CANADIAN PANDEMIC INFLUENZA PREPAREDNESS:
Planning Guidance for the Health Sector

Antiviral Annex
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PREAMBLE

The Antiviral Annex of the Canadian Pandemic Influenza Preparedness: Planning Guidance for the Health Sector (CPIP) is a federal, provincial and territorial (FPT) guidance document that outlines how jurisdictions will work together to ensure a coordinated and consistent health-sector approach to Canada’s antiviral strategy. CPIP’s main body and annexes are intended to be used together.

While it is anticipated that CPIP’s strategic direction and guidance will inform FPT planning to support a consistent and coordinated response across jurisdictions, provinces and territories (PT) have ultimate responsibility for planning and decision-making within their respective jurisdictions.

It is important to note that CPIP is not an actual response plan. Rather, it is a guidance document for pandemic influenza that can be used to support an FPT public health emergency response approach. While CPIP is specific to pandemic influenza, much of its guidance is also applicable to other public health emergencies, such as outbreaks of other communicable diseases.

1.0 INTRODUCTION

1.1 Background

Antiviral medications (known as antivirals) are used to treat persons with influenza or given to persons, either pre or post exposure, to prevent influenza. They are the only influenza-specific intervention that can be used to mitigate the impact of an influenza pandemic before vaccine becomes available.

Since 2004, Canadian FPT governments have been stockpiling antivirals to help ensure pan-Canadian equitable access to a secure, government-controlled supply of antivirals to be used during a pandemic.

In Canada, there are two government stockpiles of antivirals intended for pandemic influenza use:

- **The National Antiviral Stockpile (NAS)** is the collective name for the antiviral stockpiles held and managed by each PT. The NAS is intended to provide antivirals for all eligible persons living in Canada including federal populations within a jurisdiction, such as on reserve First Nations and correctional facility inmates.
The National Emergency Strategic Stockpile (NESS) is a federally owned and managed stockpile of emergency supplies, including influenza antivirals. The antivirals in the NESS are intended to provide surge capacity in support of FPT efforts to manage pandemic and/or avian influenza. Therefore, if PTs exhaust their own NAS supply, they may request access to NESS antivirals.

Canada’s antiviral strategy includes stockpiling antivirals to help to ensure equitable and coordinated access to a secure government-controlled supply of safe and effective antivirals, sustainable antiviral stockpile procurement and management approaches, provision of guidance on antiviral use and other best practices relating to antiviral use during a pandemic. This Annex describes the many components involved in planning to make antivirals accessible to those who may need them during an influenza pandemic.

1.2 Purpose

The purpose of the Antiviral Annex is to outline Canada’s national antiviral strategy and to provide antiviral-specific operational and technical guidance for the health sector. It is one of a series of CPIP technical annexes.

The primary audiences for the Antiviral Annex are the FPT ministries of health together with other federal government departments that have responsibilities for the health care of select populations. The Annex also serves as a reference document for other government departments, non-governmental organizations engaged in health and other stakeholders.

1.3 Changes in This Version

This version of the Antiviral Annex is considerably changed from the 2009 version in both format and content. Lessons learned from the 2009 influenza pandemic have been incorporated, including information on antiviral supply and best practices in stockpile management. Canada’s antiviral strategy is described, including updated recommendations on NAS use, composition and size. Antiviral-specific objectives, assumptions and FPT roles and responsibilities with respect to the antiviral strategy have also been updated.

The underlying principles and approaches outlined in CPIP are highlighted throughout this Annex and the CPIP pandemic risk management approach has been incorporated. The CPIP planning scenarios are used to identify antiviral-specific risk management considerations in pandemics of varying impact along with potential mitigation approaches. Antiviral-specific triggers for action and key decisions are outlined.

The Antiviral Prioritization Framework (Appendix A) has been updated to provide more guidance on its use. Appendix B provides an example of clinical guidance on antiviral use during a pandemic. Appendix C provides a detailed summary of the updated expert recommendations on NAS use, composition and size and their rationale.
2.0 CONTEXT FOR PLANNING

2.1 Role of Antivirals in Prevention and Treatment of Pandemic Influenza

Antivirals can be used to treat persons with influenza illness and for prophylaxis (prevention) of influenza. According to the currently available scientific evidence, antiviral treatment provides clinical benefit in both previously healthy and high-risk individuals. The use of antivirals for treatment and prevention of influenza is supported by clinical experts and is part of the standard of care for persons with suspected or confirmed influenza infection who are at higher risk of complications or who require hospitalization.

Antivirals authorized in Canada for influenza treatment and prophylaxis fall into two classes: neuraminidase inhibitors (NIs) - oseltamivir, peramivir and zanamivir; and M2 ion channel blockers - amantadine. There are important differences between these two classes of antivirals.

NIs are currently preferred to the M2 ion channel blockers because of their superior adverse event profile and lower rate of antiviral drug resistance. Of the NIs, oseltamivir is preferable because it is administered orally, can be used with all age groups and has been studied the most extensively. In addition, it is recommended as the drug of choice for patients with severe or progressive clinical illness and for pregnant women. Zanamivir can be used as a substitute for oseltamivir, if necessary, in persons seven years of age and older without contraindications. Peramivir, administered as a single dose infusion, is the only intravenous formulation licensed in Canada.

Amantadine is generally not recommended for the treatment of influenza because of its side effects and widespread antiviral resistance that has developed over the past decade to this drug.

### 2.2 Uncertainties and Unpredictability

Antivirals play an important role during an influenza pandemic, especially before an effective vaccine becomes available. Given the risk management approach on which the CPIP is based, it is important for health sector planners to be aware of the potential uncertainties associated with antiviral use during a pandemic:

- **Extent of antiviral resistance** - Resistance of influenza viruses to antiviral drugs can occur spontaneously in the population or arise during the treatment of someone who is ill, especially if the patient is immunocompromised. Resistant influenza viruses have also been found in persons who had been on antiviral prophylaxis.¹¹

- **Antiviral effectiveness** - Until a novel influenza strain emerges, it won’t be known how effective NIs will be for treatment and prevention of pandemic influenza. In addition to antiviral susceptibility of the novel virus strain, the optimal effectiveness of antivirals can be affected by delays in administration (their efficacy is strongly inversely correlated with time of initiation relative to onset of symptoms).

- **Ability to target antiviral treatment to true influenza cases** - Without a laboratory confirmation, it is sometimes difficult to clinically differentiate influenza-like illness (ILI) due to influenza infection from ILI due to other respiratory viruses, especially during the fall and winter when other respiratory viruses are co-circulating. It is not known to what extent rapid and accurate influenza diagnostic tests will be available during a pandemic.

- **Supply and demand** - The availability of antivirals during a pandemic will depend on several factors, including the size and composition of the stockpiles at that time, antiviral availability in the commercial market, patterns of antiviral drug resistance and public demand for treatment. There are several influencing factors that could potentially increase the demand for antiviral treatment, such as the epidemiological characteristics of the pandemic (e.g., age groups affected, clinical severity, virus transmissibility), implementation and effectiveness of other public health interventions, and media coverage of deaths.

- **Antiviral safety issues** - Adverse events can occur with any medication. Although antivirals are known to have a favourable safety profile, when a medication is given to thousands of people within a relatively short period, rare and sometimes unexpected adverse events may be detected.

Section 3.5 Key Elements of the Response provides details on the steps being taken to address these uncertainties. Section 3.6.2 Risk Management Considerations for the Antiviral Strategy outlines potential mitigation strategies.

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2.3 Lessons Learned From the 2009 Pandemic

2.3.1 SCIENTIFIC FINDINGS

Antiviral studies conducted during and after the 2009 influenza pandemic produced many key findings that have informed Canada’s antiviral strategy. These include:

- Early initiation of treatment (i.e., within 48 hours of symptom onset) showed net benefit in reducing lower respiratory tract complications, hospitalizations, duration of illness and mortality compared to no treatment in a range of patient groups (e.g., immunocompromised individuals, pregnant women and the critically ill).\(^\text{12,13,14,15}\)

- Treatment of hospitalized patients reduced severe outcomes and death.\(^\text{16,17,18,19,20}\)

- Treatment of pregnant women with oseltamivir reduced complications\(^\text{21}\) and was safe for both the women and their fetuses.\(^\text{22,23}\)

- Early treatment with oseltamivir shortened the duration of viral shedding, thereby possibly reducing transmission\(^\text{24}\).

- Understanding of oseltamivir pharmacokinetics (i.e., the drug’s absorption, distribution, metabolism and excretion within the body) in morbidly obese adults,\(^\text{25}\) children under two years of age\(^\text{26}\) and pregnant women was improved.\(^\text{27}\) Adequate oseltamivir absorption was demonstrated after nasogastric administration to patients on ventilators.\(^\text{28}\)

- There was little antiviral resistance (less than two percent of isolates overall). Most resistant influenza viruses were detected in immunocompromised patients receiving oseltamivir treatment. There were also instances of resistant viruses found in individuals who had received antiviral prophylaxis or in those with no history of antiviral exposure.\(^\text{29}\)


\(^\text{16}\) Muthuri SG et al. Op cit.


Oseltamivir was given to over 18 million persons worldwide over the course of the pandemic. Adverse events experienced by patients taking oseltamivir were not unexpected, given their underlying medical conditions, complications due to infection with the pandemic virus or were consistent with the drug’s known safety profile.\textsuperscript{30}

Dosing regimens for NIs were refined as to duration and dose size.

### 2.3.2 Programmatic Lessons Learned

The NAS was deployed for the first time during the 2009 influenza pandemic; however, it was not fully deployed until the second wave of the pandemic for the following reasons:

- Lack of consensus among PTs on the trigger for releasing the NAS during the first wave.
- There were antivirals available in the commercial market (e.g., retail pharmacies), which decreased the demand for the NAS in some jurisdictions.
- The relatively mild illness in most persons may have also contributed lower demand for antivirals.

In Canada, antiviral prescribing rates and patient access to antivirals increased during the second wave after the NAS was released and clinical treatment guidelines were disseminated. Post-pandemic analyses suggest that the increased use of antivirals during the second wave may have contributed to better outcomes in Canada.\textsuperscript{31}

Additional challenges with the antiviral strategy were identified through the 2009 pandemic experience:

- Logistical issues included rapid transportation of antivirals to communities, maintenance of proper environmental storage conditions and mechanisms for reimbursement of dispensing fees in pharmacies.
- Lack of knowledge or experience with emergency compounding (converting capsules into liquid) in the absence of the commercially-prepared oseltamivir suspension for children or those who required liquid formulations.
- Regulatory considerations regarding expanding the authority of certain health professionals (e.g., registered nurses) to prescribe and dispense antivirals.
- Inconsistencies in how and when PTs were using the NAS.
- Lack of real-time tracking and monitoring mechanisms for antiviral use.


Many of the key programmatic lessons learned have been incorporated in the Antiviral Annex, such as the need for:

- Clear triggers to release the NAS.
- Strategies to ensure timely access to the NAS, especially for persons at high-risk of complications from influenza (e.g., pregnant women, persons chronic health conditions, Indigenous peoples) and vulnerable populations (as defined in the main body of CPIP, Section 2.4).
- Special antiviral formulations and guidance (e.g., appropriate paediatric formulations and instructions for compounding suspension).
- Best practices in antiviral stockpile management.
- Comprehensive and tested PT plans to deploy antivirals within a jurisdiction on a large scale.
- Robust electronic tracking and surveillance systems to monitor antiviral distribution and dispensing.

More details on Canada's lessons learned from the 2009 influenza pandemic can be found in the reports from the Government of Canada and the Standing Senate Committee on Social Affairs, Science and Technology.

2.4 Program Delivery in the Canadian Context

During an influenza pandemic, eligible persons will be provided with NAS antivirals from the province or territory in which they reside, including on reserve First Nations communities. Some federal departments or agencies (i.e., Department of National Defence, Global Affairs Canada, Correctional Services Canada and Indigenous Services Canada) also have a role to provide antivirals for and/or administer antivirals to specific federal populations (as defined in the main body of CPIP, Section 3.4.2).

The planning guidance provided to PTs throughout this Annex is also meant for these federal departments or agencies.

As outlined in the main body of CPIP, Canada's geographic features and population diversity can create challenges in mounting an effective response to a public health emergency including access to clinical assessment and early treatment with antivirals.

Canada's vast and variable geography can present challenges for remote and isolated communities where adverse weather conditions may impact transportation and distribution of antivirals during a pandemic. In addition, health care services, especially acute care for critically ill patients, may not be readily available in remote and isolated settings (including on reserve First Nations communities). For these reasons, pre-positioning antivirals is an important consideration for jurisdictions with remote and isolated communities.

In communities without onsite licensed prescribers, consideration could be given to:

- Delegating prescribing authority to onsite registered nurses.
- Telephone assessment and prescribing by licensed prescribers.
- Advance (standing) orders, written by a licensed prescriber that would allow registered nurses to administer antivirals to individuals under specific circumstances.

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Research has shown that in densely populated areas or with overcrowded housing, the rate of viral transmission is increased.\textsuperscript{34,35}

There are individuals in any community whose needs are not be fully addressed by standard services or resources, which may make them more vulnerable in a pandemic (see examples in the main body of CPIP, Section 2.4). These individuals may need alternative options for accessing assessment and treatment. These options could include offering home visits, reaching homeless people through shelter or community health centre-based clinics and engaging multilingual family members or interpreters, if available, to assist with communication. There may also be a need to increase the quantity of paediatric formulations in jurisdictions where there are communities with a high proportion of children.

Other aspects of Canada’s diversity that may affect an antiviral program are language barriers, culture, ethnicity and religious/spiritual beliefs. Specific planning considerations are important so that all populations and communities can access early antiviral treatment.

FOR PRACTICAL ADVICE RELATING TO POPULATIONS WITH ACCESS VULNERABILITIES, SEE:

For practical advice relating to populations with access vulnerabilities, see: Flu season and the most vulnerable people. Preparing your organization, staff, volunteers and clients for seasonal and pandemic flu. The Preparedness Guidebook is available here.

2.5 Ethical Considerations

CPIP’s ethical principles and societal values are an important part of decision-making for the antiviral strategy. These principles and values include trust and solidarity, reciprocity, stewardship, equity and fairness. An ethical approach to decision-making also involves following the good decision-making processes outlined in the main body of CPIP, such as openness and transparency, accountability, inclusiveness and reasonableness. These should guide all decision-making about antiviral use, including recommendations for prioritized use of antivirals from government stockpiles in the event of a shortage.

Several aspects of the antiviral strategy have significant ethical considerations. These include:

- **Equitable access** - Government antiviral stockpiles help ensure that antivirals will be available during a pandemic. Stewardship of this valuable resource has been entrusted to governments and its good management influences public trust. However, stockpiling antivirals is not enough to ensure access. Ensuring equitable access includes making antivirals readily available, including to remote and isolated communities (e.g., on reserve First Nations) and for other vulnerable populations.

- **Scarcity of supply** - As outlined in Section 2.2, scarcity of antivirals is a planning consideration. Should shortages occur, the Antiviral Prioritization Framework (Appendix A) provides ethical guidelines for fair and equitable allocation of a limited supply of antivirals.


2.6 Legal Considerations

Legal issues that may arise during an influenza pandemic should be identified by responsible levels of government to the extent possible, ideally during the interpandemic period. Legal considerations related to antiviral prioritization are addressed in Appendix A, Section 3.4.1. Other legal considerations include:

- Regulatory mechanisms for providing access to antivirals through the Food and Drugs Act, administered by Health Canada, include:
  - clinical trials,
  - drug review,
  - Ministerial Interim Orders (e.g., permitting antiviral use in an age group for whom the medication is not licensed during a public health emergency),
  - Special Access Programme,
  - Access to Drugs in Exceptional Circumstances, includes a list of drugs eligible for importation and sale under this regulatory pathway,
  - post approval regulatory compliance and enforcement,
  - evaluating, monitoring and providing information on the safety of drugs,
  - availability of generic products (also governed by the Patent Act).

- Antiviral providers - PTs may wish to expand the scope of practice for practitioners (e.g., pharmacists, nurses) to permit them to prescribe, compound and dispense antivirals.

- Data collection and sharing - It is recommended that jurisdictions establish the capacity and legal authority where needed, to collect and to share critical information on antivirals, including data on inventory status, distribution and utilization.
3.0 CANADA'S ANTIVIRAL STRATEGY

3.1 Objectives

Canada's multifaceted antiviral strategy is intended to ensure timely access to a sufficient quantity of safe and effective antiviral drugs during an influenza pandemic. The antiviral strategy supports Canada's goals for pandemic preparedness and response, which are:

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

The supporting objectives of the antiviral strategy are to:

1. Minimize serious illness and overall deaths by
   • maintaining and providing timely access to a supply of antivirals,
   • reducing the severity of disease (e.g., complications, hospitalization and death) through early treatment (as early as possible within 48 hours of symptom onset) of influenza cases,
   • controlling outbreaks of pandemic influenza in closed health care facilities and other closed facilities (e.g., correctional facilities) and other settings (e.g., remote and isolated communities) where people at higher risk for severe outcomes reside, and
   • possibly reducing transmission of the influenza virus by reducing the level and duration of viral shedding.

2. Minimize societal disruption by
   • reducing the severity and duration of illness through early treatment, and
   • reducing the impact of influenza-related absenteeism in the workplace due to worker illness or family caregiving.
In 2015, a review of Canada's antiviral strategy began, to take into account emerging scientific evidence on NI effectiveness, the expiry of antiviral drug patents and contracts, and the introduction of generic antiviral products into the Canadian market. The CPIP Task Group undertook this review and developed updated recommendations for NAS use, composition and size. These recommendations were informed by:

- A systematic review of the evidence on the safety and effectiveness of NI in the context of seasonal, pandemic and novel influenza, which reaffirmed the importance of antivirals in reducing morbidity and mortality from pandemic influenza,
- A review of the antiviral product landscape in Canada,
- A status update on antiviral drug resistance globally,
- Updated mathematical modeling on the optimal size of the NAS, and
- International antiviral stockpile policies and practices.

In 2017, the CPIP Task Group's NAS recommendations were provided to the Pan Canadian Public Health Network (PHN) Council. Appendix C describes these recommendations and their rationale.

Subsequent to the Task Group's work, further analysis was undertaken to recommend a range for NAS size that ultimately received PHN Council's agreement, with the understanding that further details would be worked out in the procurement process. Table 1 summarizes the elements that comprise Canada's antiviral strategy, including the agreed upon NAS use, composition and size.

**TABLE 1 – ELEMENTS OF CANADA’S ANTIVIRAL STRATEGY**

<table>
<thead>
<tr>
<th></th>
<th>Stockpiling antivirals in the NAS and NESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAS</td>
<td>PT held and managed,</td>
</tr>
<tr>
<td></td>
<td><strong>Size:</strong> should be sufficient to provide antiviral treatment for between 17.14 and 23.19% of the population over the course of a pandemic.</td>
</tr>
<tr>
<td></td>
<td>• This range represents the projected treatment needs during a pandemic with high clinical severity and moderate to high transmissibility,</td>
</tr>
<tr>
<td></td>
<td>• Each PT makes its own decision regarding the size of stockpile.</td>
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<tr>
<td></td>
<td><strong>Composition:</strong> should contain oseltamivir (adult and paediatric doses) as well as other antivirals with different resistance profiles in the event of oseltamivir resistance; zanamivir is the only licensed antiviral fitting this criterion.</td>
</tr>
<tr>
<td></td>
<td>• The recommended proportion of zanamivir should be between 18 and 25% of total stockpile size.</td>
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<tr>
<td></td>
<td><strong>Use:</strong></td>
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<tr>
<td></td>
<td>• The event of a novel/pandemic influenza virus with sustained transmission first detected in Canada should trigger the provision of real time advice on the use of antivirals, based on available data to optimize the use of the stockpile. Early antiviral treatment of all identified cases is recommended initially. Post-exposure prophylaxis (PEP) of close contacts of cases during this period may be considered based on the characteristics (e.g., clinical severity and transmissibility) of the evolving pandemic.</td>
</tr>
<tr>
<td></td>
<td>• The event of a novel/pandemic virus with sustained transmission and widespread activity, within the PT/locally should trigger empiric antiviral treatment of persons with ILI, as early as possible, and when there is evidence that the pandemic influenza virus is circulating in the community, e.g., from either laboratory or surveillance data. The use of the NAS for outbreak control (i.e., treatment of cases and PEP of close contacts) in closed health care facilities and other closed facilities (e.g., correctional facilities) and other settings (e.g., remote and isolated communities) where high-risk people reside is recommended.</td>
</tr>
<tr>
<td>NESS</td>
<td>Federally held and managed antiviral supply,</td>
</tr>
<tr>
<td></td>
<td>Intended to provide surge capacity to PT NAS,</td>
</tr>
<tr>
<td></td>
<td>Current target size of antiviral holdings is the equivalent of 2.5% population coverage.</td>
</tr>
</tbody>
</table>

2. **Ensuring timely distribution** of antivirals so that treatment can begin as early as possible, ideally within 24-48 hours from symptom onset.

3. **Incorporating best practices in stockpile management**, including creative stockpile management, bulk procurement and other strategies supporting a well-managed and efficient stockpile system.

4. **Providing guidance** to clinicians on the use of antivirals and communicating with target groups (e.g., high-risk individuals, remote and isolated communities and other vulnerable populations) regarding how to use antivirals and where they can be accessed.

5. **Monitoring** antiviral safety and effectiveness data and responding accordingly.
3.2 Guiding Principles and Approaches
The CPIP guiding principles and approaches are inherent in the antiviral strategy:

- Collaboration of all levels of government and health care stakeholders is needed to ensure stockpiled antivirals are used in an effective, consistent and coordinated way and guidance is developed and disseminated using pan-Canadian approaches.

- Evidence-informed decision-making is essential when developing virus-specific clinical guidance during a pandemic, as well as recommendations for prioritization.

- Flexibility is needed to develop creative mechanisms and alternate approaches to ensure access to antivirals (e.g., in remote and isolated communities and for vulnerable populations). Health care workers may need to be flexible in their approaches to assessment and treatment (e.g., establish standing orders, train nurses or other front-line health care providers to dispense antivirals). This flexibility is described further in Section 3.5.4 of this Annex. In addition, clinical guidance may evolve throughout a pandemic as new information becomes known.

- A precautionary/protective approach must be used when evidence to inform decision-making on antiviral use early in a pandemic is limited, but timely and reasonable preventive action is needed. It should be communicated that initial recommendations on antiviral use may change as the pandemic evolves and new information becomes available.

- Use of established practices and systems to the extent possible means using best practices in stockpile management in the interpandemic period, using antivirals during seasonal outbreaks, and enhancing clinician familiarity with antiviral prescribing during seasonal influenza outbreaks. During a pandemic, existing mechanisms should primarily be used to distribute and dispense (e.g., pharmacies, on reserve First Nations nursing stations) and monitor uptake, adverse reactions and effectiveness of antivirals, emphasizing that timeliness of these mechanisms is critical during a pandemic. During a pandemic, the existing logistical and scientific expertise that contributed toward influenza planning during the interpandemic will be leveraged as much as possible.

- Ethical decision-making is an important element in the development of guidance for distribution and use of antiviral stockpiles, especially when there is a need to prioritize antivirals in a shortage situation. Ethical principles, in accordance with societal values, should be explicitly identified, considered and communicated throughout the process. During a pandemic, it becomes especially important to ensure that all actions respect ethical guidelines tailored to the concerns of public health, while at the same time respecting the rights of individuals as much as possible.
3.3 Antiviral-Specific Assumptions

Identifying planning assumptions is a way to address uncertainty. While these assumptions are not predictions, they provide a useful framework for planning that is rooted in evidence to the highest extent possible. As an influenza pandemic unfolds, emerging evidence replaces these assumptions to further guide the response.

The main body of CPIP contains two key assumptions relevant to the antiviral strategy:

1. Persons at high risk for complications from seasonal influenza will also be at increased risk of severe disease and complications from pandemic influenza infection, although additional risk groups may emerge.
2. The non-specific nature of ILI will result in the antivirals being used to some extent for persons who do not have influenza.

There are additional assumptions specific to the antiviral strategy:

- Antiviral treatment will serve as an important bridging mechanism until the widespread availability of an effective vaccine. Given current technology, it will take four to six months for vaccine to become available.
- Timely treatment with effective antivirals will reduce complications (e.g., pneumonia), hospitalization and progression of illness to severe disease and death.
- The best results are achieved when antivirals are started as soon as possible after illness onset, but benefits are seen even when antivirals are started later than 48 hours from onset of illness in inpatients.
- The risk of the emergence of viral resistance to the stockpiled antivirals is a real possibility; however, the risk is lower for zanamivir than for oseltamivir.
- Outreach efforts to treat all illness in some high-risk sub-populations (e.g., pregnant women) may result in an increased proportion of cases seeking medical attention.
- The extent to which antivirals will be commercially available at the onset of a pandemic is unknown and commercial supply should not be relied upon. Instead, it should be monitored and leveraged strategically. Stockpiling antivirals reduces the risk of relying on commercial sources.

3.4 Pandemic Roles and Responsibilities

The pandemic antiviral strategy requires a collaborative approach with clearly defined roles and responsibilities. The roles and responsibilities of the FPT governments are set out in Table 2. This section should be read in conjunction with CPIP main body Section 3.4.2. Note that some roles and responsibilities are beyond the scope of this Annex. These include FPT decision-making processes, work plans and fiscal arrangements. Stakeholder groups such as health professional organizations are not included in this table but also play an important role in pandemic preparedness and response.

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### TABLE 2 – FPT GOVERNMENTS’ ROLES AND RESPONSIBILITIES FOR ANTIVIRALS

<table>
<thead>
<tr>
<th>LEVEL OF GOVERNMENT</th>
<th>ROLES AND RESPONSIBILITIES</th>
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<tbody>
<tr>
<td><strong>FEDERAL GOVERNMENT IS RESPONSIBLE FOR:</strong></td>
<td>• providing regulatory authorization to conduct clinical trials and to market antivirals in Canada,</td>
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<tr>
<td></td>
<td>• acting as the focal point for international regulatory collaboration,</td>
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<tr>
<td></td>
<td>• negotiating with manufacturers and establishing contracts for the FPT bulk purchase of antivirals for pandemic purposes,</td>
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<tr>
<td></td>
<td>• establishing guidelines for NESS allocation as surge capacity for the PT stockpiles,</td>
</tr>
<tr>
<td></td>
<td>• national monitoring of adverse reactions to antivirals, and</td>
</tr>
<tr>
<td></td>
<td>• providing antivirals to federal populations not covered by arrangements for PT provision.</td>
</tr>
<tr>
<td><strong>PT GOVERNMENTS ARE RESPONSIBLE FOR:</strong></td>
<td>• In their respective jurisdiction:</td>
</tr>
<tr>
<td></td>
<td>• maintaining antivirals,</td>
</tr>
<tr>
<td></td>
<td>• monitoring antivirals,</td>
</tr>
<tr>
<td></td>
<td>• administering antivirals, and</td>
</tr>
<tr>
<td></td>
<td>• distributing antivirals, including distribution to most federal populations, but this varies by federal population and jurisdiction (see the main body of CPIP, Section 3.4.2 F: Federal populations).</td>
</tr>
<tr>
<td></td>
<td>• Working collaboratively to:</td>
</tr>
<tr>
<td></td>
<td>• provide antivirals to recommended populations, and</td>
</tr>
<tr>
<td></td>
<td>• share information regarding their antiviral stockpiles, including distribution and use of antivirals in their respective jurisdiction.</td>
</tr>
<tr>
<td><strong>FPT GOVERNMENTS WILL WORK COLLABORATIVELY TO:</strong></td>
<td>• establish and support pan-Canadian policies and recommendations on the use of antivirals during a pandemic,</td>
</tr>
<tr>
<td></td>
<td>• facilitate the development of clinical guidance for use of antivirals during the pandemic,</td>
</tr>
<tr>
<td></td>
<td>• disseminate clinical guidance on the use of antivirals during the pandemic, and</td>
</tr>
<tr>
<td></td>
<td>• develop strategies to mitigate the effects of insufficient or delayed antiviral drug supply, should such a situation arise.</td>
</tr>
</tbody>
</table>
3.5 Key Elements of the Response

This section details the key elements of Canada's antiviral strategy for pandemic influenza. Extensive collaboration is essential among manufacturers, regulators, clinicians and public health personnel at all levels to achieve success.

3.5.1 REGULATION OF ANTIVIRALS

HC has the authority to evaluate the safety, efficacy and quality of medications to be used in Canada. Antivirals and governments that stockpile them are regulated under the Food and Drugs Act (FDA) and its regulations.

There could be circumstances where antivirals not authorized for sale in Canada (i.e., products approved in other countries or investigational products) may be required to treat seriously ill patients who are not responding to traditional treatment approaches, or where indications for use exclude certain age groups (e.g., oseltamivir use in infants less than one year of age). There are some legal mechanisms that HC can use to make certain drugs available expediently during a pandemic. These include:

- authorization under regulations for Extraordinary Use New Drugs.
- an Interim Order issued by the federal Minister of Health under the FDA.
- Special Access Programme that authorizes limited use of drugs on a case by case basis to treat patients with serious or life-threatening conditions when conventional therapies have failed, are unsuitable or are unavailable.
- Access to Drugs in Exceptional Circumstances is a regulatory pathway that enables access to drugs which have been authorized for sale in certain foreign jurisdictions, but are not available in Canada, to address an urgent public health need. Details of drugs eligible for importation and sale under this pathway appear on the List of Drugs for an Urgent Public Health Need.
- authorization of use of investigational drugs in clinical trials.

Suspicions of counterfeit antivirals will be investigated by HC’s Regulatory and Regions Branch in collaboration with national and international partners. HC has developed an anti-counterfeit strategy for drugs and medical devices and has laboratory capacity to test samples suspected to be counterfeit or those of unknown origin.

To report suspicions of counterfeit antivirals, call 1-800-267-9675 to be directed to the nearest operational centre.
3.5.2 ANTIVIRAL SUPPLY

**Government stockpiles** - As previously indicated, government purchases of antivirals intended for pandemic influenza have gone into the NAS and the NESS. The two antivirals held in the NAS and the NESS, oseltamivir and zanamivir, are now off patent (since 2016 and 2014 respectively). In 2016, the first generic oseltamivir product received regulatory authorization in Canada.

Antiviral procurement for government stockpiles encompasses contracting, purchasing and replenishment activities. Purchasing antivirals for FPT pandemic stockpiles is usually done through group supply contracts. Through these contracts, jurisdictions can place orders for product; the manufacturers ship orders directly to jurisdictions. The length of time it takes for production and delivery of new product varies between manufacturers and depends on the quantity ordered. Each PT makes its own antiviral procurement decisions, based on jurisdiction-specific considerations.

Currently, the NAS and NESS hold oseltamivir in 75 mg, 45 mg and 30 mg capsules, and in some cases oseltamivir oral suspension, as well as zanamivir dry powder for inhalation. For children over one year of age, paediatric oseltamivir capsules (30 and 45 mg) are preferred over oral suspension for stockpiles due to their longer shelf-life, smaller storage requirements and the ability to mix them with household sweetened liquids for administration. If required, pharmacists can compound oral suspension from capsules according to directions provided by the manufacturer. However, stockpiling a small quantity of commercial powder for oral suspension in the stockpiles may be prudent for areas where pharmacists are not available to compound (e.g., remote and isolated communities).

**Commercial availability of antivirals** - As of 2017, there is no domestic production of antivirals in Canada. Maintaining stockpiles of antivirals is a strategy that has been adopted by Canada and many other resourced countries to mitigate the risk of limited access to commercial supplies of antivirals at the time of a pandemic.

Despite the unexpected commercial availability of some antiviral formulations during the 2009 pandemic, there are significant risks associated with reliance on the commercial availability of antivirals in the future, particularly for a moderate to high-impact pandemic scenario where global demand could be high. Risk assessments have concluded that it is improbable that sufficient supply would be available from commercial markets alone during a pandemic for a variety of reasons, including risk of embargo, a long transportation cycle, queuing of orders (if multiple customers place orders) and commercial supply shortfall.

However, if accessing commercial supply is considered as a component of a jurisdiction's antiviral strategy, stringent risk mitigation measures must be in place to address a number of challenges:

- **Access for all Canadians**: A mechanism would have to be in place to ensure that antivirals from a commercial source would be available to Canadians of all socioeconomic status (e.g., ensure that antivirals are covered by all PT drug formularies).
- **Timely access**: Commercial sources must have the capacity to supply antivirals for early treatment. Commercial supplies from retail sources may be limited or non-existent in some parts of Canada, particularly in northern or remote and isolated communities so stockpiling antivirals is a more prudent approach. See Section 3.5.4 for more information.
- **Price of commercial product**: Reliance on commercial supply would have significant financial implications for governments, as antivirals purchased commercially are considerably more expensive than the price offered in FPT bulk procurement contracts.
3.5.3 CLINICAL RECOMMENDATIONS FOR ANTIVIRAL USE

Clinical guidance - Virus-specific clinical guidance and treatment protocols should be developed at the onset of the pandemic, based on pandemic epidemiology and available scientific evidence.

Clinical guidance for antiviral use for pandemic influenza may differ in some ways from seasonal influenza recommendations. Definitive decisions will be based on a risk assessment at the time of a pandemic and may evolve over the course of the pandemic as new information emerges. Existing scientific expertise should be leveraged to develop clinical guidance and be engaged in ongoing assessments. Appendix B provides an example of clinical guidance on antiviral use that was developed for and distributed to clinicians across Canada during Pandemic H1N1 in 2009.

Clinical guidance for antiviral use should include:

- Recommended recipients - who are expected to benefit from treatment.
- Drugs of choice and formulations available - including management of infections due to antiviral-resistant virus.
- Dosage and duration of treatment - dosing in children and in people with renal impairment, whether longer treatment regimens or the use of combination therapy will be of benefit in certain individuals with severe disease.
- Timing of treatment - optimal timing (e.g., within 48 hours of onset of disease and ideally within 12 to 24 hours) and any window beyond which treatment is not expected to be effective.
- Treatment for special populations - treatment of pregnant women, children (including children less than one year of age), persons with immune compromising conditions, persons with renal disease, etc.
- Laboratory confirmation versus empiric treatment - indications for laboratory testing will be provided at the time of the pandemic and are likely to focus on situations where the results of the test may influence decisions regarding care and treatment, infection control and management of close contacts. These situations include confirmation of an atypical presentation when it will affect a treatment decision, admission to hospital, non-response to treatment in the hospital setting (for early detection of a resistant influenza strain) and confirmation of the etiology of an institutional outbreak.
- Presumptive treatment - early presumptive treatment, rather than post-exposure prophylaxis (PEP), may be indicated for situations where influenza infection appears prevalent and persons at very high risk of influenza complications (i.e., profoundly immunosuppressed individuals) are exposed. Early presumptive treatment requires initiation of therapy with oseltamivir or zanamivir twice daily (versus once daily as recommended for PEP) after exposure to an infectious contact even before symptoms begin.

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41 Aoki FY et al. Op cit.
Outbreak control in closed facilities and settings

The use of NAS antivirals to control outbreaks of pandemic influenza in closed health care facilities and other closed facilities and settings where people at high-risk reside will involve both treatment of cases as well as PEP for contacts (e.g., residents, staff, volunteers and others who provide services in these facilities and settings). PEP is offered to all susceptible residents regardless of their vaccination status. For unvaccinated staff and other contacts, the use of NAS for PEP may be considered based on a risk assessment of the characteristics of the pandemic. Because pandemic vaccine is not expected to be available for four to six months in a pandemic, influenza outbreaks in closed facilities and settings may be more difficult to control than during seasonal influenza outbreaks when most residents have been vaccinated.

Jurisdictional guidelines for managing respiratory outbreaks in closed health care facilities can be modified if necessary for other types of closed facilities or settings where persons at high-risk for complications of influenza reside. PTs may wish to use the following criteria in deciding which types of settings in their jurisdiction might be eligible for the use of antiviral prophylaxis for outbreak control:

- The facility is "closed", i.e., has a fixed residential population with limited turnover; a hospital has units or wards that are [or can be] closed.
- The facility has patients or residents at high-risk.
- 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).
- The facility can manage an antiviral regimen with adequate medical expertise and minimal public health assistance.

A list of potential settings and indications for the use of antiviral prophylaxis for outbreak control during a pandemic is shown in Table 3. Provincial and territorial policies may vary.
### TABLE 3 – POTENTIAL SETTINGS FOR USE OF ANTIVIRAL PROPHYLAXIS FOR THE CONTROL OF INFLUENZA OUTBREAKS DURING AN INFLUENZA PANDEMIC

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>TYPE OF FACILITY</th>
<th>DOES IT MEET THE CRITERIA FOR ANTIVIRAL PROPHYLAXIS?</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEALTH CARE FACILITIES</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acute care hospitals</td>
<td>Yes, if the affected unit or ward is closed. Antiviral prophylaxis for outbreak control would be restricted to the unit or ward where transmission is occurring.</td>
</tr>
<tr>
<td></td>
<td>Long-term care facilities (LTCFs)</td>
<td>Yes. In smaller LTCFs outbreak control measures may involve the entire facility; in large LTCFs only units where transmission is occurring would be included.</td>
</tr>
<tr>
<td></td>
<td>Speciality hospitals, e.g., complex continuing care, rehabilitation, psychiatric</td>
<td>Yes, provided the affected unit or ward can be closed (as antiviral prophylaxis for outbreak control would likely be restricted to the unit or ward where transmission is occurring) and there is adequate medical supervision to support antiviral use.</td>
</tr>
<tr>
<td>OTHER CLOSED FACILITIES</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Correctional facilities</td>
<td>Yes, on the basis that these are closed facilities with persons at high-risk (e.g., persons with immune compromising conditions) and have adequate medical supervision to support antiviral use.</td>
</tr>
<tr>
<td></td>
<td>Retirement homes, lodges</td>
<td>Possibly. They may meet the criterion of persons at high-risk but may not meet criteria for a closed facility or adequate medical supervision to support antiviral prophylaxis.</td>
</tr>
<tr>
<td></td>
<td>Homes for special care and group homes</td>
<td>Unlikely. They may meet the criterion for persons at high-risk but may not meet criteria for a closed facility or adequate medical supervision to support antiviral prophylaxis.</td>
</tr>
<tr>
<td>OTHER SETTINGS</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Remote and isolated communities</td>
<td>Yes, to the extent that these communities have fixed populations with limited turnover with persons at high-risk and have adequate medical supervision to support antiviral prophylaxis.</td>
</tr>
</tbody>
</table>
Consent and off-label use - It is recommended that potential recipients of antivirals be provided written information about the medications, 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 Canadian product monographs for each of the antiviral drugs. Educational materials should be translated into relevant languages.

Advanced written consent is commonly sought in long-term care settings to facilitate rapid use of antiviral prophylaxis for outbreak control.

Some pandemic antiviral usage may be off-label (e.g., use in pregnant women and children under one year of age). The term off-label describes the use or intended uses of a drug for indications other than those that have received regulatory authorization. A clinician may use his or her discretion in prescribing a drug off-label, but this common practice should be 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. It is important to understand the authorized indications versus off-label use for antivirals and to make sure that patients understand the risks and benefits, and that they consent to taking the prescribed drug.

Recommendations for short supply - Circumstances such as high demand or antiviral resistance could mean that the available supply of antivirals is insufficient for the intended uses. The Antiviral Prioritization Framework (Appendix A) has been developed to guide the process of determining national priorities for use when antivirals are anticipated to be in short supply. It provides a framework to identify and consider the relevant factors when making recommendations, including ethical considerations. At a minimum, persons who are severely ill and those at higher risk of complications from influenza should receive antivirals.

3.5.4 TIMELY ACCESS TO ANTIVIRALS

It is important for PTs to use health service delivery models that provide rapid patient access to assessment and free antiviral treatment through multiple distribution routes. Jurisdictions will want to consider the unique needs of vulnerable populations in accessing treatment and make special arrangements as needed for assessment and delivery of medications. Aggressive antiviral treatment markedly reduced the impact of a pandemic-related outbreak in an isolated First Nations community in 2009\(^42\) and modeling studies suggest that public health strategies in remote communities should focus on the wider availability and timely distribution of antiviral treatment of clinical illness.\(^43\)

FOR PRACTICAL ADVICE RELATING TO POPULATIONS WITH ACCESS VULNERABILITIES, SEE:

Flu season and the most vulnerable people. Preparing your organization, staff, volunteers and clients for seasonal and pandemic flu. The Preparedness Guidebook is available here.


Depending on the jurisdiction, antivirals can be distributed to, and subsequently dispensed from, community pharmacies, district health authorities, hospitals, community health centres, on reserve First Nations communities nursing stations, influenza assessment centres and correctional facilities.

There are a variety of options that jurisdictions can consider to facilitate timely access to antivirals:

- Enhancing physician capacity by establishing special fee codes for telephone assessment and prescribing.
- Delegating authority to prescribe and to dispense antivirals to other health care providers such as registered nurses or pharmacists. This option may be particularly useful for assessment centres or remote and isolated communities and should be accompanied by the provision of pandemic-specific clinical practice guidelines.
- Identifying mechanisms for access in communities without physicians, registered nurses or pharmacists.
- Providing prescriptions in advance (e.g., to pregnant women) to be followed by a telephone assessment if the patient develops ILI.

It is important to provide health care workers with timely guidelines for antiviral use and to emphasize the urgency of initiating treatment, especially for patients at high risk, to maximize benefit.

Communications should be developed for the public so they are made aware of the availability of antiviral treatment and the need for those with moderate to severe illness or underlying health conditions to contact their health care provider as soon as illness develops.

### 3.5.5 STOCKPILE MANAGEMENT

As described in Section 2.3.2, the NAS was used for the first time during the 2009 influenza pandemic. Lessons learned from this experience highlighted the need for well-established practices for all aspects of stockpile management. Antiviral stockpiles require ongoing maintenance because, as with all drugs, antivirals have a finite shelf-life. As they reach their expiry date, decisions need to be made about stockpile replenishment.

Antiviral stockpile management has three main components: storage, distribution and inventory management. While all these components come into play during a pandemic, real-time inventory management is particularly important to make informed decisions about stockpile deployment and the need for surge capacity.

Key considerations include determining:

- Whether and when there might be shortages,
- Whether adjustments might be needed to national recommendations for the use of antivirals, and
- Allocation of antivirals for surge.

Pandemic stockpile-related issues that may arise, including logistical concerns and possible procurement of additional antivirals, would be best addressed by a task group with expertise in antiviral stockpile management.
Storage - It is recommended that antivirals be stored according to Good Manufacturing Practices (GMP).  

It is important that each party in the storage and transportation chain ensures that the required conditions are met through their respective activities. It applies to all dispensing as well as storage locations. PTs may want to consider external suppliers to provide the appropriate controlled storage, transportation and record maintenance.

Security of supply should also be addressed in storage and distribution plans. NAS implementation plans should also consider storage capacity for antivirals, including dispensing locations. Jurisdictions in close geographical proximity could consider combining their individual requirements for storage.

### BEST PRACTICES FOR ANTIVIRAL STORAGE

- Adherence to DEL and GMP guidelines (e.g., environmental storage conditions, segregation of expired products, security, periodic audits, recording, quality assurance and control protocols) in all storage locations, including dispensing sites.
- Application of quality assurance protocols to deployed stock, with records kept on storage and handling conditions to support decision-making around the potential restocking of these items.

### Stockpile distribution

An effective stockpile distribution strategy bridges the gap between antivirals in central storage depots and the dispensing location. The importance of distribution logistics cannot be overemphasized. The diversity among Canada’s PTs means that each jurisdiction needs to tailor its own distribution strategy, to ensure that antivirals are at the required location in sufficient time to be used effectively.

The timing of stockpile deployment (i.e., the release and initial positioning of NAS) will be based on jurisdictional risk assessments that consider anticipated pandemic timing and impact and the need to ensure access to antivirals from the start of pandemic activity in the jurisdiction. In some locations, pre-positioning of antivirals may be warranted well in advance or even during the interpandemic phase e.g., locations that are remote or isolated or face inclement weather conditions that could interfere with transportation.

The distribution strategy selected by a jurisdiction should be governed by overarching principles and enablers (e.g., use of contractors, private sector service providers, regional health care workers, pharmacists, nurses) to adapt to urban, rural, and remote and isolated settings and their related distribution requirements.

Distribution can be carried out through coordinated arrangements and planning at the PT or regional health authority level or with local suppliers or commercial entities such as pharmacies. Distribution planning considerations include time requirements associated with the treatment schedule, geography,

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**Sources:**


business continuity planning considerations, distance and transportation networks, population dispersion, availability and capability of commercial distributors. (See also Section 3.5.4 on timely access). Consider making arrangements for compensation, ordering and billing procedures, reimbursement of pharmacy dispensing fees and required data collection.

**BEST PRACTICES FOR ANTIVIRAL DISTRIBUTION**

- Using temperature monitoring devices to ensure the integrity of the antivirals during shipment.
- Accompanying shipments to locations where receiving and handling expertise is limited.
- Utilizing existing distribution systems during a pandemic (e.g., those internal to the PT, pharmaceutical wholesalers, or commercial healthcare/service providers).
- Ensuring that distribution options factor in environmental and geographical conditions for timely distribution (e.g., pre-positioning antivirals in remote and isolated communities in advance of wider distribution).

**Inventory management** – Efficient inventory management requires knowledge of what stock is being held and where, knowing specific information about each unit of stock in the inventory and controlling the flow of stock in and out of inventory. Essential elements of an inventory management system include the ability to record and access the needed data in real time and an inventory tracking mechanism that accurately captures relevant drug information (e.g., drug type, dosage form, expiry date, lot number) in a way that can be easily updated and retrieved. Various tools are available to facilitate inventory management and sophisticated automated systems exist in some larger Canadian jurisdictions.

Currently, there is no standardized method to collect NAS inventory data, so each jurisdiction must develop and implement its own method of tracking antiviral deployment and utilization. Where retail pharmacies are used to dispense NAS antivirals, jurisdictions can leverage existing administrative drug formulary systems that provide prompt reporting on dispensed antivirals. As current antiviral unit packaging does not include bar codes, scanner inventory technology cannot be utilized. Non-pharmacy dispensing locations are typically not able to provide automated reporting on the quantity of antivirals being dispensed and may have to produce paper-based reports.

**BEST PRACTICES FOR INVENTORY MANAGEMENT**

- FPT collaboration on monitoring of NAS/NESS holdings during the interpandemic period.
- Capacity within jurisdictions to obtain real-time information about the status of the NAS (e.g., holdings and rate of depletion) from all dispensing locations, to determine the need for surge capacity during a pandemic.
- An FPT reporting process to provide a national overview on NAS capacity to inform decision-makers during a pandemic.
- Leveraging existing capabilities of pharmaceutical wholesalers and distributors or government systems regarding real-time inventory management in lieu of creating new systems.
- Capacity of pharmacy surveillance systems to differentiate NAS from commercial supply to avoid overlapping data and accurately reflect pandemic antiviral uptake.
3.5.6 ANTIVIRAL SAFETY
Available data suggest that NIs are reasonably safe to use, however serious adverse reactions can occur. A serious adverse reaction is defined as a noxious and unintended response to a drug or natural health product that occurs at any dose and that requires in-patient hospitalization or prolongation of existing hospitalization, causes congenital malformation, results in persistent or significant disability or incapacity, is life-threatening or results in death.

In the event of an influenza pandemic, any serious adverse reaction that follows administration of influenza antiviral drugs should be reported to HC’s Marketed Health Products Directorate (MHPD). As part of its mandate, MHPD will conduct post-market safety surveillance aiming at monitoring, identifying and assessing possible safety issues related to antivirals, developing risk mitigation measures as needed and communicating on related safety issues identified for these products in a timely and expedited fashion.

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

During a pandemic, MHPD will continue to use the existing Canada Vigilance database to monitor and analyze adverse events to antivirals. 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 HC MedEffect web site.

MHPD will work with the Public Health Agency of Canada (PHAC) to issue regular reports to national bodies and PTs to provide assurance of continuing drug safety or to flag the possible need to modify recommendations should problems arise.

3.5.7 MONITORING ANTIVIRAL UTILIZATION, RESISTANCE AND EFFECTIVENESS
Monitoring antiviral utilization – In addition to tracking drug inventory and status of the NAS (as discussed in Section 3.5.5 on stockpile management), it is important for PTs to monitor who is provided with antivirals to determine whether they are reaching the recommended target groups in a timely way. As a priority, usage in high-risk groups (e.g., pregnant women) and hospitalized patients with ILI should be tracked to monitor use and timeliness of treatment. Sub-optimal antiviral use should be addressed through reinforcement of guidelines, additional public and provider education and adoption of strategies to remove identified barriers.

On an ongoing basis, HC receives pharmacy-based surveillance data on the sales of prescription drugs (including antivirals) to hospitals and from retail pharmacies. However, this system would have limited utility in monitoring antiviral utilization in an influenza pandemic situation as these data are only reported on a monthly basis and not all hospitals and pharmacies participate.

Most PTs have administrative pharmacy systems in place to monitor antiviral utilization.

48 Food and Drug Regulations, Part C, section C01.001 (1).
Monitoring for antiviral drug resistance and effectiveness – It is important to know the effectiveness of antivirals for the treatment of pandemic influenza. The susceptibility of a novel or pandemic influenza virus strain to antivirals will be monitored on an ongoing basis. This testing will be carried out primarily at the National Microbiology Laboratory (NML), which is responsible for similar resistance monitoring of seasonal influenza strains and at some provincial public health laboratories. Plans call for a proportion of specimens from provincial laboratories to be tested for genotypic 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 antivirals have failed to control. For more details see the CPIP Laboratory Annex. This information is also summarized on a weekly basis in the interpandemic period in FluWatch.

3.6 Risk Management Approach

3.6.1 OVERVIEW

Risk management is a systematic approach to setting the best course of action in an uncertain environment by identifying, assessing, acting on and communicating risks. Given the inherent uncertainties in the antiviral strategy, a risk management approach provides a useful framework for pandemic planning and response and supports the CPIP planning principles and approaches of evidence-informed decision-making, proportionality, flexibility and a precautionary, protective approach. The CPIP proposes the use of assumptions (see Section 3.3) and planning scenarios as risk management planning tools.

3.6.2 RISK MANAGEMENT CONSIDERATIONS FOR THE ANTIVIRAL STRATEGY

The antiviral strategy is subject to numerous risks, including the possibility that the pandemic influenza strain is or becomes resistant to the stockpiled antivirals. Considerable efforts have been made to identify and mitigate these risks, such as diversifying the stockpile to hold two different antivirals.

Table 4 describes potential implications for the antiviral strategy for pandemics of varying impact, using the four planning scenarios described in the main body of CPIP. Factors that can affect each scenario, such as antiviral resistance or lack of age-related population immunity, are addressed in Table 5. It is expected that communication on the pandemic antiviral strategy will need to be adjusted based on the implications of each scenario.
### TABLE 4 – IMPLICATIONS AND POTENTIAL ADJUSTMENTS TO THE ANTIVIRAL STRATEGY FOR PANDEMICS OF VARYING IMPACT

<table>
<thead>
<tr>
<th>Scenario A</th>
<th>Scenario B</th>
<th>Scenario C</th>
<th>Scenario D</th>
</tr>
</thead>
</table>
| LOW | - Anticipate low demand for antivirals  
- Timing of NAS deployment based on jurisdictional risk assessment  
- Stockpiles should be adequate in quantity to meet demand  
- Treatment might not be needed for uncomplicated illness in those without risk factors (as per seasonal recommendations) | - Anticipate moderately-high demand for antivirals  
- Probable rapid NAS deployment  
- Treatment might not be needed for uncomplicated illness in those without risk factors (as per seasonal recommendations) | - Anticipate high demand for antivirals in light of large number of severely ill patients  
- Rapid and broad deployment of NAS needed  
- Antiviral demand might exceed supply  
- May need to activate mechanisms for surge capacity to access more antivirals (e.g., request for NESS antivirals)  
- May need to prioritize access to antivirals  
- Pandemic vaccine availability of critical importance |
| LOW CLINICAL SEVERITY | HIGH |
| LOW | HIGH |

**Scenario A**
- Anticipate low demand for antivirals
- Timing of NAS deployment based on jurisdictional risk assessment
- Stockpiles should be adequate in quantity to meet demand
- Treatment might not be needed for uncomplicated illness in those without risk factors (as per seasonal recommendations)

**Scenario B**
- Anticipate moderately-high demand for antivirals
- Probable rapid NAS deployment
- Treatment might not be needed for uncomplicated illness in those without risk factors (as per seasonal recommendations)

**Scenario C**
- Anticipate high demand for antivirals in light of severity of disease
- Timing of NAS deployment based on jurisdictional risk assessment
- Treatment could be recommended for all suspect and confirmed cases in light of clinical severity

**Scenario D**
- Anticipate high demand for antivirals in light of large number of severely ill patients
- Rapid and broad deployment of NAS needed
- Antiviral demand might exceed supply
- May need to activate mechanisms for surge capacity to access more antivirals (e.g., request for NESS antivirals)
- May need to prioritize access to antivirals
- Pandemic vaccine availability of critical importance
Table 5 provides a more detailed outline of the risks and events that could affect the antiviral strategy, their implications and potential mitigation or response should the risk or event occur. Timely and transparent risk communications to health care providers and the general public should be an integral part of the response to each factor/event.

**TABLE 5 - RISKS AFFECTING THE ANTIVIRAL STRATEGY, THEIR IMPLICATIONS AND POTENTIAL MITIGATION OR RESPONSE**

<table>
<thead>
<tr>
<th>FACTOR/EVENT</th>
<th>IMPLICATIONS</th>
<th>POTENTIAL MITIGATION/RESPONSE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTIVIRAL SUPPLY</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Supply of antivirals becoming depleted | • Will not be able to treat as many people as anticipated (will impact on pandemic objectives)  
• Health care provider and public distress  
• May not be able to ensure equitable access | • Activate measures for surge capacity (e.g., expedited purchases through contracts or advance purchase agreements, NESS, interjurisdictional loans)  
• May need to prioritize antiviral use |
| Shortage of some specific formulations or products | • May not be able to provide optimal treatment regimens | • Monitor NAS/NESS holdings closely to allow for timely restocking  
• Activate measures for surge capacity, including procurement of needed formulations if available  
• Combine other strengths or compound suspensions to obtain required dose(s)  
• Adjust recommendations and prioritize use |
| Viral resistance to stockpiled antiviral drugs | • Dramatic reduction of available supply of effective antivirals  
• Resistance to all antivirals would effectively remove antiviral treatment option  
• Some groups may be disproportionately impacted, e.g., zanamivir not authorized in young children | • Include antivirals with different resistance profiles in NAS  
• Adjust antiviral recommendations and prioritize use  
• Procure effective antivirals if available  
• If there is resistance to oseltamivir, consider authorizing lower age for zanamivir diskhaler use  
• Engage rapid clinical research into effective regimens |
<p>| <strong>ANTIVIRAL EFFECTIVENESS</strong> | | |</p>
<table>
<thead>
<tr>
<th>FACTOR/EVENT</th>
<th>IMPLICATIONS</th>
<th>POTENTIAL MITIGATION/RESPONSE</th>
</tr>
</thead>
</table>
| Inability to deliver antivirals in timely manner (i.e., within 48 hours of symptom onset) | • Worse clinical outcomes in untreated patients or those with delayed treatment  
• Possible increase in hospitalization and deaths | • Make antivirals available in advance in hard to reach areas with populations at higher risk for severe disease, such as remote and isolated communities (including some on reserve First Nations communities)  
• Adjust policies and strategies to remove barriers to improve timeliness of assessment and antiviral provision |
| Lack of effectiveness against pandemic strain                                  | • Patients not responding to recommended drug regimen  
• Increase in hospitalizations and deaths | • Engage in rapid clinical research into more effective regimens, combination therapy, etc.                                                                                   |
| POPULATION RISK FACTORS                                                      |                                                                                                                                             |                                                                                                                                                                           |
| New risk factors identified for severe or complicated disease                | • Additional individuals could benefit from antiviral treatment  
• Needs to be communicated to health care providers and public  
• Potential for increased demand for stockpile | • Revise clinical guidance accordingly  
• Communicate in timely way to jurisdictions and health care providers (nurses, pharmacists, MDs, etc.)  
• Consider impact on NAS; activate mechanisms for surge capacity if needed  
• Consider as part of prioritization recommendations |
| Some settings or parts of country are affected more severely than others      | • Antiviral supplies could be depleted in some jurisdictions | • Activate mechanisms for surge capacity (e.g., expedited purchases through contracts or advance purchase agreements, NESS, interjurisdictional loans) |
| No pre-existing population immunity                                           | • Might see increased demand for antiviral treatment. | • Activate mechanisms for surge capacity if needed  
• May need to adjust antiviral recommendations and prioritize use if shortage occurs |
| ANTIVIRAL SAFETY                                                             |                                                                                                                                             |                                                                                                                                                                           |
| Unexpected safety signals emerge in Canada                                   | • Affects risk-benefit considerations for antiviral recommendations  
• May require lot recalls  
• Could affect health care provider and public confidence in antiviral treatment | • Ensure ongoing monitoring mechanisms are in place  
• Investigate promptly  
• Reassess risk and benefit and re-evaluate antiviral recommendations  
• Communicate Canadian status  
• Ensure that a tracking process is in place for rapid tracing and recall of specific lots |
<table>
<thead>
<tr>
<th>FACTOR/EVENT</th>
<th>IMPLICATIONS</th>
<th>POTENTIAL MITIGATION/RESPONSE</th>
</tr>
</thead>
</table>
| Unexpected safety signals emerge in other countries | • May also be occurring in Canada  
• Could affect health care provider and public confidence in Canada’s antiviral treatment | • Activate international information-sharing protocols between national regulatory agencies  
• Investigate Canadian situation promptly  
• Communicate international and Canadian status  
• Reassess Canadian recommendations as required |
| Rumours or reports of unexpected adverse reactions | • Could affect health care provider and public confidence  
• Could decrease antiviral acceptance | • Investigate promptly  
• Communicate with public and health care providers to counter misinformation |
| Media coverage (e.g., reports of severe illness) | • Possible sudden increase in health care provider visits and demand for antiviral treatment | • Plan for surges in clinical assessment and demand for antivirals; there may be a need to prioritize antiviral use |
| Demand for antivirals for purposes beyond the agreed upon NAS use (e.g., for prophylaxis by some occupational groups) | • Issues of equity if there is PT inconsistency  
• Could cause workplace issues | • Communicate with public and health care providers on the scope of NAS use  
• Advance workplace education about risks, prevention and antiviral use  
• Ensure protective measures are available and in place to address workplace risks (e.g., personal protective equipment)  
• Individual organizations can make own decisions or conduct risk assessments regarding antiviral stockpiling for business continuity purposes |
| Different antiviral strategies in other countries | • Public and provider perception that other countries’ approaches are superior | • Communicate with public and health care providers  
• Acknowledge differences and provide rationale for Canadian approach |
3.7 Triggers for Action and Key Decisions and Activities

Key decisions needed to implement the antiviral strategy for pandemic influenza and their associated triggers are shown in Table 6. Note that communications to the public and HCWs about the antiviral strategy and its implementation should take place at all stages.

### Table 6 - Triggers and Key Decisions for the Antiviral Strategy

<table>
<thead>
<tr>
<th>TRIGGERS/TIMELINES</th>
<th>KEY DECISIONS/ACTIVITY</th>
<th>CONSIDERATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novel virus is causing human cases detected somewhere in the world (no or limited transmission)</td>
<td>• Assess NAS stockpile status and options for surge capacity (e.g., NESS)</td>
<td>• Assess sufficiency of NAS holdings, options for surge capacity including NESS, commercial supply, potential availability of other antivirals (international or investigational) and related enabling regulatory mechanisms&lt;br&gt;• Requires engagement of health professional organizations with appropriate expertise to develop guidance&lt;br&gt;• Initial guidance likely based on limited available evidence for novel virus and seasonal influenza&lt;br&gt;• PEP may be considered for contacts of cases due to novel virus&lt;br&gt;• Requires stakeholder dissemination strategy</td>
</tr>
<tr>
<td>TRIGGERS/TIMELINES</td>
<td>KEY DECISIONS/ACTIVITY</td>
<td>CONSIDERATIONS</td>
</tr>
<tr>
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</tr>
<tr>
<td>Novel virus with sustained human transmission detected somewhere in the world or in Canada</td>
<td>• Procure additional antivirals as needed</td>
<td>• Based on jurisdictional risk assessment including potential pandemic impact</td>
</tr>
<tr>
<td></td>
<td>• Invoke regulatory mechanisms required for additional antiviral uses and access to investigational drugs.</td>
<td>• Authorization for oseltamivir for children less than one year of age, access to intravenous NIs</td>
</tr>
<tr>
<td></td>
<td>• Develop allocation plan for the NESS</td>
<td>• Should include the process for accessing the NESS and allocating antivirals</td>
</tr>
<tr>
<td></td>
<td>• Facilitate development or updating of clinical guidance for pandemic virus cases</td>
<td>• Update as relevant information becomes available (e.g., emerging epidemiology)</td>
</tr>
<tr>
<td></td>
<td>• Deploy NAS within the jurisdiction</td>
<td>• May precede formal declaration of a pandemic</td>
</tr>
<tr>
<td></td>
<td>• Review and enhance (as needed) antiviral safety monitoring plan</td>
<td>• Timing based on a jurisdictional risk assessment</td>
</tr>
<tr>
<td></td>
<td>• Specific pandemic guidelines posted on MedEffect website</td>
<td></td>
</tr>
<tr>
<td>Novel/pandemic virus detected in PT or local jurisdiction</td>
<td>• Antiviral prescribing and dispensing</td>
<td>• Based on clinical guidance and individual clinical judgment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Public health should alert clinicians when there is lab evidence that pandemic virus is circulating locally</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Timely communications needed for health care providers (nurses, doctors, pharmacists, etc.) as well as the public</td>
</tr>
<tr>
<td>Ongoing/ following each pandemic wave</td>
<td>• Closely monitor FPT and commercial supply of antivirals and source additional supplies if needed</td>
<td>• Potential use of NESS for PT surge supply</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Coordination of provider and public messaging with manufacturers as required</td>
</tr>
<tr>
<td>Development of significant antiviral resistance or depletion of antiviral supply</td>
<td>• Adjust antiviral strategy and guidance</td>
<td>• May have to prioritize use if antiviral resistance develops or supply is depleted</td>
</tr>
<tr>
<td>Detection of a safety signal</td>
<td>• Investigate safety signal and act as needed</td>
<td>• Potential actions could include further monitoring, revised antiviral guidance or antiviral recall</td>
</tr>
</tbody>
</table>
4.0 INTEGRATION WITH OTHER RESPONSE COMPONENTS

4.1 Surveillance

Timely surveillance information is needed for antiviral decision-making, particularly when developing clinical guidance for antiviral use and prioritization in a shortage situation during a pandemic. PHAC is responsible for collating and analyzing surveillance information from across Canada and other countries to produce risk assessments and provide decision-makers with timely and relevant surveillance data.

Surveillance information required for antiviral decision-making includes the following (together with laboratory data outlined in Section 4.2 below):

- An early estimate of pandemic epidemiological parameters and potential impact, repeated as necessary throughout the pandemic.
- Data to support development of clinical guidance for antiviral use, including:
  - Indicators of transmissibility and severity of clinical disease,
  - Rates of illness, severe disease and death by age and risk groups, and risk of severe disease in those affected,
  - Risk factors for severe illness, hospitalization and death (including settings with increased risk), and
  - Proportion of severe disease in persons with and without underlying health conditions.
- Antiviral uptake by age and risk groups on an ongoing basis.

For further details on surveillance during a pandemic, see the CPIP Surveillance Annex.

4.2 Laboratory Response

Laboratory surveillance will be conducted by the NML and other public health laboratories and will support the antiviral strategy for pandemic influenza through:

- Identification of circulating influenza virus in local jurisdictions,
- Identification of co-circulating viral pathogens,
- Laboratory confirmation of influenza outbreaks in closed facilities, and
- Ongoing influenza strain monitoring to identify antiviral resistance.
Clinical and public health laboratories also support the clinical use of antivirals through testing of patients with ILI. As the pandemic progresses, resources will be constrained and clinical testing priorities will need to be re-evaluated. Once the novel strain becomes widespread in the community, testing may not be indicated for clinical management of uncomplicated ILI, for which empiric treatment may be indicated. At that stage, testing for clinical purposes should be focused on hospitalized patients (including those who are not improving and in whom antiviral resistance is suspected) and those with risk factors for severe disease. In these cases, test results may influence clinical decisions regarding care and treatment, infection control and management of close contacts.

For further details on laboratory response during a pandemic, see the CPIP Laboratory Annex.

4.3 Health Care Services

Antivirals are primarily a clinical, rather than a public health, intervention. Therefore, it is important to ensure that plans to distribute and administer antivirals are closely aligned with plans to provide clinical services for influenza assessment and treatment. It is also essential to ensure that health care providers are informed about antiviral availability and are provided with the latest clinical guidance for use, including issues of antiviral resistance.

For further details on health care services during a pandemic, see the CPIP (Section 4.7).

4.4 Pandemic Vaccine

It is expected to take four to six months for vaccine to be produced using current technologies and during this period antivirals play a pivotal role. The need for antivirals should decline sharply once an effective pandemic influenza vaccine program has been implemented. Delayed vaccine availability or poor vaccine uptake could increase the demand for antivirals and possibly stress antiviral supplies. Similar to seasonal influenza vaccine, pandemic vaccine is not expected to be 100% effective, which could result in some vaccinated persons developing influenza. Therefore, vaccinated individuals with ILI should still be treated.

Antiviral administration does not interfere with the immune response to inactivated influenza vaccines but can interfere with the response to live attenuated influenza vaccine.

For further details on Canada’s pandemic vaccine strategy, see the CPIP Vaccine Annex.

4.5 Communication

All levels of government in the health sector, HCWs and NGOs will be involved in pandemic influenza communications; therefore, it is important that messaging be coordinated and consistent. Communication about antivirals will need to be included in overall pandemic influenza communications planning. The federal government will address the national antiviral strategy, together with regulatory and safety issues, while the FPT PHN Communications Group will provide risk communications and social marketing advice. PTs will focus on implementation within their own jurisdictions while regional and local health departments will provide local details to the public and HCWs.


Public communication - The lessons learned in the 2009 pandemic apply to both content and use of effective communication strategies. Effective strategies are needed to communicate risk and changing recommendations. Key elements of effective risk communication include transparency, stakeholder coordination and collaboration, evidence-based risk messages that address uncertainty and motivate personal action, and flexible strategies that are responsive to public risk perception.

Communication about antiviral use will need to happen early during a pandemic. Given that antivirals are known to be most effective when begun as soon as possible after symptom onset, early public and clinician education is important on topics such as:

- How, when and where to be assessed if a person develops ILI.
- How antivirals may help those who are ill, including risks and benefits.
- For whom antivirals are intended.

Multiple modalities should be used to provide information, including traditional media and social media. Tailored approaches may be needed for specific populations, such as provision of information in relevant languages, the use of Braille for the visually impaired and the use of text-to-speech (TTS) for the hearing impaired. Jurisdiction-specific accessibility legislation will need to be taken into account when preparing information for the public. Community leaders can be engaged to disseminate key information. Involvement of stakeholders, such as Indigenous organizations, can help ensure communications materials and strategies are appropriate and acceptable for target audiences.

Special outreach efforts should be considered (e.g., advance prescribing) for populations at high-risk, such as pregnant women and persons with severe underlying health conditions, for whom early treatment is specifically recommended, so that they can begin treatment quickly if they develop ILI.

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Health care sector communications - Communicating antiviral information to the health care sector in a pandemic is a shared responsibility and should be coordinated to ensure consistency of messaging to the extent possible:

- The federal government’s pandemic website (found at Canada.ca) will include links to antiviral fact sheets, clinical guidance for antiviral use and products for health care professionals, including product information leaflets for antivirals and instructions for compounding capsules to liquid formulations. FluWatch will provide ongoing surveillance information about the novel or pandemic virus activity within Canada, as well as information on any resistance of circulating influenza viruses to antivirals.

- PTs will want to provide information to HCWs within their jurisdiction that is jurisdiction-specific (e.g., locations for assessment and treatment, how to obtain antivirals and how to report an adverse reaction). They should ensure that ordering, compounding, dispensing and reporting arrangements are understood by pharmacies and other organizations responsible for dispensing.

- Regional and local public health authorities can ensure that recommendations are disseminated to local health care providers and provide details about how to access antivirals locally. They should alert health care providers when the pandemic virus is circulating in the region, making empiric treatment appropriate.

- Health professional organizations may provide support through dissemination of recommendations for antiviral use to their members.

- Manufacturers in collaboration with PHAC and HC will communicate commercial supply issues and drug shortages and any measures being taken to mitigate these situations.

It is particularly important that the health care sector receive significant program information and updates ahead of when information is released to the public, so that health care providers can be ready to respond to queries.

For further details on communications and stakeholder engagement during a pandemic, see the CPIP Communications and Stakeholder Liaison Annex.
5.0 RESEARCH

Ongoing antiviral research benefits both seasonal and pandemic influenza management. Although much can be done during the interpandemic period, a pandemic also presents unique opportunities for research.

5.1 Infrastructure and Logistics

Networks created to conduct research during the interpandemic period are well placed to facilitate pandemic research during or after an influenza pandemic. Many international networks have been established to study influenza including some that focus on antiviral issues such as resistance and clinical management. These networks include the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) and the International Society for Influenza and other Respiratory Virus Diseases (ISIRV) Antiviral Group. Canadian intensive care researchers have developed international clinical networks, such as the International Forum for Acute Care Trialists (InFACT) that will establish open access protocols, data-sharing processes and ethical frameworks to streamline the response to a new emerging disease or pandemic. Within Canada, mathematical modeling networks collaborate with public health in areas relevant to the antiviral strategy. Existing Canadian immunization and surveillance research networks could also be leveraged.

Researchers will need access to epidemiological, laboratory and clinical data to conduct their research. Data-sharing agreements and protocols for this anticipated research access should be developed to expedite the required collaborations. The main body of CPIP, Section 4.10 provides advice for pre-planning research that will be conducted rapidly during a pandemic.

5.2 Antiviral Research Needs

Although some antiviral research was conducted during the 2009 influenza pandemic, questions remain. While certain research activities can only be conducted when the pandemic strain emerges, others can be addressed during the interpandemic period.

Research needs pertaining to antiviral drugs include:\(^{52}\)

- Methodology and protocols for evaluating the effectiveness of antivirals.
- Ongoing research on the effectiveness of NIs in reducing complications, hospitalization and mortality (more robust data needed);

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• Antiviral use protocols in the management of severely ill patients, e.g., optimal dose and mode of administration, duration and make-up of therapy.
• Ongoing randomized controlled trials of intravenous NIs and other new antivirals.
• Whether antiviral therapy reduces transmission of influenza.
• Whether antiviral therapy mitigates disease without reducing the immune responses to infection and hence, provides future protection against drift virus variants.
• Whether PEP has advantages over early initiation of treatment.
• The safety and effectiveness of prolonged antiviral prophylaxis.
• Most effective strategies for reducing the risk of antiviral resistance development and transmission.
• Public and health care provider attitudes to antiviral use, including prioritization scenarios.
• Modelling to assess pandemic wave activity and impact and to analyze the impact of various strategies to deploy antivirals.
• Optimal patient assessment and diagnosis (e.g., rapid laboratory testing methods; predictors of severity).

5.3 Knowledge Translation

The knowledge translation process involves many steps: synthesis of research findings, dissemination to the appropriate audiences using tailored messages and media, and interaction between knowledge users and researchers which results in mutual learning and ethically-sound application of knowledge. Evidence-informed decision-making requires strong\textsuperscript{53} knowledge translation strategies to ensure that research findings are taken into account in antiviral decision-making. Health professional organizations can play a major role in this regard, e.g., in the development of clinical guidance and its dissemination to clinicians.

To assist the knowledge translation process, situational awareness should be maintained on new antiviral studies. Processes for rapid review and dissemination of emerging antiviral-related research findings during an influenza pandemic should be based on those used during the interpandemic period.

6.0 ASSESSMENT AND EVALUATION

During the interpandemic period, clinicians, pharmacists and other HCWs should increase their familiarity with the use of antivirals for seasonal outbreaks of influenza to support clinical practices during a pandemic. As such, periodic studies of health care provider attitudes and antiviral prescribing patterns could be conducted and would help inform ongoing educational efforts to encourage effective antiviral prescribing.

The interpandemic period also provides an opportunity for PTs to refine their stockpile management practices and develop and test their pandemic distribution, inventory monitoring and tracking procedures.

Following a pandemic, the antiviral program should be thoroughly evaluated in each jurisdiction to draw pan-Canadian lessons learned and identify best practices for future antiviral strategy discussions. Evaluation activities could include:

- Documentation of all antiviral activities including distribution, inventory management and communication strategies used.
- Collection of data on antiviral use by age and risk groups.
- Assessment of adverse reactions and events.
- Feedback on clinical tools and algorithms used during the pandemic.
- Surveys of public opinion.
- Assessment of the effectiveness of outreach to target groups.
- Studies of antiviral effectiveness, if possible.
APPENDIX A - ANTIVIRAL PRIORITIZATION FRAMEWORK

1.0 INTRODUCTION

Canada has established stockpiles of antivirals for use during an influenza pandemic. Canada’s antiviral strategy provides that they will be used during a pandemic primarily for the early treatment of cases of pandemic influenza, together with control of laboratory-confirmed outbreaks in closed health care and other facilities (e.g., correctional facilities) and settings (e.g., remote and isolated communities) where persons at high-risk for severe outcomes reside. However, circumstances such as high demand or viral resistance to one of the stockpiled antiviral drugs could result in a shortage of antivirals. The Antiviral Prioritization Framework has been developed to guide the process of determining priorities for use when antivirals are anticipated to be in short supply.

The Antiviral Prioritization Framework was adapted from the Pandemic Vaccine Prioritization Framework (CPIP Vaccine Annex, Appendix A) that was successfully used to develop sequencing guidelines for the rollout of pandemic vaccine in fall 2009. Both are based on the Erickson De Wals framework which is familiar to public health planners in Canada.

2.0 ANTIVIRAL PRIORITIZATION FRAMEWORK

The Antiviral Prioritization Framework consists of a series of criteria, organized into four major categories: scientific evidence, ethical considerations, program issues and additional policy considerations. Key questions are identified for each of the criteria (see Table A1). While scientific evidence is the key underpinning, all criteria are relevant in the development of recommendations.

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<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>CRITERIA</th>
<th>KEY QUESTIONS</th>
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<tbody>
<tr>
<td></td>
<td>1. SCIENTIFIC EVIDENCE</td>
<td>a. Disease characteristics and burden</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• What is the anticipated pandemic impact in terms of numbers ill and severity of illness?</td>
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<td></td>
<td></td>
<td>• Who is most affected in terms of illness, complications and death?</td>
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<td></td>
<td></td>
<td>• Are there ways to predict who will develop severe disease?</td>
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<tr>
<td></td>
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<td>b. Antiviral characteristics</td>
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<td>• What is known about antiviral effectiveness, especially in reducing severe outcomes? Does the effectiveness differ between antivirals?</td>
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<td>• Are there any differences in effectiveness by age or risk group?</td>
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<td>• Are there any proposed alterations to treatment schedules (e.g., dose, duration, combination therapy)</td>
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<td></td>
<td>• Is there resistance to any of the antivirals?</td>
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<td></td>
<td>• Are there any drug safety concerns?</td>
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<tr>
<td></td>
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<td>• What are the approved indications for use?</td>
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<td></td>
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<td>• Is there effective post-market surveillance?</td>
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<td></td>
<td>2. ETHICAL CONSIDERATIONS</td>
<td>Ethical considerations</td>
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<tr>
<td></td>
<td></td>
<td>• How do the relevant ethical principles and values inform the decision?</td>
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<tr>
<td></td>
<td></td>
<td>• Are the recommendations fair and equitable?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Are they being developed in a fair and equitable way?</td>
</tr>
<tr>
<td>CATEGORY</td>
<td>CRITERIA</td>
<td>KEY QUESTIONS</td>
</tr>
<tr>
<td>--------------------------------</td>
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<td>---------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| 3. PROGRAM CONSIDERATIONS      | a. Antiviral strategies   | • What strategies and potential target groups might be considered?  
• Do the proposed strategies support Canada’s 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 epidemiology, stage of pandemic wave activity, availability of pandemic vaccine)? |
|                                | b. Logistics              | • What quantities of antivirals are available to which the pandemic virus is susceptible, in both government stockpiles and the commercial supply chain?  
• What mechanisms are in place to control use?  
• What is the size and anticipated antiviral utilization of each potential priority group?  
• Are there barriers to access to antivirals for targeted populations? |
|                                | c. Program acceptability  | • What are the public and stakeholder values that can inform decisions about antiviral 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 there be any controversy associated with the prioritization plan, within Canada and in an international context? |
3.0 CONSIDERATIONS FOR ANTIVIRAL PRIORITIZATION

The process of developing prioritization recommendations begins by considering the evidence related to each of the criteria in the prioritization framework and their associated key questions as outlined in Table A1. The Canadian pandemic goals provide strong direction if choices have to be made in implementing the antiviral strategy, because of antiviral shortages. Consideration of ethical principles and values, and understanding of public and stakeholder values will help when alternative choices are weighed.

Potential data and information needs for each of the criteria in the prioritization framework are outlined in Appendix A1 and discussed in more detail in the following sections.

3.1 Scientific Evidence

3.1.1 DISEASE CHARACTERISTICS AND BURDEN (PANDEMIC EPIDEMIOLOGY)

Knowledge of the epidemiology of the pandemic is important when developing recommendations for prioritization of antiviral use. Ideally these recommendations will be based on Canadian epidemiological data; however, decision-making cannot be delayed if these data are not available. When Canadian data become available, they can be used to validate or adjust the recommendations.

Epidemiological data are important both for understanding who is most at risk for severe outcomes and for anticipating antiviral utilization. Key epidemiological measures that could affect prioritization include:

- Attack rates - A high attack rate or prolonged pandemic wave could increase the overall need for antivirals, especially if these occur before vaccine is available. High attack rates in children could increase the need for paediatric formulations.
- Clinical severity of illness - If the spectrum of illness includes more severe disease (e.g., hospitalization, admission to intensive care (ICU), need for ventilator management, or death) than anticipated, the number of individuals seeking treatment or needing to be hospitalized will be increased.
- Pattern of severe illness and mortality - Identification of the groups at high-risk of severe outcomes will allow targeting of those most likely to need antivirals. Settings with persons at high-risk of severe outcomes from influenza might also be identified, such as remote and isolated communities, which were considered at high-risk in the 2009 influenza pandemic because of frequent crowded living conditions, high proportions of persons with underlying medical conditions and limited access to medical care.
- Outbreaks in closed facilities - 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 influenza pandemic, few outbreaks occurred in LTC homes for the elderly.

3.1.2 ANTIVIRAL CHARACTERISTICS

There are several key factors to consider regarding the antivirals themselves:

- Effectiveness - The latest scientific evidence should be collated on treatment effectiveness, in particular, reduction of severe outcomes (e.g., pneumonia, hospitalization, admission to ICU or death). It is possible that effective treatment for pandemic illness will require longer duration of treatment, higher doses or combination therapy, all of which would affect drug availability. Anticipated antiviral impact on shortening the duration of illness is a consideration in whether to prioritize treatment of health care or other critical infrastructure workers.
• Safety - When drugs are given to large numbers of persons, unexpected side effects may be detected. This may alter the risk-benefit ratio and suggest re-evaluation of the recommendations for use.

• Resistance profile - Antiviral resistance may occur spontaneously or may emerge during or following antiviral treatment. Should widespread oseltamivir resistance develop, zanamivir would be the only remaining treatment option among the antivirals currently stockpiled in Canada. This would pose serious challenges because zanamivir makes up a relatively small proportion of the NAS and it cannot be used as broadly as oseltamivir. Emergence of influenza virus strains with resistance to both oseltamivir and zanamivir is also possible.

3.2 Ethical Considerations

The Ethical Considerations Section 2.5 of the main body of CPIP identifies the ethical principles and values that underpin national pandemic planning. The following ethical considerations are most relevant to antiviral prioritization:

• Stewardship - Stockpiled antivirals are a valuable resource; therefore, those entrusted with their care must plan responsibly for their use in accordance with the pandemic goals and act with integrity and accountability.

• Trust and solidarity - Public and stakeholder acceptance of prioritization recommendations is built on trust and relationships, with open communication and collaboration. Trust also involves using ethical and transparent decision-making processes (as outlined in CPIP). National solidarity is important in implementing the antiviral strategy.

• Reciprocity - Reciprocity is the provision of societal support for those who face disproportionate burdens in their duty to protect the public. Provision of priority access to antiviral treatment for health care workers if they become ill is an example of the application of reciprocity.

• Equity and fairness - Using fair criteria for prioritization and transparency and reasonableness of decision-making processes are important when distributing a potentially scarce resource such as antivirals. Whenever possible, decisions should take health inequities into account and try to minimize them.

3.3 Program Issues

3.3.1 ANTVIRAL STRATEGIES AND POTENTIAL TARGET GROUPS

If prioritization is necessary, there are many ways to focus the use of scarce supplies to address pandemic goals and antiviral objectives. Strategies will vary depending on:

• Pandemic impact - In a low impact pandemic (with low clinical severity and virus transmissibility), the focus would be primarily minimizing serious illness and overall deaths. Societal disruption is most likely to occur during a pandemic with moderate or high impact because of high absenteeism of the workforce. In this scenario, providing priority treatment to health care workers, first responders (police, fire, ambulance) and other critical infrastructure workers could minimize the additional impact of the loss of these services.

• Reason for the short supply - Heavier than anticipated demand for treatment might require 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 to ensure best use of the limited supplies of zanamivir and other available antivirals.
• Vaccine availability - Once vaccine is available, the need for antiviral treatment will be reduced; conversely if there is a delay in vaccine availability, there will be ongoing demand for antivirals that could exceed supply.

Mathematical modeling can be very helpful in the choice of antiviral use strategies. Existing modeling studies have addressed the potential impact of different approaches to prioritizing use of antivirals during a pandemic.\(^{55,56,57,58,59}\) Timely modeling, using epidemiological characteristics of the pandemic in progress, should be conducted to assist in the prioritization decision-making.

**Potential Target Groups** - Potential target groups to consider in the prioritization process are outlined in Table A2. In each category, antiviral treatment would only be provided if the person(s) develops ILI.

**TABLE A2- POTENTIAL TARGET GROUPS FOR ANTIVIRAL PRIORITIZATIONS**

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>POTENTIAL TARGET GROUP</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PERSONS WITH SEVERE ILLNESS</td>
<td>• Hospitalized patients</td>
<td>• Persons at high-risk of complications from seasonal influenza as defined by the National Advisory Committee on Immunization (NACI)(^60) will likely be at high-risk during a pandemic.</td>
</tr>
<tr>
<td>PERSONS AT HIGH-RISK OF SEVERE OUTCOMES</td>
<td>• Persons with underlying health conditions including pregnancy</td>
<td>• Pandemic epidemiology may identify additional risk factors or predictors of severe outcome.</td>
</tr>
<tr>
<td></td>
<td>• Age groups at increased risk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Indigenous peoples</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Vulnerable populations as outlined in CPIP</td>
<td></td>
</tr>
<tr>
<td>PERSONS CAPABLE OF TRANSMITTING INFECTION TO PERSONS AT HIGH-RISK OF SEVERE OUTCOMES</td>
<td>• Health care workers</td>
<td>• Early treatment could help reduce the risk of transmission to high-risk persons.</td>
</tr>
<tr>
<td></td>
<td>• Household and close contacts of high-risk persons</td>
<td>• If vaccine is available, the latter category could be narrowed to contacts of persons who can’t be immunized (e.g., infants &lt; 6 months of age) or who are unlikely to respond to vaccine (e.g., immunosuppressed persons).</td>
</tr>
</tbody>
</table>

\(^{55}\) Greer AL, Schanzer D. Using a dynamic model to consider optimal antiviral stockpile size in the face of pandemic influenza uncertainty. PLoS ONE. 2013;8:e67253.


<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>POTENTIAL TARGET GROUP</th>
<th>COMMENTS</th>
</tr>
</thead>
</table>
| SELECTED SETTINGS | • Closed health care facilities and other closed facilities where persons at high-risk reside (e.g., correctional facilities)  
• Remote and isolated communities  
• Homeless shelters, etc. | • Consider all persons within the setting for prioritization - residents, staff, volunteers etc.  
• Consider whether to prioritize for treatment or to include outbreak control. (See next row) |

| OUTBREAK CONTROL | • Closed health care facilities and other closed facilities where persons at high-risk reside (e.g., correctional facilities) | • Involves treatment of cases and prophylaxis of close contacts. |

| CRITICAL INFRASTRUCTURE WORKERS | • HCWs involved with the pandemic response or delivery of essential health services in all settings, including:  
• community,  
• health care facilities,  
• long-term and palliative care,  
• public health, and  
• laboratory.  
• Critical infrastructure (CI) workers:  
• Emergency first responders  
• military  
• other CI workers | • In health care settings, 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  
• Emergency first responders who are functioning in a health care provider capacity (e.g., police and fire personnel who are providing medical first response) should be prioritized along with HCWs.  
• Need clear definitions for national consistency in application.  
• Provide services essential to the health, safety, security or economic well-being of Canadians and the effective functioning of government.  
• PT differences in organization of CI could affect consistent approach. |

3.3.2 LOGISTICAL ISSUES
Appropriate decision-making relies on a robust and timely monitoring program for antiviral utilization and stockpile depletion during an influenza pandemic. Key logistical considerations include identifying the available quantities of antivirals, predicting the anticipated utilization by ill persons in the proposed target groups and assessing the feasibility of implementing the proposed prioritization recommendations.

**Identifying the available quantities of antivirals** - It is important to identify all antivirals that could potentially be used, given the resistance profile of the pandemic virus. Potential sources include government stockpiles, private stockpiles (e.g., held by some large employers or health care facilities) and the commercial supply chain (e.g., manufacturers, wholesalers and retail pharmacies). Emergency authorization may be used to allow access to antivirals not sold in Canada.

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Predicting utilization - Demand and utilization are difficult to predict. In addition to epidemiological factors such as clinical severity and disease transmissibility, utilization is influenced by provider and public awareness and accessibility to assessment and treatment. Public education to promote timely medical care could lead to higher utilization, which may be desirable if treatment is to be recommended for all ill persons with certain underlying risk conditions. Targeting hospitalized patients reaches those with severe illness but may mean that treatment starts later in the illness than is ideal.

Estimates should also take into account a certain amount of drug wastage, including unavoidable treatment of persons with ILI who are infected with another respiratory virus, rather than influenza.

Feasibility - Prioritization plans should assess the feasibility of implementing recommendations in a way that provides some control without impeding timely target group access. If there are only enough drugs for the most severely ill, it may be reasonable to restrict access to hospitals. If those with early illness and underlying risk factors are also to be treated, consider the best ways to reach them quickly, whether through family doctors or special clinics. If hard-to-reach areas with residents who are at high-risk of severe outcomes are to be prioritized, prepositioning drugs may improve timely access. The choice of drug depots for antiviral distribution within a jurisdiction may also have an impact - if fewer sites are selected to hold antiviral drugs, it may be easier to control inventory when it is in short supply.

3.3.3 PROGRAM ACCEPTABILITY
The values and perceptions of the public and stakeholders should be considered when developing antiviral priority use recommendations including how the proposed recommendations will be accepted. Involving stakeholders in the process of developing prioritization recommendations provides an opportunity for them to have their concerns addressed. Some public and stakeholder views that may be anticipated include:

- General unfamiliarity with antivirals by the public.
- General acceptability of the priority groups (tied to public perceptions about mortality and value of life).
- Placement of children on the priority list.
- Perceived risk or benefit of antiviral treatment.
- Public response if there are reports of severe adverse drug reactions.
- Need for treatment during a pandemic that is perceived as mild.

Appendix A2 outlines several sources of information about how the public feels about prioritization of resources during an influenza pandemic.

3.4 Additional Policy Considerations

3.4.1 LEGAL CONSIDERATIONS
There are many factors that must be carefully considered in the development and use of an antiviral prioritization framework. If governments choose to designate priority groups for the receipt of antivirals, they could face Charter of Rights and Freedoms challenges. When designating priority groups, governments should retain evidence showing that the decision was based on sound scientific, social, logistical and ethical policy rationales. Governments should be able to demonstrate that priority group decision-making was based on reasonable, fair and rational considerations. Further, the policy decision to prioritize specific groups should be communicated widely in a clear, transparent and consistent manner and the Antiviral Prioritization Framework should be followed carefully and precisely.
3.4.2 CONFORMITY OF PROGRAMS
Recommendations from WHO and other countries and their rationale should be considered. However
differences in the Canadian situation in terms of factors such as antiviral supply or identification of high-
risk groups unique to the Canadian situation may lead to Canadian recommendations that vary to some
extent from other jurisdictions. Acknowledging these differences and providing the rationale for the
Canadian approach is important to generate understanding and support by health care providers and
the public.

A pan-Canadian approach to antiviral prioritization is desirable. Working collaboratively to establish and
support pan-Canadian policies and agreed-upon uses for the NAS during a pandemic has been identified
as role for FPT governments. (See Section 3.4 of the Antiviral Annex)

3.4.3 POLITICAL CONSIDERATIONS
Political considerations may include the possibility of controversy, within Canada or in an international
context that is associated with the proposed prioritization plan such as the choice and placement of
some potential target groups.

4.0 PROCESS FOR DEVELOPING RECOMMENDATIONS
The mandate to develop prioritization recommendations will need to be assigned to a group under the
Public Health Network with the appropriate expertise. PHAC will provide support and ensure that the
required information is available. The process should follow the ethical guidelines for good decision-
making set out in CPIP. A brief description of the proposed process and some further considerations are
outlined below.

Developing the prioritization recommendations - The process of developing prioritization
recommendations involves several steps:

- Review of the assembled scientific evidence for each of the criteria in the prioritization framework
  and discussion of the key questions (Table A1).
- Review of the pandemic goals and objectives for the pandemic antiviral strategy, considering the
  epidemiology and projected pandemic impact.
- Identification of potential target groups and settings and selection of the best strategy to address
  the pandemic goals.
- Ordering the proposed target groups and settings, followed by adjustment based on ethical, logistical
  and other considerations, together with projected antiviral quantities.
- Consolidation of the recommendations and provision of a written rationale.

Involvement of partners and stakeholders - It is recommended that key partners and relevant
stakeholders are included in the development of prioritization recommendations to obtain their input
and allow their concerns to be addressed. If time permits, further stakeholder consultation should be
carried out before recommendations are finalized.

Consistency - Consistency in PT implementation is necessary to support the selected strategies and
avoid public confusion. It will be facilitated by discussing the optimal balance of standardization, PT
flexibility in implementing the recommendations, ensuring consistent understanding of target group
definitions and interpretations and agreement on areas where PT flexibility is appropriate.
Communicating the prioritization recommendations - A communication plan should be prepared to convey the prioritization recommendations. Communications should clearly outline the process used to arrive at prioritization recommendations, the ethical principles informing decisions, who was involved in making them and the rationale for the recommendations. The communication strategy should be prepared to explain proactively why there may be PT differences in implementation of the prioritization recommendations.

APPENDIX A1 - INFORMATION NEEDS FOR ANTIVIRAL PRIORITIZATION DECISION-MAKING

The following table outlines the data and information requirements of the prioritization process. This information should be gathered, analyzed and presented in advance to the expert group that will be developing the prioritization recommendations. This will provide them an opportunity to identify any additional analyses or information required for decision-making.

TABLE A2- POTENTIAL TARGET GROUPS FOR ANTIVIRAL PRIORITIZATIONS

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>CRITERIA</th>
<th>KEY QUESTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCIENTIFIC INFORMATION</td>
<td>Pandemic epidemiology</td>
<td>• Attack rate (age-specific if known)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Case fatality rate (age-specific)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Indicators of disease severity, e.g., rates of hospitalization, ICU admission and ventilator use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Risk factors and predictors for severe illness, hospitalization and death</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Population susceptibility - age-specific seroprevalence and immunization data to ascertain population immunity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Predictions for future pandemic waves</td>
</tr>
<tr>
<td>Antiviral information</td>
<td></td>
<td>• Antiviral effectiveness data by age and risk status</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Antiviral susceptibility and resistance data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Antiviral safety data, including any age-specific effects</td>
</tr>
<tr>
<td>ETHICAL CONSIDERATIONS</td>
<td>Ethical considerations</td>
<td>• Ethical principles from CPIP and other relevant sources</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Results of public and stakeholder consultations</td>
</tr>
<tr>
<td>CATEGORY</td>
<td>CRITERIA</td>
<td>KEY QUESTIONS</td>
</tr>
<tr>
<td>----------</td>
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<td>---------------</td>
</tr>
</tbody>
</table>
| PROGRAM ISSUES | Antiviral strategies | • Identification of potential options  
• Summary of evidence base and modeling of different strategies |
|          | Logistics | • Canadian and international antiviral availability, including size and composition of government stockpiles  
• Size of Canadian and PT populations by age and sex (5-year groupings)  
• Size of all proposed target groups and risk categories  
• Estimates of anticipated need and utilization |
|          | Acceptability | • Results of public and stakeholder consultations, media scans and opinion surveys |
| ADDITIONAL POLICY CONSIDERATIONS | Conformity of programs | • Antiviral distribution plans from other countries, especially the United States of America |
|          | Legal and political considerations | • Identification of other potential significant issues with policy analysis and legal opinion as needed (including liability issues) |
APPENDIX A2 - PUBLIC CONSULTATIONS REGARDING PRIORITIZATION

The results of several public consultations regarding prioritization of resources during a pandemic are summarized below.

1. Canadian Program of Research Ethics in a Pandemic (Canprep) Projects[^62][^63]

Three projects were carried out to elicit the perspectives of Canadians and other stakeholders regarding ethical issues during a pandemic. These included national opinion surveys, town hall meetings and a national stakeholder forum. Key findings relevant to prioritization:

Main goal of the pandemic response - reduce influenza-related mortality, with reduction of global mortality an important dimension of this objective.

Key ethical considerations in priority setting:

- Ethical goals are legitimacy, fairness and equity together with trust, solidarity and stewardship.
- Criteria for priority setting decisions should be made in advance, with engagement of stakeholders including the public.
- Governments and health care sector officials should provide an explicit rationale for resource allocation decisions, including the access of priority groups to limited health care resources and services. The rationale should be publicly accessible, justified in relation to the defined criteria and explain any deviation from the pre-determined criteria.
- There should be formal mechanisms in place for stakeholders to bring forward new information, to appeal or raise concerns about particular allocation decisions and to resolve disputes.
- HCWs should be prioritized for access to some health care resources, with children a second priority.

2. University of Alberta Survey on Allocation of Scarce Resources During an Influenza Pandemic[^64]

A web questionnaire was administered to students, support and academic staff at the University of Alberta. Respondents were asked to rank eleven different groups for access to scarce resources and to select one of seven priority access plans.

Ranking of groups for access to scarce resources:

- The highest priority was given to HCWs (89% of participants), closely followed by emergency workers.
- Children were given higher priority than persons with underlying health conditions.

Preferred priority access plan:

- The top choice was to save the most lives.
- Next choices were to save people according to a priority ranking system, followed by those most likely to die.
- First come, first served approach was least acceptable.

3. **Goals and Values from the Antiviral Deliberative Dialogue Process**

The Task Group on Antivirals for Prophylaxis Deliberative Dialogue Process explored public and stakeholder beliefs and values in relation to antiviral prophylaxis.

Participants supported three goals:

1. To ensure that normal societal functions are maintained.
2. To minimize public fear and panic.
3. To reduce serious illness and death during a pandemic.

Priority recipients if antiviral prophylaxis were available:

- HCWs 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 HCWs and consider ease of delivery.
- Fairness and equity - consistency across country, avoid inequities of access.
- Compassion for the vulnerable.
- Public awareness/engagement - to gain understanding and support.
- A strong role for government; trust and confidence - government to lead, responsibility to protect vulnerable and workers who will be exposed.

4. **Institute of Medicine’s (IOM) Public Engagement on Facilitating Access to Antiviral Medications and Information in an Influenza Pandemic**

The IOM designed and convened a series of workshops in 2012 to explore the American public’s perception of potential strategies to facilitate access to antiviral medications and treatment advice during an influenza pandemic. In response to a scenario where there was a shortage of antivirals and delivery systems were overwhelmed, the common goals and values cited by participants included:

- Equity and fairness - ensuring equitable access by vulnerable populations; preventing favoritism, bias and discrimination in the distribution of resources both between and within communities; and ensuring equal access to communications about antiviral treatment.
- Integrity - compliance with prescribing protocols and priorities; encouragement of public trust, acceptance and cooperation.
- Prioritization - allocation of antivirals for certain groups.
- Transparency - accurate, consistent information sharing by authorities.

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### Clinical Recommendations for Patients Presenting with Respiratory Symptoms during the 2009–2010 Influenza Season

**Clinical ILI:**
- Does the patient have the clinical features of an influenza-like illness (ILI)?
- **Yes:** Sudden onset of cough and fever
- **No:** Usual: Sudden onset of cough and fever, Common: Sore throat, Coryza, Fatigue/malaise/prostration, Myalgias/arthritis, Headache, Decreased appetite

**Presence of pH1N1:**
- Is the pandemic (H1N1) 2009 virus known to be circulating in your community?
- **Yes:** PCR or antigen test is needed
- **No:** Clinical assessment

**Severity Indicators:**
- Does the patient display any severity indicators?
- **Yes:** Shortness of breath, wheezing, rapid or difficulty breathing, Chest pain, Signs of pneumonia, Sudden dizziness, Confusion/disorientation, Severe or persistent vomiting, High fever lasting more than 3 days, Hypotension, Bloody or coloured sputum, Blush or grey skin color
- **No:** Usual care

**Risk Factors:**
- Does the patient have any risk factors for complications from pH1N1?
- **Yes:** Antiviral medications and hospitalizations are needed
- **No:** Self-isolation at home until symptom-free and well enough to resume normal activities

**Recommendations**

1. If ILI + any severity indicators → Antiviral medications and hospitalizations are needed.
   - **Antiviral medications are most effective if started within 24-48 hours of the onset of symptoms.**
   - **Note:** During the first wave of pH1N1, people aged 55+ and particularly those >65 were less likely to become infected than adults under 55. However, when infected, older people had a proportionally higher risk of hospitalization and death.

2. If ILI + risk factors and other considerations → Antiviral medications and close follow-up are appropriate.
   - Nasopharyngeal swab may be done to assess treatment decision.
   - **Adults:** Oseltamivir (Tamiflu®) 75 mg bid x 5 days or Zanamivir (Relenza®) 2 inhalations bid x 5 days. Pediatric dosing of oseltamivir is by weight.
   - **Children:** Oseltamivir: 30-70 mg/m² bid x 5 days. Zanamivir: 8 mg oral spray bid x 5 days.
   - **Children under 2 with suspected pH1N1:** Treatment with antiviral medications is advised.
   - **Children aged 2-5 with any other risk factors (such as a history of asthma):** Treatment with antiviral medications is advised.
   - **Children aged 2-5 with no other risk factors:** Clinical discretion regarding need for treatment is indicated.

3. If ILI + no risk factors → Self-isolation at home until symptom-free and well enough to resume normal activities.

**Education**

Patients in groups 2 and 3 need to be informed of the risk of rapid deterioration and advised that if any severity indicators develop, to get re-assessed immediately.

A patient information resource, *Your H1N1 Preparedness Guide*, highlights the list of severity indicators and includes information on how to look after someone at home with pH1N1.

Clinical judgment is always indicated; look to local/regional public health authorities for additional guidance.

www.fightflu.ca  1 800 0-CANADA (1-800-622-6232)
Appendix B - Endnotes

(a) Epidemiologic data on pH1N1 in Canada (from April to August 2009) showed that in laboratory confirmed patients: almost 100% of children under age 2 presented with fever; 90% of pregnant women presented with fever; and approximately 50% of people >65 presented without fever. Overall, fever and cough were present in 70%, cough without fever was present in less than 12%, and GI symptoms were rare in people over 65. Atypical presentations were most common in infants, and elderly and immunocompromised persons. People with chronic lung conditions may present with a new or worsening cough.

(b) Information on whether pH1N1 is in the community or not can usually be obtained through contacting local/regional public health or assessing the geographic map of influenza in the weekly FluWatch reports (www.phac-aspc.gc.ca/fluwatch/index-eng.php). In remote and isolated areas, point of care testing may help to detect an outbreak (negative result is not very specific; positive result suggests influenza is likely in the community). We expect the pH1N1 influenza virus to predominate, but seasonal H1N1, H3N2 and other respiratory viruses may also circulate. As of the end of September 2009, 98% of the positive influenza A subtyped specimens were pH1N1.

(c) These severity indicators are based on Canadian epidemiologic data and case series of patients in intensive care from pH1N1 published in the medical literature as of August 2009. The most common severity indicators were shortness of breath and chest pain.

(d) These risk factors are based on both Canadian and international data from the pH1N1 virus as of August 2009. The most common chronic conditions associated with pH1N1 have been asthma, diabetes and heart disease.

(e) These are overlapping groups that may reflect other factors, such as limited access to health care, high prevalence of chronic diseases and poor living conditions. However, preliminary epidemiologic data suggest that these groups are at greater risk of severe disease. Therefore, at this time, early treatment with antivirals is advised. Check www.phac-aspc.gc.ca for upcoming guidelines on the clinical management of persons with pH1N1 in remote and isolated communities.

(f) Increased risk of hospitalization and death is partially explained by the increasing prevalence of chronic disease with age.

(g) An NP swab is indicated in patients requiring hospitalization, those with ILI who have been on prophylaxis or when there is no response to treatment. NP swabs should be sent for PCR testing at a public health laboratory, local/regional public health can facilitate this if necessary. In critically ill patients, NP swabs may be negative. An endotracheal aspirate is indicated.

Note: pH1N1 is almost always susceptible to oseltamivir (Tamiflu); seasonal H1N1 is virtually 100% resistant to oseltamivir.

(h) Pediatric dosing of oseltamivir is by weight. See Product Monograph at: www.rochecanada.com/portal/epif/ca/portal/roche/consumer_information?paf_gear_id=17700009&paf_pageId=re7191019&glossary_id=static/glossary/re7300002/re77300002/re7730003/re753001/Definition_01049.content.

<table>
<thead>
<tr>
<th>Body Weight in kg</th>
<th>Body Weight in lbs</th>
<th>Recommended Dose for 5 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 15 kg</td>
<td>≤ 33 lbs</td>
<td>30 mg twice daily</td>
</tr>
<tr>
<td>&gt; 15 kg to 23 kg</td>
<td>&gt; 33 lbs to 51 lbs</td>
<td>45 mg twice daily</td>
</tr>
<tr>
<td>&gt; 23 kg to 40 kg</td>
<td>&gt; 51 lbs to 88 lbs</td>
<td>60 mg twice daily</td>
</tr>
<tr>
<td>&gt; 40 kg</td>
<td>&gt; 88 lbs</td>
<td>75 mg twice daily</td>
</tr>
</tbody>
</table>

Oseltamivir can be used in infants <1. See: www.phac-aspc.gc.ca/alert-alerte/h1n1/guidance-orientation-07-20-eng.php. Current guidance is 2 mg/kg BID; treatment up to 3 mg/kg BID is under consideration. Zanamivir is indicated in people 7 years or older. See Product Monograph at: www.gsk.ca/english/docs-pdf/Relenza_PM_20080515_EN.pdf.


(k) Your H1N1 Preparedness Guide can be obtained from: www.fightflu.ca or ordered by phone at: 1 800 O-CANADA (1-800-622-6232).
APPENDIX C- EXPERT RECOMMENDATIONS FOR THE NATIONAL ANTIVIRAL STOCKPILE

In 2015-2016, the Canadian Pandemic Influenza Preparedness (CPIP) Task Group undertook a review of Canada’s antiviral strategy, to take into account emerging scientific evidence on the effectiveness of neuraminidase inhibitors (NIs), the expiry of antiviral drug patents and contracts, and the introduction of generic antiviral products into the Canadian market. This review included:

- A systematic review of the evidence on the safety and effectiveness of NIs in the context of seasonal, pandemic and novel influenza, which reaffirmed the importance of antivirals in reducing morbidity and mortality from pandemic influenza;\textsuperscript{67,68}
- A review of the antiviral product landscape in Canada;
- A status update on antiviral drug resistance globally;
- Updated mathematical modeling on the optimal size of the National Antiviral Stockpile (NAS) (see Section 2.2);
- International antiviral stockpile policies and practices.

In 2017, the CPIP Task Group provided the Pan-Canadian Public Health Network Council with updated recommendations on NAS use, composition and size. The Task Group recognized that, in a pandemic, antiviral stockpiles provide a bridge until vaccine becomes available. The timing of vaccine availability affects NAS size and use and how it is used in a pandemic will depend on the specific scenario.

This document outlines the CPIP Task Group’s updated NAS recommendations (Section 1.0) as well as the additional background information (Section 2.0) on how the CPIP planning scenarios and modelling data were used in determining optimal NAS size.

1.0 Updated NAS Recommendations

<table>
<thead>
<tr>
<th>TABLE C1. UPDATED NAS RECOMMENDATIONS</th>
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</table>

**USE**

The event of a novel/pandemic influenza virus with sustained transmission first detected in Canada should trigger:

- A rapid response structure, which would provide real time advice on use of antivirals, based on available data, to optimize the use of the stockpile,
- Early antiviral treatment of cases is recommended initially and post-exposure prophylaxis (PEP) of close contacts of cases may be considered based on the characteristics (e.g. clinical severity and transmissibility) of the evolving pandemic.

The event of a novel/pandemic virus with sustained transmission and widespread activity, within the PT/locally should trigger:

- Antiviral treatment of persons with influenza-like illness (ILI), as early as possible, and when there is evidence that the pandemic influenza virus is circulating in the community, e.g., from either laboratory or surveillance data,
- Use antivirals for outbreak control, including treatment of cases and PEP of close contacts of cases in closed health care facilities and other closed facilities (e.g. correctional facilities) and other settings (e.g. remote and isolated communities) where high-risk people reside.

#### TABLE C1. UPDATED NAS RECOMMENDATIONS

| SIZE | Based on a balancing of the risk scenarios (Table C2), costs and ethical considerations, a NAS size to cover 17.14% of Canadian population will be sufficient for all except the worst case of Scenario D. These calculations are based on anticipated cases of pandemic influenza in the twelve month period after onset of pandemic in Canada.
|      | This recommendation takes into account the following assumptions:
|      | • Health seeking behaviour of the population is directly related to clinical severity. However, it is difficult to predict and there may be modifying factors such as mortality and media coverage which may affect risk perception and health seeking behaviour.
|      | • An effective vaccine will be available at six months; if available sooner it will reduce the need for antivirals; if vaccine is delayed, antiviral need will increase.
|      | • There is no effect of antiviral treatment on transmissibility; it is possible that antiviral treatment could reduce transmissibility, therefore reducing the need.
|      | • There is limited resistance to stockpiled antivirals; if there is substantial antiviral resistance, this would render a portion of the stockpile ineffective.
|      | • There is perfect allocation of antiviral treatment to true cases of pandemic influenza; it is expected that there will be wastage early in the pandemic related to the use of antivirals for individuals with ILI caused by a pathogen other than influenza.
|      | • There is no rapid access to additional antivirals from other sources, e.g., commercially available; if additional access is possible, this may reduce the size of stockpile required.
|      | Additional considerations:
|      | • The two stockpiled antivirals are no longer under patent; if lower cost generic versions become available, this may decrease cost.
|      | • The strategy for management of the NAS should be renegotiated to allow for a provincial or vendor-managed stockpile.
|      | • Optimally, the NAS would be used for seasonal outbreaks and replaced on an ongoing basis.
| COMPOSITION | • The NAS should contain both oseltamivir and other antivirals with different resistance profiles. Currently, the only other antiviral licensed in Canada meeting this criterion is zanamivir. Future consideration should be given to new antivirals as they are licensed in Canada.
|      | • The recommended proportion of zanamivir should be between 18 and 25% if total stockpile size covers 17.14% of the population.
|      | • This recommendation is based on expert opinion, taking into account modeling of antiviral use in individuals with conditions that place them at high-risk of severe outcomes who present for care, the difficulty in predicting the probability of resistance, proportion of the population for whom zanamivir is indicated and international stockpile strategies.
|      | • The recommended proportion of the second antiviral may vary in the future as new antivirals become available.
|      | • The NAS should include both adult and paediatric formulations of oseltamivir (capsules and suspension).
|      | • Intravenous (IV) antivirals are not recommended for the NAS; however, mechanisms for rapid access to IV antivirals (preferably zanamivir) should be established. Consider stockpiling a small amount in the National Emergency Strategic Stockpile.
2.0 Background on Antiviral Stockpile Optimization Using Pandemic Planning Scenarios and Modeling Data

CPIP planning scenarios were used to describe strategies for antiviral use that would optimize the NAS (Table C2). Modeling was employed to evaluate the size of NAS that would be needed in each scenario (see Section 2.2).

2.1 Planning Scenarios and NAS Optimization

<table>
<thead>
<tr>
<th>TRANSMISSION</th>
<th>CLINICAL SEVERITY</th>
<th>Scenario B</th>
<th>Scenario D</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGH</td>
<td>LOW</td>
<td>High transmissibility/ low clinical severity: optimization of the AV stockpiles would be to treat all at high risk of severe illness or complications. Low clinical severity would translate into fewer people presenting for care and higher transmissibility would mean a greater number of people infected earlier (prior to vaccine availability). Based on this scenario and modeling: the maximum size of stockpile needed is 2.44% of Canadian population. (See Modeling Table C4)</td>
<td>High transmissibility/ high clinical severity: optimization of AV stockpiles would be to treat all who present for care. High transmissibility would mean greater numbers of people infected and high clinical severity would translate into larger number of people presenting for care. Based on this scenario and modeling; the maximum size of stockpile needed is 23.19% of Canadian population coverage. (See Modeling Table C3)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>LOW</th>
<th>LOW</th>
<th>Scenario A</th>
<th>Scenario C</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOW</td>
<td>LOW</td>
<td>Low transmissibility/low clinical severity: optimization of AV stockpiles would be to treat all at high risk of severe illness or complications. Low clinical severity would translate into fewer people presenting for care and lower transmissibility would mean slower rate of infection and fewer people infected prior to anticipated vaccine availability. Based on this scenario and modeling; the maximum size of an AV stockpile needed would be sufficient to cover 1.85% of Canadian population. (See Modeling Table C4)</td>
<td>Low transmissibility/ high clinical severity: optimization of AV stockpiles would be to treat all who present for care. Low transmissibility would mean fewer people infected however high clinical severity would translate into larger number of people presenting for care. Based on this scenario and modeling; the maximum size of stockpile needed is 17.14% of Canadian population coverage. (See Modeling Table C3)</td>
</tr>
</tbody>
</table>
2.2 Modeling of Optimal NAS Size

Table C3 and C4 are excerpts from dynamic modeling that was undertaken to consider the optimal NAS size in the face of pandemic uncertainty. The full modeling report is available upon request to the Public Health Agency of Canada.

**MODELING TABLE C3: TREAT ALL SCENARIO (ABSENCE OF VACCINE)**

<table>
<thead>
<tr>
<th>PROPORTION OF INFECTED CANADIANS SEEKING MEDICAL ATTENTION</th>
<th>CANADIAN POPULATION REQUIRING ANTIVIRALS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RO = 1.3</td>
</tr>
<tr>
<td>0.500(^{69})</td>
<td>12.8</td>
</tr>
<tr>
<td>0.170(^{70,71})</td>
<td>4.5</td>
</tr>
<tr>
<td>0.050(^{72})</td>
<td>1.4</td>
</tr>
<tr>
<td>0.005(^{73})</td>
<td>0.1</td>
</tr>
</tbody>
</table>

**MODELING TABLE C4: TREAT HIGH RISK (ABSENCE OF VACCINE)**

<table>
<thead>
<tr>
<th>PROPORTION OF INFECTED CANADIANS SEEKING MEDICAL ATTENTION</th>
<th>CANADIAN POPULATION REQUIRING ANTIVIRALS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RO = 1.3</td>
</tr>
<tr>
<td>0.500</td>
<td>4.8</td>
</tr>
<tr>
<td>0.170</td>
<td>1.4</td>
</tr>
<tr>
<td>0.050</td>
<td>0.4</td>
</tr>
<tr>
<td>0.005</td>
<td>0.0</td>
</tr>
</tbody>
</table>

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