Maternal Influenza Immunization at WHO

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Outline

- WHO Position Paper
- Mother’s Gift Trial
- GAVI Review
- Potential Effect on Newborn Birth Weights
- WHO/PATH Maternal Influenza Immunization Project
- Conclusion
Policy recommendations aim at protecting vulnerable high risk groups against severe influenza

For the first time, WHO showed a preference:
- “For countries considering the initiation or expansion of programmes for seasonal influenza vaccination, WHO recommends that pregnant women should have the highest priority.”

Other risk groups: children aged 6–59 months, the elderly, individuals with specific chronic medical conditions, and health-care workers
Mother’s Gift Trial: Dhaka, Bangladesh

The Study:
- Bangladesh, 2004-05
- RCT
- 340 pregnant women (3rd trimester)
  - inactivated influenza vaccine
  - pneumococcal polysaccharide vaccine
- Follow-up through pregnancy and six months after birth

Outcomes:
- Febrile respiratory illness among infants and mothers
- Lab-confirmed influenza among infants

Zaman, et. al. NEJM 2008
Effectiveness of Maternal Influenza Vaccination in Dhaka, Bangladesh

- IIV decreased respiratory illness with fever by 29% among infants and 36% among their mothers
- Vaccine efficacy against laboratory-confirmed influenza among newborns was 63%
<table>
<thead>
<tr>
<th>BMGF-Sponsored Maternal Immunization Trials</th>
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<tbody>
<tr>
<td><strong>Nepal (Steinhoff)</strong></td>
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<td><strong>RCT Endpoint</strong></td>
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<td><strong>Years</strong></td>
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<td><strong>Sample Size</strong></td>
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<td><strong>Vaccines</strong></td>
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<td><strong>Geography</strong></td>
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<td><strong>Infant Mortality</strong></td>
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<td><strong>HIV prevalence</strong></td>
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<td><strong>Climate/Flu Seasonality</strong></td>
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In 2013, GAVI Alliance Reviewed Maternal Influenza Vaccine Investment

GAVI estimates IIV in pregnancy could avert around 45 deaths per 100K vaccinated

http://www.gavialliance.org/about/governance/gavi-board/minutes/2013/11-june/minutes/06---vaccine-investment-strategy/.
“The projected impact of influenza vaccination on maternal mortality alone is insufficient to justify GAVI support at this time.”

“The case for GAVI involvement would be significantly strengthened by stronger evidence of impact on infants and the fetus.”
Influenza in Low Resource Countries: Bangladesh

- The Study:
  - Bangladesh, 2004-05
  - RCT
  - 340 pregnant women (3rd trimester)
    - inactivated influenza vaccine
    - pneumococcal polysaccharide vaccine
  - Follow-up through pregnancy and six months after birth

- Exploratory Outcomes:
  - Newborn birth weights
  - Newborns Small for Gestational Age (SGA)
Birth Weights of Babies Born Outside and Inside the Influenza Season, by Vaccine

Steinhoff MC. CMAJ. 2012.
# Fetal Risk Averted by Maternal Immunization

<table>
<thead>
<tr>
<th>Study</th>
<th>Site/Design</th>
<th>Case</th>
<th>Comparison</th>
<th>Results</th>
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<tr>
<td>Steinhoff</td>
<td>Bangladesh 2004-05 / RCT</td>
<td>Maternal influenza immunization (172)</td>
<td>No maternal influenza immunization (168)</td>
<td>Newborns exposed to vaccine were 200 gm larger, 34% less likely to be small for gestational age</td>
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<tr>
<td>(Mother’s Gift)</td>
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<td>Omer</td>
<td>USA 2004-06 / Retrospect. Cohort</td>
<td>Maternal influenza immunization (578)</td>
<td>No maternal influenza immunization (3,748)</td>
<td>Newborns exposed to vaccine had 70% less small for gestational age</td>
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<td>PLoS Med 2011</td>
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<td>Fell AJPH</td>
<td>Canada 2009-10 / Retrospect. Cohort</td>
<td>Maternal influenza immunization (23,340)</td>
<td>No maternal influenza immunization (32,230)</td>
<td>Newborns exposed to vaccine had 10% lower small for gestational age, 25% less preterm birth, and 33% less fetal death</td>
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<td>2012</td>
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<td>Dodds JOGC</td>
<td>Canada 2006-09 / Retrospect. Cohort</td>
<td>Maternal influenza immunization (1,957)</td>
<td>No maternal influenza immunization (7,824)</td>
<td>Newborns exposed to vaccine had 20% lower small for gestational age, 25% less low birth weight</td>
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GAVI Estimate of Potential Deaths Averted if IIV Birth Weight Effect

- If IIV can avert 17% preterm birth complications, GAVI estimates 4x greater impact on infant deaths.

- Estimates over next 15 years:
  - *Without* fetal vaccine effect: 170,000 deaths
  - *With* fetal vaccine effect: 900,000 deaths

Maternal Influenza Immunization Project: Building an immunization platform in conjunction with antenatal care in low- and middle-income countries

- To provide an enabling environment for country decision-making concerning the introduction of maternal influenza vaccine, and to address several barriers that affect the availability and supply of vaccines

- Collaborating Institutions:
  - WHO Initiative for Vaccine Research
  - PATH Vaccine Access and Delivery Global Program

- 3 year project

- Funding from Bill & Melinda Gates Foundation
WHO/PATH Maternal Influenza Immunization Project

1. Desk Reviews
2. Country Case Studies
3. Address Global Barriers
Activity 1 (Desk Reviews)

- Reviews of disease burden in <6 months and vaccine impact on birth outcomes

- Exploring options for encouraging unpublished safety data to be analyzed and made public
  - Encourage manufacturer to publish vaccine safety data
  - Explore ways to access regulatory data (redacted CSRs, post-licensure surveillance, other) for analysis

- Review adverse event definitions for pregnancy and newborn period

- Determine best options for pharmacovigilance in low-income settings
Activity 2 (Case Studies)

- Detailed case studies covering all aspects of immunization including:
  - operational, organizational, political structures, funding sources and budget, communications and sensitization activities, training of health care workers, monitoring and evaluation, and program acceptance by target populations

- Two case studies in countries with existing maternal influenza immunization programs (WPRO/PAHO)

- One case study in a country that uses tetanus toxoid vaccine as part of routine antenatal care, but no influenza (AFRO)
Activity 3 (Global Barriers)

- **Labeling guidelines:**
  - Consultations to reach a scientific consensus on data needs and acceptable types of studies to provide assurance of the safety of IIVs in pregnant women for the purpose of product labeling
  - Consider how WHO can use prequalification process to ensure such data needs are met and that package inserts reflect actual risks/benefits
Activity 3 (Global Barriers)

- **Vaccine supply-related activities:**
  - Develop strategies to support year-round availability of IIVs, and advocate for their implementation
  - Review implications of extending expiration dates of IIVs on product labels
  - Assess manufacturing flexibility in support of all-year influenza vaccine supply
  - Develop strategic forecasting tool
Activity 4 (Global Guidance)

- To develop technical guidance document to assist countries to introduce maternal influenza immunization into routine programs (expected in 2016)
What the WHO/PATH Maternal Influenza Immunization Project Does Not Do

- No implementation of programs
- Limited engagement with communities
- No communications or advocacy
- Limited economic analyses
- Limited pharmacovigilance
Some Other WHO Maternal Immunization Activities through Cooperative Agreement with CDC

- Develop/Harmonize AE definitions (for clinical trials and AEFI surveillance)
- Write AEFI guidance for monitoring pregnant women and newborns
- Develop survey of vaccine confidence and use
- Review investment case in late 2014 / early 2015
- Coordinating with other WHO offices to monitor progress of maternal immunization platform
Conclusion

- Maternal immunization is a platform with the potential to provide life saving vaccines against high burden pathogens in the newborn period
- BMGF-funded WHO/PATH partnership moving immunization agenda forward by addressing obstacles to implementation
- CDC support also critical to advancing maternal immunization platform
- We will engage manufacturing community to discuss issues of labels, supply, and safety in the coming years