

**GUIDANCE ON THE MANAGEMENT OF PANDEMIC H1N1 IN  
IMMUNOCOMPROMISED INDIVIDUALS**

## SUMMARY OF KEY GUIDANCE

This document summarizes important issues relating to the management of immunocompromised individuals who are infected with the pandemic strain of H1N1. It is acknowledged that there is the need for additional data on several issues relating to the management of influenza illness among the expanding spectrum of immunocompromised hosts. A summary of key guidance with evidence rating (1) is provided below.

- Clinicians should make every effort to obtain expert advice on the management of influenza illness in the immunocompromised host, particularly when special circumstances are present (e.g., atypical illness, neonates, infants, recent organ transplantation, use of new immunosuppressants). **(Strong recommendation, very low quality evidence)**.
- Among immunocompromised individuals, knowledge of surrogate markers of severity of the net state of immunosuppression is important, given the potential for severe illness and complications in the more profoundly immunosuppressed hosts **(Strong recommendation, very low quality evidence)**.
- Clinicians should be aware that influenza illness, including pandemic H1N1, may have atypical clinical features at presentation or during the course of illness **(Strong recommendation, moderate quality evidence)**.
- Clinicians should be aware that immunocompromised individuals may have prolonged illness, which may be accompanied by periodic exacerbations of symptoms and prolonged viral shedding **(Strong recommendation, moderate quality evidence)**.
- Given that immunocompromised individuals might have a suboptimal immune response to immunization, the immunization of household and other closer contacts is an important strategy in the prevention of transmission of influenza to the immunocompromised person **(Strong recommendation, moderate quality evidence)**.
- Immunocompromised individuals who have uncomplicated illness due to confirmed or strongly suspected H1N1 infection are among those known to be at risk of developing severe or complicated illness and thus should be treated with oseltamivir or zanamivir as soon as possible **(Strong recommendation, low quality evidence)**.
- Some immunocompromised individuals qualify for antiviral chemoprophylaxis in exceptional circumstances, as outlined in the text of this document **(Strong recommendation, very low quality evidence)**.  
Prolonged use of antiviral agents should generally be avoided due to the potential for antiviral resistance **(Strong recommendation, very low quality evidence)**.
- Among immunocompromised hosts with prolonged or recurrent illness, there is a higher risk of antiviral resistance. Appropriate infection control and prevention vigilance to prevent transmission of resistant strains of pandemic H1N1 is required. **(Strong recommendation, low quality evidence)**.
- Laboratory testing for pandemic H1N1 and other respiratory pathogens may guide the management of immunocompromised patients with influenza-like illnesses. In this regard, the threshold for laboratory testing should be lower than that for healthy patients **(Strong recommendation, very low quality evidence)**.

## **INTRODUCTION**

Community acquired respiratory viruses have long been recognized to be important pathogens in immunocompromised individuals (2-3). Seasonal epidemics of respiratory syncytial virus, parainfluenza virus and influenza virus occur each year, affecting variable numbers of immunocompromised individuals. Infection with these viruses may be acquired from within the community or from within health care institutions. Among the above viruses, influenza A is unique in that it undergoes antigenic change every year or two and that vaccines and antivirals are readily available for its prevention and management. Specifically, the 2009 pandemic H1N1 influenza A, which emerged as a result of quadruple reassortment, is a novel strain to which most of our population has limited immunity. This novel strain contains genomic components of swine, avian and human influenza A viruses (4-6). An important feature of influenza A epidemics is that such occurrences are associated with excess or premature mortality.

This document provides guidance on the prevention and treatment of pandemic H1N1 influenza A illness among immunocompromised individuals. Wherever appropriate, we have addressed general principles, recognizing the need for clinical judgment given the heterogeneity of the populations of immunocompromised hosts. While this document relates to pandemic H1N1, the major principles also apply to the management of influenza A illness in the interpandemic period. Several individuals and organizations have developed documents that relate to selective aspects of the issues outlined in this document. As such, these documents are referenced as appropriate. The focus is on individuals with a spectrum of immune deficits, ranging from congenital immunodeficiencies, selective acquired deficiencies and immunodeficiencies secondary to organ/tissue transplantation and immunoablative or immunosuppressive and myelosuppressive chemotherapy. In table 1, special issues relating to each group of immunocompromised patients are summarized.

## **EPIDEMIOLOGY**

As of March 2010, two waves of pandemic H1N1 have been recognized in Canada. While the full extent of the epidemiology of pandemic H1N1 remains to be defined, what is known about the epidemiology of seasonal influenza A serves as a frame of reference. Influenza A is spread primarily by respiratory droplets. Contact with droplet-contaminated surfaces is another potential mode of transmission, as is transmission by aerosol. Pandemic H1N1 has proven to be as readily transmitted as seasonal influenza. The incubation period of pandemic H1N1 has been observed to be 3-4 days with a range of 1 to 7 days. Viral shedding in nasal secretions usually peaks during the first 3 days of illness and ends by 7 days, resulting in a period of communicability of 7 days. However, shedding may be prolonged in young children (typically up to 10 days) and immunocompromised individuals in whom shedding may last for weeks to months (7-8).

The risk factors for seasonal influenza A have been defined and additional risk factors have been confirmed for pandemic H1N1. However, within populations of immunocompromised individuals, risk factors for pandemic H1N1 have not been fully defined. It has been suggested that patients after hematopoietic stem cell transplantation, after lung transplantation, and those receiving chemotherapy for leukemia are at highest risk, while the risk for human immunodeficiency virus-infected individuals seems to be relatively low (9). This notwithstanding, it is expected the risk of adverse outcomes might be increased with increasing immune suppression, cell-mediated immune defects and the presence of co-morbidities (e.g., underlying chronic lung disease).

## **CLINICAL PRESENTATION AND OUTCOMES**

Among adult patients, influenza typically starts with the sudden onset of fever, often accompanied by chills or rigors, headache, malaise, myalgia and nonproductive cough. As the illness progresses,

respiratory signs and symptoms include sore throat, nasal congestion, rhinitis and an increasingly prominent cough. Other manifestations may be present, including gastrointestinal symptoms (one or more of nausea, vomiting or diarrhea) which commonly occur with pandemic H1N1. Infants and young children may present with atypical features of influenza, manifested as a non-specific illness. In this context, similar atypical manifestations may be present in immunocompromised individuals. For example, some immunocompromised individuals may present with fever as the only manifestation of influenza illness. However, it is recognized that such individuals may be afebrile or normothermic (10).

The complications seen in previously healthy individuals may be seen in immunocompromised hosts. Invasive secondary infections due to *Streptococcus pneumoniae*, *Staphylococcus aureus*, group A streptococcus and other bacterial pathogens may occur. Patients with asplenia are known to be at increased risk of severe invasive pneumococcal disease; thus the consequences of influenza illness are potentially devastating for these individuals. Prolonged illness is a feature of infection in immunocompromised individuals. In some of the more immunocompromised individuals, the virus may be persistently present in the respiratory tract for several weeks (sometimes months), which may be accompanied by periodic exacerbations of illness (11-12). In this regard, cell-mediated immune response is important in viral clearance and promoting recovery (13) and the major cellular immune response is CD8 T-lymphocyte-mediated cytotoxicity. Reductions in T-cell number or function by acquired or congenital means will likely produce an increased likelihood of a more severe and prolonged illness.

## **PREVENTION OF H1N1 IN IMMUNOCOMPROMISED PATIENTS AND CONTACTS**

### **Immunization**

Providing the immunocompromised host can mount an adequate immune response, the importance of influenza immunization as a key preventive strategy cannot be overemphasized. Immunocompromised patients > 6 months of age (including hematopoietic and solid organ transplant candidates) should receive H1N1 and seasonal influenza vaccines. As the immunogenicity of influenza vaccine is reduced in immunocompromised hosts, household contacts should also be vaccinated to decrease the risk of household exposure. Given that immune protection might not be achieved following natural H1N1 infection in the immunocompromised patient, some experts have suggested pandemic H1N1 vaccine should still be considered even if such individuals have previously had H1N1.

Among solid organ transplant recipients, the seasonal influenza vaccine is generally recommended to be given no sooner than 3-6 months after organ transplant (14). Given the rapid spread of H1N1 virus, transplant recipients may begin to receive H1N1 vaccine as soon as one month post-transplant (14). However, the immune response to early vaccination may only be partially protective and re-vaccination at a later time point, when immunosuppressive therapy has been decreased to maintenance doses, should be considered. In this regard, concurrent chemoprophylaxis for 7-14 days should be considered after influenza immunization.

Given that influenza virus infection in cancer patients may impact on the ability to administer potentially curative systemic therapy, and produce excess morbidity and mortality, influenza immunization has been recommended for such patients and has been the subject of various studies; albeit limited randomized trials (15). Reported influenza case: fatality rates have ranged from 11% to 33% depending upon type of malignancy (11, 16). Serologic responses to influenza vaccines have varied by influenza virus type (A/H1N1 versus A/H3N2 versus influenza B), by malignancy, and by systemic therapy regimens (17). For example, hemagglutination inhibition titres of 1:40 or more have been achieved after influenza immunization in only approximately 1:5 myeloma patients compared to

three-quarters of lung cancer patients (18). Chemotherapy regimens sufficiently intense to produce neutropenia have been associated with a serological response approximately 50% lower than for less intensive regimens when immunization occurred at a minimum of one week prior to chemotherapy (17). For some regimens such as those associated with monoclonal antibodies (rituximab or alemtuzumab), serological responses have been quite variable (17, 19).

Recommendations for the timing of immunization for chemotherapy recipients have focused on administration before a systemic chemotherapy course is begun or after it has been completed. There have been no published guidelines recommending the timing of influenza immunization for patients who are already receiving chemotherapy at the time of a community outbreak. The concerns about increased risk of complications due to pandemic influenza virus, together with concerns about antiviral drug resistance associated with chemoprophylaxis (20) may compel physicians to recommend influenza immunization of cancer patients at highest risk for influenza-related complications during the course of systemic therapy, despite the risks of poor serological responses (21).

Many systemic chemotherapy regimens, particularly for lymphoreticular and solid tissue malignancies, are administered in 28-day, 21-day, 14-day, and 7-day cycles over a prolonged multi-cycle course. Poor vaccine responses (defined by failure to achieve a hemagglutination-inhibition (HAI) titre of  $\geq 1:40$  or failure to achieve fourfold seroconversion) have been related to administration of chemotherapy within 7 days prior to influenza immunization (22-23). Given that a B-cell-mediated immune response to influenza virus antigens requires a 7-14 day period to develop (24), and that serologic responses do occur in chemotherapy recipients even if vaccine is administered at least one to two weeks before the next cycle of chemotherapy (17, 23) an immunization schedule for use in patients already receiving cyclical chemotherapy, and where remaining “on-time” is deemed important, may be suggested as follows: administer influenza vaccine between day 14 and day 21 of a 28-day cycle, between day 7 and day 14 of a 21-day cycle, or on day 7 of a 14-day cycle. Administration of vaccine to patients receiving a weekly cycle of chemotherapy may require consideration of delay in the treatment cycle by one to two weeks to optimize the serologic response potential, of a two-week course of neuraminidase inhibitor-based chemoprophylaxis, or of forgoing immunization altogether at the discretion and recommendation of the attending physician in consultation with the patient. The administration of a second dose of influenza vaccine at approximately 4 weeks after the first has not enhanced serological response (17). Ideally, influenza vaccine should be administered between courses of chemotherapy wherever possible.

Influenza immunization for hematopoietic stem cell transplant (HSCT) recipients has been recommended for administration after 6 months post-transplant (23) based upon the low serological response rates observed prior to that time (24). In the setting of a community outbreak, all HSCT recipients should be immunized if they are > 4 months post-HSCT (25).

### **Pre and Post Exposure Prophylaxis**

Due to limited data concerning efficacy, concerns regarding the risk of resistance development and difficulty determining indications to start and end prophylaxis, **routine pre-exposure or seasonal chemoprophylaxis with oseltamivir (or other antivirals) is NOT recommended as this has been associated with development of antiviral resistance.**

In the setting of a defined, significant exposure (e.g. household contact or healthcare associated exposure such as shared hospital accommodation) of an immunocompromised patient to a proven or suspect case of influenza, post-exposure prophylaxis with oseltamivir is advisable in consultation with

an Infectious Diseases specialist. In this setting, prophylaxis should be instituted as soon as the exposure is recognized and continued for 10 days post exposure.

In the setting of a community or institutional outbreak, oseltamivir prophylaxis for 14 days after influenza immunization may be considered for high-risk patients less than 6 months post-HSCT (3, 25).

Outside of such a defined, significant exposure, an immune compromised patient who has been exposed to a known case of influenza (e.g. classroom or workplace exposure) should be counseled to watch for early signs and symptoms of influenza which should prompt timely medical evaluation and initiation of early treatment. This can be done via instruction to report ILI symptoms without delay to a clinician, preferably without presentation to clinic setting unless symptoms are severe. Initiation of treatment at the earliest sign of symptoms of ILI is recommended.

### **Infection Prevention and Control**

Comprehensive guidance for Infection Prevention and Control of H1N1 in all sectors of health care is available from the PHAC web site:

([http://www.phac-aspc.gc.ca/alert-alerte/h1n1/guidance\\_lignesdirectrices-eng.php#3](http://www.phac-aspc.gc.ca/alert-alerte/h1n1/guidance_lignesdirectrices-eng.php#3)) (26).

These guidance documents review appropriate measures to be taken in patients with proven or suspect H1N1 infection, including those who are immune compromised with respect to:

1. Source Control
2. Respiratory Hygiene (also known as Respiratory Cough Etiquette)
3. Hand Hygiene
4. Accommodation
5. Contact Precautions
6. Droplet Precautions/Respiratory Protection

### **Advice for Patients and Families**

Immunocompromised patients are at higher risk for severe disease due to influenza and presumably also from the novel H1N1 virus. For this reason, it is recommended they avoid contact with persons with ILI. Strict hand hygiene is advocated as an important means for reducing transmission of H1N1. Cough etiquette should be practiced; cover the nose and mouth with a tissue when coughing or sneezing and then wash hands after sneezing; or if no tissue is available the person should cough or sneeze into their sleeve to avoid contaminating their hands. Patients and families should be directed to the PHAC H1N1 preparedness guide at: <http://www.phac-aspc.gc.ca/alert-alerte/h1n1/guide/index-eng.php> for additional information on how H1N1 is spread and its prevention. As in the general population, immunocompromised patients with ILI should put on a surgical mask immediately when presenting for clinical assessment (<http://www.phac-aspc.gc.ca/alert-alerte/h1n1/guidance-orientation-amb-07-16-eng.php>).

## **Advice for Healthcare Workers and Programs**

Healthcare workers providing care to immunocompromised patients, and their employers should be familiar with PHAC Occupational Health Guidance regarding fitness to work ([http://www.phac-aspc.gc.ca/alert-alerte/h1n1/guidance\\_lignesdirectrices/humpan-eng.php](http://www.phac-aspc.gc.ca/alert-alerte/h1n1/guidance_lignesdirectrices/humpan-eng.php)).

A HCW or other staff would be considered unfit-for-work if he/she:

Has symptoms compatible with ILI suspected or confirmed to be due to Pandemic (H1N1) 2009 Flu Virus;

**Or**

Is still in the period of communicability (communicability in untreated immunocompetent adults is up to 7 days after symptoms develop; it may be shorter in those who are treated with oseltamivir or zanamivir, and longer in those who are immunocompromised).

A HCW may be considered fit-for-work with restrictions in some circumstances. The period of exclusion takes into consideration the risk setting, symptomatology and severity of the pandemic. Refer to PHAC Guidance for further details. All HCWs working with immunocompromised patients are recommended to be immunized against seasonal and H1N1 influenza.

## **DIAGNOSIS OF PANDEMIC INFLUENZA A/H1N1**

### **Definition of Severe Immunosuppression**

A state of immunosuppression exists when one or more domains of the host defence system become sufficiently impaired to result in an increased risk for infection. Such states may be suspected by a number of laboratory, clinical and treatment-related surrogate markers. Examples of such states are presented in table 2. Severe immunosuppression may be said to be present when severe neutropenia or lymphopenia (see table 2 “Laboratory-based Markers”) is present with, but may be not limited to, any of the entities suggested in table 2 under either “Clinical States” or “Treatment-related Markers”. Such states impart increase risks for acquisition of infection, progression to more severe and potentially life-threatening consequences of infection, and for an impaired ability to develop immunity or resistance to infection following subsequent exposure to a pathogen or its component antigens.

### **Clinical Definitions**

Pandemic H1N1 Influenza infection should be considered in immunocompromised patients presenting with an influenza-like illness (ILI) defined by an elevated oral or tympanic temperature thermometry (> 37.8°C) in the absence of oral mucositis, (27-28) and symptoms of respiratory tract infection (cough, rhinorrhoea, coryza, sore throat, myalgias or arthralgias, malaise, prostration), when influenza is known to be circulating in the community, or suspected or confirmed exposure to pandemic influenza, and in the absence of alternative explanations for the syndrome. Patients who present with ILI and who manifest symptoms including, but not limited to shortness of breath and difficulty breathing, are regarded as having more severe illness. In immunocompetent patients, the case definitions for ILI, particularly fever and cough when applied during periods when influenza is circulating in the community have reported positive predictive values of approximately 80%, or higher especially when the temperature is above 38°C (29-30)

Severely immunosuppressed patients with influenza infection, such as recipients of HSCT, may be afebrile at presentation in half of cases (10). Influenza infection in immunosuppressed patients may also have a natural history different than for immunocompetent hosts. For example, the duration of symptoms among allogeneic HSCT recipients may be prolonged compared to immunocompetent patients (median 14 days compared to 4-5 days) (10-31).

Influenza-related upper respiratory tract infection is defined by the detection of influenza virus in upper respiratory tract secretions in association with symptoms of upper respiratory tract infection (10, 31). Influenza lower respiratory tract infection is defined as hypoxia and or new pulmonary infiltrates plus the detection of influenza virus in either upper or lower respiratory tract secretions in the absence of other identifiable causes (10, 32).

### **Specific Testing for H1N1**

The general principles relating to testing for H1N1 in non-immunocompromised hosts apply to immunocompromised hosts. However, in the latter group, the threshold for testing is lower and as mentioned above prolonged shedding might be present. The mean duration of influenza virus shedding from the nasopharynx in infected normal hosts is approximately 5 days (31). Among HSCT recipients and profoundly immunosuppressed hosts (e.g., infants with severe combined immunodeficiency) shedding of influenza may be prolonged beyond two weeks (median 11 days, interquartile range 8-13 days) (10). The absolute lymphocyte count, as a surrogate marker of immunosuppression, appears to be inversely related to duration of shedding (10).

The ideal specimen for testing is a nasopharyngeal specimen or aspirate (32-33). (For an instructional video see <http://www.youtube.com/watch?v=TFwSefezIHU>). However, in critically ill patients, it is recommended that a deeper specimen such as a BAL or endotracheal aspirate be acquired to rule out infection because clinical experience has shown that NPS may be falsely negative in some critically ill patients (34-35). Routine surveillance of asymptomatic patients post-HSCT for viral shedding does not affect routine treatment decisions and should only be done in the context of a clinical trial (26).

There are four categories of laboratory testing for influenza viruses.

1. **Isolation of the virus in cell culture** can identify the presence of a virus but identifying the isolate as influenza A requires immunofluorescence microscopy and determination of the pandemic subtype can be performed by hemagglutination inhibition testing using reference sera. Although the traditional “gold standard” by which other tests for influenza viruses have been measured, this approach does not lend itself to providing timely results taking 2-10 days before results become available.
2. **Genomic detection by reverse transcriptase polymerase chain reaction (RT-PCR)** is the test of choice because it is the most sensitive and specific diagnostic test for influenza and can be configured to both identify influenza A virus and determine the pandemic subtype (3, 30). Results may be available in 4-6 hours of receipt of specimen by the laboratory. It does however require a well developed laboratory infrastructure for nucleic acid based testing.
3. **Direct or indirect immunofluorescence microscopy** can be used to identify influenza antigen in respiratory specimens (nasopharyngeal swabs or aspirates, and nasal swabs). This test can be more sensitive than cell culture and can generate a result within 2-4 hours (36). However, optimal results require specimens that contain adequate numbers of infected respiratory epithelial cells and require a fluorescent microscope and highly trained laboratory personnel. This approach is not as yet suitable for identification of the pandemic subtype (37).
4. **Rapid influenza detection tests (RIDT)** for viral antigen are attractive because they can provide results within 30 minutes. However, the performance characteristics of the test are highly dependant on specimen quality. Sensitivities and specificities for seasonal influenza have ranged 69-72% and 82-97%, respectively, when compared to isolation in cell culture (which is

less sensitive than RT-PCR) (36). False-negative tests appear common during periods of peak influenza activity; therefore influenza cannot be ruled out with a negative RIDT. As such, patients with ILI and negative rapid tests require further testing with RT-PCR (38). The usefulness of these tests is further limited by the fact that they cannot distinguish between the 2009 pandemic H1N1 and seasonal H1N1 or H3N2 influenza A viruses (39). The sensitivity of these RIDT is particularly poor for pandemic H1N1. Although the specificity of RIDTs is reasonable, it is the poor sensitivity that limits the usefulness of RIDTs in the management of individual patients. Data suggests the clinical sensitivity of these assays for detecting pandemic H1N1 is poor, ranging from 10 - 69% (37, 40-46). Moreover, there does exist the potential for false positive test results, especially if the tester is inexperienced or at times of low disease prevalence. Hence, RIDT tests should never be used to inform clinical decisions about diagnosis and treatment in individual pandemic H1N1 patients (33).

Influenza detection tests are influenced by the prevalence of influenza activity in the community in which the tests are being conducted, the characteristics of the test, quality control of the test procedures, the quality of the procurement and transport of respiratory specimens for testing, the presence or absence of ILI signs and symptoms, and the timing of collection with respect to viral shedding (3). The interpretation of the results is influenced by the prevalence of the infection in the community (47).

Influenza virus testing is recommended in circumstances where the results will impact upon clinical or public health decision-making (3). The limitations on laboratory resources have compelled public health authorities to recommend restriction of testing for pandemic influenza to those patients with ILI being admitted to hospital, those with underlying conditions at risk for influenza-related complications, those with progressive ILI, or those with nosocomial ILI. The recommendation for diagnostic testing among patients sufficiently ill to warrant hospitalization is based upon the poor predictive value of ILI for influenza under such circumstances (39). This recommendation is extended to patients admitted to the critical care services with non-specific respiratory infections. The recommended specimens for testing are nasopharyngeal swabs or aspirates (33).

## **ANTIVIRAL TREATMENT**

Immunocompromised patients who meet the definition of an ILI, should be considered for immediate empiric treatment with oseltamivir, or zanamivir, as appropriate. The decision to treat is largely a clinical one that is made prior to the availability of laboratory proof of influenza infection. Factors that influence the decision to treat include, but are not limited to, the prevalence of pandemic H1N1 or other seasonal strains of influenza in the community, and severity indicators.

In previously healthy individuals with uncomplicated influenza, efficacy of early antiviral treatment (<48 hours from illness onset) has been demonstrated. In hospitalized patients with seasonal influenza or 2009 H1N1, observational studies indicate that initiation of oseltamivir treatment after 48 hours of onset is associated with survival benefit compared to no treatment. (47-51) Current expert opinion suggests that symptomatic immunocompromised patients with evidence of viral replication (positive culture, rapid antigen, or PCR-based testing), even if symptoms have extended beyond 48 hours are also likely to benefit from therapy. The decision to initiate therapy will depend on the degree of the immunocompromised state, notably cell-mediated immunity.

Tables 3-4 show the recommended doses of the antiviral agents including for the treatment of infants less than 1 year of age and individuals with renal impairment (52-53). The relative cautions and contraindications are included for each drug. The optimal duration of therapy for influenza has not

been well established, but courses longer than the currently approved 5 days are recommended by many experts based on clinical severity. Indeed, some experts recommend continuing antiviral therapy until viral replication (as documented by PCR or culture) has ceased; however as noted, this may take weeks or even months and prolonged therapy has been associated with the emergence of antiviral resistance. In the case of organ transplant recipients, lung transplant patients with impaired lung function may need longer duration of treatment than other organ recipients (15).

Intravenous antiviral therapy may be considered in those individuals who are severely ill and have progressed despite oral therapy or in whom there is concern about the absorption of oral therapies or about the distribution of inhaled zanamivir. There is limited availability of intravenous agents through Health Canada's Special Access Program or clinical trials. Whilst theoretical concerns about oral absorption of oseltamivir in critically ill adult patients have prompted some experts to consider a doubling of the dose (that is, increased to 150 mg bid), recent evidence suggests this might not be necessary (54). In patients with significant disease, a reduction in immunosuppression is recommended in keeping to the usual approach to the management of severe infections in individuals receiving immunosuppressive medications. The extent of this reduction will vary from patient to patient and takes into account the risks versus benefit of such reduction.

### **ANTIVIRAL RESISTANCE**

Antiviral resistance in the immunocompromised host should be suspected if there is progression of disease or failure of resolution of symptoms after 7 to 10 days of therapy, in the setting of ongoing viral shedding, and where there is nosocomial transmission in clinical areas with immunosuppressed patients. A request for specific testing to identify oseltamivir resistance should be coordinated with an appropriate microbiology laboratory such as the provincial health laboratory. Given the clinical complexities in such circumstances, consultation with an infectious disease specialist is strongly recommended. Patients with severe illness in whom there is clinical suspicion of oseltamivir resistance should be treated with zanamivir as activity of this agent is maintained.

Observations of A/H1N1 influenza viruses during the influenza season from October 2007 to March 2008 in Europe and the United States and Canada noted the circulation of oseltamivir-resistant strains characterized by a single cytosine to thymine base mutation at position 823 of the pandemic neuraminidase gene resulting in a histidine to tyrosine substitution at residue #275 of the neuraminidase (N1) protein (H275Y) (55-56). These oseltamivir-resistant influenza viruses are sufficiently robust as to permit person-to-person transmission (57-58). This resistant form of influenza H1N1 virus was the dominant agent in late 2008 and early 2009 in our setting.

Similar mutations have been reported rarely among pandemic influenza isolates around the world and have been primarily linked to prolonged treatment or prophylaxis with oseltamivir (59). Despite the relative rarity of oseltamivir resistance among pandemic influenza isolates, high mortality rates continue to be a function of interactions between pre-existing co-morbidities and severe clinical disease (60) and quite independent of anti-viral resistance.

Antiviral resistance to neuraminidase inhibitors may be detectable using a neuraminidase inhibition assay on clinical isolates (61-62). This requires isolation of the virus and confirmation of resistance by sequencing the neuraminidase gene (63), a process that does not yet lend itself to routine clinical monitoring applications. Recently, more effective assays for the detection of the H275Y mutation have been implemented at the reference laboratory level. These include the detection of the mutation by a single nucleotide polymorphism assay (SNP) or by sequence analysis of the neuraminidase gene which can be efficiently performed by pyrosequencing.

**TABLE 1**

**SUMMARY OF SPECIAL CONSIDERATIONS**

	<b>Epidemiology/ Transmission</b>	<b>Clinical</b>	<b>Vaccination</b>	<b>Antivirals</b>
SOT Recipient	Potential for donor-derived influenza	Lung transplant recipients likely at increased risk  Postpone SOT if symptomatic; preferably 14 days asymptomatic	Vaccinate after first month post-transplant	Antiviral medications compatible with transplant medications
HSCT Recipient	Highest risk among autografts are T-cell depletions by CD34 selection of stem cell product  The duration of shedding is inversely related to the degree of lymphopenia.	Prolonged clinical illness  Postpone SCT if symptomatic at time of conditioning.  Establish diagnosis for symptomatic SCT patients	Vaccinate if > 4 months post-transplant.  If < 6 months, 2 <sup>nd</sup> dose may be considered.  No augmentation of GvHD or graft failure.	Treatment of SCT patient with influenza URI for 5 days.  Prophylaxis for 2 weeks after vaccination during outbreak
Cancers/ Leukemias	Risk of progression from URI to LRI and death is higher for lymphopenic and neutropenic patients	Vaccine response is poor and is related to timing of systemic therapy	Vaccine responses vary by viral antigen within an individual	Early intervention in high-risk patients even with minimal symptoms
Congenital immunodeficiencies	Patients with cell mediated deficits at increased risk	Prolonged infection and shedding with intercurrent co-infections possible	Vaccinate if 6 months of age or greater	Special considerations for use of antiviral in age infants < 1 year
HIV/AIDS	Importance of adherence to antiretrovirals to	In those with low CD4 counts, illness may progress rapidly	Vaccinate regardless of CD4 count	Antiviral medications compatible with antiretroviral

	maintain/improve immune function should be emphasized, as risk of severe infection in those with lower CD4 counts (<200)	and be complicated by secondary bacterial infections		medications
Corticosteroids ( $\geq 2$ mg/kg or $\geq 20$ mg/d for $\geq 1$ month of prednisone equivalent if $> 10$ kg body weight), disease modifying anti-rheumatic drugs (DMARDs), and biological response modifiers	Exact type and severity of immune dysfunction that correlates with risk of influenza-associated complications not well defined	Secondary bacterial infections possible, particularly in those with underlying chronic lung disease	As for all immunocompromised hosts, live attenuated influenza vaccine contraindicated (not available in Canada as of January 2010)	Antiviral medications compatible with corticosteroids

TABLE 2

EXAMPLES OF SURROGATE MARKERS OF IMMUNOCOMPROMISED STATES

Laboratory-based Markers	Clinical States	Treatment-related Markers
<p>Circumstances leading to the following:</p> <ul style="list-style-type: none"> <li>• Severe neutropenia (ANC &lt; 0.5 x 10<sup>9</sup>/L), and/or,</li> <li>• Severe lymphopenia (ALC &lt; 0.5 x 10<sup>9</sup>/L)</li> </ul>	<ul style="list-style-type: none"> <li>• Individuals with malignancies receiving active cytotoxic chemotherapy,</li> <li>• Acute leukemia patients,</li> <li>• HSCT recipients,</li> <li>• SOT recipients (e.g. lung, heart, kidney)</li> <li>• Individuals with congenital immunodeficiency states</li> <li>• Individuals with acquired immunodeficiency states (e.g. Human Immunodeficiency Virus infection, plasma cell dyscrasias, B-lymphocyte malignancies)</li> <li>• Individuals with rheumatic diseases or autoimmune disorders (e.g. RA or SLE)</li> <li>• Individuals with GI diseases receiving immunosuppressive drugs (e.g. IBD),</li> <li>• Individuals on renal dialysis Programmes</li> <li>• Individuals with asthma or COPD receiving corticosteroid therapy.</li> </ul>	<p>A history of ongoing myelosuppressive and/or immunosuppressive therapies such as:</p> <ul style="list-style-type: none"> <li>• Corticosteroid therapy (i.e., &gt; 700 mg cumulative dose (64) of prednisone equivalent on an ongoing basis and at the time of clinical evaluation),</li> <li>• Cytotoxic therapy (e.g., <i>anthracyclines</i> such as doxorubicin or epirubicin; <i>purine analogues</i> such as azathiaprine, thioguanine, mercaptopurine, fludarabine, pentostatin, or cladribine; <i>pyrimidine analogues</i> such as flurorouracil, cytarabine, capecitabine, or gemcitabine; <i>anti-folate agents</i> such as methotrexate or premetrxed; <i>alkylating agents</i> such as the nitrogen mustards (cyclophosphamide or ifosphamide), nitrosoureas (carmustine, lomustine, semustine, streptozotocin), and platinum analogues (cis-platin, carboplatin, or oxaliplatin); <i>taxanes</i> such as docetaxel or paclitaxel; <i>topoisomerase I inhibitors</i> such as irinotecan),</li> <li>• Immunomodulator therapies: <ul style="list-style-type: none"> <li>▪ <i>Calcineurin inhibitors</i> (e.g., cyclosporine, tacrolimus, sirolimus),</li> <li>▪ <i>Guanine synthesis inhibitors</i> (e.g., Mycophenolate mofetil),</li> <li>▪ <i>Anti-B lymphocyte therapy</i> (e.g., rituximab),</li> <li>▪ <i>Anti-T lymphocyte therapy</i> (e.g., anti-thymocyte globulin or anti-CD3),</li> <li>▪ <i>Anti- B and T cell therapy</i> (e.g., alemtuzumab, basiliximab, daclizumab),</li> </ul> </li> </ul>

		<ul style="list-style-type: none"><li>▪ <i>Anti-TNF therapy</i> (e.g., infliximab or etanercept),</li><li>▪ Alpha-interferon therapy</li></ul>
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**Abbreviations:** ANC, absolute neutrophil count; ALC, absolute lymphocyte count; HSCT, haematopoietic stem cell transplant; SOT, solid organ transplant; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; GI, gastrointestinal; IBD, inflammatory bowel disease; COPD, chronic obstructive airways disease; TNF, tissue necrosis factor

**TABLE 3**

**DOSAGE GUIDELINES FOR OSELTAMIVIR (TAMIFLU®) IN ADULTS**

<b>Oseltamivir Dosing in Adults –standard treatment duration 5 days</b>	
<b>Renal function</b>	<b>Oseltamivir Dose</b>
CrCl >30 mL/min	75 mg PO BID
CrCl 10-30 mL/min	75 mg PO DAILY
CrCl <10 mL/min (Hemodialysis)	75 mg loading dose then up to 75 mg after each dialysis run x 3 doses <sup>¶</sup>
CRRT (high-flux dialysis)	30 mg daily or 75 mg every 48 hours <sup>¶¶</sup>

CRRT = continuous renal replacement therapy

<sup>¶</sup>Based on citation # 65.

<sup>¶¶</sup>Data are limited on the dosing of oseltamivir in patients with renal impairment, including those receiving CRRT. We recommend consultation with a expert in this regard.

**TABLE 4**

**DOSAGE GUIDELINES FOR OSELTAMIVIR (TAMIFLU®) IN INFANTS,  
CHILDREN AND YOUTH (41)**

<b>Age or Body Weight</b>	<b>Treatment Dosage*</b>	<b>Prophylaxis Dosage*</b>
≥ 13 years (or 40 kg)	75 mg capsule Twice daily X 5 days	75 mg capsule Once daily X 10 days after last known exposure
1 year to 12 years		
< 15 kg	30 mg capsule or oral solution# twice daily X 5 days	30 mg capsule or oral solution# once daily X 10 days
> 15 to 23 kg	45 mg capsule or oral solution# Twice daily X 5 days	45 mg capsule or oral solution# Once daily X 10 days
24 to 40 kg	60 mg capsule or oral solution# Twice daily X 5 days	60 mg capsule or oral solution# Once daily X 10 days
<b>Birth to 12 months</b>		
< 1 month	2 mg/kg oral solution# Twice daily X 5 days	Not currently recommended for infants < 3 months due to limited data on use in this age group.
1 – 3 months	3 mg/ kg oral solution#	
> 3 to 9 months	3 mg/ kg oral solution# Twice daily X 5 days	3 mg per kg oral solution# Once daily X 10 days
> 9 to 12 months	3 mg/ kg oral solution# Twice daily X 5 days	3 mg per kg oral solution# Once daily X 10 days

\* **CAUTION:** Dosage adjustment required in renal failure if creatinine clearance < 30 mL/min  
 # **CAUTION: oral solution is prescribed in milligrams (mg) of solution (not milliliters, mL).** Errors have been made when parents interpreted mg as mL. The dosing dispenser packaged with oseltamivir (Tamiflu®) has markings only in 30, 45 and 60 mg. This works well for those over 15 kg and over 1 year. If under 1 year or less than 15 kg, a ml dropper or ml oral syringe needs to replace the prepackaged dosing dispenser with clear instructions to the parent on mls prescribed <[http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/\\_2009/tamiflu\\_2\\_hpc-cps-eng.php](http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/_2009/tamiflu_2_hpc-cps-eng.php)>.

**Note:** Dosage recommendations may be changed as new information becomes available. Please refer to reference sources for updates on dose recommendations. Current weight-based dosing recommendations are not intended for premature infants. Please seek consultation from a pediatric infectious disease clinician or pediatrician if treatment is being considered for such infants.

***What if there is no oral suspension (liquid formulation) and there are no pediatric doses of oseltamivir (Tamiflu®) capsules available?***

Emergency preparation of a suspension may be done in accordance with the Roche (*Tamiflu*®) product monograph (approved November, 2009). Options as per directions in the monograph approved by Health Canada include:

(a) compounding with Ora-Sweet®SF: Stable for 5 weeks (35 days) when stored at 25°C.

(b) compounding with Cherry Syrup (Humco®): Stable for 5 weeks (35 days) when stored in a refrigerator at 2° to 8°C.

(c) compounding with purified water containing 0.1% w/v sodium benzoate added as a preservative: Room temperature storage conditions: Stable for 3 weeks (21 days) when stored at room temperature. Do not store above 25°C.

Refrigerated storage conditions: Stable for 6 weeks when stored at 2-8°C.

## TABLE 5

### DOSAGE GUIDELINES FOR ZANAMIVIR (RELENZA®)

Available as powder for inhalation

Age > 7 years:

Treatment: 2 inhalations (10 mg) twice daily for 5 days

Prophylaxis: 2 inhalations (10 mg) once daily for 10 days

Zanamivir is relatively contraindicated in people with underlying respiratory disease, including asthma.

## REFERENCES

1. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:)
2. Hall CB, Powell KR, MacDonald NE, Gala CL, Menegus ME, Suffin SC, Cohen HJ. Respiratory syncytial viral infection in children with compromised immune function. *N Engl J Med.* 1986 Jul 10;315(2):77-81.
3. Harper SA, Bradley JS, Englund JA, File TM, Gravenstein S, Hayden FG, McGeer AJ, Neuzil KM, Pavia AT, Tapper ML, Uyeki TM, Zimmerman RK; Expert Panel of the Infectious Diseases Society of America. Clin Seasonal influenza in adults and children--diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. *Infect Dis.* 2009 Apr 15;48(8):1003-32.
4. Scalera NM, Mossad SB. The first pandemic of the 21st century: a review of the 2009 pandemic variant influenza A (H1N1) virus. *Postgrad Med.* 2009;121(5):43-7.
5. Outbreak of swine-origin influenza A (H1N1) virus infection – Mexico, March-April 2009 *MMWR: April 30, 2009 / 58(Dispatch);1-3*
6. Update: Swine influenza A (H1N1) infections --- California and Texas, April 2009. *MMWR April 24, 2009 / 58(15);400-402.*
7. American Academic of Pediatrics. Influenza. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2009 Report on Infectious Diseases.* 28<sup>th</sup> ed. Elk Grove Village, IL. American Academy of Pediatrics; 2009: 400-412.
8. Thorner AR, Hirsch MS, McGovern BH. Epidemiology, clinical manifestations, and diagnosis of pandemic H1N1 influenza ('swine influenza'). Up-To-Date. [www.uptodate.com](http://www.uptodate.com). Accessed January 17, 2010.
9. Lapinsky SE. H1N1 novel influenza A in pregnant and immunocompromised patients. *Crit Care Med* 2010 Vol. 38, No. 3 (Suppl.); S1-S6
10. Khanna N, Steffen I, Studt JD, et al. Outcome of influenza infections in outpatients after allogeneic hematopoietic stem cell transplantation. *Transpl Infect Dis.* 2009;11:100-105.
11. Couch RB, Englund JA, Whimbey E: Respiratory viral infections in immunocompetent and immunocompromised persons. *Am J Med* 1997; 102:2-9
12. Gooskens, J., Jonges, M., Claas, E.C., Meijer, A., and Kroes, A.C. 2009. Prolonged influenza virus infection during lymphocytopenia and frequent detection of drug-resistant viruses. *J Infect Dis* 199:1435-1441.
13. Cohen-Daniel, L., Zakay-Rones, Z., Resnick, I.B., Shapira, M.Y., Dorozhko, M., Mador, N., Greenbaum, E., and Wolf, D.G. 2009. Emergence of oseltamivir-resistant influenza A/H3N2 virus with altered hemagglutination pattern in a hematopoietic stem cell transplant recipient. *J Clin Virol* 44:138-140.
14. American Society of Transplantation (AST) Infectious Diseases Community of Practice / Transplant Infectious Disease Section of The Transplantation Society (TTS) Guidance On Novel Influenza A/H1N1. [http://www.a-s-t.org/files/pdf/ast\\_h1n1\\_guidance.pdf](http://www.a-s-t.org/files/pdf/ast_h1n1_guidance.pdf). accessed January 16, 2010.
15. [Goossen GM](#), [Kremer LC](#), [van de Wetering MD](#). Influenza vaccination in children being treated with chemotherapy for cancer. *Cochrane Database Syst Rev.* 2009 Apr 15;(2):CD006484.
16. Schepetiuk S, Papanoum K, Qiao M. Spread of influenza A virus infection in hospitalised patients with cancer. *Aust N Z J Med.* 1998;28:475-476.
17. Ljungman P, Nahi H, Linde A. Vaccination of patients with haematological malignancies with one or two doses of influenza vaccine: a randomised study. *Br J Haematol.* 2005;130:96-98.

18. Ring A, Marx G, Steer C, Harper P. Influenza vaccination and chemotherapy: a shot in the dark? *Support Care Cancer*. 2002;10:462-465.
19. Takata T, Suzumiya J, Ishikawa T, Takamatsu Y, Ikematsu H, Tamura K. Attenuated antibody reaction for the primary antigen but not for the recall antigen of influenza vaccination in patients with non-Hodgkin B-cell lymphoma after the administration of rituximab-CHOP. *J Clin Exp Hematop*. 2009;49:9-13.
20. Poland GA, Jacobson RM, Ovsyannikova IG. Influenza virus resistance to antiviral agents: a plea for rational use. *Clin Infect Dis*. 2009;48:1254-1256.
21. Kunisaki KM, Janoff EN. Influenza in immunosuppressed populations: a review of infection frequency, morbidity, mortality, and vaccine responses. *Lancet Infect Dis*. 2009;9:493-504.
22. Robertson JD, Nagesh K, Jowitt SN, et al. Immunogenicity of vaccination against influenza, *Streptococcus pneumoniae* and *Haemophilus influenzae* type B in patients with multiple myeloma. *Br J Cancer*. 2000;82:1261-1265.
23. Ortals DW, Liebhaber H, Presant CA, Van Amburg AL, 3rd, Lee JY. Influenza immunization of adult patients with malignant diseases. *Ann Intern Med*. 1977;87:552-557.
24. Ljungman P, Avetisyan G. Influenza vaccination in hematopoietic SCT recipients. *Bone Marrow Transplant*. 2008;42:637-641.
25. Zaia J, Baden L, Boeckh MJ, et al. Viral disease prevention after hematopoietic cell transplantation. *Bone Marrow Transplant*. 2009;44:471-482.
26. [http://www.phac-aspc.gc.ca/alert-alerite/h1n1/guidance\\_lignesdirectrices-eng.php#3](http://www.phac-aspc.gc.ca/alert-alerite/h1n1/guidance_lignesdirectrices-eng.php#3)
27. Mackowiak PA, Bartlett JG, Bordon BC, et al. Concepts of fever: recent advances and lingering dogma. *Clinical Infectious Diseases*. 1997;35:119-138.
28. Ciuraru NB, Braunstein R, Sulkes A, Stemmer SM. The influence of mucositis on oral thermometry: when fever may not reflect infection. *Clin Infect Dis* 2008;46:1859-63.
29. Boivin G, Hardy I, Tellier G, Maziade J. Predicting Influenza Infections during Epidemics with Use of a Clinical Case Definition. *Clinical Infectious Diseases*. 2000;31:1166-1169.
30. Monto AS, Gravenstein S, Elliott M, Colopy M, Schweinle J. Clinical signs and symptoms predicting influenza infection. *Arch Intern Med*. 2000;160:3243-3247.
31. Carrat F, Vergu E, Ferguson NM, et al. Time lines of infection and disease in human influenza: a review of volunteer challenge studies. *Am J Epidemiol*. 2008;167:775-785.
32. Ljungman P, Ward KN, Crooks BN, et al. Respiratory virus infections after stem cell transplantation: a prospective study from the Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant*. 2001;28:479-484.
33. Centers for Disease Control and Prevention: Interim Guidance on specimen collection, processing, and testing for patients with suspected novel influenza A (H1N1) virus infection. Atlanta, GA: US Department of Health and Human Services, CDC, 2009. <http://www.cdc.gov/h1n1flu/specimencollection.htm>.
34. PILPN [http://www.cphln.ca/CPHLN/src/documents/EN\\_H1N1\\_Best\\_Practice\\_Final\\_Version.pdf](http://www.cphln.ca/CPHLN/src/documents/EN_H1N1_Best_Practice_Final_Version.pdf) (last accessed February 9, 2010)34.
35. J. Rello, A. Rodríguez, P Ibañez, L Socias, J Cebrian, A Marques, J Guerrero, S Ruiz-Santana, Marquez, F Del Nogal-Saez, F Alvarez-Lerma, S Martínez, M Ferrer, M Avellanas, R Granada, E Maraví-Poma, P Albert, R Sierra, L Vidaur, P Ortiz, I P del Portillo, B Galván,, C León-Gil. Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain. *Crit Care*. 2009; 13(5): R148 Published online 2009 September 11. doi: 10.1186/cc8044.
36. Uyeki TM. Influenza diagnosis and treatment in children: a review of studies on clinically useful tests and antiviral treatment for influenza. *Pediatr Infect Dis J*. 2003;22:164-177.
37. Ginocchio CC, Zhang T, Manji R, et al. Evaluation of multiple test methods for the detection of novel 2009 influenza A (H1N1) during the New York city outbreak. *J Clin Virol* 2009;45:191-195.

38. Vadoo S, Stevens J, Singh K. Rapid antigen tests for diagnosis of pandemic (Swine) influenza A/H1N1. *Clin Infect Dis* 2009;49:1090-1093.
39. Boggild AK, McGeer AJ. Laboratory diagnosis of 2009 H1N1 influenza A virus. *Crit Care Med* 2010;38:(Suppl):S000-000.
40. Balish, Warnes CM, Wu K et al. Evaluation of rapid influenza diagnostic tests for detection of novel influenza A (H1N1) Virus - United States. *MMWR* 2009; 58: 826-9.
41. Leblanc JJ, Li Y, Bastien N, Forward KR, Davidson RJ, Hatchette TF. Switching gears for a pandemic: validation of a duplex RT-PCR for simultaneous detection and confirmation of the novel influenza A (H1N1) variant. *J Clin Microbiol.* 2009; 47:3805-13.
42. Faix DJ, Sherman SS, Waterman SH. Rapid-test sensitivity for novel swine-origin influenza A (H1N1) virus in humans. *N Eng J Medicine*, 2009; 361:728-9
43. Hurt AC, Baas C, Deng YM, Roberts S, Kelso A, Barr IG. Performance of influenza rapid point-of-care tests in the detection of swine lineage A (H1N1) influenza viruses. *Influenza and Other Respiratory Viruses*, 2009; 3: 171-6.
44. Sandora TJ, Smole SC, Lee GM, Chung S, Williams L, McAdam AJ. Test characteristics of commercial influenza assays for detecting pandemic influenza a (H1N1) in children. *Pediatr Infect Dis J.* 2009 Nov 20. [Epub ahead of print]
45. Drexler JF, Helmer A, Kirberg H, Reber U, Panning M, Müller M, Höfling K, Matz B, Drosten C, Eis-Hübinger AM. Poor clinical sensitivity of rapid antigen test for influenza A pandemic (H1N1) 2009 virus. *Emerg Infect Dis.* 2009 Oct;15(10):1662-4.
46. Kok J, Blyth CC, Foo H, Patterson J, Taylor J, McPhie K, Ratnamohan VM, Iredell JR, Dwyer DE. Comparison of a rapid antigen test with nucleic acid testing during cocirculation of pandemic influenza A/H1N1 2009 and seasonal influenza A/H3N2. *J Clin Microbiol.* 2010 Jan;48(1):290-1. Epub 2009 Nov 4.
47. Hatchette TF, Bastien N, Berry J, Booth TF, Chernesky M, Couillard M, Drews S, Ebsworth A, Fearon M, Fonseca K, Fox J, Gagnon JN, Guercio S, Horsman G, Jorowski C, Kuschak T, Li Y, Majury A, Petric M, Ratnam S, Smieja M, Van Caesele P. Pandemic Influenza Laboratory Preparedness Network. The limitations of point of care testing for pandemic influenza: what clinicians and public health professionals need to know. *Can J Public Health.* 2009;100: 204-7.
48. Lee N, Cockram CS, Chan PK, Hui DS, Choi KW, Sung JJ. Antiviral treatment for patients hospitalized with severe influenza infection may affect clinical outcomes. *Clin Infect Dis* 2008;46:1323-1324.
49. Hanshaoworakul W, Simmerman JM, Narueponjirakul U, et al. Severe human influenza infections in Thailand: oseltamivir treatment and risk factors for fatal outcome. *PLoS One* 2009;4(6):e6051.
50. Jain S, Kamimoto L, Bramley AM, et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. *N Engl J Med* 2009;361:1935-1944.
51. Domínguez-Cherit G, Lapinsky SE, Macias AE, et al. Critically ill patients with 2009 influenza A(H1N1) in Mexico. *JAMA* 2009;302:1880-1887.
52. Guidance for expanded use of oseltamivir (Tamiflu®) in children under one year of age in the context of Pandemic (H1N1) 2009. [www.phac-aspc.gc.ca/alert-alerte/h1n1/guidance-orientation-07-20-eng.php](http://www.phac-aspc.gc.ca/alert-alerte/h1n1/guidance-orientation-07-20-eng.php). Accessed January 16, 2010.
53. Questions and Answers on Pandemic (H1N1) 2009 Influenza: The illness and Antiviral Drugs. [http://www.cps.ca/english/H1N1\\_IllnessAntiviral.htm](http://www.cps.ca/english/H1N1_IllnessAntiviral.htm). accessed January 16, 2010.
54. Ariano RE, Sitar DS, Zelenitsky SA, et al. Enteric absorption and pharmacokinetics of oseltamivir in critically ill patients with pandemic (H1N1) influenza. *CMAJ* 2010. DOI10.1503/cmaj.092127
55. Meijer A, Lackenby A, Hungnes O, et al. Oseltamivir-resistant influenza virus A (H1N1), Europe, 2007-08 season. *Emerg Infect Dis.* 2009;15:552-560.

56. Dharan NJ, Gubareva LV, Meyer JJ, et al. Infections with oseltamivir-resistant influenza A(H1N1) virus in the United States. *JAMA*. 2009;301:1034-1041.
57. Hauge SH, Dudman S, Borgen K, Lackenby A, Hungnes O. Oseltamivir-resistant influenza viruses A (H1N1), Norway, 2007-08. *Emerg Infect Dis*. 2009;15:155-162.
58. Stephenson I, Democratis J, Lackenby A, et al. Neuraminidase inhibitor resistance after oseltamivir treatment of acute influenza A and B in children. *Clin Infect Dis*. 2009;48:389-396.
59. Deyde VM, Nguyen T, Bright RA, et al. Detection of molecular markers of antiviral resistance in influenza A (H5N1) viruses using a pyrosequencing method. *Antimicrob Agents Chemother*. 2009;53:1039-1047.
60. Zarychanski R, Stuart TL, Kumar A, et al. Correlates of severe disease in patients with 2009 pandemic influenza (H1N1) virus infection. *CMAJ*.
61. Gubareva LV, Webster RG, Hayden FG. Detection of influenza virus resistance to neuraminidase inhibitors by an enzyme inhibition assay. *Antiviral Res*. 2002;53:47-61.
62. Sheu TG, Deyde VM, Okomo-Adhiambo M, et al. Surveillance for neuraminidase inhibitor resistance among human influenza A and B viruses circulating worldwide from 2004 to 2008. *Antimicrob Agents Chemother*. 2008;52:3284-3292.
63. Deyde VM, Sheu TG, Trujillo AA, et al. Detection of molecular markers of drug resistance in the 2009 pandemic influenza A (H1N1) viruses using pyrosequencing. *Antimicrob Agents Chemother*. 2009.
64. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. *Rev Infect Dis*. 1989;11:954-963.
65. Smith JR, Ariano RE, Toovey S. The use of antiviral agents for the management of severe influenza. *Crit care Med* 2010;38, No. 3 (suppl). DOI: 10.1097/CCM.ob01e3181c85229