

This document is developed by the Pandemic/Influenza A H1N1 Expert Advisory Resource Team. The recommendations are interim and based on information available at the time of development. This document is subject to review and change as new information becomes available, given the emerging situation of Influenza A Pandemic (H1N1) 2009 Virus.

## Interim Prevention and Treatment Recommendations for Pandemic H1N1 in Pregnant & Breastfeeding Women and their Infants in the context of Pandemic (H1N1) 2009 Virus

### Background:

- Pregnant women are at no greater risk of infection with influenza, but once infected have been identified as a group at increased risk for severe disease from influenza, and of influenza-related complications, both with seasonal influenza viruses, and with Pandemic (H1N1) 2009 Virus. Risk of severe disease appears to increase throughout pregnancy and continues in the early post partum period.
- Pregnant women with underlying health conditions<sup>1</sup> appear to be at additional risk for severe influenza illness.
- Newborns have been identified as a group at increased risk for severe disease from influenza.
- Although underlying illness and pregnancy increase the relative risk of severe influenza illness, the absolute risk of severe illness in any individual patient remains low.
- Fever (from any cause) in pregnancy has been associated with an increased incidence of congenital anomalies.
- Neuraminidase inhibitors oseltamivir and zanamivir have been deemed effective treatment options in the context of Pandemic (H1N1) 2009 Virus infection.
- Oseltamivir and zanamivir are both rated risk category C (FDA) in pregnancy
- Confirmatory laboratory testing is recommended for patients with severe influenza illness who may require hospital admission. Results are unlikely to be available to clinicians at the time when initiation of antivirals is most likely to be of benefit (within 48 hours of onset of symptoms).

### Definitions:

**Influenza-Like-Illness (ILI)** means new cough or change in existing cough plus one or more of: fever, sore throat, joint pain, muscle aches, prostration.

**Underlying health conditions** means cardiac or pulmonary disorders (including bronchopulmonary dysplasia, cystic fibrosis and asthma), diabetes mellitus and other metabolic diseases cancer, immunodeficiency, immunosuppression (due to underlying disease and/or therapy) renal disease anemia or hemoglobinopathy.

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<sup>1</sup> Canada's National Advisory Committee for Immunization 2008: Significant co-morbidities include cardiac or pulmonary disorders (including bronchopulmonary dysplasia, cystic fibrosis and asthma), diabetes mellitus and other metabolic diseases cancer, immunodeficiency, immunosuppression (due to underlying disease and/or therapy) renal disease anemia or hemoglobinopathy.

### **A1. Interim Recommendations for advice to all pregnant women in the context of Pandemic (H1N1) 2009 Virus circulating in the community**

1. All pregnant women should be cautioned to practice personal protective behavior, including frequent handwashing, respiratory etiquette and avoiding contact with sick individuals.
2. All pregnant women should be counseled concerning the risks and benefits of influenza immunization and provided with information to access vaccine when it becomes available.
3. All pregnant women should be counseled in the identification of fever and the use of antipyretics.
4. All pregnant women should be aware of the symptoms of influenza-like illness and advised to report symptoms of influenza to their care provider as soon as possible.

### **A2. Interim Recommendations for treatment of pregnant women with Influenza-Like Illness (ILI) or confirmed\* Pandemic (H1N1) 2009 Virus infection.**

1. Pregnant women with ILI or confirmed Pandemic (H1N1) 2009 Virus infection should be counseled about the increased risk of severe illness and influenza-related complications in pregnant women, and they should be offered treatment in this context. Confirmatory laboratory testing is not needed when determining the need for antiviral treatment.

#### **It is recommended that antiviral treatment:**

- be **offered** to women in their first trimester of pregnancy
- be **recommended** to women in the second trimester
- be **strongly recommended** for women in their third trimester or first month postpartum
- be **strongly recommended** to pregnant women who have underlying health conditions which predispose to severe influenza illness

2. Treatment should ideally be initiated within 48 hours of symptom onset and as soon as possible, but may be considered after 48 hours of onset of illness in severe cases. *nb. In situations where pregnant women are cared for by providers who cannot prescribe antiviral drugs (e.g. midwives) arrangements should be made to facilitate prompt access to antiviral drug therapy when clinically indicated.*

3. Treatment with either zanamivir or oseltamivir is considered acceptable choices in pregnancy.

4. Pregnant women should be offered the choice of either inhaled zanamivir or oral oseltamivir. Zanamivir ***may be the preferred choice*** for many pregnant women as it is administered by inhalation and is poorly absorbed systemically.

***In cases of severe disease, oseltamivir may be the preferred choice*** based on a theoretical risk of systemic viremia.

Oseltamivir may also be preferred for patients with a history of severe asthma or severe reactive airways to avoid potential bronchospasm which could be associated with zanamivir use.

Infectious Disease specialist consultation is advised if further assistance is needed in choosing the most appropriate treatment plan.

*\* Laboratory confirmation of influenza A Pandemic (H1N1) 2009 Virus infection with or without clinical symptoms is by one or more of the following tests: RT-PCR, viral culture, or a four-fold rise in influenza Pandemic (H1N1) 2009 Virus specific neutralizing antibodies.. Public Health may consider treatment of symptomatic household contacts of confirmed cases of Pandemic (H1N1) 2009 Virus, if the ill household contact is at an increased risk of complications related to influenza (including pregnant women).*

### **A3. Interim Recommendations for treatment of pregnant women who are close or household contacts of ILI or confirmed cases of Pandemic (H1N1) 2009 Virus**

Public Health recommends **early treatment** of close or household contacts of confirmed cases of Pandemic (H1N1) 2009 Virus if the contact:

- has typical influenza-like illness (fever and cough or myalgias or sore throat), and
- is at high risk for influenza-related complications, and
- presents within 48 hours of symptom onset.

**Pregnant women are at high risk for influenza-related complications and should be offered early treatment if they meet the other criteria.** (Refer to the treatment recommendations for pregnant women with confirmed Pandemic (H1N1) 2009 Virus infection for specific anti-viral recommendations.)

### **B1. Interim Recommendations for treatment of breastfeeding women with confirmed Pandemic (H1N1) 2009 Virus**

1. Breastfeeding women should be counseled about the modes of transmission of influenza, about effective hand washing, and to consider using a mask when breastfeeding to protect their nursing child from respiratory infection. They should be encouraged to **continue** breastfeeding. (Please refer to recommendations for breastfeeding practices below).
2. Treatment is indicated for most symptomatic breastfeeding women on the basis that their household contacts (children under 24 months of age) are identified as vulnerable contacts. They should be counseled about the theoretical risks and benefits of antiviral therapy in breastfeeding, and offered treatment in this context.
3. When treatment is indicated for breastfeeding women, either zanamivir or oseltamivir would be considered acceptable, but the **preferred** agent is zanamivir. Oseltamivir may be considered as an alternative when zanamivir is not well tolerated, or when the mother is known to have severe reactive airway disease, or severe influenza infection.

### **B2. Interim Recommendations for breastfeeding practices in the context of Influenza A Pandemic (H1N1) 2009 Virus**

Though there is no specific information about breastfeeding and this new influenza virus, the following recommendations are based on experience from seasonal influenza. The risk of transmission of virus through breast milk is unknown but thought to be very small because reports of viremia that could result in influenza virus in breast milk during seasonal influenza are extremely rare.

1. Various agencies (CDC and the Academy of Breastfeeding Medicine) recommend that breastfeeding mothers who have ILI or confirmed influenza A Pandemic (H1N1) 2009 Virus continue to breastfeed and even increase feeding because breastfeeding can limit the

severity of respiratory infections in infants. Clinicians should promote this recommendation during influenza outbreaks.

2. Infants who are ill with ILI or confirmed Pandemic (H1N1) 2009 Virus should continue to breastfeed for the same reason.
3. If mother or infant are too ill to breastfeed, breast milk should be pumped and given as expressed milk to the infant.
4. A mother who is ill may use a mask to reduce the risk of transmission to her nursing infant. Respiratory etiquette should be practiced at all times, avoiding coughing or sneezing into the infant's face.
5. Parents should limit close contact of the infant to non-caregivers, and avoid taking the infant out into crowds.

Good hygiene measures should be practiced:

- washing adult and infant hands frequently with soap and water, especially after infants place their hands in their or others' mouths
- limit the sharing of toys and other items that have been in infants' mouths, and cleaning them after use
- keeping pacifiers out of adults' mouths or other infants' mouths prior to giving to the infant

### **B3. Recommendations for Antiviral Prophylaxis of Pregnant Women in the context of Influenza A Pandemic (H1N1) 2009 Virus**

Due to frequent opportunities for exposure to influenza A virus in the community, the low absolute risk of severe influenza illness, and the availability of effective early treatment, it is recommended that antiviral drugs NOT routinely be used as prophylaxis for pregnant women.

### **C1. Interim Recommendations for treatment of newborns in the context of Influenza A Pandemic (H1N1) 2009 Virus**

Infants and particularly newborns are at high risk for severe influenza illness and those under 6 months of age are not eligible for influenza immunization. In the context of Pandemic (H1N1) 2009 Virus Health Canada has produced an Interim Order permitting the use of Oseltamivir for children < 1 year old. Treatment can be considered for infants with ILI symptoms but based on limited evidence in this age group, benefits are uncertain and side effects such as vomiting and diarrhea may be an issue. Expert opinion supports **recommending** oseltamivir treatment for infants who require hospital admission or for those with underlying comorbid conditions.

Pediatric Infectious Disease specialist consultation is advised if further assistance is needed in choosing the most appropriate treatment plan.

#### **Recommended Antiviral Treatment Dose by Age for Pediatric Patients less than 1 year for Oseltamivir**

<b>Age</b>	<b>Recommended Treatment Dose for 5 Days</b>
6-11 months	25 mg twice daily
3-5 months	20 mg twice daily
< 3 months	12 mg twice daily

### Recommended Antiviral Treatment Dose by Weight for Pediatric Patients less than 1 year for Oseltamivir

Age	Recommended Treatment Dose for 5 Days
> 9 months	3.5 mg/kg/dose twice daily
less than 9 months	3.0 mg/kg/dose twice daily

Based on <http://www.cdc.gov/h1n1flu/recommendations.htm> (accessed October 21, 2009)

#### **Antiviral Chemoprophylaxis**

Prophylactic treatment for infants other than for outbreak control in a closed setting is NOT routinely recommended. Pediatric Infectious Disease specialist consultation is advised if further assistance is needed in assessing risks and benefit of prophylaxis.

#### **Adverse Reaction Reporting**

Reports of adverse reactions to antiviral medications in pregnant or breastfeeding women and their newborns is important as there is limited safety data available for these groups. It is recommended to promptly report any suspected serious adverse reactions involving an antiviral medication to Health Canada at: Adverse reaction reporting, Marketed Health Products or call: 1-866-234-2345.

#### **D1. Interim Recommendations for Infection Control in Obstetric and Perinatal Care Settings**

Guidelines for Management of Pregnant Women with Confirmed, Probable, or Suspected H1N1 Illness in facility settings can be found at:

<http://www.albertahealthservices.ca/files/ns-guidelines-management-pregnant-women-h1n1-directive-01-003.pdf>

#### **D2 Interim Recommendations for Infection Control in Community Obstetric Practice**

Providers should routinely practice meticulous hand hygiene and respiratory etiquette (cover mouth and nose with coughing and sneezing).

Providers shall self isolate and avoid contact with patients when suffering a fever and cough illness. In anticipation of seasonal influenza and Influenza A Pandemic (H1N1) 2009 virus, providers should make plans for alternate coverage to ensure that clinical care is not disrupted during the provider's absence due to illness.

Detailed recommendations for infection control measures in community clinical settings can be found at: <http://www.albertahealthservices.ca/files/ns-source-control-to-prevent-transmission-directive-01-004.pdf>

<http://www.phac-aspc.gc.ca/alert-alerte/h1n1/guidance-orientation-amb-07-16-eng.php>

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- Academy of Breastfeeding Medicine. Breastfeeding and H1N1 Influenza A – Information for Physicians. <http://www.bfmed.org/Media/Files/Documents/H1N1%20and%20Breastfeeding%20-%20for%20physicians1.pdf> . May 7, 2009. Accessed September 16, 2009
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<b>Medications and selected background information</b>		
<b>Medication</b>	<b>zanamivir</b>	<b>oseltamivir</b>
<b>Pregnancy risk category</b>	<p><b>Rating C (FDA)</b></p> <p>Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.</p> <p><b>from Micromedix:</b></p> <p><b>A) Teratogenicity/Effects in Pregnancy</b>  <b>1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Relenza®, 2003) (All Trimesters)</b>  <b>a)</b> Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.            See Drug Consult reference: <a href="#">PREGNANCY RISK CATEGORIES</a>  <b>2) Crosses Placenta: Unknown</b>  <b>3) Clinical Management</b>  <b>a)</b> Zanamivir has been shown to cross the placenta in rats and rabbits (Prod Info Relenza®, 2003). There is insufficient clinical experience with zanamivir to confirm its safety in human pregnancy. Zanamivir should only be used in women during pregnancy if the maternal benefit justifies the potential risk to the fetus (Prod Info Relenza®, 2003).  <b>4) Literature Reports</b>  <b>a)</b> No reports describing the use of zanamivir during human pregnancy have been located. According to the manufacturer, fertility studies in rats did not show adverse reproductive effects in males and females given intravenous doses of up to 90 mg/kg/day. It was estimated that this dose would produce blood concentrations (AUC) more than 300 times the human dose in humans using inhalation therapy. No malformations, maternal toxicity, or embryotoxicity were observed in pregnant rats or rabbits and their fetuses using a similar dose. Zanamivir crosses the placenta in rats and rabbits, although fetal blood concentrations are considerably lower than those in the mother (Prod Info Relenza(R), 2003). <b>b)</b> The offspring of rats given zanamivir doses of 1, 9, or 80 mg/kg three times daily (highest dose approximates 1000 times the maximum recommended human exposure) from days 7 to 17 of gestation showed an increased incidence of minor skeletal alterations. However, the individual incidence rates of the malformations remained within that normally expected in the population (Prod Info Relenza(R), 2003).</p>	<p><b>Rating C (FDA)</b></p> <p>Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.</p> <p><b>from Micromedix:</b></p> <p><b>A) Teratogenicity/Effects in Pregnancy</b>  <b>1) U.S. Food and Drug Administration's Pregnancy Category: Category C (Prod Info Tamiflu®, 2001a) (All Trimesters)</b>  <b>a)</b> Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.            See Drug Consult reference: <a href="#">PREGNANCY RISK CATEGORIES 2</a>) Crosses Placenta: Unknown <b>3) Clinical Management</b>  <b>a)</b> There is insufficient clinical experience with oseltamivir to confirm its safety in pregnancy. Until additional data are available, caution should be exercised with the use of oseltamivir in pregnant women.  <b>4) Literature Reports</b>  <b>a)</b> No human studies of pregnancy outcomes after exposure to oseltamivir have been published, and there have been no reports of outcomes after inadvertent exposure during pregnancy.</p>

	<p><b>from Lexidrugs:</b> PREGNANCY IMPLICATIONS — Zanamivir has been shown to cross the placenta in animal models, however, no evidence of fetal malformations has been demonstrated. There are no adequate and well-controlled studies in pregnant women.</p>	<p><b>from Lexidrugs:</b> PREGNANCY IMPLICATIONS — There are insufficient human data to determine the risk to a pregnant woman or developing fetus. Studies evaluating the effects on embryo-fetal development in rats and rabbits showed a dose-dependent increase in the rates of minor skeleton abnormalities in exposed offspring. The rate of each abnormality remained within the background rate of occurrence in the species studied.</p>
<b>Breastfeeding</b>	<p><b>from Lexidrugs:</b> LACTATION — Excretion in breast milk unknown/use caution  BREAST-FEEDING CONSIDERATIONS — Zanamivir has been shown to be excreted in the milk of animals, but its excretion in human milk is unknown. Caution should be used when zanamivir is administered to a nursing mother.</p>	<p><b>from Lexidrugs:</b> LACTATION — Enters breast milk/not recommended  BREAST-FEEDING CONSIDERATIONS — Oseltamivir and its carboxylate metabolite have been detected in breast milk. Breast milk samples were obtained from a single patient (~9 months post-partum) over the course of 5 days of treatment. The maximum total concentration of oseltamivir (expressed as parent drug and metabolite) was 81.6 ng/mL. Using a milk concentration of 81.6 ng/mL, the estimated exposure to the breastfeeding infant would be ~0.5% of the weight adjusted maternal dose (in a 60 kg woman).</p>
	<p><b>from Micromedix:</b>  <b>B) BREASTFEEDING</b> <b>1) Thomson Lactation Rating:</b> Infant risk cannot be ruled out. <b>a)</b> Available evidence and/or expert consensus are inconclusive or are inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding. <b>2) Clinical Management</b> <b>a)</b> It is not known if zanamivir is excreted into human breast milk, although it has been shown to be present in the milk of lactating rats (Prod Info Relenza®, 2003a). The effects on the nursing infant from possible exposure to the drug in milk are unknown. Zanamivir should be used with caution in nursing women (Prod Info Relenza®, 2003a). <b>3) Literature Reports</b> <b>a)</b> No reports describing the use of zanamivir during human lactation or measuring the amount, if any, of the drug excreted into milk have been located.</p>	<p><b>from Micromedix:</b>  <b>B) BREASTFEEDING</b> <b>1) Thomson Lactation Rating:</b> Infant risk cannot be ruled out. <b>a)</b> Available evidence and/or expert consensus are inconclusive or are inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding. <b>2) Clinical Management</b> <b>a)</b> It is not known whether oseltamivir is excreted into human breast milk and the potential for adverse effects in the nursing infant from exposure to the drug are unknown. <b>3) Literature Reports</b> <b>a)</b> No reports describing the use of oseltamivir during human lactation or measuring the amount, if any, of the drug excreted into milk have been located. Oseltamivir and oseltamivir carboxylate are excreted into the milk of lactating rats (Prod Info Tamiflu®2001). <b>4) Drug Levels in breast milk</b> <b>a) Active Metabolites</b> <b>1) oseltamivir carboxylate (Prod Info Tamiflu®, 2001)</b></p>
<b>Adverse effects</b>	<p><b>from Lexidrugs:</b> WARNINGS / PRECAUTIONS  Concerns related to adverse effects:  Allergic reactions: Allergic-like reactions, including anaphylaxis, oropharyngeal edema, and serious skin rashes have been reported.  Neuropsychiatric events: Rare occurrences of neuropsychiatric events (including confusion, delirium, hallucinations, and/or self-injury) have been reported from post marketing surveillance; direct causation is difficult to establish (influenza infection</p>	<p><b>from Lexidrugs:</b> ADVERSE REACTIONS SIGNIFICANT  &gt;10%: Gastrointestinal: Vomiting (2% to 15%)  1% to 10%: Gastrointestinal: Nausea (3% to 10%), abdominal pain (2% to 5%)  &lt;1% (Limited to important or life-threatening): Allergy, anaphylactic/anaphylactoid reaction, arrhythmia, confusion, dermatitis, diabetes aggravation, eczema, erythema multiform, hepatitis, liver function tests abnormal, neuropsychiatric events (self-injury, confusion, delirium), rash, seizure,</p>

	<p>may also be associated with behavioral and neurologic changes).</p> <p>Respiratory effects: Bronchospasm, decreased lung function, and other serious adverse reactions, including those with fatal outcomes, have been reported in patients with and without airway disease; discontinue with bronchospasm or signs of decreased lung function. For a patient with an underlying airway disease where a medical decision has been made to use zanamivir, a fast-acting bronchodilator should be made available, and used prior to each dose.</p> <p>Disease-related concerns:</p> <p>Renal impairment: Safety and efficacy of use in patients with severe renal impairment have not been established.</p> <p>Respiratory disease: Not recommended for use in patients with underlying respiratory disease, such as asthma or COPD, due to lack of efficacy and risk of serious adverse effects.</p>	<p>Stevens-Johnson syndrome, swelling of face or tongue, toxic epidermal necrolysis, urticaria</p> <p>CONTRAINDICATIONS — Hypersensitivity to oseltamivir or any component of the formulation</p> <p>WARNINGS / PRECAUTIONS</p> <p>Concerns related to adverse effects:</p> <p>Anaphylaxis/hypersensitivity: Rare but severe hypersensitivity reactions (anaphylaxis, severe dermatologic reactions) have been associated with use.</p> <p>Neuropsychiatric events: Rare occurrences of neuropsychiatric events (including confusion, delirium, hallucinations, and/or self-injury) have been reported from post marketing surveillance; direct causation is difficult to establish (influenza infection may also be associated with behavioral and neurologic changes).</p> <p>Disease-related concerns:</p> <p>Cardiovascular disease: Use with caution in patients with chronic cardiac disease; efficacy has not been established.</p> <p>Hepatic impairment: Use with caution in patients with severe hepatic impairment; safety and efficacy have not been established.</p> <p>Renal impairment: Use with caution in patients with renal impairment; dosage adjustment is required for creatinine clearance &lt;30 mL/minute.</p> <p>Respiratory disease: Use with caution in patients with respiratory disease; efficacy has not been established.</p>
<p><b>Approximate cost for an Alberta regional hospital pharmacy:</b></p>	<p>\$35.70 for one treatment course.</p>	<p>\$ 39.00 for one treatment course.</p>
<p><b>Pharmacody Namics / Kinetics</b></p>	<p><b>from Lexidrugs:</b></p> <p>Absorption: Inhalation: ~4% to 17%</p> <p>Protein binding, plasma: &lt;10%</p> <p>Metabolism: None</p> <p>Half-life elimination, serum: 2.5-5.1 hours</p> <p>Excretion: Urine (as unchanged drug); feces (unabsorbed drug)</p>	<p><b>from Lexidrugs:</b></p> <p>Absorption: Well absorbed</p> <p>Distribution: Vd: 23-26 L (oseltamivir carboxylate)</p> <p>Protein binding, plasma: Oseltamivir carboxylate: 3%; Oseltamivir: 42%</p> <p>Metabolism: Hepatic (90%) to oseltamivir carboxylate; neither the parent drug nor active metabolite has any effect on the cytochrome P450 system</p> <p>Bioavailability: 75% as oseltamivir carboxylate</p> <p>Half-life elimination: Oseltamivir: 1-3 hours; Oseltamivir carboxylate: 6-10 hours</p> <p>Excretion: Urine (&gt;90% as oseltamivir carboxylate); feces</p>