamivir (Tamiflu®) and zanamivir (Relenza®) are the two currently available neuraminidase inhibitors (NAI) (others are under development). They are active against both influenza A and B. Both drugs are licensed in Canada for treatment and prophylaxis.

Meta-analyses have shown that when administered within 48 hours of symptom onset, NAIs reduce the duration of illness by approximately one day (Cooper et al. 2003; Matheson et al. 2003; Jefferson et al. 2006). These drugs are also effective in preventing lower respiratory tract complications requiring antibiotics (Cooper et al. 2003; Matheson et al. 2003; Jefferson et al. 2006). A 59 per cent reduction in hospitalizations with oseltamivir use was demonstrated in one study (Kaiser et al. 2003). No data on reduction in mortality due to NAI treatment are currently available.

Resistance is less likely to develop than when using amantadine.

Inhaled zanamivir is recommended for treatment and prophylaxis of pregnant women and nursing mothers as there is less drug absorption. Zanamivir may remain effective if resistance to oseltamivir develops. Limitations to the use of zanamivir are that all people may not be able to use the inhalation device successfully and that the drug would not be effective if the virus replicates systemically rather than only in the respiratory tract.

The liquid formulation of oseltamivir is recommended for children and adults who cannot swallow capsules (e.g., intubated). The bioavailability if capsules are opened and the contents administered with applesauce or other substances has not been studied.

Use of the Antiviral Drug Stockpile

During the pandemic alert period (Phases 3, 4, and 5), if a novel influenza virus with pandemic potential is causing illness in Canada prior to the declaration of a pandemic, antiviral drugs will be used for domestic containment: that is, for both treatment of cases and post-exposure prophylaxis of close contacts.

During the pandemic period (Phase 6), antiviral drugs will be used for early treatment of people with influenza-like illness (ILI) who present for assessment within 48 hours of symptom onset and who are ill enough to require medical care. If, during a pandemic, it is necessary to prioritize to whom antiviral drugs will be administered (e.g., a larger dose than anticipated is necessary thereby reducing the number of people who can be treated), priority will be given to those who are deemed to be most at risk of serious morbidity and mortality based on the current epidemiologic data.

Recent evidence and modelling studies suggest that early treatment of patients with ILI is the most efficient way to prevent hospitalization and death of both high-risk patients and the general public.

Storage and Distribution

Antiviral drugs will be stored and distributed through the Provincial Drug Distribution Program (PDDP). During an influenza pandemic, PDDP will courier the drugs to one hospital pharmacy in each district health authority. The districts are responsible for storage and distribution beyond that point.

Security

Security for the antiviral drug stockpile during storage and transportation and in clinics will be provided by the RCMP and municipal police forces. Plans are being developed with the RCMP and the Department of Justice.

Clinical Guidelines

National and provincial clinical guidelines will be developed for the use of antiviral drugs.

Adverse Reaction Monitoring

Adverse reactions associated with antiviral drugs are monitored by the Marketed Health Products Directorate (MHPD) of Health Canada (http://www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/mhpd-dpsc/index_e.html). Currently, health professionals and patients voluntarily report data on adverse reactions; while it is mandatory for manufacturers to report serious reactions.

In order to deal with adverse reactions to antiviral drugs prescribed during an influenza pandemic, MHPD is modifying this system, including reporting, monitoring, signal identification and prioritization, assessment, risk management, and risk communication.

Health professionals and patients can report data on adverse reactions to the MHPD. The report form is available at <http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/ar-ei_form_e.pdf>.

Reports should be mailed, faxed or phoned to:

Atlantic Regional AR Centre
 c/o Drug Information Centre
 Queen Elizabeth II Health Sciences Centre
 Room 2421, 1796 Summer Street
 Halifax NS B3H 3A7
 adr@cdha.nshealth.ca
 Telephone: 1-866-234-2345
 Fax: 1-866-678-6789

Antiviral Drug Susceptibility Monitoring

A protocol for monitoring the susceptibility of the pandemic influenza strain to antiviral drugs is being developed by the National Microbiology Laboratory.

Roles and Responsibilities

(Outstanding issues are italicized)

Federal

- Approve and license antiviral drugs.
- *Coordinate national purchases of antiviral drugs—ongoing* (Public Works and Government Services Canada).
- *Coordinate a national antiviral strategy—ongoing* (Public Health Agency of Canada).
- *Develop a plan for containment activities during the pandemic alert period* (Public Health Agency of Canada).
- *Review and update the system for monitoring adverse drug reactions* (Marketed Health Products Directorate, Health Canada).
- *Coordinate a plan for antiviral drug susceptibility monitoring* (National Microbiology Laboratory).

- *Develop a plan for monitoring the shelf life of antiviral drugs* (Public Health Agency of Canada).

Provincial (Department of Health)

- Purchase and store antiviral drugs.
- *Arrange for security during storage and transportation, as well as in district health authority clinics* (Department of Health, RCMP, Department of Justice).
- *Develop clinical guidelines for the use of antiviral drugs* (Department of Health).
- *Develop a protocol for the use of diagnostic tests in guiding antiviral treatment* (Department of Health).
- *Develop a protocol for monitoring antiviral drug susceptibility* (Department of Health).
- *Develop a protocol for monitoring antiviral drug adverse reactions* (Department of Health).
- During an influenza pandemic:
 - Distribute drugs to the district health authorities.
 - Monitor the use and wastage of antiviral drugs in the province (Department of Health).
 - Monitor antiviral drug susceptibility and adverse drug reactions (Department of Health).

District

- Develop plans for the storage and distribution of antiviral drugs within the district health authority.
- Develop plans to rapidly administer antiviral drugs to patients.
- During an influenza pandemic,
 - Implement provincial clinical care guidelines for the use of antiviral drugs.
 - Implement the provincial protocol for the use of diagnostic tests in guiding antiviral treatment.
 - Report adverse drug reactions.
 - Implement provincial protocol for monitoring antiviral drug susceptibility.
 - Track antiviral drug use and wastage; report to the Department of Health.

Activities by Pandemic Phase

Canadian Pandemic Phase	Activities
Interpandemic Period	
1.0 No new virus subtype is present in humans. Subtype that has caused human infection may be present in animals <u>outside</u> Canada. Risk to humans is low.	<input type="checkbox"/> Usual public health practice for seasonal influenza.
1.1 No new virus subtype is present in humans. Subtype that has caused human infection is present in animals <u>inside</u> Canada. Risk to human is low.	<input type="checkbox"/> Usual public health practice for seasonal influenza.
2.0 No new virus subtype is present in humans. Animal influenza virus subtype that poses substantial risk to humans is circulating in animals <u>outside</u> Canada.	<input type="checkbox"/> Usual public health practice for seasonal influenza.
2.1 No new virus subtype is present in humans. Animal influenza virus subtype that poses substantial risk to humans is circulating in animals <u>inside</u> Canada.	<input type="checkbox"/> Usual public health practice for seasonal influenza.

Canadian Pandemic Phase		Activities
Pandemic Alert Period		
3.0	New virus subtype is present in humans <u>outside</u> Canada (single cases). No or rare instances of human-to-human spread.	<ul style="list-style-type: none"> <input type="checkbox"/> Assess size of antiviral drug stockpile. <input type="checkbox"/> Review storage and distribution plans.
3.1	New virus subtype is present in humans <u>inside</u> Canada (single cases). No or rare instances of human-to-human spread.	<ul style="list-style-type: none"> <input type="checkbox"/> Carry out limited antiviral drug distribution to district health authorities. <input type="checkbox"/> Treat cases with antiviral drugs. Antiviral drug prophylaxis for contacts is not necessary unless human-to-human transmission cannot be ruled out. <input type="checkbox"/> Monitor adverse drug reactions according to protocol. <input type="checkbox"/> Monitor antiviral drug susceptibility according to protocol. <input type="checkbox"/> Monitor use and wastage of antiviral drugs.
4.0	New virus subtype is present in humans <u>outside</u> Canada (small clusters). Limited human-to-human spread.	<ul style="list-style-type: none"> <input type="checkbox"/> Reassess antiviral drug strategy based on available epidemiologic data. Revise recommendations for antiviral drug use if necessary.
4.1	New virus subtype is present in humans <u>inside</u> Canada (single cases; no clusters). Limited human-to-human spread.	<ul style="list-style-type: none"> <input type="checkbox"/> Treat cases with antiviral drugs. <input type="checkbox"/> Treat contacts prophylactically with antiviral drugs. <input type="checkbox"/> Monitor adverse drug reactions according to protocol. <input type="checkbox"/> Monitor antiviral drug susceptibility according to protocol. <input type="checkbox"/> Monitor use and wastage of antiviral drugs.
4.2	New virus subtype is present in humans <u>inside</u> Canada (small localized clusters). Limited human-to-human spread.	<ul style="list-style-type: none"> <input type="checkbox"/> As for Phase 4.1.

Canadian Pandemic Phase		Activities
Pandemic Alert Period cont'd		
5.0	New virus subtype is present in humans outside Canada (large clusters). Localized human-to-human spread.	<ul style="list-style-type: none"> <input type="checkbox"/> Reassess antiviral drug strategy based on available epidemiologic data. Revise recommendations for antiviral drug use if necessary.
5.1	New virus subtype is present in humans inside Canada (single cases; no clusters).	<ul style="list-style-type: none"> <input type="checkbox"/> Treat cases with antiviral drugs. <input type="checkbox"/> Treat contacts prophylactically with antiviral drugs. <input type="checkbox"/> Monitor adverse drug reactions according to protocol. <input type="checkbox"/> Monitor antiviral drug susceptibility according to protocol. <input type="checkbox"/> Monitor use and wastage of antiviral drugs.
5.2	New virus subtype is present in humans inside Canada (large clusters). Localized human-to-human spread.	<ul style="list-style-type: none"> <input type="checkbox"/> As for Phase 5.1.
Pandemic Period		
6.0	New virus subtype is present in humans <u>outside</u> Canada (in the general population). Sustained human-to-human spread.	<ul style="list-style-type: none"> <input type="checkbox"/> Carry out large-scale antiviral drug distribution to district health authorities. <input type="checkbox"/> Reassess antiviral drug strategy based on available epidemiologic data. Revise recommendations for antiviral use if necessary. <input type="checkbox"/> Review recommended dosage and duration of treatment. <input type="checkbox"/> Treat cases with antiviral drugs according to clinical guidelines. <input type="checkbox"/> Monitor adverse drug reactions according to protocol. <input type="checkbox"/> Monitor antiviral drug susceptibility according to protocol. <input type="checkbox"/> Monitor use and wastage of antiviral drugs. <input type="checkbox"/> Provide ongoing information on antiviral drug effectiveness, adverse reactions, and resistance (if available) to health-care providers. <input type="checkbox"/> Provide ongoing information to the public and media about protocols for antiviral drug use.
6.1	Pandemic virus subtype is present in humans <u>inside</u> Canada (single cases; no clusters).	
6.2	Pandemic virus subtype is present in humans <u>inside</u> Canada (localized or widespread activity). Sustained human-to-human spread.	

Annex 5-A: People at High Risk of Seasonal Influenza-Related Complications (NACI 2005)

- Adults and children with chronic cardiac or pulmonary disorders (including bronchopulmonary dysplasia, cystic fibrosis, and asthma) that are severe enough to require regular medical follow-up or hospital care
- People of any age who are residents of nursing homes and other chronic care facilities
- Adults and children with chronic conditions, such as diabetes mellitus and other metabolic diseases, cancer, immunodeficiency, immunosuppression (due to underlying disease and/or therapy), renal disease, anemia, and hemoglobinopathy
- People aged over 65 years
- Adults and children with any condition that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk of aspiration
- Healthy children aged 6 to 23 months (Children in this age group are at increased risk of influenza-associated hospitalization, compared with healthy older children and young adults.)
- Children and adolescents (aged 6 months to 18 years) with conditions treated for long periods with acetylsalicylic acid

Annex 5-B: Recommended Doses of Antiviral Drugs

Table 1: Recommended pediatric and adult doses of antiviral drugs for the prophylaxis and treatment of influenza

Drug (trade name)	Prophylaxis doses	Treatment doses	Level of evidence and grade of recommendation*
Oseltamivir (Tamiflu®)	Adults and children >13 years ^a 75 mg once a day ^b	Children > 1 year ^c See Table 2 Adults 75 mg twice a day for 5 days	Children Prophylaxis no data Treatment IA Adults Prophylaxis IA Treatment IA
Zanamivir (Relenza®)	Adults and children >7 years ^{d,e} 10 mg (2 puffs) once a day ^f	Adults and children >7 years ^e 10 mg (2 puffs) twice a day for 5 days	Children Prophylaxis pending Treatment IA Adults Prophylaxis IA Treatment IA
Amantadine (Symmetrel®)	See Table 3	Not recommended	Children Prophylaxis IA Adults Prophylaxis IA
<p>^a Oseltamivir is not indicated for prophylaxis of influenza in pediatric patients less than 13 years of age.</p> <p>^b The safety and efficacy of oseltamivir for prophylaxis of influenza in patients >13 years of age have been demonstrated for up to 6 weeks.</p> <p>^c Oseltamivir should not be used for treatment of influenza in pediatric patients less than 1 year of age (see www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2004/tamiflu_hpc-cps_e.html for Important Safety Information regarding Tamiflu® (oseltamivir phosphate) and Prescription in Children Less than 1 Year of Age).</p> <p>^d Zanamivir was recently approved for prophylaxis in Canada; recommendations for its use are pending.</p> <p>^e The safety and efficacy of zanamivir for the prophylaxis and treatment of influenza in pediatric patients less than 7 years of age have not been established.</p> <p>^f The safety and efficacy of zanamivir for prophylaxis of influenza in patients less than 7 years of age have been demonstrated for up to 4 weeks.</p>			

*See Table 4.

Table 2: Recommended dose of oseltamivir for children 1 year of age and older for the treatment of influenza

Body Weight (kg)	Dosage
≤15	30 mg twice daily
>15–23	45 mg twice daily
>23–40	60 mg twice daily
>40	75 mg twice daily
<ul style="list-style-type: none"> • Oseltamivir is not indicated for treatment of influenza in patients less than 1 year of age. 	
<ul style="list-style-type: none"> • Duration of therapy is 5 days. 	
<ul style="list-style-type: none"> • Dose should be reduced by one-half in patients with creatinine clearance <30mL/min 	

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Table 3: Recommended adult and pediatric doses of amantadine for the prophylaxis of influenza

Age	Dosage	
NO RENAL IMPAIRMENT		
1–9 years	5 mg/kg once daily, or divided doses twice daily, total daily dose not to exceed 150 mg	
10–64 years	200 mg once daily, or divided doses twice daily	
>=65 years	100 mg once daily	
RENAL IMPAIRMENT		
Creatinine clearance (mL/min)	Dosage	
	10–64 years	>=65 years
>=80	100 mg twice a day	100 mg once a day
60–79	Alternating daily doses of 200 mg and 100 mg	Alternating daily doses of 100 mg and 50 mg
40–59	100 mg once a day	100 mg every 2 days
30–39	200 mg twice weekly	100 mg twice weekly
20–29	100 mg three times a week	50 mg 3 times a week
10–19	Alternating weekly doses of 200 mg and 100 mg	Alternating weekly doses of 100 mg and 50 mg

Table 4: Levels of evidence and grades of recommendation

Level	Type of evidence
I	Evidence is obtained from meta-analysis of multiple, well-designed, controlled studies.
II	Evidence is obtained from at least one well-designed experimental study.
III	Evidence is obtained from well-designed, quasi-experimental studies such as non-randomized, controlled single-group, pre-post, cohort, time, or matched case-control series.
IV	Evidence is from well-designed, non-experimental studies such as comparative and correlational descriptive and case studies.
V	Evidence is from case reports and clinical examples.
Grade	Grading of recommendation
A	There is evidence of type I or consistent findings from multiple studies of types II, III, or IV
B	There is evidence of types II, III, or IV and findings are generally consistent
C	There is evidence of types II, III, or IV but findings are inconsistent
D	There is little or no systematic empirical evidence

Annex 5-C: Adverse Reactions

Table 1: Adverse reactions of antiviral drugs

Adverse reaction	Drug		
	Oseltamivir	Zanamivir ^a	Amantadine ^b
Gastrointestinal	Nausea Vomiting (less severe if taken with food)		Anorexia Nausea Vomiting
Neurological			Nervousness Anxiety Insomnia Seizures Delirium Hallucinations
Cardiovascular			Arrhythmias (in overdose)
Respiratory		Bronchospasm Exacerbation of underlying chronic respiratory disease	
^a Zanamivir is not recommended in individuals with asthma or chronic obstructive pulmonary disease; however, if the benefit outweighs the risks, the drug can be used with caution and under proper monitoring.			
^b Side-effects of amantadine are usually mild and diminish or disappear after taking the drug for a week. Toxicity is observed more frequently in individuals with renal insufficiency or seizure disorders, in the elderly, or after higher doses.			

Annex 5-D: Oseltamivir: Patient Handout

Information about Tamiflu® (oseltamivir)

What is Tamiflu®?

Tamiflu® is a prescription drug effective both in preventing and treating influenza. It belongs to a class of antiviral drugs called neuraminidase inhibitors.

Tamiflu® is approved in Canada for treating influenza in people one year of age or older and for preventing influenza in people 13 years of age or older.

How is Tamiflu® administered?

Tamiflu® is available as a capsule that is taken orally (by mouth). For adults, it is taken twice daily for 5 days to treat influenza. For children, the dose depends on the child's weight. A liquid suspension of Tamiflu® can be taken by children or adults who cannot swallow a capsule.

How much do these drugs help?

Studies have shown that Tamiflu® can reduce the duration of influenza symptoms by one day if taken within two days of the onset of the illness. There is no information about how effective the drug is if treatment is started more than two days after the onset of symptoms.

What are the side-effects?

The most common side-effects are nausea and vomiting. These effects do not occur often and do not last long. Taking Tamiflu® with food may help to reduce these side-effects.

Who should not take Tamiflu®?

You should not take this medication if you have had a previous severe allergic reaction to Tamiflu®.

The dose of Tamiflu® may need to be adjusted if you have kidney disease.

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