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Disclosures
I will not discuss off-label use of pharmaceuticals

My department is funded in part by the WV Perinatal Partnership for outreach activities and quality initiatives.
Zika

- Flavivirus
- Transmitted by mosquitoes
- Approximately 80% asymptomatic
- Viremia duration sufficient for infection transmission to mosquitoes and contact infection
- Neurotropic
History of Zika Virus

- 2007: Zika spreads from Africa and Asia, first large outbreak on Pacific island of Yap
- 2012: Researchers identify two distinct lineages of the virus, African and Asian
- 2013–14: Zika outbreaks in French Polynesia, Easter Island, the Cook Islands and New Caledonia. Retrospective analysis shows possible link to birth defects and severe neurological complications in babies in French Polynesia
- March 2, 2015: Brazil reports illness characterized by skin rash in northeastern states
- July 17: Brazil reports detection of neurological disorders in newborns associated with history of infection
The most frequent method of ZIKV transmission is vector-borne

*Aedes aegypti*
Aedes albopictus

- Aggressive daytime feeder
- Multiple bites before resting
- Container breeder
- Competent vector for:
  - Chikungunya
  - Dengue
  - Zika
Zika
How the Zika Virus Enters the Human Population

The virus originates with nonhuman primates in tropical rainforests but can infect humans. Warm, urban environments with standing pools of water attract mosquitoes, and can lead to the virus's spread.

- **Sylvatic Cycle**
  - Chimpanzees
  - Monkeys
  - Baboons
  - Mosquitoes (Ae. africanus, Ae. furcifer-taylori, Ae. dalzieli)

- **Urban Cycle**
  - Mosquitoes (Ae. aegypti, Ae. albopictus)
  - Human Population

It appears that Zika can be transmitted through sexual intercourse, blood transfusion, and in utero.

Sources: CDC, PLOS, Reuters  Credits: David Foster, Laurie Garrett, Doug Halsey, Gabriella Meltzer
Symptoms of Zika Virus Infection

- Low Grade Fever
- Rashes
- Joint Pain, Muscle Pain & Headache
- Conjunctivitis (Red Eyes)
- Arthralgia

Hospitalization is uncommon and symptoms usually last for several days up to a week.
Zika Adult Sequelae

- Guillain-Barre Syndrome (GBS)
  - Association of increased frequency with Zika infection
  - GBS increase seen in multiple counties
- Disease affecting peripheral nerves
- Autoimmune process post-infection

Symptoms of GBS
- Symmetric ascending weakness
- Sensory component common
- Affects adults more than children
- Recovery may be protracted
- Mortality up to 20%
Zika and GBS - Venezuela

- 578 total GBS cases during time period
- First Zika case with GBS confirmed in November 2015

Source: PAHO
Neurotropic

- **Fetal damage**
  - First to early second trimester most severe
  - May be receptor mediated in rapidly growing cells
  - Microcephaly in 1-13% of early exposed fetuses
  - Later damage is still found in newborn without major primary injury
    - CDC guidelines established for neonatal follow up
    - 3 year follow up planned in Puerto Rico
    - WW--enroll child into “Birth To Three” program
Zika virus (light blue) spreads through a three-dimensional model of a developing brain. Credit: Max Salick and Nathaniel Kirkpatrick/Novartis
Zika Virus in the US & Territories

- **Zika Virus Disease Cases Reported to ArboNET***
  - US States and DC: 5,534
  - US Territories: 37,088

- **Pregnant Women with Any Lab Evidence of Zika Virus Infection***
  - US States and DC: 2,197
  - US Territories: 4,504

*Source: ArboNET as of October 11, 2017

*Source: Pregnancy Registries as of September 13, 2017
Zika Cases in West Virginia (Cont’d)

Reported Symptoms Among Cases (N=11)

<table>
<thead>
<tr>
<th>Symptom</th>
<th># of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>11 (100)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>7 (63.6)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>7 (63.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (63.6)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>6 (54.5)</td>
</tr>
<tr>
<td>Retro-orbital pain</td>
<td>4 (36.4)</td>
</tr>
<tr>
<td>Fever</td>
<td>4 (36.4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (18.2)</td>
</tr>
</tbody>
</table>
Zika

- CDC has websites and handouts
  - www.cdc.gov/zika
- WV has an active program
- WV has most testing within the state and is moving to add to its capabilities

CDC has a wide range of material from children’s literature to scientific studies.
Zika Virus Disease

Zika is a disease that is spread by mosquitoes (Aedes albopictus and Aedes aegypti). These mosquitoes also spread chikungunya and dengue. Symptoms of Zika include fever, rash, joint pain, and redness of the eyes. Muscle pain and headache also occur. These symptoms usually last for several days to a week. Hospitalization and death are not common with Zika infections. Currently in the United States and in West Virginia, Zika is associated with travel to countries where transmission is being reported (e.g. countries in the Caribbean, Central America, and South America). Read more...
Fetal Brain Anomalies

- Microcephaly
- Hydrocephalus/hydranencephaly
- Absent structures: (CC, pons, cerebellar vermis)
- Neuronal migration disorders (lissencephaly)
- Fetal brain disruption sequence
- Cerebral calcifications
- Brain asymmetry
Zika
Associated Pregnancy Outcomes

- Fetal loss/miscarriage, stillbirth
- Fetal growth abnormalities
- Fetal brain anomalies
  - Microcephaly
  - Ventriculomegaly
  - Intracranial calcifications
- Eye abnormalities
- Neurologic
  - Hypertonia
  - Arthrogryposis
  - Seizures
  - Neurobehavioral anomalies

Miranda-Filho et al, AJPH April 2016, Vol 106 No. 4
Slide courtesy of NICHD.
Zika-Related Arthrogryposis
Zika Virus
Zika and Microcephaly in Brazil

Was there increased prevalence of reported microcephaly cases from January 1, 2015 to January 7, 2016 compared to the time period 2000-2014?

<table>
<thead>
<tr>
<th>Time Period</th>
<th># of Microcephaly Cases Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000-2014</td>
<td>157.3 (yearly average)</td>
</tr>
<tr>
<td>January 1, 2015 – January 7, 2016</td>
<td>574</td>
</tr>
</tbody>
</table>

2015-2016
- 336 (58.5%) cases from 2015-2016 were female
- Average head circumference was 29.0 cm (SD=1.4 cm)
Cumulative cases of Zika infection in pregnant women

Note: Data for states, territories, and D.C. are from the U.S. Zika Pregnancy Registry. Data for Puerto Rico are from the Zika Active Pregnancy Surveillance System.

Source: Centers for Disease Control and Prevention
Biweekly cases of Zika-infected pregnancies

Summer 2016 vs. summer 2017

Note: Data for states, territories, and D.C. are from the U.S. Zika Pregnancy Registry. Data for Puerto Rico are from the Zika Active Pregnancy Surveillance System.

Source: Centers for Disease Control and Prevention
Long Term Pregnancy Outcomes: Evolving

- Emerging reports and series of long-term functional motor and sensory abnormalities
  - van der Linden et al, *BMJ* 8/16: 7 infants with microcephaly and abnormal MRI: also with arthrygryposis: neurologic not muscular
  - Pestorius et al, CDC, 8/4/16: “late-onset microcephaly” in series from Brazil: normal head size at birth, abnormal by 6 months

- Anticipate a spectrum of outcomes?
  - Developmental delay
  - Intellectual impairments
  - Mental disorders – autism, schizophrenia, etc
  - Motor abnormalities
Zika Virus

- Vaccines
- Odd stuff
  - Glioblastoma “treatment”
- Treatment IV Ig Drugs
Zika Virus

What is the CDC saying?

Does it make sense in view of the known history of RNA positive testing?

What does it “allow” individuals to do?
**Updated Interim Pregnancy Guidance: Asymptomatic Pregnant Women with Possible Zika Virus Exposure**

**Testing Recommendations and Interpretation of Results for Healthcare Providers**

**Ask pregnant women about**

- **Travel to or residence in any area with risk for Zika virus transmission before and during the current pregnancy**
- **Possible sexual exposure before and during the current pregnancy**
- **A diagnosis of laboratory-confirmed Zika virus infection before current pregnancy**
- **Symptoms of Zika virus disease during current pregnancy** (e.g., fever, rash, conjunctivitis, arthralgia)
- **If symptoms are reported, refer to symptomatic algorithm.**

**Before testing, discuss testing limitations and potential risks of misinterpretations for test results.**

**WHOM to test?**

- Asymptomatic pregnant women **with ongoing possible Zika virus exposure**
- Asymptomatic pregnant women with recent possible Zika virus exposure, **without ongoing exposure.**

**WHEN to test?**

- **Three times during pregnancy:**
  - First test at initiation of prenatal care
  - Second and third tests during pregnancy

**Which tests?**

- **Zika virus NAT (serum and urine)**

**Results**

- **Positive Zika virus NAT**
- **Negative Zika virus NAT**

**Interpretation**

**Acute Zika Virus Infection**

- **No Zika virus RNA detected. Zika virus infection during pregnancy cannot be ruled out.**

**Abbreviations:**
- IgM = Immunoglobulin M
- NAT = Nucleic acid test
- PRRNT = Plaque Reduction Neutralization test

1. Ask about type and duration of Zika virus exposure before and during the current pregnancy. Exposure prior to the current pregnancy may limit interpretation of Zika IgM antibody results; pretest counseling can help inform testing decisions.
2. Possible Zika virus exposure includes travel to or residence in an area with risk for Zika virus transmission during pregnancy or the periconceptional period (6 weeks before conception to 12 weeks after the last menstrual period), or sex without a condom during pregnancy or the periconceptional period, with a partner who traveled to, or resided in an area with risk for Zika virus transmission.
3. Zika virus testing is not routinely recommended for pregnant women with a previous diagnosis of laboratory-confirmed Zika virus infection by either NAT or serology (positive/equivocal Zika virus or dengue virus IgM and Zika virus NAT/PRRNT and dengue virus PRRNT ≤ 1:80).
4. Persons with ongoing possible exposure include those who reside in or frequently travel (e.g., daily or weekly) to an area with risk for Zika virus transmission.
5. The interval for Zika virus NAT testing during pregnancy is unknown. Preliminary data suggest that NAT might remain positive for several weeks after infection in some pregnant women. Women without a prior laboratory-confirmed diagnosis of Zika virus, NAT testing should be offered at the initiation of prenatal care, and if Zika virus NAT is not detected on clinical specimens, two additional tests should be obtained during the course of the pregnancy coincide with prenatal visits. The proportion of fetuses and infants with Zika virus–associated birth defects is highest among women with first and early second trimester infections; therefore, considering an NAT testing during the first and second trimesters might be considered to help identify infections early in pregnancy. However, adverse outcomes have been associated with infection diagnosed in the third trimester; therefore, testing every trimester might be considered.
6. Despite the high specificity of NAT, false-positive NAT results have been reported. If both serum and urine specimens are NAT positive, interpretation should be acute Zika virus infection. If NAT is only positive on serum or urine, testing should be repeated on the original NAT-positive specimen. If repeat NAT is positive, results should be interpreted as evidence of acute Zika virus infection. If repeat NAT testing is negative, results are indeterminate and healthcare providers should perform IgM antibody testing on a specimen collected ≤ 30 days after the initial specimen collection. For laboratory interpretation, see Table 1.
7. A negative Zika virus NAT result does not exclude infection during pregnancy because it represents a single point in time. Zika virus RNA levels decline over time, and the duration of the presence of Zika virus RNA in serum and urine following infection vary among pregnant women. Despite Zika virus IgM test limitations (e.g., cross-reactivity with other flaviviruses and prolonged detection for months), presenting challenges in determining the timing of infection, which should be discussed as part of pretest counseling; patients may still choose to receive Zika virus IgM testing.

https://www.cdc.gov/mmwr/volumes/66/wr/mm6629a1.htm?s_cid=mm6629a1_w
CDC’s Response to Zika
WHEN TO TEST FOR ZIKA VIRUS

As a healthcare provider, you decide if a patient should be tested for Zika virus infection. The algorithm below will help you determine whether or not to test your patient for Zika virus infection.

If your patient is...

- Experiencing or has recently experienced symptoms of Zika
  - Does your patient meet this criteria?
    - Possible Zika virus exposure through residence in or travel to an area with risk for Zika virus
      - OR
    - Possible Zika virus exposure through unprotected sex with a partner who has lived in or traveled to an area with risk for Zika virus

  - Does your patient meet this criteria?
    - Ongoing possible Zika virus exposure through residence in or frequent travel (e.g., daily or weekly) to an area with risk for Zika virus
      - OR
    - Possible Zika virus exposure AND Prenatal findings on ultrasound findings consistent with congenital Zika virus syndrome

- A pregnant woman without symptoms

NOTE:
- Asymptomatic pregnant women with recent possible Zika virus exposure (i.e., through travel or sexual exposure) who do not have ongoing exposure are not routinely recommended to have Zika virus testing. Testing should be considered using a decision-making model, one in which patients and providers work together to make decisions about testing and care plans based on a balanced assessment of risks and expected outcomes, clinical judgement, patient preferences and values, and the jurisdiction’s recommendations.
- Healthcare providers should review their local and state health jurisdiction guidelines regarding testing of patients with clinically compatible illness without known travel or sexual exposure.
- For details on which tests to order, visit https://www.cdc.gov/zika/hc-providers/testing-guidance.html

CDC does not recommend Zika virus testing for asymptomatic
- Men
- Children
- Women who are not pregnant
Zika

Detection of Zika RNA

**Blood**
- Nonpregnant
  - Serum days to a week
  - Whole blood as late as 81 days
- During French Polynesia outbreak
  - 3% of donated blood tested positive
- Pregnant
  - Serum up to 10 weeks

**Urine**
- Up to 91 days
- Replicating virus during symptoms
Detection of Zika RNA

- **Semen**
  - Up to 188 days
  - Seen when not detectable in blood
  - Sexual transmission documented at 41 days
  - Viral load may be higher than blood
    - 100,000 X blood or urine at 2 weeks
    - Asymptomatic male transmission has been reported
Detection of Zika RNA

- **Saliva**
  - Up to 91 days
  - Replicating virus at time of symptoms

- **Female genital tract**
  - Up to 14 days when not present in blood or urine

RNA detection is not replicating virus
Pregnant woman with Zika virus infection and prolonged detection of Zika virus in serum
Asymptomatic pregnant women with ongoing Zika virus exposure should be offered Zika virus NAT testing three times during pregnancy.

- IgM no longer recommended because IgM can persist for months after infection; IgM results cannot reliably determine infection during current pregnancy.
- Optimal timing and frequency of testing of asymptomatic pregnant women with NAT alone is unknown.
- For pregnant women who have received a diagnosis of Laboratory-confirmed Zika virus infection (by NAT or serology positive/equivocal Zika virus or dengue virus IgM and Zika Virus PRNT > 10 and dengue < 10 results) any time before or during the current pregnancy, additional Zika Virus testing is not recommended.
- For pregnant women without a prior laboratory-confirmed diagnosis of Zika virus, NAT testing should be offered at the initiation of prenatal care, and if Zika virus RNA is not detected on clinical specimens, two additional tests should be offered during the course of the pregnancy coinciding with prenatal visits.
Asymptomatic pregnant women who have recent possible Zika virus exposure (travel, sexual exposure) but without ongoing possible exposure are not routinely recommended to have Zika virus testing.

Testing—shared provider-patient decision making model.

Testing and care plan based on pt values, clinical judgment, balanced assessment of risks and expected outcomes and the jurisdiction’s recommendations.
Why are we not having the same problems as last year?

What is the history of infection after Zika recovery?

Is it “chicken pox” or the “common cold”?

There appears to be significant duration of immunity after a previous infection.
Zika

Protect Yourself!

Thank You!
ADDENDUM

Flu Shots for Pregnant Patients
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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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
A Potential Safety Signal Associated with Flu Vaccination of Pregnant Women

A CDC-funded study found that women vaccinated early in pregnancy with a flu vaccine containing the pandemic H1N1 (H1N1pdm09) component and who also had been vaccinated the prior season with a H1N1pdm09-containing flu vaccine had an increased risk of spontaneous abortion (miscarriage) in the 28 days after vaccination. While most miscarriages occurred in the first trimester, several occurred during the second trimester. The median gestational age at the time of miscarriage was 7 weeks. This study does not quantify the risk of miscarriage and does not prove that flu vaccine was the cause of the miscarriage. Earlier studies have not found a link between flu vaccination and miscarriage. There is an ongoing investigation to study this issue further among women who were pregnant and eligible to receive flu vaccine during the 2012-13 through 2014-15 flu seasons. Results are anticipated in late 2018 or 2019.

CDC Recommendation

CDC and its Advisory Committee on Immunization Practices (ACIP) are aware of these data, which were first presented to ACIP at a public meeting in June 2015. At this time, CDC and ACIP have not changed the recommendation for influenza vaccination of pregnant women. It is recommended that pregnant women get a flu vaccine during any trimester of their pregnancy because flu poses a danger to pregnant women and a flu vaccine can prevent influenza in pregnant women.
Flu Shot

Although evidence indicates that influenza vaccination is safe during pregnancy, data are limited for women in their first trimester, prompting a recent study that examined the incidence of miscarriage in women who received the vaccine.

The study found that women vaccinated early in pregnancy with a flu vaccine containing the pandemic H1N1 (H1N1pdm09) component who had also received the H1N1pdm09 vaccine component the previous season had an increased risk for spontaneous abortion within the 28 days after vaccination.

The CDC and its Advisory Committee on Immunization Practices continue to recommend that pregnant women get the flu vaccine at any point during their pregnancy because these women are at high risk for flu complications.
First Trimester Influenza Vaccination and Risks for Major Structural Birth Defects in Offspring

Elyse Olshen Kharbanda, MD, MPH¹, Gabriela Vazquez-Benitez, PhD¹, Paul A. Romitti, PhD², Allison L. Naleway, PhD³, T. Craig Cheetham, PharmD⁴, Heather S. Lipkind, MD, MS⁵, Nicola P. Klein, MD, PhD⁶, Grace Lee, MD, MPH⁷, Michael L. Jackson, PhD, MPH⁸, Simon J. Hambidge, MD, PhD⁹, Natalie McCarthy, MPH¹⁰, Frank DeStefano, MD, MPH¹⁰, and James D. Nordin, MD, MPH¹, for the Vaccine Safety Datalink

Objective To examine risks for major structural birth defects in infants after first trimester inactivated influenza vaccine (IIV) exposures.

Study design In this observational study, we used electronic health data from 7 Vaccine Safety Datalink sites to examine risks for selected major structural defects in infants after maternal IIV exposure. Vaccine exposures for women with continuous insurance enrollment through pregnancy who delivered singleton live births between 2004 and 2013 were identified from standardized files. Infants with continuous insurance enrollment were followed to 1 year of age. We excluded mother–infant pairs with other exposures that potentially increased their background risk for birth defects. Selected cardiac, orofacial or respiratory, neurologic, ophthalmologic or otologic, gastrointestinal, genitourinary and muscular or limb defects were identified from diagnostic codes in infant medical records using validated algorithms. Propensity score adjusted generalized estimating equations were used to estimate prevalence ratios (PRs).

Results We identified 52,856 infants with maternal first trimester IIV exposure and 373,088 infants whose mothers were unexposed to IIV during first trimester. Prevalence (per 100 live births) for selected major structural birth defects was 1.6 among first trimester IIV exposed versus 1.5 among unexposed mothers. The adjusted PR was 1.02 (95% CI 0.94-1.10). Organ system-specific PRs were similar to the overall PR.

Conclusion First trimester maternal IIV exposure was not associated with an increased risk for selected major structural birth defects in this large cohort of singleton live births. (J Pediatr 2017;187:234-9).
At its June 21-22 meeting, the CDC’s Advisory Committee on Immunization Practices (ACIP) recommended against use of live attenuated influenza vaccine (LAIV; FluMist) for the 2017-2018 flu season because of the vaccine's reduced efficacy.

The ACIP also voted to revise the influenza recommendation for pregnant women to clarify that they may receive any recommended, licensed and age-appropriate influenza vaccine, administered at any time during pregnancy, except for LAIV.
Flu Shot Report

- Study was odds ratio of influenza vaccination in women who had a miscarriage vs. those who did not.
- Study did not estimate the risk of miscarriage after flu vaccination.
- Study cannot estimate the risk of miscarriage for pregnant women who receive pH1N1 vaccine in two consecutive years.
- 2013 study showed no increased risk in women during the 2005-2006 and 2006-2007 flu season.
Perspective

2009 H1N1 Influenza and Pregnancy — 5 Years Later

Sonja A. Rasmussen, M.D., and Denise J. Jamieson, M.D., M.P.H.
Although data were available before the 2009 pandemic suggesting that pregnant women were at increased risk for influenza-associated complications, the pandemic provided solid data on this vulnerability.\(^2\) Pregnant women with 2009 H1N1 influenza were at substantially higher risk for hospitalization than the general population, and they accounted for approximately 5\% of deaths from 2009 H1N1 influenza that were reported to the Centers for Disease Control and Prevention (CDC), even though pregnant women make up only about 1\% of the population. Moreover, the 2009 pandemic virus was also bad for babies: infants born to women who had been severely ill with influenza complications had increased risk for adverse outcomes such as preterm birth or small size for gestational age.\(^2\)
Risk management of seasonal influenza during pregnancy: current perspectives

Mark H Yudin

More recently, pregnant women were again overrepresented among cases of illness and death in the 2009 global H1N1 influenza pandemic. Although only roughly 1% of the population is pregnant at any given time, in a systematic review of 120 studies reporting on 3,110 pregnant women from 29 countries with H1N1 influenza, pregnant women accounted for approximately 6% of individuals who were hospitalized, were admitted to the intensive care unit (ICU), and died as a result of H1N1.
Questions, or for more information contact

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For a presentation on Zika, Flu, preterm labor, or other topics please contact Shauna Lively, Outreach Education Director at Shauna.Lively@gmail.com or 304-516-1083