Communications: ACIP recommendations and vaccine uptake by pregnant women

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Disclosures

- Member, CDC’s Advisory Committee on Immunization Practices
- Writer, Up To Date – Herpes, Parvovirus, Rubella
Points to consider using flu vaccine as an example:

- Challenge of treating mother and fetus/newborn

- Role of labeling and ACIP recommendations when counseling about vaccines

- What factors are prioritized when considering use of a vaccine during pregnancy and postpartum
Historical Perspective

**Influenza Pandemic 1918-19**

1,350 pregnant women reported; 50% developed pneumonia (>50% died); case fatality 27%

**Asian Flu 1957**

Also noted higher than expected death rate;

Second & third trimesters particularly affected

**H1N1 Pandemic 2009**

56 deaths reported (7.1% 1st trimester, 26.8% 2nd trimester, 64.3% third trimester)
**H1N1 in pregnancy and postpartum women: CA**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pregnant (N=94)</th>
<th>Postpartum (N=8)</th>
<th>Nonpregnant (N=137)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range) — yr</td>
<td>26 (16–42)</td>
<td>28 (22–33)</td>
<td>28 (15–44)</td>
<td>0.02‡</td>
</tr>
<tr>
<td>Race or ethnic group — no./total no. (%)§</td>
<td></td>
<td></td>
<td></td>
<td>0.24†</td>
</tr>
<tr>
<td>Hispanic</td>
<td>43/78 (55)</td>
<td>3/8 (38)</td>
<td>47/116 (41)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>15/78 (19)</td>
<td>2/8 (25)</td>
<td>32/116 (28)</td>
<td></td>
</tr>
<tr>
<td>Asian or Pacific Islander</td>
<td>9/78 (12)</td>
<td>2/8 (25)</td>
<td>15/116 (13)</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>6/78 (8)</td>
<td>1/8 (12)</td>
<td>18/116 (16)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5/78 (6)</td>
<td>0</td>
<td>4/116 (3)</td>
<td></td>
</tr>
<tr>
<td>Chronic coexisting illness — no./total no. (%)¶</td>
<td>32/93 (34)</td>
<td>2/8 (25)</td>
<td>82/137 (60)</td>
<td>&lt;0.001†</td>
</tr>
</tbody>
</table>

*Young, healthy women get sick!*
### H1N1 in pregnancy and postpartum women: CA

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pregnant (N=94)</th>
<th>Postpartum (N=8)</th>
<th>Nonpregnant (N=137)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary bacterial or fungal infection — no. (%) †</td>
<td>1 (1)</td>
<td>1 (12)</td>
<td>9 (7)</td>
<td>0.05</td>
</tr>
<tr>
<td>Antiviral treatment — no./total no. (%) ‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At any time during course of illness</td>
<td>71/88 (81)</td>
<td>7/8 (88)</td>
<td>97/120 (81)</td>
<td>0.98</td>
</tr>
<tr>
<td>≤48 hr after symptom onset</td>
<td>30/60 (50)</td>
<td>3/7 (43)</td>
<td>28/82 (34)</td>
<td>0.06</td>
</tr>
<tr>
<td>Antibiotic treatment — no./total no. (%)</td>
<td>42/94 (45)</td>
<td>7/8 (88)</td>
<td>80/137 (58)</td>
<td>0.04</td>
</tr>
<tr>
<td>Median time from symptom onset to hospitalization (range) — days</td>
<td>2 (0–11)</td>
<td>6 (1–7)</td>
<td>3 (0–20)</td>
<td>0.12‡</td>
</tr>
<tr>
<td>Median hospital stay (range) — days</td>
<td>3 (1–76)</td>
<td>6 (1–36)</td>
<td>4 (1–41)</td>
<td>0.03‡</td>
</tr>
<tr>
<td>Death — no.</td>
<td>6</td>
<td>2</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Median time from symptom onset to death (range)</td>
<td>20 (14–49)</td>
<td>30 (26–33)</td>
<td>10 (3–22)</td>
<td>0.01‡</td>
</tr>
</tbody>
</table>

*Delay in antiviral treatment ➔ greater death rate!*

Louie et al. NEJM, 2010;362:27-35
Influenza Vaccine Recommendation

- All pregnant women should receive influenza vaccine every year – during any trimester of pregnancy.
ACIP and the GRADE approach

- ACIP adopted the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach in October 2010
  - Quality of evidence for benefits and harms
  - Going from evidence to recommendations

- Quality of evidence for benefits and harms is only one factor in developing a recommendation
  - Other key factors include balance of benefits and harms, values, and health economic data
  - ACIP Charter states, “shall include consideration of disease epidemiology and burden of disease, vaccine efficacy and effectiveness, vaccine safety, economic analyses and implementation issues.”
Evidence to Decision (EtD) Frameworks

- EtD frameworks were developed by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group*

- Frameworks are intended to help panels:
  - Structure discussion and identify reasons for disagreements
  - Be more systematic and explicit about the judgments that they make, the evidence used to inform each of those judgments, additional considerations, and the basis for their recommendations or decisions
  - Make the process and basis for decisions structured and transparent

- Frameworks assist users of recommendations by enabling them to understand the judgments made by the panel and the evidence supporting those judgments

*GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 1: Introduction
BMJ 2016; 353 doi: https://doi.org/10.1136/bmj.i2016 (Published 28 June 2016)
Courtesy of Wendy Carr, CDC – ACIP 2/20/18
Proposed ACIP EtR Framework: Question, Background, and Problem

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>JUDGMENTS</th>
<th>EVIDENCE</th>
<th>ADDITIONAL INFORMATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Is the problem of public health importance?</td>
<td><img src="no.png" alt="No" /></td>
<td><img src="yes.png" alt="Yes" /></td>
<td><img src="varies.png" alt="Varies" /></td>
</tr>
</tbody>
</table>
Proposed EtR Framework Criteria

- **Statement of Problem**
  - Public health importance
  - Burden of disease

- **Benefits and Harms**
  - Balance of desirable and undesirable effects
  - Certainty in evidence (evidence profiles)

- **Values and Preferences of target population**

- **Acceptability to stakeholders**

- **Resource Use**
  - Health Economic Analyses

- **Feasibility**
  - Implementation considerations

Courtesy of Wendy Carr, CDC – ACIP 2/20/18


8.1 Pregnancy

Pregnancy Category B:

A reproductive and developmental toxicity study has been performed in female rats at a dose approximately 265 times the human dose (on a mg/kg basis) and revealed no evidence of impaired female fertility or harm to the fetus due to AFLURIA. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, AFLURIA should be given to a pregnant woman only if clearly needed.

In the reproductive and developmental toxicity study, the effect of AFLURIA on embryo-fetal and pre-weaning development was evaluated in pregnant rats. Animals were administered AFLURIA by intramuscular injection twice prior to gestation, once during the period of organogenesis (gestation day 6), and once later in pregnancy (gestation day 20), 0.5 mL/rat/occasion (approximately a 265-fold excess relative to the projected human dose on a body weight basis). No adverse effects on mating, female fertility, pregnancy, parturition, lactation parameters, and embryo-fetal or pre-weaning development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis.

8.3 Nursing Mothers

AFLURIA has not been evaluated in nursing mothers. It is not known whether AFLURIA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when AFLURIA is administered to a nursing woman.
Flu vaccination coverage

Figure 1. Trend of flu vaccination coverage before and during pregnancy and prevalence of provider recommendation/offer or no recommendation for vaccination among women pregnant anytime October through January, Internet panel survey, United States, 2010-11 through 2015-2016 flu seasons

- Received provider recommendation and offer*
- Vaccination coverage†
- Received no recommendation*
Flu vaccine coverage in pregnancy

- As of early November 2017, influenza (flu) vaccination coverage among pregnant women before and during pregnancy was 35.6%.

Figure 1. Flu vaccination coverage before and during pregnancy among pregnant women by early November and mid April for 2010-11 through 2016-17 flu seasons, Internet panel survey, United States
Why are we here?

- Providers
- Patients (mothers, babies, families)
- Sources of information
- Interpretation of that information
- Decision ---- but what is rational?
Final Rule for Pregnancy and Lactation Labeling

- **Eliminates** pregnancy letter categories for all drugs.

- Includes 3 subsections for 8.1 Pregnancy and 8.2 Lactation
  - Risk summary
  - Clinical considerations
  - Human Data
  - Animal Data

- Include pregnancy exposure registry information for products with an enrolling study
Considerations specific to pregnancy

1. Pregnancy physiology – Impact of disease

2. Pregnancy immunology – Impact of vaccine

3. Safety of vaccines
   - Maternal issues
   - Fetal issues (trimester of exposure, birth defects, fetal brain development, fetal immune response)
   - Postpartum issues (exposure through breast feeding)
The vaccine monitoring system

US Department of Health and Human Services (HHS)

- Food and Drug Administration (FDA)
- Centers for Disease Control and Prevention (CDC)
- National Institutes of Health (NIH)

Immunization Safety Office (ISO)

- PRISM
- VAERS
- VSD
- CISA

VA Adverse Drug Event Reporting System (ADERS)

Military Vaccine Agency (MILVAX)
Association of spontaneous abortion with receipt of inactivated influenza vaccine containing H1N1pdm09 in 2010–11 and 2011–12

James G. Donahue, Burney A. Kieke, Jennifer P. King, Frank DeStefano, Maria A. Mascola, Stephanie A. Irving, T. Craig Cheetham, Jason M. Glanz, Lisa A. Jackson, Nicola P. Klein, Allison L. Naleway, Eric Weintraub, Edward A. Belongia

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Kaiser Permanente Northwest, 3800 N. Interstate Ave, Portland, OR 97227, United States
Kaiser Permanente Southern California, 100 S. Los Robles Ave., 2nd Floor, Pasadena, CA 91101, United States
Kaiser Permanente Colorado, 10065 E. Harvard, Suite 300, Denver, CO 80231, United States
Group Health Research Institute, 1730 Minor Avenue, Suite 1600, Seattle, WA 98101, United States
Kaiser Permanente Northern California, 1 Kaiser Plaza, 16th Floor, Oakland, CA 94612, United States
Additional safety data on flu & SAb


The response to the “signal”

It’s the first study to identify a potential link between miscarriage and the flu vaccine and the first to assess the effect of repeat influenza vaccination and risk of miscarriage. The findings suggest an association, not a causal link, and the research is too weak and preliminary, experts said, to change the advice, which is based on a multitude of previous studies, that pregnant women should get a flu vaccine to protect them from influenza, a deadly disease that may cause serious birth defects and miscarriage. But the study is likely to raise questions about the safety of the vaccine as flu season gets underway.

The new finding raises a lot of questions and is sure to provoke concern among pregnant women, who may be tempted to forgo vaccinations. But experts and even the authors themselves caution that this result is far from conclusive.
The truth about the flu shot during pregnancy

We actually do not know if the flu shot during pregnancy is safe.

The American College of Obstetricians and Gynecologists states that “no study to date has seen an adverse consequence of influenza vaccine in pregnant women and their offspring.” Well, my friends, this is because there hasn't been much research to determine its safety. (source)

In fact, the warnings on the inserts of flu vaccines clearly state that “safety and effectiveness have not been established in pregnant women or nursing mothers,” yet the shot is routinely administered to these very women for the protection of their pregnancies.

What's more, a recent found that the flu vaccine is linked to an increased risk of miscarriage.
8.1 Pregnancy

Pregnancy Category B

A developmental toxicity study has been performed in female rats at a dose approximately 40 times the human dose (on a mL/kg basis) and revealed no evidence of harm to the fetus due to BOOSTRIX. Animal fertility studies have not been conducted with BOOSTRIX. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, BOOSTRIX should be given to a pregnant woman only if clearly needed.

In a developmental toxicity study, the effect of BOOSTRIX on embryo-fetal and pre-weaning development was evaluated in pregnant rats. Animals were administered INFANRIX by intramuscular injection once prior to gestation and BOOSTRIX by intramuscular injection during the period of organogenesis (gestation Days 6, 8, 11, and 15), 0.1 mL/rat/occasion (approximately 40-fold excess relative to the projected human dose of BOOSTRIX on a body weight basis). The antigens in INFANRIX are the same as those in BOOSTRIX, but INFANRIX is formulated with higher quantities of these antigens. No adverse effects on pregnancy, parturition, lactation, embryo-fetal or pre-weaning development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis noted in this study.

Registry of Receipt of Adacel Vaccine During Pregnancy

Sanofi Pasteur Inc. maintains a surveillance registry to collect data on pregnancy outcomes and newborn health status outcomes following vaccination with Adacel vaccine during pregnancy. Women who receive Adacel vaccine during pregnancy are encouraged to contact directly or have their healthcare professional contact Sanofi Pasteur Inc. at 1-800-822-2463 (1-800-VACCINE).

8.3 Nursing Mothers

It is not known whether Adacel vaccine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Adacel vaccine is given to a nursing woman.
If there is insufficient information on the label and/or there is no clear recommendation, the assumption is the vaccine is unsafe to use in pregnancy or postpartum while breastfeeding.