

**BRITISH COLUMBIA CENTRE FOR DISEASE CONTROL (BCCDC):
INTERIM OPTIONS FOR CLINICIANS CONSIDERING INFLUENZA ANTIVIRALS
IN THE CONTEXT OF CHANGING PATTERNS OF RESISTANCE, 2008-09 SEASON**

These interim guidelines dated February 10, 2009 are based on evolving knowledge and up-to-date surveillance data for the 2008-09 influenza season, which suggest a high rate of oseltamivir resistance in A/H1N1 viruses and a continued high rate of amantadine resistance in A/H3N2 viruses. Health care providers considering the use of antivirals should consult surveillance updates to stay informed about influenza activity and antiviral resistance patterns in their area. The appropriate choice of antiviral options may change. Influenza antivirals should be used selectively and judiciously for appropriate clinical indications. Product monographs and other references should be consulted for detailed prescribing information[1-9].

A. BACKGROUND

1. General

In Canada, three antiviral medications are approved for the treatment and chemoprophylaxis of influenza: oseltamivir (Tamiflu[®]), zanamivir (Relenza[®]), and amantadine[1-4]. All require medical prescription. Oseltamivir and zanamivir are neuraminidase inhibitors; amantadine is an M2 ion channel inhibitor in the class of drugs known as adamantanes. Rimantadine is another adamantane approved in the United States but not approved for use in Canada. Oseltamivir and amantadine are oral medications whereas zanamivir is inhaled using a Diskhaler[®] device. Oseltamivir and zanamivir are options for both influenza A and B whereas amantadine is inherently ineffective against influenza B.

Until recently, **Oseltamivir** has been considered the preferred antiviral option for treatment or chemoprophylaxis of influenza among people one year of age and over. Oseltamivir is approved for treatment and post-exposure prophylaxis of influenza. It is also used off-label for pre-exposure prophylaxis in Canada[4]. In double-blind, placebo-controlled trials including children, young and elderly adults, the only adverse effect to occur significantly more often with oseltamivir compared to placebo was nausea or vomiting (2-17%) [7,10] These symptoms are generally mild, are mitigated by taking oseltamivir with food and cease on discontinuation of medication.

Zanamivir is an antiviral alternative to oseltamivir that is active against current influenza A/H1N1 (including oseltamivir-resistant viruses), A/H3N2, and influenza B. Zanamivir is approved in Canada for the treatment and chemoprophylaxis of people ≥ 7 years of age[4]. In the United States, zanamivir is approved for chemoprophylaxis indication as young as 5 years of age[5]. Zanamivir is approved for both post-exposure prophylaxis and for pre-exposure prophylaxis for up to 28 days duration in Canada; longer duration may also sometimes be warranted but would then be off-label[4]. Diskhaler[®] administration of zanamivir may be difficult in some groups such as the very old, young, or cognitively disabled[11]. No adverse effects have been significantly associated with zanamivir compared to placebo. There have been reports of bronchospasm in patients with underlying asthma/COPD taking zanamivir although clinical trials show no difference compared to placebo.

Amantadine is an antiviral alternative to oseltamivir that is active against current A/H1N1 strains but is no longer recommended for the treatment or prevention of influenza A/H3N2 due to high rates of amantadine resistance among circulating A/H3N2 viruses. Amantadine is not active against influenza B[4]. Careful dosing requirements apply to amantadine used in the elderly and those with renal conditions[6]. In otherwise healthy young adults given amantadine prophylactically, 5% to 10% report difficulty concentrating, insomnia, light-headedness, and irritability[6]. These side effects are usually mild and cease shortly after the prophylaxis is stopped; however, they occur more frequently in older populations unless a reduced dosage is used. Serious side effects (e.g. marked behavioural changes, delirium, hallucinations, agitation, seizures) have been associated with high plasma drug concentrations. These have been observed most often among those with renal insufficiency, seizure disorders, or certain psychiatric disorders, and among the elderly. Lower dosages for these people reduces the severity of such side effects[6].

2. Amantadine Resistance Patterns

During the 2007-08 season, 99% of the A/H3N2 isolates tested in Canada were resistant to amantadine whereas just 1% of the A/H1N1 isolates tested were amantadine resistant[4]. Since the start of the 2008-09 season (to February 5), the National Microbiology Laboratory (NML) has tested 72 influenza A isolates (40 A/H1N1 and 32 A/H3N2) for amantadine resistance. All of the A/H1N1 isolates were susceptible; however all of the A/H3N2 isolates were resistant to amantadine. The resistant isolates have come from Newfoundland, Quebec, Ontario, Saskatchewan, Alberta, British Columbia, and the Northwest Territories[12].

Resistance to amantadine emerges readily within days of starting treatment. Amantadine resistance is more likely to occur in semi-closed settings, such as within a family, facility, or institution (including nursing homes), where the drug is used for both prophylaxis and treatment, as opposed to prophylaxis alone. For this reason, simultaneous use of amantadine for prophylaxis and therapy within these settings is not advised. People in institutions treated with amantadine should be isolated from others until 2 days after treatment has ended. [6].

3. Neuraminidase Resistance Patterns

During the 2007-08 influenza season, oseltamivir resistance was first identified among circulating A/H1N1 viruses worldwide[4,13]. All oseltamivir-resistant strains were due to changes at position 274 in the viral neuraminidase gene (H274Y) – believed to be a spontaneous mutation conferring resistance[4,14]. The global proportion of oseltamivir-resistant A/H1N1 specimens among those tested increased from 16% during the northern hemisphere's 2007-08 season to 31% during the southern hemisphere's 2008 season[15]. In Canada, between August 26, 2007 and May 17, 2008, 481 influenza A/H1N1 isolates were tested for oseltamivir resistance by the NML and, of these, 125 (26%) were found to be resistant. All but one of the 125 oseltamivir resistant A/H1N1 viruses assessed in Canada during the 2007-08 season were sensitive to amantadine (>99%); the one virus isolate resistant to both oseltamivir and amantadine was from a person who was treated with both. Testing in the United States showed that all oseltamivir resistant A/H1N1 viruses assessed by the CDC for the 2007-08 season retained sensitivity to both zanamivir and amantadine[4,16].

During the 2008-09 season, to February 5, 2009, the NML has tested 146 influenza isolates (35 A/H1N1, 13 A/H3N2 & 98 B) for oseltamivir resistance[12]. All of the A/H3N2 and B isolates were sensitive to oseltamivir; however all of the thirty-five A/H1N1 isolates were resistant to oseltamivir due to the H274Y mutation. The thirty-five oseltamivir resistant A/H1N1 isolates came from Prince Edward Island, Nova Scotia, Ontario, Alberta, and British Columbia. All thirty-five A/H1N1 isolates that were oseltamivir-resistant were sensitive to amantadine. All 150 influenza isolates for the 2008-09 season to February 5 (39 A/H1N1, 13 A/H3N2 & 98 B) tested for zanamivir resistance have been found to be sensitive to zanamivir[9].

In addition, as of February 10, 2009, the **British Columbia** Centre for Disease Control (BCCDC) Virology laboratory has assessed 76 A/H1N1 viruses for the H274Y mutation denoting oseltamivir resistance using an innovative single nucleotide polymorphism (SNP) assay. Of these 76 A/H1N1 viruses assessed, 68 showed the oseltamivir resistance mutation (the other 8 are indeterminate and undergoing further characterization by sequence analysis of the neuraminidase gene)[12,17].

In the **United States** week 4 posting to FluView on February 6, 2009 indicates that, since October 1, 2008, 190 influenza A/H1N1, 41 influenza A/H3N2, and 77 influenza B viruses have been tested for antiviral resistance. Of the 190 A/H1N1 viruses assessed, 185 (97%) were oseltamivir-resistant, 2 (1%) were adamantane-resistant, and none was zanamivir-resistant. Of the 41 influenza A/H3N2 viruses assessed, all 41 were resistant to the adamantanes but all were sensitive to both oseltamivir and zanamivir[18].

In **Europe**, since week 40/2008 to February 4, 2009, of the 110 A/H1N1 virus isolates tested for resistance against neuraminidase inhibitors, 107 (97%) were oseltamivir-resistant, but all were sensitive to zanamivir and all of the 27 A/H1N1 viruses tested were sensitive to adamantanes. No antiviral resistance against neuraminidase inhibitors has been detected in the 138 A/H3N2 virus isolates tested so far this season in Europe. Of the 115 A/H3N2 isolates that were also tested for adamantane susceptibility, all 115 (100%) were resistant. All ten type B isolates tested were sensitive to both neuraminidase inhibitors [19].

B. INTERIM INFLUENZA ANTIVIRAL TREATMENT OPTIONS AS OF DECEMBER 28, 2008

Zanamivir, although difficult to use for some people, is active against all three human influenza types or subtypes (A/H3N2, A/H1N1, B). **Oseltamivir** is active against influenza A/H3N2 and B viruses but is not currently an effective option for A/H1N1 viruses. **Amantadine**, requiring dosage adjustment (most notably in the elderly and those with renal conditions) to minimize side effects, is active against A/H1N1 only.

Antivirals used for treatment of influenza are most beneficial when started within the first two days of illness. The effectiveness of antiviral options in reducing the duration and/or complications of influenza has been summarized in published reviews[7,8,20-25]. Data for safety and effectiveness are lacking for children less than one year of age. Treatment effectiveness data are not available for all antiviral options in all age or at-risk groups for all outcomes; more systematic evaluation is needed especially related to the benefit against serious outcomes for zanamivir and amantadine as antiviral alternatives. In the meantime, antivirals should be used selectively and judiciously for appropriate clinical indications, most notably for individuals with severe illness and those most likely to develop complications or die as a result of influenza[7].

Position papers of the Canadian Paediatric Society and Association of Medical Microbiology and Infectious Diseases (AMMI) Canada (<http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=18382639>) and the American Pediatric Society (<http://aappolicy.aappublications.org/cgi/reprint/pediatrics;119/4/852.pdf>) are readily available and valuable sources of information concerning influenza antivirals.

Choice of antiviral should be based on the type/sub-type of influenza (if known), predominant viruses circulating in the community, patient age and underlying health, anticipated antiviral benefits and adverse effects, ease of administration, contraindications/warnings/precautions and, ultimately, clinician judgment. Clinicians should consult package inserts and references for specific antiviral prescribing information[1-9].

C. DECIDING ON INFLUENZA ANTIVIRAL OPTIONS BASED ON SURVEILLANCE & TESTING

Health care providers considering influenza antivirals in the treatment of patients should take into account the following for the 2008-09 season (current to February 10, 2009):

- 1) **Vaccination** is the primary prevention strategy for influenza. In particular, note that the A/H1N1 component of the 2008-09 vaccine is a good antigenic match to current oseltamivir resistant A/H1N1 viruses. Pneumococcal vaccine for eligible persons will help prevent secondary complications. Cough etiquette, hand hygiene and limiting contact with others when ill, reduces respiratory virus transmission.
- 2) **Surveillance** for influenza antiviral resistance is ongoing in Canada. Clinicians should regularly review public health updates to determine the likelihood of type (A or B) or subtype-specific (A/H1N1, A/H3N2) influenza illness in their area. In BC, provincial influenza surveillance results are regularly updated and posted throughout the influenza season (<http://www.bccdc.org/content.php?item=35>) [17]. National profiles are posted at the FluWatch website (<http://www.phac-aspc.gc.ca/fluwatch/>) [12]. Clinicians should be alert for changes relevant to antiviral options throughout the season and consult public health as needed.
- 3) **Diagnostic test results**, and their availability, detail and timeliness:
 - a. **No influenza test results available (Figure A).**
 - b. **Rapid antigen, near patient or point-of-care (POC) testing (Figure B).**
 - i. Some rapid tests can distinguish between influenza A and B but do not provide subtype (A/H3N2 versus A/H1N1) detail. These tests can take 15 minutes to 2 hours and some can be used in the office setting.
 - ii. In general, the sensitivity of rapid tests is variable (median 70–75%) and lower than that of cell culture. Their median specificity is 90–95%. Test parameters may vary with age and other considerations.
 - iii. Because of concern related to false negative and false positive results (depending upon the stage of the season), diagnosis by rapid POC tests must be interpreted with caution and where indicated should be confirmed by direct immunofluorescence microscopy (DFA), cell culture or RT-PCR testing. Complete details regarding World Health Organization and CDC recommendations on the use of rapid influenza testing, including a review of kits, can be found at the websites in references [26,27].
 - c. **Laboratory confirmation with a diagnostic test capable of distinguishing influenza A/H1N1 versus A/H3N2 or B viruses with results available in a timely way (Figure C).**
 - i. Local availability/timeliness, either routinely or at special request, should be explored by interested clinicians.
- 4) **Chemoprophylaxis** may be warranted in some people [1-9]. Choice of antiviral should similarly be guided by the above considerations. Facility guidelines for institutional outbreak control have been separately provided to local public health authorities. Consult local public health as needed.

Figure A: No Influenza Test Results Available but Clinical Suspicion of Influenza and Indication for Treatment are Strong¹

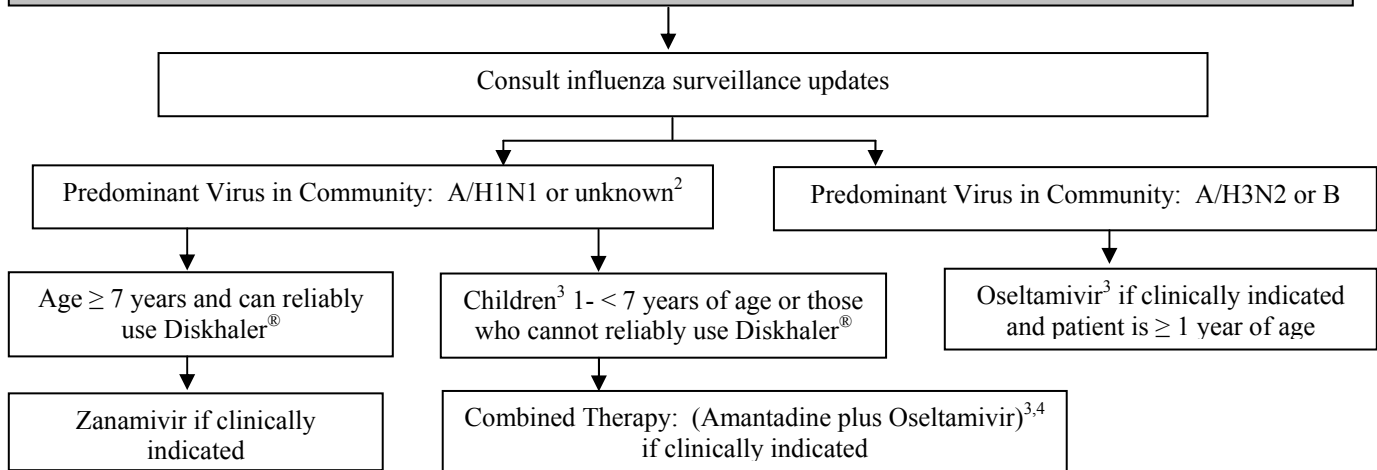
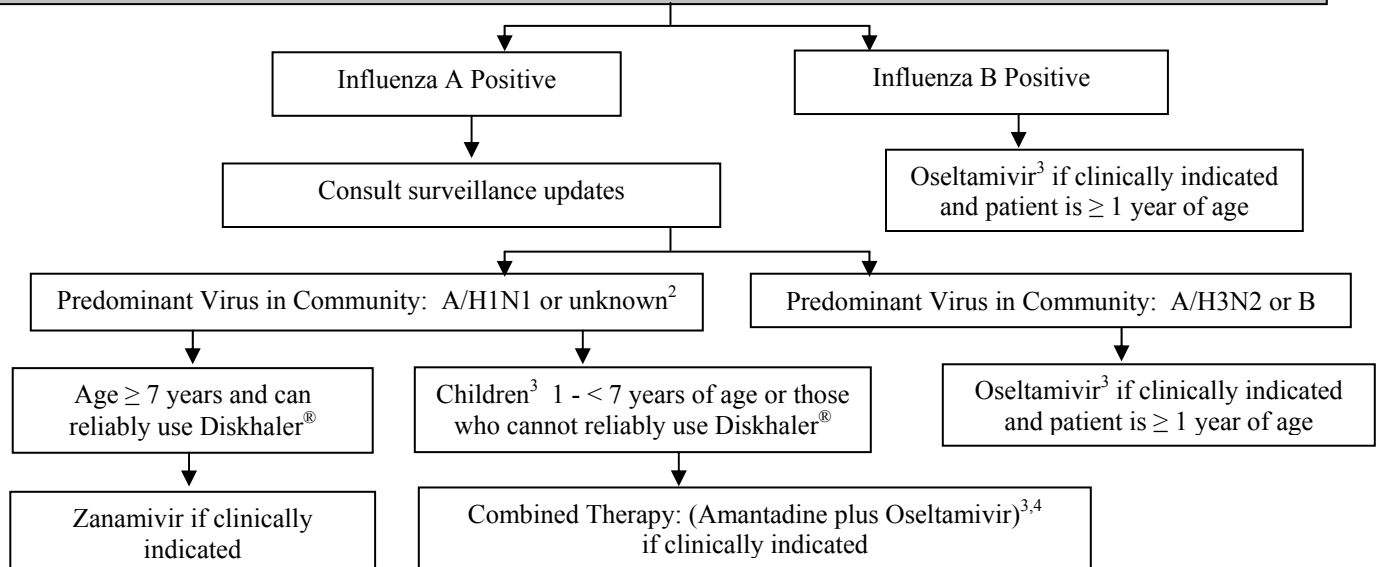


Figure B^b: Rapid Point of Care Test Results for Influenza A or B Available but Subtype Results Not Available and Strong Indication for Treatment¹



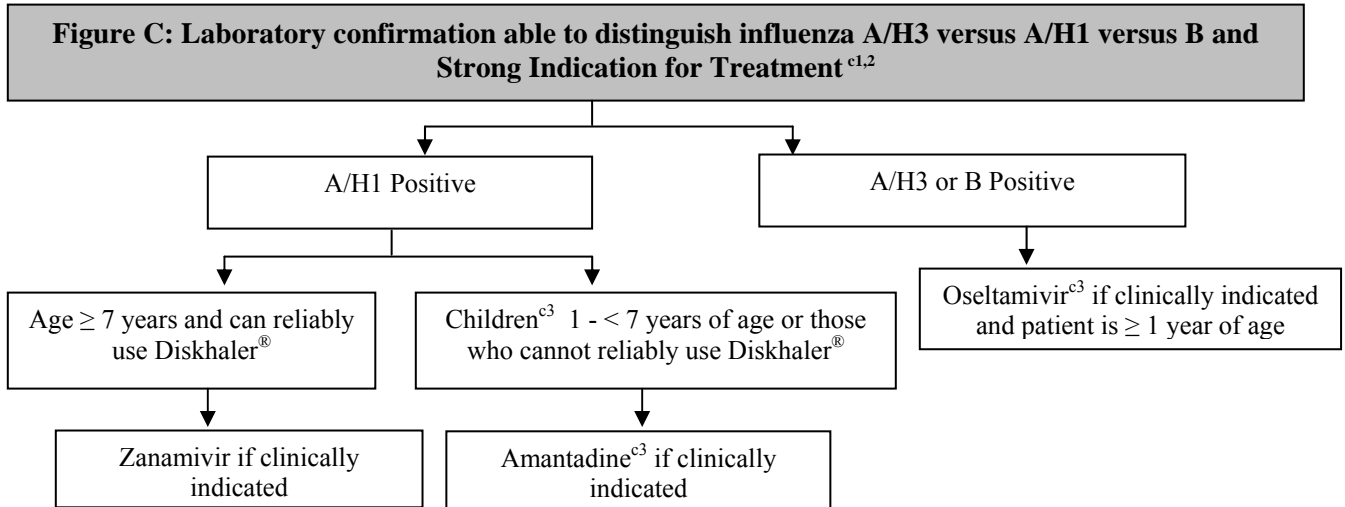
¹Antivirals used for influenza treatment are most beneficial when started within the first two days of illness. Antivirals should be used selectively and judiciously for appropriate clinical indications, most notably for individuals with severe illness and those most likely to develop complications or die as a result of influenza. See narrative section B of these guidelines and consult specific antiviral package insert and/or references for prescribing detail including dose/indications/contraindications/precautions/warnings.

²Surveillance data may be driven by younger age groups. Circulating A/H1N1 may be more likely to cause classic influenza illness and/or be reported in younger compared to elderly people and this requires consideration in treatment choice.

³Data for safety and effectiveness are lacking for children < 1 year of age and no influenza antivirals are yet approved for use in that very young age group. Expert infectious disease consultation is advised in considering pediatric antiviral treatment options, especially for hospitalized children or those with severe illness.

⁴Combined therapy with (amantadine plus oseltamivir) will address A/H1N1 (amantadine), A/H3N2 (oseltamivir) and B (oseltamivir), if multiple influenza types/subtype may be circulating. Human data are lacking to support the benefits of combination antiviral treatment of influenza; however, these interim recommendations are intended to assist clinicians treating patients who might be infected with oseltamivir-resistant influenza A/H1N1 virus when individual subtype-specific laboratory confirmation is lacking.

^bSee Narrative in Section C3b of these guidelines related to rapid antigen, point of care tests. If there is strong clinical suspicion of influenza and strong indication for treatment and the rapid test is negative, consider treatment options per Figure A above.



^{c1} Antivirals used for influenza treatment are most beneficial when started within the first two days of illness. Antivirals should be used selectively and judiciously for appropriate clinical indications, most notably for individuals with severe illness and those most likely to develop complications or die as a result of influenza. See narrative section B of these guidelines and consult specific antiviral package insert and/or references for prescribing detail including dose/indications/contraindications/precautions/warnings.

^{c2} When submitting a specimen for laboratory testing to a Virology laboratory, there will be added transportation and processing time and subtype or oseltamivir resistance results may not be routinely available/reported or provided in a timely way to guide clinical decision-making. Antiviral treatment options are time-sensitive. Local availability and timeliness of such diagnostic testing, either routinely or at special request, should be explored by interested clinicians. In such cases, treatment options can be considered per Figure A or B and revised with the availability of test results if clinically warranted.

In British Columbia, the Virology Laboratory of the BC Centre for Disease Control is able to conduct subtyping of influenza viruses for special surveillance indications and clinically upon request. If the respiratory specimen arrives before 14:00 Monday to Friday or before 10 AM on Saturday, subtype results could be made available the next business day following identification of influenza by the BCCDC laboratory, if specially requested. Clinicians requesting this detail for individual patients are required to notify the BCCDC laboratory in advance of specimen submission.

^{c3} Data for safety and effectiveness are lacking for children < 1 year of age and no influenza antivirals are yet approved for use in that very young age group. Expert infectious disease consultation is advised in considering pediatric antiviral treatment options, especially for hospitalized children or those with severe illness.

D. REFERENCES

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