

## MOTHERISK ROUNDS

# H1N1 Influenza in Pregnancy: Risks, Vaccines, and Antivirals

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## Abstract

When pregnant women are infected by the H1N1 influenza A virus, the consequences are more serious than they are in other groups of patients. It is imperative to vaccinate pregnant women against this virus. Unvaccinated women who come in contact with the virus should receive prophylactic antiviral therapy. The existing information on the safety of oseltamavir and zanamavir, the most used antivirals, is limited but reassuring.

## Résumé

Les conséquences de l'infection par le virus de la grippe A H1N1 sont plus graves pour les femmes enceintes que pour d'autres groupes de patients. Il est impératif de vacciner les femmes enceintes contre ce virus. Les femmes non vaccinées qui entrent en contact avec le virus devraient recevoir un traitement antiviral prophylactique. Les données existantes sur l'innocuité de l'oseltamavir et du zanamavir (les antiviraux les plus utilisés) sont limitées, mais rassurantes.

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## INTRODUCTION

In April 2009, a novel influenza A virus (H1N1) was determined to be the cause of outbreaks of respiratory illness in Mexico.<sup>1</sup> On April 26, 2009, the Public Health Agency of Canada reported the first six cases of H1N1 infection in Canada.<sup>2</sup> In June 2009, the WHO declared the H1N1 influenza a pandemic because of confirmed cases seen around the world, and pregnant women were among the groups stated to have an increased risk of complications.<sup>3</sup> Several studies have reported that pregnant women with seasonal influenza infection are at higher risk of complications than the general population.<sup>4-6</sup>

These same risks have been reported in women with H1N1 influenza infections. According to a report by the PHAC,

pregnant women with 2009 H1N1 influenza were more likely than non-pregnant women and people in general who contracted 2009 H1N1 influenza to be admitted to hospital, to become seriously ill, and to die, and they tended to have fewer medical conditions prior to their influenza illness. In addition, pregnant women were reported to have a greater risk of pregnancy complications, such as miscarriage or premature delivery; women in the second half of pregnancy had greater risk, and the greatest risk was seen in women in the third trimester.<sup>7</sup> The increased risk of complications is thought to be related to physiologic changes that occur during pregnancy, including alterations in the immune, cardiovascular, and respiratory systems.<sup>8</sup>

In a report from the CDC in the United States summarizing cases of infection with H1N1 virus in pregnant women, infected pregnant women were four times more likely to be admitted to hospital than pregnant women without infection. This report disclosed that 13% of deaths due to H1N1 infection were in pregnant women who were fairly healthy before their influenza illness.<sup>9</sup>

## H1N1 INFLUENZA VACCINE

The WHO, the PHAC, and the CDC are recommending that pregnant women receive the H1N1 vaccine.<sup>10-12</sup> Although studies of the safety of 2009 H1N1 vaccine have not been conducted in pregnant women, the seasonal influenza vaccine has been given to millions of pregnant women over many years. Influenza vaccines have not been shown to cause harm to pregnant women or their babies.<sup>13,14</sup> The 2009 H1N1 vaccines are produced in a manner similar to the seasonal influenza vaccine. Therefore, the 2009 H1N1 influenza vaccines are expected to have safety profiles that are similar to seasonal influenza vaccines.<sup>10</sup>

Benefits have been seen in women and their infants after influenza vaccination during pregnancy. In a study from

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Bangladesh, immunization of women with influenza vaccine in the third trimester of pregnancy was found to reduce the incidence of febrile respiratory illness in both mother and child compared with immunization of women with a pneumococcal vaccine during third trimester. Laboratory-confirmed influenza was reduced by 63% in the infants of vaccinated women up to six months of age.<sup>15</sup>

### Adjuvanted and Unadjuvanted

Two types of H1N1 influenza vaccine will be available in Canada: adjuvanted and unadjuvanted. The adjuvanted vaccine is intended to increase an individual's immune response to the vaccine, and it allows for smaller doses of the virus antigen to be used in production while providing immunogenicity that is comparable to that induced by a non-adjuvanted vaccine. Adjuvanted vaccines are included in common vaccines such as tetanus and hepatitis B. The adjuvant used in Canada's H1N1 influenza vaccine (AS03) is made up of three ingredients: squalene, a natural, biodegradable oil (10.69 mg); DL- $\alpha$ -tocopherol (vitamin E oil, 11.86 mg); and polysorbate 80 (Tween 80), an emulsifier (4.86 mg). Clinical research trials using this adjuvant have been conducted in Canada, the United States, and Europe, and have demonstrated the safety of AS03-containing vaccines.<sup>10</sup> Although exposure to an adjuvanted H1N1 pregnancy is unlikely to cause any problem, the WHO states that the unadjuvanted vaccine is the preferred vaccine for pregnant women because of the extensive experience with use of unadjuvanted vaccines in pregnancy. However, if the unadjuvanted vaccine is not available and there is active H1N1 influenza in the community, then the adjuvanted vaccine should be offered to all pregnant women.<sup>16</sup> Nevertheless, Health Canada states that only women who are more than 20 weeks' pregnant or who have a medical condition, regardless of the stage of pregnancy, should be offered the adjuvanted vaccine.<sup>10</sup>

### Thimerosal

Thimerosal is a form of mercury used in the H1N1 flu vaccine to stabilize and maintain its quality during storage. Both the adjuvanted and unadjuvanted H1N1 vaccines contain small amounts of thimerosal (5 $\mu$ g and 50 $\mu$ g, respectively).<sup>17</sup> In comparison, a 170g can of tuna contains approximately 23.8–61.2  $\mu$ g of methyl mercury.<sup>18</sup> There is no evidence that thimerosal is harmful to a pregnant

woman or her child. Large cohort studies have demonstrated that there is no increase in adverse neurodevelopmental outcomes, including autistic-spectrum disorders, in children vaccinated with thimerosal containing vaccines.<sup>19</sup> No studies have examined the safety of exposure to thimerosal-containing vaccines during pregnancy; however, thimerosal-containing influenza vaccines have been used in pregnant women for years, and adverse effects have not been reported.<sup>10</sup>

### Breastfeeding

The Advisory Committee for Immunization Practice states that neither inactive nor active vaccines are contraindicated during breastfeeding. Vaccines given to nursing women have not adversely affected the mother or her infant.<sup>20</sup>

Infants from birth to 59 months old, particularly those less than 24 months old, are considered to be at high risk for hospitalization because of H1N1 influenza. Therefore, individuals who are potentially capable of transmitting influenza to those at high risk should be immunized, regardless of whether the high-risk person has been immunized. Although there are no recommendations for the use of the H1N1 influenza vaccine specifically in nursing mothers, these mothers should be given high priority for vaccination with the H1N1 vaccine in order to protect their health and the health of their infants.<sup>10,11</sup>

### ANTIVIRAL MEDICATIONS

The 2009 H1N1 influenza virus is susceptible to the neuraminidase inhibitor antiviral medications, oseltamivir and zanamivir.<sup>21,22</sup> Although clinical data on the use of these and other antivirals during pregnancy are limited, pregnancy is not a contraindication to oseltamivir or zanamivir use.<sup>23,24</sup> A recently published review article reports that oseltamivir and zanamivir are relatively safe drugs for use in pregnant and breastfeeding women.<sup>25</sup> The review describes data from two Japanese teratogen information services that found no increased risk of birth defects among 90 pregnant women exposed to oseltamivir (75 mg twice daily for up to 5 days) during the first trimester of pregnancy. In these 90 cases, there was one malformation (a ventricular septal defect), an incidence of 1.1%. This is within the accepted incidence of major malformations in the general population (1–3%). The miscarriage rate was 3.3%, which is lower than in general population, and four births (4.4%) were premature. There are fewer data available for use of zanamivir. In one report, among three pregnancies with zanamivir exposure, one resulted in a healthy baby, one was terminated, and the third miscarried.<sup>26</sup>

The updated interim recommendations from the CDC for the use of antiviral medications indicate that pregnant

#### ABBREVIATIONS

CDC	Centers for Disease Control
PHAC	Public Health Agency of Canada
WHO	World Health Organization

women and women up to two weeks postpartum with suspected or confirmed influenza should receive prompt empiric antiviral therapy.<sup>23</sup> Oseltamivir is given orally; by contrast, zanamivir is given by inhalation and results in less systemic absorption. Oseltamivir is preferred for treatment of pregnant women because of its systemic activity. The recommended treatment regimen is the same as that recommended for adults who have seasonal influenza, i.e., oseltamivir 75 mg twice daily for five days, or zanamivir 10 mg (two 5 mg inhalations) twice daily for five days. Antiviral treatment should be initiated as soon as possible after the onset of influenza symptoms, and benefits are expected to be greatest if treatment starts within 48 hours of onset of symptoms (based on data from studies of seasonal influenza).<sup>27</sup> However, data from studies of seasonal influenza indicate benefit for hospitalized patients even if treatment is started more than 48 hours after the onset of symptoms.

The drug of choice for chemoprophylaxis may be zanamivir because of its limited systemic absorption. However, respiratory complications that may be associated with zanamivir because it is inhaled must be considered, especially in women at risk for respiratory problems.<sup>23</sup> For these reasons, and because of more safety data are available, oseltamivir is a reasonable alternative. Currently recommended chemoprophylaxis is 75 mg oseltamivir once per day for 10 days, or 10 mg (two 5 mg inhalations) zanamivir once daily for 10 days after the last known exposure to H1N1 influenza virus. In addition to specific antiviral medication, acetaminophen should be given if the patient is febrile.

### Antivirals and Breastfeeding

Use of antiviral medications for H1N1 treatment or chemoprophylaxis should not be a contraindication to breastfeeding. A recent report described a nursing mother who was given oseltamivir 75 mg by mouth twice daily for five days.<sup>28</sup> The dose in milk corresponded to 0.5% of the mother's weight-adjusted dosage. The authors calculated that the infant would receive oseltamivir 0.012 mg/kg daily, which is much less than pediatric doses (2–4 mg/kg daily). This dose is unlikely to cause any adverse effects in breastfed infants.

Zanamivir has poor systemic absorption, and it is not likely to reach the bloodstream of the infant in clinically relevant amounts. It has been estimated that an exclusively breastfed 5 kg infant would receive about 0.075 mg of zanamivir daily in breast milk after an inhaled maternal dose of 10 mg, which is less than 1% of the recommended prophylactic dose for children.<sup>25</sup>

### CONCLUSION

Pregnant women should be immunized using the unadjuvanted H1N1 vaccine, although use of adjuvanted H1N1 vaccine is not likely to be a concern. Therefore, if there is active H1N1 influenza infection in the community and unadjuvanted vaccine is unavailable, then pregnant women and their health care providers should consider use of the adjuvanted H1N1 vaccine, because pregnant women, especially those in the second half of pregnancy, are at increased risk of health and pregnancy complications. Breastfeeding mothers should be vaccinated with the adjuvanted H1N1 vaccine in order to protect themselves and their infants.

For treatment or chemoprophylaxis during the current H1N1 influenza pandemic, oseltamivir is the drug of choice because there is more evidence for its safe use in pregnancy. Zanamivir can be used if necessary, although there is less evidence for its safety in pregnant women. Neither drug appears to affect the growth and development of the fetus, although ongoing data collection is important. Both oseltamivir and zanamivir are considered to be compatible with breastfeeding.

### REFERENCES

- Centers for Disease Control and Prevention. Outbreak of swine-origin influenza A (H1N1) virus infection—Mexico, March–April 2009. *MMWR* 2009;58:467–70.
- Public Health Agency of Canada. FluWatch Weekly Report Apr 19–Apr 25, 2009 (Week 16). Available at: [http://www.phac-aspc.gc.ca/fluwatch/08-09/w16\\_09/index-eng.php](http://www.phac-aspc.gc.ca/fluwatch/08-09/w16_09/index-eng.php). Accessed October 27, 2009.
- Zarocostas J. World Health Organization declares A (H1N1) influenza pandemic *BMJ* June 12 2009;338:b2425.
- Schanzer DL, Langley JM, Tam TW. Influenza-attributed hospitalization rates among pregnant women in Canada 1994–2000. *J Obstet Gynaecol Can* 2007;29:622–9.
- Tuyishime JD, De Wals P, Moutquin JM, Frost E. Influenza-like illness during pregnancy: results from a study in the eastern townships, province of Quebec. *J Obstet Gynaecol Can* 2003;25:1020–5.
- Dodds L, McNeil SA, Fell DB, Allen VM, Coombs A, Scott J, et al. Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women. *CMAJ* 2007;176(4):463–8.
- Public Health Agency of Canada. Flu Watch: Oct 11, 2009 to October 17, 2009 (Week 41). Available at [http://www.phac-aspc.gc.ca/fluwatch/09-10/w41\\_09/index-eng.php](http://www.phac-aspc.gc.ca/fluwatch/09-10/w41_09/index-eng.php). Accessed October 26, 2009.
- Jamieson DJ, Theiler RN, Rasmussen SA. Emerging infections and pregnancy. *Emerg Infect Dis* 2006;12(11):1638–43.
- Jamieson DJ, Honein MA, Rasmussen SA, Williams JL, Swerdlow DL, Biggerstaff MS, et al.; Novel Influenza A (H1N1) Pregnancy Working Group. H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet* 2009;374:451–8.
- Public Health Agency of Canada. Guidance document on the use of pandemic influenza A (H1N1) 2009 Inactivated Monovalent Vaccine October 21, 2009. Available at: <http://www.phac-aspc.gc.ca/alert-alerte/h1n1/vacc/pdf/monovacc-guide-eng.pdf>. Accessed October 28, 2009.
- CDC. Use of influenza A (H1N1) 2009 monovalent vaccine: recommendations of the advisory committee on immunization practices

- (ACIP), 2009 MMWR 2009;58(No. RR-10):1–8. Available at: <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5810a1.htm>. Accessed October 23, 2009.
12. World Health Organization. WHO recommendations on pandemic (H1N1) 2009 vaccines Available at: [http://www.who.int/csr/disease/swineflu/notes/h1n1\\_vaccine\\_20090713/en/indexhtml](http://www.who.int/csr/disease/swineflu/notes/h1n1_vaccine_20090713/en/indexhtml). Accessed October 29, 2009.
  13. Heinonen OP, Shapiro S, Monson RR, Hartz SC, Rosenberg L, Slone D. Immunization during pregnancy against poliomyelitis and influenza in relation to childhood malignancy. *Int J Epidemiol* 1973;2:229–35.
  14. Gruslin A, Steben M, Halperin S, Money DM, Yudin MH; SOGC Infectious Diseases Committee. Immunization in pregnancy. Society of Obstetricians and Gynaecologists of Canada CPG No. 220, December 2008. *J Obstet Gynaecol Can* 2008;30:1149–54.
  15. Zaman K, Roy E, Arifeen SE, Rahman M, Raqib R, Wilson E, et al. Effectiveness of maternal influenza immunization in mothers and infants. *New Engl J Med* 2008; 359:1555–64.
  16. World Health Organization. Strategic advisory group of experts on immunization—report of the extraordinary meeting on the influenza A (H1N1) 2009 pandemic, 7 July 2009. *Wkly Epidemiol Rec* 2009;84(30):301–4.
  17. Public Health Agency of Canada. Frequently Asked Questions—H1N1 Flu Virus Available at: [http://www.phac-aspc.gc.ca/alert-alerte/h1n1/faq\\_rg\\_h1n1-eng.php#vs](http://www.phac-aspc.gc.ca/alert-alerte/h1n1/faq_rg_h1n1-eng.php#vs). Accessed October 26, 2009.
  18. Health Canada. Human health risk assessment of mercury in fish and health benefits of fish consumption. Available at: [http://www.hc-sc.gc.ca/fn-an/pubs/merc/merc\\_fish\\_poisson-eng.php](http://www.hc-sc.gc.ca/fn-an/pubs/merc/merc_fish_poisson-eng.php). Accessed Oct 29, 2009.
  19. Gerber JS, Offit PA. Vaccines and autism: a tale of shifting hypotheses. *Clin Infect Dis* 2009;48:456–61.
  20. Kroger AT, Atkinson WL, Marcuse EK, Pickering LK. General recommendations on immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2006;55(RR-15):1–48.
  21. Centers for Disease Control and Prevention. Update: drug susceptibility of swine origin influenza A (H1N1) viruses, April 2009. *MMWR Morb Mortal Wkly Rep* 2009;58:433–5.
  22. Novel swine-origin influenza A (H1N1) virus investigation team. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N Engl J Med* 2009;360(25):2605–15.
  23. Centers for Disease Control and Prevention. Updated interim recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009–2010 season. October 16, 2009 4:00 PM ET. Available at: <http://www.cdc.gov/H1N1flu/recommendations.htm>. Accessed October 28, 2009.
  24. Centers for Disease Control and Prevention. Pregnant women and novel influenza A (H1N1) virus: considerations for clinicians. June 30, 2009. Available at: [http://www.cdc.gov/h1n1flu/clinician\\_pregnant.htm](http://www.cdc.gov/h1n1flu/clinician_pregnant.htm). Accessed October 28, 2009.
  25. Tanaka T, Nakajima K, Murashima A, Garcia-Bournissen F, Koren G, Ito S. Safety of neuraminidase inhibitors against novel influenza A (H1N1) in pregnant and breastfeeding women. *CMAJ* 2009;181(1–2):55–8.
  26. Freund B, Gravenstein S, Elliott M, Miller I. Zanamivir: review of clinical safety. *Drug Saf* 1999;21:267–81.
  27. Centers for Disease Control and Prevention (CDC); Advisory Committee on Immunization Practices (ACIP). Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008. *MMWR Recomm Rep* 2008 Aug 8;57(RR-7):1–60.
  28. Wentges-van Holthe N, van Eijkeren M, van der Laan JW. Oseltamivir and breastfeeding. *Int J Infect Dis* 2008;12:451.