Maternal Immunisation: Where Do We Stand?

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My qualifications for this lecture

- My first publications suggesting a group B streptococccal (GBS) vaccine was published in 1976

- My first study of a candidate GBS vaccine for pregnant women was published in 1977
Maternal Immunisation Is Not A New Concept

- 1879: Maternal immunisation with vaccinia virus conferred protection in infants
- 1938: Maternal immunisation with whole cell pertussis vaccine protected infants from complications of pertussis
- 1961: Maternal immunisation with tetanus toxoid vaccine prevented in New Guinea; millions of mother and neonatal lives have been prevented worldwide since then
- 2011: TIV and Tdap - recommended in the USA
But It Is Complicated

- In developed countries, risk continues to overshadow benefit and obstetrical providers are not major vaccinators

- In developing countries, societal norms may pose lack of trust in government and cultural barriers

- Although many medical contacts, not an established “platform” for immunisation

- Shakespeare was correct
  - “First kill all the lawyers”
What Happened to Progress in the Past 50 Years?

- Medication tragedies harming the fetus (e.g., thalidomide) sparked concerns for the safety of anything
- Regulatory agencies still don’t have licensing pathways
- Manufacturers still concerned about liability
- Providers not educated about VPD’s, perceive unwillingness of women and are not giving recommended vaccines because of time and reimbursement issues
- “Disappearance” of VPD’s except in infants <3 months of age (the “invisible deaths”)
Immunization of Women During Pregnancy is Not New . . . For Protection of the Woman

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.

First US influenza vaccine recommendation
Maternal and Young Infant Influenza Infections in the USA

- Burden of disease substantial
  - Increased risk of complications and death in pregnant women due to pulmonary compromise
- If no maternal specific IgG, increased risk of complicated influenza in baby
- No infant vaccine
  - Until age 6 months, then requires 2 doses, 4-weeks apart for protection (uptake in 2011 ~66% for 1 or 2 doses)
- TIV recommended but 2007-2008 uptake in pregnant women ~15%; H1N1 pandemic rose to ~49%
One-Two Punch: Maternal Immunization
Risk of Adverse Fetal Outcomes Following Administration of a Pandemic Influenza A(H1N1) Vaccine During Pregnancy

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Henrik Svanström, MSc
Ditte Molgaard-Nielsen, MSc
Tyra G. Krause, MD, PhD
Hanne-Dorthe Emborg, DVM
Mads Melbye, MD, DrMedSci
Anders Hvidt, MSc, DrMedSci

The 2009 influenza A(H1N1) pandemic put pregnant women at increased risk of morbidity, mortality, and poor pregnancy outcomes. Pregnant women were among the main target groups prioritized for vaccination against influenza A(H1N1)pdm09, and an estimated 2.4 million women were vaccinated during pregnancy in the United States alone. However, assessment of the fetal safety of H1N1 vaccination in pregnancy has been limited to a few pharmacovigilance reports and descriptive cohort studies.

In a registry-based cohort study, we investigated whether exposure to an AS03-adjuvanted influenza A(H1N1) pdm09 vaccine in pregnancy was associated with increased risk of major birth defects, preterm birth, and small size for gestational age.

Context Assessment of the fetal safety of vaccination against influenza A(H1N1) pdm09 in pregnancy has been limited.

Objective To investigate whether exposure to an adjuvanted influenza A(H1N1)pdm09 vaccine during pregnancy was associated with increased risk of adverse fetal outcomes.

Design, Setting, and Participants Registry-based cohort study based on all live-born singleton infants in Denmark, delivered between November 2, 2009, and September 30, 2010. In propensity score-matched analyses, we estimated prevalence odds ratios (PORs) of adverse fetal outcomes, comparing infants exposed and unexposed to an AS03-adjuvanted influenza A(H1N1)pdm09 vaccine during pregnancy.

Main Outcome Measures Major birth defects, preterm birth, and small size for gestational age.

Results From a cohort of 53,432 infants (69.8% [13.1%] exposed to the influenza A(H1N1)pdm09 vaccine during pregnancy [345 in the first trimester and 6644 in the second or third trimester]), 660 (330 exposed) were included in propensity score-matched analyses of adverse fetal outcomes associated with first-trimester exposure. For analysis of small size for gestational age after second- or third-trimester exposure, 13,284 (6642 exposed) were included; for analyses of preterm birth, 12,909 (6543 exposed) were included. A major birth defect was diagnosed in 18 of 330 infants (5.5%) exposed to the vaccine in the first trimester, compared with 15 of 330 unexposed infants (4.5%) (POR 1.21, 95% CI 0.60-2.45). Preterm birth occurred in 31 of 330 infants (9.4%) exposed in the first trimester, compared with 24 of 330 unexposed infants (7.3%) (POR 1.32, 95% CI 0.76-2.31), and in 302 of 6643 infants (4.6%) with second- or third-trimester exposure, compared with 295 of 6366 unexposed infants (4.6%) (POR 1.00, 95% CI 0.84-1.17). Small size for gestational age was observed in 25 of 330 infants (7.6%) with first-trimester exposure compared with 31 of 330 unexposed infants (9.4%) (POR 0.79, 95% CI 0.46-1.37), and in 641 of 6642 infants (9.7%) with second- or third-trimester exposure, compared with 657 of 6642 unexposed infants (9.9%) (POR 0.97, 95% CI 0.87-1.09).

Conclusions In this Danish cohort, exposure to an adjuvanted influenza A(H1N1) pdm09 vaccine during pregnancy was not associated with a significantly increased risk of major birth defects, preterm birth, or fetal growth restriction.

JAMA. 2012;308(2):165-174
## WHO Prequalified TIV Vaccines: Package Inserts 2012

<table>
<thead>
<tr>
<th>Company/Vaccine</th>
<th>Pregnancy Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK (Flulval)</td>
<td>Animal reproduction ND; Limited data do not indicate adverse foetal outcome</td>
</tr>
<tr>
<td>Green Cross (GCFLU)</td>
<td>Animal and pregnant women studies ND; should only be given when necessary</td>
</tr>
<tr>
<td>Sanofi (FLUZONE)</td>
<td>Pregnancy category C; animal studies ND; not known if it can cause harm</td>
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Protection of Newborns Through Maternal Immunization Symposium

- Foundation Merieux and WHO sponsored a symposium at Veyrier-du-Lac December 2012
- Reviewed potential outcomes, addressed ethical and regulatory issues involved, identified future research needs, promising vaccines and public health strategies
- Addressed industrialized and developing countries
- Summary of symposium presentations were published in Vaccine in July 2003
Resource-limited countries: update on Maternal and Neonatal Tetanus Elimination initiatives; pneumococcal PS vaccine trials in Papua New Guinea and Philippines

Industrialized countries: influenza, RSV fusion protein-2, GBS type III conjugate vaccines discussed; pertussis mentioned

Societal Issues

- Barriers to recruitment of pregnant women for clinical trials
- Vaccine licensure, liability, victim compensation systems identified as the greatest barriers to development and implementation
Placental Transfer of Maternal IgG

- Placental transfer is a selective process using receptor-mediated transport
- IgG1=IgG3>IgG2>IgG4 (protein antigens elicit IgG1 and IgG3 – TIV, Td; PS antigens elicit IgG2)
- Begins at 17 weeks and increases with gestation (passive transport)
- By 33 weeks maternal equal fetal levels
- By 40 weeks total fetal IgG exceeds maternal levels (active transport)
- Placental abnormalities affect transport (eg, HIV, malaria, other infections)
Protection of Newborns Through Maternal Immunization: Conclusions

- Immune mechanisms during pregnancy differ, but allow for adequate responses to inactivated vaccines.

- Maternally-derived specific IgG does not lead to fetal tolerance and does not affect priming for later boosting.

- Societal issues:
  - Barriers to recruitment of pregnant women for clinical trials
  - Vaccine licensure, liability, victim compensation systems identified as the greatest barriers to development and implementation.
Global Causes of Child Deaths*

Maternal Mortality Per 100,000 Live Births in 2008*

Tetanus Immunisation in Pregnancy

# Current Status of Critical Information Influencing Accelerated Introduction of Selected Vaccines for Pregnant Women (High- or Low-resource Setting)

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Influenza</th>
<th>Hib</th>
<th>Pertussis</th>
<th>Pneumococcal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High resource</td>
<td>Low resource</td>
<td>High resource</td>
<td>Low resource</td>
</tr>
<tr>
<td>Disease burden, mother</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Disease burden, infant</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Vaccine safety</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Maternal Immunogenicity</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Antibody interference with routine childhood immunization</td>
<td>N/A</td>
<td>N/A</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Effectiveness in pregnant women</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Effectiveness in infants born to vaccinated mother</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Legend:**

- **++** Substantial information available
- **+** Partial information available
- **-** Little or no information available
- **N/A** Not applicable
Recommendations for Maternal Immunisation Research

- Perform detailed, age-specific burden of disease studies in various settings.

- Conduct large-scale efficacy trials of maternal immunisation in diverse populations, adequately powered to assess laboratory-confirmed outcomes.

- Perform operational research in different regions of the world to determine the feasibility and cost of delivering vaccines to pregnant women.
Recommendations for Maternal Immunisation Research

• Strengthen bacteriologic and virologic surveillance in developing & developed regions

• Perform knowledge, attitudes, and practices surveys in multiple regions in the world

• Rigorous safety and post marketing surveillance in regions where maternal immunisation is introduced
Critical Gaps in Knowledge

- Burden of illness in neonatal and early infancy period
- Burden of illness during pregnancy
- Understanding of alternative strategies
- Vaccines that can benefit both mother and infant are a win-win (2 for 1 prevention strategy)
Challenges

• Understand key drivers of maternal-child health policy decisions

• Operational research into the feasibility of including specific vaccines into routine antenatal care

• In decisions and discussions on maternal vaccine policy, involve persons with expertise in diverse areas, including: maternal-child health, immunology, vaccines and vaccine safety, health law, health systems, communications and advocacy, and regulatory affairs

• Funding
“In resource limited countries, the safety and efficacy of maternal tetanus toxoid vaccine is a story of spectacular success that was built on maternal and neonatal disease burden not barriers that would have resulted in decades of ongoing deaths”

“We can’t await another decade of deaths and disabilities to have all the evidence to make policy easy. It’s time for and education and implementation of good policy”

Carol J. Baker, MD 2012