Perinatal Services BC
An agency of the Provincial Health Services Authority

Management Guideline for Pregnant Women and Neonates Born to Women with Suspected or Confirmed Pandemic H1N1 Influenza (Swine Origin A/H1N1 Influenza)

This guideline was
developed by a multidisciplinary team
coordinated by Perinatal Services BC
(formerly BC Perinatal Health Program)

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Introduction

The purpose of this document is to provide information and advice about pandemic H1N1 (swine origin influenza A/H1N1) influenza virus in the context of the care of an obstetrical patient. It draws upon multiple documents to provide a single simple source of preliminary information for the prenatal care provider.

The Public Health Agency of Canada has developed an information sheet for pregnant women – *Pregnancy and the H1N1 Flu Virus* (www.phac-aspc.gc.ca/alert-alerte/swine-porcine/pregnancy-grossesse-eng.php).[1]

The management of an obstetrical patient in the context of the pandemic H1N1 influenza should follow the most current public health and infection control recommendations. Many of these recommendations have been assembled on the Provincial Health Officer's website for physicians at http://www.health.gov.bc.ca/pho/physh1n1.html. At the time of writing of this document the following general recommendations are in effect.

Recommendations for health care providers seeing patients in clinics or hospital facilities: screening triage for fever and respiratory symptoms

All patients, including pregnant women, who present to a health care setting (whether an office, ambulatory care clinic etc.) should be screened for fever and respiratory symptoms. This should include:

- If possible, screen for respiratory symptoms by phone when the person makes or confirms their appointment; if a person coming in for routine perinatal care has respiratory symptoms assess the need for the visit and whether they can come at a time when contact with other patients, especially pregnant women and young children is minimized.
- Passive screening: signs posted at the entrances to all health care settings (clinics, Emergency Departments) asking patients to report whether they have fever and any new or worsening respiratory symptoms, and
- Active screening: At first contact, staff asks about fever and respiratory symptoms.
- Influenza symptoms include respiratory symptoms such as cough, sore throat, coryza (runny nose), as well as headache and myalgias (general body aches).

Infection prevention and control precautions for patients

Patients who report fever and respiratory symptoms should be instructed to:

- Clean their hands with 60-90% alcohol-based hand rub (or soap and water if immediately available).
- Put on a surgical mask, and
- Be seated at least 2 metres (6 feet) away from others.
- If this is not possible in the waiting room setting, she should be placed immediately in an examining room.

Routine practices and contact precautions for clinicians

Individual facility specific infection control guidelines should be reviewed on a regular basis as recommendations are changing over time. However, the general infection control practices are indicated when assessing patients with fever and respiratory symptoms:

Before a clinical assessment:

- Ensure patient is still wearing a surgical mask.
- Perform hand hygiene (alcohol based hand rub or soap and water) before and after patient assessment.
- Put on gloves.
- A gown is needed only when there is a risk of clothing or skin contamination (such as when examining young children who may have difficulty controlling their secretions).
- Consider most appropriate respiratory protection.

Respiratory protection

Along with gloves and a gown (if needed), clinicians should wear respiratory protection when within 2 meters of a suspect influenza-like-illness (ILI) case. For most care a surgical mask and eye protection is recommended; a N95 respirator with eye protection is only recommended if you are performing an aerosol-generating medical procedure. Hospital facilities are generally recommending N95 masks for all clinical contact (Work Safe BC recommendations).[2]

After a clinical assessment:

- Eye or face protection should be removed after leaving the patient's room and disposed of in either a hands-free waste receptacle (if disposable) or in a separate receptacle to go for reprocessing (if reusable).
- The surgical mask or N95 respirator should be removed by the straps, being careful not to touch the mask or respirator itself, after leaving the woman's room and disposed of in a hands-free waste receptacle.
- Health care workers should perform hand hygiene after removing the respiratory protection and after leaving the patient's room.
- Affected surfaces that may have been contaminated with droplets need to be cleaned. Routine office cleaning products are effective for respiratory viruses including influenza; no special cleaning products are needed.[3]

Overview of Pandemic H1N1 Influenza (Swine Origin A/H1N1 Influenza)

Pandemic H1N1 (swine origin A/H1N1) influenza is a novel influenza virus that has established person-to-person transmission and spread globally. On June 11, 2009 the World Health Organization declared the first pandemic of the 21st century due to this novel virus – the first pandemic in more than 40 years. Pandemic H1N1 influenza causes illness that is clinically indistinguishable from human influenza viruses. In the early reports, there was apparent worse severity in Mexico but as the outbreak has spread to many countries and the cases in Mexico have been reviewed, the level of severity has been comparable across regions. Like classic influenza, symptoms include fever, cough, sore throat, fatigue, and lack of appetite. Some people, particularly younger individuals have reported vomiting and diarrhea.[4, 5] Elderly persons appear to be less frequently infected by pandemic H1N1 influenza. Unlike seasonal human influenza, pandemic H1N1 is associated with increased rates of serious outcomes such as hospitalization and death in children and young adults, rather than the elderly. The risk factors associated with serious outcomes are chronic health conditions including cardiac or pulmonary disorders (including bronchopulmonary dysplasia, COPD, cystic fibrosis and asthma), diabetes mellitus, other metabolic diseases, cancer, immunodeficiency or immunosuppression, renal disease, anemia or hemoglobinopathies and conditions that compromise the management of respiratory secretions and are associated with an increased risk of aspiration.

Reports from the Public health Agency of Canada up to August 22, 2009, show that pregnant women made up 5% of cases of all reproductive aged women with H1N1 infection but were 30% of hospitalized patients and 30% of women of childbearing age who died were pregnant.

Because pandemic H1N1 is antigenically quite distinct from recent human influenza viruses, the seasonal influenza vaccine administered in 2008-2009 is not anticipated to provide protection against pandemic H1N1. Early immunogenicity studies show little effect of seasonal vaccine on pandemic H1N1 antibody levels pre- and post-immunization among young adults.[6] Manufacturers globally are working with the WHO and public health to develop a specific vaccine against pandemic H1N1 but this will likely take many months. Antiviral therapy can be used for treatment and in some cases for prophylaxis (see later section on antivirals in pregnancy).

Review of Epidemiology to date

The epidemiology of this infection is changing rapidly and up to date reporting is being posted on Public Health Agency of Canada (http://www.phac-aspc.gc.ca/alert-alerte/swine_200904-eng.php), the BC Centre for Disease Control websites as well as on the PHSA website. (www.bccdc.org, www.phsa.ca) International information is available on the World Health Organization (WHO) website as well as the Centre for Disease Control (Atlanta, Georgia).[7,8,9,10,11]

Because the pandemic H1N1 virus has already established easy person-to-person transmission and has spread globally, neither the WHO nor Canada are advising restriction of regular travel or closure of borders. It is considered prudent for people who are ill to delay

international travel and for people developing symptoms following international travel to seek medical attention, in line with guidance from national authorities.

There is no risk of infection from this virus from consumption of well-cooked pork and pork products. Individuals are advised to wash hands thoroughly with soap and water on a regular basis and stay home if they develop any symptoms of influenza-like illness. If they think they may need medical attention and are in B.C., they can call HealthLink BC at 8-1-1 for advice.[12]

Clinical guideline on specimen collection and testing for pandemic H1N1

In British Columbia – and to meet national notification requirements – public health emphasizes testing of all patients hospitalized with suspect influenza H1N1 – notably those admitted with influenza-like illness. Persons with severe respiratory illness will be the highest priority for testing.

Clinicians should test suspected cases of pandemic H1N1 among those hospitalized with influenza-like illness or otherwise with severe manifestations by obtaining an upper respiratory specimen, preferably with a nasopharyngeal swab. Where appropriate, bronchoalveolar lavage (BAL) may also be submitted from severe cases. A confirmed case of pandemic H1N1 is defined as detection by PCR, culture or four-fold rise in specific antibody titre based on acute compared to convalescent sera.

It is unknown how long viral shedding continues with pandemic H1N1 but current guidelines suggest that shedding is 2 days prior to the illness and until 7 days from illness onset OR until fever has resolved, whichever happens last.

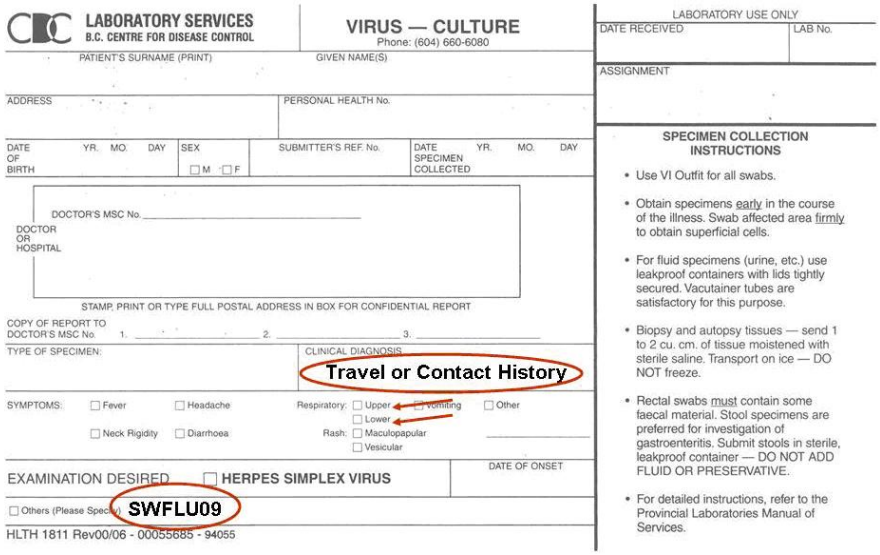
In BC, testing can be done at the BCCDC laboratories but require mandatory information be completed on the lab requisitions.

Lab Requisitions:

Please complete the requisition as thoroughly as possible. Medical mandatory requirements are outlined below and must be used on our regular BCCDC Virology-Culture (HLTH 1811) requisitions (including use with ILI outbreak form):

- Please provide **medical mandatory information** including the following if present:
    - Fever
    - Lower Respiratory Tract Infection / Pneumonia / Severe Respiratory Infection (SRI) / Hospitalized
    - Upper Respiratory Tract Infection
    - Degree of severity – i.e., hypoxia, requiring mechanical ventilation

- In the "Other (Please Specify)" area, please use the code **SWFLU09** as a unique Outbreak/Alert Identifier and highlight SRI or hospitalized as applicable.



LABORATORY SERVICES
B.C. CENTRE FOR DISEASE CONTROL

VIRUS — CULTURE
Phone: (604) 660-6080

PATIENT'S SURNAME (PRINT) GIVEN NAME(S)

ADDRESS PERSONAL HEALTH No.

DATE OF BIRTH YR. MO. DAY | SEX ☐ M ☐ F | SUBMITTER'S REF. No. | DATE SPECIMEN COLLECTED YR. MO. DAY

DOCTOR OR HOSPITAL
DOCTOR'S MSC No.
STAMP, PRINT OR TYPE FULL POSTAL ADDRESS IN BOX FOR CONFIDENTIAL REPORT

COPY OF REPORT TO DOCTOR'S MSC No. 1. 2. 3.

TYPE OF SPECIMEN: CLINICAL DIAGNOSIS

Travel or Contact History

SYMPTOMS: ☐ Fever ☐ Headache ☐ Neck Rigidity ☐ Diarrhoea
Respiratory: ☐ Upper ☐ Lower ☐ Vomiting ☐ Other
Rash: ☐ Maculopapular ☐ Vesicular

EXAMINATION DESIRED ☐ HERPES SIMPLEX VIRUS DATE OF ONSET

☐ Others (Please Specify) SWFLU09

HLTH 1811 Rev00/06 - 00055685 - 94055

LABORATORY USE ONLY
DATE RECEIVED LAB No.
ASSIGNMENT

SPECIMEN COLLECTION INSTRUCTIONS

- Use VI Outfit for all swabs.
- Obtain specimens early in the course of the illness. Swab affected area firmly to obtain superficial cells.
- For fluid specimens (urine, etc.) use leakproof containers with lids tightly secured. Vacutainer tubes are satisfactory for this purpose.
- Biopsy and autopsy tissues — send 1 to 2 cu. cm. of tissue moistened with sterile saline. Transport on ice — DO NOT freeze.
- Rectal swabs must contain some faecal material. Stool specimens are preferred for investigation of gastroenteritis. Submit stools in sterile, leakproof container — DO NOT ADD FLUID OR PRESERVATIVE.
- For detailed instructions, refer to the Provincial Laboratories Manual of Services.

Specimens:

Optimal specimens continue to be **Nasopharyngeal Swabs (COPAN flocked swabs**) BUT Starplex® non-flocked swabs are also acceptable for nasopharyngeal and nasal samples. **For those offices and clinics that do not have ready access to these swabs, the swabs and transport media used for genital herpes culture/PCR are acceptable.** DO NOT use the wire shaft pertussis swab as it interferes with the test and may give false negative results.

Specimen Collection:

a) For personal protection, it is recommended that gloves, gown, eye protection, be worn while collecting specimens.

b) Patients with copious discharge should be requested to gently clean their nose by washing or with tissue.

c) Incline the patient's head as required and insert the cotton swab perpendicular to the face to a depth of 2–3 cm into the nostril. Swab around the inside of the nostril

and along the floor of the nasal cavity by rotating the swab shaft between the fingers,

d) Break or cut off the swab shaft and place into the accompanying vial of transport media and tighten the lid securely.

e) **Label** the container with the patient's **full name** and **date of birth**.

Transport/Alerts

Standard transportations procedures used to transport to BCCDC can be utilized.

BCCDC Tests/Results

Testing for Influenza using RT-PCR will take place in the BCCDC Virology Lab regularly depending on the volume and stage of the outbreak/epidemic. Please ensure that correct, reachable phone numbers are included on the requisition,

As noted the Medical Microbiologists on-call is 604-661-7033 for other issues.[13]

Clinical guideline for management of pregnant women

There are insufficient data available at this point to determine who is at higher risk for complications of pandemic H1N1. Pregnant women have been noted to be at higher risk of dying during the pandemics of 1918 and 1957. Adverse pregnancy outcomes were also highlighted during the 1918 pandemic, with increased rates of spontaneous abortion and preterm birth reported, especially among women with pneumonia. Pregnant women, especially those in third trimester, are also known to be at higher risk of complications requiring hospitalization due to seasonal influenza.

Early reports suggest that pregnant women are at higher risk of complications due to pandemic H1N1.[14,15] Specific reports regarding the pattern of pandemic H1N1 illness in pregnancy are only just being made available. Prior to this outbreak, there was a report from 1988 of a previously healthy 32-year-old pregnant woman who was hospitalized for pneumonia and died 8 days later after infection with another variant of swine influenza. A recent report from MMWR (May 12, 2009),[16] stated that to date in the U.S. there have been 20 cases of pandemic H1N1 in pregnancy. Mean age was 26 years (range 15-39), 3 cases were hospitalized and one woman died. In Canada, there has been one death reported to date in a pregnant woman at 28 weeks gestation.

Clinical Presentation

Pregnant women with pandemic H1N1 may present with typical acute respiratory illness (e.g., fever/feverishness, cough, sore throat, fatigue). Many pregnant women will go on to have a typical course of uncomplicated influenza. However, for some pregnant women, illness might progress rapidly, and might be complicated by secondary bacterial infections including pneumonia. Fetal distress associated with severe maternal illness can occur. Pregnant women, especially those in third trimester, should be instructed to seek early care if they develop influenza-like symptoms in the context of pandemic H1N1 circulating in their community – particularly if they have known contact with a case. Pregnant women who have suspected pandemic H1N1 should be tested as described above. Of note, in some facilities a rapid viral respiratory illness testing – VIRAP – is available that permits the diagnosis of other viral pathogens that might aid in differential diagnoses. Rapid tests, however, should not be

considered to rule out pandemic H1N1 where it is otherwise suspected on clinical or epidemiologic grounds.

General Management

Pregnant women with mild influenza like illness should be managed at home but should self isolate and call their prenatal care provider. They can also be advised to call HealthLink BC at 8-1-1 for advice if they have any questions, if their condition deteriorates, or if they fail to improve within a few days. If assessment in office or clinic is required they should be advised to call ahead and on arrival should put on a mask and sanitize or wash their hands, mask and be seen in a separate room from other patients, ideally at the end of a clinic. If assessment or admission to hospital is required, again women and/or their care providers should alert infection control and primary staff that they are coming and ideally should be shown into a separate room for assessment following hospital infection control procedures for respiratory isolation. These guidelines may change as the epidemic evolves so consultation with local infection control staff is important.

Antiviral Information

Oseltamivir and zanamivir are neuraminidase inhibitors active against pandemic H1N1 but the current seasonal influenza is resistant in many cases to these antivirals. Their mechanism of action involves a crucial step in the life cycle of influenza A and B. A viral surface glycoprotein (hemagglutin) binds to sialic acid residues on respiratory epithelial surface glycoproteins, which is necessary for the initiation of infection. After the virus replicates, it is also attached to the host cell the same way until neuraminidase cleaves this link and frees the new virions.[17,18]

Zanamivir is inhaled as a dry powder (10 mg bid for five days for treatment) and oseltamivir is an oral drug (75mg po bid for five days for treatment). The major side effects are nausea and vomiting, but there has been some concern with respiratory distress associated with zanamivir, particlulary in asthmatic persons.[19,20]

Antiviral Treatment for Pandemic H1N1 in Pregnancy

The currently circulating pandemic H1N1 is sensitive to the neuraminidase inhibitor antiviral medications zanamivir (Relenza) and oseltamivir (Tamiflu), but is resistant to the adamantane antiviral medication, amantadine. Pregnant women with moderate or severe influenza like illness with symptoms that include cough, fever, myalgias, respiratory distress (with or without nausea and vomiting), should be tested for pandemic H1N1 and offered empiric antiviral therapy. Early treatment should especially be considered for pregnant women in third trimester since they are at highest risk of serious outcomes. Individuals with mild disease and other co-morbid conditions such as severe asthma can also be considered for early antiviral therapy.

As is recommended for other persons who are treated, antiviral treatment with oseltamivir or zanamivir should be initiated as soon as possible after the onset of influenza symptoms, with benefits expected to be greatest if started within 12 hours of onset based on data from studies of seasonal influenza. Benefit declines when therapy is started more than 48 hours after illness onset. However, some data from studies on seasonal influenza suggest there may be benefit for hospitalized patients even if treatment is started more than 48 hours after onset.[21] **Of note, treatment in the second and third trimester of pregnancy is believed to be of particular importance as data on increased complications due to influenza appears to be primarily in later pregnancy**.

Antiviral Treatment for pandemic H1N1 in Pregnancy – Benefit/Risk Considerations

Choice of antiviral regimen needs to be consistent with current public health recommendations and based on availability of antivirals. Because of the limited information available related to effects of influenza antiviral drugs on pregnant women and their fetuses, oseltamivir or zanamivir should be used during pregnancy when the potential benefit justifies the potential risk to the embryo or fetus. Women in third trimester are at greater risk of serious complications due to influenza, including pandemic H1N1 and, furthermore, any theoretical safety concerns to the fetus are lowest in third trimester. However, where illness warrants treatment, antivirals should not be withheld from pregnant women because of undue safety concerns, regardless of gestational age. Early evidence suggests pregnant women may be at higher risk for severe complications from pandemic H1N1, and the benefits of treatment or chemoprophylaxis with oseltamivir or zanamivir likely outweigh the theoretical risks of antiviral use.

Although, both oseltamivir and zanamivir are FDA Category C drugs indicating there is no human data,[22, 23] there are no proven human pregnancy risks or complications so they can be used at the clinicians' discretion in pregnancy.[24, 25, 26] There is limited pregnancy data with animal studies with doses 100 times that of treatment doses, demonstrating minor skeletal alterations in rats when pregnant rats are given zanamivir and there are similar findings in pregnant rabbits given oseltamivir.

A recent review of the safety of influenza antivirals in pregnancy published in the Canadian Medical Association Journal emphasizes that limited data suggest oseltamivir is not a major human teratogen and, because of more data about its safety in pregnancy, the use of oseltamivir may be preferred over zanamivir during pregnancy. First choice in pregnancy for a women with mild/moderate and critical illness would be oseltamivir. Zanamivir may also be used, but there are less data available about its safety and/or efficacy in pregnant women. Because there is less systemic absorption of zanamivir, some have suggested it may be used preferentially on theoretical grounds in women in their first trimester if they do not have a history of asthma.

Several studies have shown that fever during pregnancy is associated with an increased risk of birth defects and other adverse outcomes. For this reason, fever in pregnant women should be treated. Acetaminophen appears to be the best option for treatment of fever during pregnancy.

Antiviral Dosing Regimens

Recommendations for use of antivirals for pregnant women might change as additional data on the benefits and risks of antiviral therapy in pregnant women become available. Current dosing recommendations for **treatment** are per usual as:

Oseltamivir – 75mg po bid x 5 days
Zanamivir – 10mg (2 inhalations) inhaled, twice daily x 5 days.[27]

Breastfeeding Considerations

Breastfeeding is encouraged as there may be a theoretical advantage to the neonate of passive transmission of antibodies to influenza virus from an exposed or infected mother.

Women who are breastfeeding can continue while receiving antivirals. However, women who are ill with pandemic H1N1 should take steps to minimize the exposure to their infants, including frequent hand washing and possibly wearing a mask.

Although the risk for pandemic H1N1 transmission through breast milk is unknown, reports of transmission of seasonal influenza infection are rare.

A handout from the CDC that might be useful:[28] http://www.cdc.gov/h1n1flu/infantfeeding.htm

Clinical guideline for management of the neonate

It is recommended that neonates of mothers with an influenza-like illness be observed closely for signs of respiratory illness. Isolation of these infants from others by rooming in with the mother is generally the appropriate approach. Neonates requiring admission to a nursery should be isolated as per standard NICU respiratory precautions. If neonates become ill with possible influenza like illness, consultation with a pediatrician and/or infectious diseases is recommended.

The characteristics of human infections with pandemic H1N1 are still being studied, and it is not known whether infants are at higher risk for complications associated with pandemic H1N1 infection compared to older children. Limited safety data on the use of oseltamivir (or zanamivir) is available from children less than one year of age, and oseltamivir is not licensed for use in children less than 1 year old.

Oseltamivir use for children less than 1 year old was recently approved in the US by the FDA under an Emergency Use Authorization (EUA), and dosing for these children is age-based. Recommended doses of oseltamivir antiviral medication for infants <3 months is 12 mg twice daily, however dose adjustments in this age group may need to be modified based on weight. Consultation with an expert is recommended.[29] The Canadian Pediatric Society Guideline provides a helpful reference to general management of children and youth.[30]

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