AMMI CANADA GUIDELINE

Use of antiviral drugs for seasonal influenza: Foundation document for practitioners—Update 2019

Fred Y Aoki MD[1], Upton D Allen MBBS[2,3,4], Samira Mubareka MD[5], Jesse Papenburg MD[6,7], H Grant Stiver MD[8], Gerald A Evans MD[9]

This document updates the previous AMMI Canada Foundation Guidance (2013) on the use of antiviral therapy for influenza.

KEYWORDS: influenza, guidelines, antivirals

Le présent document est une mise à jour des précédentes directives d'AMMI Canada (2013) sur l'utilisation des antiviraux contre la grippe.

MOTS-CLÉS : grippe, directives, antiviraux

[1]Medical Microbiology and Pharmacology & Therapeutics, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba; [2]Department of Pediatrics, University of Toronto, Toronto, Ontario; [3]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario; [4]Division of Infectious Diseases, Department of Pediatrics, Hospital for Sick Children, Toronto, Ontario; [5]Department of Laboratory Medicine and Molecular Diagnostics, Sunnybrook Health Sciences Centre, and Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Ontario; [6]Division of Pediatric Infectious Diseases, Department of Pediatrics, Montreal Children's Hospital, McGill University Health Centre, Montréal, Québec; [7]Division of Microbiology, Department of Clinical Laboratory Medicine, Montreal Children's Hospital, McGill University Health Centre, Montréal, Québec; [8]Division of Infectious Diseases, Department of Medicine, University of British Columbia, Vancouver, British Columbia; [9]Division of Infectious Diseases, Department of Medicine, Kingston Health Sciences Centre, Queen's University, Kingston, Ontario

Correspondence: Gerald A Evans, Division of Infectious Diseases, Department of Medicine, Queen's University, Room 3013, Etherington Hall, 98 Stuart Street, Kingston, Ontario K7L 2V6. Telephone: 613-533-6619. E-mail: evansg@queensu.ca

I. PURPOSE

The purpose of this document is to provide information for clinicians on the use of antiviral drugs for the prevention and treatment of seasonal influenza. It is provided as a foundation document that, with supplements to be published as needed to describe new developments, is intended to replace the 2013 foundation document (1). This document focuses on the use of antiviral drugs for seasonal, not pandemic, influenza.

As of August 2018, three antiviral drugs are licensed in Canada for the treatment and prophylaxis of influenza: amantadine (oral) and two neuraminidase inhibitors (NAIs), oseltamivir (oral) and zanamivir (dry powder for inhalation). The efficacy and safety of these agents has been demonstrated in randomized, placebo-controlled trials with largely healthy ambulatory adults and children with relatively mild seasonal influenza, but the clinical importance of prescribing antiviral drugs for influenza on the basis of these data has been the subject of some controversy (2). However, in high-risk patients with seasonal (or pandemic) influenza, both oral oseltamivir and inhaled zanamivir may reduce hospitalization, and oseltamivir may reduce mortality (3). Limited data from studies in which the effectiveness of oseltamivir and zanamivir were directly compared in individuals with seasonal influenza do not suggest a clear advantage of either agent (see section IV.B).

Other antiviral drugs are licensed internationally, but not in Canada, including intravenous peramivir (licensed in the United States and other countries), inhaled laninamivir (licensed in Japan), oral favipiravir (licensed in Japan), and oral baloxavir marboxil (licensed in Japan and the United States). These four agents may be accessed via Health Canada's Special Access Program.

Recently circulating seasonal influenza A viruses (A[H1N1], A[H3N2]) show a high rate of resistance to amantadine; therefore,

the subsequent discussion is limited to the NAI drugs. 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 on the basis of the quality of the evidence and the determination of benefit versus harm arising from the recommendation (4). In situations for which high-quality evidence is not available but the 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: The benefits of the treatment approach clearly exceed the harms; quality of evidence is high (Grade A), moderate (Grade B), or exceptional (Grade X).

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

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

No recommendation: Pertinent evidence is lacking or quality is very low, and the balance between benefits and harms is unclear.

Impact of recommendation strength on practising 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 clinician's judgment. Patient preference should play a substantially influential 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 substantially influential role.

III. THE DISEASE

A. Influenza viruses

The influenza strains that 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, influenza vaccine composition from NACI, and antiviral resistance from the CDC (5–7).

B. Clinical aspects

Seasonal influenza viruses share similar clinical features. The influenza virus is transmitted from infected to susceptible persons by droplets. The relative contributions of small particle aerosols and fomites in transmission are uncertain, although emission of infectious virus in fine particles with airborne potential by humans has been demonstrated (8). The basic reproductive number (mean number of secondary cases

Table 1: GRADE evidence quality versus recommendation grading and benefit-to-harm ratio (4)

Quality of evidence	Preponderance of benefit or harm	Balance of benefit and harm
A: Well-designed RCTs or diagnostic studies of 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 in which validating studies cannot be done, and the preponderance of benefit or harm is clear	Strong recommendation / Recommendation	

GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCT = randomized controlled trial

transmitted by a single index case to susceptible contacts) is 1.28 (interquartile range 1.19 to 1.37), and the median incubation period of seasonal influenza A illness is 1.4 days (95% C 1.3 to 1.5 d) (9,10).

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 5–7 days, although it is commonly accepted that some persons, particularly young children and immunocompromised persons, may shed virus for longer periods (11). For the 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.

Infection due to influenza virus can be asymptomatic or range from mild, uncomplicated, and self-limited to the upper respiratory tract to a serious complicated illness dominated by exacerbation of a comorbid, underlying medical condition or to severe viral or bacterial pneumonia with or without multiple organ failure (12).

In adults, influenza typically begins with fever; respiratory symptoms such as a cough or sore throat; and systemic symptoms, such as myalgia, arthralgia, and headache. Gastrointestinal symptoms, notably diarrhea, have more commonly been described as manifestations of seasonal influenza A in children than in adults (13,14).

Although older children and adolescents show the typical clinical features of influenza illness, among those aged younger than 10 years, the clinical features may be atypical. Indeed, among children aged younger than 5 years, 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 aged younger than 6 months are more likely to present with rhinorrhea and dehydration than with cough and pneumonia, and among those aged younger than 3 months, fever alone or fever with dehydration are common presenting features (11). Diarrheal illness may be observed. Some clinical signs in infants, children, and youth warrant urgent medical attention. Familiarity with these signs is advised (Box 1).

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 may develop several days after illness onset. The epidemiology of bacterial co-infections associated with seasonal influenza remains difficult to assess, although data from recent pandemics suggest there is regional variation and that rates of co-infection may be as high as 44% of influenza cases. *Streptococcus pneumoniae* and methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* co-infection can be associated with fulminant pneumonia (12,15,16). Clinicians should be aware of this potential complication, particularly in immune-compromised patients and in critical care settings. 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%–38% of cases (12).

Box 1: 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

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 clinical presentation (due to secondary bacterial infection); and neurological complications (17). The latter include febrile seizures, status epilepticus, encephalitis or 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 Box 2, which is adapted from the Canadian National Advisory Committee on Immunization (12,13,19).

Box 2: At-risk groups and comorbid medical conditions that predispose individuals to severe influenza (adapted from 12,13,19)

- 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 CD4 is $< 200 \times 10^6$/L) or iatrogenic, due to medication
- Neurological disease and neurodevelopmental disorders that compromise handling of respiratory secretions (cognitive dysfunction, spinal cord injury, seizure disorders, neuromuscular disorders, cerebral palsy, metabolic disorders)
- Children aged younger than 5 years*
- Individuals aged 65 years 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 postpartum regardless of how the pregnancy ended†
- Individuals aged younger than 18 years who are on chronic aspirin therapy
- Obesity with a BMI ≥40 or a BMI >3 z-scores above the mean for age and gender
- Children and adolescents (age 6 months–18 years) undergoing treatment for long periods with acetylsalicylic acid because of the potential increase in Reye's syndrome associated with influenza
- Indigenous peoples

** Children aged 2–4 years also have a higher rate of complications than older children; however, the risk for these children is lower than the risk for children aged younger than 2 years*

† The risk of influenza-related hospitalization increases with length of gestation; ie, it is higher in the third trimester than in the second

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 temperature 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% (20). However, among non-immunized healthy young 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) is predictive of influenza confirmed by laboratory testing in 60%–71% of cases (20–22). Among immunized patients aged 60 years and older, the combination of fever, coughing, and acute onset has a predictive value of 44% for laboratory-confirmed diagnosis of influenza (23). Conversely, the absence of fever and cough has been shown to reliably exclude a diagnosis of influenza in patients attending an emergency department (24).

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 (25). The common presenting findings of fever, cough, and rhinorrhea do not distinguish influenza illness from illness due to other respiratory viruses, especially among children aged younger than 4 years. 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, comorbid conditions, and immunocompetence.

IV. TREATMENT OF INFLUENZA ILLNESS

A. NAIs

NAIs competitively bind the influenza virus neuraminidase (NA) active site, thus impeding sialidase activity and virus release from cells. NAIs differ in their side chains, affecting bioavailability and NA active site binding. For both zanamivir and oseltamivir, we describe some uses that exceed the authorizations provided by Health Canada, as outlined in the Canadian product monographs (26,27).

1. Oseltamivir

The NAI drug oseltamivir (Tamiflu®) is authorized by Health Canada for the treatment of uncomplicated influenza A and B in patients aged 1 year or older who have been symptomatic for no more than 2 days. Oseltamivir is also authorized in Canada for the prevention of influenza A and B in adults and children aged 1 year and older who are in close contact with an individual with characteristic symptoms of influenza. In the United States, oseltamivir is approved for the treatment of influenza in infants aged 2 weeks or older (28).

Oseltamivir is formulated as oseltamivir phosphate in capsules containing 30, 45, or 75 mg per capsule or as a suspension containing 6 mg/mL. Intravenous oseltamivir is no longer available in Canada. Oseltamivir phosphate is well absorbed after ingestion or after administration via gastric tube to critically ill, ventilated patients (29). After absorption, it is extensively converted by hepatic and intestinal epithelial cell esterases 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 (28).

Influenza B viruses are approximately 10- to 20-fold less susceptible to oseltamivir carboxylate than are influenza A viruses, and these in vitro differences may explain the lesser efficacy of oseltamivir for treatment of influenza B virus infections than influenza A virus infections (30–32).

Treatment and prophylaxis regimens of oseltamivir and zanamivir for adults and for children by age and weight are detailed in Table 2 (33,34). Doses do not need to be adjusted in obese adults, elderly persons, or people with mild or moderate hepatic impairment (26,33). Dose reduction is advised for pharmacokinetic reasons in persons with creatinine clearance

Table 2: Oseltamivir and zanamivir treatment of influenza

Medication	Treatment (5 days)	Chemoprophylaxis (10 days)*
Oseltamivir†		
Adults and adolescents aged ≥13 y	75 mg twice daily	75 mg once daily
Children aged ≥12 mo–12 y, body weight (kg/lb)		
≤15/≤33	30 mg twice daily	30 mg once daily
>15–23/>33–51	45 mg twice daily	45 mg once daily
>23–40/>51–88	60 mg twice daily	60 mg once daily
>40 kg/>88	75 mg twice daily	75 mg once daily
Children aged 3 mo to <12 mo*	3 mg/kg twice daily	3 mg/kg once daily
Children aged <3 mo‡	3 mg/kg twice daily	Not recommended unless situation judged critical because of the limited data on use in this age group
Zanamivir§		
Adults and children aged ≥7 y	10 mg twice daily (two 5 mg inhalations)	10 mg (two 5 mg inhalations) once daily

Note: Treatment regimens are adapted from (28,51)

* *Safety has been demonstrated for up to 12 weeks in immunocompromised patients (21)*

† *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 6 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. Please note that antivirals are not authorized in Canada for the routine treatment of seasonal influenza illness in infants aged younger than 1 year. Such use may be considered on a case-by-case basis*

‡ *Please note that antivirals are not authorized in Canada for the routine treatment of seasonal influenza illness in infants aged younger than 1 year. Such use may be considered on a case-by-case basis*

§ *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*

of less than 60 mL/min, although the drug has a wide margin of safety and causes no serious, dose-related adverse effects. Doses for patients with impaired renal function are detailed in Table 3 (35–38).

In adults, oral oseltamivir is generally well tolerated. Mild, rapidly reversible nausea and vomiting have been observed among approximately 5%–10% more persons taking oseltamivir than taking placebo. Nausea and vomiting are more common among young adults taking 150 mg twice daily (12%–15%) than taking 75 mg twice daily (8%–11%) or placebo (3%–7%) (27). No other side effects occurred significantly more frequently among oseltamivir than placebo recipients. Influenza A and B viruses rarely cause central nervous system (CNS) symptoms, including convulsions and coma (39). A causal relationship between oseltamivir and such adverse effects or a wider spectrum including delirium with hallucinations has not been definitively established (40). Close monitoring of treated patients is advised (31).

For adults with seasonal influenza of less than 36 hours duration, there appears to be no advantage to combining oseltamivir and zanamivir (41). The administration of higher doses of oseltamivir to patients with seasonal influenza is not supported by available data (42). A randomized comparison of a standard versus a double dose of oseltamivir for treatment of ambulatory patients with seasonal influenza A and B illness indicated that the higher dose caused more adverse events but offered no benefit over the standard dose, although the study was limited by a small sample size (41).

For children, data on the safety and efficacy of oseltamivir exist for those aged 1 year and older (43). 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 (44). A liquid formulation was shown in a randomized placebo-controlled trial to be safe and well accepted by healthy children aged 1–12 years and children with asthma aged 6–12 years (42). Emesis occurred in 14.3% of children receiving

Table 3: Recommended oseltamivir regimens for prevention and treatment of patients with renal impairment (25,34–37)

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	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 at the time of onset of influenza symptoms, then 30 mg after each dialysis session	30 mg before dialysis, then 30 mg after alternate dialysis sessions
	High-flux HD: 75 mg after each dialysis session	No data
	CAPD dialysis: 30 mg once before the start of dialysis	30 mg before dialysis, then 30 mg once weekly
	CRRT high-flux dialysis: 30 mg daily or 75 mg every second day	No data
<10 mL/min (renal failure)*	Single 75 mg dose for the duration of illness	No data

The following dosing regimen has been suggested for children on the basis of limited data:

In children aged older than 1 year, 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

Although this may provide a framework for guidance, it is strongly suggested that an infectious disease physician or clinical pharmacist be consulted.

* *Experience with the use of oseltamivir in patients with renal failure is limited. These regimens have been suggested on the basis of the limited available data and the manufacturer's recommendation (*21,23,31–33*). Consultation with an infectious disease physician or clinical pharmacist is recommended*

CAPD = continuous automated peritoneal dialysis; CRRT = continuous renal replacement therapy; HD = hemodialysis

oseltamivir 2 mg/kg twice per day for 10 doses (maximum 100 mg/dose) and 8.5% receiving placebo. Discontinuation rates because of adverse events were not different—1.8% and 1.1%, respectively, for the treatment and placebo arms (42).

The safety and efficacy of oseltamivir in infants aged younger than 1 year have not been established. This is clearly an area in which additional research is needed. A caution was issued as a result of deaths observed in 7-day-old mice receiving extremely high doses of the drug (45). The mice were fed a dose that was about 250 times the dose recommended for children. The concentrations of the pro-drug in the brain were 1,500 times those of 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. On the basis of the animals' age and the stage of the development of their blood–brain barrier, the human equivalent was felt to be infants aged younger than 1 year. However, recent reports from Japan have not shown CNS toxicity in infants aged younger than 1 year who were treated with oseltamivir.

In November 2005, adverse neuropsychiatric events and deaths were reported among Japanese children receiving oseltamivir. The US Food and Drug Administration reviewed the available information and concluded that the increased reports of neuropsychiatric events among Japanese children were most likely related to an increased awareness of influenza-associated encephalopathy, increased access to oseltamivir among that population, and a coincident period of intensive monitoring for adverse events (46). They were not able to conclude that a causal relationship existed between oseltamivir and pediatric deaths. Analyses of neuropsychiatric events among patients with influenza in three large US administrative databases and a recent report from Japan arrived at the same conclusion (47–50).

Drug interactions during co-administration of oseltamivir are unlikely because drug interactions involving competition for esterases have not been extensively reported. Oseltamivir carboxylate is eliminated largely unchanged in the urine by glomerular filtration and renal tubular secretion by an anionic transporter and does not cause dose-related adverse effects even at high doses (28). The manufacturer states in the product monograph that oseltamivir food and herb interactions have not been established (25).

2. Zanamivir

Zanamivir (Relenza®) is authorized by Health Canada for the treatment of uncomplicated influenza A and B in patients aged 7 years or older who have been symptomatic for no more than 2 days. It is also authorized for the prevention of influenza A and B in patients aged 7 years or older. Inhaled zanamivir is not generally recommended for treatment of patients with severe underlying airway disease because of the risk of serious adverse events, including bronchospasm, decline in respiratory function, and respiratory arrest, and because efficacy has not been demonstrated in this population (26).

In vitro influenza A and B viruses exhibit similar susceptibility to zanamivir (28). In observational studies of children and young adults with influenza A or B virus infection treated with either oseltamivir or zanamivir, no difference was found between treatments in duration of fever among children aged 4–16 years (30). However, in older children and adults (mean age 15 [SD 12] y) with influenza B virus infection, the duration of fever was significantly less in individuals treated with zanamivir versus oseltamivir (32). In a small observational study that directly compared the efficacy of zanamivir in ill persons of unspecified age with influenza A or influenza B virus infection, no differences in duration of fever were observed (51). 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 (52). Approximately 80% of an inhaled dose is deposited onto the upper respiratory tract lining, and 13% is deposited in the bronchi and lungs, where it exerts its antiviral effect. Approximately 10%–20% of inhaled drug is absorbed and eliminated unchanged in 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 were treated with zanamivir Diskhaler powder in water, administered by nebulizer and resulting in bronchospasm and obstruction of ventilator filters (53). Intravenous zanamivir is not available in Canada.

Although practitioners are advised to beware of bronchospasm in zanamivir-treated patients, one study of index-case family members who inhaled zanamivir once daily as prophylaxis found no increase in asthma exacerbations in asthmatic contacts receiving zanamivir (6%) versus placebo (11%; 54,55). Another double-blind placebo-controlled trial of zanamivir treatment of influenza in patients aged 12–88 years (median 38 y) with asthma or chronic obstructive pulmonary disease (COPD) did not find an increased incidence of bronchospasm in the zanamivir group (56). In fact, the morning and evening peak expiratory flow rates were significantly increased in the zanamivir group (57).

Despite these data, there have been reports of acute bronchospasm in patients taking zanamivir, so the Advisory Committee on Immunization Practices of the US CDC advised caution in using zanamivir with patients with asthma or COPD and advised that these patients should have a short-acting bronchodilator available during treatment. Drug interactions between zanamivir and other drugs co-administered

systemically are neither likely nor expected because of the minimal absorption of zanamivir after oral inhalation (51).

3. Combination therapy

The clinical utility of combination therapy for treating influenza remains uncertain. The effects of combined treatment with oseltamivir and zanamivir in patients with seasonal influenza have been studied in two controlled trials. In adults with seasonal influenza due mainly to A(H3N2), combined oseltamivir–zanamivir treatment appeared less effective than oseltamivir monotherapy and not significantly more effective than zanamivir monotherapy (40). Nausea and vomiting tended to be more frequent in the combination arm (40). In the other controlled trial, combined treatment of index cases in households with standard doses of oseltamivir plus zanamivir appeared to be more efficacious than either oseltamivir and zanamivir monotherapy for reduction of secondary household cases of influenza, but only in a subgroups analysis (58). Combined treatment with 500 mg clarithromycin, 200 mg naproxen, and 75 mg oseltamivir twice daily for 2 days, followed by 75 mg oseltamivir alone twice daily for 3 days among hospitalized patients in an open-label randomized study reduced 30- and 90-day mortality more than oseltamivir alone (59). This study has not yet been replicated, so its results remain to be confirmed. A Cochrane review was not able to determine whether a corticosteroid should be recommended concomitantly or in combination with antiviral therapy for seasonal influenza (60).

Overall, the available data do not yet support a strong recommendation for combining standard doses of oseltamivir and zanamivir for treatment of adults with seasonal influenza and, in particular, individuals with high-risk conditions.

Resistance of influenza A or B viruses to oseltamivir and zanamivir arises uncommonly during therapy or prophylaxis in immunocompetent individuals (28,51). After the introduction of NAI drugs in the 1990s, resistance first became prevalent in 2007 when the seasonal A(H1N1) virus was supplanted by an oseltamivir-resistant A(H1N1) strain with resistance mediated by a H275Y mutation in the enzymatic cleft on the NA enzyme, seemingly in the absence of widespread global oseltamivir use or pressure. In 2009, this A(H1N1) oseltamivir-resistant virus was displaced by the oseltamivir-sensitive A(H1N1)pdm09 virus. After the pandemic ended, this virus persisted as the current seasonal A(H1N1) virus. In A(H3N2) and influenza B strains, oseltamivir resistance levels have remained low since its introduction, and zanamivir resistance has rarely been identified even in treated immunocompromised patients. In immunocompromised patients with influenza treated with oseltamivir, resistance to it has developed frequently and relatively early during therapy with resulting treatment failure.

Recent data on NAI resistance are available. NAI resistance has been uncommon. In the 2017–2018 US influenza season in the United States, the CDC reported 1.0% (11 of 1,147) A(H1N1)pdm09 isolates were resistant to oseltamivir and none were resistant to zanamivir or peramivir. None of 2,354 A(H3N2) isolates and 1,118 influenza B isolates were resistant to any of the three NAI drugs (61). In the 2017–2018 Canadian influenza season, all but 8 of 1,607 A(H3N2) isolates and all 325 A(H1N1)pdm09 isolates were resistant to amantadine. Of 596 A(H3N2) isolates, 1 was resistant to oseltamivir; of 277 A(H1N1)pdm09 isolates, 1 was resistant to oseltamivir (H275Y mutation), as was 1 of 878 influenza B isolates. All 592 A(H3N2) and 277 A(H1N1)pdm09 isolates were sensitive to zanamivir; 2 of 878 influenza B isolates were resistant by genotypic testing (personal communication with Y Li, PhD, Canadian National Microbiology Laboratory, August 1, 2018).

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 because of influenza A viruses, in otherwise healthy children aged older than 1 year and adults (2,62). A meta-analysis concluded that these drugs seemed to reduce total influenza-related complications but could not distinguish between mild and serious complications (63). NAIs have been shown to reduce the frequency of otitis media as a complication of influenza in pediatric patients (61). NAI treatment of hospitalized patients with seasonal influenza may reduce the duration of hospitalization and mortality (64).

Clinical trials have demonstrated differences in effectiveness of oseltamivir and zanamivir in patients with influenza A or B virus infection. In observational studies, oseltamivir has been more effective for the treatment of influenza A than influenza B virus infection among children and adults (33,65). Inhaled zanamivir is equally efficacious for treatment of both influenza A and B virus infections (51,66). When compared directly in patients with influenza A virus infection, oseltamivir was found to be both more effective than zanamivir or not different (31,41). In patients with influenza B virus infection, zanamivir was found to be both more effective than oseltamivir and not more effective (30,31). Thus, there are no consistent efficacy results to support selection of oseltamivir in preference to zanamivir or vice versa.

Inasmuch as a number of respiratory tract viral pathogens can cause an influenza-like illness, anti-influenza drug therapy will invariably result in the treatment of some persons whose influenza-like illness is not due to influenza virus. At present, no data suggest that such treatment is ecologically harmful. Because 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 comorbid medical conditions
3. Interval between onset of illness and initiation of antiviral therapy
4. Likely influenza types 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 (67):

- *Mild or uncomplicated illness*—characterized by typical symptoms such as 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, and sometimes diarrhea and vomiting but no shortness of breath and little change in chronic health conditions
- *Moderate or progressive illness*—characterized by typical symptoms plus signs or symptoms suggesting more than mild illness: chest pain, poor oxygenation (e.g., tachypnea, hypoxia, laboured 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, COPD, chronic renal failure, diabetes, or cardiovascular disease)
- *Severe or complicated illness*—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 3 days).

2. Presence of risk factors or comorbid medical conditions

Patients with risk factors such as age, ethnicity, or a comorbid medical condition have been identified as being at greater risk for complications of influenza on the basis of extensive experience during seasonal influenza outbreaks and recent experience during the A(H1N1)pdm09 pandemic (see Box 2).

Notwithstanding the association of the aforementioned medical conditions as risk factors for severe influenza, 20%–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.

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 only in shortening symptom duration. Optimal benefits are obtained if treatment is initiated as early as possible after the onset of symptoms (61,68). Thus, starting treatment within 12 hours of illness onset should be a practice goal.

4. Likely influenza types 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 2009–2010, the predominant influenza viruses have been sensitive to NAIs; however, it is important to maintain awareness in case oseltamivir-resistant seasonal influenza viruses reappear.

D. Treatment of children

Although some aspects of influenza prevention and treatment in adults can be extrapolated to children, there are several areas in which special pediatric considerations are necessary. In general, fewer data are available to guide the management of care for children, most notably young infants, than are available for adults.

The incidence of seasonal influenza in healthy children ranges from 10% to 40% each year, but low rates (e.g., 3%) have been reported, presumably based on which strain of influenza virus is circulating. Roughly half of all fatalities are among previously healthy children (13,69). During community outbreaks of seasonal influenza, the highest attack rates occur among 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 before 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 (65,70).

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; 66).

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 as many as 50% of reported influenza-related hospitalizations and deaths. Influenza B has been identified in a disproportionate number of pediatric seasonal influenza-associated deaths (33%–62%; 71).

Children at the highest risk of adverse outcomes from influenza illness include those aged younger than 5 years (72). Hospitalizations occur more frequently among those aged younger than 2 years than among older children, with the highest hospitalization rates being among those aged younger than 6 months (13). This does not necessarily translate into a recommendation to use antiviral therapy in those aged younger than 2 years (see Section V).

Among the currently available antiviral agents, three are approved for use with children in Canada: amantadine (which is not currently useful because of resistance) for influenza A, and oseltamivir and zanamivir for influenza A and B. Clinical trials supporting the use of NIs in children have been summarized in a systematic review (73).

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%) (74). 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 more than 24 hours after the onset of symptoms (75). No benefit was demonstrated for patients with influenza B, although the number of children with influenza B was small compared with the number of those with influenza A (19,72,76). A benefit of reducing asthma exacerbations among oseltamivir-treated children has also been demonstrated in a randomized controlled trial (77).

Since the earlier studies on NAIs, additional studies have been reported or are in progress, and experience with the use of NAIs has increased (78–80). However, there exists a relative paucity of new data from randomized trials with infants and young children. The role of NAIs with children has been the subject of recent meta-analyses (61,70). 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 (70). A recent meta-analysis involving individual patient data from published and unpublished studies indicates that early treatment with oseltamivir significantly reduced the duration of illness by 17.6 to 29.9 hours in children with influenza and lowered their risk of developing otitis media by 34% (81).

Studies have provided valuable safety data as well as data on the use of oseltamivir with premature newborns (82,83). In the United States, oseltamivir is approved for the prevention of influenza in patients aged 1 year and older and for the treatment of acute uncomplicated influenza in patients aged 2 weeks and older who have been symptomatic for no more than 2 days (27). Although oseltamivir was temporarily approved for use in infants aged younger than 1 year on the basis of a favourable risk-to-benefit ratio during the 2009 H1N1 pandemic, antivirals are not currently authorized in Canada for the treatment of seasonal influenza in infants aged younger than 1 year, 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 aged younger than 1 year vary within a reasonably narrow range and have been updated for seasonal influenza (84–86). Current dosing recommendations are shown in Table 2, but clinicians should be aware of possible dose changes as more information becomes available for young infants.

The benefit of inhalational zanamivir for children aged at least 7 years was demonstrated in a double-blind, randomized, placebo-controlled trial (87). Its impact on secondary complications such as otitis media and antibiotic usage was not demonstrated in this trial. A recent systematic review of treatment studies using zanamivir in children and adults evaluated 737 children aged 5–12 years. Although no significant treatment benefit was found, we should note that the analysis included children who were symptomatic but did not have laboratory-proven influenza illness (88).

E. Treatment of immunocompromised patients

This group includes individuals with a wide range of congenital and acquired immunodeficiencies. The heterogeneity of populations of immunocompromised patients is well recognized, resulting in varying degrees of risk for adverse outcomes from influenza illness. In this context, Table 4 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 (89). The presence of these markers suggests increased risk for the acquisition of infection, progression to more severe and potentially

life-threatening consequences of infection, and an impaired ability to develop immunity to infection after subsequent exposure to influenza virus (86).

In addition to the well-recognized variability in the clinical manifestations of influenza illness, atypical clinical features may be present in immunocompromised individuals. For example, immunocompromised individuals may present with fever as the sole manifestation of influenza illness, or they may present with respiratory symptoms without fever (90,91).

The complications seen among persons with a normal immune system may also be seen in immunocompromised patients. Invasive secondary bacterial infections caused by *S. pneumoniae*, *S. aureus*, *Streptococcus pyogenes*, and other bacterial pathogens may occur and can be devastating for the immunocompromised patients.

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 (92,93). This persistent shedding may be accompanied by periodic exacerbations of illness (89,90). Cell-mediated immunity is important in mediating protection from influenza illness, viral clearance, and recovery from illness (94–98). 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 (91,92). The risk for immunocompromised persons is compounded if they have comorbid medical conditions 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 because of differences in the nature and intensity of their immunosuppressive therapies (99,100).

Table 4: Selected surrogate indices of immunocompromised states

Laboratory-based indices	Clinical states	Treatment-related indices
Significant risk: • Severe neutropenia ANC < 0.5×10^9/L) • Severe lymphopenia (ALC < 0.5×10^9/L)	Significant but variable risk due to heterogeneity in clinical states: • Individuals with malignancies receiving active cytotoxicchemotherapy • Acute leukaemia patients • HSCT recipients • SOT recipients (e.g., lung, heart, kidney) • Individuals with congenital immunodeficiency states • Individuals with acquired immunodeficiency states (e.g., HIV, plasma cell dyscrasias, B-lymphocyte malignancies) • Individuals with rheumatic diseases or autoimmune disorders (e.g., RA or SLE) • Individuals with GI diseases (e.g., IBD) receiving immunosuppressive drugs • Individuals on renal dialysis • Individuals with asthma or COPD receiving corticosteroid therapy	Significant but variable risk due to heterogeneity in nature and intensity of treatments, such as a history of ongoing myelosuppressive or immunosuppressive therapies, such as: • Corticosteroid therapy (70) (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 (71), ≥2 mg/kg per day of prednisone or its equivalent or ≥20 mg/d if they weigh more than 10 kg. administered for 14 days or more) • Cytotoxic therapy* • Immunomodulator therapies†

Note: Adapted from Allen, Doucette, and Bow (89)

* *Examples of cytotoxic therapy include but are not limited to 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); and 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), and alpha-interferon therapy*

ALC = absolute lymphocyte count; ANC = absolute neutrophil count; COPD = chronic obstructive airways disease; GI = gastrointestinal; HSCT = haematopoietic stem cell transplant; IBD = inflammatory bowel disease; RA = rheumatoid arthritis; SLE = systemic lupus erythematosis; SOT = solid organ transplant; TNF = tumour necrosis factor

The importance of early treatment of influenza illness in immunocompromised patients (e.g., organ transplant recipients) is well documented, as summarized in a recent prospective multicentre study over 4 consecutive years (101). 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 for influenza in immunocompromised patients (97). Antiviral resistance should be considered if there is a lack of response to antiviral therapy, especially when antiviral administration is recent. Accordingly, practitioners should consult with experts and be vigilant to 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 3. 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 (102). Moreover, the rates of hospitalization were comparable to those observed in individuals with other recognized comorbid conditions that increase the risk of influenza-related complications (99). As a result of such data, pregnancy is now recognized as a risk factor that underscores the need for annual influenza immunization. During the 2009 A(H1N1)pdm09 pandemic, not only were increased rates of hospitalization observed among healthy pregnant women, especially in the second and third trimester, but so too was an increased rate of death compared with that among non-pregnant women (103). Such excess mortality had previously been observed during the 1918 and 1957 pandemics. A recent meta-analysis demonstrated that women who were less than 4 weeks post-partum were at the greatest risk of death (104). New evidence indicates that a significant increase in stillbirths, premature deliveries, and infant mortality occurs among women who have influenza in the third trimester (105).

Oseltamivir pharmacokinetics in pregnant women with influenza are not different from one trimester to another (106). These observations support the recommendation to treat influenza in pregnant women in all trimesters and, perhaps, up to 4 weeks postpartum, with oseltamivir in standard doses as soon as possible after the onset of influenza-like symptoms (107). Oseltamivir is excreted in breast milk at low concentrations (108). The clinical importance of this observation is not yet known.

Oseltamivir and zanamivir are listed by the Food and Drug Administration 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 pregnant women or fetuses have been observed as a result of treatment with oseltamivir during pregnancy (109,110).

Some authorities recommend oseltamivir in preference to zanamivir during pregnancy because it is systemically absorbed (111). 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 the 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 because the benefits of treatment are much greater with initiation at less than 12 hours than with initiation 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 X evidence**)
  ii. the illness is progressive, severe, or complicated, regardless of previous health status (**Strong Recommendation, Grade X evidence**)
  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 hours 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 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 C 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 zanamivir is an option (**Option, Grade D evidence**)
- Zanamivir may be preferred to oseltamivir in the following situations:
  i. Patients not responding to oseltamivir therapy (**Recommendation, Grade D evidence**)
  ii. Patients with illness despite oseltamivir prophylaxis (**Recommendation, Grade D evidence**)
  iii. When influenza B is confirmed or strongly suspected (**Recommendation, Grade C 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 in Appendix A.

- For individuals with mild disease, no risk factors, and:
  - illness of less than 48 hours' duration, treatment with oseltamivir or inhaled zanamivir may be considered (**Option, Grade A evidence**)
  - illness of more than 48 hours' duration, antiviral treatment is not generally recommended (**Recommendation, Grade C evidence**).
- For individuals with mild disease, risk factors, and:
  - illness of less than 48 hours' duration, initiate oseltamivir or inhaled zanamivir therapy immediately (**Strong Recommendation, Grade X evidence**)
  - 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 in Appendix B.

- Consider hospitalization (**Recommendation, Grade C evidence**)
- Immediately initiate 75 mg oseltamivir twice daily orally or by nasogastric tube (**Recommendation, Grade C evidence**)
- Oseltamivir should be started even though the interval between symptom onset and initial administration of antiviral is longer than 48 hours (**Recommendation, Grade C evidence**)
- Treatment with zanamivir instead of oseltamivir may 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. when influenza B is confirmed or strongly suspected (**Option, Grade C evidence**).
- In the case of (i) and (ii), patients should also 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 in Appendix C.

- Mild disease, no risk factors other than age:
  i. *Aged younger than 1 year:* 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 aged younger than 6 months are not eligible for influenza vaccination, immunization of people in 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 pregnant women may also provide protection for infants during the first 6 months of life (**Option, Grade D evidence**).
  ii. *Aged 1 year to younger than 5 years:* Although children aged younger than 5 years are classified as a high-risk group (with those aged younger than 2 years at 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. *Aged 5 years 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**).
- Mild disease and risk factors other than age:
  i. *Aged younger than 1 year:* 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. *Aged 1 year and older:* for illness of less than 48 hours' duration, treatment with oseltamivir or, if age appropriate, inhaled zanamivir (**Recommendation, Grade B evidence**).
  iii. *Aged 1 year and older:* for 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**).

E. Treatment of infants, children, and youth with moderate, progressive, severe, or complicated influenza illness with or without risk factors

- Consider hospitalization (**Recommendation, Grade C evidence**).
- Start treatment immediately with oseltamivir or zanamivir (if age appropriate) in appropriate doses (see Table 2; **Strong Recommendation, Grade B evidence**).
- Oseltamivir or zanamivir should be started even if the interval 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. patients not responding to oseltamivir therapy (**Recommendation, Grade C evidence**)
  - ii. patients with illness despite oseltamivir prophylaxis (**Recommendation, Grade C evidence**)
  - iii. when influenza B is confirmed or strongly suspected (**Option, Grade C evidence**).
    - In circumstances (i) and (ii), the patient should also be tested for oseltamivir resistance, if possible.
- Although oseltamivir was approved temporarily for use in infants aged younger than 1 year on the basis of a favourable risk-to-benefit ratio during the recent 2009 H1N1 pandemic and is now authorized in the United States, it is not authorized in Canada for the routine treatment of seasonal influenza illness in infants aged younger than 1 year. 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

1. Immunocompromised individuals who have uncomplicated influenza illness are at risk of developing severe or complicated illness and should thus 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 beyond 10 days should be avoided among immunocompromised individuals, if possible, because of the potential for antiviral resistance (**Option, Grade D evidence**).
4. Early initiation of therapy for symptomatic infection among immunocompromised patients is preferred over post-exposure prophylaxis (112). In the setting of a defined, significant exposure (e.g., household contact or health care–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 in Section VI.ii) may be initiated before 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 Table 3 for treatment recommendations for adults and children with renal impairment as a risk factor.

H. Treatment of pregnant women

Oseltamivir in standard doses is recommended for treatment of women with influenza during pregnancy and up to 4 weeks post-partum on the basis of epidemiological data demonstrating an association between pregnancy and the immediate post-partum period and an increased risk of severe influenza combined with data demonstrating the extensive safe use of oseltamivir to treat such patients during the 2009 H1N1 pandemic (**Strong Recommendation, Grade C evidence**).

VI. CHEMOPROPHYLAXIS VERSUS EARLY THERAPY

Antiviral prophylaxis with NAIs has been demonstrated to be efficacious and well tolerated. We detailed three chemoprophylactic strategies in our previous publications (1,2): 1) seasonal prophylaxis, 2) post-exposure prophylaxis (PEP) or contact exposure, and 3) outbreak control. Chemoprophylaxis is recommended only in very select circumstances:

1. 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 clinical trial setting, the practicality and effectiveness of such seasonal prophylaxis in practice have not been established (113). 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*. This strategy should not be considered for individuals receiving live influenza vaccine (Flumist), which may interfere with its immunogenicity.

2. PEP is an efficacious strategy when initiated in the first 48 hours after exposure to a contact with suspected or lab-confirmed influenza. Contacts are considered infectious for the interval beginning 24 hours before illness onset until the time fever ends. However, it is recommended that the strategy of early treatment be used in place of PEP because of reports of oseltamivir resistance arising during PEP. Early presumptive therapy may be appropriate for situations in which influenza infection appears prevalent and persons at very high risk of influenza complications are exposed (71,81). 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.
3. 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 (101,114). Closed facilities include nursing homes and other long-term care facilities that house patients at high risk of influenza complications (100,112), as well as correctional institutions that pose special other risks and considerations with respect to influenza outbreaks because of their unique environment; these factors mandate consideration of the same measures for outbreak management in both (101,115). 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 (116). A similar lack of interference with oseltamivir would be expected. Nasal attenuated live influenza vaccine (Flumist) should not be used in these situations because 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 (112) (**Recommendation, Grade D evidence**)
- An early treatment strategy should involve counselling together with arrangements for contacts to have medication on hand (**Option, Grade D evidence**)
- The selective use of pre-exposure prophylaxis can be considered 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 when inactivated vaccine is used
  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 or quadrivalent 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 (does not include individuals with chicken or egg allergy) and who are likely to have ongoing close exposure to unimmunized persons at high risk, including infants and toddlers aged younger than 24 months (117).
- Early therapy is preferred over post-exposure prophylaxis because of concerns regarding drug resistance (**Option, Grade D evidence**)

An algorithm for prophylaxis is provided in Appendix D.

- Post-exposure prophylaxis may be considered in family settings for persons who cannot be reliably protected by immunization (eg, aged younger than 6 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 C evidence**)
- Neither early treatment nor PEP should be prescribed
  - for groups of healthy individuals on the basis of possible exposure in the community
  - if the close contact did not occur during the infectious period (from 1 day before the onset of symptoms until 24 hours after fever ends) of the person with suspected or confirmed influenza
  - if more than 4 days have elapsed since the last infectious contact. (**Option, Grade D evidence**).

ACKNOWLEDGEMENTS: The authors acknowledge the critical review of the parent version of this document by the Public Health Agency of Canada Antiviral Scientific Advisory Group and the Infectious Diseases & Immunization Committee of the Canadian Paediatric Society and its review and endorsement by the Association of Medical Microbiology and Infectious Disease Canada Guidelines Committee. The authors also extend appreciation to Ms Sheila Ang for secretarial assistance.

CONTRIBUTORS: Conceptualization, FYA, UDA, HGS, and GAE; Methodology, FYA, UDA, and GAE; Writing – Original Draft, FYA, UDA, HGS, GAE, SM, and JP; Writing – Review & Editing, FYA, UDA, HGS, GAE, SM, and JP. All authors approved the final draft.

FUNDING: No funding was received for this work.

DISCLOSURES: Upton D Allen reports research grants from Hoffmann La Roche Inc. H Grant Stiver reports honoraria from Hoffman La Roche Inc. and advisory board participation at Hoffman La Roche Inc. Jesse Papenburg reports honoraria from BD Diagnostics and Cepheid and research grants from BD Diagnostics, MedImmune, and Hoffman La Roche Inc.

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APPENDIX A

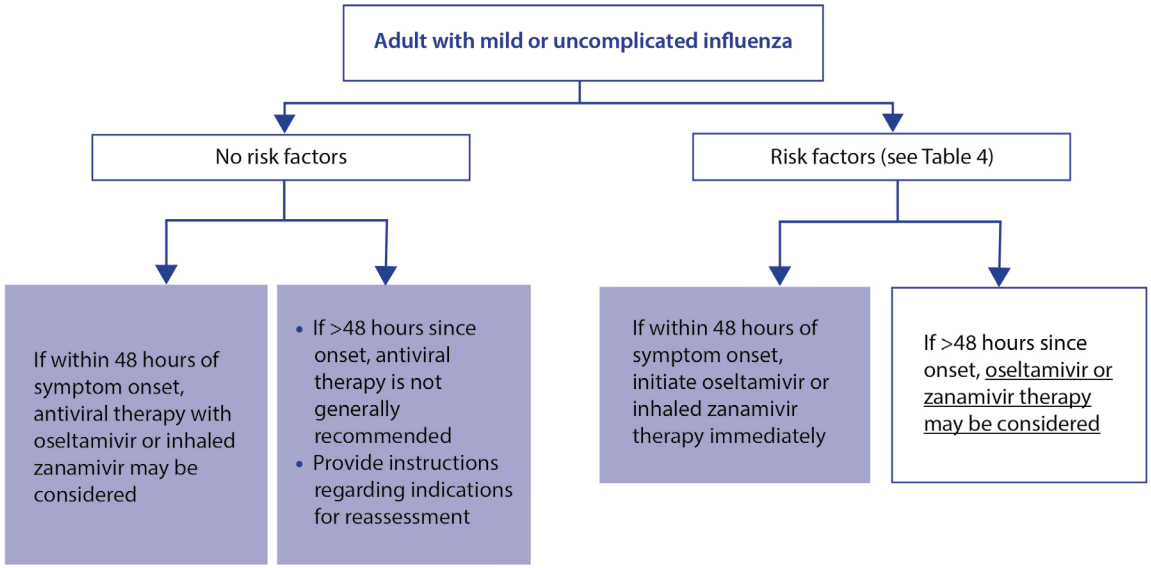

Figure A.1: Algorithm for oseltamivir and zanamivir treatment of mild or uncomplicated influenza in adults

APPENDIX B

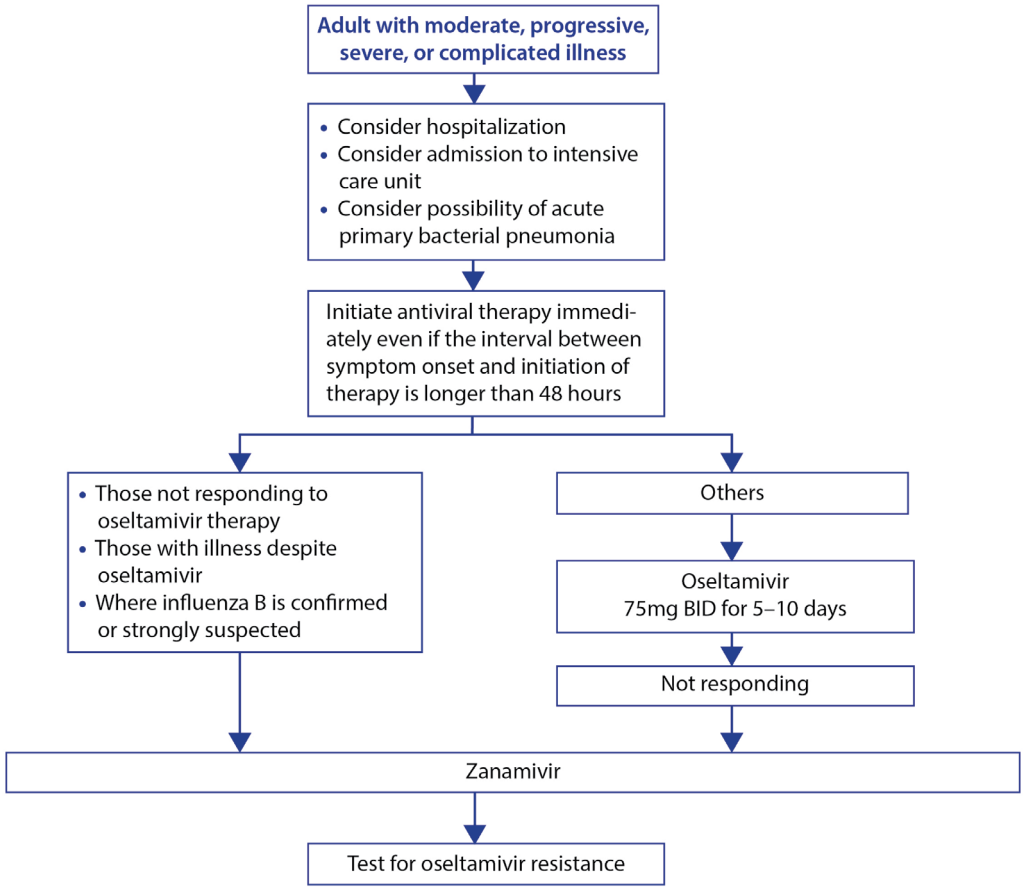

Figure B.1: Algorithm for oseltamivir and zanamivir treatment of moderate, progressive, severe, or complicated influenza in adults

APPENDIX C

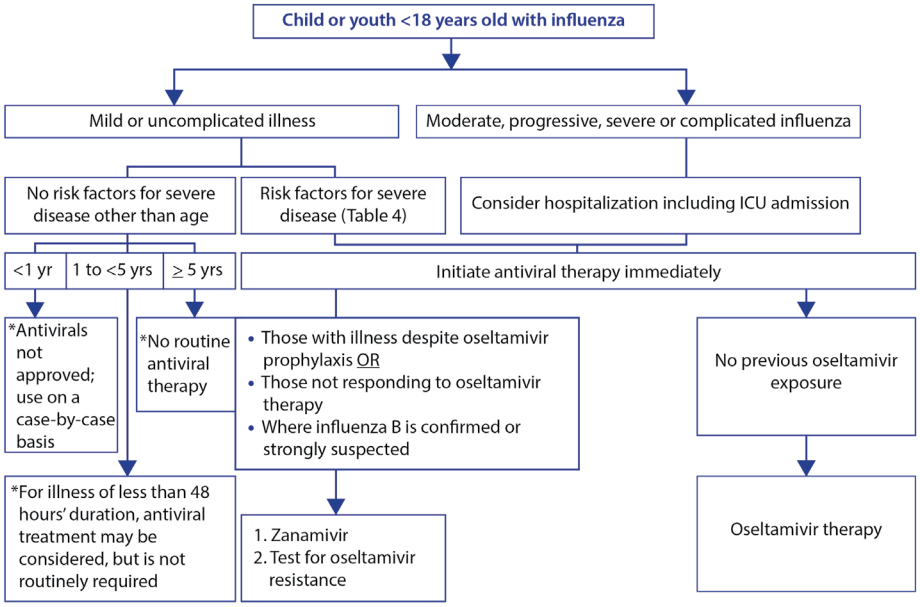

Figure C.1: Algorithm for oseltamivir and zanamivir treatment of influenza in children and youth (<18 y)

* *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 more than 48 hours. Treatment with oseltamivir or, if appropriate, zanamivir may be considered on a case-by-case basis even if symptoms have been present for more than 48 hours. In Canada, antivirals are not authorized for infants aged younger than 1 year but may be considered on a case-by-case basis. See Table 2, footnote 2*

APPENDIX D

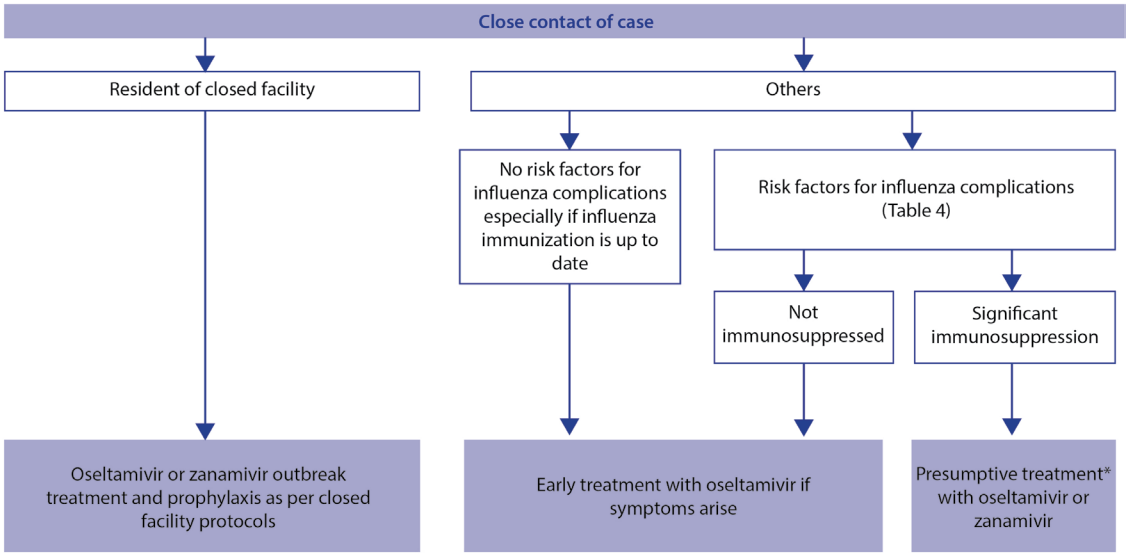

Figure D.1: Algorithm for oseltamivir and zanamivir prophylaxis or early treatment in close contacts of suspected or lab-confirmed cases

* *Presumptive treatment is therapy with twice-daily doses of oseltamivir or zanamivir initiated before the onset of influenza symptoms in close contact with an individual with suspected or lab-confirmed influenza illness*