

Antiviral Medication for the Prevention and Treatment of Influenza

December 2010

Public Health Protection and Prevention Branch
Public Health Division
Ministry of Health and Long-Term Care

Note: This document replaces Section 4.7 Antiviral
Medication in *A Guide to the Control of Respiratory Infection
Outbreaks in Long-Term Care Homes*, October 2004

Acknowledgements

The Ministry of Health and Long-Term Care would like to thank the following people for their contribution to the revision of Section 4.7 and its related appendices.

Working Group Members

Irene Armstrong, MD, MSc, CCFP, FRCPC

Associate Medical Officer of Health
Communicable Disease Control
Toronto Public Health

Sofia da Silva, BSc, BScN, RN (Chair)

Nurse Consultant
Public Health Division
Ministry of Health and Long-Term Care

Valerie F. Krym, MD, MPH, CCFP(EM), FCFP

Senior Medical Consultant
Medical Group
Public Health Division
Ministry of Health and Long-Term Care

Associate Professor, Department of Family and Community Medicine
Associate Professor, Dalla Lana School of Public Health
University of Toronto

Emergency Physician
Sunnybrook Health Sciences Centre

Colin Lee, MD, MSc, CCFP(EM), FRCPC

Public Health Physician
Infectious Diseases Prevention and Control
Ontario Agency for Health Protection and Promotion

Associate Medical Officer of Health
Simcoe Muskoka District Health Unit

Glenn McAuley, BSc, BSP, R.Ph

Senior Pharmacist, Drug Program Services
Ontario Public Drug Programs
Ministry of Health and Long-Term Care

Allison McGeer, MSc, MD, FRCPC

Microbiologist & Infectious Disease Consultant

Professor, Laboratory Medicine and Pathobiology
University of Toronto

Director, Infection Control
Mount Sinai Hospital

Anna M. Miranda, MES, BASc, CPHI(C)

Manager, Communicable Disease Liaison Unit
Toronto Public Health

Roxana Nassiri, MSc, BASc., CPHI(C), CIC

Public Health Inspector
Infectious Disease Team
Huron County Health Unit

Anne-Luise Winter, RN, BScN, MHSc, CIC

Senior Epidemiologist
Ontario Agency for Health Protection and Promotion

Contributors

Vincent Teo, BScPHM, PharmD

Clinical Pharmacist, Emergency Department
Sunnybrook Health Sciences Centre

Mary Vearncombe, MD, FRCPC

Medical Director, Infection Prevention & Control
Sunnybrook Health Sciences Centre

4.7 Antiviral Medication for the Prevention and Treatment of Influenza

Vaccination is recognized as the cornerstone for preventing or attenuating influenza for those at high risk of serious illness or death from influenza infection and its complications. Health care workers and their employers should actively promote, implement and comply with influenza immunization recommendations in order to decrease the risk of infection and complications among the vulnerable populations for whom they care. For immunization recommendations, please refer to the current season's National Advisory Committee on Influenza (NACI) statement of seasonal influenza vaccine available at: <http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10vol36/acs-6/index-eng.php>.

Antiviral prophylaxis should not replace annual influenza immunization.

Antiviral medication is recommended for the management of institutional outbreaks of influenza A and/or influenza B. Antivirals play a key role in outbreak management and control. Research has shown that antiviral drugs are effective for both the prevention (prophylaxis) and early treatment of influenza infection. The use of antiviral medication, in conjunction with other outbreak control measures, can quickly bring influenza outbreaks in health care facilities under control. While influenza vaccination alone is adequate to protect healthy adults from illness due to influenza, vaccination provides incomplete protection to the elderly and those with immuno-compromising illnesses. Antiviral medications offer protection that is additive to that of annual influenza immunization in these populations. Antiviral medications are also effective in the prevention of influenza in unvaccinated young healthy adults.

Three antiviral drugs are available in Canada for the treatment and prophylaxis of influenza in two classes: the M2 ion channel inhibitor (i.e. amantadine) and the neuraminidase inhibitors (i.e. oseltamivir and zanamivir). Amantadine is NOT currently recommended for prophylaxis or treatment due to adverse side effects and the emergence of amantadine-resistant influenza A strains.

Decisions regarding influenza antiviral prophylaxis or treatment should be made based on current data of circulating influenza strains, including antiviral resistance. Testing of influenza for antiviral resistance is performed as part of the routine surveillance program at the Ontario Agency for Health Protection and Promotion (OAHPP) and the National Microbiology Laboratory (NML), and is reported by the Laboratory-Based Respiratory Pathogen Report and the national FluWatch program respectively.

Please refer to Appendix A for current antiviral medication recommendations.

Health care providers are advised to refer to updates on influenza activity and resistance patterns in ongoing surveillance reports disseminated in the Ministry

of Health and Long-Term Care's (MOHLTC) weekly Ontario Influenza Bulletin at: http://www.health.gov.on.ca/english/providers/program/pubhealth/flu/flu_09/flubul_mn.html and the OAHPP's Laboratory-Based Respiratory Pathogen Report at: <http://oahpp.ca/h1n1/>.

If antiviral drug resistance is detected or suspected in a facility outbreak (i.e. if an outbreak appears poorly controlled despite proper antiviral use), or is reported to be wide-spread in the community, local and provincial health authorities should be contacted for up-to-date advice on antiviral use.

4.7.1 Antivirals as Part of an Influenza Outbreak Preparedness Plan

An outbreak plan should include measures that will expedite the administration of antiviral medication for staff and patients. Since treatment is most effective when started early, it is recommended that the following measures be in place in the event of an outbreak to ensure that there are no delays in providing medication:

- Consent for antiviral medication use should be obtained from residents/patients or their substitute decision-makers in advance of the influenza season. For long-term care homes, this consent may be obtained at the same time that consent is obtained for influenza immunization.
- In long-term care homes, advance orders for antiviral medication for residents should be obtained from medical staff at the beginning of each influenza season, or a plan should be in place to obtain physician's orders quickly in the event of an outbreak. Advance orders can substantially expedite administration of antiviral medications.
- Staff that are unable/unwilling to be immunized should obtain a prescription for a neuraminidase inhibitor at the beginning of the influenza season. Staff should be advised upon hiring, and annually thereafter, that they will be excluded from working in an outbreak area/unit if they are unvaccinated and/or refuse to take antiviral prophylaxis as part of outbreak management and control.

4.7.2 Antiviral Medication for Prevention (Prophylaxis)

During a public health-confirmed influenza outbreak, antiviral medication for prevention shall be offered to:

- all residents/patients in the outbreak-affected area who are not already ill with influenza, whether previously vaccinated or not, until the outbreak is declared over.
- all unvaccinated asymptomatic staff who work in the area of the facility where the influenza outbreak is occurring, until the outbreak is declared over.

During a confirmed influenza outbreak, when the circulating strain is not well-matched by the vaccine, antiviral prophylaxis should be offered to all staff, regardless of vaccination status, until the outbreak is declared over. The local public health unit will notify the facility when this is necessary.

Antiviral prophylaxis should be initiated as soon as an influenza outbreak is declared. In almost all situations, it is prudent to wait for laboratory confirmation of influenza before initiating prophylaxis and treatment. Once the specimen reaches the appropriate laboratory, the results of rapid antigen detection testing and PCR testing are usually available within 24 hours.

Institutions should consult with local public health unit representatives on the outbreak management team when starting antiviral prophylaxis and treatment. **Antivirals will not be reimbursed by the Ontario Drug Benefit Program unless the outbreak has been confirmed by the local Medical Officer of Health or designate.**

Recommendations regarding influenza antiviral prophylaxis:

- It is reasonable to allow unvaccinated staff to work with residents or patients as soon as they start antiviral prophylaxis. Unless there is a contraindication, staff should also immediately be immunized against influenza.
- In healthy adults, it takes two weeks to develop antibodies to the influenza virus after receiving the influenza vaccine. Staff who have been vaccinated for less than two weeks at the time the influenza outbreak is declared should take antiviral prophylaxis for two weeks after vaccination or until the outbreak is declared over (whichever comes first). Note: Antiviral medications do not interfere with the immune response to vaccine.
- Staff must be alert to the symptoms and signs of influenza, particularly within the first 48 hours after starting antiviral prophylaxis, and should be excluded from working in any health care setting if symptoms develop. Staff illness should immediately be reported to the supervisor, infection control practitioner and/or occupational health.
- Prophylaxis may be discontinued once the outbreak is declared over.
- Prophylaxis may also be given during influenza season in non-outbreak institutional settings to unvaccinated individuals at high-risk of influenza-related complications, at the discretion of the treating physician.
- If a person taking a neuraminidase inhibitor (i.e. oseltamivir or zanamivir) for prophylaxis of influenza develops symptoms of an influenza-like illness, the neuraminidase inhibitor can be continued, however, the neuraminidase inhibitor should be increased to the treatment dose.

4.7.3 Antiviral Medication for Treatment

Treatment decisions for the residents/patients are the responsibility of the attending physicians. Treatment decisions for health care staff that work in the facility rest with their health care provider and as such, obtaining prescriptions for antiviral treatment is the responsibility of the staff.

Treatment should be started within 48 hours (or less) of onset of symptoms for maximum effectiveness. This may also decrease complications of influenza infection. Since treatment is most effective when started early, it is recommended that all long-term care homes have pre-authorized orders for antiviral medication for treatment and prophylaxis of residents in the event of outbreaks, to ensure that there are no delays in providing medication.

Recommendations regarding antiviral treatment:

- Antiviral treatment should be started for ill residents/patients (who meet the outbreak case definition), as soon as possible and preferably within 48 hours of symptom onset. Treatment should be given for a total of five days.
- Ill residents/patients are to remain in their rooms for the duration of antiviral treatment.
- Once an outbreak has been laboratory-confirmed as influenza, additional laboratory confirmation of each new case is not required in order to initiate antiviral treatment in individuals who meet the outbreak case definition.

4.7.4 Antiviral Use Decision-Making: Answers to Common Questions

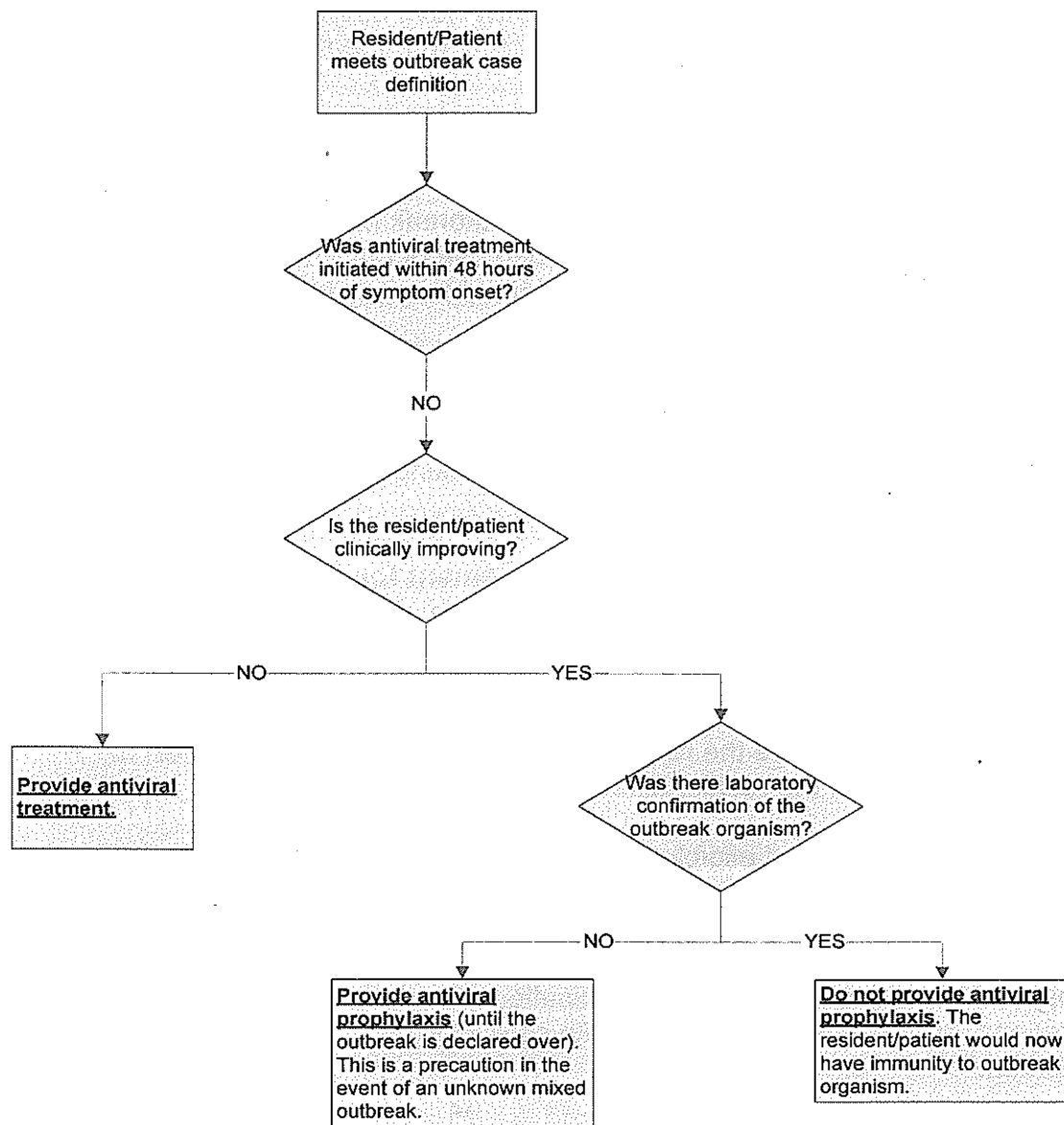
A. If a resident/patient meets the outbreak case definition AND has been symptomatic for more than 48 hours AND antiviral treatment has not been started, the following recommendations in Diagram 1 are made, based on expert opinion.

B. If the outbreak is ongoing when the five-day treatment course ends AND antiviral prophylaxis is being used for outbreak control AND the resident did not have laboratory-confirmed influenza:

- the resident/patient should be switched to a course of antiviral prophylaxis until the outbreak is declared over.

This measure is suggested as a precaution in the event an unknown mixed outbreak (i.e. more than one virus causing the outbreak) and is not required if the resident/patient has laboratory confirmation of influenza.

Diagram 1. Antiviral Use Recommendations in Influenza Outbreaks if Treatment is not Initiated within 48 hours of Symptom Onset



4.7.5 When Antiviral Use Does Not Control the Outbreak

As discussed above, it is prudent to wait for laboratory confirmation of the causative agent of an outbreak before initiating antiviral prophylaxis or treatment. If new cases of influenza-like illness continue to occur 72-96 hours after the initiation of antiviral use, one or more of the following may be occurring:

- The new cases could be caused by an agent other than influenza (i.e. RSV);
- There may be compliance issues;
- Resistance to the antiviral medication may have developed in the circulating influenza strain (this is less likely with the neuraminidase inhibitors oseltamivir and zanamivir)

In the event that the outbreak is not controlled with antiviral use, the following actions should be taken:

- The public health representative on the outbreak management team should be consulted regarding continued use of antivirals.
- Nasopharyngeal swabs should be obtained for virus isolation from new cases, including staff cases.
- Sensitivity testing may be done in consultation with the Ontario Public Health Laboratory if resistance is suspected and no other organism is identified in the outbreak. The results, however, may not be received within a time-frame to influence decision-making regarding the continued use of antivirals to control the outbreak.

4.7.6 Procedures for Obtaining Reimbursement for Antiviral Medications from the Ontario Drug Benefit (ODB) Program

All long-term care residents are eligible for prescription drug coverage under the Ontario Drug Benefit (ODB) Program. Prescriptions for antiviral medications, as for all other medications, are the responsibility of the medical directors or attending physicians of the residents.

Health care workers are not eligible for prescription drug coverage under any circumstances from the ODB Program. Under very specific circumstances, immunized health care workers may be eligible for reimbursement. In all other circumstances, health care workers are responsible for their own antiviral-related expenses. Prescriptions for antiviral medications for staff, as for all other medications, are obtained from their health care provider or another source, as appropriate.

General information regarding the ODB Program is available at:
http://www.health.gov.on.ca/english/providers/program/drugs/odbf_mn.html.

A searchable eFormulary with information on the conditions for reimbursement of the neuraminidase inhibitors oseltamivir and zanamivir is available at:
http://www.health.gov.on.ca/english/providers/program/drugs/odbf_eformulary.html.

Full details of the reimbursement criteria are below in Table 1. Reimbursement for institutionalized individuals/long-term care residents applies only during a public health-confirmed influenza outbreak for patients requiring treatment (up to

five days of therapy) and for patients requiring prophylactic therapy (up to six weeks of therapy for prophylaxis).

Oseltamivir (Tamiflu®) Reimbursement

Oseltamivir is available as a Limited Use (LU) benefit and is the recommended drug of choice for both prophylaxis and treatment in an influenza outbreak. The Ministry of Health and Long-Term Care reimburses long-term care homes for the use of oseltamivir for prophylaxis and treatment only during public health-confirmed influenza outbreaks. Long-term care homes include nursing homes and homes for the aged (not retirement homes). Refer to Table 1 for the clinical criteria to obtain reimbursement under the ODB Program.

Zanamivir (Relenza®) Reimbursement

Zanamivir is available as a LU benefit for both prophylaxis and treatment in an influenza outbreak when the predominant circulating strain is resistant to oseltamivir. Zanamivir is reimbursed in a similar manner when the predominant circulating strain is resistant to oseltamivir. Refer to Table 1 for the clinical criteria to obtain reimbursement under the ODB Program.

Amantadine reimbursement

Amantadine is NOT currently recommended for prophylaxis or treatment due to its adverse side effects and the emergence of amantadine-resistant influenza A strains. Amantadine, however, is available as a General Benefit in the ODB Formulary.

Table 1. Limited Use (LU) Criteria for Oseltamivir (Tamiflu®) and Zanamivir (Relenza®)

LU Code	Drug	Clinical Criteria
371	Oseltamivir (Tamiflu®) 75 mg capsule	For the prophylaxis (max: 75 mg daily) of institutionalized individuals during confirmed outbreaks of influenza A or influenza B. Supply is limited to a maximum of 6 weeks. The outbreak must be confirmed by Public Health.
372	Oseltamivir (Tamiflu®) 75 mg capsule	For the treatment (max: 75 mg twice daily) of institutionalized individuals during confirmed outbreaks due to influenza A or influenza B. Supply is limited to 5 days. The outbreak must be confirmed by Public Health.

414	Zanamivir (Relenza®) 5 mg inhalation	For treatment: 2 inhalations of 5 mg (10 mg) twice daily for 5 days. For the treatment of institutionalized individuals during confirmed outbreaks due to influenza A or influenza B when the predominant circulating strain is resistant to oseltamivir or for the prophylaxis of influenza A, where new cases have developed despite oseltamivir prophylaxis. The outbreak must be confirmed by Public Health.
415	Zanamivir (Relenza®) 5 mg inhalation	For prophylaxis: 2 inhalations of 5 mg (10 mg) once daily for 10 days For the prophylaxis of institutionalized individuals during confirmed outbreaks due to influenza A or influenza B when the predominant circulating strain is resistant to oseltamivir or for the prophylaxis of influenza A, where new cases have developed despite oseltamivir prophylaxis. The outbreak must be confirmed by Public Health.

Under the general LU process, an individual LU prescription must be completed for each patient and kept on file at the dispensing pharmacy. Note that the LU form has been discontinued; LU codes are now written directly onto the prescription. Recognizing that this could result in a delay in therapy in institutions with large numbers of residents, the MOHLTC has created an exception to this requirement for oseltamivir ONLY.

The MOHLTC will accept a single LU prescription to be completed for multiple patients who require treatment or prophylaxis and meet one of the approved criteria. All institutions are eligible for the exemption provided the outbreak was confirmed by Public Health. Once confirmation of an outbreak is received and an attending physician decides to prescribe oseltamivir or zanamivir, the prescribing physician must complete a LU prescription by filling in the appropriate LU code, date, CPSO number and signing the form. The name of the home should be written in under "Patient's name". The completed LU prescription must then be attached to a list of affected patients and forwarded to the dispensing pharmacy. One LU prescription should be used for patients requiring treatment and a separate LU prescription must be completed for patients requiring prophylactic therapy during the influenza outbreak. The standard LU process (i.e. one completed LU prescription for each patient) is also acceptable.

Appendices

Appendix A: Oseltamivir (Tamiflu®) and Zanamivir (Relenza®) Prophylaxis and Treatment Recommendations

Appendix B: National Microbiology Laboratory (NML) Antiviral Susceptibility Testing Results

Appendix C: Neuraminidase Inhibitors: Oseltamivir (Tamiflu®) and Zanamivir (Relenza®)

Appendix D: M2 Ion Channel Inhibitor: Amantadine (Amantadine is NOT currently recommended for prophylaxis or treatment)

