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

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INDEX

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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.

Definitions of the strength of evidence for the recommendations

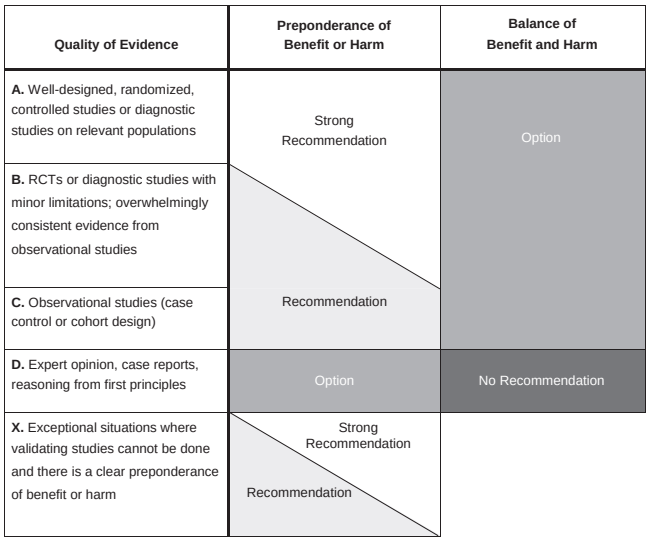
Strong Recommendation: Benefits of treatment approach clearly exceed harms; quality of evidence is high **(Grade A)** or moderate **(Grade B)** or exceptional **(Grade X)**.

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.

TABLE 1
GRADE Evidence Quality versus Benefit to Harm Ratio and Recommendation Grading[5]



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®[6], influenza vaccine composition from NACI[7] and antiviral resistance from CDC.[8]

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

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

shed virus for longer periods.[9] For purposes of post-exposure prophylaxis, the infectious period is considered to extend from one day before onset of symptoms until 24 h after fever ends.

Illness caused by influenza virus can range from asymptomatic to mild, uncomplicated, self-limited upper respiratory tract infection to serious complicated illness dominated by exacerbation of a co-morbid, underlying medical condition or severe viral lower respiratory tract infection (pneumonia) with or without multiorgan failure.[9]

In adults, influenza typically begins with fever, respiratory symptoms such as cough or sore throat and systemic symptoms, such as myalgia, arthralgia and headache. Gastrointestinal symptoms, notably diarrhea, have been described uncommonly as manifestations of seasonal influenza A.

While the typical clinical features of influenza illness appear in older children and youth, among those younger than 10 years of age, the clinical features may be atypical. Indeed, among children younger than five years of age, influenza illness is often non-specific and may be indistinguishable from illness due to other respiratory viruses. Young infants may present with a sepsis-like picture. Infants younger than six months of age are more likely to present with rhinorrhea and dehydration than cough and pneumonia and among those younger than three months of age, fever alone or fever with dehydration are common presenting features.[9] Diarrheal illness may be observed. Some clinical signs in infants, children and youth warrant urgent medical attention. Familiarity with these signs is advised (Table 2).

Severe lower respiratory tract disease encompasses diffuse primary viral pneumonia, which often develops directly from progression of initial symptoms, and secondary bacterial pneumonia, which may arise after a period of initial improvement. Acute respiratory distress syndrome (ARDS) may develop several days after illness onset. The importance of secondary bacterial infections in influenza is further illustrated by the fact that among fatal cases of A(H1N1)pdm09, concomitant bacterial pneumonia was demonstrated in 26% to 38% of cases.[10] These bacteria included *Streptococcus pneumoniae*, methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* (MRSA).

Influenza-related complications in infants, children and youth include severe hemorrhagic viral pneumonia, secondary bacterial pneumonia (due to *S. pneumoniae*, *S. aureus*, or group A Streptococcus), mixed viral and bacterial pneumonia, localized viral pneumonia, severe laryngotracheobronchitis (croup) and exacerbation of chronic pulmonary disease. Non-pulmonary complications include acute myositis, myocarditis or pericarditis, toxic shock-like picture (due to secondary bacterial infection) and neurologic complications. The latter include febrile seizures, status epilepticus, encephalitis/encephalopathy, Reye's syndrome and Guillain-Barré syndrome.[11]

Conditions that place individuals (including infants, children and youth) at risk of severe outcomes from influenza illness are shown in Table 3, which is adapted from the Canadian National Advisory Committee on Immunization[12] and incorporates recently published data.[13]

C. Clinical diagnosis of influenza illness

The accuracy of clinical diagnosis varies substantially. However, when influenza is circulating in the community, the presence of cough and a fever of 37.8°C or higher in otherwise healthy adults has a positive predictive value of 86.8% for a laboratory-confirmed diagnosis of influenza, although the negative predictive value is poor at 39.3%.[14] Among non-immunized young healthy adults, the combination of a fever of 37.8°C or higher plus at least one respiratory symptom (sore throat, cough or nasal symptoms) and one constitutional symptom (myalgia, headache, sweats, chills or fatigue) are predictive of influenza confirmed by laboratory testing in 60% to 71% of cases.[14,15,16] Among immunized patients 60 years of age and older, the combination of fever, coughing and acute onset have a predictive value of 44% for laboratory-confirmed diagnosis of influenza.[17]

Diagnosing influenza illness by clinical criteria in infants and young children is more problematic than in adults because they cannot articulate their symptoms as readily and the signs and symptoms of influenza illness are often non-specific. Studies evaluating the sensitivity and specificity of a clinical diagnosis of influenza in children compared with a laboratory gold standard are limited.[18] The common presenting findings of fever, cough and rhinorrhea do not distinguish influenza illness from that due to other respiratory viruses. Thus, in diagnosing influenza in a patient and arriving at a treatment decision, practitioners should be guided by knowledge of whether influenza virus is circulating in their community as well as their clinical assessment of the individual patient, taking into account factors that may influence the presentation such as extremes of age, co-morbid conditions and immunocompetence.

V. TREATMENT OF INFLUENZA ILLNESS

A. Antiviral drugs

For both zanamivir and oseltamivir, 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.[19]

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/acces/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.[20]

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[20] and this *in*

vitro difference may explain differences in clinical efficacy of oseltamivir for treatment of influenza A and B virus infections in children[21,22] and adults.[23]

Treatment and prophylaxis regimens of oseltamivir and zanamivir for adults and for children by age and weight are detailed in Table 4.[24] Doses do not need to be adjusted in obese adults.[25] 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.[26-29]

In adults, oral oseltamivir is generally well tolerated. 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%).[20] No 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.[30] A causal relationship between oseltamivir and such adverse effects or a wider spectrum including delirium with hallucinations has been suspected but not definitively established.[31,32] 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.[33] 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.[34] Oseltamivir 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.[35]

In children, data on the safety and efficacy of oseltamivir exist for those one year of age and older.[36] 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.[36] 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.[36]

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.[37] 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.[38] 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.[39]

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.[20]

2. 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.[40] 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.[22] 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.[23] 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.[41]

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.[40] 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.[42]

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/dhp-mps/acces/drugs-drogues/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.[43] 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%).[44] 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.[45] In fact the morning and evening peak expiratory flow rates were significantly increased in the zanamivir group.[46] 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.[40]

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.[47] 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.[3,49] 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.[49] 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 infection[53] and treating oseltamivir-resistant A(H1N1) pdm09 pneumonitis[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 CDC[57]:

- **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 3
At-risk groups and co-morbid medical conditions that predispose to severe influenza (adapted from references 12 and 13)

- Asthma and other chronic pulmonary disease, including bronchopulmonary dysplasia, cystic fibrosis, chronic bronchitis and emphysema
- Cardiovascular disease (excluding isolated hypertension; including congenital and acquired heart disease such as congestive heart failure and symptomatic coronary artery disease)
- Malignancy
- Chronic renal insufficiency
- Diabetes mellitus and other metabolic diseases
- Hemoglobinopathies such as sickle cell disease
- Immunosuppression or immunodeficiency due to disease (e.g. HIV infection, especially if CD_4 is $<200\times10^6$/L), or iatrogenic, due to medication
- Neurologic disease and neurodevelopmental disorders that compromise handling of respiratory secretions (cognitive dysfunction, spinal cord injury, seizure disorders, neuromuscular disorders, cerebral palsy, metabolic disorders)
- Children younger than 5 years of age*
- Individuals 65 years of age or older
- People of any age who are residents of nursing homes or other chronic care facilities
- Pregnant women and women up to 4 weeks post partum regardless of how the pregnancy ended
- Individuals <18 years of age who are on chronic aspirin therapy
- Obesity with a BMI $\geq$40 or a BMI >3 z-scores above the mean for age and gender
- Aboriginal peoples

** 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 4
Oseltamivir and zanamivir treatment of influenza (treatment regimens adapted from reference 24).
The Use of Antiviral Drugs for Influenza: A Foundation Document for Practitioners

Medication		Treatment (5 days)	Chemoprophylaxis (10 days)
Oseltamivir[1]			
		Adults	
		75 mg twice daily	75 mg once daily
		Children ≥12 months	
Body Weight (kg)	Body Weight (lbs)		
≤15 kg	≤33lbs	30 mg twice daily	30 mg once daily
>15 kg to 23 kg	>33 lbs to 51 lbs	45 mg twice daily	45 mg once daily
>23 kg to 40 kg	>51 lbs to 88 lbs	60 mg twice daily	60 mg once daily
>40 kg	>88 lbs	75 mg twice daily	75 mg once daily
		Children 3 months to <12 months[2*]	
		3 mg/kg/dose twice daily	3 mg/kg/dose once per day
		Children <3 months[3*]	
		3 mg/kg/dose twice daily	Not recommended unless situation judged critical due to limited data on use in this age group
Zanamivir[4]			
		Adults	
		10 mg (two 5 mg inhalations) twice daily	10 mg (two 5 mg inhalations) once daily
		Children (≥7 years or older)	
		10 mg (two 5 mg inhalations) twice daily	10 mg (two 5 mg inhalations) once daily

**Please note that antivirals are not authorized in Canada for the routine treatment of seasonal influenza illness in infants younger than one year of age. Such use may be considered on a case-by-case basis.*

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.

When dispensing commercially manufactured Oseltamivir (TAMIFLU) Powder for Oral Suspension (6 mg/mL or 12 mg/mL), pharmacists should ensure the units of measure on the prescription instructions match the dosing device.

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 full 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 solutions. Zanamivir is not recommended for persons with chronic respiratory diseases such as asthma or 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.[49,58] 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 in 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.

The attack rates for seasonal influenza in healthy children range from 3% to 30% with 1% requiring hospitalization.[59,60] During community outbreaks of seasonal influenza, the highest attack rates occur in school-age children. Children are a common source from which infection is spread to other household members. The shedding of virus usually starts 24 h prior to the onset of overt symptoms and generally ceases at seven days.

Influenza illness may be indistinguishable from illness due to other respiratory viruses. The atypical and non-specific nature of influenza illness in young children is evidenced by Canadian surveillance data that suggest that among hospitalized children, fever and cough are the most common presenting features.[61]

The pulmonary and non-pulmonary influenza-related complications in infants, children and youth are generally similar to those in adults with the exception that some conditions are more likely to be seen in children (sepsis-like illness, diarrhea, otitis media, severe laryngotracheobronchitis (croup), febrile seizures, Reye's syndrome, and refusal to walk due to myositis.[59]

In general, children with pre-existing high-risk medical conditions are more likely to have adverse outcomes. However, previously healthy children may also experience adverse consequences. In this regard, in some influenza seasons previously healthy children may account for up

TABLE 5
Recommended oseltamivir regimens for prevention and treatment of adult patients with renal impairment (26-29, Tamiflu[R] Canadian Product Monograph, 2012)

Creatinine clearance	Treatment for 5 days	Prophylaxis until outbreak is over
>60 mL/min	75 mg twice daily	75 mg once daily
>30–60 mL/min	75 mg once daily OR 30 mg suspension twice daily OR 30 mg capsule twice daily	75 mg on alternate days or 30 mg once daily
10-30 mL/min	30 mg once daily	30 mg on alternate days
<10 mL/min (renal failure)*	Single 75 mg dose for the duration of illness	No data
Dialysis patients*	Low-flux HD: 30 mg after each dialysis session	30 mg after alternate dialysis sessions
	High-flux HD: 75mg after each dialysis session	No data
	CAPD dialysis: 30 mg once weekly	30 mg once weekly
	CRRT high-flux dialysis: 30 mg daily or 75 mg every second day	No data
The following dosing regimen has been suggested for children based on limited data (29):		
In children older than one year of age, after alternate HD sessions as follows:		
• 7.5 mg for children weighing >15 kg		
• 10 mg for children weighing 16–23 kg		
• 15 mg for children weighing 24–40 kg		
• 30 mg for children weighing >40 kg		
While this may provide a framework for guidance, it is strongly suggested that an infectious disease physician or clinical pharmacist should be consulted.		

**Experience with the use of oseltamivir in patients with renal failure is limited. These regimens have been suggested based on the limited available data[27,28,29] Consultation with an infectious physician or clinical pharmacist is recommended*

to 50% of reported influenza-related deaths.[62] Influenza B has been identified in a disproportionate number of pediatric influenza-associated deaths (38%).[62]

Children at the highest risk of adverse outcomes from influenza illness include those younger than five years of age.[63] 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.[61] 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. [49,64] 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.[64]

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%).[65] 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.[66] A benefit on asthma exacerbations among oseltamivir-treated children has also been demonstrated in a randomized controlled trial.[67]

Since the earlier studies on NAIs, additional studies have been reported or are in progress and experience with their use has increased.[68-71] However, there exists a relative paucity of new data from randomized trials in infants and young children. Recent studies have provided valuable safety data[72] as well as data on the use of oseltamivir in premature newborns.[73] 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.[74-76] 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.[77] 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.[77]

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[78] or may present with respiratory symptoms without fever.[79]

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.[80,81] This persistent shedding

TABLE 6
Selected surrogate indices of immunocompromised states

Laboratory-based Indices	Clinical States	Treatment-related Indices
Significant risk	Significant but variable risk due to heterogeneity in clinical states	Significant but variable risk due to heterogeneity in nature and intensity of treatments
• 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 therapy[71] (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 flurorouracil, cytarabine, capecitabine, or gemcitabine; *anti-folate agents* such as methotrexate or pemetrexed; *alkylating agents* such as the nitrogen mustards (cyclophosphamide or ifosphamide), nitrosoureas (carmustine, lomustine, semustine, streptozotocin), 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 erythematosis; GI, gastrointestinal; IBD, inflammatory bowel disease; COPD, chronic obstructive airways disease; TNF, tissue necrosis factor

may be accompanied by periodic exacerbations of illness.[80,81] Cell-mediated immunity is important in mediating protection from influenza illness, viral clearance and recovery from illness.[81-85] Thus, reductions in T-cell number or function as a result of acquired or congenital immunodeficiency states may result in an increased likelihood of a more severe and prolonged illness and an increased risk of antiviral resistance.[81,82] The risk for immunocompromised persons is compounded if they have co-morbid states that are themselves risk factors for adverse outcomes from influenza illness (e.g., underlying chronic lung disease). The risk among these individuals may be variable due to differences in the nature and intensity of their immunosuppressive therapies.[86,87]

The importance of early treatment of influenza illness in immunocompromised hosts (e.g., organ transplant recipients) is well documented. Protracted illness and virus shedding may prompt physicians to prolong antiviral therapy with oseltamivir. However, the increased likelihood of antiviral resistance is a major concern with prolonged oseltamivir therapy of influenza in immunocompromised patients.[88] Antiviral resistance should be considered if there is a lack of response to antiviral therapy, especially in the setting of recent antiviral administration. Accordingly, practitioners should consult with experts and be vigilant for antiviral resistance when treating such patients.

F. Treatment of patients with renal impairment

Recommended oseltamivir regimens for treatment and prophylaxis of patients with renal impairment or failure are presented in Table 5.[26-29]

No dosage adjustments are required for inhaled zanamivir treatment in patients with renal impairment.

G. Treatment of pregnant patients

During seasonal influenza epidemics, healthy pregnant women with influenza, especially those in the third trimester of pregnancy, experienced rates of hospitalization in excess of those observed in age-matched non-pregnant women with influenza.[89] Moreover, the rates of hospitalization were comparable to those observed in individuals with other recognized co-morbid conditions that increase the risk of influenza-related complications.[89] As a result of such data, pregnancy is now recognized to be a risk factor that warrants annual influenza immunization. During the 2009 A(H1N1)pdm09 pandemic, not only were increased rates of hospitalization observed in healthy pregnant women, especially in the second and third trimester, but also an increased rate of death compared to that in non-pregnant women.[90] Such excess mortality had previously been observed during the 1918 and 1957 pandemics. A recent meta-analysis demonstrated that women who were less than four weeks post-partum were at greatest risk of death.[91] New evidence indicates that there is a significant increase in stillbirths, premature deliveries, and infant mortality when women have influenza in the third trimester.[92]

Oseltamivir pharmacokinetics in pregnant women with influenza are not different from one trimester to another.[93] Oseltamivir is excreted in breast milk, but at concentrations below that required to inhibit current influenza A and B strains.[94] These observations taken together support the recommendation to treat influenza in pregnant women in all trimesters with oseltamivir in standard doses as soon as possible after the onset of influenza-like symptoms.[95]

Oseltamivir and zanamivir are listed by the FDA as Pregnancy Category C drugs, reflecting the fact that no controlled trials have been done to assess their safety during pregnancy. No adverse effects on the pregnant woman or fetus have been observed as a result of treatment with oseltamivir during pregnancy.[96,97]

Some authorities recommend oseltamivir in preference to zanamivir during pregnancy because it is systemically absorbed.[98] Systemically absorbed oseltamivir would likely be delivered to virus-infected respiratory tract tissues more consistently than would inhaled zanamivir, especially in the later stages of pregnancy when diaphragmatic excursion, limited by the gravid uterus, may impair necessary distribution of inhaled zanamivir through the respiratory tract. Oseltamivir is now recommended for the treatment of influenza in pregnant women.

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 less than 12 h than at 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 **(Recommendation, Grade C 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:
  - illness with onset within 48 h, treatment with oseltamivir or inhaled zanamivir may be considered. (**Strong recommendation**, **Grade A evidence**)
  - 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:
  - illness with onset within 48 h, initiate oseltamivir or inhaled zanamivir therapy immediately. **(Strong Recommendation, Grade X evidence)**
  - 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: NAIs 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: NAIs 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.
  ii. One year of age and older: illness with onset within 48 h, treat with oseltamivir or if age appropriate, inhaled zanamivir **(Recommendation, Grade B 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)**

- Treatment with zanamivir instead of oseltamivir should be considered for:
  i) Patients not responding to oseltamivir therapy, **(Recommendation, Grade X evidence)**
  ii) Patients 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.
- Although oseltamivir was approved temporarily for use in infants under one year of age on the basis of a favourable risk-to-benefit ratio during the recent 2009 H1N1 pandemic and is now authorized in the U.S., it is not authorized in Canada for the routine treatment of seasonal influenza illness in infants less than one year of age. Such use in this population for seasonal influenza should be handled on a case-by-case basis, based on severity of illness. **(Option, Grade D evidence)**

F. Treatment of immunocompromised patients:
Recommendations

1. Immunocompromised individuals who have uncomplicated influenza illness are at risk of developing severe or complicated illness and thus should be treated with oseltamivir as soon as possible without regard to the duration of illness. **(Recommendation, Grade C 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 X 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[1,2]: (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 h after exposure to a contact with suspected or lab-confirmed influenza. Contacts are considered infectious for the interval beginning 24 h 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.[74] 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.[99] Closed facilities include nursing homes and other long-term care facilities that house patients at high risk of influenza complications[99] 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.[99] 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.[100] A similar lack of interference with oseltamivir would be expected. Nasal attenuated live influenza vaccine (Flumist^{R}) 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)[101] 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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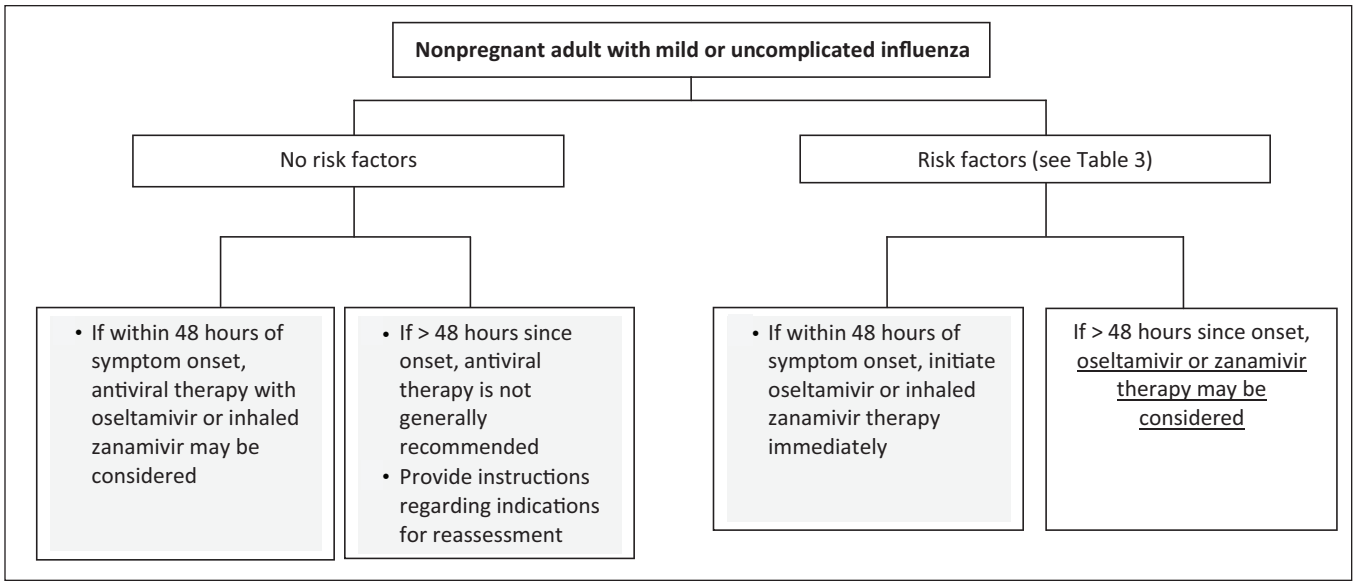
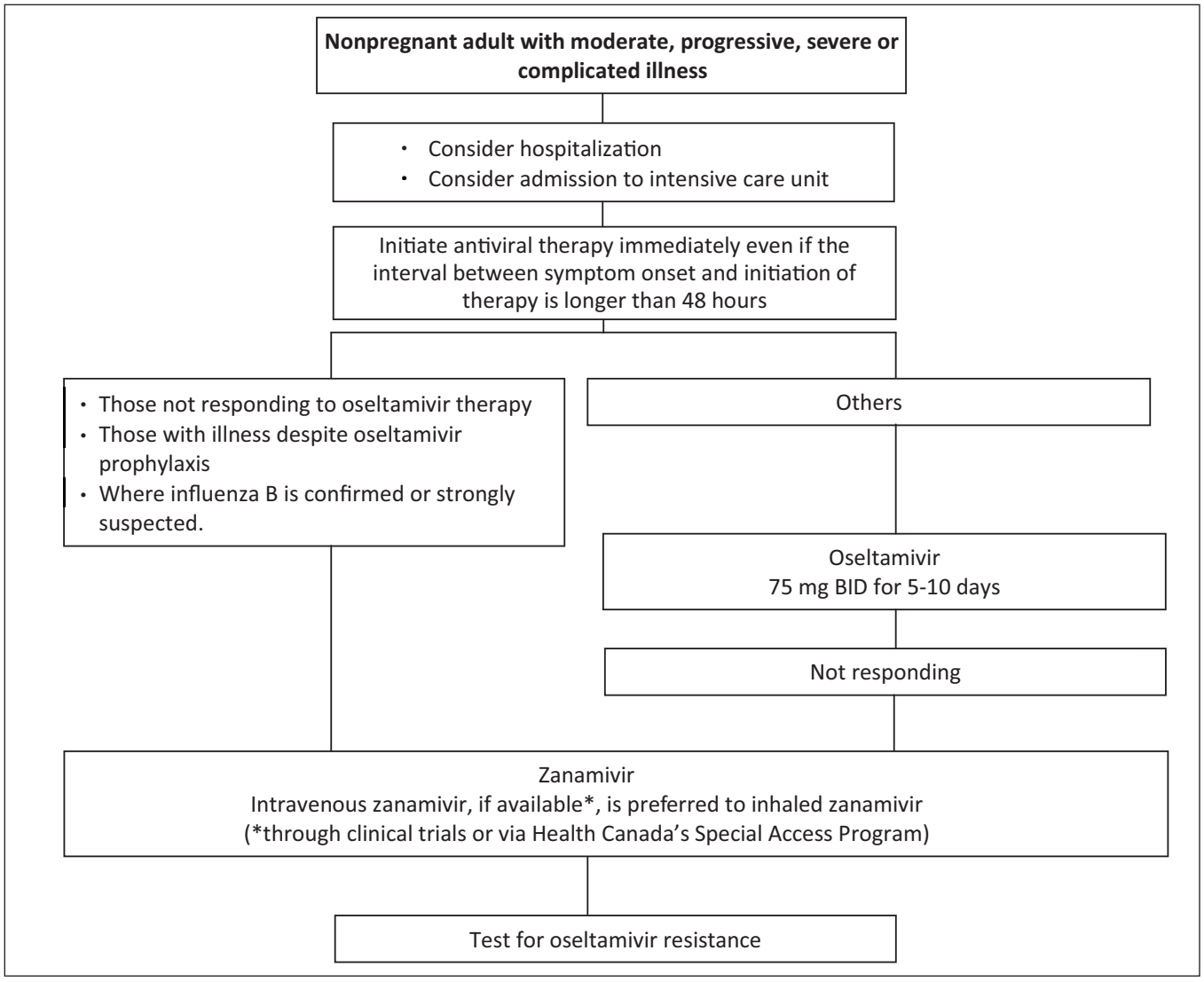
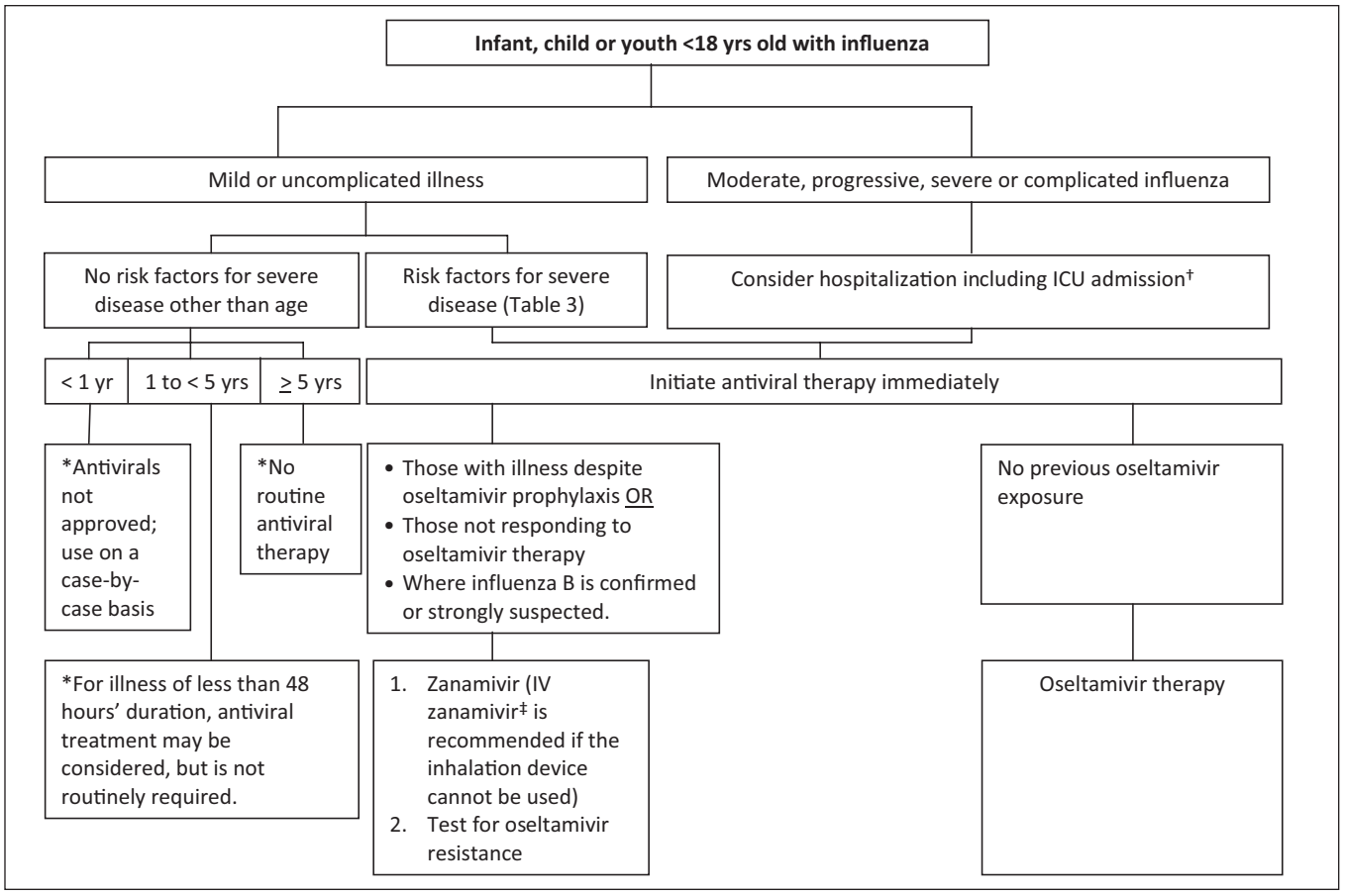


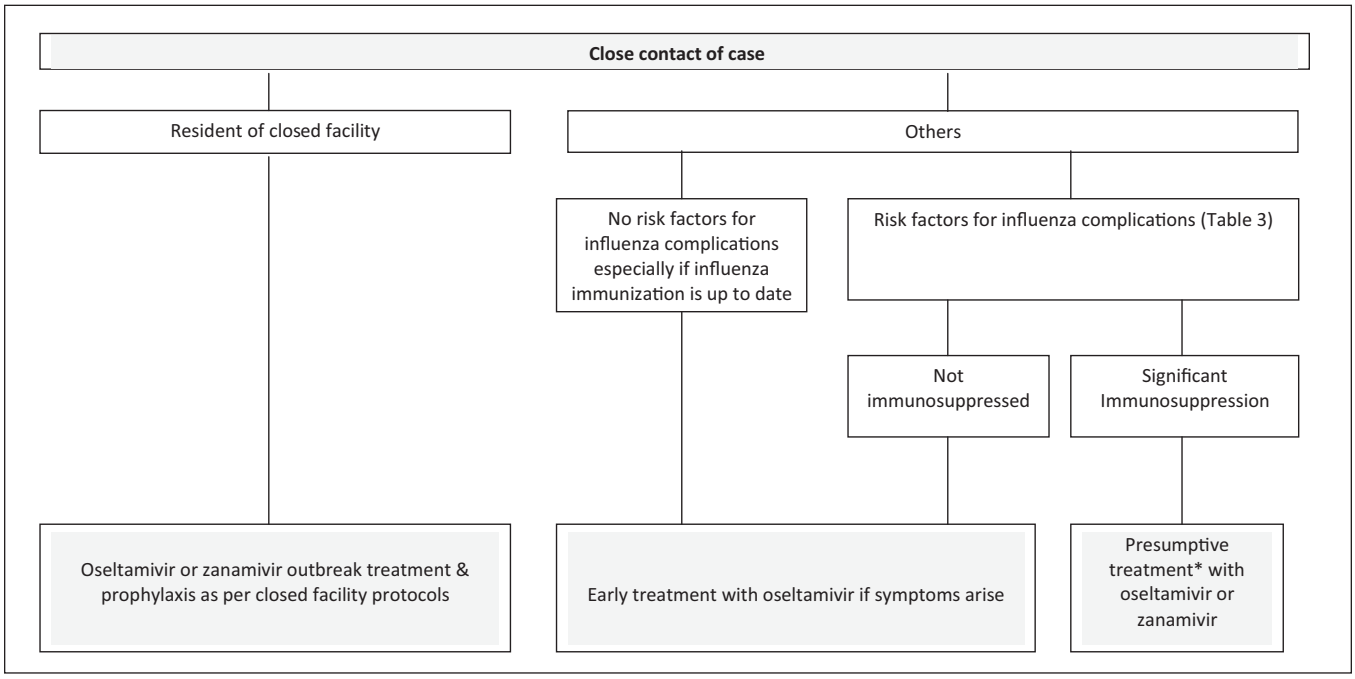
Appendix A) *Algorithm for oseltamivir and zanamivir treatment of mild or uncomplicated influenza in nonpregnant adults. The Use of Antiviral Drugs for Influenza:A Foundation Document for Practitioners*



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*