The use of antiviral drugs for influenza: A foundation document for practitioners

Fred Y Aoki MD1, Upton D Allen MBBS2, H Grant Stiver MD3, Michel Laverdière MD4, Gerald A Evans MD5

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1Professor of Medicine, Medical Microbiology and Pharmacology & Therapeutics, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba; 2Professor, Department of Pediatrics & Institute of Health Policy, Management and Evaluation, Senior Associate Scientist, Research Institute, Chief, Division of Infectious Diseases, Department of Pediatrics, Hospital for Sick Children, University of Toronto, Toronto, Ontario; 3Professor Emeritus of Medicine, Division of Infectious Diseases, Department of Medicine, University of British Columbia, Vancouver, British Columbia; 4Department of Microbiology-Infectious Diseases, Hôpital Maisonneuve-Rosemont, Montreal, Quebec; 5Professor of Medicine, Biomedical & Molecular Sciences and Pathology & Molecular Medicine, Chair, Division of Infectious Diseases, Department of Medicine, Kingston General Hospital, Queen’s University, Kingston, Ontario
Correspondence: Dr Gerald A Evans, Division of Infectious Diseases, Department of Medicine, Room 3013, Etherington Hall, 94 Stuart Street, Queen’s University, Kingston, Ontario K7L 3N6. Telephone 613-533-6619, fax 613-533-6825, e-mail evansg@queensu.ca
I. PURPOSE
The purpose of this document is to provide information for clinicians on the use of antiviral drugs for the prevention and treatment of seasonal influenza. It is provided as a foundation document which, with brief supplements published as needed to describe new developments, is intended to replace the annual Guidance publications.1,2

The efficacy and safety of antiviral drugs has been demonstrated in controlled trials but the clinical importance of prescribing them for the treatment of seasonal influenza in largely healthy ambulatory adults and children has been the subject of some ongoing controversy.3 However, in high-risk patients with seasonal or pandemic influenza, both oral oseltamivir and inhaled zanamivir may reduce hospitalization and oseltamivir may reduce mortality.4 As of August 2013, three antiviral drugs are licensed in Canada for treatment and prophylaxis of influenza: amantadine (oral) and two neuraminidase inhibitors (NAI), oseltamivir (oral) and zanamivir (dry powder for inhalation). Other antiviral drugs are available internationally (licensed or investigational), including intravenous formulations of oseltamivir, zanamivir and peramivir. These drugs have been available in Canada in specific situations for clinical use but are currently not licensed. Another NAI, laninamivir, a long-acting orally inhaled powder, has been approved in Japan as a single dose treatment, for the therapy of influenza A and B infection.

Drug or virus-specific recommendations will be published, if needed, to complement this document. Other aspects of influenza management, such as laboratory diagnosis, infection control, immunization and non-pharmacological interventions, are beyond the scope of this article.

The susceptibility of recently circulating seasonal influenza viruses to amantadine (AH1N1, AH3N2, influenza B) shows high rates of resistance, therefore subsequent discussion is limited to the neuraminidase inhibitor drugs.

II. PROCESS STATEMENT
The development of this guideline paper arose in early 2013 from two sources: a previous guidance authored in 2012 by AMMI Canada members (FA, UA, GS, GE) and following a suggestion from the Public Health Agency of Canada’s Antiviral Scientific Advisory Group that a generic Canadian guideline be developed for the use of antivirals for seasonal influenza. The concept was then approved by the Guidelines Committee of AMMI Canada. A first draft was co-written by all the authors (FA, UA, GS, GE). Subsequently, all the authors reviewed, revised and approved the document before submission to PHAC for further review and feedback. The AMMI Canada Guidelines Committee approved the final document prior to submission to the Journal for publication.

III. GRADING OF RECOMMENDATIONS
A grading system is used to qualify recommendations based on the quality of evidence and the determination of benefit versus harm arising from the recommendation as defined below.5 In situations where high-quality evidence is not available but anticipated benefits strongly outweigh the harm, the recommendation could be based on lesser evidence. See Table 1 for categories of evidence and their relationship to recommendations. As more data on efficacy are published, the grades of recommendation may change.

![Image](https://via.placeholder.com/150)

**Definitions of the strength of evidence for the recommendations**

**Strong Recommendation**: Benefits of treatment approach clearly exceed harms; quality of evidence is high (Grade A) or moderate (Grade B) or exceptional (Grade X).

**Recommendation**: Benefits exceed harms, but quality of evidence is moderate (Grade B), or low (Grade C) or exceptional (Grade X).

**Option**: Quality of evidence is very low (Grade D) or well-done studies (Grade A, B or C) show little clear advantage.

**No Recommendation**: There is a lack of pertinent evidence or quality is very low and there is an unclear balance between benefits and harms.

### Impact of recommendation strength on practicing clinicians

**Strong recommendations** should be followed unless a clear and compelling reason for an alternate approach is present.

**Recommendations** should generally be followed, but clinicians should remain alert to new information and patient preferences.

**Option** reflects flexibility in decision-making regarding treatment according to the judgment of the clinician. Patient preference should play a substantial influencing role.

**No recommendation** reflects no constraints on decision-making, and clinicians should remain alert to new evidence that clarifies the balance of benefit and harm. Patient preference should play a substantial influencing role.

IV. THE DISEASE

A. Influenza viruses

The influenza strains that will predominate in Canada in any given season are unpredictable. Their identification and knowledge of their antiviral drug susceptibility profiles are fundamental to the rational prescribing of antiviral drugs for the prevention and treatment of influenza because antiviral drug resistance patterns of influenza viruses demonstrated in vitro generally correlate with treatment outcomes. Relevant information is usually compiled from different sources each year. Practitioners can find current information about circulating influenza strains from FluWatch,7 influenza vaccine composition from NACI7 and antiviral resistance from CDC.5

B. Clinical aspects

Seasonal influenza viruses share similar clinical features.

| Virus is transmitted from infected to susceptible persons through respiratory secretions containing suspensions of virus, especially airborne droplets generated by coughing and sneezing. The relative contributions of small particle aerosols and fomites in transmission are uncertain. The basic reproductive number [Ro] (mean number of secondary cases transmitted by a single index case to susceptible contacts) ranges from 1.3 to 1.7. The incubation period of seasonal influenza A illness is one to four days with a mean of two days.9 |
| In otherwise healthy patients with uncomplicated illness, virus in nasopharyngeal secretions is shed beginning 24 h (1 day) before onset of symptoms, peaks in the first two to three days of illness and declines over five to seven days, although it is commonly accepted that some persons, particularly young children and immunocompromised persons, may become infected and shed virus for longer periods of time. |

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**TABLE 1**

<table>
<thead>
<tr>
<th>Quality of Evidence</th>
<th>Preponderance of Benefit or Harm</th>
<th>Balance of Benefit and Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Well-designed, randomized, controlled studies or diagnostic studies on relevant populations</td>
<td>Strong Recommendation</td>
<td>Option</td>
</tr>
<tr>
<td>B. RCTs or diagnostic studies with minor limitations; overwhelmingly consistent evidence from observational studies</td>
<td>Recommendation</td>
<td>Option</td>
</tr>
<tr>
<td>C. Observational studies (case control or cohort design)</td>
<td>Option</td>
<td>No Recommendation</td>
</tr>
<tr>
<td>D. Expert opinion, case reports, reasoning from first principles</td>
<td>Strong Recommendation</td>
<td></td>
</tr>
<tr>
<td>X. Exceptional situations where validating studies cannot be done and there is a clear preponderance of benefit or harm</td>
<td>Option</td>
<td>No Recommendation</td>
</tr>
</tbody>
</table>

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TABLE 2
Clinical signs warranting urgent medical attention in infants, children and youth with suspected or proved influenza

| Infants and toddlers (<1 year and 1–3 years, respectively) | Rapid breathing and difficulty breathing |
| Bluish skin colour or change in skin colour |
| Not drinking enough fluids |
| Not waking up or not interacting |
| Being so irritable that child does not want to be held |
| Flu-like symptoms improve but then return with fever and a worse cough |
| Fever with a rash |
| Seizures |

| Children and youth (>3 to <12 years and 12–18 years, respectively) | Rapid breathing, difficulty breathing or shortness of breath |
| Bluish skin colour, bloody or coloured sputum |
| Flu-like symptoms improve but then return with fever and a worse cough |
| Confusion, listlessness, altered consciousness |
| Severe or persistent vomiting |
| Fever with a rash |
| Severe chest pain or abdominal pain |
| Seizures |

The use of antiviral drugs for influenza

A. Antiviral drugs

For both oseltamivir and zanamivir, this document describes some uses that are outside of the authorizations provided by Health Canada, as outlined in the Canadian Product Monographs, as of August 2013.

1. Oseltamivir – The NAI drug oseltamivir (Tamiflu®) is authorized by Health Canada for the treatment of uncomplicated influenza A and B in patients one year of age or older who have been symptomatic for no more than two days. Oseltamivir is also authorized in Canada for prevention of influenza A and B in adults and children one year of age and older who are close contacts of an individual with characteristic symptoms of influenza. In the United States, oseltamivir is also approved for the treatment of influenza in infants two weeks of age or older.

Oseltamivir is formulated as oseltamivir phosphate in capsules containing 30 mg, 45 mg or 75 mg per capsule or as a suspension containing 6 mg/mL or 12 mg/mL. Intravenous oseltamivir may be obtained either through clinical trials (if available) or in specific circumstances through the Special Access Program of Health Canada (http://www.hc-sc.gc.ca/dhp-mps/access/drugs-drogues/index-eng.php).

Oseltamivir phosphate is well absorbed and extensively converted by hepatic and intestinal epithelial cells to oseltamivir carboxylate, which is the active antiviral molecule. It is eliminated almost completely as unchanged drug in the urine by glomerular filtration and renal tubular secretion.

In part due to lack of further metabolic transformation, oseltamivir carboxylate has little potential for drug-drug interactions and this expectation has been borne out by limited clinical studies. Influenza B viruses are approximately 10- to 20-fold less susceptible to oseltamivir carboxylate than are influenza A viruses and this in...


viro difference may explain differences in clinical efficacy of oseltamivir for treatment of influenza A and B virus infections in children and adults. Treatment and prophylaxis regimens of oseltamivir and zanamivir for adults and for children by age and weight are detailed in Table 4. Doses do not need to be adjusted in obese adults. Dose reduction is advised for pharmacokinetic reasons in persons with creatinine clearance <10 mL/min although the drug has a wide margin of safety and causes no serious, dose-related adverse effects. Dose reduction is advised for patients with impaired renal function, as detailed in Table 5. In adults, oral oseltamivir is generally welltolerated. Mild, rapidly reversible nausea and/or vomiting have been observed in approximately 5% to 10% more persons taking oseltamivir versus placebo. Nausea and/or vomiting are more common in young adults taking 150 mg twice daily (12% to 15%) than 75 mg twice daily (8% to 11%) compared to placebo (3% to 7%). Other side effects occurred significantly more frequently in oseltamivir than placebo recipients. Influenza A and B viruses rarely cause central nervous system symptoms including convulsions and coma. A causal relationship between oseltamivir and such adverse effects or a wider spectrum including delirium with hallucinations has been suspected but not definitively established. Close monitoring of treated patients is advised. For adults with seasonal influenza of less than 36 h duration, there appears to be no advantage of combining oseltamivir and zanamivir. Administering higher doses of oseltamivir to critically ill patients with influenza is not warranted. Preliminary analysis from a randomized comparison of 150 mg BID and 75 mg BID oseltamivir for treatment of patients seriously ill with influenza, including A(H1N1)pdm09 viruses, suggested that the higher dose was safe but offered no benefit over the standard dose regimen, as evaluated by reductions in viral shedding at day 5 of treatment. Osel tamivir was used to treat critically ill patients during the 2009 H1N1 pandemic. Such use included treatment with higher doses administered for longer periods than the approved five-day regimen of 75 mg BID. In critically ill ventilated patients with A(H1N1)pdm09, oseltamivir administered via a gastric tube was well absorbed, yielding plasma concentrations that exceed the inhibitory concentration of influenza A virus. In children, data on the safety and efficacy of oseltamivir exist for those one year of age and older. Pharmacokinetic data show that 2 mg/kg twice daily resulted in drug exposures within the range associated with tolerability and efficacy in adults who were administered approximately 1 mg/kg twice daily. A liquid formulation was shown in a randomized placebo controlled trial to be safe and well accepted by healthy children one to 12 years of age and children with asthma six to 12 years of age. Emesis occurred in 14.3% of children receiving oseltamivir 2 mg/kg/dose BID for 10 doses (maximum 100 mg/dose) and 8.5% receiving placebo. Discontinuation rates due to adverse events were not different, being 1.8% and 1.1%, respectively. The safety and efficacy of oseltamivir in infants younger than one year of age have not been established. This is clearly an area where additional research is needed. A caution was issued due to deaths observed in seven-day old mice receiving extremely high doses of the drug. These animals were fed a dose that was about 250 times the dose recommended for children. The concentrations of the pro-drug in the brain were 1500 times those of the adult animals exposed to the same dose. Thus, it was felt that an immature blood-brain barrier may have caused the toxicity in these animals. Based on the ages of the animals and the stage of the development of their blood-brain barrier, the human equivalent was felt to be infants younger than one year of age. However, recent reports from Japan did not show CNS toxicity in infants younger than one year of age who were treated with oseltamivir. In November 2005, there were reports of neuropsychiatric events and deaths in Japanese children receiving oseltamivir. The United States FDA reviewed the available information and concluded that the increased reports of neuropsychiatric events in Japanese children are most likely related to an increased awareness of influenza-associated encephalopathy, increased access to oseltamivir in that population, and a coincident period of intensive monitoring of adverse events. They were not able to establish a causal relationship between oseltamivir and the reports of pediatric deaths. Of note, deaths occurred in children two years of age and older but the ages of those with neuropsychiatric manifestations were not reported.

Drug Interactions: Interactions during co-administration of oseltamivir with other drugs are unlikely as it is eliminated largely unchanged into urine by glomerular filtration and renal tubular secretion by an anionic transporter and does not cause dose-related adverse effects even at high doses.

1. Zanamivir – Zanamivir (Relenza®) is authorized by Health Canada for the treatment of uncomplicated influenza A and B in patients seven years of age or older who have been symptomatic for no more than two days. It is also authorized for the prevention of influenza A and B in patients seven years of age or older.

In vitro, influenza A and B viruses exhibit similar susceptibility to zanamivir. In observational studies of children and young adults with influenza A or B virus infection treated with either oseltamivir or zanamivir, there was no difference in duration of fever between treatments in young children four to 16 years of age. However, in older children and adults (mean ± SD age 15±12 years) with influenza B virus infection, the duration of fever was significantly less in individuals treated with zanamivir versus oseltamivir. In a small, observational study in persons of unspecified age directly comparing the efficacy of zanamivir in ill persons with influenza A or influenza B virus infection, no differences in duration of fever were observed.

No data are available on the comparative effects of oseltamivir and zanamivir on influenza B virus infection in older adults and those in high-risk groups.

Zanamivir is marketed as a powder in a proprietary inhalational device that delivers 5 mg of zanamivir per inhalation. Approximately 80% of an inhaled dose is deposited onto the upper respiratory tract lining and 13% in the bronchi and lungs, where it exerts its antiviral effect. Ten per cent to 20% of inhaled drug is absorbed and eliminated unchanged into the urine.

No dose reductions are recommended for any patient population. There have been case reports of mechanically ventilated patients with A(H1N1)pdm09 influenza who had been treated with zanamivir diskhaler powder in water administered by nebulizer, resulting in bronchospasm and obstruction of ventilator filters.

Intravenous formulations of zanamivir are under clinical investigation but are not authorized for use in Canada. Intravenous zanamivir may be obtained either through clinical trials (if available) or in specific circumstances through the Special Access Program of Health Canada (http://www.hc-sc.gc.ca/dfhp-mps/acces/drugs-droges/index-eng.php).

Zanamivir is safe and well tolerated as evidenced by studies revealing no adverse effects after intravenous injection of 1200 mg/day to adult volunteers for five days. Although practitioners are advised to beware of bronchospasm in zanamivir-treated patients, in one study of zanamivir inhaled once daily as prophylaxis of family members of index cases there was no increase in asthma exacerbations in asthmatic contacts receiving zanamivir (6%) versus placebo (11%). Another double-blind placebo-controlled trial of zanamivir treatment of influenza in patients 12 to 88 years of age (median 38 years of age) with asthma or chronic obstructive pulmonary disease did not find an increased incidence of bronchospasm in the zanamivir group. In fact the morning and evening peak expiratory flow rates were significantly increased in the zanamivir group. Despite these data there have been reports of acute bronchospasm in patients taking zanamivir, so that the Advisory Committee on Immunization Practices of the US Centers for Diseases Control and Prevention advised caution in using zanamivir for asthmatic and COPD patients and advised that the patient should have a short acting bronchodilator available during treatment. Drug Interactions: Interactions between zanamivir and other drugs co-administered systemically are neither likely nor expected due to the minimal absorption of zanamivir after oral inhalation.
3. Combination therapy – The clinical utility of combination therapy for treating influenza remains uncertain. A retrospective cohort study compared a triple combination of drugs (oseltamivir, amantadine & ribavirin) with oral oseltamivir in adults with serious influenza illness requiring ventilator support.57 Both regimens were similarly effective in reducing mortality. A modeling study using three antiviral drugs with different mechanisms of action suggested that this therapeutic strategy could delay the emergence of resistance better than treatment with a single influenza inhibitor.48

B. Benefits of antiviral treatment
NAI therapy of patients ill with infection due to seasonal influenza viruses has been demonstrated in controlled trials to reduce the duration and severity of uncomplicated, self-limited laboratory-confirmed influenza, largely due to influenza A viruses, in otherwise healthy children older than one year of age and adults.49 A meta-analysis concluded that these drugs seemed to reduce total influenza-related complications but could not distinguish between mild and serious complications.50 NAIs have been shown to reduce the frequency of otitis media as a complication of influenza in pediatric patients.51 NAI treatment of hospitalized patients with seasonal influenza may reduce the duration of hospitalization and mortality.51

In a number of observational studies of patients with A(H1N1)pdm09 infection, it was reported that treatment with NAIs, chiefly oseltamivir, reduced the progression and severity of illness in the general population as well as in vulnerable groups. These groups include pregnant women and solid organ transplant recipients.52

As noted above, in vitro and available clinical data from observational studies,21-23 but not randomized, controlled trials, suggest that inhaled zanamivir may be more efficacious than oral oseltamivir for the treatment of influenza B virus infection in older, but not younger children.

Investigational intravenous zanamivir 600 mg BID has been reported to be efficacious for preventing experimental human influenza A virus infection53 and treating oseltamivir-resistant A(H1N1)pdm09 pneumonia,54,55 as well as critically ill patients with A(H1N1)pdm09 influenza.56 Based on these data, intravenous zanamivir is recommended for antiviral therapy of patients severely ill with suspected or confirmed oseltamivir-resistant influenza who are unable to use the inhalational device.

Inasmuch that a number of respiratory tract viral pathogens can cause an influenza-like illness, anti-influenza drug therapy will invariably result in treatment of some persons whose influenza-like illness is not due to influenza virus. At present, there are no data to suggest that such treatment is ecologically harmful. Since NAIs are specific inhibitors of only influenza virus neuraminidase, such treatments are unlikely to engender resistance in other microorganisms. Moreover, influenza viruses are not constituents of the normal flora of humans.

C. Considerations in selecting treatments
The indications for treatment may be structured around the following considerations:
1. Severity of illness;
2. Presence of risk factors or co-morbid conditions;
3. Interval between onset of illness and diagnosis;
4. Likely influenza type(s) causing infection (see Section III).

1. Severity of illness:
Useful definitions of the range of clinical illness caused by influenza viruses have been adapted from those published by the CDC57:
• Mild or uncomplicated illness is characterized by typical symptoms like fever (although not everyone with influenza, especially at the extremes of age, will have a fever), cough, sore throat, rhinorrhea, muscle pain, headache, chills, malaise, sometimes diarrhea and vomiting, but no shortness of breath and little change in chronic health conditions.

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>At-risk groups and co-morbid medical conditions that predispose to severe influenza (adapted from references 12 and 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Asthma and other chronic pulmonary disease, including bronchopulmonary dysplasia, cystic fibrosis, chronic bronchitis and emphysema</td>
<td></td>
</tr>
<tr>
<td>- Cardiovascular disease (excluding isolated hypertension; including congenital and acquired heart disease such as congestive heart failure and symptomatic coronary artery disease)</td>
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<tr>
<td>- Malignancy</td>
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<td>- Chronic renal insufficiency</td>
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<tr>
<td>- Diabetes mellitus and other metabolic diseases</td>
<td></td>
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<tr>
<td>- Hemoglobinopathies such as sickle cell disease</td>
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<tr>
<td>- Immunosuppression or immunodeficiency due to disease (e.g. HIV infection, especially if CD4 is &lt;200×10^6/L), or iatrogenic, due to medication</td>
<td></td>
</tr>
<tr>
<td>- Neurologic disease and neurodevelopmental disorders that compromise handling of respiratory secretions (cognitive dysfunction, spinal cord injury, seizure disorders, neuromuscular disorders, cerebral palsy, metabolic disorders)</td>
<td></td>
</tr>
<tr>
<td>- Children younger than 5 years of age*</td>
<td></td>
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<tr>
<td>- Individuals 65 years of age or older</td>
<td></td>
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<tr>
<td>- People of any age who are residents of nursing homes or other chronic care facilities</td>
<td></td>
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<tr>
<td>- Pregnant women and women up to 4 weeks post partum regardless of how the pregnancy ended</td>
<td></td>
</tr>
<tr>
<td>- Individuals &lt;18 years of age who are on chronic aspirin therapy</td>
<td></td>
</tr>
<tr>
<td>- Obesity with a BMI ≥40 or a BMI &gt;3 z-scores above the mean for age and gender</td>
<td></td>
</tr>
<tr>
<td>- Aboriginal peoples</td>
<td></td>
</tr>
</tbody>
</table>

* Children who are two through four years of age also have a higher rate of complications compared to older children; however, the risk for these children is lower than the risk for children younger than two years of age

- Moderate or progressive illness is characterized by typical symptoms plus signs or symptoms suggesting more than mild illness: chest pain, poor oxygenation (e.g. tachypnea, hypoxia, labored breathing), cardiopulmonary insufficiency (e.g. low blood pressure), CNS impairment (e.g. confusion, altered mental status), severe dehydration, or exacerbations of chronic conditions (e.g. asthma, chronic obstructive pulmonary disease, chronic renal failure, diabetes or cardiovascular disease).

- Severe or complicated illness is characterized by signs of lower respiratory tract disease (e.g., hypoxia requiring supplemental oxygen, abnormal chest radiograph, mechanical ventilation), CNS abnormalities (encephalitis, encephalopathy), complications of low blood pressure (shock, organ failure), myocarditis or rhabdomyolysis, or invasive secondary bacterial infection based on laboratory testing or clinical signs (e.g. persistent high fever and other symptoms beyond three days).

2. Presence of risk factors or co-morbid medical conditions:
- Patients with risk factors such as age, ethnicity or co-morbid medical conditions have been identified as being at greater risk for complications of influenza based on extensive experience during seasonal influenza outbreaks and the recent experience during the A(H1N1)pdm09 pandemic (see Table 3).

Notwithstanding the above association of the aforementioned medical conditions as risk factors for severe influenza, 20% to 40% of patients with severe A(H1N1)pdm09 influenza admitted to intensive care units were previously healthy persons not belonging to any known high-risk group. The corollary is that practitioners must be vigilant in their evaluation of otherwise healthy individuals in whom seasonal influenza illness appears to be mild but may be progressing.
Table 1: Oseltamivir and zanamivir treatment of influenza (treatment regimens adapted from reference 24).

<table>
<thead>
<tr>
<th>Medication</th>
<th>Treatment (5 days)</th>
<th>Chemoprophylaxis (10 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>Body Weight (lbs)</td>
<td></td>
</tr>
<tr>
<td>≤15 kg</td>
<td>≤33 lbs</td>
<td>75 mg twice daily</td>
</tr>
<tr>
<td>&gt;15 kg to 23 kg</td>
<td>&gt;33 lbs to 51 lbs</td>
<td>30 mg twice daily</td>
</tr>
<tr>
<td>&gt;23 kg to 40 kg</td>
<td>&gt;51 lbs to 88 lbs</td>
<td>45 mg twice daily</td>
</tr>
<tr>
<td>&gt;40 kg</td>
<td>&gt;88 lbs</td>
<td>60 mg twice daily</td>
</tr>
<tr>
<td>Children ≥12 months</td>
<td></td>
<td>75 mg twice daily</td>
</tr>
</tbody>
</table>

Children 3 months to <12 months

<table>
<thead>
<tr>
<th>Adults</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Weight (kg)</td>
<td>Body Weight (lbs)</td>
<td></td>
</tr>
<tr>
<td>10 mg (two 5 mg inhalations) twice daily</td>
<td>10 mg (two 5 mg inhalations) twice daily</td>
<td></td>
</tr>
<tr>
<td>10 mg (two 5 mg inhalations) once daily</td>
<td>10 mg (two 5 mg inhalations) once daily</td>
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</tr>
</tbody>
</table>

1. Oseltamivir is administered orally without regard to meals, although administration with meals may improve gastrointestinal tolerability. Oseltamivir is available in 30 mg, 45 mg, and 75 mg capsules, and as a powder for oral suspension that is reconstituted to provide a final concentration of either 6 mg/mL or 12 mg/mL. If the commercially manufactured oral suspension is not available, the capsules may be opened and the contents mixed with a sweetened liquid to mask the bitter taste or a suspension can be compounded by retail pharmacies.

2. Weight-based dosing is preferred. However, if weight is not known, dosing by age for treatment of influenza (give two doses per day) or prophylaxis (give one dose per day) in full-term infants younger than one year of age may be necessary: 0 to 3 months = 12 mg per dose for treatment (not for prophylaxis); 3 to 5 months = 20 mg per dose; 6 to 11 months = 25 mg per dose.

3. Current weight-based dosing recommendations are not intended for premature infants. Premature infants may have slower clearance of oseltamivir due to immature renal function, and doses recommended for term infants may lead to very high drug concentrations in this age group. Very limited data from a cohort of premature infants demonstrated that oseltamivir concentrations among premature infants given 1 mg/kg body weight twice daily were similar to those observed with the recommended treatment doses in term infants (3 mg/kg body weight twice daily). Observed drug concentrations were highly variable among premature infants. The IDSA 2011 recommendations for pediatric pneumonia suggest 2 mg/kg/day divided twice daily. Currently available data are insufficient to recommend a specific dose of oseltamivir for premature infants; it is strongly suggested that an infectious disease physician or clinical pharmacist be consulted.

4. Zanamivir is administered by inhalation using a proprietary "Diskhaler" device distributed together with the medication. Zanamivir is a dry powder, not an aerosol, and should not be administered using nebulizers, ventilators, or other devices typically used for administering medications in aerosolized solution. Zanamivir is not recommended for persons with chronic obstructive pulmonary disease that increase the risk of bronchospasm.

3. Interval between onset of illness and initiation of antiviral therapy.

Initiation of treatment of uncomplicated seasonal influenza in healthy adults and children with NAI within 36 h to 48 h of illness onset is efficacious. Optimal benefits are obtained if treatment is initiated as early as possible after the onset of symptoms. Thus, starting treatment within 12 h of illness onset should be a practice goal.

4. Likely influenza type(s) causing infection:

Practitioners should be mindful of reports from the Public Health Agency of Canada's FluWatch (<http://www.phac-aspc.gc.ca/fluwatch/> and reports from their provincial or territorial public health departments. Since 2009-10, the predominant influenza viruses have been sensitive to NAIs; however it remains important to maintain awareness in case oseltamivir-resistant seasonal influenza viruses reappear.

D. Treatment of children

While some aspects of influenza prevention and treatment in adults can be extrapolated to children, there are several areas where special pediatric considerations are necessary. In general, when compared to adults, there are fewer data to guide the management of children, notably young infants.
to 50% of reported influenza-related deaths. Influenza B has been identified in a disproportionate number of pediatric influenza-associated deaths (38%).

Children at the highest risk of adverse outcomes from influenza illness include those younger than five years of age. Hospitalizations occur more frequently among those younger than two years of age compared with older children, with the highest hospitalization rates being among those younger than six months of age. This does not necessarily translate into a recommendation to use antiviral therapy in those younger than two years of age; such children with mild influenza illness and in the absence of risk factors other than age do not usually need treatment.

Among the currently available antiviral agents, three are approved for use for children in Canada: amantadine (which is not currently useful because of resistance) for influenza A; oseltamivir and zanamivir for influenza A and B. Clinical trials supporting the role of the NAIs in children were previously summarized and have been the subject of recent meta-analyses. One meta-analysis suggested that NAIs shorten the duration of illness in children with seasonal influenza and reduce household transmission, but that they have little effect on asthma exacerbations or the use of antibiotics.

Data from the only double-blind, randomized, controlled trial of oseltamivir for the treatment of influenza in previously healthy children, indicated significant reductions in physician-diagnosed complications requiring antibiotic therapy (relative risk-reduction 40%) and in the likelihood of developing otitis media (relative risk reduction 44%). Another randomized trial among children aged one to three years, indicated an 85% reduction in acute otitis media when oseltamivir was started within 12 h after the onset of influenza illness, but no reduction when treatment was started at >24 h after the onset of symptoms. A benefit on asthma exacerbations among oseltamivir-treated children has also been demonstrated in a randomized controlled trial.

Since the earlier studies on NAIs, additional studies have been reported or are in progress and experience with their use has increased. However, there exists a relative paucity of new data from randomized trials in infants and young children. Recent studies have provided valuable safety data as well as data on the use of oseltamivir in premature newborns. In the United States, oseltamivir is approved for the prevention of influenza in patients one year and older and the treatment of acute uncomplicated influenza in patients two weeks of age and older who have been symptomatic for no more than two days. (Tamiflu USA Product Monograph Revised December 2012). Oseltamivir was temporarily approved for use in infants less than one year of age on the basis of a favourable risk-to-benefit ratio during the 2009 H1N1 pandemic. However, antivirals are not currently authorized in Canada for the treatment of seasonal influenza in infants younger than one year of age and their use in infants should be handled on a case-by-case basis, based on severity of illness. Recommendations for oseltamivir dosing for infants less than one year of age varied within a reasonably narrow range and have been updated for seasonal influenza. Current dosing recommendations are shown in Table 4, but clinicians should be aware of possible dose changes as more information becomes available for young infants.

**E. Treatment of immunocompromised patients**

This group includes individuals with a wide range of congenital and acquired immunodeficiencies. The heterogeneity of populations of immunocompromised hosts is well recognized, resulting in varying degrees of risk for adverse outcomes from influenza illness. In this context, Table 6 summarizes selected clinical, laboratory and other markers that help to categorize various immunodeficiency states and identify patients who might be at the greatest risk of adverse outcomes from influenza illness. The presence of these markers suggest increased risk for acquisition of infection, progression to more severe and potentially life-threatening consequences of infection, and for an impaired ability to develop immunity to infection following subsequent exposure to influenza virus.

In addition to the well-recognized variability in the clinical manifestations of influenza illness, atypical clinical features may be present in immunocompromised individuals. For example, immunocompromised individuals may present with fever as the sole manifestation of influenza illness or may present with respiratory symptoms without fever.

The complications seen among persons with normal immune systems may also be seen in immunocompromised hosts. Invasive secondary bacterial infections caused by *S. pneumoniae*, *S. aureus*, *S. pyogenes* and other bacterial pathogens may occur and can be devastating for the immunocompromised host. For example, asplenic individuals are known to be at increased risk of severe invasive pneumococcal disease.

Prolonged illness and viral shedding are features of infection in immunocompromised individuals. Indeed, in some of the more immunocompromised individuals, the virus may be persistently present in the respiratory tract for several weeks or months. This persistent shedding...
TABLE 6
Selected surrogate indices of immunocompromised states

<table>
<thead>
<tr>
<th>Laboratory-based Indices</th>
<th>Clinical States</th>
<th>Treatment-related Indices</th>
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| **Severe neutropenia**  
(ANC <0.5×10^9/L), and/or,  
**Severe lymphopenia**  
(ALC <0.5×10^9/L) | Individuals with malignancies receiving active cytotoxic chemotherapy  
Acute leukemia patients  
HSCT recipients  
SOT recipients (e.g. lung, heart, kidney)  
Individuals with congenital immunodeficiency states  
Individuals with acquired immunodeficiency states (e.g. Human Immunodeficiency Virus infection, plasma cell dyscrasias, B-lymphocyte malignancies)  
Individuals with rheumatic diseases or autoimmune disorders (e.g. RA or SLE)  
Individuals with GI diseases receiving immunosuppressive drugs (e.g. IBD)  
Individuals on renal dialysis  
Individuals with asthma or COPD receiving corticosteroid therapy. | A history of ongoing myelosuppressive and/or immunosuppressive therapies such as:  
Corticosteroid therapy71 (i.e., among adult patients >700 mg cumulative dose of prednisone equivalent on an ongoing basis and at the time of clinical evaluation; among pediatric patients,72 ≥2 mg/kg per day of prednisone or its equivalent, or ≥20 mg/day if they weigh more than 10 kg administered for 14 days or more)  
Cytotoxic therapy*  
Immunomodulator therapies** |

*Examples of cytotoxic therapy include, but are not limited to:  
(e.g., anthracyclines such as doxorubicin or epirubicin; purine analogues such as azathioprine, thioguanine, mercaptopurine, fludarabine, pentostatin, or cladribine; pyrimidine analogues such as flurouracil, cytarabine, capecitabine, or gemcitabine; anti-folate agents such as methotrexate or pemetrexed; alkylating agents such as the nitrogen mustards (cyclophosphamide or ifosfamide), nitrosoureas (carmustine, lomustine, semustine, streptozocin), and platinum analogues (cis-platin, carboplatin, or oxaliplatin); taxanes (e.g., docetaxel, paclitaxel); topoisomerase I inhibitors (e.g., irinotecan).  
**Examples of immunomodulator therapy include, but are not limited to:  
Calcineurin inhibitors (e.g., cyclosporine, tacrolimus, sirolimus), Guanine synthesis inhibitors (e.g., Mycophenolate mofetil), Anti-B lymphocyte therapy (e.g., rituximab), Anti-T lymphocyte therapy (e.g., anti-thymocyte globulin or anti-CD3), Anti-B and T cell therapy (e.g., alemtuzumab, basiliximab, daclizumab), Anti-TNF therapy (e.g., infliximab or etanercept), Alpha-interferon therapy

Adapted from: Allen et al (reference 77). Abbreviations: ANC, absolute neutrophil count; ALC, absolute lymphocyte count; HSCT, haematopoietic stem cell transplant; SOT, solid organ transplant; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; GI, gastrointestinal; IBD, inflammatory bowel disease; COPD, chronic obstructive airways disease; TNF, tissue necrosis factor
VI. RECOMMENDATIONS FOR TREATMENT

A. General Principles:
- Treatment should be initiated as rapidly as possible after onset of illness as the benefits of treatment are much greater with initiation at least less than 12 h after 48 h. (Strong recommendation, Grade B evidence)
- Antiviral therapy should be initiated even if the interval between illness onset and administration of antiviral medication exceeds 48 h if:
  i. The illness is severe enough to require hospitalization (Strong recommendation, Grade X evidence),
  ii. The illness is progressive, severe or complicated, regardless of previous health status (Strong recommendation, Grade X evidence), or
  iii. The individual belongs to a group at high risk for severe disease (Strong recommendation, Grade X evidence).
- Otherwise healthy patients with relatively mild, self-limited influenza are not likely to benefit from NAI therapy initiated more than 48 h after illness onset. Clinical judgment should be used. (Option, Grade D evidence)
- Patients for whom antiviral therapy is not initially recommended should be advised of symptoms and signs of worsening illness that might warrant reassessment. (Recommendation, Grade X evidence)
- Treatment duration should routinely be five days (Strong recommendation, Grade A evidence), but may be continued longer than five days if clinically indicated. (Option, Grade D evidence)
- Intubated patients with influenza illness should receive oseltamivir through a nasogastric tube. (Recommendation, Grade C evidence)
- For patients unable to tolerate or receive oral oseltamivir, inhaled or intravenous zanamivir (see Zanamivir section V 2 for how to access) is a suitable option. (Option, Grade D evidence)
- Zanamivir may be preferred to oseltamivir in the following situations:
  i. Patients not responding to oseltamivir therapy (Option, Grade D evidence)
  ii. Patients with illness despite oseltamivir prophylaxis (Option, Grade D evidence)
  iii. Where influenza B is confirmed or strongly suspected (Option, Grade D evidence)
- For severely ill patients, zanamivir administered intravenously is preferred to inhaled drug. (Recommendation, Grade X evidence)
- In ventilated patients, zanamivir should only be administered intravenously. (Strong recommendation, Grade X evidence)
- In the above circumstances i and ii, virus should be tested for oseltamivir resistance, if possible. (Option, Grade D evidence)

B. Treatment of non-pregnant adults with mild or uncomplicated influenza illness:
A treatment algorithm is provided as Appendix A.
- For individuals with mild disease, no risk factors and:
  o illness with onset within 48 h, treatment with oseltamivir or inhaled zanamivir may be considered. (Strong recommendation, Grade A evidence)
  o illness of more than 48 h duration, antiviral treatment is not generally recommended. (Recommendation, Grade X evidence)
- For individuals with mild disease, risk factors and:
  o illness with onset within 48 h, initiate oseltamivir or inhaled zanamivir therapy immediately. (Strong recommendation, Grade X evidence)
  o illness of more than 48 h duration, treatment with oseltamivir or inhaled zanamivir may be considered. (Recommendation, Grade X evidence)

C. Treatment of non-pregnant adults with moderate, progressive, severe or complicated influenza illness with or without risk factors
A treatment algorithm is provided as Appendix B.
- Consider hospitalization and admission to ICU. (Recommendation, Grade C evidence)
- Oseltamivir 75 mg BID orally or by nasogastric tube should be initiated immediately. (Recommendation, Grade C evidence)
- Oseltamivir should be started even though the window between symptom onset and initial administration of antiviral is longer than 48 h. (Recommendation, Grade C evidence)
- Treatment with zanamivir instead of oseltamivir should be considered for
  i) Those not responding to oseltamivir therapy, (Recommendation, Grade X evidence)
  ii) Those with illness despite oseltamivir prophylaxis, (Recommendation, Grade X evidence)
  iii) Where influenza B is confirmed or strongly suspected (Recommendation, Grade C evidence)
- In the above circumstances i and ii, virus should be tested for oseltamivir resistance, if possible.

D. Treatment of infants, children and youth with mild or uncomplicated influenza illness:
A treatment algorithm is provided as Appendix C.
- For those with mild disease, no risk factors other than age:
  i. Younger than one year of age: NAI s are currently not approved in Canada for the routine treatment of seasonal influenza illness; antiviral use may be considered on a case-by-case basis. Given that infants less than six months of age are not eligible for influenza vaccination, immunization of their household and other close contacts is important in protecting them against influenza, thereby potentially leading to reduced need for antiviral therapy. Influenza immunization of the pregnant woman may also provide protection for her infant during the first six months of life. (Option, Grade D evidence)
  ii. One to less than five years of age: Although children under five years of age are classified as a ‘high risk’ group (with those younger than two years of age having the highest risk), those who are otherwise healthy and have mild disease not requiring hospitalization do not routinely require antiviral therapy. For these children, treatment is optional. (Option, Grade D evidence)
  iii. Five years of age or older: antiviral therapy is not routinely recommended for children and youth who are otherwise healthy and have mild disease not requiring hospitalization. (Option, Grade D evidence)
  For those with mild disease and risk factors other than age:
  i. Younger than one year of age: NAI s are currently not approved in Canada for the routine treatment of seasonal influenza illness. Such use may be considered on a case-by-case basis. (Option, Grade D evidence)
  ii. One year of age and older: illness with onset within 48 h, treatment with oseltamivir or if age appropriate, inhaled zanamivir may be considered on a case-by-case basis. (Option, Grade D evidence)
  iii. One year of age and older: illness of more than 48 h duration, treatment with oseltamivir or if age appropriate, inhaled zanamivir may be considered on a case-by-case basis. (Option, Grade D evidence)

E. Treatment of infants, children, and youth with moderate, progressive, severe, or complicated influenza illness with or without risk factors:
- Consider hospitalization and admission to ICU. (Recommendation, Grade C evidence)
- Start treatment immediately with oseltamivir or zanamivir (if age appropriate) in appropriate doses (see Table 4). (Strong recommendation, Grade B evidence)
- Oseltamivir or zanamivir should be started even though the interval between symptom onset and initial administration of antiviral is longer than 48 h. (Recommendation, Grade C evidence)
1. Immunocompromised individuals who have uncomplicated infection should be treated with zanamivir, if possible without regard to the duration of illness. (Recommendation, Grade X evidence)

2. Immunocompromised patients should be treated with zanamivir, if they have recently received or are currently receiving oseltamivir as prophylaxis or therapy. (Recommendation, Grade C evidence)

3. Prolonged antiviral therapy should be avoided in immunocompromised individuals if possible due to the potential for antiviral resistance. (Option, Grade D evidence)

4. Early initiation of therapy for symptomatic infection in immunocompromised patients is preferred over post-exposure prophylaxis. In the setting of a defined, significant exposure (e.g. household contact or healthcare associated exposure such as shared hospital accommodation) of an immunocompromised patient to a suspected or lab-confirmed case of influenza, post-exposure prophylaxis may be considered. (Option, Grade D evidence)

5. In exposed, susceptible, profoundly immunosuppressed individuals at very high risk of complications, presumptive treatment (as defined below in VII.ii) may be initiated prior to the onset of symptomatic illness. (Option, Grade D evidence)

6. For early presumptive treatment, oseltamivir is preferred. (Option, Grade D evidence)

G. Treatment of patients with renal impairment

See the relevant sections above and Table 5 for treatment recommendations of adults and children with renal impairment as a risk factor.

H. Treatment of pregnant patients

Oseltamivir in standard doses is recommended for treatment of pregnant women with influenza based on the extensive safe use of oseltamivir to treat pregnant women during the 2009 H1N1 pandemic. (Strong recommendation, Grade C evidence). See also V. G Treatment of pregnant patients.

VII. RECOMMENDATIONS FOR CHEMOPROPHYLAXIS VERSUS EARLY THERAPY

An algorithm for prophylaxis is provided as Appendix D.

Antiviral prophylaxis with NAIs has been demonstrated to be efficacious and well tolerated. Three chemoprophylactic strategies were first detailed in our previous publications: (i) seasonal prophylaxis, (ii) post-exposure prophylaxis (PEP) or contact exposure and (iii) outbreak control. Antiviral chemoprophylaxis is recommended only in very selected circumstances:

i. Seasonal prophylaxis involves continuous (usually daily) administration of antiviral medication for all or part of an influenza season to prevent influenza illness. This may include circumstances in which effective vaccine is not available or vaccine is contraindicated. Although efficacious in the setting of clinical trials, the practicality and effectiveness of such seasonal prophylaxis in the field have not been established. Two weeks of prophylaxis initiated at the time of administration of injected, inactivated influenza vaccine during the influenza season may be considered to prevent influenza until vaccine-induced immunity develops, a strategy referred to as bridging prophylaxis.

ii. PEP is an efficacious strategy when initiated in the first 48 hours after exposure to a contact with suspected or lab-confirmed influenza. Contacts are considered infectious for the interval between 24 hours before illness onset until the time fever ends. However, it is recommended that the strategy of early treatment be used in place of PEP because of reports of oseltamivir resistance arising during PEP. Early presumptive therapy may be appropriate for situations where influenza infection appears prevalent and persons at very high risk of influenza complications are exposed. Early presumptive treatment requires initiation of therapy with oseltamivir or zanamivir twice daily (versus once daily as recommended for PEP) initiated after exposure to an infectious contact even before symptoms begin.

iii. Outbreak control. Chemoprophylaxis combined with antiviral treatment of ill persons plus other measures is recommended for controlling outbreaks of influenza in closed facilities. Closed facilities have a fixed residential population with limited turnover or units that can be closed. Closed facilities include nursing homes and other long-term care facilities that house patients at high risk of influenza complications as well as correctional institutions that pose special other risks and considerations with respect to influenza outbreaks due to their unique environment; these factors mandate consideration of the same measures for outbreak management in both. Chief among these additional measures is the concurrent administration of inactivated influenza vaccine parenterally. Zanamivir does not interfere with the hemagglutination antibody response to injected vaccine. A similar lack of interference with oseltamivir would be expected. Nasal attenuated live influenza vaccine (Flumist) should not be used in these situations, as oseltamivir and zanamivir would be expected to interfere with its immunogenicity.

Recommendations for Antiviral Prophylaxis

- Early therapy is preferred over routine seasonal pre-exposure prophylaxis (Recommendation, Grade X evidence).
- An early treatment strategy should involve counseling together with arrangements for contacts to have medication on hand. (Option, Grade D evidence)
- The selective use of pre-exposure prophylaxis can be suggested for the following scenarios (Option, Grade D evidence) during community outbreaks of influenza illness:
  i. As a bridge to vaccine-induced immunity during the 14-day period after immunization of high-risk individuals.
  ii. Protection of high-risk persons for whom vaccination is contraindicated or deemed likely to be ineffective.
  iii. Protection of patients at high risk and their family members and close contacts when circulating strains of influenza virus in the community are not matched with trivalent seasonal influenza vaccine strains, based on current data from the local or national public health laboratories.
  iv. Protection of family members or health care workers for whom influenza immunization is contraindicated (e.g., known anaphylaxis to chicken or egg protein) and who are likely to have ongoing close exposure to unimmunized persons at high risk.

...
including infants and toddlers who are younger than 24 months of age. [http://www.cps.ca/english/statements/ID/ID11-06.htm]

- Early therapy is preferred over post-exposure prophylaxis due to concerns regarding drug resistance. (Option, Grade D evidence)
- Post-exposure prophylaxis may be considered in family settings for persons who cannot be reliably protected by immunization (e.g., age less than six months, immunocompromised or vaccine contraindicated). (Option, Grade D evidence)
- To control outbreaks in closed facilities, antiviral drug prophylaxis, combined with treatment and inactivated vaccine administration, is indicated. (Strong Recommendation, Grade X evidence)
- Neither early treatment nor PEP should be prescribed:
  - For groups of healthy individuals based on possible exposure in the community
  - If the close contact did not occur during the infectious period of the person with suspected or confirmed influenza which extends from 1 day before the onset of symptoms until 24 h after fever ends
  - If >4 days have elapsed since the last infectious contact (Option, Grade D evidence)

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CONFLICT OF INTEREST DECLARATION: Dr. Fred Y. Aoki: Honoraria: Hoffmann La Roche Inc., GlaxoSmithKline and Merck; Advisory Board: GlaxoSmithKline, Hoffmann La Roche Inc.; Research: GlaxoSmithKline, Hoffmann La Roche Inc., Biocryst Inc., Merck; Dr. Upton D. Allen: Research: Hoffmann La Roche Inc.; Dr. H. Grant Stiver: Honoraria: Hoffmann La Roche Inc.; Advisory Board: Hoffmann La Roche Inc.; Dr. Gerald A. Evans: Research: Biocryst Inc.
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The use of antiviral drugs for influenza

Aoki et al

Nonpregnant adult with mild or uncomplicated influenza

- No risk factors
  - If within 48 hours of symptom onset, antiviral therapy with oseltamivir or inhaled zanamivir may be considered
  - If > 48 hours since onset, antiviral therapy is not generally recommended
  - Provide instructions regarding indications for reassessment

- Risk factors (see Table 3)
  - If within 48 hours of symptom onset, initiate oseltamivir or inhaled zanamivir therapy immediately
  - If > 48 hours since onset, oseltamivir or zanamivir therapy may be considered

Appendix A) Algorithm for oseltamivir and zanamivir treatment of mild or uncomplicated influenza in nonpregnant adults. The Use of Antiviral Drugs for Influenza: A Foundation Document for Practitioners

Nonpregnant adult with moderate, progressive, severe or complicated illness

- Consider hospitalization
- Consider admission to intensive care unit

Initiate antiviral therapy immediately even if the interval between symptom onset and initiation of therapy is longer than 48 hours

- Those not responding to oseltamivir therapy
- Those with illness despite oseltamivir prophylaxis
- Where influenza B is confirmed or strongly suspected.

Others

Oseltamivir
75 mg BID for 5-10 days

Not responding

Zanamivir
Intravenous zanamivir, if available*, is preferred to inhaled zanamivir (*through clinical trials or via Health Canada’s Special Access Program)

Test for oseltamivir resistance

Appendix B) Algorithm for oseltamivir and zanamivir treatment of moderate, progressive, severe or complicated influenza in nonpregnant adults. The Use of Antiviral Drugs for Influenza: A Foundation Document for Practitioners
Appendix C) Algorithm for oseltamivir and zanamivir treatment of influenza in children and youth (<18 years of age). The Use of Antiviral Drugs for Influenza: A Foundation Document for Practitioners. *In children of any age with mild or uncomplicated illness, antiviral treatment is not routinely recommended and should not be used if symptoms have been present for >48 h. †Treatment with oseltamivir or, if appropriate, zanamivir may be considered on a case-by-case basis even if symptoms have been present for >48 h. In Canada, antivirals are not authorized for infants <1 year of age but should be considered. See Table 5, Footnote 2. ‡Accessed through available clinical trials or via Health Canada’s Special Access Program.

Appendix D) Algorithm for oseltamivir and zanamivir prophylaxis or early treatment in close contacts of suspected or lab-confirmed case. The Use of Antiviral Drugs for Influenza: A Foundation Document for Practitioners. *Presumptive treatment is therapy with twice daily doses of oseltamivir or zanamivir initiated before the onset of influenza symptoms in close contact of individual with suspected or lab-confirmed influenza illness.