

**The Use of Antiviral Drugs for Influenza: Guidance for Practitioners
2011-2012**

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SUMMARY

This Guidance addresses the use of antiviral drugs in the management of seasonal influenza illness for the 2011-2012 season. It updates our documents published in 2006¹ and 2010.² Noteworthy Guidance changes since 2010 include:

- Seasonal influenza in 2011-2012 is predicted to be caused by two influenza A and, one influenza B strain, all of which are anticipated to be generally susceptible to oseltamivir.
- Additional data now support the conclusion that initiation of antiviral therapy more than 36 to 48 hours after onset of symptoms appears to be beneficial in patients hospitalized with complicated influenza and severe illness.
- Oseltamivir is recommended for the treatment of influenza in pregnant women.
- Pre-exposure prophylaxis may be initiated concurrently with vaccine administration, especially in the setting of influenza outbreaks in institutions to provide bridging protection until vaccine-induced immunity develops.
- Zanamivir may be more efficacious than oseltamivir when illness is due to influenza B virus.
- Intravenous zanamivir is the recommended antiviral treatment for patients seriously ill with suspected or confirmed oseltamivir-resistant influenza infection who are unable to administer zanamivir using the inhalational device

I. PURPOSE OF THIS GUIDANCE

The purpose of this document is to provide recommendations for clinicians on the use of antiviral drugs for the prevention and treatment of influenza during the 2011-2012 influenza season in Canada. Other aspects of influenza management, such as laboratory diagnosis, infection control, immunization and non-pharmacological interventions are beyond the scope of this article.

II. GRADING OF RECOMMENDATIONS

A grading system is used to qualify recommendations based on the quality of evidence and the determination of benefit vs. harm arising from the recommendation as defined below.³ 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.

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**).

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

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.

III. THE DISEASE

A. Influenza viruses

For the 2011-2012 influenza season, it is expected that the circulating influenza strains will be those contained in the trivalent inactivated influenza vaccines for 2011-2012:

1. Pandemic H1N1 [A/California/07/2009 (H1N1)-like], hereafter referred to as pH1N1, 2. A/Perth/16/2009 (H3N2)- like, and 3. B/Brisbane/60/2008-like.⁴ Influenza

A/Brisbane/59/H1N1-like viruses (so called seasonal influenza A/H1N1 viruses) appear to

have been completely displaced during and since the 2009-2010 pandemic by a pH1N1

strain that has become the new seasonal H1N1 virus. It is referred to by the WHO, and,

hereafter as A(H1N1)pdm09.⁵ In Canada, during the 2010-2011 influenza season, 63% of 10,095 influenza isolates were A/H3N2, 27%, influenza B and 10%, pH1N1 viruses.⁶

However, during the current influenza season in Australia, 49% of 11,044 influenza isolates

were pH1N1, 43%, influenza B and 8%, A/H3N2.⁶ Thus, it seems probable that influenza

illness during the coming season will be caused by both influenza B and A viruses and that

the latter will likely be A(H1N1)pdm09 virus.⁶ The influenza strain that will predominate is

uncertain.

Influenza B viruses cause more illness in children than adults.⁷ In Canada in 2010-2011, 28% of 2,317 influenza B isolates were obtained from children less than 5 years old, 35% from persons 5-19 years old and 37% from persons aged 20 years or more,⁶ supporting the view that influenza B viruses are more common causes of illness in children than in adults.

Antiviral drug resistance patterns of influenza viruses demonstrated in vitro generally correlate with treatment outcomes. Oseltamivir resistance rates remained low in all pandemic H1N1 viruses, comprising less than one percent of Canadian isolates tested

between September 2010 and August 2011.⁶ Resistant viruses have been isolated from patients who were receiving oseltamivir prophylaxis,⁸ or longer term oseltamivir treatment (usually in critical care units),⁹ and immunosuppressed patients who had prolonged virus shedding during oseltamivir therapy.¹⁰ All A(H1N1)pdm09 strains remain susceptible to zanamivir.⁶ Globally, as of March 2011, 1.5% of 5814 influenza A(H1N1)09 viruses were oseltamivir-resistant. All were susceptible to zanamivir.¹¹ Based on these in vitro data, oseltamivir and zanamivir are likely to be similarly efficacious in the management of A(H1N1)pdm09 disease.

The susceptibility of current seasonal influenza viruses to the neuraminidase inhibitor drugs, oseltamivir and zanamivir, and amantadine are shown in Table 2.¹² Since all of these strains (A/pH1N1 and A(H1N1)pdm09, A/H3N2, influenza B) are resistant to amantadine, subsequent discussion is limited to the neuraminidase inhibitor drugs. Recommendations for laboratory testing of influenza viruses for antiviral resistance testing have been published. (Available at:

http://www.cphln.ca/pdf/EN_H1N1_Best_Practice_Final_Version.pdf)

B. Clinical aspects

Seasonal influenza A viruses share similar clinical features with the recently described pH1N1 virus.¹³

The transmission characteristics of the above two groups of influenza virus are similar.- 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 1 to 4 days with a mean of 2 days, which is generally similar to pH1N1.¹⁴ However, in a minority of pH1N1 cases, the

incubation period was observed to be up to 7 days.¹³ This may also apply to seasonal influenza illnesses, including those due to current strains of the pH1N1 virus.

In otherwise healthy patients with uncomplicated illness, virus in nasopharyngeal secretions is shed beginning 24 hours (1 day) before onset of symptoms, peaks in the first 2-3 days of illness and declines over 5 to 7 days although it is commonly accepted that some persons, particularly young children and immunocompromised persons, may shed virus for longer periods. For purposes of post-exposure prophylaxis, the infectious period is considered to extend from 1 day before onset of symptoms until 24 hours after fever ends.¹⁵

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.¹⁴

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. However, as many as 25% of persons with pH1N1 reported diarrhea and up to 32%, abdominal pain or vomiting.

While the typical clinical features of influenza illness appear in older children and youth, among those less than 10 years of age, the clinical features may be atypical. Indeed, among children less than 5 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 less than 3 months of age, fever alone or fever with dehydration are common presenting features.¹⁴ Diarrheal illness may be observed. Some clinical signs in infants, children and youth warrant urgent medical attention. Familiarity with these signs is advised (Table 3).

Severe lower respiratory tract disease encompasses diffuse primary viral pneumonia, which often develops directly from progression of initial symptoms, and a 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 cases of pH1N1, concomitant bacterial infection was demonstrated in 20-30% of cases of pH1N1 disease with pneumonia.¹³ These bacteria included *S. 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 *Streptococcus pneumoniae*, *Staphylococcus 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.¹⁸

Conditions that place individuals (including infants, children and youth) at risk of severe outcomes from influenza illness are shown in Table 4, which is adapted from recommendations of the WHO¹⁶ and the Canadian National Advisory Committee on Immunization.¹⁷ Table 4 has been added since our 2006 document¹ and includes pregnancy and morbid obesity as risk conditions plus First Nations, Inuit and Metis heritage as a risk factor.

C. Clinical diagnosis of influenza illness

Clinical suspicion and the accuracy of diagnosis vary 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%.¹⁹

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.^{19,20,21} 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.²²

Diagnosing influenza illness by clinical criteria in children is more problematic than in adults because they cannot articulate their symptoms as readily. Studies evaluating the sensitivity and specificity of a clinical diagnosis of influenza in children compared with a laboratory gold standard are limited.²³ The common presenting findings of fever, cough and rhinorrhea do not distinguish influenza illness from that due to other respiratory viruses.²³ 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.

IV. TREATMENT OF INFLUENZA ILLNESS

A. Antiviral drugs including off-label use

For both zanamivir and oseltamivir, these guidelines are recommending some uses that are off-label and not approved by Health Canada. Accordingly, it remains incumbent on the prescribing clinician to apprise the patient that the drug has not been approved for this indication.

1. Oseltamivir – The neuraminidase inhibitor (NAI) drug oseltamivir (Tamiflu[®]R) is authorized by Health Canada for the treatment of uncomplicated influenza in patients one

year of age or older who have been symptomatic for no more than 2 days. Oseltamivir is also authorized in Canada for prevention of influenza in adults and children ≥ 1 year old who are close contacts of an individual with characteristic symptoms of influenza.

Oseltamivir is formulated as oseltamivir phosphate in capsules containing 30, 45 or 75 mg per capsule or as a suspension containing 12 mg/ml. No injectable formulation is currently authorized for use.

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.²⁴

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 viruses²⁴ and these *in vitro* differences may explain differences in clinical efficacy of oseltamivir for treatment of influenza A and B virus infections in children^{25,26} and adults.²⁷

Treatment and prophylaxis regimens of oseltamivir and zanamivir for adults and for children by age and weight are detailed in Table 5.²⁸ 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. Mild, rapidly reversible nausea and/or vomiting have been observed in approximately 5-10% more persons taking oseltamivir versus placebo. Nausea and/or vomiting are more common in young adults taking 150 mg twice daily (12-15%) than 75 mg twice daily (8-11%) compared to placebo (3-7%).²⁴

For adults with seasonal influenza of less than 36 hours duration, there appears to be no advantage of combining oseltamivir and zanamivir.²⁹

Oseltamivir was widely used during the 2009 H1N1 pandemic. Such use included treatment with higher doses administered for longer periods than the approved 5-day regimen of 75 mg BID. In critically ill ventilated patients with pH1N1, oseltamivir administered via a gastric tube was well absorbed, yielding plasma concentrations that exceed the inhibitory concentration of influenza A virus.³⁰ Preliminary analysis from a randomized comparison of 150 mg BID and 75 mg BID oseltamivir for treatment of patients seriously ill with influenza, including pH1N1 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.³¹

A review by the drug manufacturer identified no additional safety issues associated with the extensive use of oseltamivir during the H1N1 pandemic compared to the prepandemic period.³²

More details regarding safety, tolerance, drug interactions and formulations were detailed in our previous guideline.¹

2. Zanamivir – Zanamivir (RelenzaR) is authorized by Health Canada for the treatment of uncomplicated influenza in patients 7 years of age or older who have been symptomatic for no more than 2 days. It is also authorized for the prevention of influenza in patients 7 years of age or older.

In vitro, influenza A and B viruses exhibit similar susceptibility to zanamivir.³³ 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 aged 4-16 years.²⁷ However, in older children and adults (mean age 15 ± 12 [SD] yrs) with influenza B virus infection, the duration of fever was significantly less in individuals treated with zanamivir versus oseltamivir.²⁶ 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.³⁴

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.³³ 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. Of inhaled drug, 10-20% is absorbed and eliminated unchanged into the urine. Since inhaled zanamivir may induce bronchospasm, the Canadian product monograph advises against its use in persons with severe asthma or COPD.

No dose reductions are recommended for any patient population.

There have been case reports of mechanically ventilated patients with pH1N1 influenza who had been treated with zanamivir diskhaler powder in water, administered by nebulizer resulting in bronchospasm and obstruction of ventilator filters.³⁵

Intravenous formulations of zanamivir are under clinical investigation but are not authorized for use in Canada. In specific circumstances, intravenous zanamivir may be obtained through the Special Access Programme of Health Canada (<http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/index-eng.php>).

B. Benefits of antiviral treatment

Neuraminidase inhibitor 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 greater than 1 year of age and adults.^{36,37} NAIs have been shown to reduce the frequency of otitis media as a complication of influenza in pediatric patients.³⁷ NAI treatment of hospitalized patients with seasonal influenza may reduce the duration of hospitalization and mortality.³⁸

While there are no comparable randomized controlled trials describing the benefits and risks of treating patients with influenza due to the A(H1N1)pdm09 virus, in a number of

observational studies of patients with pH1N1 infection, it was reported that treatment with NAIs, chiefly oseltamivir, was effective in reducing 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.³⁹

As noted above, *in vitro* and available clinical data from observational studies,²⁵⁻²⁷ 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 in preventing experimental human influenza A virus infection,⁴⁰ as well as for treating oseltamivir-resistant 2009 H1N1 pneumonitis.^{41,42} 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 per se. 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 CDC²⁸:

- **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.
- **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 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 recent experience during the pH1N1 pandemic (see Table 4).

Notwithstanding the above association of the aforementioned medical conditions as risk factors for severe influenza, 20-40% of patients with severe pH1N1 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.

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 36-48 hours of illness onset is efficacious. Optimal benefits are obtained if treatment is initiated as early as possible after the onset of symptoms.⁴³ Thus, starting treatment within 12 hours of illness onset should be a practice goal.

4. Likely influenza type(s) causing infection:

As discussed in Section III, it is uncertain what will be the predominant strain of influenza causing illness in the 2011-2012 influenza season. Practitioners should be mindful of reports in Public Health Agency of Canada's *FluWatch* and reports from their provincial or territorial public health departments. This may be important in case oseltamivir-resistant seasonal H1N1 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.^{44,45} 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 hours prior to the onset of overt symptoms and generally ceases at 7 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.⁴⁶

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).⁴⁴

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 the 2010-2011 influenza virus season in the USA, approximately 50% of the 115 influenza-related deaths that were reported were among previously healthy children.⁴⁷ Influenza B was identified in a disproportionate number of pediatric influenza-associated deaths (38%).⁴⁷

Children at the highest risk of adverse outcomes from influenza illness include those less than 5 years of age.⁴⁸ Hospitalizations occur more frequently among those less than 2 years of age compared with older children, with the highest hospitalization rates being among those less than 6 months of age.⁴⁶ This does not necessarily translate into a decision to uniformly use antiviral therapy in those less than 2 years of age; such children with mild influenza illness 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.^{37,49} One meta-analysis suggested that the neuraminidase inhibitors 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.⁴⁹ The challenges of pooling data from disparate studies have been acknowledged.⁵⁰

Indeed, data from the only double-blind, randomized, controlled trial on 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%).⁵¹ Another randomized trial among children aged 1-3 years, indicated an 85% reduction in acute otitis media when oseltamivir was started within 12 hours after the onset of influenza illness, but no reduction when treatment was started at > 24 hours after the onset of symptoms.⁵² A benefit on asthma exacerbations among oseltamivir-treated children has also been demonstrated in a randomized controlled trial.⁵³

Since the earlier studies on NAIs, additional studies have been reported and are in progress and experience with their use has increased.⁵⁴⁻⁵⁸ However, there exists a relative paucity of new data from randomized trials in infants and young children. Recent studies have provided valuable safety data⁵⁸ as well as data on the use of oseltamivir in premature newborns.⁵⁹ Oseltamivir was approved temporarily for use in infants under 1 year of age on the basis of a favourable risk-to-benefit ratio during the recent 2009 H1N1 pandemic. However, its use for seasonal influenza in infants should be handled on a case-by-case basis, based on severity of illness as it is not approved for this indication in Canada. During the 2009 H1N1 pandemic, 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.^{12,60,61} Current dosing recommendations are shown in table 5.²⁸

E. Treatment of immunocompromised patients

This group includes individuals with immunodeficiency states ranging from congenital immunodeficiencies, selective acquired deficiencies and immunodeficiencies secondary to organ/tissue transplantation and immunoablative, immunosuppressive or myelosuppressive chemotherapy. The heterogeneity of populations of immunocompromised hosts is well recognized. This results in varying degrees of risk of 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.⁶² 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.⁶²

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 illness⁶³ and may present with respiratory symptoms without fever.⁶⁴

The complications seen among persons with normal immune systems may also be seen in immunocompromised hosts. Invasive secondary bacterial infections caused by *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Streptococcus 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.^{65,66} This persistent shedding may be accompanied by periodic exacerbations of illness.^{65,66} Cell-mediated immunity is important in mediating protection from influenza illness, viral clearance and recovery from illness.⁶⁶⁻⁷⁰ 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.^{66,67} 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.^{71,72}

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 likelihood of antiviral resistance is a major concern with prolonged oseltamivir therapy of immunocompromised patients.⁷³ Accordingly, practitioners should consult with experts and monitor for antiviral resistance when treating such patients.

F. Treatment of patients with renal impairment

Recommended oseltamivir regimens for treatment of patients with renal impairment or failure are presented in Table 7.^{74,75}

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.⁷⁶ 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.⁷⁶ As a result of such data, pregnancy is now recognized to be a risk factor that warrants annual influenza immunization. During the 2009 pH1N1 pandemic, not only were increased rates of hospitalization again observed in healthy pregnant women, most in the second and third trimester, but also increased rates of death occurred compared to non-pregnant women.⁷⁷ Such excess mortality had previously been observed during the 1918 and 1957 pandemics. New evidence indicates that there is a significant increase in stillbirths, premature deliveries, and infant mortality when women have influenza in the third trimester.⁷⁸ Although there was no apparent benefit of oseltamivir in reducing adverse infant outcomes in one study, the number of mothers treated with antivirals was too small to exclude a beneficial effect.⁷⁹

Oseltamivir pharmacokinetics in pregnant women with influenza are not different from one trimester to another.⁷⁹ Oseltamivir is excreted in breast milk, but at concentrations below that required to inhibit current influenza A and B strains.⁸⁰ 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.⁸¹

Oseltamivir and zanamivir are listed by the FDA as Pregnancy Category C drugs, reflecting the fact that no clinical studies 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.^{82,83}

Some authorities recommend oseltamivir in preference to zanamivir during pregnancy because it is systemically absorbed.⁸⁴ 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.

V. 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 hours than at 48 hours. (**Strong recommendation, Grade B evidence**)
- Antiviral therapy should be initiated even if the interval between illness onset and administration of antiviral medication exceeds 48 hours if:
 - i. The illness is severe enough to require hospitalization (**Strong recommendation, Grade C evidence**),
 - ii. The illness is progressive, severe or complicated, regardless of previous health status (**Strong recommendation, Grade C evidence**) , or
 - iii. The individual belongs to a group at high risk for severe disease (**Strong recommendation, Grade C evidence**).
- Otherwise healthy patients with relatively mild, self-limited influenza are not likely to benefit from NAI therapy initiated more than 48 hours after illness onset. Clinical judgment should be used. (**Option, Grade D evidence**)
- Patients for whom antiviral therapy is not recommended should be advised of symptoms and signs of worsening illness that might warrant reassessment. (**Recommendation, Grade D evidence**)
- Treatment duration should routinely be 5 days (**Strong Recommendation, Grade A evidence**), but may be continued longer than 5 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 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 **(Recommendation, Grade C evidence)**
 - ii. Patients with illness despite oseltamivir prophylaxis **(Recommendation, Grade C evidence)**
 - iii. Severely immunosuppressed patients **(Option, Grade D evidence)**
- For severely ill patients, zanamivir administered intravenously is preferred to inhaled drug. **(Recommendation, Grade D evidence)**
- In ventilated patients, zanamivir should only be administered intravenously **(Strong Recommendation, Grade D evidence)**
- If patients are not responding to oseltamivir therapy, their virus should be tested for oseltamivir resistance **(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 of less than 48 hours' duration, treat with oseltamivir or inhaled zanamivir. **(Option, Grade A evidence)**
 - o illness of more than 48 hours' duration, antiviral treatment is **not** recommended. **(Recommendation, Grade C evidence)**
- For individuals with mild disease, risk factors and:
 - o illness of less than 48 hours' duration, treat with oseltamivir or

inhaled zanamivir. **(Strong Recommendation, Grade C evidence)**

- o illness of more than 48 hours' duration, treatment with oseltamivir or inhaled zanamivir may be considered. **(Option, Grade D 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 every 12 hours orally or by nasogastric tube should be started 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 hours. **(Recommendation, Grade C evidence)**
- Treatment with zanamivir instead of oseltamivir should be considered for
 - i) Those not responding to oseltamivir therapy, **(Recommendation, Grade C evidence)**
 - ii) Those with illness despite oseltamivir prophylaxis, **(Recommendation, Grade C evidence)**
 - iii) Those with significant immunosuppression **(Option, Grade D evidence)**

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. Although children under 2 years of age are classified as high risk, those who are otherwise healthy and have mild disease not requiring hospitalization do not routinely require antiviral therapy. For these children, treatment is an option. The same applies to children 2 to less than 5 years of age in whom the risk of complications is even lower than those less than 2 years of age.
(Option, Grade D evidence)
 - ii. 1 to < 5 years old: illness of less than 48 hours' duration, oseltamivir treatment may be considered, but is not routinely required in children with mild disease not requiring hospitalization.
(Option, Grade A evidence)
 - iii. 1 to <5 years old: illness of more than 48 hours' duration, treatment with oseltamivir is **not** recommended.
(Recommendation, Grade C evidence)
 - iv. ≥ 5 years old: 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)**
 - v. < 1 year old: NAIs are currently not approved for the routine treatment of seasonal influenza illness. Given that infants less than 6 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. **(Option, Grade D evidence)**

- For those with mild disease and risk factors other than age :
 - i. ≥ 1 yr old: illness of less than 48 hours' duration, treat with oseltamivir or if age appropriate, inhaled zanamivir
(Recommendation, Grade B evidence)
 - ii. ≥ 1 yr old: illness of more than 48 hours' duration, treatment with oseltamivir or if age appropriate, inhaled zanamivir may be considered on a case-by-case basis. **(Option, Grade D evidence)**
 - iii. < 1 year of age: NAIs are currently not approved for the routine treatment of seasonal influenza illness.

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 **(Strong recommendation, Grade B evidence)**
- Treat with oseltamivir or zanamivir in appropriate doses (see Table 5)
- Oseltamivir or zanamivir should be started even though the window between symptom onset and initial administration of antiviral is longer than 48 hours. **(Recommendation, Grade C evidence)**
- Treatment with zanamivir instead of oseltamivir should be considered for
 - i) Those not responding to oseltamivir therapy, **(Recommendation, Grade C evidence)**
 - ii) Those with illness despite oseltamivir prophylaxis,
(Recommendation, Grade C evidence)

iii) Those with significant immunosuppression, **(Option, Grade D evidence)**

- Although oseltamivir was approved temporarily for use in infants under 1 year of age on the basis of a favourable risk-to-benefit ratio during the recent 2009 H1N1 pandemic, its use in this population for seasonal influenza should be handled on a case-by-case basis, based on severity of illness. **(Option, Grade D)**

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. **(Option, Grade D 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 proven or suspect 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 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 for treatment recommendations of adults and children with renal impairment as a risk factor.

H. Treatment of pregnant women

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 pandemic. **(Strong recommendation, Grade C evidence)**

VI. CHEMOPROPHYLAXIS VERSUS EARLY THERAPY

Antiviral prophylaxis with NAIs has been demonstrated to be efficacious and well tolerated. Three chemoprophylactic strategies were detailed in our previous guideline:² (i) Seasonal prophylaxis including bridging prophylaxis to protect individuals for two weeks after receipt of inactivated injectable influenza vaccine until vaccine-induced immunity developed, (ii) post-exposure prophylaxis (PEP) or contact exposure and (iii) outbreak control. Antiviral chemoprophylaxis is recommended only in very selected circumstances, including bridging prophylaxis for individuals as in (i) or (iii) above, to control outbreaks in nursing homes and other long-term care facilities that house patients at high risk of influenza complications.¹² In this latter situation it should be initiated concurrently with inactivated influenza vaccine administered

parenterally. Zanamivir does not interfere with the hemagglutination antibody response to injected vaccine.⁸⁵ 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 their immunogenicity.

In the above context, in the appropriate setting, PEP is an efficacious strategy when initiated in the first 48 hours after exposure to an infectious ill contact. Contacts are considered infectious for the interval beginning 24 hours before illness onset until the time fever ends. However, it is recommended that the strategy of early treatment be used as an alternative to PEP because of reports of oseltamivir resistance arising during PEP. Early presumptive therapy with treatment doses of oseltamivir or zanamivir twice daily (versus once daily as recommended for PEP) initiated after exposure to an infectious contact even before symptoms begin may be appropriate for situations where influenza infection appears prevalent and persons at very high risk of influenza complications are exposed.¹²

For less vulnerable contacts, an early treatment strategy entailing counseling about early symptoms and signs of influenza combined with advice that they seek treatment immediately if influenza-like illness develops is appropriate. Such contacts could be provided a prescription they could fill so as to have medication on hand for early initiation of therapy, if they become symptomatic.

Recommendations for Antiviral Prophylaxis

- Early therapy is preferred over routine pre-exposure prophylaxis
(Recommendation, Grade D evidence).
- An early treatment strategy should involve counseling together with arrangements for contacts to have medication on hand. **(Option, Grade D evidence)**
- Some experts recommend the selective use of pre-exposure prophylaxis 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)⁸⁶ 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**)

An algorithm for prophylaxis is provided as Appendix D.

- Post-exposure prophylaxis may be considered in family settings for persons who cannot be reliably protected by immunization (e.g., age less than 6 months, immunocompromised or vaccine contraindicated). (**Option, Grade D evidence**)

- To control outbreaks in nursing homes and other long-term care facilities among patients at high risk of acquiring infection due to their housing arrangements and of incurring influenza complications, antiviral drug prophylaxis, combined with treatment and inactivated vaccine administration, is indicated. **(Strong Recommendation, Grade C 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 hours after fever ends
 - If > 4 days have elapsed since the last infectious contact**(Option, Grade D evidence)**

ACKNOWLEDGEMENTS

The authors thank the Public Health Agency of Canada, in particular, Dr. Barbara Raymond, Centre for Immunization & Respiratory Infectious Diseases, Sharon Smith, Pandemic Preparedness Division, Centre for Immunization and Respiratory Infectious Disease and Dr. Ken Scott, Federal Co-Chair of the Antiviral Scientific Advisory Group for their support.

We acknowledge the critical review of this document by the PHAC Antiviral Scientific Advisory Group and the Infectious Diseases and Immunization Committee of the Canadian Paediatric Society and its review and endorsement by the AMMI Canada Guidelines Committee.

The authors also extend appreciation to Ms. Angela Nelson for her excellent secretarial assistance.

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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: Hoffman La Roche Inc.; Advisory Board: Hoffman La Roche Inc.

Dr. Gerald A. Evans: Research: Biocryst Inc.

Table 1. GRADE Evidence Quality vs. Benefit to Harm Ratio and Recommendation Grading³

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

Table 2.¹² Susceptibility of influenza viruses to oseltamivir, zanamivir and amantadine as of December, 2010

	Oseltamivir	Zanamivir	Amantadine
pH1N1	S	S	R
Seasonal H1N1 (prepandemic)	R	S	S
Seasonal A H3N2	S	S	R
Influenza B	S	S	R

S = susceptible; R = resistant

Table 3. 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)
<p>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</p>
Children and Youth (>3 to < 12 years and 12-18 years, respectively)
<p>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</p>

Table 4. At-risk groups and co-morbid medical conditions that predispose to severe influenza (Adapted from 16,17)

- 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
- Chronic liver disease
- 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 $< 200 \times 10^6/L$), or iatrogenic, due to medication
- Certain rheumatologic diseases such as rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, antiphospholipid syndrome, scleroderma, spondyloarthropathies, Sjogren's syndrome, dermatomyositis, vasculitis, sarcoidosis, polyarteritis nodosa
- 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 2 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 2 weeks post partum regardless of how the pregnancy ended
- Individuals < 18 years of age who are on chronic aspirin therapy
- Morbid obesity ($BMI \geq 40$)
- First Nations, Inuit and Metis Canadians

* Children who are 2 years through 4 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 2 years

Table 5. Oseltamivir and zanamivir regimens adapted from:
<http://www.cdc.gov/h1n1flu/recommendation.htm>²⁸

Medication		Treatment (5 days)	Chemoprophylaxis (10 days)
Oseltamivir¹			
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
*Please note that antivirals are not authorized for the routine treatment of seasonal influenza illness in infants less than 1 year of age.			
Zanamivir⁴			
Adults			
		10 mg (two 5-mg inhalations) twice daily	10 mg (two 5-mg inhalations) once daily
Children (≥7 years or older for treatment, ≥7 years for chemoprophylaxis)			
		10 mg (two 5-mg inhalations) twice daily	10 mg (two 5-mg inhalations) once daily
<p>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 12 mg/mL. If the commercially manufactured oral suspension is</p>			

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 (final concentration 15 mg/mL).

When dispensing commercially manufactured Oseltamivir (TAMIFLU) Powder for Oral Suspension (12 mg/mL), pharmacists should ensure the units of measure on the prescription instructions match the dosing device. Prescribers should watch out for any changes in drug concentration in Canadian supplies of oseltamivir, as in the USA, the concentration of the oseltamivir suspension has been changed to 6 mg/mL.

2. Weight-based dosing is preferred. However, if weight is not known, dosing by age for treatment (give two doses per day) or prophylaxis (give one dose per day) of influenza in full-term infants younger than 1 year of age may be necessary: 0-3 months (treatment only) = 12 mg (1 mL of 12 mg/mL commercial suspension); 3-5 months = 20 mg once daily (1.6 mL of 12 mg/mL of commercial suspension), 6-11 months = 25 mg (2 mL of 12 mg/mL commercial suspension) once daily).
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. These data are insufficient to recommend a specific dose of oseltamivir for premature infants.
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.

Table 6. Selected surrogate indices of immunocompromised states

Laboratory-based Indices	Clinical States	Treatment-related Indices
<p style="text-align: center;">Significant Risk</p> <ul style="list-style-type: none"> • Severe neutropenia (ANC < 0.5 x 10⁹/L), and/or, • Severe lymphopenia (ALC < 0.5 x 10⁹/L) 	<p style="text-align: center;">Significant but Variable Risk Due to Heterogeneity in Clinical States</p> <ul style="list-style-type: none"> • 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. 	<p style="text-align: center;">Significant but Variable Risk Due to Heterogeneity in Nature and Intensity of Treatments</p> <p>A history of ongoing myelosuppressive and/or immunosuppressive therapies such as:</p> <ul style="list-style-type: none"> • 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**
<p>*Examples of cytotoxic therapy include, but are not limited to: (e.g., <i>anthracyclines</i> such as doxorubicin or epirubicin; <i>purine analogues</i> such as azathiapriner, thioguanine, mercaptopurine, fludarabine, pentostatin, or cladribine; <i>pyrimidine analogues</i> such as flurorouracil, cytarabine, capecitabine, or gemcitabine; <i>anti-folate agents</i> such as methotrexate or premetrexed; <i>alkylating agents</i> such as the nitrogen mustards (cyclophosphamide or ifosphamide), nitrosoureas (carmustine, lomustine, semustine, streptozotocin), and platinum analogues (cis-platin, carboplatin, or oxaliplatin); <i>taxanes</i> (e.g., docetaxel, paclitaxel);</p>	<p>**Examples of immunomodulator therapy include, but are not limited to: <i>Calcineurin inhibitors</i> (e.g., cyclosporine, tacrolimus, sirolimus), <i>Guanine synthesis inhibitors</i> (e.g., Mycophenolate mofetil), <i>Anti-B lymphocyte therapy</i> (e.g., rituximab), <i>Anti-T lymphocyte therapy</i> (e.g., anti-thymocyte globulin or anti-CD3), <i>Anti-B and T cell therapy</i> (e.g., alemtuzumab, basiliximab, daclizumab), <i>Anti-TNF therapy</i> (e.g., infliximab or etanercept), Alpha-interferon therapy</p>	

<i>topoisomerase I inhibitors</i> (e.g., irinotecan).	
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Adapted from: Allen U, Doucette K, Bow E, in reference 62

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

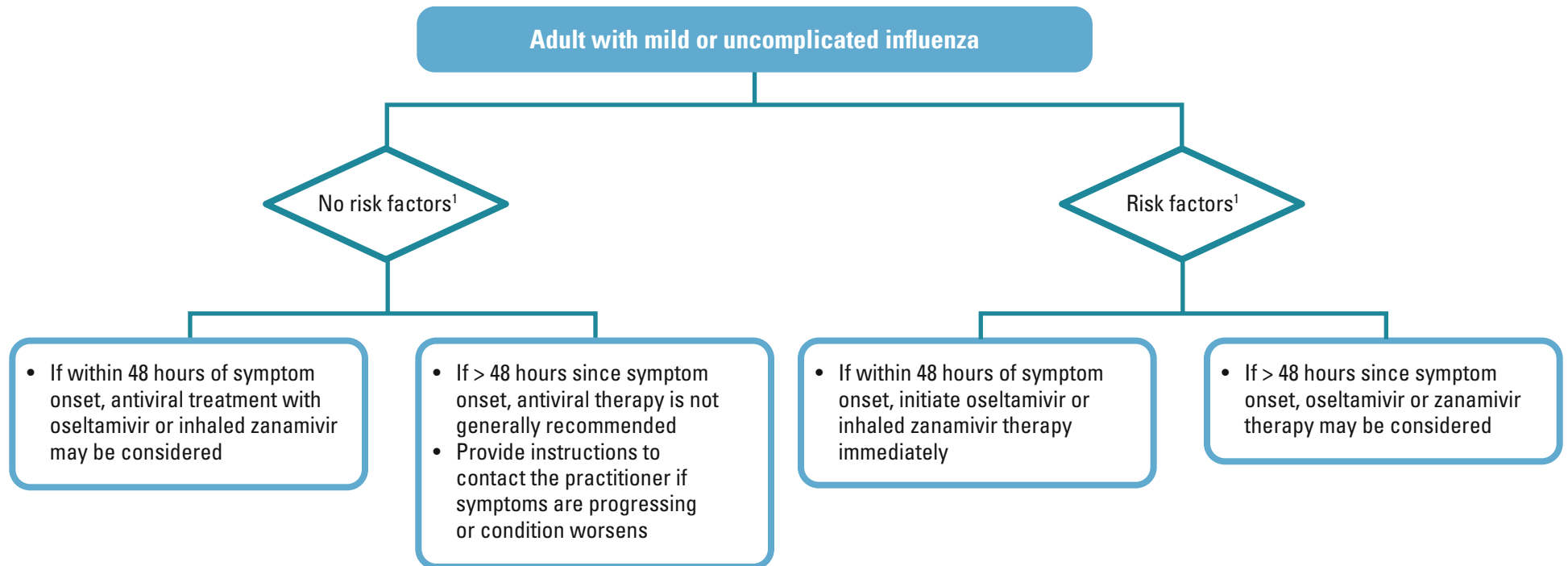
Table 7. Recommended oseltamivir regimens for treatment of adults* with renal impairment or failure

Creatinine clearance	Treatment
>30mL/min	75mg twice daily
>10–30mL/min	75mg once daily OR 30mg suspension twice daily OR 30mg capsule twice daily
≤10mL/min (renal failure)**	Single 75mg dose for the duration of illness
Dialysis patients**	Low-flux HD: 30mg after alternate dialysis sessions High-flux HD: 75mg after each dialysis session CAPD dialysis: 30mg once weekly CRRT high-flux dialysis: 30mg daily or 75mg q48hrs

*For doses for infants and children, consult with your local infectious diseases physician or clinical pharmacist

**Experience with the use of oseltamivir in patients with renal failure is limited, however these regimens have been suggested based on the limited available data^{73,74}

> Algorithm for oseltamivir and zanamivir treatment of mild or uncomplicated influenza in adults—December 2011 *From: The Use of Antiviral Drugs for Influenza: Guidance for Practitioners 2011-2012*



¹

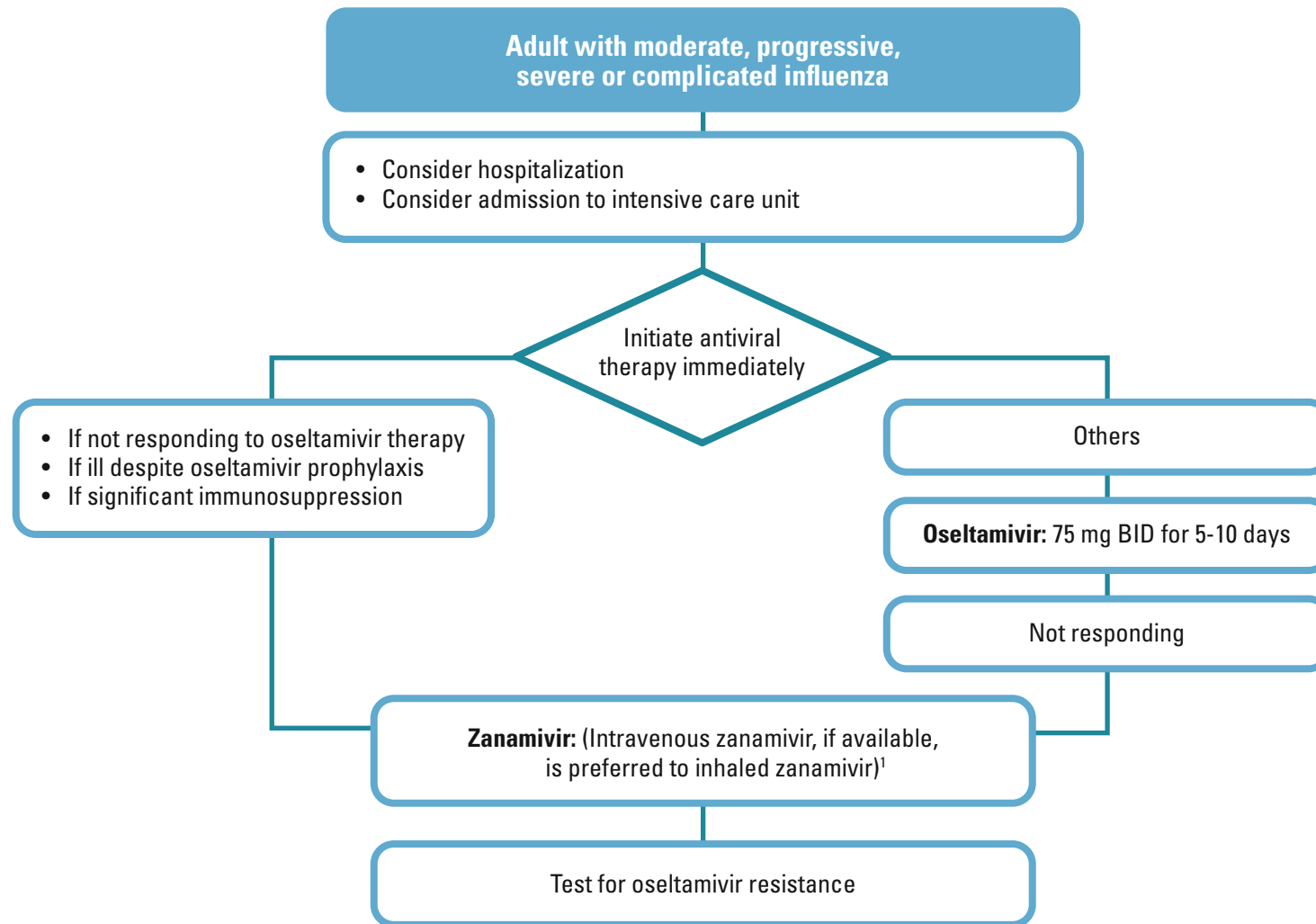
- Asthma and other chronic pulmonary disease, including bronchopulmonary dysplasia, cystic fibrosis, chronic bronchitis and emphysema
- Cardiovascular disease (excluding isolated hypertension; including congenital and acquired heart disease such as congestive heart failure and symptomatic coronary artery disease)
- Malignancy
- Chronic renal insufficiency
- Chronic liver disease
- Diabetes mellitus and other metabolic diseases

- Hemoglobinopathies such as sickle cell disease
- Immunosuppression or immunodeficiency due to disease (e.g. HIV infection, especially if CD4 is < 200 x 10⁶/L), or iatrogenic, due to medication
- Certain rheumatologic diseases such as rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, antiphospholipid syndrome, scleroderma, spondyloarthropathies, Sjogren's syndrome, dermatomyositis, vasculitis, sarcoidosis, polyarteritis nodosa
- 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 2 years of age (Children who are 2 years through 4 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 2 years)
- 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 2 weeks post partum regardless of how the pregnancy ended
- Individuals < 18 years of age who are on chronic aspirin therapy
- Morbid obesity (BMI > 40)
- First Nations, Inuit and Metis Canadians

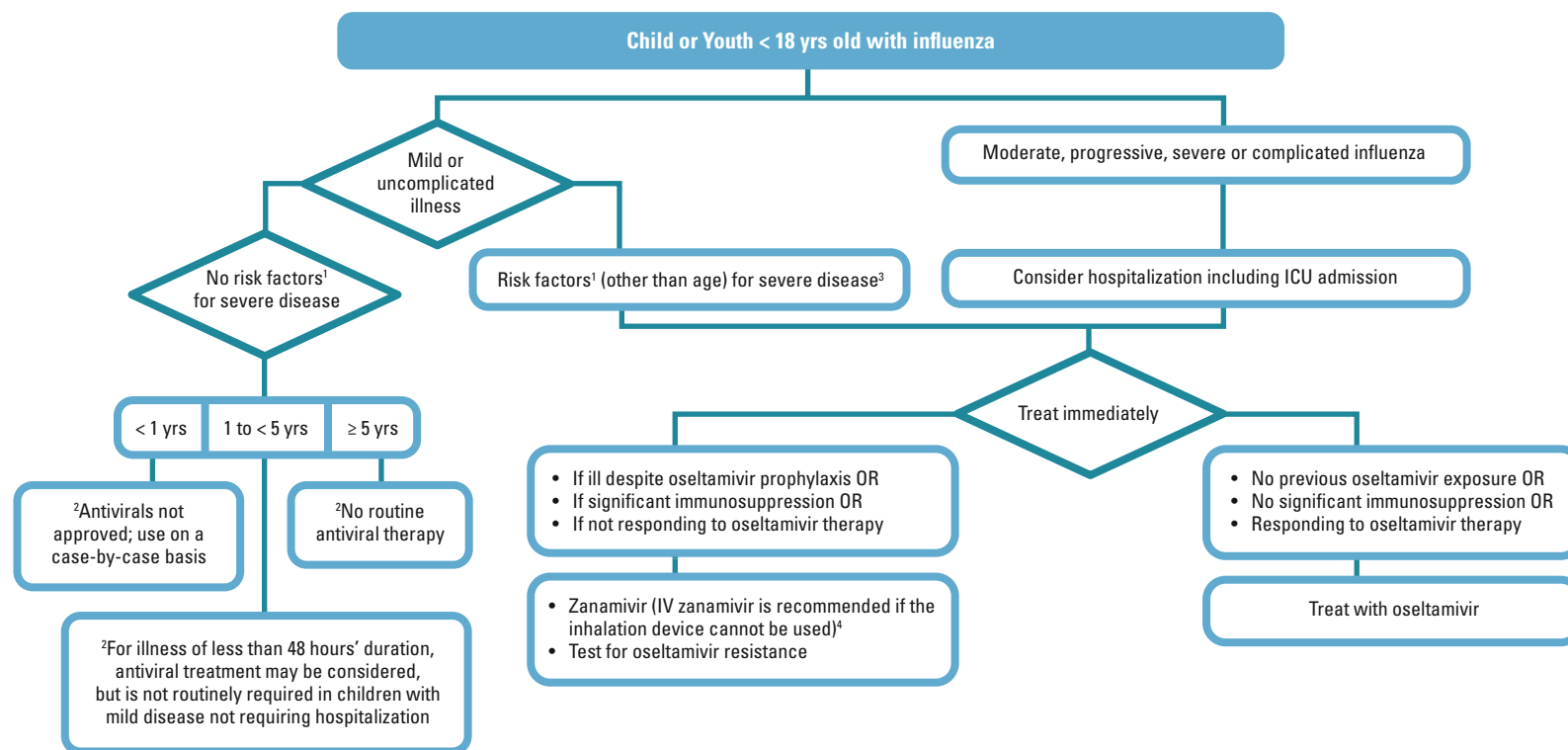
> Algorithm for oseltamivir and zanamivir treatment of moderate, progressive, severe or complicated influenza in adults—December 2011

From: *The Use of Antiviral Drugs for Influenza: Guidance for Practitioners 2011-2012*



¹ *Inhaled zanamivir cannot be administered via ventilator*

> Algorithm for oseltamivir and zanamivir treatment of influenza in children and youth (< 18 yrs old)—December 2011 *From: The Use of Antiviral Drugs for Influenza: Guidance for Practitioners 2011-2012*



¹ • 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
• Chronic liver disease
• Diabetes mellitus and other metabolic disease

• Hemoglobinopathies such as sickle cell diseases
• Immunosuppression or immunodeficiency due to disease (e.g. HIV infection, especially if CD4 is < 200 x 10⁹/L), or iatrogenic, due to medication
• Certain rheumatologic diseases such as rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, antiphospholipid syndrome, scleroderma, spondyloarthropathies, Sjogren's syndrome, dermatomyositis, vasculitis, sarcoidosis, polyarteritis nodosa
• Neurologic disease and neurodevelopmental disorders that compromise handling of respiratory secretions (cognitive dysfunction, spinal cord injury, seizure disorders, neuromuscular disorders, cerebral palsy, metabolic disorders)

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• Pregnant women and women up to 2 weeks post partum regardless of how the pregnancy ended
• Individuals < 18 years of age who are on chronic aspirin therapy
• Morbid obesity (BMI > 40)
• First Nations, Inuit and Metis Canadians

² In the above scenarios in those with mild or uncomplicated illness, treatment is not routinely recommended if ill for > 48 hrs.

³ If ill for more than 48 hours, treatment may be considered on a case-by-case basis for children ≥ 1 year of age (antivirals not approved for infants < 1 year of age).

⁴ Inhaled zanamivir cannot be administered via ventilator.

> Algorithm for oseltamivir and zanamivir treatment of influenza in children and youth (< 18 yrs old)—December 2011 *From: The Use of Antiviral Drugs for Influenza: Guidance for Practitioners 2011-2012*

Oseltamivir and zanamivir regimens adapted from: <http://www.cdc.gov/h1n1flu/recommendation.htm>

Medication		Treatment (5 days)	Chemoprophylaxis (10 days)
Oseltamivir¹			
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 months²			
		3 mg/kg/dose twice daily	3 mg/kg/dose once per day
Children < 3 months³			
		3 mg/kg/dose twice daily	Not recommended unless situation judged critical due to limited data on use in this age group
*Please note that antivirals are not approved for the routine treatment of seasonal influenza illness in infants less than 1 year of age.			
Zanamivir⁴			
Adults			
		10 mg (two 5-mg inhalations) twice daily	10 mg (two 5-mg inhalations) once daily
Children (≥7 years or older for treatment, ≥7 years for chemoprophylaxis)			
		10 mg (two 5-mg inhalations) twice daily	10 mg (two 5-mg inhalations) once daily

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 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 (final concentration 15 mg/mL).

When dispensing commercially manufactured Oseltamivir (TAMIFLU) Powder for Oral Suspension (12 mg/mL), pharmacists should ensure the units of measure on the prescription instructions match the dosing device. Prescribers should watch out for any changes in drug concentration in Canadian supplies of oseltamivir, as in the USA, the concentration of the oseltamivir suspension has been changed to 6 mg/mL.

² Weight-based dosing is preferred. However, if weight is not known, dosing by age for treatment (give two doses per day) or prophylaxis (give one dose per day) of influenza in full-term infants younger than 1 year of age may be necessary:

- 0-3 months (treatment only) = 12 mg (1 mL of 12 mg/mL commercial suspension);
- 3-5 months = 20 mg once daily (1.6 mL of 12 mg/mL of commercial suspension),
- 6-11 months = 25 mg (2 mL of 12 mg/mL commercial suspension) once daily.

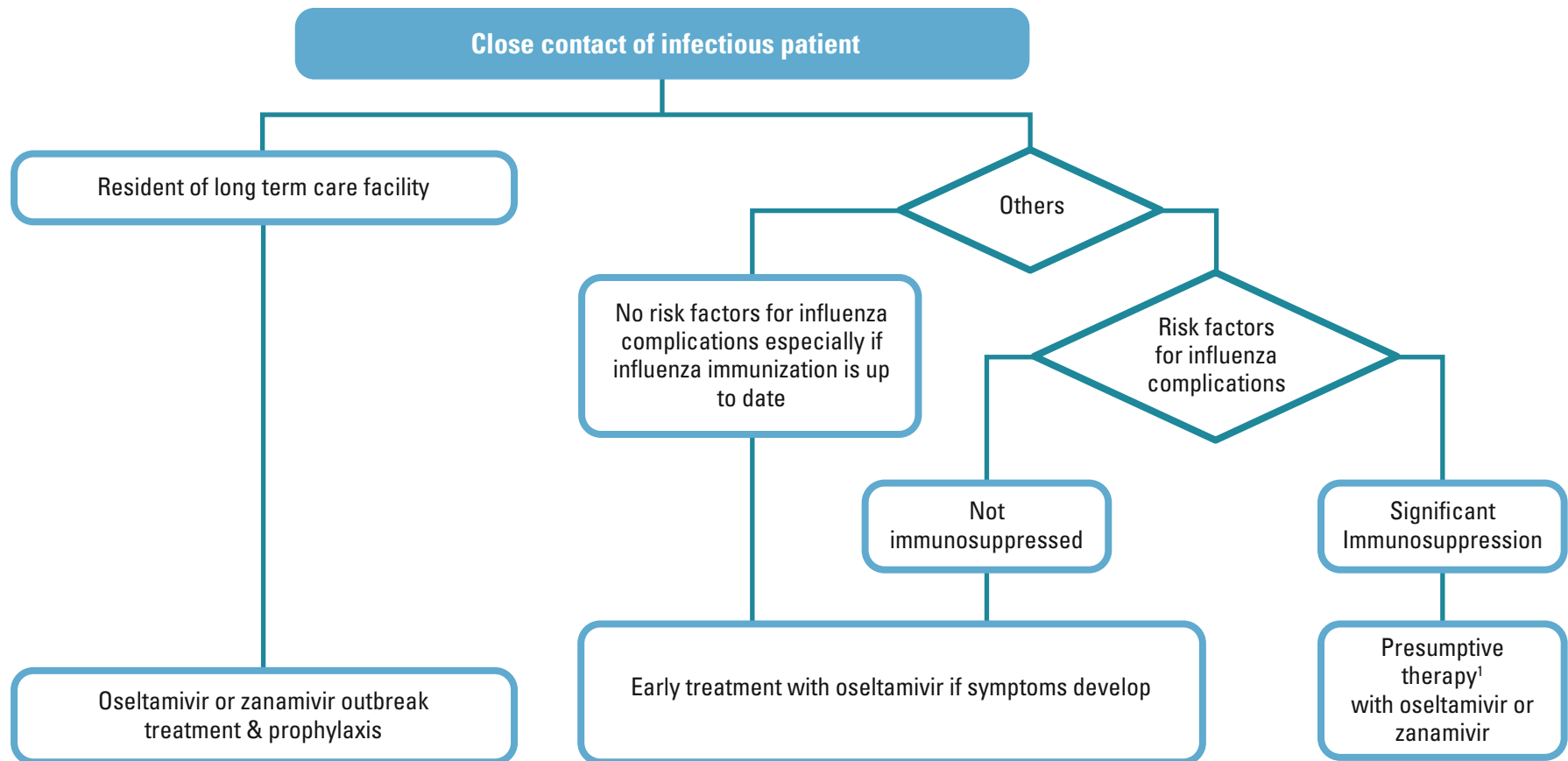
³ Current weight-based dosing recommendations are not intended for premature infants. Premature infants may have slower clearance of oseltamivir due to immature renal function, and doses recommended for full term infants may lead to very high drug concentrations in this age group. Very limited data from 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. These data are insufficient to recommend a specific dose of oseltamivir for premature infants.

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.

<http://www.ammi.ca/guidelines>

> Algorithm for oseltamivir and zanamivir prophylaxis or early therapy in close contacts of infectious patients—December 2011

From: *The Use of Antiviral Drugs for Influenza: Guidance for Practitioners 2011-2012*



¹ Presumptive treatment is therapy with twice daily doses of oseltamivir or zanamivir initiated before the onset of influenza symptoms in close contacts of individuals with suspected or proved influenza illness

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