

# Vaccine safety during pregnancy

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**Deshayne Fell, PhD**

Assistant Professor, School of Epidemiology and Public Health, uOttawa  
Scientist, CHEO Research Institute  
Adjunct Scientist, ICES



## Disclosure statement

I have no affiliation (financial or otherwise) with a pharmaceutical, medical device or communications organization.

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**BACKGROUND**

# Why vaccinate pregnant women?



Complex physical, physiological, and immunological changes during pregnancy increase maternal vulnerability to some infections



Maternal infection is one pathway to adverse birth outcomes, including: spontaneous preterm birth, spontaneous abortion, stillbirth, congenital anomalies



Immature immune system of the neonate poses an additional risk of infection and associated complications for young infants

# Why vaccinate pregnant women?

*“Immunization in pregnancy has emerged as an important and successful public health intervention globally to reduce mortality and morbidity among pregnant women, their developing fetuses and neonates, and infants.”*

*Kochhar S. Vaccine 2017; 35:6469-71.*

# Barriers and facilitators of maternal immunization

## BARRIERS

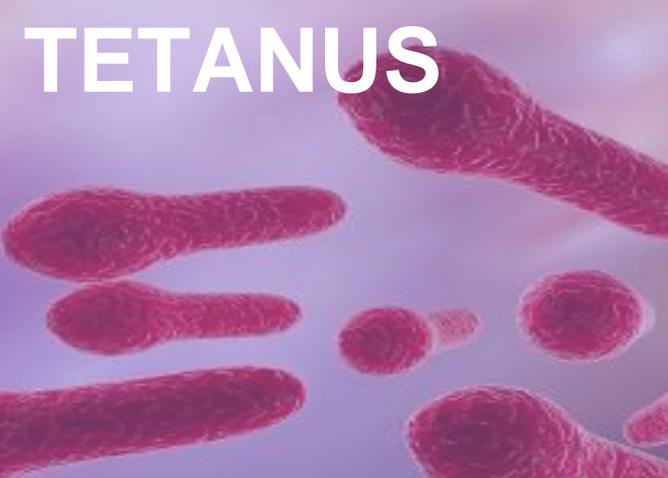
- **Vaccine safety during pregnancy (self, baby)**
- Lack of vaccine knowledge
- Low perceived severity of disease
- Lack of recommendations from healthcare personnel
- Issues with access or accessibility

## FACILITATORS

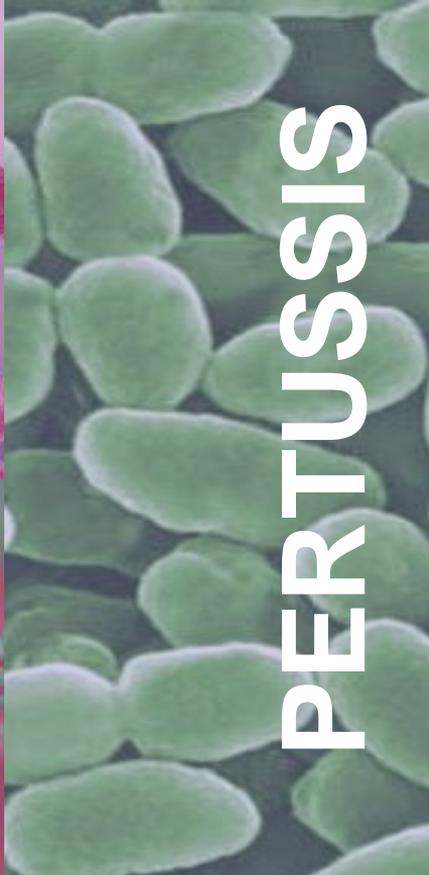
- Vaccine recommended and offered by health care provider
- **Safety information specific to vaccine administration in pregnant women**
- Robust national guidelines
- High level of vaccine knowledge
- Existing comorbidities
- Having a family doctor



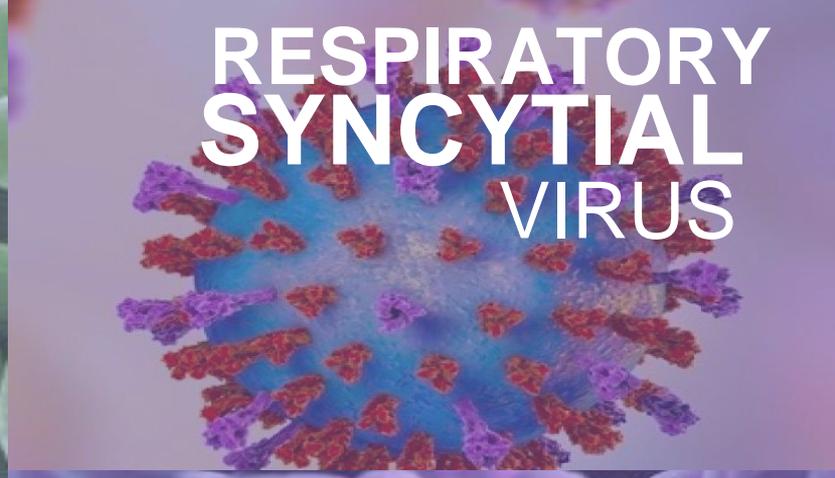
Chamberlain AT, et al. PLOS Currents Outbreaks. 2015; Edition 1; Wilson RJ, et al. Vaccine. 2015; 33(47):6240-9; Collins J, et al. Human Vaccines & Immunotherapeutics. 2014; 10(10):2922-9; MacDougall & Halperin. Human Vaccines & Immunotherapeutics 2016; 12:857-65.



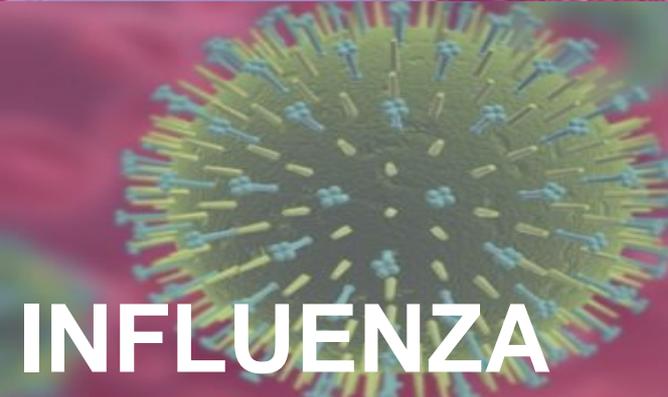
**TETANUS**



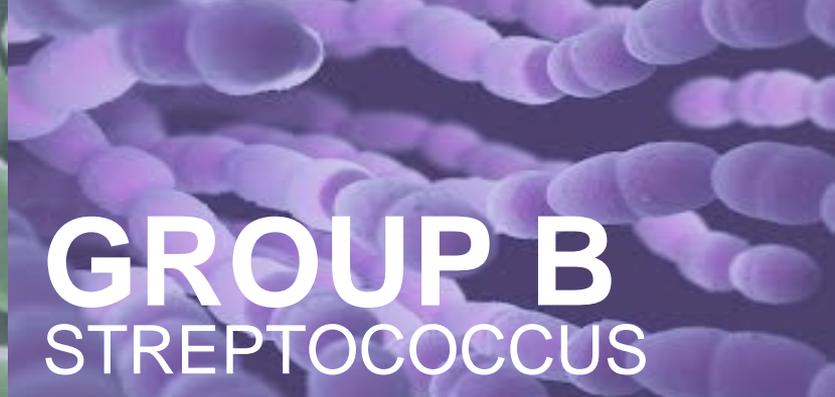
**PERTUSSIS**



**RESPIRATORY  
SYNCYTIAL  
VIRUS**



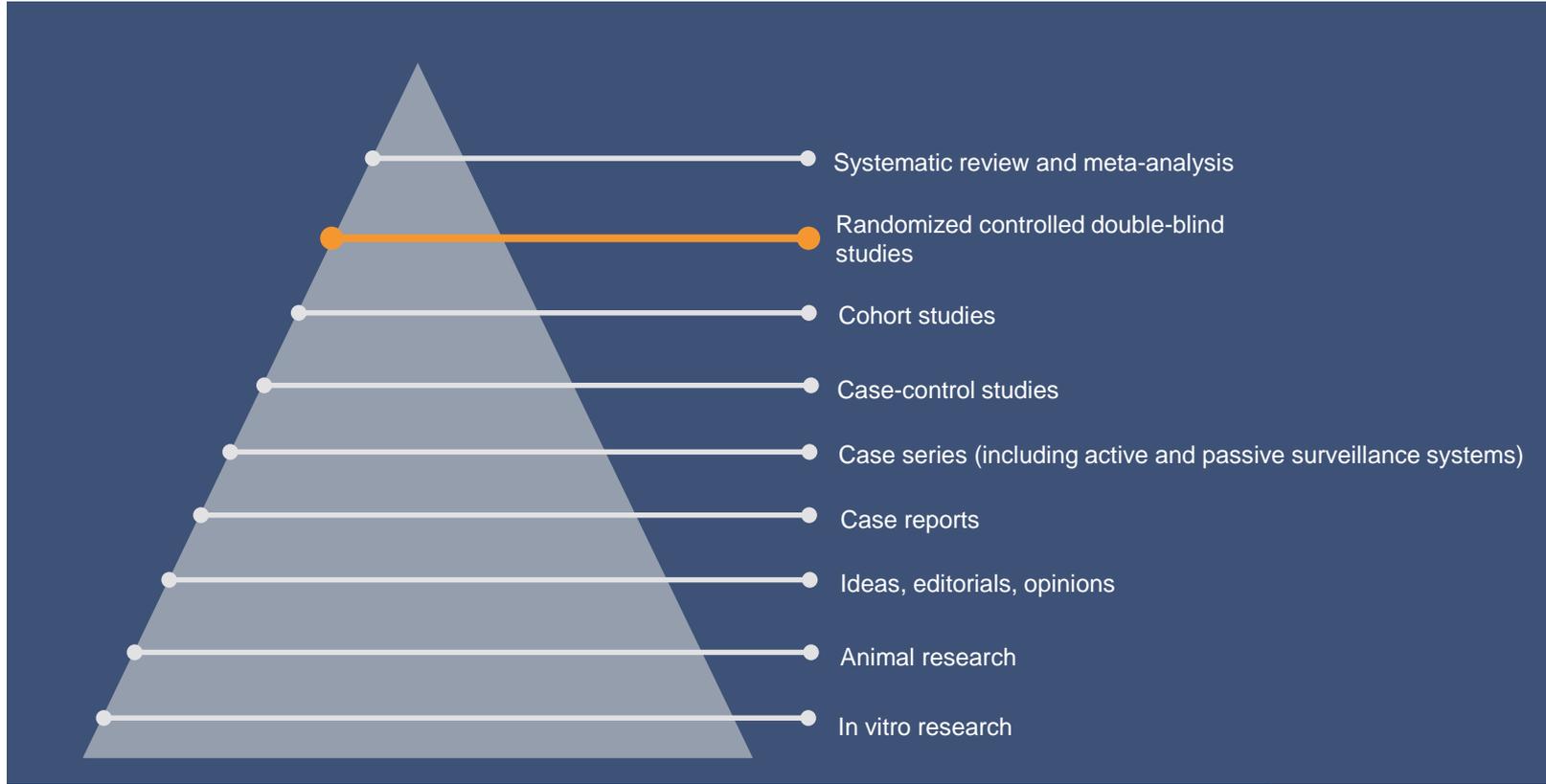
**INFLUENZA**



**GROUP B  
STREPTOCOCCUS**

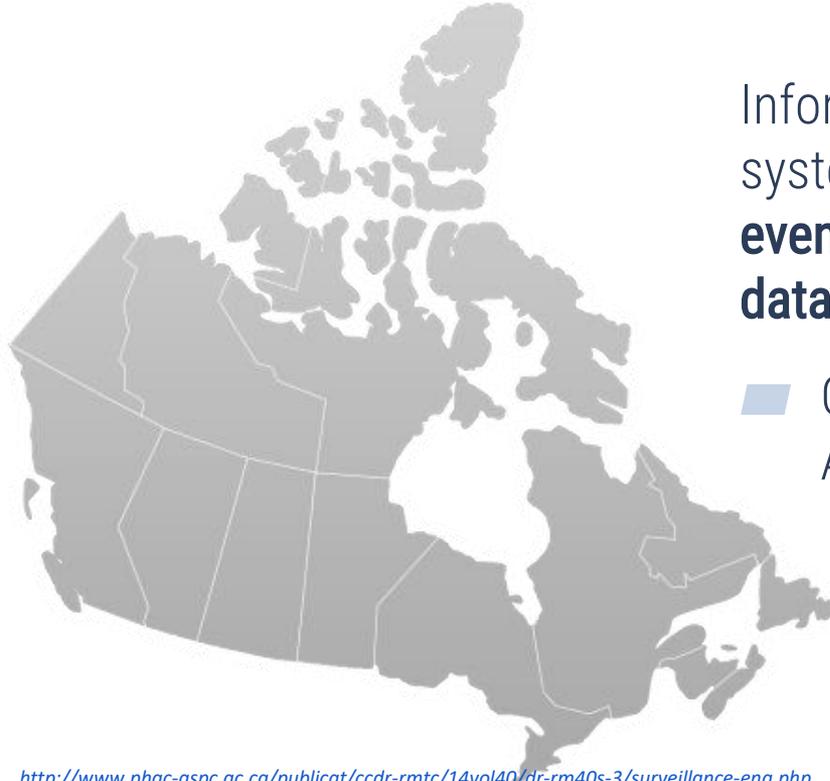
**VACCINES RECOMMENDED  
DURING PREGNANCY**

**NEW VACCINES  
UNDER DEVELOPMENT**



## HIERARCHY OF EVIDENCE

# AEFI surveillance in Canada



Information from immunization information systems may be linked to the **Canadian adverse events following immunization surveillance system database (CAEFISS)**

- CAEFISS is operated under the Public Health Agency of Canada



Public Health  
Agency of Canada

# Other AEFI surveillance databases

## Vaccine Safety Datalink (VSD)

Developed by the CDC, conducts national surveillance for AEFIs in the US



## Uppsala Monitoring Centre (UMC)

WHO organization, conducts global pharmacovigilance through collaboration with National Regulatory Agencies (e.g., CDC)



## The Yellow Card Scheme

National AEFI surveillance system in the U.K, depends on spontaneous reporting



## Vaccine Adverse Event Reporting System (VAERS)

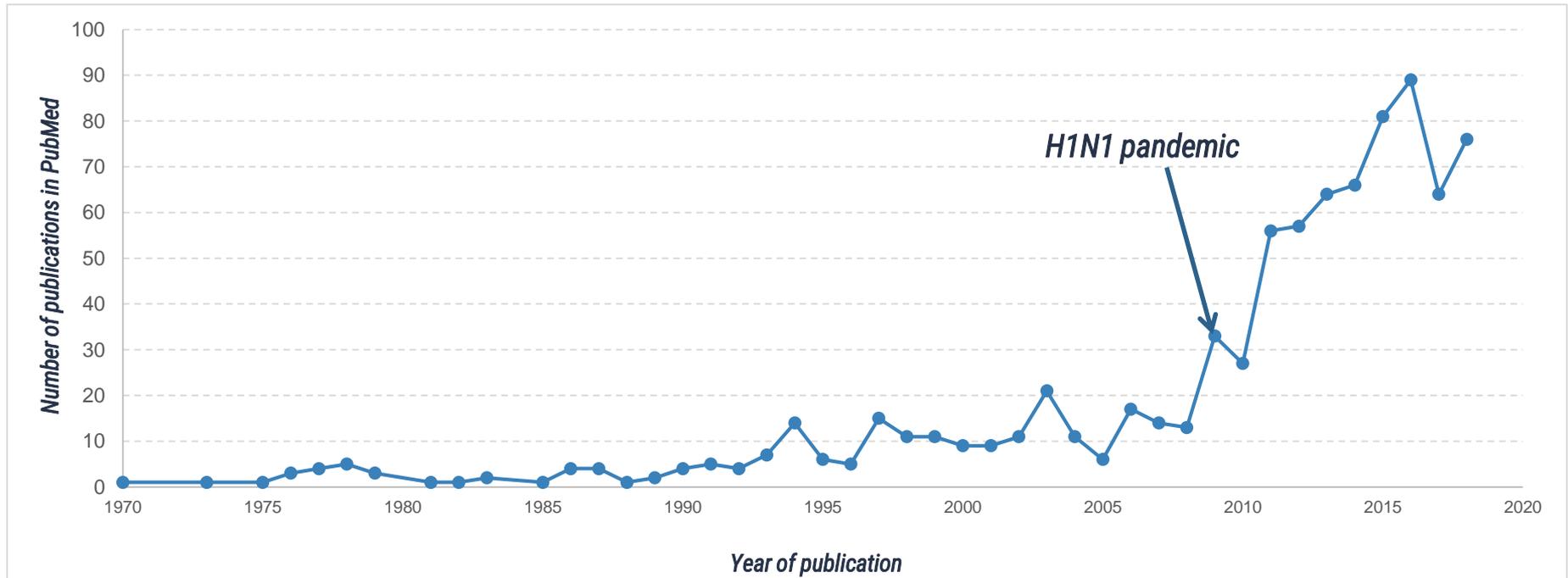


National program in the US managed by the CDC and the FDA for AEFI case reporting

# 2

## SAFETY EVIDENCE

# PubMed citations, Jan 1970 to Sept 2019



# Safety of maternal influenza immunization

## Safety of seasonal influenza and influenza A (H1N1) 2009 monovalent vaccines in pregnancy

Moro et al. Vaccine 2012; 11(8), 911–921

- Rates of spontaneous abortion, preterm birth, and major birth defects in pregnant women who received live H1N1 vaccine were similar to or lower than published background rates

### OBSTETRICS

## Adverse events following administration to pregnant women of influenza A (H1N1) 2009 monovalent vaccine reported to the Vaccine Adverse Event Reporting System

Moro et al. AJOG 2011; ;205:473.e1-9

- Review of reports to VAERS following H1N1 vaccination in pregnant women did not identify any concerning patterns of maternal or fetal outcomes

### OBSTETRICS

## Adverse events in pregnant women following administration of trivalent inactivated influenza vaccine and live attenuated influenza vaccine in the Vaccine Adverse Event Reporting System, 1990-2009

Moro et al. AJOG 2011; 204:146.e1-7

- No unusual patterns of pregnancy complications or fetal outcomes were observed in the VAERS reports of pregnant women after the administration of TIV or LAIV.

VAERS

# Safety of maternal influenza immunization

THE NEW ENGLAND JOURNAL OF MEDICINE

ORIGINAL ARTICLE

## Influenza Vaccination of Pregnant Women and Protection of Their Infants

Shabir A. Madhi, M.D., Ph.D., Clare L. Cutland, M.D., Locadiah Kuwanda, M.Sc., Adriana Weinberg, M.D., Andrea Hugo, M.D., Stephanie Jones, M.D., Peter V. Adrian, Ph.D., Nadia van Niekerk, B.Tech., Florette Treurnicht, Ph.D., Justin R. Ortiz, M.D., Marietjie Venter, Ph.D., Avy Violari, M.D., Kathleen M. Neuzil, M.D., Eric A.F. Simões, M.D., Keith P. Klugman, M.D., Ph.D., and Marta C. Nunes, Ph.D., for the Maternal Flu Trial (Matflu) Team\*

## Maternal immunisation with trivalent inactivated influenza vaccine for prevention of influenza in infants in Mali: a prospective, active-controlled, observer-blind, randomised phase 4 trial

Milagritos D Tapia, Samba O Sow, Boubou Tamboura, Ibrahim Tégoué, Marcela F Pasetti, Mamoudou Kodio, Uma Ornuochekwa, Sharon M Tennant, William C Blackwecker, Flannoc Coulibaly, Awa Traoré, Adama Mamby Kelta, Fadima Cheick Haidara, Fatoumata Diallo, Moussa Doumbia, Doh Sanogo, Ellen DeMatt, Nicholas H Schluterman, Andrea Buchwald, Karen I Kotloff, Wilbur H Chen, Evan W Orenstein, Lauren A V Orenstein, Julie Villanueva, Joseph Bresee, John Treanor, Myron M Levine

## Year-round influenza immunisation during pregnancy in Nepal: a phase 4, randomised, placebo-controlled trial

Mark C Steinhoff, Joanne Katz, Janet A Englund, Subarna K Khatri, Laxman Shrestha, Jane Kuypers, Laveta Stewart, Luke C Mullary, Helen Y Chu, Steven C LeClerg, Naoko Kazuki, Monica McNeal, Adriana M Reedy, James M Tielsch



## IIV3 vs. placebo



2116 HIV-negative women – 2<sup>nd</sup> or 3<sup>rd</sup> trimester



- Mild to moderate Injection-site reactions were more frequent among IIV3 recipients than among placebo recipients
- No other significant differences in solicited reactions between the two study groups



## IIV3 vs. quadrivalent meningococcal conjugate



4193 women – 3<sup>rd</sup> trimester



- Mild pain at the injection site was more commonly reported in women given IIV3
- No serious adverse events in infants or mothers were related to maternal vaccination



## IIV3 vs. placebo



3693 women – 2<sup>nd</sup> or 3<sup>rd</sup> trimester



- No difference in number of adverse events in infants or mothers between groups



# Safety of maternal influenza immunization

OBSERVATIONAL STUDIES

## RESEARCH AND PRACTICE

### H1N1 Influenza Vaccination During Pregnancy and Fetal and Neonatal Outcomes

Deshayne B. Fell, MSc, Ann E. Sprague, PhD, Ning Liu, MSc, Abdool S. Yasseen III, MSc, Shi-Wu Wen, PhD, Graeme Smith, MD, PhD, and Mark C. Walker, MD, MSc, for Better Outcomes Registry & Network (BORN) Ontario

Fell et al. *AJPH* 2012; e1–e8. doi:10.2105

- Ontario study of pH1N1 influenza vaccine
- Outcomes: preterm birth; fetal death; small-for-gestational-age birth
- No evidence of any adverse effect of pH1N1 influenza vaccination during pregnancy on fetal and neonatal outcomes

CMAJ

RESE

### Rates and determinants of seasonal influenza vaccination in pregnancy and association with neonatal outcomes

Alexandra Legge BSc, Linda Dodds PhD, Noni E. MacDonald MD, Jeffrey Scott MD, Shelly McNeil MD

Legge et al. *CMAJ* 2014; doi: 10.1503/cmaj.130499

- Nova Scotia study of seasonal influenza vaccine
- Outcomes: preterm birth; small-for-gestational-age birth; low birthweight
- No association with any adverse neonatal outcomes

### Health outcomes of young children born to mothers who received 2009 pandemic H1N1 influenza vaccination during pregnancy: a retrospective cohort study

Laura K. Walsh<sup>1,2</sup>, Jessy Donelle<sup>3</sup>, Linda Dodds<sup>4</sup>, Steven Hawken<sup>2,3,5</sup>, Kumanan Wilson<sup>2,3,5</sup>, Eric I. Benchimol<sup>2,3,6</sup>, Pranesh Chakraborty<sup>2,6</sup>, Astrid Guttmann<sup>3,9,11</sup>, Jeffrey C. Kwong<sup>3,7,8,9</sup>, Noni E. MacDonald<sup>4</sup>, Justin R. Ortiz<sup>10</sup>, Ann E. Sprague<sup>1,2,6</sup>, Karina A. Top<sup>4</sup>, Mark C. Walker<sup>1,2,5</sup>, Shi Wu Wen<sup>2,6</sup>, Deshayne B. Fell<sup>2,3,6</sup>

Walsh et al. Unpublished (under review)

- Ontario study of pH1N1 influenza vaccine
- Outcomes: rates of immune-mediated outcomes (infection and asthma) and SAEs up to age 5 years
- Small association with increase in asthma and decrease in GI infections; no association with mortality or cancer

# Safety of maternal influenza immunization

DOI: 10.1111/1471-0528.12977  
www.bjog.org

Systematic review

## Fetal death and preterm birth associated with maternal influenza vaccination: systematic review

DB Fell,<sup>a,b</sup> RW Platt,<sup>a</sup> A Lanes,<sup>c</sup> K Wilson,<sup>d,e,f</sup> JS Kaufman,<sup>a</sup> O Basso,<sup>a</sup> D Buckeridge<sup>a</sup>

Fell et al. BJOG 2015; 122(1):17-26

- N=27 studies
- Outcomes: preterm birth; fetal death
- No evidence of any adverse effect of influenza vaccination during pregnancy on preterm birth or late fetal death

Contents lists available at ScienceDirect



Vaccine

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

Review

Influenza vaccination during pregnancy: A systematic review of fetal death, spontaneous abortion, and congenital malformation safety outcomes

M. McMillan<sup>a,\*</sup>, K. Porritt<sup>b</sup>, D. Kralik<sup>c,1</sup>, L. Costi<sup>c</sup>, H. Marshall<sup>d</sup>

McMillan et al. Vaccine 2015; 33(18):2108-17

- N=19 studies
- Outcomes: fetal death; congenital malformations
- No evidence of any adverse effect of influenza vaccination during pregnancy

## Maternal Influenza Immunization and Birth Outcomes of Stillbirth and Spontaneous Abortion: A Systematic Review and Meta-analysis

Kristin N. Bratton,<sup>1,2</sup> Melissa T. Wardle,<sup>1,2</sup> Walter A. Orenstein,<sup>1,2,3,4</sup> and Saad B. Omer<sup>1,2,5</sup>

Bratton et al. CID 2015; 60(5):e11-9

- N=7 studies
- Outcomes: stillbirth and spontaneous abortion
- No evidence of any adverse association between influenza vaccination during pregnancy and study outcomes

## Association of spontaneous abortion with receipt of inactivated influenza vaccine containing H1N1pdm09 in 2010–11 and 2011–12

James G. Donahue<sup>a,\*</sup>, Burney A. Kieke<sup>a</sup>, Jennifer P. King<sup>a</sup>, Frank DeStefano<sup>b</sup>, Maria A. Mascola<sup>c</sup>, Stephanie A. Irving<sup>d</sup>, T. Craig Cheetham<sup>e</sup>, Jason M. Glanz<sup>f</sup>, Lisa A. Jackson<sup>g</sup>, Nicola P. Klein<sup>h</sup>, Allison L. Naleway<sup>d</sup>, Eric Weintraub<sup>b</sup>, Edward A. Belongia<sup>a</sup>

Determined if receipt of IIV vaccine containing pH1N1 was associated with **spontaneous abortion (SAB)**

- **Case-control study** over 2 influenza seasons (2010-11, 2011-12) in the Vaccine Safety Datalink
- SAB was associated with influenza vaccination receipt in the 28 day risk window (odds ratio=2.0, 95% CI 1.1-3.6). No association in other risk windows.
- **IIV-SAB association was statistically significant in 2010-11 but not 2011-12**, and only in the subgroup of women vaccinated during the previous season (pandemic)

# Case-Control Study of Inactivated Influenza Vaccine and Spontaneous Abortion in the Vaccine Safety Datalink, 2012-13, 2013-14, and 2014-15

Jim Donahue, PhD, DVM  
Marshfield Clinic Research Institute

**Advisory Committee on Immunization Practices  
February 27, 2019**

- **No significant association between influenza vaccine receipt and SAB**, regardless of prior season vaccination status
- Odds ratios were less than or close to 1.0 in all risk windows
- No significant associations in season-specific analyses
- **Findings support safety of influenza vaccine in early pregnancy**



2019

# Safety of maternal pertussis immunization

Reactogenicity and immunogenicity of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) in pregnant and nonpregnant women <sup>☆</sup>

Zheteyeva et al. *Vaccine* 2012; 11(8), 911–21

- Pregnant women were more likely to report moderate/severe pain at the Tdap injection-site compared with nonpregnant women, but did not necessitate medical visits

Enhanced surveillance of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccines in pregnancy in the Vaccine Adverse Event Reporting System (VAERS), 2011–2015

Moro et al. *AJOG* 2011; ;205:473.e1-9

- No new or unexpected vaccine AEs were noted among pregnant women who received Tdap after routine recommendations for maternal Tdap vaccination

Adverse event reports after tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccines in pregnant women

Moro et al. *AJOG* 2011; 204:146.e1-7

- During a time when Tdap was not routinely recommended in pregnancy, review of reports to VAERS in pregnant women after Tdap did not identify any concerning outcome patterns

# Safety of maternal pertussis immunization

OBSERVATIONAL STUDIES



## Association with chorioamnionitis (3 studies)

Kharbanda et al. JAMA 2014; Layton et al. Vaccine 2017;  
DeSilva et al. Vaccine 2017



## Association with post-partum hemorrhage (1 study)

Layton et al. Vaccine 2017



## No increased risk for adverse outcomes (13 studies)

Berenson et al., 2016; DeSilva et al., 2016; Donegan et al., 2014;  
Hoang et al., 2015; Kharbanda et al., 2014; Morgan et al., 2015;  
Moro et al., 2016; Munoz et al., 2014; Shakib et al., 2013;  
Sukumaran et al., 2015; Villarreal Pérez et al., 2017; Walls et al.,  
2016; Zheteyeva et al., 201

# Safety of maternal pertussis immunization

## Maternal vaccination against pertussis: a systematic review of the recent literature

Despoina Gkentzi,<sup>1,2</sup> Paraskeui Katsakiori,<sup>3</sup> Markos Marangos,<sup>2</sup> Yingfen Hsia,<sup>4</sup> Gayatri Amirthalingam,<sup>5</sup> Paul T Heath,<sup>4</sup> Shamez Ladhani<sup>5</sup>

Gkentzi D, et al. *Arch Dis Child Fetal Neonatal Ed* 2017; 102(5): F456-63

- January 2011 – May 2016
- N = 47 studies
- Prenatal vaccination induces high antibody concentrations that are efficiently transferred to the fetus
- Safe, no evidence of adverse pregnancy, birth, or neonatal outcomes

*Review*

## Safety of Tetanus, Diphtheria, and Pertussis Vaccination During Pregnancy

*A Systematic Review*

Mark McMillan, MCIsc, Michelle Clarke, BAAppSc, MPPH, Adriana Parrella, PhD, Deshayne B. Fell, PhD, MSc, Gayatri Amirthalingam, MBBS, MFPH, and Helen S. Marshall, MD, MPH

McMillan M, et al. *Obstet Gynecol* 2017; 129(3): 560-73

- Inception of database – May 5, 2016
- N = 21 studies
- Prenatal combined Tdap administered 2nd or 3rd trimester not associated with adverse outcomes in fetus or neonate
- Medically attended events in pregnant women are similar between vaccinated and unvaccinated groups

# 3

## FUTURE PERSPECTIVES

# Paradigm shift on inclusion of pregnant women in RCTs

Labelling pregnant women as **“vulnerable”**



Reclassify as **“scientifically complex”**

**“Acceptable risk”** to a woman or fetus is not well defined



Develop a **list of circumstances** justifying their participation

**Perceived legal risk** if the fetus or mother have an adverse outcome



Standardizing and reinforcing the existing **informed consent process**



# Vaccines in development: RSV & GBS



## Respiratory syncytial virus (RSV)

- **Phase 3**, observer-blind, placebo-controlled randomized trial; **>3,000 pregnant women**
- Maternal RSV vaccine reduced severe RSV hypoxemia by **60% in the first months of life**
- Vaccine appears to be **safe in mothers and infants**

THE  Prepare™ TRIAL

## Group B Streptococcus (GBS)

- **Phase I and II** trials of a trivalent GBS vaccine (serotypes Ia, Ib and III) have been conducted in >600 non-pregnant and **>500 pregnant women** in four countries



- The **Global Alignment of Immunization safety Assessment in pregnancy (GAIA)** is a working group coordinated by the Brighton Collaboration, and funded by the BMGF
- Standardization of **adverse event following immunization (AEFI)** case definitions specific to maternal and neonatal outcomes
- **9 case definitions:** Vaccine 2016; 34(40): Part I
- **11 case definitions:** Vaccine 2017; 35(48): Part II





## Future directions for safety monitoring

### **COMPLETE & ACCURATE**

maternal vaccination ascertainment

### **BACKGROUND RATES**

adverse pregnancy outcomes

### **BETTER DATA**

to study miscarriages/stillbirth

### **LONGITUDINAL DATA**

to study long-term health outcomes

### **GAIA CASE DEFINITIONS**

widespread implementation

### **ROBUST RESEARCH METHODS**

to account for biases in observational study

### **MECHANISMS FOR DATA SHARING/COMBINING**

for national and international collaboration





**Merci!**  
**Thank you!**



**Deshayne Fell**  
**[dfell@cheo.on.ca](mailto:dfell@cheo.on.ca)**