Communication: 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:

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- 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

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

Young, healthy women get sick!

Louie et al NEJM, 2010;362:27-35

H1N1 in pregnancy and postpartum women: CA

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

Delay in antiviral treatment ⟶ greater death rate!

Louie et al NEJM, 2010;362:27-35

Influenza Vaccine Recommendation

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- All pregnant women should receive influenza vaccine every year – during any trimester of pregnancy.

ACOG
The American College of Obstetricians and Gynecologists

Society for Maternal•Fetal Medicine

AAFP

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

CDC

AMERICAN COLLEGE of NURSE-MIDWIVES
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ACIP and the GRADE approach

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- **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."

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

Evidence to Decision (EtD) Frameworks

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- **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

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Question: Overarching policy question to be answered by the guideline panel (ACIP) using the Evidence to Recommendations (EtR) framework.
Population: Target population for vaccine (e.g., age range, sex, immune status, pregnancy)
Intervention: Vaccination (if applicable, dosage and schedule)
Comparison(s): No Vaccination/Placebo/Control/Standard care/An existing vaccine/Other prevention options
Outcome: Outcome(s) associated with vaccination (e.g., prevention outcomes or adverse effects)

Background: The addressed PICO question should be described in detail, and important background information for understanding the question and why a recommendation or decision is needed should be briefly provided.

	CRITERIA	JUDGMENTS	EVIDENCE	ADDITIONAL INFORMATION
PROBLEM	Is the problem of public health importance?	*No* ☐ *Probably no* ☐ *Uncertain* ☐ *Probably yes* ☐ *Yes* ☐ *Varies* ☐		

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

Proposed EtR Framework Criteria

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- **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

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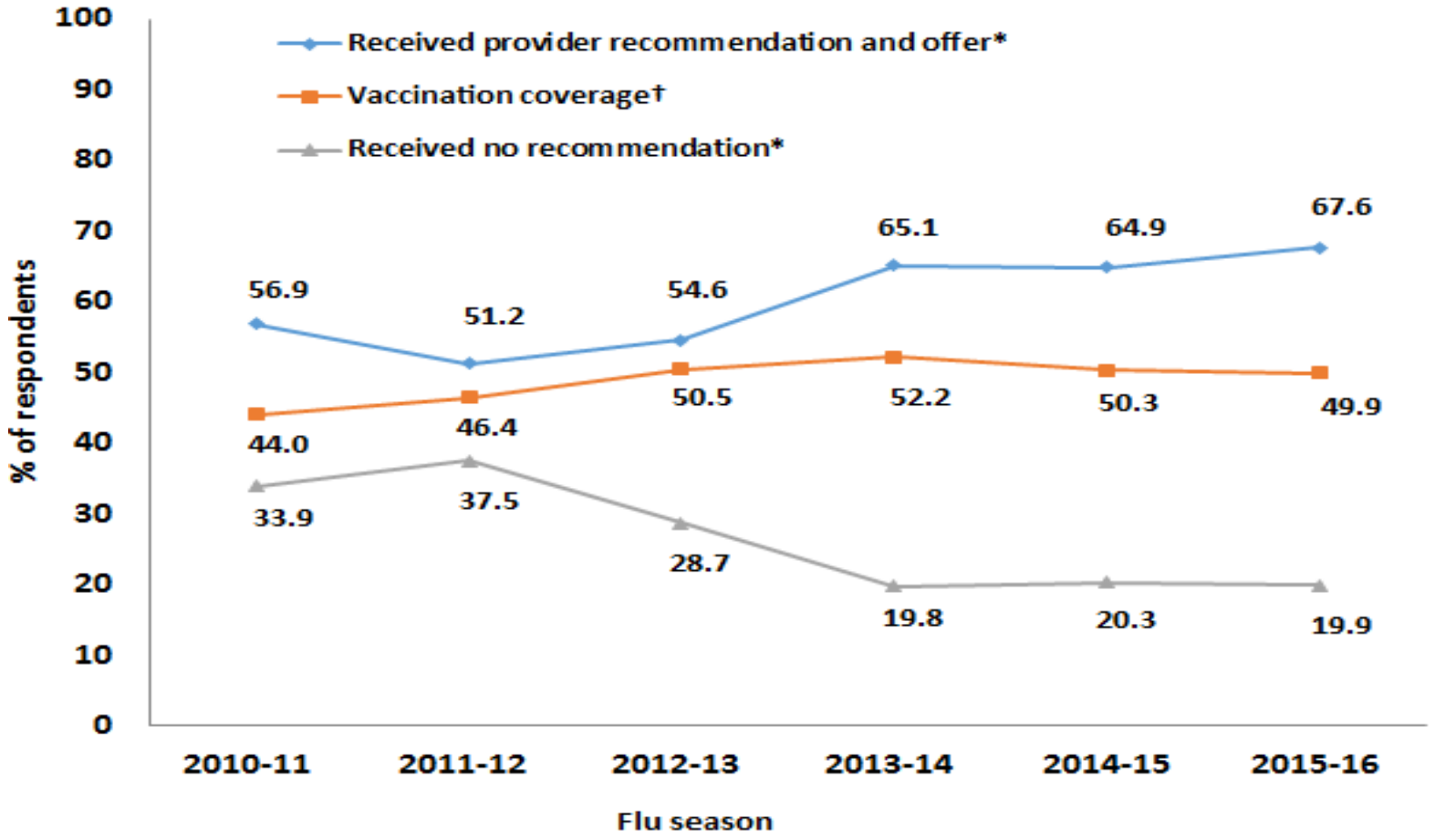
Figure 1. Trend of flu vaccination coverage before and during pregnancy and prevalence of provider recommendation / offer or no recommendation for vaccination among women pregnant anytime October through January, Internet panel survey, United States, 2010-11 through 2015-2016 flu seasons



2013–14. MMWR 2013; 62(No. RR-07)

Flu vaccine coverage in pregnancy

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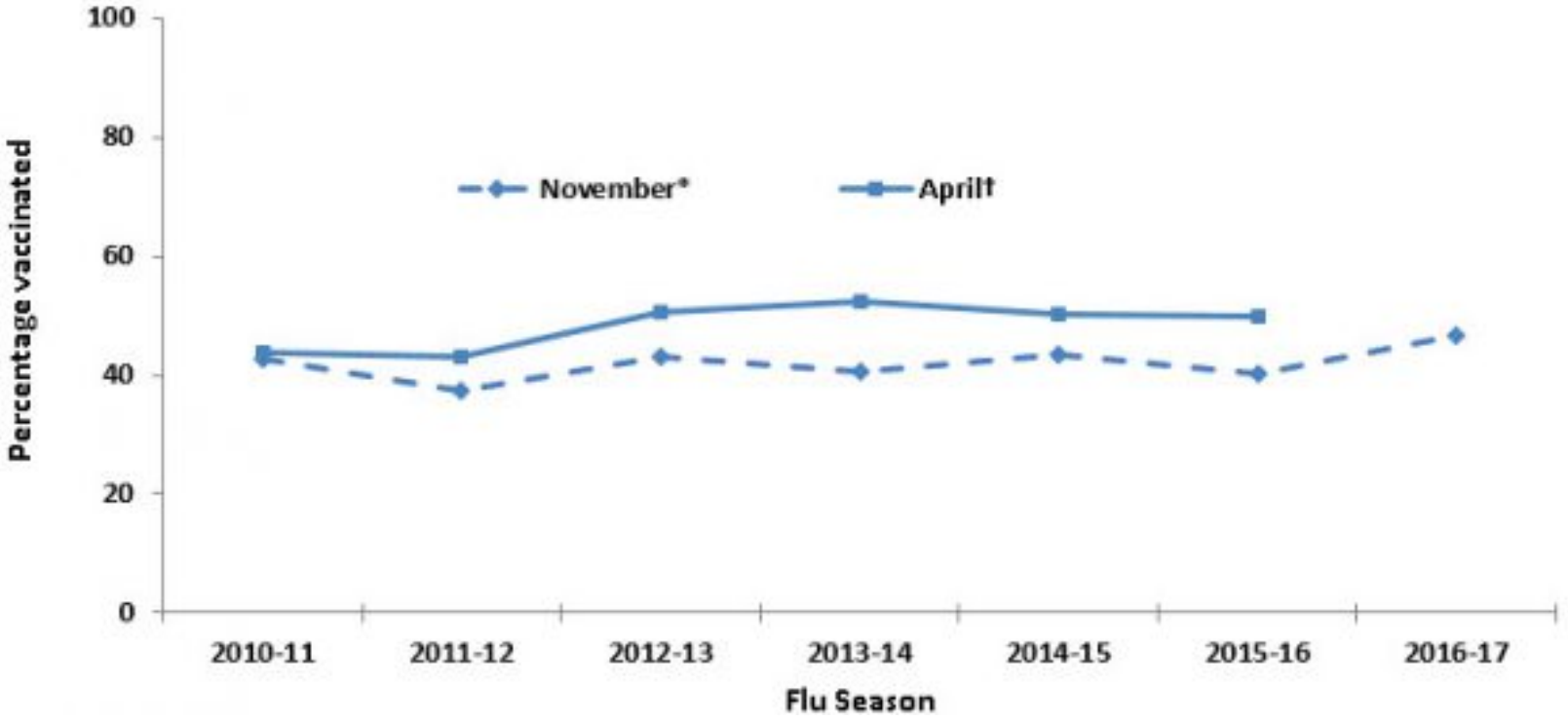
- As of early November 2017, influenza (flu) vaccination coverage among pregnant women before and during pregnancy was 35.6%.

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



MMWR Recomm Rep 2016;65(No. RR-05):1–54

Why are we here?

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- Providers
- Patients (mothers, babies, families)
- Sources of information
- Interpretation of that information
- Decision ---- but what is rational?

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

FEBRUARY 22, 2018

The Psychology of Clinical Decision Making — Implications for Medication Use

Jerry Avorn, M.D.

Final Rule for Pregnancy and Lactation Labeling

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- **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

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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

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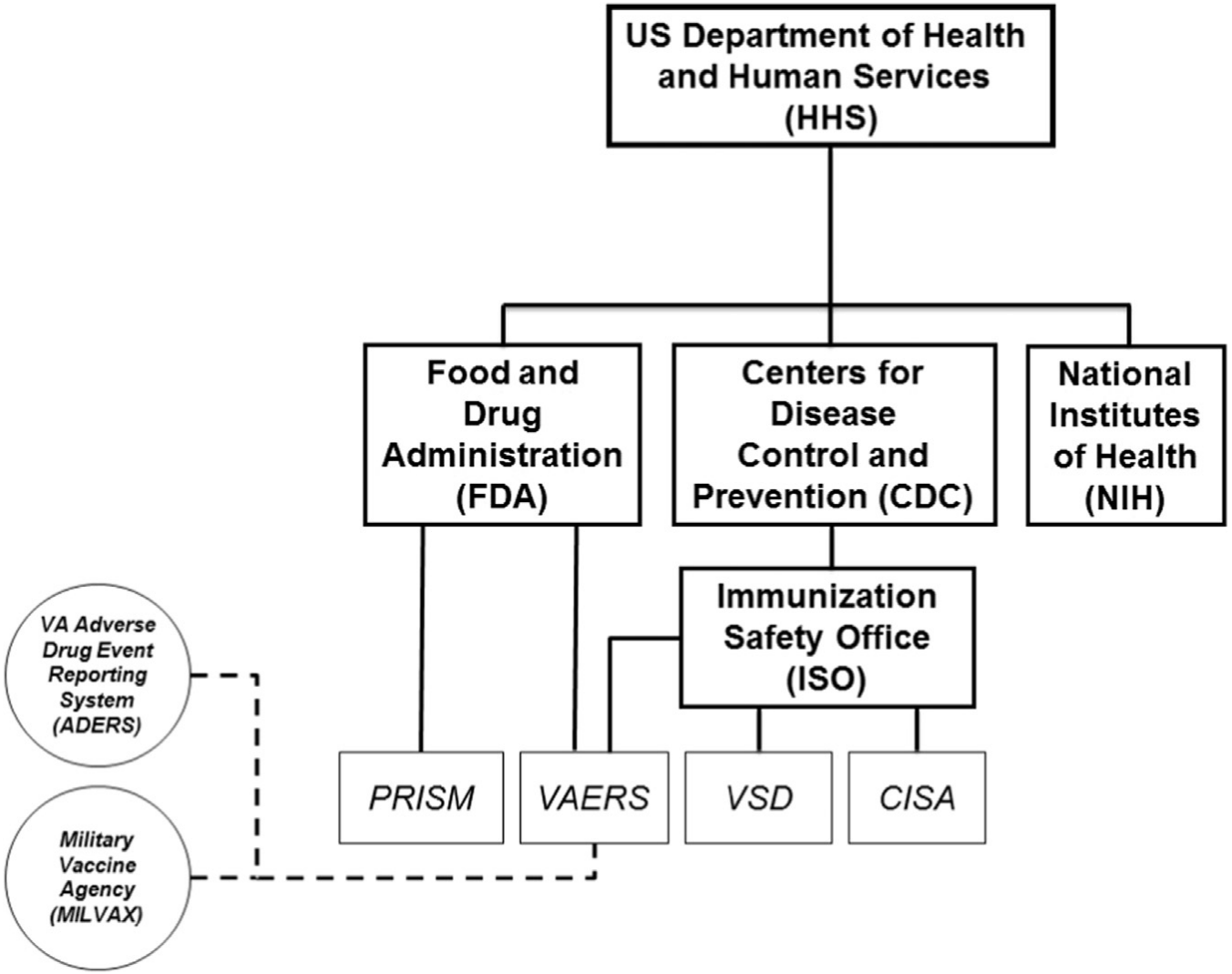

Nesin et al. Seminars in Perinatology 2015

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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

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

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Additional safety data on flu & SAb

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- Pasternack et al. Vaccination against pandemic A/H1N1 2009 influenza in pregnancy and risk of fetal death: cohort study Denmark. BMJ 2012: 344:e2794
- Chambers et al. Risks and safety of pandemic h1n1influenza vaccine in pregnancy: Birth defects, spontaneous abortion, preterm delivery and small for gestational age infants. Vaccine 2013; 31:5026-32.
- Louik et al. Risks and safety of pandemic H1N1 influence vaccine in pregnancy: exposure prevalence, preterm delivery, and specific birth defects. Vaccine 2013:31:5033-40.
- Moro et al. Surveillance of Adverse Events After Seasonal Influenza Vaccination in Pregnant Women and Their Infants in the Vaccine Adverse Event Reporting System, July 2010-May 2016. Drug Safety. 40(2):145-152, 2017 02.
- Chambers et al. Safety of the 2010-11, 2011-12, 2012-13, and 2013-14 seasonal influence vaccines in pregnancy: Birth defects, spontaneous abortion, preterm delivery, and small for gestational age infants, a study from the cohort arm of VAMPSS. Vaccine, 2016:34: 4443-4449.

The response to the “signal”

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MENU | CDC A-Z | SEARCH

Influenza (Flu)

Seasonal Influenza (Flu) > Health Professionals > Vaccination

Flu Vaccination & Possible Safety Signal

Information & Guidance for Health Care Providers

The Washington Post
Democracy Dies in Darkness

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.

STAT

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.

NEWS

It’s far too soon to say the vaccine actually did cause miscarriages, and they say the study, paid for by the Centers for Disease Control and Prevention, did not find anything definite. Only 17 women had miscarriages that might be linked with vaccination. But it’s a troubling signal that they are following up on.

In the meantime, pregnant women are still urged to get flu vaccines because they and their unborn babies are at high risk from actually getting flu — and that’s something that’s been confirmed by many studies over a long time in tens of thousands of women.

Blogs…

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Holistic Squid
healthy living demystified

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.

Package inserts for Tdap

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8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with Adacel vaccine. It is also not known whether Adacel vaccine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Adacel vaccine should be given to a pregnant woman only if clearly needed.

Animal fertility studies have not been conducted with Adacel vaccine. The effect of Adacel vaccine on embryo-fetal and pre-weaning development was evaluated in two developmental toxicity studies using pregnant rabbits. Animals were administered Adacel vaccine twice prior to gestation, during the period of organogenesis (gestation day 6) and later during pregnancy on gestation day 29, 0.5 mL/rabbit/occasion (a 17-fold increase compared to the human dose of Adacel vaccine on a body weight basis), by intramuscular injection. 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 health-care 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.

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 woma 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 INFANRI is formulated with higher quantities of these antigens. No adverse effects on 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.

Pregnancy Registry

GlaxoSmithKline maintains a surveillance registry to collect data on pregnancy outcomes and newborn health status outcomes following vaccination with BOOSTRIX during pregnancy. Women who receive BOOSTRIX during pregnancy should be encouraged to contact GlaxoSmithKline directly or their healthcare provider should contact GlaxoSmithKline by calling 1-888-452-9622.

8.3 Nursing Mothers

It is not known whether BOOSTRIX is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BOOSTRIX is administered 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.