

# Teratology and Public Health: Working Together to Make Recommendations for Pregnant Women in the Face of Uncertainty

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**Centers for Disease Control and Prevention (CDC), Atlanta, GA**

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**Brent Lecture**  
**Teratology Society Annual Meeting, Bellevue, WA**



*The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.*



U.S. Department of Health and Human Services  
Centers for Disease Control and Prevention

## Disclosure

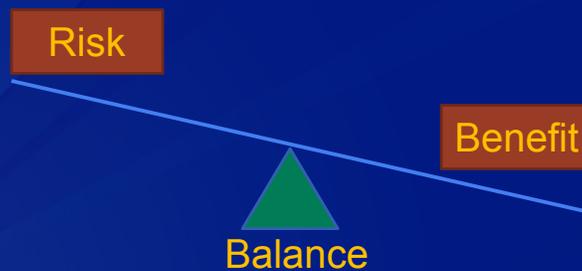
**This presenter has no financial or other interests that pose a conflict of interest.**

## Examples of Public Health Decisions

- Rubella vaccine to prevent congenital rubella syndrome
- Folic acid to prevent neural tube defects
- Prevention and treatment of influenza

## Public Health Decisions: Weighing the Risk and Benefit

- Prospect of clinical benefit – probability of preventing harm (depends on disease risk)
- Potential risk – probability x magnitude of harm
- Benefit of intervention >>> Potential risk of harm



## Rubella Vaccine to Prevent Congenital Rubella Syndrome



Rash associated with rubella

## Congenital Rubella Syndrome



Rubella infection in pregnancy can lead to fetal death, preterm delivery, birth defects, spontaneous abortion, and visual, hearing and cognitive impairment

## History of Congenital Rubella Syndrome

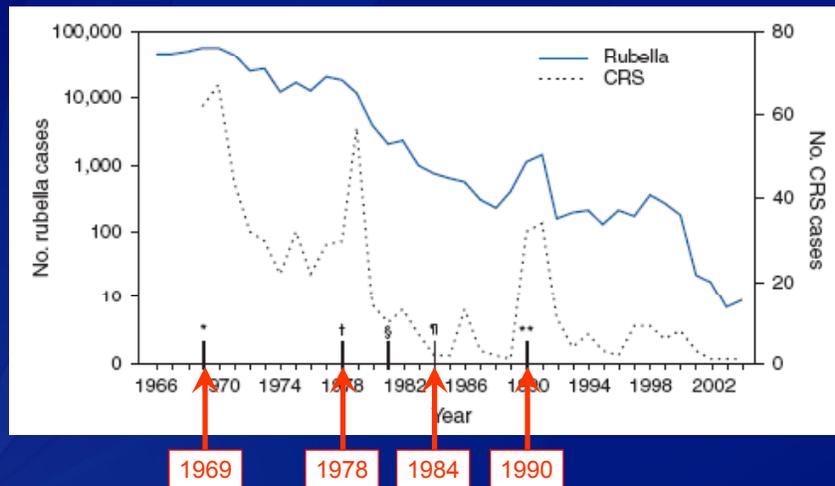
- In 1941, Gregg recognized the effects of maternal rubella on the fetus
- 1962-1965 worldwide rubella epidemic
  - 12.5 million cases of rubella in the US
  - 11,250 fetal deaths
  - 2,100 neonatal deaths
  - 20,000 infants born with congenital rubella syndrome
- Rubella vaccine developed and licensed (1969)

## Decisions about Vaccination Strategies

- Vaccinate adolescent females – initially used in UK
- Vaccinate children to abolish reservoir for disease – initially used in US

*Plotkin SA, Clin Infect Dis 43:S164-168, 2006*

## Trends in Rubella and Congenital Rubella Syndrome in the US, 1966-2002



MMWR Morb Mortal Wkly Rep 54:279-82, 2005

## Key Changes in Recommendations

- **1969** – Recommendation for use of rubella vaccine (age 1 to puberty)
- **1978** – Expanded to include adolescents and certain adults, particularly females
- **1984** – Vaccination of certain workers; prenatal testing and postpartum vaccination of susceptible women
- **1990** – 2-dose schedule for MMR vaccine implemented

MMWR Morb Mortal Wkly Rep 54:279-82, 2005

# MMWR™

**Morbidity and Mortality Weekly Report**

*Achievements in Public Health*

**Elimination of Rubella and Congenital  
Rubella Syndrome — United States,  
1969–2004**

*MMWR Morb Mortal Wkly Rep 54:279-82, 2005*

## **Update on Global Rubella Elimination - 1**

- In 2012 – total of 94,030 rubella cases reported to WHO from 174 Member States (86% decrease from 670,894 cases reported in 2000 from 102 Member States)

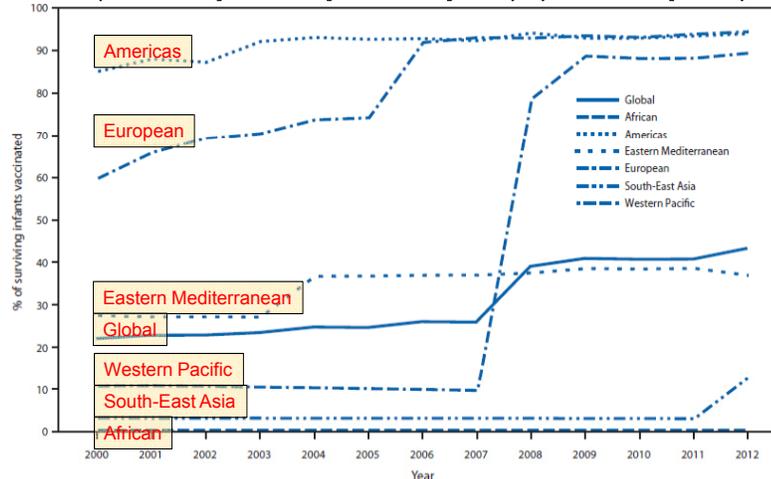
*WHO, Weekly Epidemiological Record, 49:521-32, 2013*

## Update on Global Rubella Elimination - 2

- As of December 2012, 132 of 194 WHO Member States had introduced rubella-containing vaccine
  - 3/46 (7%) in African Region
  - 35/35 (100%) in the Region of the Americas
  - 14/22 (64%) in the Eastern Mediterranean Region
  - 53/53 (100%) in the European Region
  - 5/11 (45%) in the South-East Asia Region
  - 22/27 (81%) in the Western Pacific Region

*WHO, Weekly Epidemiological Record, 49:521-32, 2013*

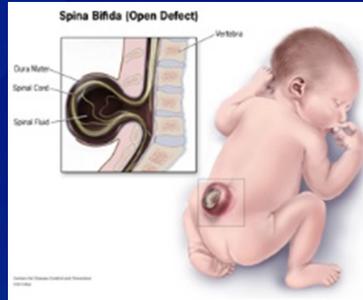
FIGURE 1. Proportion of surviving infants receiving rubella-containing vaccine (RCV) – World Health Organization (WHO) regions, 2000–2012\*



\* Based on WHO–United Nations Children's Fund (UNICEF) estimates of rubella coverage. Note: China introduced RCV into its immunization schedule in 2008.

*WHO, Weekly Epidemiological Record, 49:521-32, 2013*

## Folic Acid to Prevent Neural Tube Defects



## History of Folic Acid Fortification: Key Studies

- Trial of periconceptional multivitamin (with 360 mcg folic acid) supplementation for women with previous child with an NTD
  - Rate among fully supplemented mothers was 0.6%, compared to 5.0% among unsupplemented mothers ( $p < 0.01$ )
- Trial of periconceptional multivitamin (containing 800 mcg folic acid, minerals, trace elements) supplementation for NTD occurrence prevention
  - Rate among vitamin supplement group was 0/2052, compared to 6/2104 among trace-element supplement group ( $p=0.029$ )

Smithells et al., *Lancet* 1:339-40, 1980  
Czeizel & Dudas, *N Engl J Med* 327:1832-5, 1992

## Decisions about Folic Acid

- **Supplementation vs. Fortification**
- **Level of Fortification**
- **Potential risks**
  - Masking of vitamin B12 deficiency
  - Increased pregnancy loss
  - Increased risk of twinning
  - Colon cancer
  - Dementia

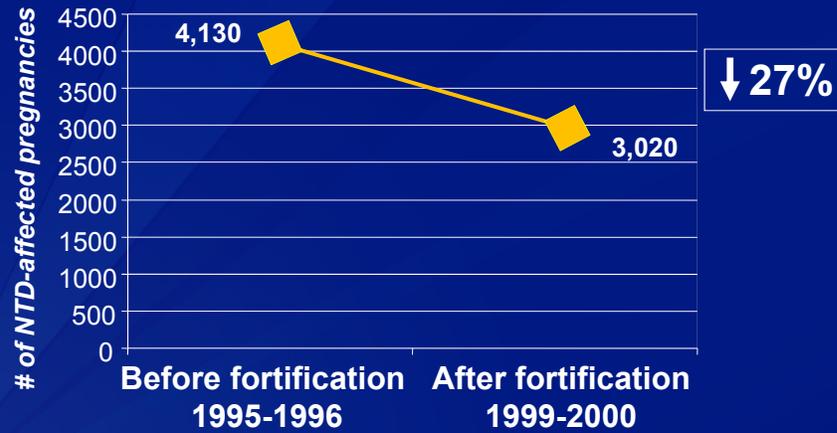
**Crider et al., *Nutrients* 3:370-384, 2011**

## Recommendations to Prevent NTD Occurrence

- In 1992, the Public Health Service recommended that all women of childbearing age who are capable of becoming pregnant consume 400 mcg of folic acid daily
- In March 1996, FDA mandated that cereal grains labeled as "enriched" have folic acid added at level of 140 mcg/100g of product by January 1, 1998

***MMWR Recomm Report* 41:1, 1992**  
**Food and Drug Administration, *Federal Register* 61:8781-97, 1996**

## NTD-Affected Pregnancies per Year Before and After Fortification, United States



MMWR Morb Mortal Wkly Rep 53:362-365, 2004

## Update on Global Prevention of Folic Acid-Preventable NTDs

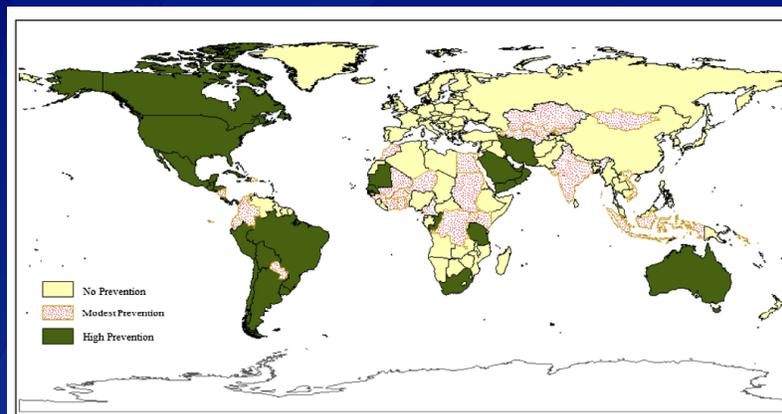


Figure 1. The status of global prevention of folic acid-preventable spina bifida and anencephaly, 2012 [1].

Kancherla et al., *Sem Fetal & Neonatal Med* 19:153-160, 2014

## Prevention and Treatment of Influenza



## Effects of Influenza on the Pregnant Woman

- Changes in a pregnant woman's immune, respiratory, cardiovascular and other systems place her at increased risk for influenza-associated complications
- Increased morbidity and mortality from influenza during previous pandemics
- Increased risk of complications related to seasonal influenza

*Rasmussen, Jamieson and Bresee, Emerg Infect Dis 14:95-100, 2008*

## Effects of Influenza on the Embryo or Fetus

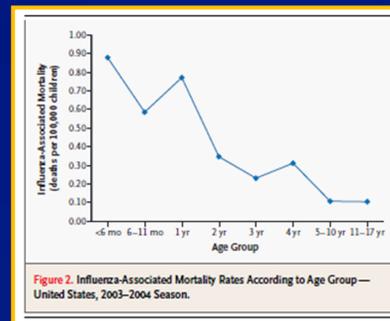
- Effects of influenza on the embryo or fetus are unknown
- Viremia infrequent and placental transmission rare; however, adverse effects may still occur (e.g., hyperthermia)
- Increased risk of pregnancy loss and possibly preterm birth observed in previous pandemics
- Increased risk of certain birth defects seen



*Rasmussen, Jamieson and Bresee, Emerg Infect Dis 14:95-100, 2008*

## Effects of Influenza on the Infant

- Immune system of a newborn is immature – most of its serum immunoglobulins are from maternal IgG transfer across the placenta
- Infants have increased susceptibility to viral infections, including influenza
- Influenza vaccines are not approved for use in children aged <6 months
- Chemoprophylaxis and treatment options are limited



**Figure 2.** Influenza-Associated Mortality Rates According to Age Group—United States, 2003–2004 Season.

*Bhat et al, N Engl J Med. 353:2559-67, 2005*

## Prophylaxis and Treatment of Influenza in Pregnant Women

- Effects of anti-influenza medications (oseltamivir and zanamivir) on the embryo or fetus unknown
  - Oseltamivir (Tamiflu®) – human data limited to 61 reports of exposed pregnancies in marketing period
  - Zanamivir – human data limited to 3 zanamivir-exposed pregnancies during clinical trials



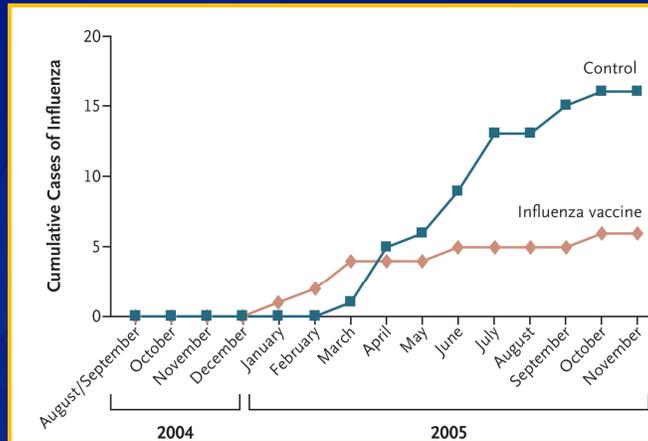
*Rasmussen, Jamieson and Bresee, Emerg Infect Dis 14:95-100, 2008*

## Influenza Vaccination of Pregnant Women

- Influenza vaccine protects pregnant women and their infants up to 6 months of age from influenza
- Influenza vaccine has been used during pregnancy since the 1960s and no maternal or fetal problems have been seen in association with influenza vaccination
- Advisory Committee on Immunization Practices and American College of Obstetricians and Gynecologists have recommended inactivated influenza vaccine for women who will be pregnant during influenza season for many years, regardless of pregnancy trimester, but adherence has been low (<30%)

*Rasmussen, Jamieson and Bresee, Emerg Infect Dis 14:95-100, 2008*

## Influenza Vaccine during Pregnancy Protects Infants < 6 Months of Age from Laboratory-Proven Influenza



Zaman et al., *N Engl J Med* 359:1555-64, 2008

## Decisions about Influenza and Pregnancy

- Should pregnant women with pandemic influenza be treated with an antiviral medication? Should treatment vary by pregnancy trimester? Which medication?
- Should pregnant women receive a pandemic influenza vaccine? Should vaccination recommendations vary by pregnancy trimester? Which vaccine?

Rasmussen, Jamieson and Bresee, *Emerg Infect Dis* 14:95-100, 2008

Department of Health and Human Services  
Centers for Disease Control and Prevention  
In partnership with:  
March of Dimes  
Association of Maternal & Child Health Programs

# Pandemic influenza

## Special considerations for pregnant women

April 3-4, 2008, Roybal Campus, Atlanta, Georgia




S248 | Influenza Preparedness and Response | Peer Reviewed | Rasmussen et al. | American Journal of Public Health | Supplement 2, 2009, Vol 99, No. S2

## Pandemic Influenza and Pregnant Women: Summary of a Meeting of Experts

Pandemic Influenza: Special Considerations for Pregnant Women was a meeting convened by the Centers for

Sorja A. Rasmussen, MD, MS, Denise J. Jamieson, MD, MPH, Kitty MacFarlane, CNM, MPH, Janet D. Cragan, MD, MPH, Jennifer Williams, MSN, MPH, and Zsakeba Henderson, MD; for the Pandemic Influenza and Pregnancy Working Group

CDC Home Search Health Topics A-Z

# MMWR

Dispatch  
April 21, 2009 / 58 (Dispatch);1-3

## Swine Influenza A (H1N1) Infection in Two Children --- Southern California, March--April 2009

## **2009-2010 Treatment Recommendations**

- **Treatment recommended for pregnant women and women up to 2 weeks postpartum with suspected or confirmed influenza, regardless of trimester of pregnancy**
  - Oseltamivir (Tamiflu®) - BEST if started as soon as possible (i.e., <48 hours of symptom onset), but later treatment also of benefit
  - Considering severity of disease, treatment benefit outweighs potential risk
  - Acetaminophen for fever
- **Do not delay treatment because of a negative rapid influenza diagnostic test or inability to test or while awaiting test results**

## **2009-2010 Vaccine Recommendations**

- **Pregnant women should receive both 2009 H1N1 and seasonal inactivated vaccines**
- **Live attenuated vaccine not licensed for use in pregnant women, but can be used postpartum**

## 2009 H1N1 Influenza and Pregnancy

- Illness and deaths seen in all three trimesters
- Pregnant women 4 times more likely to be hospitalized
- 5% of deaths in US from 2009 H1N1 influenza were among pregnant women, even though pregnant women account for ~1% of the US population
- Most women who died were previously healthy
- Early treatment was associated with fewer ICU admissions and fewer deaths

*Jamieson et al., Lancet 374:451-8, 2009*  
*Siston et al., JAMA 303:1517-1525, 2010*

## Maternal Influenza and Newborn Outcomes - 1

- Study of women with 2009 H1N1 admitted to ICU/died in US
  - Delivery during flu hospitalization - infants at increased risk for preterm birth, low 5-minute Apgar scores, and NICU admission
  - Delivery after discharge from flu hospitalization – infants at increased risk for small for gestational age (SGA) and NICU admission

*CDC, MMWR Morb Mortal Wkly Rep 60:1193, 2011*

## Maternal Influenza and Newborn Outcomes - 2

- Study of hospitalized women in Nova Scotia
  - Infants born to hospitalized women more likely to be born SGA and to have lower mean birth weight than infants born to women who were not hospitalized
- Study of women with lab-confirmed 2009 H1N1 in US
  - No difference in outcomes among all women with H1N1 compared to matched controls
  - Hospitalized women had higher incidence of SGA infants

*McNeil et al., Am J Obstet Gynecol 204:S54-7, 2011*

*Naresh et al., J Perinatol 33:939-43, 2013*

## Maternal Influenza and Birth Defects

- Systematic review and meta-analysis of the association between 1<sup>st</sup> trimester influenza exposure and birth defects

Birth Defect	Pooled Odds Ratio
Any birth defect	2.00 (1.62-2.48)
Neural tube defects	3.33 (2.05-5.40)
Hydrocephaly	5.74 (1.10-30.00)
Congenital heart defects	1.56 (1.13-2.14)
Cleft lip +/- cleft palate	3.12 (2.20-4.42)
Digestive system	1.71 (1.09-2.69)
Limb deficiencies	2.03 (1.27-3.27)

*Luteijn et al., Human Reprod 29:809-23, 2014*

## Safety of Neuraminidase Inhibitors

- **Safety of neuraminidase inhibitors evaluated in several studies**

(Greer et al., 2010; Svensson et al. 2011; Saito et al., 2013; Xie et al., 2013; Dunstan et al., 2014; Beau et al., 2014)

- **None have shown evidence of harm, except for one study which showed an association with late transient hypoglycemia**

## Safety of Influenza Vaccine

- **Safety of influenza vaccine (seasonal and pH1N1) evaluated in several studies**

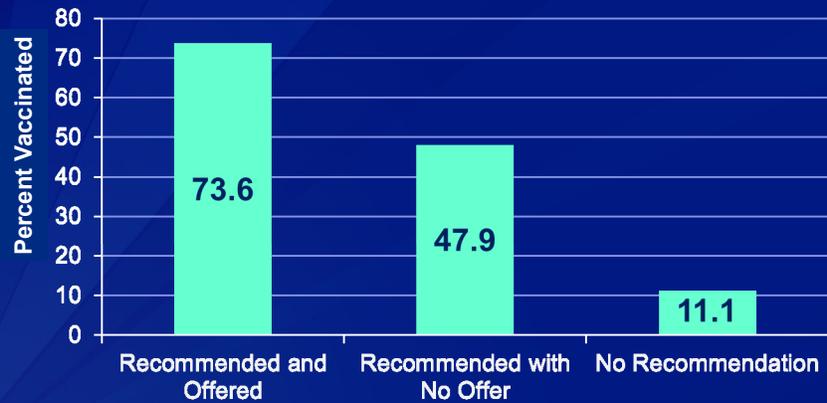
(Moro et al., 2011a; Moro et al., 2011b; Moro et al., 2013; Chambers et al., 2013; Louik et al., 2013; Nordin et al., 2014)

- **None have shown evidence of harm, except for two studies that showed an association with preterm birth with pH1N1-containing vaccines (<3 days decrease in gestational age)**

- **Several studies have shown benefits of influenza vaccine on birth outcomes (lower risk of preterm birth, low birth weight, SGA)**

(Steinhoff et al., 2012; Omer et al., 2011; Fell et al., 2012; Richards et al., 2013; Legge et al., 2014)

## Provider recommendation is one of the strongest predictors of influenza vaccination among pregnant women



*CDC, MMWR Morb Mortal Wkly Rep 61(38):758-763, 2012*

## Patient Barriers to Influenza Vaccination during Pregnancy

- Safety concerns
- Lack of knowledge about influenza (unfamiliar with recommendations)
- Fear of needles
- Vaccination history (no previous flu vaccination)
- General mistrust of the medical establishment
- Lacking an established relationship with an ob/gyn as a vaccine provider
- Access to care

*Shavell et al., Am J Obstet Gynecol 207:S67-74, 2012*

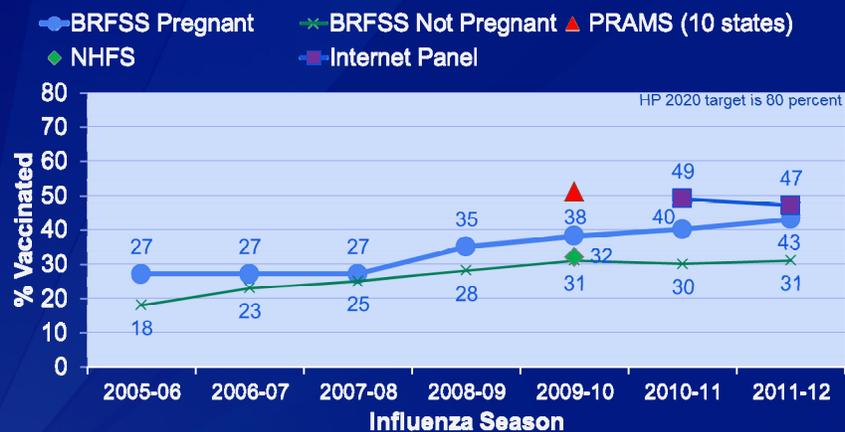
## Update on Vaccine Recommendations

- All people  $\geq 6$  months of age are recommended to receive influenza vaccination - priority groups include:
  - Pregnant women
  - Household contacts and caregivers of children  $<5$  years, with particular emphasis on contacts of infants  $<6$  months of age



Grohskopf et al., *MMWR Rec Reports*, 62(RR07);1-43, 2013.

## Estimated Influenza Vaccination (trivalent) Coverage, Pregnant Women\*



\* Behavioral Risk Factor Surveillance (BRFSS) data from December-February interviews only, for women 18-44 years pregnant or not pregnant when interviewed. Differences in influenza vaccination coverage between pregnant and not pregnant women were statistically significant ( $p < 0.05$ ) only for the 2009-10, 2010-11, and 2011-12 seasons. Other estimates for pregnant women from PRAMS (MMWR December 3, 2010;59(47):1541-1545); NHFS (Ding et al. Am J Obstet Gynecol June 2011 Supplement); and internet panel survey (MMWR August 19, 2011;60(32):1078-1082; MMWR September 28, 2012;61(8):758-63).

## Update on Treatment Recommendations

- Treatment with oseltamivir recommended for pregnant women and women up to 2 weeks postpartum with suspected/confirmed influenza
  - Regardless of trimester of pregnancy
  - Regardless of whether woman received influenza vaccine
  - Early treatment (<48 hours) best, but later treatment also of benefit
  - Do not delay treatment because of negative rapid influenza diagnostic test or inability to test or while awaiting test results



<http://www.cdc.gov/flu/protect/vaccine/pregnant.htm>

## Pregnant Women in the 2013-2014 Flu Season



## Conclusions

- **Public health recommendations require weighing the risks and benefits of planned intervention**
  - Often data on risks and benefits are incomplete
- **Based on experience from these 3 examples:**
  - Engage experts and partners
  - Be transparent about what you know and don't know
  - Collect data on outcomes to guide future interventions
  - Alter course based on data collected

## Acknowledgments

Margaret (Peggy) Honein, PhD, MPH

## **Questions**

**Contact information:  
skr9@cdc.gov**

## Effectiveness of Neuraminidase Inhibitors

- Meta-analysis of NAI effectiveness in reducing mortality of hospitalized patients (published online March 19, 2014)
  - Pregnant women (n=2166) – Treatment any time vs. none - AOR 0.46, 0.23-0.89
  - Pregnant women (n=917) – Early vs late treatment - AOR 0.27, 0.11-0.63
  - Pregnant women (n=1303) – Early treatment vs none - AOR 0.16, 0.04-0.67
- Cochrane review –reviewed data from 20 oseltamivir and 26 zanamivir randomized controlled trials (released April 10, 2014)
  - Pregnant women excluded from RCTs

*Muthuri et al., Lancet Resp Dis, online*  
*Jefferson et al., Cochrane Database Systematic Reviews 2014*

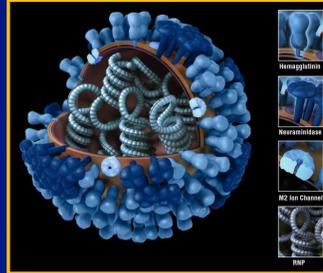
## Maternal Outcomes (ICU Admissions and Deaths) by Timing of Antiviral Treatment, US, April--August 21, 2009

Timing of treatment after symptom onset	Relative Risk (95% CI)	
	ICU Admissions	Deaths
>4 days vs. ≤2 days	6.0 (3.5-10.6)	53.5 (7.3-391.7)
3-4 days vs. ≤2 days	2.4 (1.2-4.8)	9.9 (1.1-87.2)

*Siston et al., JAMA 303:1517-1525, 2010*

## Timeline of 2009 H1N1 Influenza Outbreak - 1

- April 15, 17, 2009 – CDC identifies novel influenza A (H1N1) virus from 2 patients, US government notifies WHO
- April 25, 2009 – WHO declares public health emergency of international concern
- April 26, 2009 – US declares public health emergency



## Timeline of 2009 H1N1 Influenza Outbreak - 2

- April 27, 29, 2009 – WHO raises global pandemic alert to phases 4/5
- May 4, 2009 – 2<sup>nd</sup> documented death in the US from 2009 H1N1 was a healthy pregnant woman
- June 11, 2009 – WHO raises global pandemic alert to phase 6
- August 10, 2010 – WHO declares end to 2009 H1N1 influenza pandemic



## What We Knew before 2009 H1N1

### **Pandemic Influenza and Pregnant Women**

Sonja A. Rasmussen,\* Denise J. Jamieson,\* and Joseph S. Bresee\*

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 14, No. 1, January 2008

*Rasmussen, Jamieson and Bresee, Emerg Infect Dis 14:95-100, 2008*

## Infant Outcomes among Severely Ill Pregnant Women with 2009 H1N1 Influenza

Live singleton births n=143\*

- Delivered during maternal influenza hospitalization n=85
  - 23 mothers died
- Delivered after maternal influenza hospitalization n=54
  - Median days from discharge to delivery = 85
  - Range = 5-187 days

\*Missing delivery timing information n=4

*CDC, MMWR Morb Mortal Wkly Rep 60:1193, 2011.*

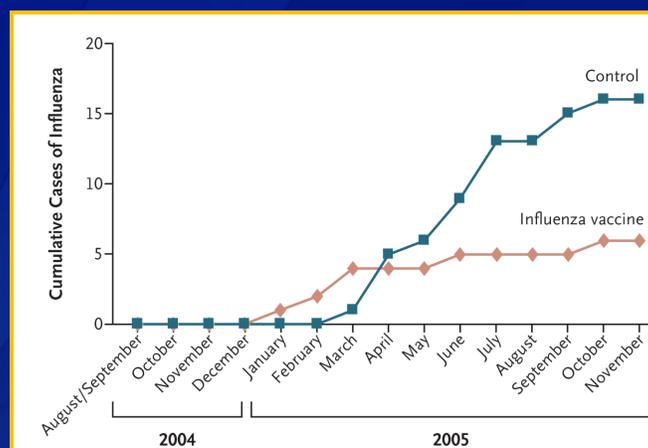
## Infant Outcomes among Severely Ill Pregnant Women with 2009 H1N1 Influenza

Infant Outcomes	Delivery during maternal hospitalization for influenza illness	Delivery after discharge from influenza illness hospitalization	US Estimate
	N (%; 95% CI)*	N (%; 95% CI)*	
Preterm Birth	49 (64%; 52–74%)	10 (21%; 11–35%)	12%
SGA	3 (4%; 0–2%)	13 (25%; 14–39%)	10%
Low Birthweight	32 (44%; 32–56%)	10 (19%; 10–33%)	8%
Low 5-Minute Apgar Score	21 (29%; 19–41%)	1 (2%; 0–11%)	2%
NICU Admission	50 (69%; 58–80%)	11 (22%; 12–36%)	6%

\*Exact 95% Confidence Interval

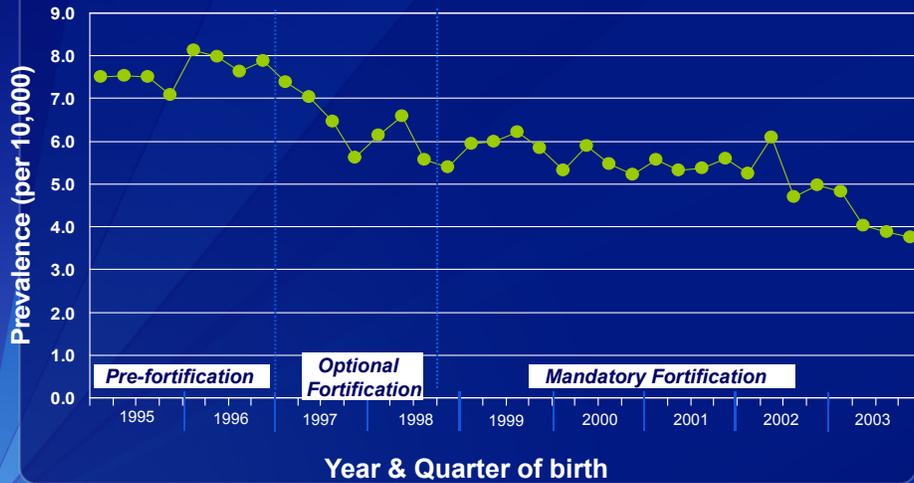
CDC, MMWR Morb Mortal Wkly Rep 60:1193, 2011

## Influenza Vaccine during Pregnancy Protects Infants < 6 Months of Age from Laboratory-Proven Influenza



Zaman et al., N Engl J Med 359:1555-64, 2008

## Prevalence of Neural Tube Defects, 24 Surveillance Programs, National Birth Defects Prevention Network



## What We Know Now

CDC Home Search Health Topics A-Z

**MMWR**

Dispatch  
May 12, 2009 / 58(Dispatch);1-3

**Novel Influenza A (H1N1) Virus Infections in Three Pregnant Women --- United States, April--May 2009**

Articles

**H1N1 2009 influenza virus infection during pregnancy in the USA** ➔

Denise J Jamieson, Margaret A Honein, Sonja A Rasmussen, Jennifer L Williams, David L Swerdlow, Matthew S Biggerstaff, Stephen Lindstrom, Janice K Louie, Cara M Christ, Susan R Bohm, Vincent P Fonseca, Kathleen A Ritger, Daniel J Kuhles, Paula Eggers, Hollianne Bruce, Heidi A Davidson, Emily Lutterloh, Meghan L Harris, Colleen Burke, Noelle Cocoros, Lyn Finelli, Kitty F MacFarlane, Bo Shu, Sonja J Olsen, and the Novel Influenza A (H1N1) Pregnancy Working Group\*

## Pandemic 2009 Influenza A(H1N1) Virus Illness Among Pregnant Women in the United States

Alicia M. Sison, PhD

Sonja A. Rasmussen, MD

Margaret A. Honein, PhD

Alicia M. Sison, MD

**Context** Early data on pandemic 2009 influenza A(H1N1) suggest pregnant women are at increased risk of hospitalization and death.

**Objective** To describe the severity of 2009 influenza A(H1N1) illness and the association with early antiviral treatment among pregnant women in the United States.

## Acetaminophen Use during Pregnancy - 1

Reproductive Toxicology 30 (2010) 508-519

Contents lists available at ScienceDirect



ELSEVIER

Reproductive Toxicology

journal homepage: [www.elsevier.com/locate/reprotox](http://www.elsevier.com/locate/reprotox)



Review

Childhood asthma and use during pregnancy of acetaminophen. A critical review

Anthony R. Scialli<sup>a,b,\*</sup>, Robert Ang<sup>c</sup>, James Breitmeyer<sup>c</sup>, Mike A. Royal<sup>c</sup>

<sup>a</sup> Tetra Tech Sciences, Arlington, VA, United States

<sup>b</sup> The Reproductive Toxicology Center, Bethesda, MD, United States

<sup>c</sup> Cadence Pharmaceuticals, Inc., San Diego, CA, United States

- “At present, the evidence is inconclusive that any such association is causal.”

*Scialli et al., Reprod Toxicol 30:508-19, 2010*

## Acetaminophen Use during Pregnancy - 2

Research

Original Investigation

### Acetaminophen Use During Pregnancy, Behavioral Problems, and Hyperkinetic Disorders

Zeyan Liew, MPH; Beate Ritz, MD, PhD; Cristina Rebordosa, MD, PhD; Pei-Chen Lee, PhD; Jern Olsen, MD, PhD

EDITORIAL

### Antenatal Acetaminophen Use and Attention-Deficit/Hyperactivity Disorder: An Interesting Observed Association But Too Early to Infer Causality

Miriam Cooper, MRCPsych, MSc; Kate Langley, PhD; Anita Thapar, FRCPsych, PhD

*Liew et al., JAMA Pediatr 168:313-20, 2014*  
*Cooper et al., JAMA Pediatr 168:306-7, 2014*

## Information on Safety of Neuraminidase Inhibitors during Pregnancy - 1

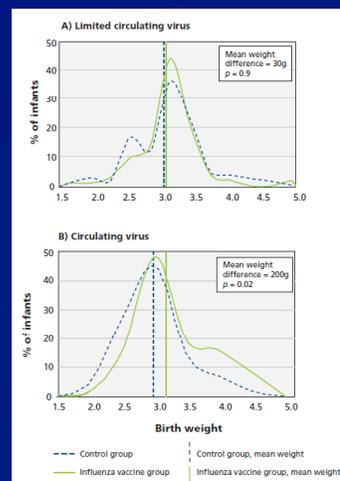
Study	Design	Numbers exposed/unexposed	Results
Greer et al., 2010	Retrospective cohort, Parkland Hospital, 2003-2008	Oseltamivir - 135 Unexposed - 82,097	No increased risk for preterm birth, premature rupture of membranes, gestational diabetes, preeclampsia, low birth weight, major or minor malformations
Svensson et al. 2011	Retrospective cohort, national registers, Sweden, 2005-2007	Oseltamivir - 81 Zanamivir - 2 Both - 3 Unexposed - 860 (matched by infant birth year, sex)	Increased risk of late transient hypoglycemia (crude OR 4.0, 1.3-12.8). No increased risk of low Apgars, congenital malformations, SGA, low birth weight, preterm birth or birth-related death
Saito et al., 2013	Case series study, Japan, 2009-2010	Oseltamivir - 619 Zanamivir - 50	No increased risk of malformations, miscarriage, preterm birth, neonatal death, low birthweight, SGA, NEC, IVH, seizures

## Information on Safety of Neuraminidase Inhibitors during Pregnancy - 2

Study	Design	Numbers exposed/unexposed	Results
Xie et al., 2013	Retrospective cohort, maternal newborn database, Ontario, 2009-2010	Oseltamivir – 1,237 Unexposed – 54,118	Infants exposed to oseltamivir were less likely to be SGA (10 <sup>th</sup> centile) – ARR 0.77 (0.70-0.98). No increased risk of SGA (3 <sup>rd</sup> centile), preterm birth, very preterm birth, low Apgar scores
Dunstan et al., 2014	Prospective cohort, UK teratology information service during 2009 H1N1 pandemic	Zanamivir – 180 Oseltamivir - 27 Unexposed – 575	No increased risk of major malformations, preterm delivery, low birth weight
Beau et al., 2014	French prescription database 2004-2010,	Oseltamivir - 337 Unexposed - 674 (matched by age, month, delivery year)	No increased risk for pregnancy loss, preterm birth, neonatal pathology, congenital defects

## Maternal Influenza Vaccine's Effects on Fetus/Newborn - 1

- Randomized controlled trial in Bangladesh -- pregnant women received inactivated influenza vaccine vs. pneumococcal
- Higher birth weights ( $p=0.02$ ) and lower risk of small for gestational age (SGA) ( $p=0.03$ ) among infants whose mothers received influenza vaccine



Steinhoff et al., CMAJ 184:645-53, 2012

## Maternal Influenza Vaccine's Effects on Fetus/Newborn - 2

- **Observational study from Georgia PRAMS**
  - Infants born during the putative influenza season (1 October-31 May) to mothers who received influenza vaccine prenatally were less likely to be preterm (aOR=0.60, 95% CI 0.38-0.94) and SGA (aOR= 0.31, 95% CI 0.13-0.75) compared to unvaccinated women.
- **Observational study from Ontario**
  - Infants born to mothers who received H1N1 vaccine prenatally were less likely to be SGA (aRR=0.90; 95% CI 0.85, 0.96) or preterm (<32 weeks) (aRR = 0.73; 95% CI = 0.58, 0.91). Fetal death was also less likely (aRR = 0.66; 95% CI = 0.47, 0.91).

*Omer et al., PLoS Med 8:e1000441, 2011*  
*Fell et al., Am J Public Health 102:e33-40, 2012*

## Maternal Influenza Vaccine's Effects on Fetus/Newborn - 3

- **Observational study from Kaiser Permanente GA and Mid-Atlantic**
  - Infants born to mothers who received H1N1 vaccine prenatally had 37% lower odds of being born preterm than infants of unvaccinated mothers. Mean birth weight difference of 45.1 g (1.8-88.3) between infants of H1N1-vaccinated mothers and of unvaccinated mothers. No significant association between H1N1 influenza immunization and LBW or SGA.
- **Observational study from Nova Scotia**
  - Odds of preterm delivery among infants of vaccinated women were lower than those of nonvaccinated women (aOR=0.75, 0.60-0.94). Rate of low birthweight infants was also lower among vaccinated women (aOR=0.73, 0.56-0.95).

*Richards et al., Clin Infect Dis 56, 1216-22, 2013*  
*Legge et al., CMAJ 186:E1577-164, 2014*

## Information on Safety of Influenza Vaccines during Pregnancy - 1

Study	Design	Numbers exposed/unexposed	Results
Moro et al., 2011	Review or reports of adverse events to VAERS, US, 1990-2009	148 reports of adverse events after TIV and 16 after LAIV	No unusual patterns of pregnancy complications or fetal outcomes
Moro et al., 2011	Review of reports of adverse events to VAERS, US, 2009-2010	294 reports of adverse events after 2009 H1N1 inactivated vaccine	No concerning patterns of maternal or fetal outcomes
Moro et al., 2013	Review of reports of adverse events to VAERS, US, 2009-2010	113 reports of adverse events after 2009 H1N1 LAIV	No concerning patterns of medical conditions in infants

## Information on Safety of Influenza Vaccines during Pregnancy - 2

Study	Design	Numbers exposed/unexposed	Results
Chambers et al., 2013	Prospective cohort	- 841 exposed to pH1N1-containing vaccine - 191 unexposed to any influenza vaccine	No meaningful evidence of increased risk for major birth defects, spontaneous abortion or SGA. Increased risk of PTD – AHR=3.28, 1.25-8.63 (decrease in gestational age ~3 days)
Louik et al., 2013	Birth defects – case-control Preterm delivery – cohort 4 regions in US, 2009-2011	Birth defects - 3104 cases - 1098 controls PTD - 378 exposed to pH1N1-containing vaccines - 573 unexposed	41 specific birth defects – most AORs ~1.0, 3 defects - AORs >2.0 and 4 defects - AORs <0.5, wide 95% CIs PTD - 2009-2010 season – AHR=2.82, 1.16-6.86 (decrease in gestational age <2 days) - 2010-2011 season – AHR=0.22, 0.06-0.83
Nordin et al., 2014	Retrospective matched cohort, 7 US sites, 2004-2009	57,749 vaccinated 92,440 unvaccinated	No increased or decreased risk for PTD or SGA

**PANDEMIC INFLUENZA REVISITED:  
Special Considerations for  
Pregnant Women and Newborns**

August 12 - 13, 2010  
Roybal Campus, Atlanta, Georgia  
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Sponsored by Centers for Disease Control and Prevention (CDC):  
• National Center on Birth Defects and Developmental Disabilities  
• National Center for Chronic Disease Prevention and Health Promotion  
• National Center for Immunization and Respiratory Diseases  
• Influenza Coordination Unit

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• Association of Maternal and Child Health Programs  
• March of Dimes



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SUPPLEMENT

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**Preparing for influenza after 2009 H1N1: special  
considerations for pregnant women and newborns**

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and the Pandemic Influenza and Pregnancy Working Group

*Rasmussen et al., Am J Obstet Gynecol 204:S13-20, 2011*

## **Current Treatment Recommendations - 1**

- All pregnant women with suspected influenza should receive prompt empiric treatment with appropriate influenza antiviral medications
- Pregnant women with suspected influenza should be treated, regardless of influenza vaccination status
- Currently available diagnostic tests should not be used to guide initial treatment decisions

## **Current Treatment Recommendations - 2**

- Prophylaxis recommendations should be the same as those for other groups at high risk for influenza-associated complications (can be considered)
- Recommendations for treatment /prophylaxis should apply to women for at least 2 weeks following the end of pregnancy
- Acetaminophen for fever

## **Strategies to Improve Immunization Coverage**

- Use reminder/recall systems
- Enter information regarding vaccine administration into immunization information systems
- Use standing orders
- Review immunization status at each patient visit
- Educate health care providers who administer vaccines
- Regularly assess provider coverage rates
- Improve public and provider awareness to increase demand

*Shavell et al., Am J Obstet Gynecol 207:S67-74, 2012*