In compliance with continuing education requirements, all presenters must disclose any financial or other associations with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters as well as any use of unlabeled product(s) or product(s) under investigational use.

CDC, our planners, content experts, and their spouses/partners wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters. Planning committee discussed conflict of interest with each presenter to ensure there is no bias.

Content will not include any discussion of the unlabeled use of a product or a product under investigational use with the exception of the following speakers:

Karen Broder of the Centers for Disease Control and Prevention will discuss two CDC-supported clinical research studies involving administration of a repeated dose of Tdap. The Tdap package inserts indicate that Tdap is approved by FDA for use as a single dose. CDC’s Advisory Committee on Immunization Practices (ACIP) recommends that pregnant women receive a dose of Tdap in every pregnancy (this includes women who previously received a prior Tdap dose). Both studies are registered at ClinicalTrials.gov.

CDC did not accept commercial support for this continuing education activity.
Maternal Influenza and Tdap vaccine safety monitoring at CDC – Clinical Immunization Safety Assessment (CISA) Project

Karen R. Broder, MD
Immunization Safety Office
Centers for Disease Control and Prevention (CDC)

National Immunization Conference, May 17, 2018
Disclaimer

- The findings and conclusions in this presentation are those of the authors and do not necessarily represent the official position of the CDC or FDA
- Trade names are used for identification purposes
CDC vaccine safety monitoring

CISA
Clinical Immunization Safety Assessment (CISA) Project

7 participating medical research centers¹

- assist U.S. healthcare providers with complex vaccine safety questions about their patients (CISAeval@cdc.gov)²
- conduct clinical research

1. Boston Medical Center, MA; Cincinnati Children’s Hospital Medical Center, OH; Columbia University, NY; Duke University, NC; Johns Hopkins University, MD; Kaiser Permanente Northern California, CA; Vanderbilt University TN
## CISA Project sites and principal/senior investigators

<table>
<thead>
<tr>
<th>CISA Project Site</th>
<th>Principal and Senior Investigators</th>
</tr>
</thead>
</table>
| Boston Medical Center, MA                              | Elizabeth Barnett, MD  
                      Stephen Pelton, MD  |
| Cincinnati Children's Hospital Medical Center, OH       | Steven Black, MD  
                      Elizabeth Schlaudecker, MD, MPH  
                      Mary Staat, MD, MPH  |
| Columbia University, NY                                 | Anne Gershon, MD  
                      Philip LaRussa, MD  
                      Melissa Stockwell, MD, MPH  |
| Duke University, NC                                     | Emmanuel “Chip” Walter, MD, MPH  
                      Geeta Swamy, MD  
                      Ken Schmader, MD  |
| Johns Hopkins University, MD                            | Neal Halsey MD  
                      Kawsar Talaat, MD  |
| Kaiser Permanente Northern California, CA               | Nicola Klein, MD, PhD  |
| Vanderbilt University Medical Center, TN                | Kathryn M. Edwards, MD  
                      Buddy Creech, MD, MPH  |
# CISA Project research: strengths and limitations

## Strengths
- Can implement prospective, multi-site clinical studies (hundreds of subjects)
- Expertise in vaccine safety and clinical trials in many clinical areas
- Access to subspecialists and special populations, including pregnant women
- Can collect detailed clinical data on patients and biological specimens
- Ability to recruit controls

## Limitations
- Sample size limited to assess risk for rare adverse events
- Potential challenges to recruit and retain subjects
- May be challenging to verify vaccine history for vaccines given outside site prior to study
- Clinical studies may be labor and resource-intensive
CISA clinical research studies  
September 2012- May 2018  
by life stage and influenza vaccine status

<table>
<thead>
<tr>
<th>Life stage</th>
<th>Number of influenza vaccine studies (N=10)</th>
<th>Number of non-influenza vaccine studies (N=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant Women</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Infants and young children</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Children and adolescents</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Non-pregnant adults</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Older adults</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
CISA clinical research: maternal studies

1. PregText: Feasibility of monitoring influenza vaccine safety in pregnant women using text messaging
   - ClinicalTrials.gov (NCT01974050)
   - Completed and published*

2. Clinical study of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine (Tdap) safety in pregnant women
   - ClinicalTrials.gov (NCT02209623)

3. Safety and immunogenicity of simultaneous Tdap and inactivated influenza vaccine (IIV) in pregnant women
   - ClinicalTrials.gov (NCT02783170)

* Stockwell M. American Journal of Preventive Medicine, 2017
Study 1 - CISA PregText study: design*

- Observational study of pregnant women <20 weeks gestation at enrollment receiving IIV as part of routine care during 2013-14 at Columbia University clinics
- Pregnant women received text messages at scheduled time points to assess health events
- Chart review performed to confirm health, pregnancy, and neonatal outcomes

* Stockwell M. American Journal of Preventive Medicine. 2017; study registered at ClinicalTrials.gov (NCT01974050)
CISA PregText study: * example text message string

Msg 9: PregText: Are you still pregnant? Reply 1 or 2:
1 = No, I am no longer pregnant
2 = Yes, I am still pregnant

Reply #2 to Msg 1

Reply #1 to Msg 1

Go to Fig B

Msg 10: Since we last texted, did you have a health problem of any kind?
Reply 1 or 2:
1 = No, had no problems;
2 = Yes, had a problem

* Stockwell M., personal communication May 2018
CISA PregText study results*

- Demonstrated the feasibility of text messaging for influenza vaccine safety surveillance sustained throughout pregnancy

- In 166 women receiving IIV during pregnancy (85% first trimester)
  - Post-vaccination fever was infrequent
  - Typical pattern of maternal and neonatal health outcomes was observed

*Stockwell M. American Journal of Preventive Medicine. 2017
## CISA PregText results: pregnancy outcomes*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Text Message Reported Outcome**</th>
<th>Electronic Medical Record Abstracted Outcome**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous abortion</td>
<td>5.0% (2.4, 9.9)</td>
<td>4.2% (1.9, 8.9)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>6.3% (3.2, 11.9)</td>
<td>7.4% (4.1, 13.1)</td>
</tr>
<tr>
<td>Low birth-weight</td>
<td>8.2% (4.6, 14.1)</td>
<td>9.9% (6.0, 15.9)</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>4.6% (2.1, 9.7)</td>
<td>7.8% (4.4, 13.1)</td>
</tr>
<tr>
<td>Major birth defects</td>
<td>1.5% (0.4, 5.3)</td>
<td>2.8% (1.1, 7.0)</td>
</tr>
</tbody>
</table>

*Stockwell M. American Journal of Preventive Medicine. 2017

**95% confidence interval shown in parenthesis
Study 2 - CISA Tdap safety in pregnant women study

- Observational study

*Study Registered at ClinicalTrials.gov (NCT02209623)
CISA Tdap safety in pregnant women study: design*

- Women aged 18-45 years enrolled at Vanderbilt and Duke University clinics
  - Pregnant women at ≥20 and ≤34 weeks gestation receiving Tdap for routine care followed through delivery
  - Nonpregnant women receiving Tdap for usual care or as a research procedure and followed through 1 month after vaccination
- Prior Tdap/Td/TT history assessed by subject report and/or medical record/registry
- Reactions assessed for 1 week after Tdap – presented to the Advisory Committee on Immunization Practices (ACIP), June 2016
- Pregnancy and infant outcomes assessed – analysis in progress

*Study Registered at ClinicalTrials.gov (NCT02209623)
**CISA Tdap safety in pregnant women study: reaction grade definitions**

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain and tenderness</td>
<td>Interferes with activity but did not necessitate medical visit or absenteeism</td>
<td>Prevents daily activity and resulted in medical visit or absenteeism</td>
</tr>
<tr>
<td>Swelling and redness</td>
<td>10-34 mm</td>
<td>≥ 35 mm</td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>≥ 100.4 - &lt; 102.2° F</td>
<td>≥ 102.2° F</td>
</tr>
<tr>
<td>Other symptoms</td>
<td>Same as Pain/tenderness</td>
<td>Same as Pain/tenderness</td>
</tr>
</tbody>
</table>

*K. Edwards presentation to ACIP June 2016*
CISA Tdap safety in pregnant women study: preliminary results*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pregnant Women N= 374</th>
<th>Nonpregnant women N= 225</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>28.9</td>
<td>28.3</td>
</tr>
<tr>
<td>Median gestational age at enrollment (weeks)</td>
<td>29.2</td>
<td>N/A</td>
</tr>
<tr>
<td>Non-white</td>
<td>35.4%</td>
<td>21.3%</td>
</tr>
<tr>
<td>Prior Tdap receipt</td>
<td>52.9%</td>
<td>65.3%</td>
</tr>
<tr>
<td>Received Tdap Adacel®</td>
<td>97.3%</td>
<td>92.4%</td>
</tr>
</tbody>
</table>

*K. Edwards, presentation to ACIP June 2016 and K. Edwards, Personal communication May 2018
## CISA Tdap safety in pregnant women study: preliminary results

<table>
<thead>
<tr>
<th>Local Reaction (moderate/severe)</th>
<th>Pregnant Women N=367</th>
<th>Nonpregnant women N=223</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain²</td>
<td>67 (18%)</td>
<td>25 (11%)</td>
</tr>
<tr>
<td>Tenderness³</td>
<td>71 (19%)</td>
<td>38 (17%)</td>
</tr>
<tr>
<td>Swelling³</td>
<td>21 (6%)</td>
<td>13 (6%)</td>
</tr>
<tr>
<td>Redness³</td>
<td>21 (6%)</td>
<td>12 (5%)</td>
</tr>
</tbody>
</table>

1. K. Edwards, presentation to ACIP June 2016
2. Moderate/severe pain was statistically higher in pregnant vs. nonpregnant women (did not meet non-inferiority criteria); no woman sought medical care for injection-site pain
3. Moderate/severe local reactions were not statistically higher in pregnant vs. nonpregnant women (met non-inferiority criteria)
## CISA Tdap safety in pregnant women study: preliminary results

1. K. Edwards, presentation to ACIP June 2016
2. No moderate/severe systemic reactions were statistically higher in pregnant vs. non-pregnant women (all met non-inferiority criteria)

<table>
<thead>
<tr>
<th>Systemic Reaction (moderate/severe)</th>
<th>Pregnant Women N (%) N=367</th>
<th>Nonpregnant women N (%) N=223</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>2 (1%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Malaise</td>
<td>39 (11%)</td>
<td>11 (5%)</td>
</tr>
<tr>
<td>Body ache</td>
<td>29 (8%)</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>Headache</td>
<td>27 (7%)</td>
<td>20 (9%)</td>
</tr>
</tbody>
</table>
CISA Tdap safety study in pregnant women: preliminary results
Rates of moderate/severe reactions among pregnant women with and without prior Tdap receipt within 7 days after vaccination*

All comparisons for moderate/severe reactions met non-inferiority criteria
K. Edwards, presentation to ACIP June 2016
Study 3 - CISA simultaneous Tdap and IIV in pregnant women study*

- Randomized clinical trial
  - Pilot study
  - Open-label

*Study Registered at ClinicalTrials.gov (NCT02783170)
CISA Tdap and IIV in pregnant women study: design*

- Pregnant women aged 18-45 years who planned on receiving Tdap and IIV during the current pregnancy enrolled
  - Duke University and Cincinnati Children’s Medical Center clinics during 2016-17 and 2017-18 seasons
  - ≥26 and ≤32 weeks gestation

- Randomize 1:1 to
  - Simultaneous: Tdap (Boostrix®) and IIV (Fluzone Quadrivalent®) at visit 1 (N=41)**
  - Sequential: IIV at visit 1 then Tdap ~3 weeks later at visit 2 (N=40)**

*Study Registered at ClinicalTrials.gov (NCT02783170)
** Personal communication with G. Swamy, May 2018
CISA Tdap and IIV in pregnant women study: data collected*

- **Mother**
  - **Clinical:**
    - Reactions after vaccines and serious adverse events after vaccines
    - Pregnancy outcomes (e.g., preterm birth)
  - **Lab**
    - Blood for immunogenicity to vaccine antigens
    - Placenta (for pathological evidence of chorioamnionitis)

- **Infant**
  - Clinical outcomes at birth
  - **Lab**
    - Umbilical cord blood for immunogenicity to vaccine antigens
CISA maternal research: challenges

- Selection of control group for routinely recommended vaccines
  - Not ethical to use a placebo vaccine
- When uptake of vaccines is low in pregnant women, it may be challenging to recruit sufficient numbers of women
- Obtaining accurate vaccine history from before pregnancy may be challenging (e.g., prior Tdap status)
- Prospective clinical studies are resource intensive; need lengthy follow-up to assess pregnancy and infant outcomes
CISA maternal research: potential future directions

- Safety of different influenza vaccine products
  - Recombinant influenza vaccine (Flublok®)
- Safety of influenza vaccine in first trimester
- Immune and inflammatory responses after maternal vaccination
- Safety of simultaneous maternal vaccination
- New vaccines
  - Respiratory syncytial virus vaccine (RSV)
  - Group B streptococcal vaccine
CISA maternal research: summary

- CDC clinical studies complement other systems to provide data on maternal vaccine safety
- Clinical study of pregnant women receiving IIV showed a typical pattern of maternal and neonatal health outcomes after vaccination
- Clinical study of Tdap in pregnant women showed rates of moderate/severe reactions after Tdap were not higher in those receiving repeat Tdap vs. first-time Tdap
- CISA well-suited to conduct clinical studies to address questions arising as new maternal vaccines are introduced
# Acknowledgements

**CISA**
- Steven Black
- Buddy Creech
- Kathryn Edwards
- Kimberly Fortner
- Philip LaRussa
- Elizabeth Schlaudecker
- Melissa Stockwell
- Geeta Swamy
- Chip Walter

**CDC**
- Frank DeStefano
- Maria Cano
- Lisa Grohskopf
- Theresa Harrington
- Fiona Havers
- Pedro Moro
- Oidda Museru

**National Vaccine Program Office**
- Karin Bok

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**THANKS**
Maternal Influenza and Tdap vaccine safety monitoring at CDC: Vaccine Safety Datalink

Lakshmi Sukumaran, MD, MPH
Medical Officer
Immunization Safety Office
Disclaimer

- The findings and conclusions in this presentation are those of the author and do not necessarily represent the official position of the CDC.
OUTLINE

- Studying pregnancy in the Vaccine Safety Datalink (VSD)
- Results of VSD inactivated influenza vaccine (IIV) and tetanus, diphtheria, and acellular pertussis (Tdap) safety studies in pregnancy
Maternal vaccine safety in the VSD
CDC vaccine safety monitoring

VSD

Vaccine Safety Datalink

8 participating healthcare organizations
1. Evaluate the safety of newly licensed vaccines
2. Evaluate the safety of new vaccine recommendations for existing vaccines
3. Evaluate clinical disorders following immunizations
4. Assess vaccine safety in special high risk populations
5. Develop and evaluate methods for vaccine safety assessment
6. Evaluate and study the safety of the immunization schedule

VSD Strategic Priorities
Identifying pregnancies in the VSD

- VSD uses an validated algorithm\textsuperscript{1} to identify pregnancy outcomes and start and end dates from electronic health records
- VSD data can be used to link pregnant women to their children
- VSD annual cohort \textasciitilde3\% of US population\textsuperscript{2}
  - \textasciitilde125,000 pregnancies per year
  - \textasciitilde90,000 live births per year
- Additional pregnancy data: Height and weight, education, marital status, prior pregnancy history, smoking and alcohol use, plurality, delivery type, Apgars, last menstrual period, estimated due date

\textsuperscript{1} Naleway AL et al. Vaccine (2013).
\textsuperscript{2} McNeil MM et al. Vaccine (2014).
Pregnancy episode file: outcome, start date, end date, gestational age

Standardized VSD files: demographics, vaccination, diagnosis and procedure codes

FAMID file: mother-infant linkages

PREG file: Additional pregnancy and delivery information on pregnancies ending in live births
Types of VSD pregnancy studies
- Cohort
- Case-control
- Methods

Vaccines
- Influenza
- Tdap
- Other (HPV, hepatitis, etc.)

Maternal Outcomes
- Local reactions
- Allergic reactions
- Neurologic outcomes

Pregnancy outcomes
- Spontaneous abortion
- Stillbirth
- Pregnancy complications

Birth Outcomes
- Preterm
- Small for gestational age
- Low birth weight

Infant Outcomes
- Birth defects
- Neonatal complications
- Hospitalization
- Death
VSD Influenza vaccine safety studies
VSD maternal influenza studies – maternal outcomes

- Medically attended maternal acute events\textsuperscript{1,2}
  - Outcomes included allergic reactions, fevers, local reactions, neurologic events
  - No increased risk following IIV or monovalent H1N1 vaccines

1. Nordin JD et al. Vaccine (2014)
VSD maternal influenza studies – pregnancy outcomes

- Spontaneous abortion (SAB)\textsuperscript{1,2}
  - No increased risk of SAB in the 28 days following IIV exposure during 2005-2007 influenza seasons\textsuperscript{1}
  - Increased risk of SAB in the 28 days following IIV exposure during 2010-2012 influenza seasons\textsuperscript{2}
    - Risk seen in women vaccinated with pandemic 2009 H1N1 containing vaccine in prior influenza season
    - Follow up study evaluating subsequent influenza seasons in progress

VSD maternal influenza studies – pregnancy outcomes

- Adverse obstetric events\textsuperscript{1,2}
  - Outcomes included hyperemesis, gestational hypertension, gestational diabetes, proteinuria, urinary tract infection
  - No increased risk following IIV or monovalent H1N1 vaccines

- Adverse birth outcomes\textsuperscript{3}
  - No increased risk of preterm birth or small for gestational age following IIV

\textsuperscript{1} Kharbanda EO et al. Obstet Gynecol (2013)
\textsuperscript{2} Nordin JD et al. Vaccine (2014)
\textsuperscript{3} Nordin JD et al. J Pediatr (2014)
VSD maternal influenza studies – infant outcomes

- Major structural birth defects\(^2\)
  - No increased risk after first trimester IIV exposure

- Infant mortality and hospitalizations\(^3\)
  - No increased risk of infant death, hospitalization or hospitalizations from respiratory causes following maternal IIV exposure

VSD Tdap vaccine safety studies
VSD maternal Tdap studies – maternal outcomes

- Medically attended maternal acute adverse events\(^1-^3\)
  - Outcomes included local reactions, fevers, allergic reactions, neurologic events
  - No increased risk following Tdap vaccine, concomitant Tdap and IIV, or following repeated doses of tetanus-containing vaccines

VSD maternal Tdap studies – pregnancy outcomes

- Adverse obstetric events\(^1\)
  - Small statistically significant increased risk of chorioamnionitis
    - Follow-up study evaluating infant morbidity showed no signals (next slide)
    - No increased risk of hypertensive disorders of pregnancy

- Adverse birth outcomes\(^{1,2,3}\)
  - No increased risk of preterm delivery, small for gestational age following Tdap vaccine, concomitant Tdap and IIV, or following repeated doses of tetanus-containing vaccines

VSD maternal Tdap studies – infant outcomes

- Infant morbidity\(^1\)
  - Slight increase in chorioamnionitis after maternal Tdap
  - However, no increased risk of tachypnea of newborn, neonatal sepsis, neonatal pneumonia, respiratory distress syndrome, newborn convulsions

- Birth defects\(^2\)
  - No increased risk of microcephaly or other structural birth defects
    - Response to concerns of increase in microcephaly in Brazil related to Zika

- Infant mortality and hospitalizations\(^3\)
  - No increased risk for infant death, hospitalizations or respiratory hospitalizations after maternal Tdap

---

2. DeSilva M et al. JAMA (2016)
VSD maternal vaccine safety summary
Published VSD pregnancy studies

Published VSD pregnancy studies (cont.)

Published VSD pregnancy studies (cont.)

Published VSD pregnancy studies (cont.)

Future directions for VSD pregnancy work

- Calculating background rates of adverse events during pregnancy in preparation for new vaccines (i.e. Zika virus, Respiratory Syncytial Virus, Group B Strep)
- Exploration of additional covariates to include in safety studies
  - Pre-conception visits, infertility treatments
- Developing methods to rapidly identify pregnant women for future VSD studies
- Studying safety of repeated Tdap or influenza vaccines in pregnancy
- Developing and incorporating standardized outcome definitions
  - Using GAIA\(^1\) initiative definitions
  - Algorithm for birth defects (ICD-10)

1. GAIA: Global Alignment of Immunization safety Assessment in pregnancy project
Recap

- Maternal vaccination safety is a priority of the Immunization Safety Office and VSD
- The VSD has unique methods to study vaccine safety in pregnancy and conducts high quality epidemiologic studies
- VSD studies support the safety of influenza and Tdap vaccines in pregnancy and are consistent with larger body of evidence
Acknowledgements

CDC Immunization Safety Office
VSD pregnancy working group
VSD project managers and data managers

For more information, contact CDC
1-800-CDC-INFO (232-4636)

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