Vaccinating pregnant women: New data and new Healthy People goal

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Outline
- Historical Context
- Recommendations and Healthy People 2020 Goal
- Influenza Burden and Vaccine Effectiveness in Pregnant Women
- Influenza Burden and Effectiveness of Maternal Vaccination in Infants
- Influenza Vaccine Safety
- Influenza Vaccine Cost Effectiveness
- Conclusions—What We Know Now
Early Recognition that Pregnancy Confers Increased Risk for Severe Pandemic Influenza

- Harris et al. published first case series of 1350 pregnant women with clinical influenza from the 1918 pandemic more than 10 years before isolation of the influenza virus.

Pregnant Women Have Been a Target Group for Influenza Vaccination Since the First Recommendations

The high-risk groups who contribute most to the excess deaths and who the Public Health Service believes should be routinely immunized each year are:

1. Persons of all ages who suffer from chronic debilitating disease, in particular: (a) rheumatic heart disease, especially mitral stenosis; (b) other cardiovascular diseases, such as arteriosclerotic heart disease or hypertension—especially patients with evidence of frank or incipient insufficiency; (c) chronic bronchopulmonary disease, for example, chronic asthma, chronic bronchitis, bronchiectasis, pulmonary fibrosis, pulmonary emphysema, or pulmonary tuberculosis; (d) diabetes mellitus; (e) Addison’s disease.

2. Pregnant women.

3. All persons 65 years or older.

All women who are pregnant or who might be pregnant in the upcoming influenza season should receive influenza vaccine

- Vaccine can be given during any trimester of pregnancy
- All forms of inactivated influenza vaccine (IIV) approved for use in pregnant women
  - Intramuscular and intradermal
  - Trivalent and quadrivalent

Healthy People 2020 Goal

- Increase the percentage of pregnant women who are vaccinated against seasonal influenza
  - Target: 80%
  - Baseline: 28% in 2008*

*Based on National Health Interview Survey (NHIS), CDC/NCHS

https://www.cdc.gov/flu/fluavview/pregnant-coverage_1516estimates.htm
WHO SAGE Working Group on Influenza Vaccines and Immunization Position Papers

- In 2005
  - Few countries with influenza vaccination programs
  - Very limited global vaccine supply
  - Pregnant women mentioned as one of several groups that may be considered for influenza vaccination

- In 2012
  - More globally representative epidemiologic and surveillance data
  - Informed by experience and knowledge from 2009 H1N1 pandemic
  - Pregnant women identified as highest priority target group for vaccination

Influenza Burden and Vaccine Effectiveness in Pregnant Women
Impact of Seasonal Influenza on Pregnant Women

- Pregnant women have a higher risk of influenza-associated hospitalization than non-pregnant women (Neuzil, K. et al. Am J Epidemiol 1998;148:1094-102)
  - Risk comparable with adults with high risk conditions
  - Risk increases by trimester
- Mortality attributed to influenza observed among pregnant women from 1998-2005 in the US, particularly in the 3rd trimester (Callaghan, Obstetric Gynecol 2010; 115: 919-23)

Odds of Acute Cardiopulmonary Hospitalization Increases by Trimester vs. Postpartum Period, 1974-1993

Impact of Laboratory-Confirmed Influenza vs. Other Respiratory Illness during Pregnancy

- Case-control study of pregnant women hospitalized with respiratory illness with vs. without laboratory-confirmed influenza

- Influenza associated with higher symptom severity, more frequent fever, and higher self-perceived impairment


Impact of Seasonal Influenza during the First Trimester and Congenital Anomalies

- Systematic review and meta-analysis of 22 published studies

- Exposure defined as any reported influenza, influenza-like illness, fever with influenza, regardless of laboratory-confirmation

<table>
<thead>
<tr>
<th>Defect</th>
<th>Pooled Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any birth defect</td>
<td>2.00 (1.62-2.48)</td>
</tr>
<tr>
<td>Neural tube defect</td>
<td>3.33 (2.05-5.40)</td>
</tr>
<tr>
<td>Hydrocephaly</td>
<td>5.74 (1.10-30.00)</td>
</tr>
<tr>
<td>Congenital heart defects</td>
<td>1.56 (1.13-2.14)</td>
</tr>
<tr>
<td>Cleft lip</td>
<td>3.12 (2.20-4.42)</td>
</tr>
<tr>
<td>Limb reduction defects</td>
<td>2.03 (1.27-3.27)</td>
</tr>
</tbody>
</table>

Luteijn et al., Human Reprod 29:809-23, 2014
Impact of Seasonal Influenza on Adverse Pregnancy and Perinatal Outcomes

- Recent review evaluated 16 published studies of preterm birth, SGA, fetal death
- Heterogeneity across studies prohibited meta-analysis for preterm birth, fetal death
- Some evidence that severe 2009 A/H1N1 pandemic influenza was associated with preterm birth and fetal death
- Insufficient data on impact of seasonal influenza on adverse perinatal outcomes

Immunogenicity of Influenza Vaccine in Pregnant Women and Antibody Transfer to Infant

- IIV induces protective levels of antibody in pregnant women (Sumaya, CV. et al. JID 1979;140:141-6)
  - both HIV-uninfected and HIV-infected (Madhi SA. et al. NEJM 2014;371:918-31)
Influenza VE Against Laboratory-Confirmed Influenza in Pregnant Women

- Four RCTs of IIV in pregnant women*

<table>
<thead>
<tr>
<th>Setting</th>
<th>Years</th>
<th>VE</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangladesh</td>
<td>2004-05</td>
<td>36%</td>
<td>Resp illness + fever</td>
</tr>
<tr>
<td>South Africa</td>
<td>2011-12</td>
<td>50% HIV-uninfected 58% HIV-infected</td>
<td>RT-PCR + influenza</td>
</tr>
<tr>
<td>Mali</td>
<td>2011-13</td>
<td>77%</td>
<td>RT-PCR + influenza</td>
</tr>
<tr>
<td>Nepal</td>
<td>2011-13</td>
<td>Not published</td>
<td>RT-PCR + influenza</td>
</tr>
</tbody>
</table>

- Case-control study of pregnant women with ARI showed 44% reduction in RT-PCR-confirmed influenza (Thompson MG. et al. CID 2014;58:449-57)


Influenza VE Against Adverse Pregnancy and Perinatal Outcomes

- Mixed findings from retrospective observational studies
  - Two studies reporting VE against preterm birth and differences in birthweight between infants of vaccinated vs. unvaccinated mothers (Omer SB. et al. PloS Med 2011;8:e1000441; Steinhoff M. et al. CMAJ 2012;184:645-53)

- Studies are limited by their retrospective design and potential biases

- RCTs from South Africa and Mali did not show VE against preterm birth or differences in birth weight between treatment groups
Influenza Burden and Effectiveness of Maternal Vaccination in Infants


### TABLE 1. RATES OF HOSPITALIZATION FOR ACUTE CARDIOPULMONARY CONDITIONS ATTRIBUTABLE TO INFLuenza

<table>
<thead>
<tr>
<th>AGE</th>
<th>NO. OF PERSON-YEARS</th>
<th>NO. OF HOSPITALIZATIONS FOR ACUTE CARDIOPULMONARY CONDITIONS PER 10,000 PERSON-YEARS</th>
<th>NO. OF INFLUENZA-ATTRIBUTABLE HOSPITALIZATIONS PER 10,000 PERSON-YEARS</th>
<th>AVERAGE EXCESS NO. OF HOSPITALIZATIONS PER 10,000 CHILDREN PER YEAR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6 mo</td>
<td>117,205</td>
<td>1064</td>
<td>1497</td>
<td>608</td>
</tr>
<tr>
<td>6 to &lt;12 mo</td>
<td>82,997</td>
<td>1117</td>
<td>854</td>
<td>403</td>
</tr>
<tr>
<td>1 to &lt;3 yr</td>
<td>224,900</td>
<td>464</td>
<td>387</td>
<td>233</td>
</tr>
<tr>
<td>3 to &lt;5 yr</td>
<td>302,344</td>
<td>232</td>
<td>193</td>
<td>138</td>
</tr>
<tr>
<td>5 to &lt;15 yr</td>
<td>1,207,697</td>
<td>120</td>
<td>105</td>
<td>86</td>
</tr>
</tbody>
</table>

*Values are differences in rates between the influenza season and the peri-influenza season (the baseline values).

†Values are weighted averages of annual excess hospitalizations for a population of 10,000 persons within the specified age group. The excess hospitalizations were calculated for each stratum by multiplying the stratum-specific difference in hospitalization rate by the proportion of the study year covered by the influenza season. CI denotes confidence interval.

‡The weighted average differences in rate between the influenza season and the peri-influenza season were calculated with stratum-specific person-years in all seasons as weights; strata were defined by age group, study year, race, and residence.


Influenza VE Against Laboratory-Confirmed Influenza in Infants of Vaccinated Mothers

- Four RCTs of IIV all evaluating RT-PCR-confirmed influenza in infants <6 months

<table>
<thead>
<tr>
<th>Setting</th>
<th>Years</th>
<th>Vaccination Timing</th>
<th>VE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangladesh</td>
<td>2004-05</td>
<td>3rd trimester</td>
<td>69%</td>
</tr>
<tr>
<td>South Africa</td>
<td>2011-12</td>
<td>Late 2nd/3rd trimester</td>
<td>49% HIV-uninfected mothers No significant VE in infants of HIV-infected mothers</td>
</tr>
<tr>
<td>Mali</td>
<td>2011-13</td>
<td>3rd trimester</td>
<td>68% during first 4 months 33% during first 6 months</td>
</tr>
<tr>
<td>Nepal</td>
<td>2011-13</td>
<td>2nd/3rd trimester</td>
<td>Not published</td>
</tr>
</tbody>
</table>

Pooled Analyses from Gates-Funded RCTs of IIV Efficacy Among Infants of Vaccinated Mothers

- Three RCTs in South Africa, Mali, and Nepal
- Will pool data across sites to evaluate
  - IIV impact on birth outcomes and neonatal mortality
  - IIV impact on infant pneumonia
  - Rare adverse events

Box 1: The list of expected pooled analyses.

- Estimating overall pooled efficacy of maternal influenza immunization against infant and maternal lab confirmed influenza.
- This analysis may also focus on determinants of variability in vaccine efficacy by site, season, and vaccine composition.
- Impact of maternal influenza immunization on birth outcomes such as pre-term and small for gestational age births.
- Immunogenicity of maternal TIV by site and antigen, dynamics of mother to infant antibody transfer. This analysis may also focus on determinants of variability in vaccine immunogenicity by site, vaccine composition, and maternal and infant characteristics.
- Analysis of safety outcomes in mothers and infants— with a particular focus on endpoints too rare to be evaluated in individual trials (e.g., miscarriage, stillbirth).
- Impact of maternal TIV on neonatal mortality— all causes and, where possible, cause specific mortality.
- Impact of maternal TIV on maternal mortality.
- Infant growth by maternal vaccination status.
- Indirect "herd" effects of maternal TIV. Influenza-like illness and laboratory confirmed influenza among household contacts (Kail and Nepal only).
- Impact of maternal TIV on Infant Pneumonia.
- Impact of maternal TIV on (a) Medically Attended Acute Respiratory Illness (MAARI) among mothers and infants, and (b) Severe acute respiratory illness (mothers only). The working group might decide to recommend separate analyses for mothers and infants.


Influenza Vaccine Safety in Pregnant Women
Safety of Influenza Vaccination during Pregnancy

  - None identified maternal or fetal problems with influenza vaccination

- Several studies during and since 2009 influenza pandemic have evaluated seasonal and pH1N1 vaccines (Moro et al., 2011a; Moro et al., 2011b; Moro et al., 2013; Chambers et al., 2013; Louik et al., 2013; Nordin et al., 2014; Naleway et al, 2014)
  - None showed evidence of harm, except for two studies that showed an association with preterm birth with pH1N1-containing vaccines (<3 days decrease in gestational age) (Chambers et al., 2013; Louik et al., 2013)

Safety of Influenza Vaccination during Pregnancy

- Systematic review of 19 observational studies that evaluated fetal outcomes (fetal death, spontaneous abortion, congenital malformations) (McMillan M. et al., Vaccine 2015 Apr 27;33(18):2108-17)
  - 5 studies of seasonal influenza vaccine; 14 of A/H1N1pdm09 vaccine
  - No observed association between influenza vaccination and adverse outcomes
  - Women vaccinated in the first trimester under-represented
Influenza Vaccine Cost Effectiveness

Cost Effectiveness of IIV Use in Pregnant Women in the United States

- Decision analytic model based on hypothetical cohort of 5.2 million pregnant women during 2010-2013 seasons

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Averted hospitalization</td>
<td>21,000</td>
<td>1,111</td>
<td>3,020</td>
</tr>
<tr>
<td>Averted outpatient visits</td>
<td>46,668</td>
<td>33,528</td>
<td>114,217</td>
</tr>
<tr>
<td>Infants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Averted hospitalization</td>
<td>1,265</td>
<td>704</td>
<td>1,099</td>
</tr>
<tr>
<td>Averted outpatient visits</td>
<td>33,972</td>
<td>17,809</td>
<td>41,789</td>
</tr>
<tr>
<td>Total</td>
<td>116,618,240</td>
<td>45,092,614</td>
<td>162,206,155</td>
</tr>
<tr>
<td>Direct medical cost saved (US$)</td>
<td>4,622,804</td>
<td>1,724,501</td>
<td>5,205,207</td>
</tr>
<tr>
<td>Indirect cost saved (US$)</td>
<td>120,641,044</td>
<td>46,727,115</td>
<td>167,411,162</td>
</tr>
<tr>
<td>Societal cost saved (US$)</td>
<td>77,660,368</td>
<td>77,600,368</td>
<td>77,620,368</td>
</tr>
<tr>
<td>Program cost (US$)</td>
<td>43,040,676</td>
<td>(10,873,233)</td>
<td>89,810,994</td>
</tr>
<tr>
<td>Net savings/costs (US$)</td>
<td>305</td>
<td>123</td>
<td>619</td>
</tr>
<tr>
<td>QALY saved</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost per QALY saved</td>
<td>Cost-saving</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost values are given in 2013 dollars.</td>
<td></td>
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</tbody>
</table>

Xu J. et al. Vaccine 2015;34:3149-3155
Conclusions

- Pregnant women are at increased risk of hospitalization with influenza
  - some effect of lower threshold for admission
- Influenza vaccine is immunogenic in pregnant women
- Influenza vaccine is effective at preventing
  - laboratory-confirmed influenza among pregnant women
  - laboratory-confirmed influenza among infants of vaccinated mothers
- Influenza vaccine is safe for use in pregnant women
- Influenza vaccine is cost effective during moderate to severe influenza seasons in the United States
- Influenza vaccine may prevent adverse maternal and fetal outcomes
  - more data needed
Thank you

Questions?

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.