

Annex E

Canadian Pandemic Influenza Plan *for the Health Sector*

The Use of Antiviral Drugs During a Pandemic

At the time of an outbreak with a novel virus or a pandemic, these recommendations need to be considered in the context of this situation and changes made to strategies on the basis of the emerging epidemiology or other data (e.g. antiviral resistance, optimal treatment course).

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Summary of key changes:

- Contains updated scientific data, regulatory information, policy decisions and knowledge based on experience acquired since the last version (2006), including:
 - Updated information on the size, use and composition of the National Antiviral Stockpile;
 - A summary of the August 2008 Report on Antivirals for Prophylaxis;
 - Implementation advice for the antiviral early treatment strategy;
 - October 19, 2009: Addition of Pandemic H1N1 Updates;
 - May 7, 2010: Addition of Appendix 2: *Antiviral Drug Prioritization Framework*.

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Pandemic H1N1 Updates

With the emergence of the pandemic (H1N1) 2009 influenza virus, the following guidance documents were created that contain different advice to that offered in this Annex. Here is a list of H1N1 guidance documents and how they differ from Annex E:

Interim Guidance for Ambulatory Care of Influenza–Like–Illness in the Context of H1N1 Influenza Virus

Annex E recommends antivirals for all who need it, based on a moderate pandemic scenario. Due to the mild nature of the pandemic H1N1, antiviral treatment is recommended for those with severe disease, or those who have influenza-like illness and risk factors for complications, including: pregnant women, children 6-23 months and persons with certain chronic health conditions. Antivirals are not recommended to treat mild disease in persons who are otherwise healthy.

Interim Guidance for Emergency Use of Oseltamivir (Tamiflu) in Children Under 1 Year of Age in the Context of 2009 H1N1 Pandemic

Annex E does not recommend the use of oseltamivir for infants under 1 year as it is a contraindication in the product monograph (based on limited safety data available at the time of drug approval by Health Canada). Infants have been identified as being at increased risk of morbidity and mortality from pandemic H1N1 influenza. Based on this as well as current scientific evidence and expert opinion, Health Canada released an Interim Order to permit the expanded use of oseltamivir as a treatment or prophylaxis for children less than 1 year of age.

Interim Clinical Guidance for Pregnant and Breastfeeding Women with Influenza-Like Illness in the Context of H1N1 Pandemic

In Annex E zanamivir is noted as the treatment of choice for pregnant women. For pandemic H1N1 influenza, oseltamivir is recommended as the treatment of choice; zanamivir may be useful if nausea and vomiting are present.

Interim Guidance for the Management of Pandemic H1N1 Influenza Outbreaks in Closed Facilities

This document expands on Annex E's recommendations for antiviral use in outbreak control in closed facilities. This guidance document includes recommendations for early detection measures; triggers for outbreak investigation; as well as antiviral treatment and prophylaxis strategies depending on the severity of the disease and the risk profile of the resident population.

1.0 Introduction

The purpose of this annex is to provide information and recommendations that will assist pandemic planners with the development and implementation of their antiviral strategies. The recommendations of the Pandemic Influenza Committee are intended to facilitate consistent use of antivirals across Canada at the time of an influenza pandemic and to form the basis for an effective, equitable, flexible and informed national antiviral strategy. It will be necessary for planners to review all recommendations and implementation plans once a pandemic strain has emerged so that appropriate changes can be made in the implemented strategy on the basis of emerging epidemiology or other data (e.g. antiviral resistance, optimal treatment course).

2.0 Role of Antivirals

Antivirals (anti-influenza drugs) will be the only specific medical intervention on hand during the initial pandemic response until pandemic vaccine becomes available, which will take at least 4 to 6 months. Antiviral drugs can be used to treat cases that are identified early in their illness and can also be used to prevent influenza (prophylaxis). When used for treatment, there is good evidence that antivirals reduce the complications of and mortality from influenza. When antivirals are taken for prophylaxis, their protection is virtually immediate. Taking antivirals does not interfere with the immune response to inactivated influenza vaccines.

To date there has been relatively little practitioner or public experience with antiviral drugs in Canada. During annual influenza seasons, they are used primarily to control outbreaks in health care and long-term care institutions; they are seldom prescribed in the primary care setting. During several recent domestic avian influenza outbreaks in Canada, they have been used for prophylaxis of individuals exposed to avian influenza (e.g. cullers) because of their roles in outbreak control.

3.0 Classes of Antiviral (Anti-Influenza) Drugs

Two classes of antiviral drugs are currently authorized in Canada for prevention and/or treatment of influenza infection: neuraminidase inhibitors and M2 ion channel blockers. There are important differences in the pharmacokinetic characteristics, side effects and rates of drug resistance between these two classes of antivirals. Such performance characteristics and the costs should be considered in selecting the specific drugs to be used for prophylaxis or treatment. Summary information on these drugs is presented in Table 1 and more detailed information follows:

When reviewing Table 1, it is important to note the distinction between:

- Pre-exposure prophylaxis – prolonged and preventive use of antivirals in advance of expected exposure (usually for 4 weeks or more); and
- Post-exposure prophylaxis – preventive use of antivirals following close contact with an infected person (usually for 10 days).

Table 1 - Antiviral (Anti-Influenza) Drugs Currently Approved for Use in Canada

Drug	Trade Name & Manufacturer	Class	Authorized Indications (as per product monograph)	Formulation(s)	Shelf Life/Stability	Proposed Use(s) During Pandemic
Oseltamivir	Tamiflu®, Hoffmann-La Roche Inc.	Neuraminidase Inhibitor	Treatment of influenza A and B in persons 1 year of age and older who have been symptomatic for no more than 2 days Prevention of influenza A and B in persons 1 year of age and older after close contact with an infected individual for post-exposure prophylaxis (10 days)	Capsules (30 mg, 45 mg and 75 mg): 10 capsules per blister pack 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 of capsules: 7 years for new government stockpile orders (previously 5 years) Shelf life of powder for suspension: 2 years Stability: Once reconstituted, 10 days in refrigerator (at 2°-8° C)	Capsules (adult and paediatric) for early treatment of ill persons and for outbreak control (treatment and post-exposure prophylaxis) in health care and other closed facilities where high-risk persons reside Oral suspension not included in the national stockpile
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 Prevention of influenza A and B in persons 7 years of age and older (post-exposure prophylaxis and up to 28 days' pre-exposure prophylaxis)	ROTADISK® consisting of a circular foil disk with four blisters each containing 5 mg of zanamivir. A DISKHALER® inhalation device is provided to administer the medication (through inhalation). One box contains 5 disks, which is equivalent to one treatment course	Shelf life: 5 years	Early treatment of ill persons and outbreak control (treatment and prophylaxis) in health care and other closed facilities where high-risk persons reside Preferred treatment for pregnant and nursing women
Amantadine	Symmetrel® syrup, Bristol-Myers Squibb <i>Generic amantadine manufacturers:</i> Dominion Pharmacal, GenPharm, Medican Pharma, Pharmed, Pharmascience	M2 ion Channel blocker (cyclic amines or adamantanes)	Treatment of influenza A in persons 1 year of age and older Prevention of influenza A in persons 1 year of age and older	Capsules (100 mg/capsule): bottles of 100 capsules Syrup (10 mg/mL): bottles of 500 mL	Shelf life of capsules: 3.5 to 4 years depending on manufacturer* Shelf Life of syrup: 2 years	For use as combination therapy (with a neuraminidase inhibitor) for the treatment of severe disease Prophylaxis if strain is known to be susceptible to amantadine

* **Note:** In one study amantadine was found to be stable after 25 years of uncontrolled storage on the shelf.¹ The 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 could be used to determine whether the drugs are still potent.

3.1 Neuraminidase Inhibitors

Oseltamivir (Tamiflu®) and zanamivir (Relenza®) are the two neuraminidase inhibitors that are currently approved for use in Canada for the treatment of influenza A or B. Both are also approved for post-exposure prophylaxis, i.e. 10 days of daily treatment after close contact with an infected individual. Zanamivir, but not oseltamivir, is also approved for pre-exposure (or seasonal) prophylaxis during community outbreaks, but for up to 28 days only. Oseltamivir and zanamivir are currently the only neuraminidase inhibitors in the global market; however, other agents such as peramivir, an injectable neuraminidase inhibitor, are under development.

Oseltamivir and zanamivir inhibit the neuraminidase enzyme of influenza A and B viruses. This action interferes with virus replication by causing aggregation and clumping of budding virions, impeding their release and thereby limiting spread of virus to contiguous uninfected cells in the respiratory epithelium. The drugs are well tolerated and have been used effectively for the treatment and prophylaxis of seasonal influenza A and B infections. Although there can be no certainty, neuraminidase inhibitors are expected to be effective against pandemic viruses. Data from uncontrolled clinical trials of oseltamivir treatment of H5N1- infected persons suggest improved survival, although the optimal dosage and duration of therapy are uncertain.²

Neuraminidase inhibitors are effective as treatment when administered within 48 hours of onset of illness, but for optimal benefit treatment should begin as early as possible.³ Current estimates of the benefits of early oseltamivir therapy include a 25% to 30% reduction in symptom duration plus a reduction in illness severity, a 59% reduction in hospitalizations (range: 30% to 70%), a 63% reduction in anti-microbial drug use (range: 40% to 80%) and a 1-day reduction in work days lost under treatment (range: 0.5 to 1.5 days).⁴ In a prospective cohort study of patients hospitalized with influenza in southern Ontario, treatment with antiviral drugs was associated with a significant reduction in mortality (odds ratio, 0.21; $p = 0.03$).⁵

Evidence is limited on the effects of neuraminidase inhibitors in reducing influenza complications in individuals with high-risk conditions. The available evidence supporting such a benefit derives from analyses of pooled data from multiple independent studies.⁶

Both oseltamivir and zanamivir have similar effectiveness, of 70% to 90%, compared with placebo in preventing laboratory-confirmed influenza illness.⁷ A detailed review of the effectiveness of neuraminidase inhibitors for the prevention of influenza was conducted by the Canadian Agency for Drugs and Technologies in Health.⁸ This report reviewed studies of pre-exposure (seasonal) prophylaxis, post-exposure prophylaxis (e.g. in family settings) and outbreak control in closed settings (e.g. nursing homes). Data are limited or absent for prophylaxis among very young children, pregnant women, immunocompromised persons and for specific occupational groups such as health care workers. There are no randomized controlled trial data on oseltamivir and only two trials on zanamivir for control of outbreaks in long-term care facilities. Of the two trials on zanamivir one showed a significant difference between the placebo and treatment groups, and one did not. Observational studies support the use of oseltamivir for outbreak control in these settings.

Data on whether viral shedding is reduced by early treatment with neuraminidase inhibitors are inconsistent. The duration of viral shedding was reduced in one study that employed experimental infection; however, other studies have not demonstrated any reduction in the duration of viral shedding.⁹ A re-analysis of four household-based, randomized clinical trials (two oseltamivir and two zanamivir) showed that the efficacy of oseltamivir against the infectiousness of treated cases was significant, whereas the efficacy of zanamivir was not.¹⁰ The authors caution against over-interpreting these results because of the small samples.

In most cases neuraminidase inhibitor prophylaxis does not suppress the antibody response to influenza infection if an individual acquires infection during prophylaxis.¹¹ This is felt to be an advantage, as this acquired protection will persist after prophylaxis has been stopped.

Oseltamivir and zanamivir are generally well tolerated, and experience to date suggests that serious side effects are very rare. Relatively common side effects with oseltamivir are nausea and vomiting, but this seldom leads to discontinuation of the drug. Inhalation of zanamivir has been rarely associated with bronchospasm, which may be severe in patients with bronchial asthma and chronic obstructive pulmonary disease. There have been post-marketing reports, mainly from Japan, of delirium and self-injury, in some cases fatal, in patients with influenza who were receiving neuraminidase inhibitors. These events were reported primarily in children. The contribution of the antiviral therapy to these events has not been established, and influenza itself is known to be associated with a variety of neurological and behavioural symptoms. Close monitoring for signs of abnormal behavior during antiviral treatment is advised.

Development of resistance is a risk with any drug. Current evidence suggests that the development of resistance during influenza treatment is less likely with neuraminidase inhibitors (oseltamivir and zanamivir) than with amantadine.¹² Resistance to the neuraminidase inhibitors occurs by different mechanisms, and viruses that are resistant to oseltamivir generally remain sensitive to zanamivir.

Until recently, global surveillance had detected only very low levels of resistance to the neuraminidase inhibitors.⁸ In 2008, however, oseltamivir-resistant influenza A (H1N1) strains were detected in many countries, particularly in Europe and North America, including Canada, and investigation suggested that they were readily transmissible, in contrast to earlier experience with oseltamivir-resistant strains.¹³ This occurrence did not appear to be connected with oseltamivir use either in individuals or in the countries involved. Ongoing, intensified monitoring of antiviral resistance will help clarify the situation over time. The risk of a pandemic virus being resistant from the outset or becoming resistant to oseltamivir is unknown.

3.1.1 Interchangeability of Neuraminidase Inhibitors

Use of oseltamivir and zanamivir for treatment or prophylaxis is expected to be interchangeable in most cases. They cannot, however, be used interchangeably in the following circumstances:

- Zanamivir is *preferred* for pregnant and nursing women as it is administered by inhalation and is poorly absorbed systemically;
- Zanamivir is *not suitable* for:
 - Children under the age of 7;
 - Persons with reactive airways disease;
 - Persons who cannot use the inhaler, e.g. some elderly and nursing home patients and small children;
 - Persons with severe respiratory disease, because absorption would be impeded; and
 - Treatment of seriously ill persons if there is evidence that the pandemic virus replicates outside of the respiratory system.

3.1.2 Treatment Schedules

The standard dosages for treatment and prophylaxis with oseltamivir and zanamivir are shown in Table 2. It is possible that the dosage and/or duration of treatment might need to be modified for a novel or pandemic virus; this will be monitored closely during the pandemic.

Table 2 - Standard Dosages for Neuraminidase Inhibitor Treatment and Prophylaxis

		Oseltamivir (Tamiflu®)	Zanamivir (Relenza®)
Treatment	Adults	75 mg twice daily for 5 days	2 inhalations (10 mg) twice daily for 5 days
	Children	15 kg or less: 30 mg twice daily for 5 days >15-23 kg: 45 mg twice daily for 5 days >23-40 kg: 60 mg twice daily for 5 days (given as two 30 mg capsules) >40 kg: 75 mg twice daily for 5 days Adolescents 13 years and older: 75 mg twice daily for 5 days	Age 7 and above: 2 inhalations (10 mg) twice daily for 5 days
Prophylaxis*	Adults	75 mg daily	2 inhalations (10 mg) once daily
	Children	15 kg or less: 30 mg once daily >15-23 kg: 45 mg once daily >23-40 kg: 60 mg once daily (given as two 30 mg capsules) >40 kg: 75 mg once daily	Age 7 and above: 2 inhalations (10 mg) once daily
Renal impairment: adult	Creatinine clearance of 10-30 mL/min	Treatment: 75 mg once daily for 5 days Prophylaxis: 75 mg every other day or 30 mg once daily	No dosage adjustment necessary
	Renal dialysis (treatment or prophylaxis)	Low flux hemodialysis: 30 mg orally every second hemodialysis session Continuous ambulatory peritoneal dialysis: 30 mg orally once a week	No dosage adjustment necessary

* Duration of prophylaxis is determined by the circumstances. Standard post-exposure prophylaxis is given for 10 days. For outbreak control, prophylaxis is continued until the outbreak is over, usually 10 to 14 days. Pre-exposure prophylaxis generally continues for the duration of exposure. Note: Pre-exposure use for oseltamivir and use beyond 28 days for zanamivir are not approved indications.

3.2 M2 Ion Channel Blockers (Cyclic Amines or Adamantanes)

M2 ion channel blockers (amantadine and rimantadine) interfere with the replication cycle of influenza A but are not effective against influenza B. Rimantadine has fewer side effects than amantadine but is not currently approved for use in Canada.

Amantadine is approximately 70% to 90% effective in preventing illness from influenza A infection, providing the strain is amantadine susceptible. When administered within 2 days of onset of illness, it can reduce the duration of uncomplicated influenza A illness by approximately 1 day, but its ability to reduce the complications of influenza has not been studied. Amantadine resistance 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.¹⁴ In recent years, the majority of circulating H3N2 viruses in many parts of the world have been resistant to M2 blockers. Resistance of the H5N1 viruses to the M2 blockers is common but varies by geographical origin and viral clade. Fortunately, amantadine resistance to H1N1 virus remains relatively rare.

Amantadine should not be used as the sole agent for treatment because of the frequency with which resistance develops. However, in light of its proposed role in combination therapy, as described in the following section, standard dosages for amantadine treatment and prophylaxis are provided in Table 3.

Table 3* - Standard Dosages for Amantadine to be Considered in the Context of Combination Therapy

Age	Dosage†	
No renal impairment		
1-9 years or <40 kg	5 mg/kg once daily, or divided twice daily, total daily dose not to exceed 150 mg	
10-64 years	200 mg once daily, or divided twice daily Reduce to 100 mg daily for persons with seizure disorder	
≥65 years	100 mg once daily	
Renal impairment		
Creatinine clearance (mL/min/1.73 m ²)	Dosage for those 10-64 years	Dosage for those ≥65 years
≥80 mL/min	100 mg twice daily	100 mg once daily
60-79 mL/min	Alternating daily doses of 200 mg and 100 mg	Alternating daily doses of 100 mg and 50 mg
40-59 mL/min	100 mg daily	100 mg every 2 days
30-39 mL/min	200 mg twice weekly	100 mg twice weekly
20-29 mL/min	100 mg three times weekly	50 mg three times weekly
10-19 mL/min	Alternating weekly doses of 200 mg and 100 mg	Alternating weekly doses of 100 mg and 50 mg

* Adapted from: National Advisory Committee on Immunization. Statement on influenza for the 2006-07 season. *CDCR* 2006;32(ACS 7).

† Duration of treatment is 5 days or until 48 hours after recovery, whichever is shorter.

Duration of prophylaxis is determined by the circumstances. Standard post-exposure prophylaxis is given for 10 days. For outbreak control, prophylaxis is continued until the outbreak is over, usually 10 to 14 days. Pre-exposure prophylaxis generally continues for the duration of exposure.

These dosages are based on a 2006 statement by the National Advisory Committee on Immunization related to monotherapy for seasonal influenza outbreaks (see Table 3 footnote reference). It is possible, on the basis of additional studies and experience, that the dosages used in combination may need to be adjusted to reduce adverse reactions and achieve better therapeutic effects. For outbreaks in long-term care facilities, once-daily dosing and the use of amantadine syrup may make this regimen easier to administer.

3.3 Combination Therapy and Other New Approaches

The World Health Organization (WHO) recommends the consideration of combination therapy (amantadine and oseltamivir) for persons with avian influenza (H5N1) who are seriously ill in areas of the world where the viruses are likely to be susceptible to amantadine.² Drug combination therapy uses drugs with different mechanisms of action to provide greater benefit than single drugs, reduce the risk of resistance and potentially allow for lowered doses, thus reducing adverse effects. Various combinations of M2 blockers, neuraminidase inhibitors, interferon and ribavirin have been suggested for the treatment of influenza. There have been several preliminary reports of combination therapy with an M2 blocker and neuraminidase inhibitor that are promising;^{15,16} however, further studies are indicated. Studies of combination therapy are being monitored, and their applicability to the pandemic stockpile is under assessment.

Because oral medications are not always suitable for seriously ill patients, parenteral products could play an important role, especially in a hospital setting. Intravenous versions of the existing neuraminidase inhibitors are under development. Clinical trials are under way for peramivir, another neuraminidase inhibitor administered by the intramuscular or intravenous route. When available, parenteral products will be assessed for inclusion in the stockpile. Similarly, as other new antivirals become available their potential role will be evaluated.

4.0 The National Antiviral Strategy

4.1 Goals of the National Antiviral Strategy

The goals of the national antiviral strategy are to support the Canadian pandemic goals of minimizing serious illness and overall deaths and minimizing societal disruption by:

- Reducing the severity and duration of illness (including a decrease in the occurrence of complications, hospitalization and death);
- Mitigating societal disruption by reducing the impact of absenteeism due to illness in the critical infrastructure sectors; and
- Reducing the level and duration of viral shedding, thereby possibly reducing transmission.

4.2 Antiviral Stockpiles

National stockpiles of antiviral drugs help ensure that there is equitable access across Canada to a secure, government-controlled supply of antivirals for pandemic influenza. Without such stockpiling it is unlikely that there would be any antiviral drugs available at the time of a pandemic. The antivirals purchased by the government have largely gone into two stockpile systems in Canada: the National Antiviral Stockpile and the National Emergency Stockpile System.

4.2.1 National Antiviral Stockpile (NAS)

The National Antiviral Stockpile (NAS) was created in the fall of 2004 and contained 16 million doses of oseltamivir. In February 2006, it was decided that the size (and diversity) of the stockpile should be increased to 55.7 million doses to support a national early treatment strategy, namely, to provide antivirals to all Canadians expected to need treatment during a pandemic. The calculations were based on assumptions of a clinical attack rate of 35% over the course of a pandemic of moderate severity, with half of those clinically ill seeking medical care and receiving a standard 5-day course of antiviral treatment. At the time of publication of this annex, the stockpile consists of 48.7 million adult oseltamivir capsules, 2 million paediatric oseltamivir capsules and 5 million doses of zanamivir.

The National Antiviral Stockpile contains enough antivirals to treat 17.5% of the population. It has been distributed on a per capita basis to each of the provinces/territories and is under P/T care and control under the terms of a national agreement for use. Some provinces/territories have chosen to purchase additional quantities of antivirals.

4.2.2 National Emergency Stockpile System (NESS)

The National Emergency Stockpile System (NESS) is a federally owned stockpile of emergency supplies that is managed by the Public Health Agency of Canada (PHAC). It contains a number of emergency supplies for different types of emergencies. At the time of publication of this annex, NESS contains approximately 14.9 million doses of antivirals made up of 8.0 million adult oseltamivir capsules, 2.0 million paediatric oseltamivir capsules, 4.9 million zanamivir doses and 70,000 capsules of amantadine. Additional doses of amantadine, zanamivir and paediatric oseltamivir are being purchased. These NESS antivirals are intended for multiple purposes, including rapid response to an emerging pandemic and provision of surge capacity in support of P/T efforts to manage pandemic/avian influenza.

4.2.3 Other Government Stockpiles

Other federal government departments (e.g. Canadian Forces for active duty personnel, Department of Foreign Affairs and International Trade for mission staff overseas) hold a stockpile of antiviral drugs to meet the anticipated needs of their staff. In addition, some provinces have chosen to augment their portion of the NAS.

4.3 Proposed Uses of Antiviral Drugs

The proposed uses of antivirals from the national stockpiles are summarized in Table 4 and described more fully in the following sections. Note that the prophylaxis indications in the last column of this table are presented for planning purposes and are based on recommendations received by the Public Health Network Council.

For antiviral use in domestic avian influenza outbreaks, see *Human Health Issues related to Avian Influenza in Canada*: <http://www.phac-aspc.gc.ca/publicat/daio-enia/index-eng.php>.

Table 4 - Proposed Uses of Government-Stockpiled Antiviral Drugs in Canada

Pandemic Phase	Use	
	Early Treatment	Post-exposure Prophylaxis
Pandemic alert period (Phases 4 and 5)	Cases with novel virus infection	Close contacts of persons with novel virus infection
Pandemic period (Phase 6)	Cases of pandemic influenza	Control of laboratory-confirmed influenza outbreaks in closed health care facilities and other closed facilities where high-risk persons reside

4.3.1 Early Treatment Strategy

The NAS will be used at the time of a pandemic for treatment purposes (indications for use see section 5.3). Modeling suggests that stockpiles that cover 20% to 25% of the population (as is the case in Canada when all stockpiles are included) would be sufficient to treat most of the clinical cases and could lead to 50% to 77% reduction in hospitalization.¹⁷ A focus on early treatment (in contrast to prophylaxis) is the most efficient way to use antiviral drugs and, according to the estimated impact of a pandemic, antiviral treatment is expected to be cost-saving to the economy.⁴

Indirect benefits of early treatment include the possible reduction of transmission of infection to close contacts and the positive impact on maintaining the critical infrastructure by shortening the duration of illness, thereby reducing absenteeism. The policy recommendations on the use of antivirals for prophylaxis (which are described in detail in the next section) recommend that during the implementation of the early treatment strategy, critical infrastructure workers, including health care workers, have access to rapid assessment and early treatment in order to minimize societal disruption. See Appendix 1 for a list of critical infrastructure sectors.

The principal challenge of a treatment-focused strategy is the 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 to 24 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 and is discussed further in section 5 of this annex.

Antiviral treatment of ill persons infected with a novel virus that has pandemic potential is also recommended during the pandemic alert period (Phases 4 and 5), together with antiviral prophylaxis of their contacts. The Public Health Measures annex (Annex M) provides more detail on control measures during these phases.

While it is anticipated that the NAS will be sufficient to treat all persons who could benefit, on the basis of the assumptions described earlier, there could be developments that will merit reconsideration of this approach. The stockpile could be depleted faster than expected if the attack rate is higher than anticipated or the illness so severe that a higher proportion of ill persons seek care. Treatment could require more than 10 doses, or antiviral resistance could restrict the use of a stockpiled drug. Also, an unknown proportion of antivirals could be “wasted” because some of the patients treated for influenza-like illness will turn out to have other respiratory viruses instead of influenza. Furthermore, should oseltamivir resistance arise, this would reduce our treatment options to zanamivir. Assessment of stockpile adequacy will need to be made as the pandemic progresses and its clinical features become known. If prioritization for treatment is necessary, it is recommended that a national approach be taken using guidelines for the use of antivirals in short supply.

4.3.2 Prophylaxis Recommendations

The Task Group on Antivirals for Prophylaxis was struck in 2006 to conduct a comprehensive review of the provision of antivirals for prophylaxis (prevention) and to advise the Public Health Network Council on whether governments should stockpile antivirals for this purpose for use during an influenza pandemic. In August 2008, after careful analysis and pan-Canadian consultations, the Public Health Network Council published the *National Policy Recommendations on the Use of Antivirals for Prevention During an Influenza Pandemic*.¹⁸ The recommendations reflect current public health advice, given the scientific evidence available at the time of publication, and will be reviewed periodically to take into account new evidence.

These policy recommendations were received by P/T governments and will be used to inform federal, provincial and territorial policies pertaining to the use of antivirals for prophylaxis. Currently it is assumed that the limited use of antivirals for prophylaxis as described below can be covered by the NAS with back-up from the NESS. Any decision by a province or territory to provide prophylaxis beyond these recommendations will require additional purchases beyond the current NAS/NESS supplies.

The recommendations are as follows:

Pandemic Alert Period (Phases 4 and 5):

- As part of an early response strategy, provide post-exposure prophylaxis of close contacts of cases, together with treatment of cases.

Pandemic Period (Phases 6):

- Focus on early treatment of people with influenza and no post-exposure prophylaxis of close contacts of cases;
- Provide rapid access to antivirals and early treatment to critical infrastructure workers to minimize societal disruption;
- Use antivirals for outbreak control, including treatment of cases and prophylaxis of close contacts of cases in closed health care facilities and other closed facilities where high-risk people reside; and
- No use of antivirals from government stockpile for pre-exposure prophylaxis.

The widespread use of antivirals for *pre-exposure prophylaxis* during a pandemic was not recommended because of a number of factors. The relative paucity of clinical trial data was noted. The unknown health and safety risks of administering a drug with known side effects to a large number of healthy people for a prolonged period was a concern, as well as the difficulties of guaranteeing compliance with prolonged use. The risks of resistant strains of the virus developing were identified. It was concluded that the decision to undertake extensive pre-exposure prophylaxis required stronger scientific evidence, such as that obtained from population-based trials.

The use of antivirals from government stockpiles for post-exposure prophylaxis during an influenza pandemic was not recommended. Once a pandemic starts, this measure would require enormous quantities of antivirals and would be very resource intensive to administer. It was noted that during a pandemic, the entire health system would be challenged, and efforts should be focused on the needs of the ill.

The use of antiviral drugs to control outbreaks of influenza in health care settings, such as long-term care facilities and hospitals, is standard practice in Canada. It was recommended that this practice continue in a pandemic along with its consideration for other types of closed facilities, such as correctional facilities, where high-risk persons reside. Effective control of influenza outbreaks in these settings is expected to provide significant benefits in terms of hospitalizations averted and lives saved.

Private stockpiles (individual or corporate) of antivirals for prophylaxis are beyond the scope of this annex, but it is recognized that some organizations have undertaken this as part of their pandemic preparedness or business continuity planning efforts.

4.3.3 Rapid Containment Strategy

The WHO has developed a protocol for a rapid containment strategy to be implemented by national authorities with the assistance of WHO and international partners.¹⁹ Its purpose is to stop the development of pandemic influenza when it is initially detected and before the virus has been able to spread more widely. Mathematical modelling studies suggest that containment of a pandemic might be possible in the early stages if the initial outbreak of human cases is localized and antiviral prophylaxis, movement restrictions and non-pharmaceutical interventions are implemented in the

affected area within the first 3 weeks.^{20,21} The basic containment strategy uses a geographically based approach in which antiviral medications and non-pharmaceutical measures are used in a defined area surrounding the initial cases (i.e. the Containment Zone) to restrict the virus from spreading beyond that Containment Zone. There is also a surrounding Buffer Zone, where intensive surveillance for possible “break-through” cases would be done to evaluate whether the containment operation is succeeding.

While it is unlikely that the new pandemic will originate in Canada, it is anticipated that PHAC will lead the development of the containment strategy for Canada in the context of commitments under the North American Plan for Avian and Pandemic Influenza and in accordance with the WHO interim protocol on this issue.

4.4 Stockpile Management

Canada’s antiviral stockpiles are constantly being reassessed by F/P/T governments for size, composition (type of antiviral) and relative proportion of the stockpile in line with new science, technologies and formulations; changing resistance rates; disease epidemiology; and changing populations. In addition, all drugs have a shelf-life or an amount of time specified by the manufacturer during which the drug is documented to be stable and potent. This necessitates the development of a stockpile management approach that allows for the regular replacement of stock.

4.4.1 Recent Recommendations on Composition and Mix

The Public Health Network Council has recently approved the following recommendations that will be implemented over time by the provinces and territories:

- diversify the stockpile to 80% oseltamivir and 20% zanamivir (41 million doses of adult oseltamivir and 10.7 million doses of zanamivir for adults and children);
- increase the number of paediatric oseltamivir capsules to 9.2 million; and
- add 5.8 million capsules of amantadine.

More zanamivir will be used as a hedge against resistance. The additional paediatric oseltamivir capsules will provide sufficient quantities for paediatric treatment based on 2005 population data and on the same assumption used for adults (i.e. that 17.5% of the paediatric population will be ill enough that their parents seek medical treatment). Amantadine will be used in combination therapy to treat severe illness targeted for hospitalized patients.

4.4.2 Sustainability Strategy

By 2010, over 50% of the oseltamivir in the current NAS (28.4 million doses of adult oseltamivir) will meet its stated shelf-life of 5 years. An Antiviral Stockpile Management Task Group was established in June 2008 to provide options and recommendations on the management of the NAS with a focus on addressing impending expiring stock and general best practices for stockpile management.

Scientific data indicate that oseltamivir is a very stable drug, and new oseltamivir purchased by the government will have a shelf-life of 7 years. This does not apply to drugs that have already been purchased.

A number of options were considered regarding how to manage the expiring stock, in conjunction with the recent recommendations on composition and mix. Options considered were:

- Participating in a time-limited exchange program with the manufacturer that allows almost expired stock to be exchanged to meet both adult and paediatric targets;
- Replacing some of the expired oseltamivir for zanamivir; and
- Temporarily holding some expiring oseltamivir (with ongoing stability testing).

A final report of the Antiviral Stockpile Management Task Group is planned for release in 2009. Good stockpile management includes careful consideration of storage conditions. All antivirals require storage in a dry place at room temperature (15° to 30° C). Amantadine should be stored in a light-resistant container. A best practice for oseltamivir and zanamivir storage is temperature monitoring and documentation to demonstrate that an average temperature of 20° to 25° C has been maintained for the antiviral stockpiles and that there is no variation beyond 15° to 30° C.

5.0 Implementation Planning

The provinces and territories, together with their regional and local partners, are responsible for implementing the antiviral strategy in their own jurisdictions. Since the current antiviral supplies have been allocated on a per capita basis, antivirals should be provided through the local distribution point to all residents, including those who live on First Nations reserves.

While some differences in implementation plans are anticipated, it is expected that the provinces and territories will remain consistent in their uses of antivirals in terms of overall approach, eligibility for drugs, approach to off-label use and communications messages, etc. This will be facilitated by clear national guidelines in these areas. A national forum on implementation of the antiviral strategy was held in October 2007 (summary available from PHAC upon request) and focused specifically on early treatment. Presentations and input from that meeting have informed the guidelines that follow.

5.1 Components of an Implementation Plan

Common elements of a P/T antiviral implementation plan include the following:

- Storage and handling;
- Distribution within the province/territory – secure and efficient delivery system, taking into account the needs of remote and First Nations communities;
- Trigger for release of the antivirals – e.g. release from central depots in advance of anticipated pandemic activity; local use to begin when there is laboratory evidence that the pandemic virus is circulating locally;
- Clinical assessment – service delivery model and accompanying tools;
- Dispensing – who and where, tied to service delivery model;
- Laboratory capacity and guidelines for clinical testing;
- Surveillance and monitoring – uptake/usage, effectiveness, adverse events, antiviral resistance;
- Communications – public, health care professionals and other groups;

- Roles and responsibilities, including potential role of public health in distributing antivirals, promoting or monitoring their use;
- Documentation of distribution, dispensing, etc.;
- Training and exercises; and
- Evaluation of outcomes.

5.2 Antiviral Use in the Pandemic Alert Period

As already outlined, early treatment of cases and post-exposure prophylaxis of close contacts should be offered in Canada during the Pandemic Alert Period (Phase 4 & 5) as part of the rapid response strategy. While these phases could occur as a result of a novel virus originating in Canada, it is more likely that a novel virus would emerge in another country.

Detailed advice for case and contact management in the pandemic alert period is found in the Public Health Measures annex (Annex M) of the Canadian Pandemic Influenza Plan.

5.3 Implementation of the Early Treatment Strategy

It is intended that the NAS will be used at the time of a pandemic (Phase 6) for early treatment of persons:

- With influenza-like illness;
- Assessed within 48 hours of the onset of symptoms; and
- When there is laboratory evidence that the pandemic influenza virus is known to be circulating in the community.

Putting this policy into operation requires consideration of a number of issues.

5.3.1 Timing of Treatment

Since replication of influenza virus in the respiratory tract peaks between 24 and 72 hours after the onset of the illness, neuraminidase inhibitors (which act at the stage of viral replication) must be administered as early as possible. This is ideally within 12 to 24 hours of the start of illness. Evidence suggests that there is no benefit in using antivirals to treat community cases of seasonal influenza more than 48 hours from onset of illness. It is important to note that experience with the novel or pandemic virus may differ and result in changes in these recommendations.

It is recognized that adopting a 12 to 24 hour target to begin treatment puts considerable strain on the health care delivery system and probably means incorporating alternative models for providing clinical assessment and dispensing drugs. However, it is only by optimizing the early treatment strategy that we will achieve the desired results of preventing complications, hospitalizations and deaths.

In the hospital setting however, where more seriously ill persons are seen, clinicians should be allowed clinical latitude on the 48 hour rule, as there is some evidence for the value of delayed treatment in hospitalized patients.⁵ Immunocompromised persons may have prolonged viral replication and might also be expected to benefit from delayed treatment.

5.3.2 Assessment and Treatment Options

P/T planning for early access to antiviral drugs involves a number of considerations and options:

- Can the existing ambulatory care system assess and deliver drugs to the expected number of persons with influenza within the 12 to 48 hour target? What are the infection control implications?
- Should the existing services be supplemented or replaced by additional services like influenza assessment and treatment centres? Who will provide assessment and treatment services in these centres?
- Will medical directives be used for expansion of prescribing capacity, or could the provinces/territories consider extending prescribing rights to pharmacists or other health professionals?
- How will vulnerable populations be served?
- Could the response and role of telephone advice lines be expanded?
- What is the role for self-assessment?
- Will distribution of antivirals be under local public health control?

The Clinical Care annex (Annex G, Clinical Care Guidelines and Tools) contains a clinical algorithm for the assessment and management of persons with influenza-like illness. It is anticipated that in ambulatory care settings like influenza centres, nurses and potentially other health professionals will provide assessment using algorithms, and treatment using medical directives. In any triage/assessment setting, the Antiviral Working Group recommends that certain categories of persons be referred to a clinician for assessment and treatment (subject to modification at the time of the pandemic):

- Persons who are seriously ill or appear to be developing complications;
- Persons who are not responding to treatment;
- Persons with serious underlying health conditions, e.g. chronic cardiac or pulmonary disorders (except hypertension); diabetes mellitus and other metabolic diseases; renal disease; cancer; immunodeficiency and immunosuppression (due to underlying disease and/or therapy); anemia or haemoglobinopathy; and conditions that compromise the management of respiratory secretions and are associated with an increased risk of aspiration;
- Infants and very young children;
- Pregnant women; and
- Any additional high-risk groups identified in the pandemic.

Some of the tools needed to support the early treatment strategy can be found in Annex G. These tools may need modification when the pandemic virus emerges and its characteristics are known. Other national tools to support the early treatment strategy are under development.

5.3.3 Role of Laboratory Testing

The Laboratory annex (Annex C, Pandemic Influenza Laboratory Guidelines) outlines the role that laboratories will play in influenza testing, particularly in surveillance. Once the presence of pandemic influenza has been established in an area, laboratory testing in the ambulatory care setting will decrease in order to conserve laboratory resources for surveillance purposes and monitoring of antiviral resistance and effectiveness. Routine patient diagnosis will be made primarily on clinical grounds, using clinical algorithms that are modified for the pandemic presentation.

The Clinical Care annex (Annex G) contains recommendations for the role of laboratory testing in individual diagnosis and suggests that indications for limited laboratory testing throughout the pandemic include the following:

- Confirmation of an atypical presentation of pandemic influenza, including young children, when it will affect a treatment decision;
- Confirmation of the etiology of an institutional outbreak;
- Non-response to treatment in the hospital setting (for early detection of a resistant strain in a hospital); and
- Admission to the intensive care unit, to enable cohorting of patients.

5.3.4 Prescribing and Dispensing Antivirals

There are several ways to expedite early treatment with antivirals. The use of medical directives is already widely applied in health care settings; these are instructions by physicians to certain health care providers that pertain to any patient meeting the criteria set out in the medical directive. In addition, some provinces/territories have the option of extending prescribing rights to pharmacists or other health professionals.

Dispensing is normally supervised by pharmacists, although P/T legislation may allow others to dispense as well. In the interests of providing widespread access, dispensing antiviral drugs where patients are seen – for example, at influenza centres (if established) or emergency departments – could help to reduce exposure time to infected persons and expedite patient care. An examination of P/T legislation can help planners determine the best avenues to pursue with respect to prescribing and dispensing antivirals.

The option of removing antiviral drugs from prescription drug status during a pandemic is under consideration in several countries. New Zealand currently allows this during the winter season. It is not under consideration in Canada because of the regulatory assessment that identifies antiviral drugs as most appropriate for the Canadian Food and Drug Regulations' Schedule "F" (prescription drugs); to date there have been no additional data that would qualify any of the antiviral medications for removal from Schedule F.

5.4 Outbreak Control in Health Care and Other Closed Facilities

Use of antiviral drugs to control outbreaks of influenza in closed health care settings, like long-term care facilities and hospitals, is standard practice in Canada. Outbreak control involves the use of antivirals to treat cases and to provide post-exposure prophylaxis to contacts, that is, to residents, staff, volunteers and others who provide services in these facilities. Guidelines for seasonal outbreak control in institutions recommend antiviral prophylaxis for all susceptible residents, regardless of vaccination status, and for unvaccinated staff.²² Because pandemic vaccine will not be available initially, influenza outbreaks in long-term care facilities may be more severe during a pandemic than during seasonal outbreaks, when most residents are vaccinated.

In long-term care facilities, prophylactic measures generally involve the whole facility, with some exceptions when the outbreak is very small or there is very little mixing of staff or residents between units.²³ In hospitals, antiviral use for outbreak control is restricted to the unit or ward where transmission is occurring.

Early detection and confirmation of institutional outbreaks by laboratory testing will be vital during an influenza pandemic so that antivirals and other outbreak control measures can be started

immediately. This should reduce outbreak size, thereby reducing morbidity and mortality in residents and staff illness/absenteeism. Planning should ensure that there is rapid access to laboratory testing to confirm the presence of the novel virus and to antivirals for both treatment of residents and staff and for prophylaxis. Medical directives, dispensing plans and advance consent can facilitate rapid outbreak control.

Many provinces/territories have existing guidelines for managing respiratory outbreaks in health care facilities; Ontario is but one example.²⁴ Such guidelines could be modified if necessary for other types of closed facilities in which high-risk persons reside. Responsibility for guideline development or modification, dissemination and training should be assigned within the province/territory.

Pandemic planners may consider using the following criteria in deciding which types of facilities in their jurisdiction might be eligible for antiviral outbreak control:

- The facility is “closed”, i.e. has a fixed residential population with limited turnover, or in the case of a hospital has units or wards that are, or can be, closed;
- The facility has high-risk patients/residents;
- There is ongoing surveillance to detect influenza activity and outbreaks in the facility;
- It would be difficult to manage an outbreak in the setting;
- Outbreak control would reduce the burden on the health care system (e.g. prevent hospitalization or further morbidity and mortality in already-hospitalized patients); and
- The facility is able to manage an antiviral regimen with adequate medical expertise and minimal public health assistance.

A list of potential settings for the use of antivirals for outbreak control and whether they meet the criteria for limited antiviral prophylaxis is shown in Table 5 Provincial and territorial policies may vary.

Table 5 - Potential Settings for Use of Antivirals for the Control of Influenza Outbreaks During an Influenza Pandemic

Category	Type of Facility	Does it Meet the Criteria for Limited Antiviral Prophylaxis?
Health care facilities	Acute care hospitals	Yes, if the affected unit or ward is closed. Antiviral use for outbreak control would be restricted to the unit or ward where transmission is occurring.
	Long-term care facilities (LTCFs)	Yes. In smaller LTCFs outbreak control measures may involve the entire facility; in large LTCFs only units where transmission is occurring would be included.
	Speciality hospitals, e. g. complex continuing care, rehabilitation, psychiatric	Yes, provided facility is closed and there is adequate medical supervision to support antiviral use; would likely be restricted to the unit or ward where transmission is occurring.

Other closed facilities	Correctional facilities	Yes, on the basis that these are closed facilities with high-risk persons (e.g. immunosuppressed) and have the adequate medical supervision to support antiviral use.
	Retirement homes, lodges	Possibly not, on the basis that they may meet the criterion of high-risk persons but may not meet the criterion of a closed facility or adequate medical supervision to support antiviral use.
	Homes for special care and group homes	Unlikely; may meet the criterion for high-risk persons but may not meet criteria for a closed facility or adequate medical supervision to support antiviral use.

5.5 Consent and Off-label Use

It is recommended that potential recipients of antiviral drugs be given written information about the drugs, including information about potential adverse effects, what to do if adverse events occur and how to report them. Consumer information sheets are attached to the product monographs for both Tamiflu® and Relenza®. Educational materials will need to be translated into multiple languages. Advanced written consent is commonly sought in long-term care facilities to facilitate rapid use of antivirals for outbreak control.

As identified below, some of the proposed pandemic uses for antiviral drugs may be “off-label”. The term “off-label” describes the use of a drug for indications (or intended uses) other than those that have received regulatory authorization. All drugs that are for sale in Canada have received approval by Health Canada before their release on the market. The indications (or intended uses) of each drug are well specified and supported by scientific evidence. An authorized indication generally includes not only the condition to be treated but also for whom the drug is indicated and for how long. However, at the discretion of the clinician, drugs may be prescribed for purposes other than the authorized indications.

Clinicians decide to prescribe drugs off-label for different reasons. In some circumstances, there is good clinical trial evidence to support off-label use. For example, there is good clinical trial evidence to support the use of low-dose aspirin to prevent myocardial infarction. However, this evidence has never been submitted for regulatory review, and thus it is not an authorized indication. In other circumstances, there is no clinical trial evidence to support off-label use, but there is great patient need and a sound medical rationale. For example, anti-seizure medications may need to be prescribed for a pregnant woman with epilepsy even though there no trials for these medications in pregnant women.

It is common practice for physicians to prescribe drugs off-label, but this is informed by evidence, need, a sound clinical rationale and an assessment of the potential risks and benefits of a particular drug for a particular patient. What is important is that there is transparency about what an authorized indication is and what is not. In addition, it is important that patients understand the risks and benefits and consent to taking the prescribed drug.

In summary, this is the recommended approach to off-label use with respect to antiviral medications:

1. It needs to be clear to planners, clinicians and patients alike what an authorized indication of an antiviral drug is and what off-label is.
2. The decision to prescribe an antiviral off-label rests with clinicians after a careful risk/benefit assessment for an individual patient has been undertaken.

3. Transparency is important; guidelines and written patient materials that propose off-label use should include the clinical rationale as well as potential risks and benefits.
4. There should be informed consent.

Some considerations for limited off-label use of oseltamivir and zanamivir during a pandemic are as follows:

Neuraminidase inhibitors for pregnant women: Pregnant women are known to be at increased risk of complications and death from influenza, both for seasonal influenza and during past pandemics. If neuraminidase inhibitors are prescribed, zanamivir is the preferred drug as there is little systemic absorption.

Longer treatment courses: Recent studies on severely ill patients and H5N1 infections suggest potential benefit from longer treatment regimens or the use of combination therapy. More studies are under way to examine this.

Antivirals used beyond their stated shelf life: Oseltamivir and amantadine are known to be stable drugs. A number of countries have extended the functional shelf life of current stockpiles of oseltamivir from 5 to 7 years.

Note: Oseltamivir is currently contraindicated in children less than 1 year of age; however, studies in this age group are under way. The risks and benefits of treating children less than 1 year of age will need to be carefully assessed at the time of a pandemic when more data may be available.

5.6 Monitoring Adverse Reactions

Serious adverse reactions (or side effects) to neuraminidase inhibitors have been very rare. During a pandemic it will be essential to look for, and respond to, the occurrence of known serious adverse reactions and unexpected serious adverse reactions that may be recognized with widespread use of the drugs. Health Canada's existing adverse reaction surveillance system, known as the Canada Vigilance Program, will be used during a pandemic.

The Canada Vigilance Program collects and assesses reports of adverse reactions to drugs and health products. The Marketed Health Products Directorate (MHPD) of Health Canada is responsible for post-market surveillance, risk management and risk communication for drugs and other health products or medical devices. Adverse reaction reports are submitted by health professionals and consumers on a voluntary basis either directly to Health Canada or through the manufacturer. Manufacturers are required to report serious and unexpected adverse reactions that come to their attention.

The Canada Vigilance Program is supported by seven Canada Vigilance Regional Offices, which provide a regional point-of-contact for health professionals and consumers. Reports are collected by the regional offices before being forwarded to the Canada Vigilance National Office for further analysis. The Canada Vigilance Program provides a variety of tools for health professionals and consumers to report suspected adverse reactions. Reporting is simple and can be done on line, by phone or by submitting the Canada Vigilance Reporting Form by fax or mail.

During a pandemic, MHPD will continue to use the existing system to monitor adverse events to antiviral drugs. The spontaneous reporting system will be "stimulated" as health care professionals, institutions and the public are given information about "what to" and "how to" report adverse reactions to antivirals. Specific pandemic reporting guidelines for health professionals and

consumers have been developed and will be posted on Health Canada's MedEffect web site (<http://www.hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>).

MHPD will use its Canada Vigilance database to monitor and analyze the reported adverse reactions. In addition, MHPD has been developing plans to enhance its capacity for monitoring adverse reactions and for timely risk management and communication of related safety issues identified for these products. MHPD will work with PHAC to issue regular reports to national bodies and provinces/territories to provide assurance of continuing drug safety or to flag the possible need to modify recommendations should problems arise.

Suspensions of counterfeit antiviral drugs will be investigated by the Health Products and Food Branch Inspectorate of Health Canada, in collaboration with partners in the Health Products and Food Branch and other national and international partners. The Inspectorate has developed an anti-counterfeit strategy for drugs and medical devices, and has laboratory capacity to test samples that are suspected to be counterfeit or those of unknown origin. To report a problem, call 1-800-267-9675 to be directed to the nearest operational centre.

5.7 Antiviral Resistance and Effectiveness Monitoring

The susceptibility of a novel strain or the pandemic virus to antiviral drugs (both during the Pandemic Alert Period and the Pandemic Period) will be monitored on an ongoing basis. Monitoring for drug resistance is essential to know whether or not antiviral drugs will have the desired effect. This will be carried out at the National Microbiology Laboratory, which is responsible for similar resistance monitoring of seasonal influenza strains. More limited antiviral resistance testing may also be performed in some provincial public health laboratories. Plans call for a proportion of specimens from P/T laboratories to be tested for resistance to amantadine, oseltamivir and zanamivir on an ongoing basis, as well as samples from clinical situations in which drug resistance is suspected, such as outbreaks that antivirals have failed to control. For more details see the Laboratory annex (Annex C).

It will also be important to evaluate the effectiveness of antiviral treatment or prophylaxis so that clinical guidelines can be adjusted as necessary. Methodology and protocols for evaluating effectiveness, in real-time if possible, still need to be developed, and work is ongoing in this regard.

6.0 Outstanding Issues

There are a number of outstanding antiviral issues to be addressed:

- Completion of P/T antiviral implementation plans;
- Advancing a national antiviral prophylaxis strategy and facilitating the development of a national prophylaxis implementation plan;
- Identification of process and triggers for modifying the antiviral strategy during the pandemic: developing clinical guidelines based on new epidemiological data, identifying at what point in a severe pandemic we will need to switch to a prioritized treatment strategy, and creating a rapid response plan in the event of significant adverse events (shared responsibility with surveillance planners);
- Development of protocols for monitoring antiviral drug effectiveness;

- Considerations for stockpiling of antivirals by individuals or private industry for personal use or business continuity purposes;
- Development of tools for the early treatment strategy, including communication materials for health care providers and the public on the appropriate use of antiviral drugs;
- Completion of protocols for monitoring antiviral drug resistance (shared responsibility with laboratory and surveillance planners);
- Guidelines for the use of antivirals in short supply; and
- Ongoing assessment of the size, composition and uses of the NAS based on new scientific evidence, modeling studies, new antiviral agents and formulations, and new international best practices.

7.0 Considerations for Future Research

At a national Influenza Research Priorities Workshop held in 2005, research aimed at the development and use of antivirals for both treatment and prophylaxis was identified as a priority. This included studies of novel approaches with existing antiviral medications as well as research aimed at the development and evaluation of new antiviral agents. Subsequently the Canadian Institutes of Health Research have developed a funded pandemic research program that has sparked considerable Canadian research effort and the development of networks of Canadian researchers. Similar research efforts are under way in other countries. There are now several international networks actively monitoring antiviral resistance, and a Southeast Asian Influenza Clinical Research Network was recently established in response to the H5N1 situation.

Some of the important questions about effective treatment protocols can only be answered when the pandemic strain emerges. Rapid clinical trials will be critical to guide the most appropriate use of antiviral drugs. In Canada, an Emerging Infectious Diseases Research Network is being developed. This would bring government and academic researchers together in advance of a mass emergency like a pandemic to develop research protocols along with advance ethical approvals or mechanisms for rapid ethical approval, so that research studies could be rapidly launched when needed.

Outstanding antiviral research issues include the following.

7.1 Prepandemic

- Protocols for rapid epidemiological studies at the time of the pandemic to identify risk groups, attack rates, presentations, etc. (also need to determine potential researchers and networks, funding mechanisms, ethics reviews, etc).
- Protocols for rapid clinical studies at the time of the pandemic (similar determination of potential researchers and networks, funding mechanisms, ethics reviews, etc).
- Patient assessment and diagnosis:
 - How to improve clinical diagnosis;
 - Improved diagnostic tests; and
 - Predictors of severity or futility of treatment.
- Antiviral treatment:
 - Safety and effectiveness of antivirals for the treatment and prophylaxis of infants under the age of 1 year and select high-risk groups, such as pregnant women, immunocompromised persons, the elderly with underlying disease;

- More robust data on the effectiveness of neuraminidase inhibitors in reducing complications, hospitalization and mortality;
- Benefit of delayed treatment; and
- Use of combination therapy in different populations.
- Antiviral prophylaxis – the safety and effectiveness of prolonged prophylaxis.
- Antiviral resistance:
 - Mechanisms for resistance to both classes of antivirals;
 - Assessment of the biological consequences (e.g. infectiousness, virulence) of resistance; and
 - How to prevent or limit resistance.
- Development of new antiviral drugs.
- Effectiveness of antiviral delivery strategies.
- Public and health care worker attitudes to antiviral use, including prioritization scenarios.
- Adverse events – occurrence, predictors, mechanisms.

7.2 At the Time of the Pandemic/Postpandemic

- Rapid epidemiological studies to identify risk groups, attack rates, presentations etc.
- Rapid clinical studies to determine the effectiveness of treatment regimens (including combination therapy) against the pandemic strain and the need for any modifications or benefit of delayed treatment.
- Patient assessment and diagnosis:
 - How to improve clinical diagnosis;
 - Improved diagnostic tests; and
 - Predictors of severity or futility of treatment.
- Investigation of serious adverse reactions.
- Effectiveness of antiviral delivery strategies.

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Appendix 1 – Definition of Critical Infrastructure

According to Public Safety Canada, “critical infrastructure” refers to those physical and information technology facilities, networks, services and assets that, if disrupted or destroyed, would have a serious impact on the health, safety, security or economic well-being of Canadians or the effective functioning of governments in Canada. The following is a list of the 10 sectors in the National Critical Infrastructure Assurance Program,* which provides sample subsectors for each sector.

1. Energy and utilities (e.g. electrical power, natural gas, oil production and transmission systems)
2. Communications and information technology (e.g. telecommunications, broadcasting systems, software, hardware and networks, including the Internet)
3. Finance (e.g. banking, securities and investment)
4. Health care (e.g. hospitals, health care and blood supply facilities, laboratories and pharmaceuticals)
5. Food (e.g. safety, distribution, agriculture and food industry)
6. Water (e.g. drinking water and wastewater management)
7. Transportation (e.g. air, rail, marine, surface)
8. Safety (e.g. chemical, biological, radiological and nuclear safety; hazardous materials; search and rescue; emergency services; and dams)
9. Government (e.g. services, facilities, information networks, assets and key national sites and monuments)
10. Manufacturing (e.g. defence industrial base, chemical industry)

National planning for critical infrastructure protection is under way. Some provinces and territories may be using modified definitions of the critical infrastructure sectors, but the concepts are similar.

* Public Safety Canada. *About Critical Infrastructure*. Available at: <http://www.publicsafety.gc.ca/prg/em/ci/index-eng.aspx>. Accessed Dec. 23, 2008.

Appendix 2 – Antiviral Drug Prioritization Framework

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1.0 Introduction

Canada has established stockpiles of antiviral drugs for use in an influenza pandemic. However, circumstances like high demand or antiviral resistance could mean that not enough antiviral drugs are available for the intended uses. This Antiviral Drug Prioritization Framework has been developed to guide the process of determining priorities for use when antiviral drugs are anticipated to be in short supply. It provides a framework for identifying and considering the relevant factors in making recommendations.

The Antiviral Drug Prioritization Framework has been adapted from the Pandemic Vaccine Prioritization Framework¹ which was successfully used to develop sequencing guidelines for the rollout of pandemic H1N1 vaccine in fall 2009. Both frameworks are based on the Erickson De Wals framework² which is familiar to public health planners in Canada.

2.0 Antiviral Drug Prioritization Framework

The Antiviral Drug Prioritization framework (see Table 1) consists of a series of criteria which are organized into four major categories: scientific evidence, ethical considerations, program issues and additional policy considerations. Key questions are identified for each of the criteria. While scientific evidence is the key underpinning, all criteria are relevant for development of recommendations.

Table 1 - Antiviral Drug Prioritization Framework

Category	Criteria	Key Questions
1. Scientific evidence	a. Disease characteristics and burden	What is the anticipated impact in terms of numbers ill and severity of illness? Who is most affected in terms of illness, complications and death? Are there predictors of disease severity?
	b. Antiviral drug characteristics	What is known about drug efficacy, especially in reducing severe outcomes? Are there any age or risk condition-specific differences? Are there any proposed alterations to treatment schedules (e.g. dose, duration, combination therapy) Is there resistance to any of the antiviral drugs? Are there any drug safety concerns? What are the approved indications for use? Is there effective post-market surveillance?
2. Ethical considerations	Ethical considerations	What ethical principles and values should be applied? How do they inform the decision? Are the recommendations fair and equitable?
3. Program considerations	a. Antiviral strategies	What strategies might be considered (e.g. based on modeling studies)? Do the proposed strategies support the pandemic goals, and how? Are there important knowledge gaps that affect choice of strategies, and can these be addressed through timely research? What other factors might affect the strategies (e.g. pandemic stage, availability of pandemic vaccine)?
	b. Logistics	What quantities of antiviral drugs are available to which the pandemic virus is susceptible? What proportion of the drugs are in government stockpiles? What mechanisms are in place to control use? What is the size and anticipated antiviral drug utilization of each potential priority group? Are the target populations accessible in a timely way?
	c. Program acceptability	What are the public and stakeholder values that can inform decisions about antiviral drug prioritization? Should there be any alterations because of public or provider perceptions of disease severity or risk of the antivirals?
4. Additional policy considerations	a. Legal considerations	Are there any applicable legal considerations?
	b. Conformity of programs	What are other countries doing? What degree of provincial/territorial variation is acceptable?
	c. Political considerations	Will the proposed prioritization plan be free of controversy, within Canada and in an international context?

3.0 Considerations in Applying the Antiviral Drug Prioritization Framework

Annex E of the CPIP – The Use of Antiviral Drugs during a Pandemic³– identifies early antiviral treatment of clinical cases as the primary Canadian antiviral pandemic strategy. Considering all stockpiles, there are enough antivirals to treat 20-25% of the Canadian population. The other recommended pandemic use is control of laboratory-confirmed outbreaks in closed health care facilities and other closed facilities where high risk persons reside, as occurs with seasonal influenza outbreaks. In the pandemic alert period, proposed uses include treatment of novel virus cases and post-exposure prophylaxis of close contacts. Other prophylactic use is not recommended during the pandemic.

The Canadian pandemic goals provide strong direction if choices have to be made in implementing the pandemic antiviral drug program. These goals are set out in the Canadian Pandemic Influenza Plan for the Health Sector (CPIP)⁴:

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

While the most likely approach to prioritization is to restrict treatment to the most seriously ill (or those likely to become seriously ill), the strategies may vary depending on the circumstances leading to the potential shortfall and need for prioritization. Modelling may be of help in identifying the best strategies to optimize outcomes with the available drugs.

The process of using the framework to develop a specific antiviral prioritization plan involves consideration of the evidence related to each of the criteria and the applicable key questions in Table 1, followed by integration of the results as they apply to potential target groups. Developing recommendations for prioritization may not be straightforward. Not all of the necessary information is or will be available. Integrating target groups based on severity of presentation, underlying risk condition or age (which might be suggested by pandemic epidemiology), occupational priority or setting could be challenging.

Potential data and information needs for each of the criteria are outlined in Appendix 1. Some of these data will be available only through special studies, for which protocols and arrangements should be set up in advance. Some measures, such as mortality, are open to a number of equally valid interpretations, as described in Section 3.1. Consideration of ethical principles and values, and an understanding of public and stakeholder values will help when alternative choices must be weighed.

The following sections highlight the data gaps and some of the potential pitfalls surrounding considerations of the criteria.

3.1 Disease Characteristics and Burden (Pandemic Epidemiology)

Knowledge of the epidemiology of the pandemic and its disease burden is one of the most important considerations in developing recommendations for antiviral drug use, including prioritization of recipients. Ideally one would use Canadian epidemiological data on disease characteristics; however decision-making cannot be delayed if data are not available. It is hoped that detailed epidemiological data will emerge rapidly from the areas of the world first affected by the pandemic. When available, Canadian data can be used to validate or adjust the plan.

Epidemiological data are important both for understanding who is most at risk for severe outcomes and for anticipating antiviral utilization. The key epidemiological measures that could affect prioritization include virus transmission and attack rates, and the rate and pattern of severe illness and mortality.

If the spectrum of illness includes more severe cases than anticipated, a higher proportion of those who become ill would be expected to seek medical care or need hospitalization, potentially increasing the numbers needing treatment. Similarly, fewer cases of severe illness could reduce the need for treatment. A high attack rate or extended pandemic wave could increase the overall need for antivirals, especially if this occurs before vaccine is available. There are usually age-specific differences in attack rate, with children generally having higher attack rates than adults. This could increase the need for paediatric formulations.

Identification of the groups most at risk of severe outcomes (such as hospitalization, admission to intensive care (ICU), need for a ventilator, or death) will allow targeting of those most likely to need antiviral drugs. Epidemiological analysis of surveillance data can identify underlying risk factors for severe disease, such as the existing NACI high risk conditions or new risk factors identified in the pandemic. High risk settings might also be identified; for example remote and isolated communities were considered high risk in the 2009 H1N1 pandemic because of frequent crowded living conditions, high proportions of persons with underlying medical conditions, and limited access to medical care. Epidemiological or clinical studies might also identify additional predictors of severe disease, i.e. clinical presentations that could be used in targeting treatment.

Mortality data can be expressed in different ways, e.g. as the number or rate of deaths by age or risk group, or as years of life lost (YLL), which can be further refined into years of healthy life lost or working years of life lost. The choice of one of these mortality measures implies an ethical value judgement as to whether some lives (e.g. young persons or elders) are more important than others. The use of YLL is supported by the observation that, in a pandemic, mortality is shifted to younger ages compared to seasonal influenza.⁵

Another factor for consideration is whether persons who are most likely to spread disease should be given priority in order to reduce the risk to others. Traditionally, one would consider the risk that infected health care workers could pose to their vulnerable patients and the role of children in transmitting influenza within families and the community at large. However the evidence for reduction of infectivity by early antiviral treatment is inconsistent.

Annex E suggests that antivirals continue to be used for the control of institutional outbreaks during a pandemic as for seasonal influenza outbreaks. The risk of outbreaks in long term care (LTC) settings may vary depending on the pandemic virus and its age specific patterns. For example during the 2009 H1N1 pandemic few outbreaks have occurred in LTC homes for the elderly.

3.2 Antiviral Drug Characteristics

Key factors to consider regarding the antiviral drugs themselves include efficacy, safety, and the resistance profile of the pandemic virus.

The latest information should be collated on efficacy of treatment, in particular reduction of severe outcomes such as pneumonia, hospitalization, admission to ICU or death. Studies with the new pandemic virus are needed to confirm antiviral efficacy; until these results are available, efficacy may be inferred from seasonal flu experience. Any differences in the efficacy of treatment,

e.g. for certain clinical presentations, risk groups or ages, or by timing of presentation should be noted. It is possible that effective treatment will require higher doses, longer duration of treatment and /or combination therapy, all of which would affect drug availability.

Impact on shortening the duration of illness and potentially reducing infectivity is an important consideration in whether to prioritize treatment of health care workers or other critical infrastructure workers.

When drugs are given to large numbers of persons, unexpected side effects may be detected. This may alter the risk benefit ratio suggesting re-evaluation of treatment recommendations.

Antiviral resistance may occur spontaneously or may emerge during or following antiviral treatment. The risk of resistance is greatest with the M2 blockers (which are not recommended for sole treatment use) and least with zanamivir. Should widespread resistance develop to oseltamivir, zanamivir would be the only remaining treatment option. This would present severe challenges because zanamivir makes up only about 20% of the current stockpile (enough for about 5% of the population) and it cannot be used as broadly as oseltamivir. Zanamivir is not suitable for: children under age seven; persons with reactive airways disease; persons who cannot use the inhaler, e.g. some elderly and nursing home patients and small children; persons with severe respiratory disease (because bioavailability would be impeded); and treatment of seriously ill persons if there is evidence that the pandemic virus replicates outside of the respiratory system.

Appropriate decision-making relies on a robust and timely monitoring program for antiviral utilization, resistance and effectiveness as antivirals are used. The rate of depletion of the stockpile should be monitored along with the types of patients who are being treated, in order to assess the extent to which high risk individuals and other targeted groups (e.g. health care workers) are being reached.

3.3 Ethical Considerations

WHO has recently published guidance on ethical considerations in developing a response to pandemic influenza.⁶ Chapter 3 of the WHO guidelines deals with priority-setting and equitable access to therapeutic and prophylactic measures. The key recommendations include establishing a process for setting priorities and promoting equitable access that involves society and relevant stakeholders and that incorporates pre-established mechanisms for revising decisions, and providing timely and accurate information to the public.

WHO identifies the following key principles that need to be taken into account in developing criteria for use in prioritization:

- utility (the principle of acting to maximize aggregate welfare) - whether for individual or community benefit;
- equity (the fair distribution of benefits and burdens) - this principle may sometimes conflict with utility considerations;
- age – e.g. the “fair innings” argument (the idea that everyone is entitled to some “normal” span of life years). WHO notes that opinions were mixed on this criterion and that age-based prioritization criteria should be adopted only after wide public consultation;
- non-discrimination against individuals based on inappropriate characteristics such as gender, race and ethnicity, religion, political affiliation, national origin and social or economic status;
- the goals of the antiviral drug strategy (noting that possible goals may compete with each other).

Many jurisdictions (e.g. Australia, New Zealand, UK, USA) have developed an ethical framework to assist their pandemic planning.⁷⁻¹⁰ Similarly, the CPIP contains a section called Ethics and Pandemic Planning, which identifies the ethical principles that have been used in national planning.

Some Canadian provinces, for example Quebec and Alberta,^{11,12} have developed their own comprehensive ethical advice for pandemic planning, while others have adopted the ethical framework for pandemic planning prepared by the University of Toronto Joint Centre for Bioethics.^{13,14} The ethical principles and values identified in this framework and in the CPIP are summarized in Appendix 2.

Numerous relevant ethical discussions are found in the literature.¹⁵⁻²⁰ A full analysis of the ethical issues surrounding the antiviral drug prioritization question is beyond the scope of this document, but issues related to the principles of equity (including access to drugs without financial constraint) and their application to prioritization decisions must be highlighted. Both the WHO and the CPIP identify equity as an important ethical principle informing pandemic planning. However, there are other ethics principles that also need to be brought to bear, such as utility and optimizing the risk/benefit ratio.

3.4 Antiviral Strategies

The overall pandemic goals were outlined at the start of Section 3.0. In order to support the overall goals, Annex E sets out the goals of the national antiviral strategy as follows:

- reducing the severity and duration of illness (including a decrease in the occurrence of complications, hospitalization and death);
- mitigating social disruption by reducing the impact of absenteeism due to illness in critical infrastructure sectors; and
- reducing the level and duration of viral shedding, thereby possibly reducing transmission.

If prioritization is necessary, choices must be made about the relative importance of these goals. For example in a mild pandemic, one might wish to focus primarily on the first goal, and within that goal on the reduction of severity of illness rather than its duration. A mild pandemic would be unlikely to cause social disruption, making the second goal less important.

If treatment cannot be offered to everyone who is ill as proposed in Annex E, antiviral drugs could be used in a variety of ways to address the goals. For example, to minimize serious illness and overall deaths one could concentrate first on those most likely to get sick or to die, and/or one could include health care workers to maintain the functioning of the health care system and maximize everyone's chance for optimal health care. Societal disruption is most likely to occur in a moderate to severe pandemic as a result of high absenteeism of the workforce. Providing priority treatment to first responders (police, fire, ambulance) and other critical infrastructure workers could minimize the additional impact of the loss of these services; however this approach might not be necessary in a mild pandemic.

Strategies will also vary depending on the reason for the anticipated short supply of antivirals. Heavier demand than anticipated might need only modest adjustments to the treatment strategy combined with appropriate health care provider and public communication. If drug resistance precludes use of oseltamivir, more drastic prioritization would be required for best use of the limited supplies of zanamivir. If treatment regimes prove ineffective or drugs can't be delivered in a timely way, reconsideration of prophylaxis strategies might be warranted.

Modeling of the impact of different strategies can be extremely helpful in identifying the best ways to optimize outcomes.²¹⁻²⁵ Useful models and relevant publications may be available from the Canadian or WHO pandemic modeling networks.

Antiviral strategies also need to take into account the other pandemic interventions, especially the availability of vaccine. Once vaccine is available the need for antiviral treatment will be sharply reduced; conversely if vaccine availability is delayed there will be ongoing demand for antiviral drugs that could exceed supply.

3.5 Logistical Issues

Key logistical considerations include identifying the quantities of antiviral drugs available, predicting the anticipated utilization by ill persons in the proposed target groups, and assessing the feasibility of implementing the proposed prioritization recommendations.

It is important to identify all antivirals that could potentially be used, given the resistance profile of the pandemic virus. Potential sources include the national stockpiles, additional provincial stockpiles, and private stockpiles (e.g. held by some large employers or health care facilities). Manufacturers may have additional supplies for sale to government or available commercially. It may be more difficult, however, to control use of antivirals that are available outside of government stockpiles. Emergency authorizations may be used to allow unapproved uses (e.g. oseltamivir below age one) or access to novel drugs (e.g. IV peramivir).

Demand and utilization are difficult to predict. In addition to epidemiological factors like pandemic severity, utilization is influenced by accessibility of the target populations and factors that influence timely presentation for care, like the delivery strategies chosen. The 50% rate of presentation for care on which the national stockpile size was modeled comes from the Meltzer model and is based primarily on US experience during the pandemics of 1957 and 1968.²⁶ It is not known if this older US experience is realistic for Canada and this should be reassessed as further data become available.

Antiviral effectiveness is very limited after 48 hours from onset of illness, except in seriously ill or immunocompromised patients. Effective implementation of the early treatment strategy relies on public and provider awareness of the need to begin treatment within 48 hours of onset of illness, preferably within 12-24 hours, and ready access to the antiviral drugs. Public education to promote timely medical care could lead to higher utilization. This is not an issue if treatment is to be recommended for all ill persons with certain underlying risk conditions. However apart from the presence of underlying risk conditions, it may be difficult at early stages to predict which individuals will experience severe illness.

Estimates should also take into account a certain amount of drug wastage, including unavoidable treatment of persons with influenza-like-illness (ILI) who in fact have infection due to another respiratory virus. It is not known to what extent other viruses, including seasonal influenza viruses, will co-circulate with the pandemic strain. The current laboratory strategy does not allow for routine testing to aid diagnosis except in selected cases. Aggressive implementation of the early treatment strategy to maximize its benefits will inevitably mean over-treatment, but the extent of this cannot be predicted.

For any prioritization plan, it is important to assess the feasibility of implementing the recommendations in a way that controls use without impeding timely target group access. The methods used by a province or territory to implement the early treatment strategy could affect access as well as the rate of utilization of antiviral drugs. If there are only enough drugs for the most severely ill, restricting access to hospitals is reasonable. If those with early illness and underlying risk factors are also to be treated, then it is important to look at how best to reach them quickly, whether through family doctors or special clinics. In high risk settings that are to be prioritized, pre-positioning drugs can help improve timely access.

Strict public health control with rigid application of clinical algorithms may preserve antiviral supply, but allowing some clinical judgment may benefit more patients.

Telephone triage and prescribing may be practical ways to deal with large numbers of patients within the treatment window but are probably not useful strategies if priority use is restricted to seriously ill persons. The choice of drug depots for antiviral distribution within a jurisdiction could also have an impact – the fewer sites that are selected to hold antiviral drugs, the easier it is to control inventory in situations of short supply.

3.6 Program Acceptability

Some of the specific concerns about program acceptability by public and stakeholders include the following:

- general unfamiliarity with antiviral drugs by public and medical community;
- general acceptability of the priority choices (tied to public perceptions about mortality and value of life);
- placement of children on the priority list;
- perceived risk or benefit to antiviral treatment;
- use of drugs with limited safety and minimal clinical efficacy data;
- public response to reports of severe adverse drug reactions;
- need for treatment in a pandemic that is perceived as mild.

The TGAP (Task Group on Antivirals for Prophylaxis) deliberative dialogue process²⁷ explored public and stakeholder beliefs and values in relation to antiviral prophylaxis. The key values emphasized for decision-making were practicality, fairness and equity, compassion for the vulnerable, public awareness and engagement, and government leadership (see Appendix 3).

The University of Toronto Joint Centre for Bioethics, through its Canadian Program of Research Ethics in a Pandemic (<http://www.canprep.ca/>), has engaged in pandemic research projects that include stakeholder forums and public consultation about ethical values related to pandemic issues. These and similar initiatives (e.g. government-commissioned survey data) can provide helpful guidance about public and stakeholder opinions.

3.7 Legal Considerations

There are many factors that must be carefully considered in the development and use of an antiviral drug prioritization framework. If governments choose to create priority groups for the receipt of antiviral drugs, they could face Charter of Rights and Freedoms challenges under section 15 (equality rights) and/or under section 7 (life, liberty and security of the person). It is important for governments that decide to create priority groups, therefore, to retain evidence that the decision to create the lists was based on a sound scientific, social, logistical and ethical policy rationale. Governments should be able to demonstrate that the composition of the lists was based on reasonable, fair and rational considerations. Further, the policy decision to create priority lists should be communicated widely in a clear and consistent manner, and the prioritization framework should be followed carefully and precisely unless necessary modifications due to new evidence justify a change.

3.8 Potential Priority Groups

There are a number of possible approaches to the identification of potential target groups for prioritization. The following comments are organized under the existing antiviral goals from Annex E (outlined in Section 3.4); however it is understood that the antiviral goals might also need to be modified.

Reducing the severity and duration of illness (including a decrease in the occurrence of complications, hospitalization and death)

Addressing this goal would involve the consideration of the following potential priority groups:

- Persons who are seriously ill – e.g. hospitalized patients or those with symptoms that are indicative of more serious illness (e.g. shortness of breath, chest pain or altered consciousness)
- Persons at high risk of poor outcome – identifying persons and groups at high risk of poor outcome will depend on epidemiological analysis of who is most likely to develop complications, require hospitalization or die as a result of infection with the pandemic virus. The existing NACI recommendations²⁸ identify high risk groups for seasonal influenza based on age and underlying medical conditions* which are likely to also place persons at high risk during a pandemic. Review of pandemic epidemiology may identify additional risk factors for poor outcome (e.g. morbid obesity, asthma)
- Healthy persons (children, adults, seniors) – Certain age groups may be found to be at higher risk of severe outcomes during the pandemic or, conversely, relatively spared. For example, if an H2 pandemic were to occur, persons born before 1968 who were exposed to circulating H2 viruses between 1957 and 1968 might have some pre-existing immunity
- Persons capable of transmitting infection to high risk persons – early treatment of health care workers or household and close contacts of high risk persons might help reduce the risk of spread of infection to the high risk persons. If vaccine is available, the latter category could be narrowed to contacts of persons who can't be vaccinated (e.g. infants < 6 months of age) or who are unlikely to respond to vaccine (e.g. immunosuppressed persons)

* Persons with underlying chronic disease, residents of long-term care homes, persons aged 65+, healthy children aged 6-23 months and pregnant women

- Selected settings – this category could include remote and isolated communities, closed health care facilities, and other closed settings like correctional facilities. Strategies for consideration in a prioritization plan could include outbreak control as outlined in Annex E (treatment and post-exposure prophylaxis) or treatment only.

Mitigating social disruption by reducing the impact of absenteeism due to illness in critical infrastructure sectors

Disease severity and anticipated absenteeism will be the major influences in the degree of social disruption caused by the pandemic, and therefore the extent to which treatment of critical infrastructure workers (some or selected groups) might need to be prioritized. The concept of including the person doing the task (who could be a volunteer or family member), not just the person with the job title, needs emphasis in occupational settings.

The critical infrastructure sectors are outlined in Appendix 4. For prioritization consideration the following groupings are proposed:

- Health care workers – maintenance of a well-functioning health care system contributes heavily to the first pandemic goal of reducing severe morbidity and mortality, both due to the pandemic virus and for other critical illness or injury. Prioritization of health care workers also helps prevent spread of infection to vulnerable patients and prevent outbreaks. The principle of reciprocity is also relevant as health care workers will be asked to expose themselves to more risk than usual by caring for persons with the pandemic virus. For consistency, consider using the same definition for health care workers as used for vaccine prioritization: *All health care system workers involved with the pandemic response or delivery of essential health services*²⁹
- First responders – first responders (police and firefighters) often attend emergency health situations with Emergency Medical Services (EMS)
- Military - consideration should be given to military involved in critical missions
- Other critical infrastructure workers – consider as needed to maintain essential services.

Reducing the level and duration of viral shedding, thereby possibly reducing transmission

Achievement of this goal is more speculative; however it is part of the rationale for prioritizing health care workers.

4.0 Using the Antiviral Drug Prioritization Framework

The Clinical Care and Antiviral Task Group has the responsibility for making recommendations for antiviral drug prioritization (if necessary) for consideration by the Public Health Network. These will be based on a situational analysis specific to the pandemic.

Suggestions for this process include the following steps:

- Decide if additional persons/groups (e.g. ethicists, modelers) should be invited to participate in the process. It is particularly important to have provincial/territorial involvement to address implementation and logistical feasibility of the proposed recommendations
- Decide on a meeting format and whether a face-to-face meeting is required
- Decide if there will be stakeholder or other consultation before the plan is finalized
- Assemble all of the background information for presentation to the Task Group

- Task Group process:
 - o Review all of the information and discuss the questions posed for each of the criteria
 - o Confirm or define the goals/objectives for the revised program
 - o Consider potential target groups and antiviral uses
 - o Order (at least group) the proposed target group/antiviral uses
 - o Adjust proposed target group/antiviral uses to the quantities available
- Conduct stakeholder consultation if desired, and revise as needed
- Once the prioritization plan is implemented, continue to monitor antiviral utilization, resistance and effectiveness to ensure most effective use.

The appendices to this document provide several tools, such as a list of the data and information needs that should be assembled for the Task Group's consideration (Appendix 1), and a draft discussion tool to assist individuals in assimilating and weighing the information (Appendix 5).

It is expected that those developing the recommendations will provide a full rationale and identify the factors that weighed heavily in the decisions.

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Appendix 1 – Data and Information Needs for Antiviral Prioritization Decision-Making

Here is a list of the data and information that will be needed for the prioritization process. This should be gathered, analysed and presented in advance to the group that will be doing the prioritization, to give them the opportunity to identify any additional analyses or information needed for decision-making.

1. Scientific Information

- **Pandemic epidemiology**
 - o Attack rate (age-specific if known)
 - o Case fatality rate (age-specific)
 - o Indicators of disease severity, e.g. rates of complications and hospitalization
 - o Risk factors for severe illness, hospitalization and death; and predictors of severe outcomes
 - o Population susceptibility – age-specific serosurvey and vaccination data to ascertain population immunity
 - o Predictions for future pandemic waves
- **Antiviral drug information**
 - o Antiviral drug efficacy data by age and risk status
 - o Antiviral drug susceptibility and resistance data
 - o Antiviral drug safety data, including any age-specific effects

2. Ethical Considerations

- Ethical principles from CPIP
- Results of public consultations

3. Program Issues

- **Antiviral strategies**
 - o Identification of potential options
 - o Summary of evidence base and modeling of different strategies
- **Logistics**
 - o Antiviral drug availability, including amounts in government stockpiles
 - o Information on proposed P/T distribution and control strategies
 - o Size of Canadian and provincial/territorial populations by age and sex (5 year breakdowns)
 - o Size of all proposed sub-population groups and/or risk categories
 - o Estimates of anticipated need and utilization
- **Acceptability**
 - o Results of public and stakeholder consultations, media scan and opinion surveys

4. Additional Policy Considerations

- Antiviral distribution plans from other countries, especially the USA
- Identification of other potential significant issues with policy analysis and legal opinion as needed (including liability issues)

Appendix 2 – Relevant Ethical Principles to Consider

Ethical principle (CPIP 2006)	Applicability to antiviral prioritization strategy
Protect and promote the public's health	Underlying premise of antiviral program (but there are various strategies to do this)
Ensure equity and distributive justice (fair and equitable distribution of resources based on need)	Develop fair criteria for prioritization Multiple possible applications
Respect the inherent dignity of all persons	Use consistent approach to prioritization decisions
Use the least restrictive means (infringe on personal autonomy only to the extent necessary to ensure the public good)	Prioritization decisions might interfere with usual doctor-patient relationship in making treatment decisions
Optimize the risk/benefit ratio	Maximize the benefit and minimize the risks in prioritization decisions
Work with transparency and accountability	Justify prioritization plan and decisions Public and stakeholder consultation Widespread dissemination of prioritization framework
Additional ethical values from U of T Joint Centre for Bioethics ethical framework ¹²	
Decision-making processes are reasonable, inclusive, responsive	Fair criteria, consultation process Open to review as situation changes
Reciprocity (responsibility of society to support those who face a disproportionate burden in protecting the public good)	Prioritization for health care workers Also reciprocal responsibility of health care workers to report illness promptly so they can be treated
Trust	Build trust with stakeholders before pandemic occurs; ensure that decision-making processes are ethical and transparent
Solidarity	Communication and open collaboration with stakeholders
Stewardship	Need to consider benefit to the public good and equity

Appendix 3 – Goals and Values from the Antiviral Deliberative Dialogue Process

Participants supported three goals:

- to ensure that normal societal functions are maintained
- to minimize public fear and panic
- to reduce serious illness and death during a pandemic.

Priority recipients if antiviral prophylaxis were available:

- health care workers with close patient contact (general agreement)
- those in emergency services (opinion divided, especially about other essential services)
- the most vulnerable, including children, those in institutions, chronically ill and elderly (divided opinion; children most often flagged).

Values emphasized for decision-making:

- Practicality/efficiency/pragmatism – minimize illness and death, protect health care workers, consider ease of delivery
- Fairness and equality – consistency across country, avoid inequities of access
- Compassion for the vulnerable
- Public awareness/engagement – to gain understanding and support
- Strong role for government; trust and confidence – government to lead, responsibility to protect vulnerable and workers who will be exposed.

Source: EKOS Research Associates, Inc. for the Public Health Agency of Canada. The Use of Antivirals for Prophylaxis: Deliberative Dialogue Process. Final Findings Report²⁷

Appendix 4 – Definition of Critical Infrastructure

Public Safety Canada defines critical infrastructure as those physical and information technology facilities, networks, services and assets which, if disrupted or destroyed, would have a serious impact on the health, safety, security or economic well-being of Canadians or the effective functioning of governments and businesses in Canada.

The ten sectors of Canada's critical infrastructure consist of:

- Energy and utilities (e.g. electrical power, natural gas, oil production and transmission systems)
- Information and communications technology (e.g. telecommunications, broadcasting systems, software, hardware and networks including the Internet)
- Finance (e.g. banking, securities and investment)
- Health (e.g. hospitals, health care and blood supply facilities, laboratories and pharmaceuticals)
- Food (e.g. safety, distribution, agriculture and food industry)
- Water (e.g. drinking water and wastewater management)
- Transportation (e.g. air, rail, marine, surface)
- Safety (e.g. first responders, emergency services and dams)
- Government (e.g. services, facilities, information networks, assets and key national sites and monuments)
- Manufacturing (e.g. defence industrial base, chemical industry)

Source: Public Safety Canada. About Critical Infrastructure. Available at: <http://www.publicsafety.gc.ca/prg/em/ci/index-eng.aspx>

Appendix 5 – Antiviral Drug Prioritization Framework, Draft Discussion Tool

Category 1: Scientific Evidence

Criteria	Questions	Considerations	Notes
Disease characteristics and burden	What is the anticipated impact in terms of numbers ill and severity of illness?	<ul style="list-style-type: none"> High attack rates and/or disease severity could mean higher number of severely ill persons who could benefit from treatment Anticipated societal disruption might lead to occupational groups being made a higher priority. Pressure to treat all cases if disease severity is high 	
	Who is most affected in terms of illness, complications and death?	<ul style="list-style-type: none"> Can certain ages or risk groups be targeted to prevent severe disease? NACI and/or additional high-risk conditions? Increased occupational risk? 	
	Are there predictors of disease severity?	<ul style="list-style-type: none"> Can persons be identified who should be treated to avoid bad outcomes? 	
Antiviral drug characteristics	What is known about drug efficacy, especially in reducing severe outcomes? Are there any age or risk condition-specific differences?	<ul style="list-style-type: none"> Adjust priority for groups with most anticipated benefit 	
	Are there any proposed alterations to treatment schedules (e.g. dose, duration, combination therapy)?	<ul style="list-style-type: none"> Could affect drug supply 	
	Is there resistance to any of the antiviral drugs?	<ul style="list-style-type: none"> Would affect choice and quantity of drugs available Could affect strategies for use and targets (e.g. young children can't use zanamivir) 	
	Are there any drug safety concerns?	<ul style="list-style-type: none"> Reconsider risk/benefit for certain ages or population sub-groups 	
	What are the approved indications for use?	<ul style="list-style-type: none"> Will there be need for off label use? 	
	Is there effective post-market surveillance?	<ul style="list-style-type: none"> How will safety, effectiveness and utilization be monitored? 	

Category 2: Ethical Considerations

Criteria	Questions	Considerations	Notes
Ethical considerations	What ethical principles and values should be applied?	<ul style="list-style-type: none"> Are the ethical principles and values from the CPIP and WHO applicable? Are any of the other ethical frameworks from Canada (e.g. U of T) or elsewhere applicable? To what extent can we extrapolate societal values from the Task Group on Antiviral Prophylaxis or other public consultations? 	
	How do they inform the decision?	<ul style="list-style-type: none"> To what degree should ethical principles prevail over scientific considerations if they do not point in the same direction? 	
	Are the recommendations fair and equitable?	<ul style="list-style-type: none"> What criteria can be used to assess whether they are fair and equitable? 	

Category 3: Program Considerations

Criteria	Questions	Considerations	Notes
Antiviral strategies	What strategies might be considered (e.g. from modeling studies)? How do the proposed strategies support the pandemic goals?	<ul style="list-style-type: none"> Translation of the pandemic goals into strategy involves value judgements 	
	Are there important knowledge gaps that affect choice of strategies?	<ul style="list-style-type: none"> Can these be addressed through timely research? 	
	What other factors might affect the strategies?	<ul style="list-style-type: none"> E.g. pandemic stage, availability of pandemic vaccine 	
Logistical issues	What quantities of antiviral drugs are available to which the pandemic virus is susceptible?	<ul style="list-style-type: none"> Consider resistance profile Should match prioritization process to vaccine availability Parenteral antivirals may be needed in severe pandemic with many hospitalized patients 	
	What proportion of drugs are in government stockpiles? What mechanisms are in place to control use?	<ul style="list-style-type: none"> Successful implementation of prioritization strategies depends on ability to control distribution of drugs 	
	What is the size and anticipated antiviral drug utilization of each potential priority group?	<ul style="list-style-type: none"> What are most appropriate potential priority groups or settings? Definitions for health care or critical infrastructure workers could be problematic Possible P/T variation in uptake 	
	Are the target populations accessible in a timely way?	<ul style="list-style-type: none"> Some targets are hard to identify or access – should that affect their prioritization? Need flexibility for some settings (e.g. remote settings with poor access to health care) 	

Program acceptability	What are the public and stakeholder values that can inform decisions about antiviral drug prioritization?	<ul style="list-style-type: none"> High value for children, even if not most severely affected, identified in US planning 	
	Should there be any alterations because of public or provider perceptions of disease severity or risk of the drugs?	<ul style="list-style-type: none"> Increased occurrence of severe disease will drive demand up Unexpected adverse drug reactions will affect attitudes and utilization 	

Category 4: Other Policy Considerations

Criteria	Questions	Considerations	Notes
Legal considerations	Are there any applicable legal considerations?	<ul style="list-style-type: none"> Examples include departure from manufacturer's recommendations, use of new drugs under emergency authorization procedures Legal review desirable 	
Conformity of programs	What are other countries doing?	<ul style="list-style-type: none"> How important is this factor? (communications, political considerations) Countries may differ in terms of antiviral availability and pandemic goals and values, but rationales for variation may not be widely known Cross-border issues 	
	What degree of provincial/territorial variation is acceptable?	<ul style="list-style-type: none"> Anticipated variation in delivery methods and in critical infrastructure worker categories What if there is variation in pandemic activity? Cross-border issues 	
Political considerations	Will the proposed prioritization plan be free of controversy, within Canada and in an international context?	<ul style="list-style-type: none"> Will we be criticized for our use of antivirals if other countries are short? 	