Influenza immunization in pregnancy: observations in mother, fetus, infant

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Outline of presentation

• Summary of Bangladesh Mother'sGift trial data and recent studies

• Mechanism of fetal effects

• Considerations for policy, research
In the U.S., in some winters as many as 9% of all infants 0-6 months of age require care in a clinic, emergency room or hospital (Neuzil, 2000)

Hospitalization rates for infants 0 to 6 months in the U.S. range from 45-104/10,000 infants (Poehling 2006)

Of all U.S. children 0-5 years who are hospitalized with influenza, 48% are 0-6 months of age (Neuzil, Poehling)

Little data from resource-constrained regions
Incidence of Influenza Virus Infection in Early Infancy: A Prospective Study in South Asia
Henkle, Emily; Steinhoff, Mark C.Omer, Saad B. Roy, Eliza ; Arifeen, Shams E. ; Raqib, Rubhana McNeal, Monica Breiman, Robert F. Moss, William J. Zaman, K.

close follow-up of 131 infants in Mother’sGift trial cohort

- We evaluated infants of mothers who did not receive ‘flu vaccine
- Weekly home visits to detect respiratory illness,
- Rapid test for influenza on nasal swabs of ill children.
- Serum specimens obtained from cord, 10 weeks, 20-24 weeks
- Sera were analyzed for antibody titers to the three influenza vaccine strains

Pediatric Infectious Disease Journal:
2011;30:170-173
Findings:

10 infants had positive rapid test alone
26 had serologic response to one of the three antigens
5 had positive rapid test plus serology

Total: 41 infants with proven ‘flu infection during 0-6 months,
a cumulative incidence of 31 (95% CI: 24-41) per 100 infants;
11/100 had febrile illness

Conclusion:

these data, and reports from other centers, suggest that infants in
tropical regions with perennial influenza virus circulation (6 to 10
months/year) of multiple viral strains (6/year), likely have a greater
exposure to influenza infection in the first six months of life
5 year study of influenza admissions to Children’s Hospital, Suzhou, China

(31° N, sim. to Lahore, Cairo, New Orleans: Humid sub tropical)

Figure 1. Monthly distribution of number of influenza cases, positive rate, precipitation and mean temperature in Suzhou from 7-11 months flu circulation/year, not including H1N1 pandemic
• Though increased rates of influenza infection are recognized in 0-6 months old infants, influenza vaccines are not licensed for this age group.

• We assessed the effect of antenatal maternal influenza immunization in infants, and review recent data.
First RCT showing maternal and infant effects of antenatal ‘flu immunization

Effectiveness of Maternal Influenza Immunization in Mothers and Infants

K. Zaman, M.B., B.S., Ph.D., Eliza Roy, M.B., B.S., D.C.H.,
Shams E. Arifeen, M.B., B.S., Dr.P.H., Mahbubur Rahman, M.B., B.S., Ph.D.,
Rubhana Raqib, Ph.D., Emily Wilson, M.H.S., Saad B. Omer, M.B., B.S., Ph.D.,
Nigar S. Shahid, M.B., B.S., M.P.H., Robert E. Breiman, M.D.,
and Mark C. Steinhoff, M.D.
Maternal antepartum Influenza vaccine data

Mothers efficacy (%)

rate/ 100 subjects

- RIF: 36% * Statistically significant
- RIF > 38°: 43%
- Diarrheal disease: 19%
- Clinic visit: 25%

* Statistically significant
maternal 'flu vaccine efficacy in infants 0-6 months

rate/ 100 subjects

- RIF: 29%*
- RIF > 38°: 28%
- Diarrheal disease: 2%
- Clinic visit: 42%*
- Influenza test ordered: 49%*
- Influenza test positive: 63%*

* Statistically significant
N American studies confirm Bangladesh infant protection data

<table>
<thead>
<tr>
<th>Author</th>
<th>Site</th>
<th>Design</th>
<th>Vaccine</th>
<th>Control</th>
<th>Effect in infant a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaman et al, 2008</td>
<td>Bangladesh, 2004–2005</td>
<td>Randomized controlled trial of vaccine</td>
<td>172</td>
<td>168</td>
<td>36% ILI 69% rapid test influenza illness</td>
</tr>
<tr>
<td>Benowitz et al, 2010</td>
<td>Connecticut, 2000–2009</td>
<td>Case-control</td>
<td>91</td>
<td>156</td>
<td>91.5% DFA or PCR influenza hospitalization</td>
</tr>
<tr>
<td>Poehling et al, 2011</td>
<td>Tennessee, Ohio, New York, 2002–2009</td>
<td>Case-control</td>
<td>151</td>
<td>1359</td>
<td>45–48% viral culture or PCR in influenza hospitalization</td>
</tr>
<tr>
<td>Eick et al, 2011</td>
<td>Apache, Navajo, 2002-2005</td>
<td>Observational prospective cohort</td>
<td>573</td>
<td>587</td>
<td>41% serologically defined influenza episode</td>
</tr>
</tbody>
</table>

DFA, direct fluorescent antibody; ILI, influenza-like illness; PCR, polymerase chain reaction.

a Expressed as efficacy (percent reduction of infant outcome).

Seasonality of influenza in Dhaka

Incidence rate /100 person - months, of respiratory illness with fever > 38° for mothers and infants, and cumulative influenza virus detection,

- after Jan 31, many ‘flu isolates, plus vaccine was associated with 49% decrease of flu-like illness,

- See Brooks, PIDJ 2010, for independent Dhaka flu surveillance data
Analysis for seasonality of flu circulation, and flu vaccine effect

• The test of interaction between vaccine group and low/high influenza circulation interval with episodes of febrile disease was statistically significant (p=0.016).

• In summary, the 116 infants born in the February-June 2005 interval were *in utero* for 1-4 months while influenza virus circulated, and during clinically effective influenza vaccine protection.

• Then analyze the effect of antenatal flu vaccine on newborn outcomes
Distribution of Birth Weights during flu virus circulation in Dhaka, Bangladesh:

**FETAL EFFECT OF ANTENATAL FLU VACCINE**

Steinhoff, CMAJ, 2012
Figure 4. Mean Birth Weight by Study Interval, by Vaccine

Steinhoff, CMAJ, 2012
## Other Birth Weight Effects Seen in Prospective Randomized Trials

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Weight Difference</th>
<th>Site</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria Px</td>
<td>+159g</td>
<td>Gambia</td>
<td>Greenwood</td>
</tr>
<tr>
<td>Gonorrhea Tx</td>
<td>+155g</td>
<td>Kenya</td>
<td>Gichangi</td>
</tr>
<tr>
<td>Fe supplement</td>
<td>+280g</td>
<td>India</td>
<td>Agarwal</td>
</tr>
<tr>
<td>10,000 calories</td>
<td>+29g</td>
<td>Guatemala</td>
<td>Lechtig</td>
</tr>
<tr>
<td>Micro nutr supplement</td>
<td>+79g*</td>
<td>Nepal</td>
<td>Osrin</td>
</tr>
</tbody>
</table>
FIGURE 4
Difference in mean birthweights associated with maternal influenza vaccination or illness status

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steinhoff</td>
<td>Bangladesh</td>
<td>327</td>
</tr>
<tr>
<td>S.Omer</td>
<td>USA</td>
<td>4,168</td>
</tr>
<tr>
<td>McNeill</td>
<td>Canada</td>
<td>132,307</td>
</tr>
<tr>
<td>Mendez</td>
<td>USA</td>
<td>45</td>
</tr>
<tr>
<td>Pierce</td>
<td>UK</td>
<td>1,476</td>
</tr>
</tbody>
</table>

Overall Mean Difference: 150g

Vaccine effect
Illness effect

CI, confidence interval.

Considerations. I

• First evidence that ’flu vaccine improves fetal growth,

• Implies that maternal seasonal ‘flu infection has negative impact on fetus

• data internally valid:
  – Robust blinded RCT design, secondary analysis
  – biological effect related to vaccine clinical effect,
  – randomization was effective,
  – statistically significant, though small sample size.
Small for gestational age (SGA) status is a direct measure of reduced intra uterine growth.
Odds Ratios for SGA births to immunized vs unimmunized, and unexposed vs exposed mothers

- **Steinhoff (Bangladesh)**
  - $N = 327$

- **S.Omer (USA)**
  - $N = 4,168$

- **McNeill (Canada)**
  - $N = 132,307$

Overall Odds Ratio
- 0.47

**NNV = 5**

- **Vaccine effect**
- **Illness effect**
Summary of studies regarding fetal/newborn effects of influenza:
One RCT, 4 observational studies

<table>
<thead>
<tr>
<th>Author (reference)</th>
<th>Site/years</th>
<th>Design</th>
<th>Number of subjects</th>
<th>Newborn outcome&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steinhoff et al, 2012&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Bangladesh, 2004–2005</td>
<td>Randomized controlled trial (secondary analysis)</td>
<td>Influenza vaccine: 58</td>
<td>Pneumococcal vaccine: 58</td>
</tr>
<tr>
<td>Omer et al, 2011&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Georgia, 2004–2006</td>
<td>Cohort analysis</td>
<td>Influenza vaccine: 578</td>
<td>No vaccine: 3748</td>
</tr>
<tr>
<td>Mendez-Figueroa et al, 2011&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Rhode Island, 2009–2010</td>
<td>Prospective cohort (pH&lt;sub&gt;I&lt;/sub&gt;,N&lt;sub&gt;I&lt;/sub&gt;)</td>
<td>Laboratory-positive influenza: 16</td>
<td>ILI, laboratory negative: 25</td>
</tr>
</tbody>
</table>

<sup>a</sup> Expressed as efficacy (percent reduction of infant outcome).

Long term effects of full term SGA birth (= reduced intrauterine growth)

- Decreased adult height
- Decreased academic performance
- Decreased IQ at 18 years
- Increased adult obesity, coronary heart disease, diabetes, stroke (Gluckman, NEJM 2008)

- These adult chronic diseases represent substantial long term social costs, perhaps greater than acute flu disease
Recent report from Ontario, Canada, 55,000 pregnancies during 2009 pandemic

- A/H1N1 pdm09 adjuvanted vaccine in 2008-2009 compared:
- 23,340 immunized pregnant women, with
- 32,230 not immunized.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rel risk: flu/control</th>
<th>95% CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGA</td>
<td>0.90</td>
<td>0.85-0.96</td>
</tr>
<tr>
<td>preterm (&lt; 32 wk)</td>
<td>0.73</td>
<td>0.53-0.91</td>
</tr>
<tr>
<td>fetal death</td>
<td>0.66</td>
<td>0.47-0.91</td>
</tr>
</tbody>
</table>

Fell DB, et al. H1N1 influenza vaccination during pregnancy and fetal and neonatal outcomes.

Effect of influenza vaccine is greater during periods of flu virus circulation

Seasonal Influenza and Fetal Outcomes

- Seasonal influenza does cause increased hospitalizations among pregnant women, and some increase of poor maternal and fetal outcomes.

- Placental involvement in seasonal flu is rare: only 5 reports since the 1970s, approximately one per decade.

- Limited transplacental passage of influenza virus suggests that intrauterine growth restriction related to seasonal influenza infection is an indirect effect on the fetus.

- Influenza vaccine appears to reduce this fetal effect, when mothers are exposed to seasonal influenza.

- Mechanism of the indirect effect is not explained by the classical textbook descriptions.
Effect of Antepartum Infections on the Fetus

• Obstetric textbooks describe the mechanisms of effects of maternal infections on the fetus as:

  a. **vertical transmission**: infection of the fetus through the placenta (malaria, syphilis, CMV)

  b. **ascending infection**: fetal infection through the cervix (chlamydia, genital organisms)

• The effect of maternal influenza is usually discussed under pandemic influenza and catastrophic maternal illness with acute adverse effects on the fetus.

• Nonpandemic influenza is not mentioned as a cause of decreased birth weight, or intrauterine growth restriction.
Key Recommendations

• Need to develop data for public policy stakeholders about
  – three fold burden of flu in pregnancy (WHO recommendation)
  – safety of flu vaccine in pregnancy

• Need specific messages for parents
  ▪ flu vaccine can enhance fetal growth and reduce disease of infant up to 6 months

• Studies of pathogenesis of maternal and fetal effects of influenza needed
  o Better understanding of details of pathogenesis will lead to better specific treatment
Feasibility of antenatal flu immunization delivery

Maternal tetanus immunization has better coverage than most antenatal and neonatal programs

Figure 2: Reported and estimated degrees of current coverage of neonatal interventions in 75 countries, 2000. See webtable 2 for assumptions.

Darmstadt et al, Lancet. 2005; 365:977
Critical Data Gaps

• Little data in pregnant women for burden of ‘flu disease and fetal/infant effects
• Non-pandemic ‘flu data needed in most regions
• Long term outcome of fetal effects of maternal ‘flu should be evaluated
• Pathphysiology of maternal flu infection on fetus not well described
Tropical considerations

• While policy and vaccine strain selection have been worked out for high latitude regions,

• Policy for tropical regions needs development:
  o When to give vaccine if flu present 7-11 months?
  o Which virus strains to use in vaccine, when 3-6 strains circulate/year?
Ongoing Field Study

• **Mother'sGift Influenza Field Trial in Nepal (MaGIFT)**
  Gates Foundation support, additional studies in Mali, S Africa

• Nepal site represents S. Asia, flu present 6-9 months/year
• RCT of antenatal influenza vaccine compared to saline placebo in 3,600 mothers, follow-up for six months.
• Two annual cohorts with vaccine delivered monthly

• Current Status:

• First annual cohort completed, 2\textsuperscript{nd} ongoing
  - 2,141 mothers immunized, 1,334 births.
  - 120 influenza isolates from 2000 illness specimens evaluated
Recruitment Nepal MaGIFT study 2011-2012
Specimens and Isolates
Nepal MaGIFT

weekly isolation of influenza for 8 months; 10 months with 3 weeks off
Antenatal influenza immunization

TRIAD or

3 for 1 effect:

• Maternal
• Fetal
• Infant for 6 months post partum

Da Vinci, 1510 to 1513
Mother’s Gift Study Team
General questions for maternal antenatal immunization

1. **Disease**
   Is there disease in pregnancy/early infancy, prevented by IgG? **Yes x 2**

2. **Vaccine safety**
   Is vaccine safe in mother, fetus, infant? **Yes x 3**

3. **Immunogenicity**
   Does antenatal vaccine produce IgG in mother and infant? **yes**

4. **Efficacy**
   Does maternal immunization prevent disease in mother/infants? **Yes, Asia, N America**

5. **Economic**
   Is maternal immunization cost-effective? Sustainable? **Yes for US mothers, yes thru antenatal TT programs**

6. **Policy**
   Do national policy-makers accept all of #1 – 5? **US, Canada, UK enacted**
Merci