Overview of Maternal Immunization: Benefitting Mothers and Their Infants

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Maternal Immunization

- An innovative (but NOT new) approach to protect both the mother and the infant by immunizing woman usually in last half of pregnancy, after the fetus is fully formed.

- Practical: This benefits two individuals (mother and infant) with one intervention at a critical high risk period.
PREGNANT WOMEN

• Deserve appropriate routine medical care as medically indicated - regardless of pregnancy status. **EXAMPLES:** antibiotics/ HIV therapy

• Can help protect their infants against some diseases by medical intervention during pregnancy. **EXAMPLE:** Rh disease/Rhogam

• Have mature immune systems which are far more competent than the fetus or neonate. They respond well to protein, polysaccharide, and conjugate **vx** **EXAMPLE:** tetanus **vx**

• Have increasing access to routine prenatal care internationally, which is associated with improved maternal and infant outcomes

Thanks to my sister-in-law
## Health Service Coverage Among Pregnant Women*


<table>
<thead>
<tr>
<th>Income Group</th>
<th>At least 1 visit</th>
<th>At least 4 visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low income</td>
<td>69</td>
<td>39</td>
</tr>
<tr>
<td>Lower middle income</td>
<td>79</td>
<td>47</td>
</tr>
<tr>
<td>Upper middle income</td>
<td>94</td>
<td>75</td>
</tr>
<tr>
<td>High income</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Global</td>
<td>78</td>
<td>48</td>
</tr>
</tbody>
</table>

Immune Responses During Pregnancy*

- Many changes to pregnant women during pregnancy (especially 3rd trimester) are physiologic changes
  - Increased heart rate, stroke volume; decreased lung capacity but increase in O2 carriage
  - Decrease in concentration of IgG by hemodilution
- Decreased cell mediated immunity: relatively minor but can predispose to listeria, TB, toxoplasmosis, etc.
- No significant alteration in antibody responses to vaccines or infections

Neonates and Young Infants are at High Risk for Serious Infections

- Neonates are uniquely at risk for many serious infections.
- Neonatal infections cause much morbidity and mortality worldwide.
- Immune system of neonates is immature and relatively ineffective.
- Active immunization in neonates is not typically successful.

*Black et al. Lancet 2010*
1950’s: Routine immunization during pregnancy with diphtheria, influenza and polio vaccines to directly protect mothers.

1960’s: Worldwide use of maternal tetanus vaccine.

1970’s-90’s: Safety and benefit of polio vaccine during polio outbreaks (Finland, Israel), and meningococcal outbreaks (Brazil).

1980’s: Lack of safety and efficacy data resulted in stopping maternal vaccination except for high maternal risk in USA.

2009-10 pandemic H1N1 outbreak demonstrated risk of flu during pregnancy and benefits of flu vaccine for mother and infant.

2012-2014 pertussis epidemic emphasized high risk of neonatal pertussis deaths and benefit of maternal Tdap – mainly for infant.
CURRENT AND POTENTIAL VACCINE CANDIDATES: What has priority for maternal vaccination?

- Established maternal vaccines
  - Tetanus
  - Influenza
  - Pertusis

- Vaccine Candidates under development
  - Respiratory syncytial virus vaccine (in clinical trials)
  - Group B Streptococcal vaccine: Study sponsored by Novartis now completed in South Africa (in clinical trials)
  - New pertussis vaccines
  - Herpes simplex virus
  - Meningococcal vaccine
  - Pneumococcal vaccine – conjugate
  - Cytomegalovirus
### Who Could Benefit From What Vaccine?

<table>
<thead>
<tr>
<th>Licensed Vaccines</th>
<th>Mother</th>
<th>Infant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetanus</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Influenza</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Pertussis</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Meningococcus</td>
<td>✓</td>
<td>?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vaccines in Development</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Group B strep</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>RSV</td>
<td>?</td>
<td>✓</td>
</tr>
<tr>
<td>CMV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

October 25, 2012
NEONATAL TETANUS:
A PREVENTABLE DISEASE

- Important cause of neonatal death worldwide for centuries
  - 1960: 38% of neonatal mortality in Thailand
  - 1980: 30% of all deaths in first year of life in many developing countries

- 1961: Landmark study in New Guinea demonstrated benefit of maternal immunization with tetanus toxoid

- 1989: World Health Organization set goal to eliminate neonatal tetanus using maternal immunization – renewed X 3
38 Countries eliminated MNT between 2000 & June 2015

*(Plus Ethiopia except Somali region, 30 provinces out of 34 in Indonesia and 16 regions out of 17 in Philippines) leaving 21 countries yet to eliminate MNT

21 Countries with MNT in 2015
FACTORS AFFECTING TRANSPLENCTAL TRANSPORT OF MATERNAL ANTIBODY TO THE INFANT

- Placental abnormalities
  - Malaria
  - HIV infection
- TIME:
  - gestational age of infant
  - time between vaccination and delivery
- Maternal IgG level
- IgG subclass

Infant born in Nepal during maternal immunization trial
An abnormal placenta may not efficiently transport maternal antibodies to the fetus.

EXAMPLE: In HIV+ women in Africa, lower antibody titers to certain antigens were seen in cord blood: reduction of 15-40%
EXAMPLES OF MATERNAL IMMUNIZATION

- Pertussis
- Influenza
- RSV
Pertussis Impacts the Youngest Infants – USA Outbreak, 2012-4

Fatal Neonatal Pertussis

- National Incidence
- National Incidence without Washington
- Vaccine Received
- Acellular Only
- Transition Period
- Whole Cell and Acellular

Cases/100,000 vs Age (years)

- <1 year: 35 cases/100,000
- 1 year: 5 cases/100,000
- 2 years: 3 cases/100,000
- 3 years: 2 cases/100,000
- 4 years: 1 case/100,000
- 5 years: 1 case/100,000
- 6 years: 1 case/100,000
- 7 years: 1 case/100,000
- 8 years: 1 case/100,000
- 9 years: 1 case/100,000
- 10 years: 1 case/100,000
- 11 years: 1 case/100,000
- 12 years: 1 case/100,000
- 13 years: 1 case/100,000
- 14 years: 1 case/100,000
- 15 years: 1 case/100,000
- 16 years: 1 case/100,000
- 17 years: 1 case/100,000
- 18 years: 1 case/100,000
- 19 years: 1 case/100,000

Fatal Neonatal Pertussis

- 5th DTaP Vaccine
- Acellular Only

Transi- tion Period

Whole Cell and Acellular
Example: UK Maternal Tdap Immunization*

CONCLUSIONS:
Immunization of pregnant women with Tdap between 27-30+6 weeks associated with highest umbilical cord GMCs of IgG to PT and FHA compared with immunization beyond 31 wks.

High burden of influenza illness among pregnant women.

Excellent immunogenicity and safety profile of TIV.

Effectiveness in infants born to vaccinated mothers.

No good alternatives for neonates, young infants.

Main barriers: logistics and costs.

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Pregnant women represent the most important risk group for receipt of inactivated seasonal influenza vaccine.

The priority accord to pregnant women was based on “compelling evidence of substantial risk of severe disease in this group and evidence that seasonal influenza vaccine is safe and effective in preventing disease in pregnant women as well as their young infants, in whom disease burden is also high.”

No recommendation for timing of influenza vaccine during pregnancy.

Revision of WHO Position Paper and Grade Tables published in Nov. 2012.
Influenza Vaccination of Pregnant Women and Protection of Their Infants

Shabir A. Madhi, M.D., Ph.D., Clare L. Cutland, M.D., Locadiah Kuwanda, M.Sc., Adriana Weinberg, M.D., Andrea Hugo, M.D., Stephanie Jones, M.D., Peter V. Adrian, Ph.D., Nadia van Niekerk, B.Tech., Florette Treurnicht, Ph.D., Justin R. Ortiz, M.D., Marijette Venet, Ph.D., Ary Violari, M.D., Kathleen M. Neuzil, M.D., Eric A.F. Simões, M.D., Keith P. Klugman, M.D., Ph.D., and Marta C. Nunes, Ph.D., for the Maternal Flu Trial (Matflu) Team®

Figure 1. Kaplan–Meier Estimates of Percentages of Confirmed Cases of Influenza According to Cohort and Study Group. Confirmed influenza was defined as influenza diagnosed by means of reverse-transcriptase–polymerase-chain-reaction assay. The insets show the same data on an expanded y axis. HIV denotes human immunodeficiency virus, and IV3 trivalent inactivated influenza vaccine.
GACVS Advice: Safety of influenza vaccines in pregnancy

- Safety information for influenza vaccines continues to be reassuring.
- Significant morbidity due to vaccine-preventable diseases among women and infants could be prevented by immunization of pregnant women.
- Despite lack of apparent safety issues, precautions and contraindications limiting vaccine benefits to women are often included in product labeling, which is problematic.

Further action by GACVS:
- Continue to monitor and report adverse events in pregnant women following the use of influenza vaccine.
- Include methodological points for planning and analysis of clinical trials and post-marketing studies.
UPDATE ON SAFETY OF INFLUENZA VACCINES DURING PREGNANCY: 2015

Safety of flu vaccines assessed using:
• Prospective clinical trials
• Retrospective and database studies
• Post-marketing passive reporting systems
• VAERS or VSD in the US
• Yellow Card System in the UK
• Other vaccine safety systems using databases that link vaccination history and medical outcomes
• Post-marketing Pregnancy Registries

** Limitations:
1. Under reporting
2. In addition to number of events, calculation of a rate or attributable risk (using # persons vaccinated as denominator) is necessary to evaluate relationship or causality;
3. Confounders
4. Insufficient power

* Ortiz et al, Vaccine 2011; Blancard-Rohner, Siegrist Vaccine 2011; Munoz 2012
** Zaman NEJM 2009; Englund JID 1993
SUMMARY:

- Risks inherent in pregnancy and delivery themselves: (locale-dependent) : LOW-MODERATE
- Risk of influenza in the pregnant woman: MODERATE
- Risk of influenza in the fetus: VERY LOW
- Risks of vaccine to the woman: VERY LOW
- Risks of vaccine to the infant: VERY LOW

NOTE: Sometimes difficult to dissociate the above risks
EXAMPLE: Maternal Immunization to Prevent Infant RSV Disease

- Most urgent need for protection against RSV is during first few months of life; >75% of RSV disease hospitalization occurs in full term, healthy infants.

- Efficient RSV-specific IgG transfer from mothers to neonates.

- RSV subunit vaccines in pregnant women show good immunogenicity and lack of reactogenicity (Munoz et al Vaccine 2003).

- Studies of RSV vaccine ongoing in pregnant women in USA (Novavax).
CHALLENGES FOR MATERNAL IMMUNIZATION (1)

- Lack of effective vaccines against important common pathogens
- Immune response to some vaccines appears short-lived, necessitating intrapartum (not pre-conception) vaccination and perhaps repeated immunization
- Regulatory and legal issues
- Liability issues and issues affecting interaction with pharmaceutical companies
Lack of sufficient health care personnel to provide even routine prenatal care at crowded clinics: adding one additional shot can still be a problem.

Increasing lack of understanding and/or acceptance of vaccines by populations who no longer see vaccine-preventable disease: vaccine untruths spread via internet

Complexity of clinical trials

Perception of difficulty in obtaining licensure for a maternal vaccine
OUR GOAL: HEALTHY MOTHERS AND BABIES
# Update on Potential RSV Vaccines

## 2015 RSV Vaccine Update

*http://sites.path.org/vaccinedevelopment/files/2014/07/RSV-Vaccine-Snapshot_8July2014.pdf*
### IMPACT OF 2009 INFLUENZA A (H1N1): INFANTS

<table>
<thead>
<tr>
<th>Study</th>
<th>Site</th>
<th>Case</th>
<th>Control</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>McNeill AJOG 2011</td>
<td>Canada</td>
<td>Maternal flu season respiratory hospitalization (N=208)</td>
<td>No hospitalization (N=132,099)</td>
<td>Newborns of hosp. women: 90 gm smaller, 40% more likely SGA</td>
</tr>
<tr>
<td>Mendez-Figueroa AJOG 2011</td>
<td>USA</td>
<td>Maternal ILI with lab confirmed pandemic H1N1 (N=15)</td>
<td>Maternal ILI with neg. lab test (N=25)</td>
<td>Newborns exposed to flu were 285 gm smaller</td>
</tr>
<tr>
<td>Pierce BMJ 2011</td>
<td>UK</td>
<td>Pregnant women with lab+ confirmed pandemic H1N1 (N=256)</td>
<td>Historical comparison of pregnant women from 2005-2006 (N=1220)</td>
<td>Newborns exposed to flu were 255 gm smaller, with incr. perinatal mortality and premature birth</td>
</tr>
</tbody>
</table>
Influenza Vaccine in Pregnant Women

- Used for > 50 years
- Excellent safety profile
- Immunogenic in pregnant women
- No clinical effectiveness studies with lab-confirmed outcomes in pregnant women
- Large retrospective studies focused on safety, immunogenicity, infant benefit
- Two randomized, prospective, controlled effectiveness study in Bangladesh and South Africa.

Southwest Washington Health District, WA, USA
## Impact of 2009 Influenza A (H1N1): Mothers *

<table>
<thead>
<tr>
<th>Maternal Risk Factor</th>
<th>RR Hospitalization</th>
<th>RR Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>1.0 (0.8-1.1)</td>
<td>0.8 (0.7-1.0)</td>
</tr>
<tr>
<td>Respiratory Disease</td>
<td>3.3 (2.0–5.8)</td>
<td>7.8 (4.9–26.6)</td>
</tr>
<tr>
<td>Asthma</td>
<td>1.8 (1.2–2.6)</td>
<td>1.7 (1.5–2.1)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.9 (0.5–1.7)</td>
<td>4.0 (3.1–6.9)</td>
</tr>
<tr>
<td>Cardiac Dis.</td>
<td>2.0 (1.5–2.2)</td>
<td>9.2 (5.4–10.7)</td>
</tr>
<tr>
<td>Renal Dis.</td>
<td>4.4 (4.2–4.5)</td>
<td>22.7 (21–25.4)</td>
</tr>
<tr>
<td>Liver Dis.</td>
<td>35.7 (3.2–16)</td>
<td>17.4 (11.6–28)</td>
</tr>
<tr>
<td>Neurological Disease</td>
<td>1.1 (0.9–1.3)</td>
<td>13.1 (8.4–32.4)</td>
</tr>
<tr>
<td>Immune Compromised</td>
<td>24.3 (16.1–33)</td>
<td>27.7 (14–66.5)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>6.8 (4.5–12.3)</td>
<td>1.9 (0.0–2.6)</td>
</tr>
</tbody>
</table>

Relative Risk differed by country from 3.5 in Germany to 25.3 in France, and may reflect clinical practice variations and health care utilization.

*Van Kerkhove, Mounts PLoS Med 2011*
## Safety of Adjuvanted Influenza H1N1 vaccines in Pregnant Women, 2010-2012

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Study Group</th>
<th>Control Group</th>
<th>F/Up Period</th>
<th>Maternal Outcomes</th>
<th>Infant Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsai et al Vaccine 2010</td>
<td>Novartis trial database of MF59 adjuvanted Flu vaccines (N=23,300) and unadjuvanted (N=40,285)</td>
<td>43 pregnancies after MF59 and 60 pregnancies after nonadj flu vx; majority vx in 1st trimester</td>
<td>None</td>
<td>Delivery</td>
<td>No signals of risk but small numbers; similar rates after nonadj. &amp; MF59 adj vx</td>
<td>Not reported</td>
</tr>
<tr>
<td>Tavares et al Vaccine 2011</td>
<td>Cohort study of 267 women in all trimesters</td>
<td>267 women given ASO3-adj 2009 H1N1 vaccine</td>
<td>None</td>
<td>6 mos. Post Delivery</td>
<td>No adverse effects on pregnancy</td>
<td>No impact on fetus, infant</td>
</tr>
<tr>
<td>Gisslser et al ESPID 2012</td>
<td>Retrospective database review</td>
<td>76,043 newborn; 12,510 spon. abortions</td>
<td>No maternal vx</td>
<td>Delivery</td>
<td>Pandemrix vaccine did not affect course of pregnancy</td>
<td>Protective effect on newborns regardless of smoking hx</td>
</tr>
<tr>
<td>Mackenzie et al Br J Clin Pharm 2012</td>
<td>Safety surveillance feasibility study in Scotland</td>
<td>3754 vaccinated people, with 117 pregnant women</td>
<td>312 who declined vaccine</td>
<td>Delivery</td>
<td>No significant safety issues ; 4 miscarriages overall</td>
<td>No significant risk6 possible congenital abnormalities</td>
</tr>
<tr>
<td>Oppermann et al Vaccine 2012</td>
<td>F/up of German pregnant women given ASO3 or nonadj. flu vx</td>
<td>323 pregnant women any trimester</td>
<td>1329 controls</td>
<td>Delivery</td>
<td>No attributable risk vs. controls</td>
<td>No attributable risk vs. controls</td>
</tr>
</tbody>
</table>
Bangladesh: Maternal Immunization with Influenza Vaccine Protects Mothers and Babies*

*Babulis et al, NEJM 2008;359

Table 2. Clinical Effectiveness of Influenza Vaccine in Infants and Mothers.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Episodes</th>
<th>Clinical Effectiveness (95% CI)</th>
<th>Risk Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Influenza Vaccine</td>
<td></td>
</tr>
<tr>
<td>Mothers</td>
<td>no.</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Person-months</td>
<td>1076</td>
<td>1089</td>
<td></td>
</tr>
<tr>
<td>Respiratory illness with fever</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any fever</td>
<td>77</td>
<td>50</td>
<td>35.8 (3.7 to 57.2)</td>
</tr>
<tr>
<td>Temperature &gt;38°C</td>
<td>33</td>
<td>19</td>
<td>43.1 (-9.0 to 70.3)</td>
</tr>
<tr>
<td>Diarrheal disease</td>
<td>60</td>
<td>49</td>
<td>19.3 (-74.6 to 47.8)</td>
</tr>
<tr>
<td>Clinic visit</td>
<td>25</td>
<td>19</td>
<td>24.9 (-43.9 to 60.8)</td>
</tr>
</tbody>
</table>

Figure 2. Cumulative Cases of Laboratory-Proven Influenza in Infants Whose Mothers Received Influenza Vaccine, as Compared with Control Subjects. Testing for influenza antigen was performed from December 2004 to November 2005.

*Zaman et al, NEJM 2008;359
Houston, TX - USA

- 1998-2003: 252 pregnant women who received TIV within 6 months of delivery matched with 826 unvaccinated pregnant women\(^1\)
  - No SAE within 42 days of vaccination
  - No difference in pregnancy outcomes (C/S, premature birth) or infant medical conditions from birth to 6 months of age

- 2004-2005: 1,006 pregnant women vaccinated with TIV (all trimesters – mean GA 23.6 wk) matched with 1,495 unvaccinated pregnant women\(^2\)
  - No SAE within 42 days of vaccination
  - No difference in maternal hospitalization for reasons other than delivery, C/S, prematurity, infant medical conditions to 6 mo of age

Recent Publications on Influenza Vaccine Safety During Pandemic H1N1 Influenza Outbreak: 2009-2014

AJOG Supplement, 2012:

- Munoz FM. Safety of influenza vaccines in pregnant women.
- Khromava A et al. Manufacturers’ post-marketing safety surveillance of influenza vaccine exposure in pregnancy
- Kharbanda EO et al. Assessing the safety of influenza immunization during pregnancy: the Vaccine Safety Datalink
- Heikkinen T et al. Safety of MF-59-adjuvanted A/H1N1 influenza vaccine in pregnancy: a comparative cohort study

Reviews