What are antiviral medications for influenza?

Antiviral medications are recommended to treat and prevent influenza. Drugs currently used in Canada are oseltamivir (Tamiflu®) which is an oral medication, and zanamivir (Relenza®) which is an inhaled medication. Oseltamivir and zanamivir are neuraminidase inhibitors which work by blocking the exit of the influenza virus from respiratory cells and therefore prevent further replication of the virus. Amantadine is an older antiviral medication that is no longer used. Because antiviral medications prevent further replication of the virus, when used for treatment, they should be taken as soon as possible, ideally within 48 hours of symptom onset.

What are the recommendations for the use of influenza antiviral medications?

Influenza antiviral medications are recommended for:

- Treatment of moderate, progressive, severe or complicated influenza, such as individuals who are hospitalized with influenza-like illness.
- Treatment of those at high risk for complications of influenza, such as children less than five years of age, adults 65 years of age and over, and those with underlying medical conditions (see Appendix A for additional details).
- Treatment and prevention in influenza outbreaks in institutional settings (see below: ‘How are antiviral medications used in institutional influenza outbreaks?’).

When influenza is circulating, laboratory confirmation of influenza is not needed before initiating treatment, as waiting until influenza is confirmed will delay initiation of therapy. Although treatment is generally more beneficial if given early, it can still be considered in those at high risk for influenza complications, even if more than 48 hours has passed from symptom onset. Use of antiviral medication is also recommended, regardless of time from symptom onset, in individuals with moderate, progressive, severe or complicated influenza-like illness, such as individuals who are hospitalized with influenza-like illness.  

1
How can practitioners determine if influenza is circulating?

From November to April, Public Health Ontario posts a weekly [Ontario Respiratory Pathogen Bulletin](http://www.pho.ca) which provides information about the circulation of influenza and other respiratory pathogens in Ontario. There is an overall influenza activity assessment based on several provincial indicators, and local information is also available by public health unit jurisdiction. In addition, some local public health units produce their own surveillance reports. Once influenza is circulating in the community, those with serious illness and those at risk of complications from influenza should be started on antivirals as soon as possible after symptom onset and without laboratory confirmation. Between May and October, a condensed version of the [Ontario Respiratory Pathogen Bulletin](http://www.pho.ca) is posted every other week.

How are influenza antiviral medications used?

The following describes key features related to the use of influenza antiviral drugs.

<table>
<thead>
<tr>
<th></th>
<th>Oseltamivir</th>
<th>Zanamivir (5 mg per inhalation)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dosage for treatment</strong></td>
<td>75 mg twice daily for 5 days for adults.</td>
<td>2 inhalations twice daily (approximately 12 hours apart) for 5 days. c</td>
</tr>
<tr>
<td></td>
<td>See <a href="http://www.pho.ca">AMMI guideline</a> for pediatric dosing.a</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose adjustments may be needed if person is known to have renal impairment. See <a href="http://www.pho.ca">AMMI guidelines</a>. b</td>
<td></td>
</tr>
<tr>
<td><strong>Dosage for prevention</strong></td>
<td>75 mg daily for 10 days for adults d (or in an outbreak, until the outbreak is declared over).</td>
<td>2 inhalations twice daily (approximately 12 hours apart) for 5 days. c</td>
</tr>
<tr>
<td></td>
<td>See <a href="http://www.pho.ca">AMMI guidelines</a> for pediatric dosing.a</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose adjustments may be needed if person is known to have renal impairment. See <a href="http://www.pho.ca">AMMI guidelines</a>. b</td>
<td></td>
</tr>
<tr>
<td><strong>Age authorized for use</strong></td>
<td>1 year of age and over.</td>
<td>7 years of age and over.</td>
</tr>
<tr>
<td></td>
<td>Can be considered on a case-by-case basis for those younger than 1 year of age.a</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oseltamivir</td>
<td>Zanamivir (5 mg per inhalation)</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>Nausea, vomiting. Taking it with food may increase tolerability.</td>
<td>Allergic reactions: oropharyngeal or facial edema.</td>
</tr>
<tr>
<td></td>
<td>Post-marketing reports of serious skin reactions and sporadic, transient neuropsychiatric events (self-injury or delirium; mainly reported among Japanese adolescents and adults).</td>
<td>Adverse events: diarrhea, nausea, sinusitis, nasal signs and symptoms, bronchitis, cough, headache, dizziness, and ear, nose and throat infections.</td>
</tr>
<tr>
<td></td>
<td>See <a href="#">product monograph</a> for additional details.</td>
<td>See <a href="#">product monograph</a> for additional details.</td>
</tr>
<tr>
<td><strong>Contra-indications</strong></td>
<td>None</td>
<td>Underlying respiratory condition such as chronic obstructive pulmonary disease or asthma.</td>
</tr>
<tr>
<td></td>
<td>See <a href="#">product monograph</a> for additional details.</td>
<td>See <a href="#">product monograph</a> for additional details.</td>
</tr>
<tr>
<td><strong>Product monograph</strong></td>
<td>Tamiflu® product monograph, Relenza® product monograph</td>
<td></td>
</tr>
</tbody>
</table>

a. For pediatric dosing, see Table 4 of the [AMMI Canada Guidelines: The use of antiviral drugs for influenza: A foundation document for practitioners](#).

b. Checking creatinine clearance and dose adjustments are not required for those who are not known to have renal impairment. For those with known renal impairment, alternative dosing based on creatinine clearance is provided in Table 5 of the [AMMI Canada Guidelines: The use of antiviral drugs for influenza: A foundation document for practitioners](#).

c. A second dose (10 mg, which is 2 inhalations) should be taken on the first day of treatment whenever possible, provided there is at least 2 hours between doses (based on the [product monograph for Relenza®](#)).

d. For exposure to avian influenza, 75 mg twice a day is recommended for prevention. Based on CDC [Interim Guidance on Influenza Antiviral Chemoprophylaxis of Persons Exposed to Birds with Avian Influenza A Viruses Associated with Severe Human Disease or with the Potential to Cause Severe Human Disease](#).

e. For more information, see CDC [Influenza Antiviral Medications: Summary for Clinicians](#).
Is influenza antiviral resistance a concern?

There is very little resistance to oseltamivir or zanamivir among recently circulating strains of influenza. Influenza strains are regularly monitored for antiviral resistance with results provided in the Ontario Respiratory Pathogen Bulletin.

How are antiviral medications used in institutional influenza outbreaks?

When an influenza outbreak is declared in an institutional setting, antiviral medications are recommended for:

- treatment of residents/patients meeting the case definition, regardless of immunization status
- prophylaxis of residents/patients who are not ill with influenza symptoms, regardless of immunization status
- prophylaxis of unvaccinated staff members
- prophylaxis of vaccinated staff members when there is a mismatch between the vaccine and circulating influenza strains, based on consultation with public health officials.

Antiviral medication for treatment and prophylaxis should begin as soon as possible in an outbreak. For prevention, the antiviral drugs should be used for the duration of the outbreak. For influenza outbreaks in long-term care homes, oseltamivir is the recommended antiviral for residents. Information on prophylaxis following treatment can be found on page 62 of the document entitled A Guide to the Control of Respiratory Infection Outbreaks in Long-Term Care Homes.

What is the evidence that influenza antiviral medications are effective?

Duration of symptoms

When oseltamivir is used for treatment, it decreases the duration of symptoms by:

- Almost 17 hours in adults (16.8 hours reduction; 95% Confident interval (CI): 8.4 to 25.1) and 29 hours in children (95% CI: 12 to 47 hour reduction) based on a meta-analysis of randomized trials by Jefferson et al. And
- Almost 18 hours (17.8 hours reduction; 95% CI: to 9.3 to 27.1) in a meta-analysis by Dobson et al. using patient-level data from randomized trials where oseltamivir was given to adults within 36 hours of illness onset; in the subset of patients with laboratory-confirmed influenza, the duration of symptoms was decreased by over 25 hours (25.2 hours reduction; 95% CI: 16.0 to 36.2).
Complications of infection

The meta-analysis by Jefferson et al. did not find an effect of oseltamivir on influenza-related complications\(^3\), which may be due to the enrollment of mostly healthy individuals who often do not develop complications.\(^5\) The meta-analysis by Dobson et al. noted a 44\% reduction (risk ratio (RR) = 0.56; 95\% CI: 0.42 to 0.75) in the risk of lower respiratory tract complications requiring antibiotics and a 63\% reduction (RR = 0.37; 95\% CI: 0.17 to 0.81) in hospital admission for any cause for those infected individuals receiving oseltamivir compared to those who did not.\(^4\) Observational studies have also shown the benefits of neuraminidase inhibitors. A meta-analysis of individual-level data of hospitalized patients with laboratory-confirmed or clinical pandemic influenza (A/H1N1pdm09) in 2009-2010 showed a 19\% decrease in the risk of death (odds ratio (OR)= 0.81; 95\% CI: 0.70 to 0.93) when patients were given neuraminidase inhibitors compared to those who were not treated. More benefit was seen in persons 16 years of age and over (25\% reduction; OR=0.75; 95\% CI: 0.64 to 0.87) than in children (18\% reduction; OR=0.82; 95\% CI: 0.58 to 1.17). Early treatment (within 2 days of symptom onset) showed even more benefit.\(^6\)

Prophylaxis

Influenza antivirals medications are very effective when used for prophylaxis.

- The review by Jefferson et al. found that oseltamivir prophylaxis reduced symptomatic influenza by 55\% compared to placebo (RR= 0.45, 95\% CI: 0.30 to 0.67).\(^3\)
- A meta-analysis by Okoli et al. that assessed individual level protection of pre- and post-exposure oseltamivir found it to be 89\% effective (OR=0.11; 95\% CI: 0.06 to 0.20) at preventing laboratory-confirmed influenza.\(^7\)
- The Advisory Committee on Immunization Practices (ACIP) in the United States state that antiviral medications are approximately 68 to 89\% effective in preventing influenza.\(^8\)

Which organizations recommend influenza antiviral medications?

Antiviral medications are recommended by a number of organizations including the:

a. **Association of Medical Microbiology and Infectious Disease Canada (AMMI Canada)**

   The Use of Antiviral Drugs for Influenza: A Foundation Document for Practitioners (2013): provides treatment, prophylaxis and outbreak management recommendation with regard to influenza antiviral medications.

b. **Ontario Ministry of Health and Long-Term Care**

   A Guide to the Control of Respiratory Infection Outbreaks in Long-Term Care Homes (2016): provides guidance regarding the treatment and prophylaxis of residents of long term care facilities.
during influenza outbreaks, and also regarding prophylaxis of staff members of these facilities during influenza outbreaks.

c. **Centers for Disease Control and Prevention (CDC)**

The CDC website provides a comprehensive overview of the use of influenza antiviral medication:

- [Influenza Antiviral Medications: Summary for Clinicians](#)
- [Antiviral Drugs: Information for Health Care Providers](#)
- [Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP)](#)

d. **Infectious Diseases Society of America (IDSA)**


e. **European Centre for Disease Prevention and Control (ECDC)**

*Expert opinion on neuraminidase inhibitors for the prevention and treatment of influenza – review of recent systematic reviews and meta-analyses*: This document found that available evidence supports the use of neuraminidase inhibitors for the treatment and prevention of influenza. It concluded that neuraminidase inhibitors are a reasonable public health measure during seasonal influenza outbreaks, pandemic and zoonotic outbreaks for susceptible strains of influenza.

For additional information, please contact your local public health unit or Public Health Ontario (email: cd@oahpp.ca).
References


Citation

©Queen’s Printer for Ontario, 2017

Disclaimer
This document was developed by Public Health Ontario (PHO). PHO provides scientific and technical advice to Ontario’s government, public health organizations and health care providers. PHO’s work is guided by the current best available evidence at the time of publication.

The application and use of this document is the responsibility of the user. PHO assumes no liability resulting from any such application or use.

This document may be reproduced without permission for non-commercial purposes only and provided that appropriate credit is given to PHO. No changes and/or modifications may be made to this document without express written permission from PHO.

For Further Information
Communicable Diseases, Emergency Preparedness and Response
cd@oahpp.ca

Public Health Ontario
Public Health Ontario is a Crown corporation dedicated to protecting and promoting the health of all Ontarians and reducing inequities in health. Public Health Ontario links public health practitioners, front-line health workers and researchers to the best scientific intelligence and knowledge from around the world.

For more information about PHO, visit publichealthontario.ca.
Appendix A

List of conditions that increase the risk for influenza complications:

- chronic pulmonary disease, including asthma
- cardiovascular disease (excluding hypertension)
- malignancy
- chronic renal insufficiency
- diabetes mellitus and other metabolic disease
- anemia and hemoglobinopathies, such as sickle cell disease
- immunosuppression due to disease or medication
- neurologic and neurodevelopmental disorders
- children younger than 5 years of age
- individuals 65 years of age or older
- people of any age who live in nursing homes or other chronic care facilities
- pregnant women and up to 4 weeks post-partum
- individuals < 18 years of age who are on chronic aspirin therapy, due to the risk of Reye’s syndrome related to influenza
- morbid obesity (BMI ≥ 40) or a BMI > 3 z-scores above the mean for age and gender
- Indigenous peoples

Sources for list of conditions that increase the risk of influenza complications:

- AMMI Canada Guidelines: Table 3
- Canadian Immunization Guide chapter on influenza and statement on seasonal influenza vaccine for 2017-2018: Table 1

Public Health Ontario acknowledges the financial support of the Ontario Government.