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TORONTO INVASIVE BACTERIAL DISEASES NETWORK

# PANDEMIC H1N1 2009 INFLUENZA SURVEILLANCE UPDATE

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Pandemic H1N1 influenza virus continues to circulate globally, and transmission remains active in the tropics of Latin America, South Asia/Indian subcontinent, and Southeast Asia. To date, the World Health Organization (WHO) reports 4,735 deaths due to pandemic H1N1 influenza. In temperate regions of the southern hemisphere, cases of pandemic H1N1 influenza have declined to below baseline levels as these nations approach the end of their influenza season.

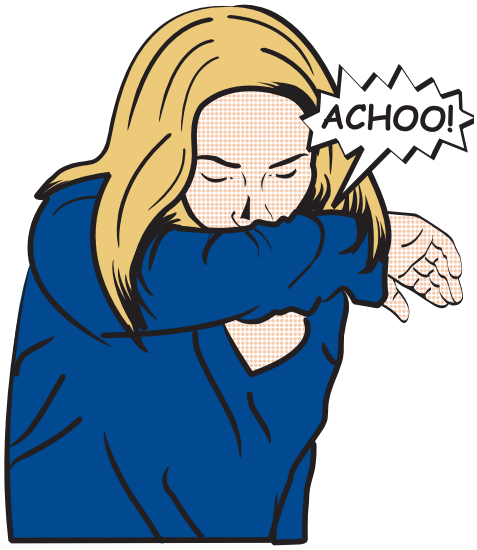
There are many lessons to be learned from the southern hemisphere experience, notably that while the overwhelming majority of those afflicted with pandemic H1N1 influenza suffered a mild course of illness, those adults who required hospitalization and ICU admission were younger than what is typically observed with seasonal influenza, and up to 50% lacked identifiable co-morbidities which would increase their risk of complicated influenza infection.

In Australia, 80% of ICU admissions due to H1N1 influenza occurred in 30-59 year olds, and in New Zealand, 12- 30% of patients hospitalized with H1N1 influenza required admission to the ICU. In general, countries of the southern hemisphere were equipped to handle pandemic H1N1 influenza, with health care worker absenteeism straining the systems' ability to respond only focally and at peak season. Surgery had to be cancelled in some hospitals, but generally only for 10-14 days.

Influenza activity continues to increase in the northern temperate zones across the world and Pandemic (H1N1) 2009 is the predominant influenza strain worldwide. In Europe, influenza activity is increasing, and in the United States, geographically widespread activity is being reported in 41 states.

In Canada, overall influenza activity has increased for a fifth consecutive week. All indicators (proportion of positive influenza tests, national ILI consultation rate, number of regions reporting widespread and localized activity and number of influenza outbreaks) were higher this week compared to the previous weeks. Four regions reported widespread activity in BC & NT and fourteen regions reported localized activity, while twenty-three regions reported sporadic activity. Of fifty-eight influenza outbreaks reported this week, 55 were in schools.

As of October 17, 2009, there have been 1,604 hospitalizations, 312 ICU admissions, and 83 deaths due to pandemic H1N1 influenza virus. 99.9% of all isolates subtyped this week were Pandemic H1N1 2009. Given increasing activity across the country, we can expect a substantial increase in influenza activity in the next few weeks. Resistance to neuraminidase inhibitors remains rare with only 3 isolates reported in Canada to date.

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## DIAGNOSTIC TESTING FOR INFLUENZA

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The recent worldwide spread of novel influenza A (H1N1) virus and the anticipated fall influenza wave has highlighted the need to ensure front line physicians have a working knowledge of influenza diagnostic testing. It is anticipated that testing supplies will be in short supply due to high numbers of influenza cases, and while jurisdictions vary in their diagnostic testing recommendations, current guidelines usually focus diagnostic efforts on patients requiring hospitalization, or those who have an underlying risk factor for severe disease (pregnancy, immunocompromised state, etc.).

Common diagnostic methodologies for influenza include rapid commercial enzyme immunoassay (EIA) tests, Direct Fluorescent Antigen (DFA) assays, reverse transcription polymerase chain reaction (rt-PCR) assays, and viral culture. All of these methods require the collection of a respiratory specimen (commonly a nasopharyngeal swab) using a specialized swab and viral transport medium (usually Minimal Essential Medium, a pink liquid). Usual bacterial culture swabs are, unfortunately, sometimes collected in error; and cannot be processed for viral testing because the cotton in the swab interferes with the test reagents. While influenza serologic testing is available, this method is used solely as an epidemiologic tool, and is not of value for individual patient care.

## INFLUENZA DIAGNOSTIC TESTS

Rapid influenza diagnostic tests (rapid tests), based on EIA (enzyme immunoassay) or DFA (direct fluorescent antigen), are appealing because the testing takes less than an hour to perform. EIA tests are similar in concept to a home pregnancy test but require some dilution and mixing of samples, and are usually licensed to be processed in a laboratory. DFA tests microscopically visualize fluorescent-labeled influenza antigen on infected respiratory epithelial cells, and require a laboratory with a fluorescence microscope and considerable technical expertise. The Centres for Disease Control and Prevention (Atlanta, GA) has recently conducted a preliminary evaluation of multiple commercial EIA tests (MMWR Morb Mortal Wkly Rep. 2009 Aug 7;58(30):826-9). Sixty-five clinical respiratory specimens collected in April/May 2009 that had previously tested positive either for novel influenza A (H1N1) or for seasonal influenza A viruses by PCR were used in the evaluation. The results showed that EIAs, although capable of detecting novel influenza A (H1N1) virus from respiratory specimens containing high levels of virus, had a low overall sensitivity (40-69%). The sensitivity of DFA tests is probably a bit better. Thus, a positive rapid test result means that the patient has influenza, but a negative result is not helpful in ruling out influenza infection. Patients with influenza-like illnesses (fever and cough and at least one other respiratory or systemic symptom) but a negative rapid test result should therefore be managed empirically based on the amount of influenza circulating in the community, level of clinical suspicion, underlying medical conditions, severity of illness, and risk for complications.

Testing with reverse-transcriptase-PCR (Rt-PCR) or virus isolation should be performed if a more definitive determination of the presence of influenza virus is required. Viral culture has the benefit of an improved sensitivity, compared to rapid tests, but requires up to 10-14 days of incubation in cell culture before a result is available. For this reason, although viral culture is critical to tracking viral evolution during a pandemic wave, it is not useful for guiding clinical practice. Rt-PCR, which detects and amplifies influenza RNA in patient samples, has the benefit of both a rapid turnaround time (several hours) and a high sensitivity (~95%) and has de facto become the gold standard for influenza testing. The drawbacks of Rt-PCR are cost and availability. Rt-PCR requires specialized equipment and laboratory staff with skills and experience in molecular techniques, and its availability has been limited to a few academic centres and public health laboratories.

## INFLUENZA SUBTYPING AND RESISTANCE TESTING

When respiratory virus testing has been requested, clinicians will usually receive a report indicating whether Influenza A and/or B was detected. In order to appropriately select antiviral therapy, clinicians must in addition know the distribution and antiviral resistance of circulating influenza strains. During the 2008/9 influenza season, for example, one of the seasonal influenza strains (H3N2) was susceptible to oseltamivir while the second (seasonal H1N1) was resistant, requiring clinicians to use a complex decision tree for determining the appropriate antiviral treatment. Fortunately, more than 99% of isolates of the 2009 H1N1 pandemic strain are so far susceptible to both oseltamivir and zanamivir, and either is effective for treatment (the strain is, however, resistant to amantadine). Reference laboratories continue to undertake strain typing and resistance testing on a systematic sample of isolates so that resistance will be detected if it arises, and to continue to inform clinicians and clinical algorithms. This testing is complex and relatively expensive. Clinicians who suspect antiviral resistance (eg. clinical deterioration while on antiviral medication) can usually request influenza A subtyping or resistance testing by directly contacting their laboratory/ microbiologist.

## DIAGNOSING AND MANAGING PATIENTS WITH SUSPECTED INFLUENZA

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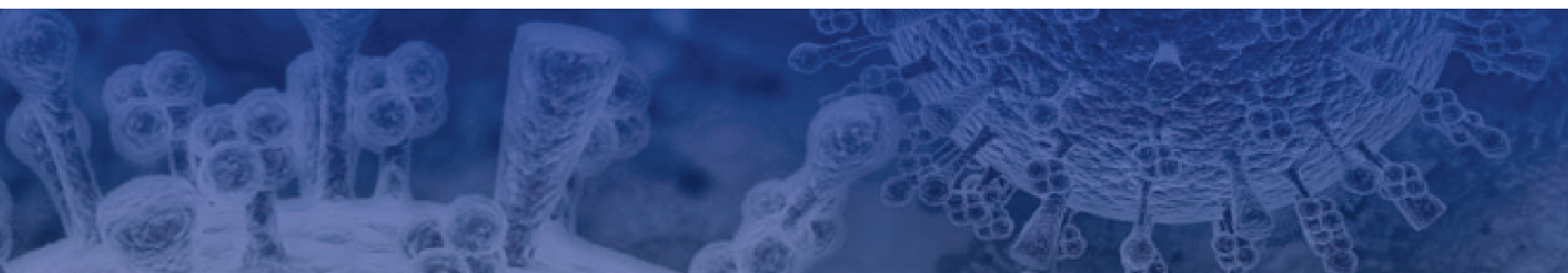
***How do you determine which patients are likely enough to have influenza that you should consider antiviral therapy?***

Most of us do not have access to any testing of out-patients for influenza. If rapid testing is available, a positive rapid test is helpful, but a negative rapid test does not significantly reduce the probability that a patient has influenza. Fortunately, during periods when influenza is circulating, laboratory testing is not necessary to identify 5-65 year olds who will benefit from therapy.

When influenza is circulating, 5-65 year olds with sudden onset of illness, fever (>38C) and early cough have an 80% chance of having influenza; generally speaking, during influenza activity, any illness with fever and either cough or sore throat has a greater than 50% chance of being influenza. It is critical to be aware of the degree of circulation of influenza – generally you can do this by being alert to messages from your local public health unit; you can also check the fluwatch website (http://www.phac-aspc.gc.ca/fluwatch/index-eng.php), or your provincial public health websites (see links on page 4 of newsletter).

Identifying influenza in young children, severely immunocompromised adults, and adults over the age of 65, is more difficult. In children, other viruses also commonly cause high fevers, and cough is less common. In older and immunocompromised adults, disease may be atypical, and they may not mount a fever. It remains true that, when influenza is active in the community, influenza like illness (fever plus cough or sore throat plus at least one other symptoms) is very likely to be influenza. However, many patients whose symptoms do not meet criteria for influenza like illness also have influenza. For instance, during influenza activity, patients requiring



hospital admission for pneumonia, exacerbation of COPD or asthma, or sepsis of uncertain origin have a 20-30% chance of having influenza. Similarly, about 20% of patients who require admission for any cardiac diagnosis (eg. myocardial infarction, new onset atrial fibrillation) and who have a fever, actually have influenza (obviously, with a complication).

### *In patients who are suspected of having influenza, who will benefit from therapy?*

If antivirals can be started within 48 hours of the onset of symptoms, it reduces symptom severity and duration by 25-40%, and the risk of complications and need for hospitalization by approximately 60%. The earlier treatment is started, the more effective it is. In an ideal world, during influenza activity due to pH1N1, all patients with influenza-like illness would be started on therapy within 48 hours of symptom onset, and this treatment would prevent most hospitalization and death. However, delivering antivirals within 48 hours of symptom onset is very difficult in our system, and disease due to this virus is usually mild. Most experts believe that the limited benefits of treating healthy patients aged 5-65 years of age does not warrant the substantial effort required to effectively deliver early therapy. In contrast, for patients with risk factors for complicated or severe influenza (eg. pregnant women, children under 2 years of age, persons with diabetes, underlying organ system disease or are immunocompromised), the Centers for Disease Control (CDC) recommends that all providers "develop methods to ensure that treatment can be started quickly after symptom onset" (http://www.cdc.gov/H1N1flu/pregnancy/antiviral_messages.htm). The Society of Obstetrics and Gynecology of Canada (SOGC) recommends that physicians "pre-position" antivirals for pregnant women. Pre-positioning means providing patients with a prescription for a treatment course of antivirals, and instructions as to when to fill the prescription and when/how to contact the healthcare system about their illness.

While most out-patients will be beginning to recover from influenza at 48-72 hours, making antiviral therapy unnecessary, there is growing evidence that patients with more severe illness (notably, those who are ill enough to require hospital admission) may benefit from antivirals even if they have been symptomatic for longer than 48 hours. Thus, patients at risk of complications from influenza who have persisting or worsening symptoms should be treated with antivirals independent of the time from onset of symptoms. Of course, it is also important to assess patients for secondary bacterial complications: in some circumstances, both antiviral and antibiotic therapy are warranted. The following table summarizes recommendations for syndromic treatment of influenza during the second wave of the pandemic .

| Patient group | Treatment recommendation during period of pH1N1 influenza activity |
|---|---|
| Patient requiring hospitalization for pneumonia, exacerbation of COPD/asthma, febrile illness of uncertain etiology, cardiac diagnosis with fever | Empiric therapy with oseltamivir |
| Influenza like illness (fever plus cough or sore throat) in a child or adult who is at risk of complications from influenza* | Empiric therapy with oseltamivir ** or zanamivir, unless patient is already clearly recovering from acute illness |
| Suspected influenza (eg acute respiratory illness in contact of lab-confirmed influenza case) in a child or adult at risk of influenza complications*, but illness does not meet criteria for influenza like illness | Consider empiric therapy |
| Influenza like illness in a previously healthy child or adult out-patient | Consider empiric therapy only if therapy can be started within 48 hours of onset of symptoms, or if fever and other symptoms are worsening after that time. |

*persons at risk of complications of pH1N1 influenza include pregnant women, children under the age of 5 years (especially children under the age of 2 years), children and adults with underlying immunocompromise, organ system disease (eg. asthma, cardiac disease, kidney or liver disease), diabetes mellitus, or neurologic conditions predisposing to aspiration. ** Oseltamivir is recommended for treatment of pregnant women.

### *What antiviral should be chosen? What dose? What duration?*

To date, >99% of pandemic 2009 H1N1 influenza viruses have been susceptible to neuraminidase inhibitors (oseltamivir and zanamivir) and resistant to amantadine. Thus, either oseltamivir or zanamivir is recommended for treatment.

Zanamivir and oseltamivir have never been directly compared; however, their effect appears to be similar. Oseltamivir is often recommended preferentially for more severely ill and high risk patients, because the systemic absorption may better protect against the development of primary viral pneumonia. Experts recommend oseltamivir specifically for pregnant women both because of the systemic absorption, and because the safety data are more robust (CMAJ. 2009 Jul &:181(1-2):55-8/ Epub 2009 Jun 15)

For adults and children over the age of 12 and without kidney disease, the treatment dose of oseltamivir is 75mg (1 capsule) orally bid for five days. This dose should be decreased to 75 mg daily in patients with estimated creatinine clearances between 10 and 35 ml/min. Doses for children, and those with end-stage renal disease can be found at (http://www.rochecanada.com/portal/eipf/ca/portal/roche/consumer_information?paf_gear_id=17700009&paf_pageId=re7191019&glossary_id=static/glossary/re7300002/re77300002/re77300003/re753001/Definition_01049.content).

Retail supplies of the 75 mg capsules of oseltamivir are adequate, and shortages are not expected this fall. In contrast, supplies of zanamivir are very limited, as are supplies of the oseltamivir liquid suspension, and the 30 and 45 mg capsules for children. Currently the reduced dose capsules are only available in government stockpiles and are not in the Canadian retail market. Should the oral suspension not be readily available, the package insert provides guidance for emergency pharmacy compounding of the capsules to produce liquid suspensions (15 mg/mL) for administration to children or adults with difficulty swallowing capsules. (http://www.rochecanada.com/portal/eipf/ca/portal/roche/consumer_information?paf_gear_id=17700009&paf_pageId=re7191019&glossary_id=static/glossary/re7300002/re77300002/re77300003/re753001/Definition_01049.content). It is also possible to open capsules and provide the medication suspended in liquid or semisolid foods such as applesauce; some pharmacies will also compound the capsules.

The most common adverse effects associated with oseltamivir are nausea and vomiting, which are reported in 2-14% of recipients. These symptoms are usually worst with the first dose, and can be mitigated to some degree by taking the medication with food. Other adverse effects were not reported more often with oseltamivir than placebo in randomized controlled trials; allergic reactions may, of course, occur, but have been rarely reported. Zanamivir is a dry powder for inhalation; the carrier powder is lactose. Case reports of bronchospasm in patients with underlying lung disease receiving zanamivir inhalations have been published, although in a randomized controlled trial of treatment of asthmatics, no impact of zanamivir on wheezing or pulmonary function could be detected. Very little zanamivir is absorbed, and systemic side effects have not been reported.

# INFLUENZA INFORMATION LINKS - 2009-2010 SEASON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