Optimizing Infant Protection: Maternal Immunization

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ADVAC 2016
June 1, 2016
My institution has received research support for clinical studies from Pfizer, GSK, and Chimerix.

I have served as a consultant for Gilead and Pfizer.

I have served and am serving on several US government and international vaccine committees.

I support influenza vaccination in healthcare workers in my hospital.
Neonates are uniquely at risk from different infections which cause substantial morbidity and mortality worldwide.

- Immune system of neonates is immature and relatively ineffective.
- Active immunization is rarely successful in newborns.
PREGNANT WOMEN

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

• Should not be excluded from beneficial treatments/potentially beneficial therapies based on pregnancy status.  EXAMPLE:  antiretroviral drugs

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

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

• Are capable to make informed consent for themselves and their unborn child (although this is country and culture-specific)
Immune Responses During Pregnancy

- Physiologic changes *
  - Increased heart rate, stroke volume; decreased lung capacity but increase in O2 carriage.
  - Alter host response to antigens (increase in estrogen and progesterone result in decreased interleukins).
  - Increase in blood cortisol levels (decreased clearance)

- Decreased cell mediated immunity: relatively minor predisposition to listeria, TB, toxoplasmosis, etc.*

- Decrease in concentration of IgG by hemodilution (18% IgG decrease from 2\textsuperscript{nd} to 3\textsuperscript{rd} trimester**)

- Historically: Th2 humoral immune response thought to predominate but now evidence of shifts between pro-inflammatory and anti-inflammatory states to facilitate implantation of blastocyst, fetal growth, and parturition (facilitated by estrogens and progesterone)***

- No significant alteration in antibody responses to vaccines or infections

** Amino N. et al  1978 Ob Gyn 52: 415  
Pregnancy and Inflammation, NK cells, and Implantation: The Good, the Bad, and the Ugly*

- Not a simple Th1/Th2 paradigm
- The good: inflammation important for implantation
  - Cytokines provide growth factors necessary for implantation of fetus in placenta
  - Adaptive immunity has potential to potentiate inflammation
  - Treg cells control some aspects of adaptive immunity
- The bad:
  - NK cell hyperactivation, IF17 have role in implantation failure
- The ugly:
  - Endometriosis from prolonged inflammation leads to infertility

*Chaouat. J Reprod Immunology 2013; 97:2-13
WHY IMMUNIZE A PREGNANT WOMAN?

- Immunization during pregnancy has the potential to protect both mother and infant during a vulnerable period in their lives.
- Pregnant women are accessible to medical care and intervention.
- Transplacental transfer of antibodies is safer and less expensive than administration of immunoglobulin preparations to the infant.
<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>

* World Health Statistics 2010.*
OBSTETRICAL CONSIDERATIONS FOR USING A VACCINE IN PREGNANT WOMEN*

- High risk for exposure of pregnant woman to disease
- Infection poses a special risk to the mother
- Infection poses a special risk to the fetus
- Vaccine is available, and unlikely to cause harm

Examples of maternal immunization to be discussed:

- Diphtheria
- Tetanus
- Influenza
- Pertussis
- (Future: RSV?)

Not discussed: SORRY!

- Group B Streptococcus
- Meningococcus
- CMV, HSV

Outline

UK Poster
1950
IMMUNIZATION DURING PREGNANCY: RECENT HISTORY

• Routine immunization during pregnancy with diphtheria, influenza and polio vaccines (50-60’s)
• Safety and benefit of polio vaccine during polio outbreaks (Finland, Israel), and meningococcal outbreaks (Brazil) between 1970 – 90’s
• Concerns of vaccine safety, vaccine components, and lack of efficacy data resulted in cessation of maternal vaccination except for high maternal risk in USA by 1980’s
• 2009-10 pandemic H1N1 outbreak demonstrated risk of flu during pregnancy and benefits of flu
• 2012-2014 pertussis epidemic emphasized high risk of neonatal pertussis deaths and benefit of maternal Tdap
DIPHTHERIA: A fatal disease in the early 1900’s

- Diphtheria causes respiratory disease due to blockage of throat with thick secretions that make breathing difficult / impossible
- Treatment in 1920’s was antitoxin
- Alaska outbreak with shortage of antitoxin – 2 children died in 1925
- Balto and Gunnar Kaasen delivered antitoxin to Nome (now the Iditarod sled race.
- Vaccine introduction in 1950’s given to both children and pregnant women

UK poster, 1950

http://www.cdc.gov/features/diphtheria/diphtheria_b200px.jpg
More maternal Ab → Less infant Ab after infant immunization
### 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


• 1989: World Health Organization set goal to eliminate neonatal tetanus using maternal immunization – renewed X 3
New Guinea, 1961: Incidence of neonatal tetanus pre-study was 80 cases per 1000 live births

<table>
<thead>
<tr>
<th># Doses Tetanus Toxoid Given To Pregnant Women</th>
<th>0 or 1 dose</th>
<th>2 doses</th>
<th>3 doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of infants with neonatal tetanus</td>
<td>16/160 (10%)</td>
<td>8/234 (3.4%)</td>
<td>1/175 (0.6%)</td>
</tr>
</tbody>
</table>
37 Countries eliminated MNT between 2000 & May 2015

*(Plus Ethiopia except Somali region, 30 provinces out of 34 in Indonesia and 16 regions out of 17 in Philippines) leaving 22 countries yet to eliminate MNT

Source: WHO/UNICEF Database
Date of slide: 26 May 2015
Map production: Immunization Vaccines and Biologicals, (IVB), World Health Organization

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

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FACTORS AFFECTING TRANSPLACENTAL 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
Maternal-Fetal IgG Transport: AN ACTIVE PROCESS

- Placental transfer is highly selective for monomeric IgG, and occurs by receptor-mediated active transport.
- Transport requires HEALTHY placenta.
- IgG1 = IgG3 > IgG4 > IgG2.
- No transfer of IgM, IgA, IgE.
- Begins at 17 wks; increases with gestation.
- By 33 weeks maternal = fetal IgG levels and by 40 weeks fetal > maternal IgG levels.


Fig. 1. Comparison of IgG concentrations in forty-six paired maternal cord sera.
PLACENTAL STRUCTURE: Reduced Transfer of Tetanus Antibodies with Malaria

Cord/Maternal IgG ratio:

<table>
<thead>
<tr>
<th>Parasite Density</th>
<th>Cord/Maternal IgG Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>No placental parasites</td>
<td>0.82</td>
</tr>
<tr>
<td>&lt;35 parasites per 200 white cells</td>
<td>0.23</td>
</tr>
<tr>
<td>&gt;35 parasites per 200 white cells</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Bair et al. Lancet 1994;343:208
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%.

<table>
<thead>
<tr>
<th>Specific Antibody</th>
<th>HIV-Infected Mother-Exposed Uninfected Infant Pairs</th>
<th>HIV-Uninfected Mother-Unexposed Infant Pairs</th>
<th>Reduction, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemophilus influenzae type b</td>
<td>0.57 (0.45-0.79)</td>
<td>0.74 (0.61-1.00)</td>
<td>23</td>
</tr>
<tr>
<td>Bordetella pertussis</td>
<td>0.91 (0.61-1.20)</td>
<td>1.51 (1.15-2.06)</td>
<td>40</td>
</tr>
<tr>
<td>Pneumococcus</td>
<td>0.62 (0.41-0.77)</td>
<td>0.73 (0.53-0.94)</td>
<td>15</td>
</tr>
<tr>
<td>Tetanus toxoid</td>
<td>0.95 (0.60-1.12)</td>
<td>1.30 (1.03-1.86)</td>
<td>27</td>
</tr>
</tbody>
</table>

Placental Transfer of Anti-Measles AB in Mothers with High Total IgG is Reduced*

- Total IgG in mothers associated with reduced efficiency of transfer of total & measles-specific IgG
- Relatively more measles Ab transferred to babies born to German mothers than Nigerian mothers

<table>
<thead>
<tr>
<th></th>
<th>Total IgG in Mother At Delivery Mean (Range) (g/L)</th>
<th>Maternal Measles NT Ab</th>
<th>Cord Measles NT Ab</th>
<th>% Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nigerian</td>
<td>15.8 (18-26)</td>
<td>6.0</td>
<td>6.0</td>
<td>100%</td>
</tr>
<tr>
<td>German</td>
<td>8.7 (4.8-16)</td>
<td>7.0</td>
<td>7.7</td>
<td>140%</td>
</tr>
</tbody>
</table>

*Harter et al. PIDJ 2000;19:635-41
NOTE: Pre-pregnancy immunization has higher % IgG transmission but decreased total IgG levels

<table>
<thead>
<tr>
<th>Timing of Hib Vaccine</th>
<th>IgG Anti-PRP (ug/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mother</td>
</tr>
<tr>
<td>Pre-Pregnancy</td>
<td>20</td>
</tr>
<tr>
<td>Sacaton, AZ$^1$</td>
<td></td>
</tr>
<tr>
<td>3rd Trimester</td>
<td>78</td>
</tr>
<tr>
<td>Houston, TX$^2$</td>
<td></td>
</tr>
<tr>
<td>The Gambia$^3$</td>
<td>4</td>
</tr>
</tbody>
</table>

Pertussis cases by age — United States, 2012

Fatal Neonatal Pertussis

National Incidence without Washington

National Incidence

Cases/100,000

Age (years)

<1

1

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

Vaccine Received*  Acellular Only  Transition  Whole Cell and Fatal Neonatal Pertussis
<table>
<thead>
<tr>
<th>Arm</th>
<th>Group</th>
<th>N</th>
<th>Antepartum</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>1</td>
<td>32</td>
<td>Tdap</td>
<td>Saline</td>
</tr>
<tr>
<td>Control</td>
<td>2</td>
<td>16</td>
<td>Saline</td>
<td>Tdap</td>
</tr>
<tr>
<td>Control</td>
<td>3</td>
<td>32</td>
<td>Single dose Tdap administered to non-pregnant women</td>
<td></td>
</tr>
</tbody>
</table>
EXAMPLE: UK Pertussis Disease and Maternal Tdap *

UK Neonatal Pertussis Epidemic, 2012

Maternal Pertussis Vx

EXAMPLE: UK Maternal Tdap Immunization*


Introduction of Maternal Pertussis Vaccination – UK, 2012-2013*

~70% rate of maternal TdapIPV uptake over time

Lancet 2014
2012: Marked increase in young infant pertussis and serious disease, K

Oct. 2012: Immunization of pregnant women started using TdapIPV

Vaccine coverage in first year = 64%

Vaccine effectiveness in infants: calculated based on cases of disease in babies in first 2-3 months of life.
**CONCLUSION:**
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.

Timing of Tdap During Pregnancy: Earlier is Better (NEW)

Maternal Immunization Earlier in Pregnancy Maximizes Antibody Transfer and Expected Infant Seropositivity Against Pertussis  

Clin Inf Dis 2016

N = 335 women, 2nd or 3rd trimester

Conclusion: Early 2nd trimester immunization significantly increased neonatal pertussis PT and FHA AB
1. Maternal Immunization Earlier in Pregnancy Maximizes Antibody Transfer and Expected Infant Seropositivity Against Pertussis

The effect of timing of maternal tetanus, diphtheria, and acellular pertussis (Tdap) immunization during pregnancy on newborn pertussis antibody levels – A prospective study

N = 61 immunized women/cords

Vaccine 32 (2014) 5787–5793

2. The optimal gestation for pertussis vaccination during pregnancy – A prospective cohort study

N = 109 immunized mat/cord prs

Am J Ob Gyn 2016
EXAMPLE: Influenza Vaccine and Pregnant Women*

- 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.

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

Legend:
++ Substantial information available
+ Partial information available
- Little or no information available
N/A Not applicable

Bangladesh: Maternal Immunization with Influenza Vaccine Protects Mothers and Babies*

*Babul et al, NEJM 2008;359
## 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>3.5.7 (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*
### 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>
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.
This recommendation is based on evidence of:

- **High risk of severe disease**

- **Safety** of seasonal influenza vaccine throughout pregnancy

- **Effectiveness** of preventing influenza in the women as well as in their young infants, in whom the disease burden is also high.

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., Marietjie Venter, Ph.D., Avy 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*

CONCLUSIONS
Influenza vaccine was immunogenic in HIV-uninfected and HIV-infected pregnant women and provided partial protection against confirmed influenza in both groups of women and in infants who were not exposed to HIV. (Funded by the Bill and Melinda Gates Foundation and others; ClinicalTrials.gov numbers, NCT01306669 and NCT01306682.)
Protection of Pregnant Women and Infants with Maternal Flu Vaccine - South Africa (Madhi et al, NEJM 2014)

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.
Maternal influenza immunization in southern Nepal:
- Sponsored by B&M Gates Foundation
- ~3500 pregnant women enrolled to receive flu vaccine or placebo
- Babies and mother outcome followed
- Influenza present nearly every month
**Efficacy of Maternal Flu Vx Immunization: Dependent on match to circulating viruses, Nepal**

<table>
<thead>
<tr>
<th></th>
<th>Vx Efficacy Cohort 1 (p value)</th>
<th>Vx Efficacy Cohort 2 (p value)</th>
<th>Vx Efficacy Cohorts 1 &amp; 2 (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal + ILI</td>
<td>7.4% (0.497)</td>
<td>33% (0.02)</td>
<td>17% (0.05)</td>
</tr>
<tr>
<td>Maternal + flu overall</td>
<td>42% (0.07)</td>
<td>-8% (0.84)</td>
<td>27% (0.18)</td>
</tr>
<tr>
<td>Infant lab - confirmed flu</td>
<td>12% (0.47)</td>
<td>60% (&lt;0.01)</td>
<td>28% (0.03)</td>
</tr>
</tbody>
</table>

Impact of Influenza B circulating strains and match to Vaccine in Immunized Pregnant Women - Nepal

Summary of Influenza circulation, immunization dates, and vaccine status
Mothers and Infants Nepal 2011-2014

Number of influenza detections/month by vaccine for each influenza subtype
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)

- US government regulation (FDA): No evidence teratogenicity in animal models (required prior to human trials)
Humanized RSV Monoclonal Antibody: Palivizumab

- Proof of principal: RSV F-protein antibody will protect high-risk infants from lower respiratory tract disease
- Palivizumab (Synagis™; MedImmune, Gaithersburg, MD) administered IM at 15 mg/kg monthly
- Approved in USA in 1998 for use in infants and children <2 years of age with chronic lung disease and babies born at <35 weeks gestation
- Cost ~$900/100 mg vial (cost for 3 kg infant: 5 doses = $2250–$4500)
Infant and Mother RSV Antibody Levels Over Time in 149 Mother/Infant Pairs (Bangladesh*)

*Chu H, Steinhoff M, Englund J. JID 2015
RSV VACCINE vs PLACEBO IN PREGNANT WOMEN*

- **Primary Endpoints:**
  - Safety in women and their offspring
  - Effect of antibody on primary RSV disease in infants

- **Secondary Endpoints:**
  - Immunogenicity
  - Efficiency of antibody transfer
  - Persistence of antibody in infants
  - Breast milk antibody

UPDATE ON POTENTIAL RSV VACCINES*

2015 RSV Vaccine Update by PATH: 62 candidates

RSV Postfusion F Nanoparticle Vaccine Currently in Clinical Trials – Novavax*

- Developed by Novavax (Gaithersburg, MD)
- Engineered RSV postfusion F protein expressed in baculovirus forms nanoparticles
- Preclinical studies in cotton rats showed protection against RSV
- Phase I studies in healthy adults (men) completed*
- Phase II placebo-controlled studies in 330 women of childbearing age and ~50 pregnant women completed

*Vaccine 2013

** Glenn GM et al JID 2016 213; 411
## Maternal Immunization with RSV F protein Vaccine (Phase 2 study, Novavax, 2016)*

### Infants: Time from Vaccination to Delivery (Days) Impacts Placental Antibody Transfer

<table>
<thead>
<tr>
<th>Assay</th>
<th>Source</th>
<th>Del. &lt; 30d post vacc., n=7*</th>
<th>Del. &gt; 30d post vacc., n=14</th>
<th>All n=21*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti F IgG</td>
<td>Cord</td>
<td>7,227</td>
<td>8,659</td>
<td>8,153</td>
</tr>
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<td>Mothers</td>
<td>12,979</td>
<td>6,993</td>
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<td>1.2</td>
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<tr>
<td>PCA</td>
<td>Cord</td>
<td>177</td>
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<td>189</td>
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<tr>
<td></td>
<td>Mothers</td>
<td>303</td>
<td>178</td>
<td>213</td>
</tr>
<tr>
<td></td>
<td>Ratio</td>
<td>0.6</td>
<td>1.1</td>
<td>0.9</td>
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<tr>
<td>RSV/A</td>
<td>Cord</td>
<td>928</td>
<td>672</td>
<td>748</td>
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<tr>
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<td>Mothers</td>
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<td>512</td>
<td>529</td>
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<td>Mothers</td>
<td>724</td>
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<td>Ratio</td>
<td>0.8</td>
<td>1.2</td>
<td>1.1</td>
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**Important Findings:**
- Maternal antibody peaks 14d after vaccination
- Period of placental transfer >30 days maximizes antibody titer in infants
- P3 recruitment window opened to 31 weeks to maximize antibody transfer

*Presented by A. August at WHO Maternal Immunization Mtg, Geneva, Switzerland, April 25, 2016

GA = gestational age
Ad hoc analysis
*Excludes 1 mother/infant pair with delivery 5 days post-immunization, late pre-term delivery
CHALLENGES OF MATERNAL RSV IMMUNIZATION

1) Placental transfer of antibody: generalizable to all populations?
   a) Impact of HIV
   b) Impact of maternal IgG

2) Timing of vaccination

3) Inhibition of secondary vaccine (if/when infant vaccines available)

4) Safety – in both mother and baby

5) Efficacy-
   a) requiring large controlled clinical studies in geographical diverse and developing/developed countries
   b) Clinical and laboratory endpoints
OTHER POTENTIAL PATHOGENS: What vaccines have priority for maternal vaccination?

- RSV fusion protein vaccine: Studies ongoing
- Group B Streptococcal vaccine: Study sponsored by Novartis now completed in South Africa
- Herpes simplex virus
- Meningococcal vaccine
- Pneumococcal vaccine – conjugate, polysaccharide
- Cytomegalovirus – perhaps pre-pregnancy
POTENTIAL OBSTACLES FOR MATERNAL IMMUNIZATION

- 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
Legal Liability for Vaccine Manufacturers

- The background rates of major congenital anomalies, spontaneous abortions, and still births without vaccination are substantial.
- Temporal relationships, rather than causation, will be difficult to prove or disprove.
- Background of a litigious society makes supporting studies difficult for manufacturers.
- Indemnification needed before companies will participate in production and testing.
OTHER POTENTIAL PATHOGENS: What has priority?

- Group B Streptococcal vaccines: Study sponsored by Novartis completed in South Africa
- Herpes Simplex virus?
- Meningococcal vaccine
- Pneumococcal vaccine – conjugate, polysaccharide
- Cytomegalovirus? – perhaps pre-pregnancy
Pregnant Homer woman joins mating call to bag moose with single shot

By CRAIG MEDRED
Alaska Dispatch News

If you’re 8½ months pregnant, craving meat and find the freezer empty, what do you do?

Well, if you’re a woman in Homer, you go out and shoot a moose. That’s what Ashley Switzer did.

The 22-year-old, soon-to-be first-time mom was home alone in early September when it came time to put food on the table. Husband Scott was off working on a fishing boat somewhere near Kodiak Island, about 130 miles to the southwest.

Ashley wasn’t sure when he’d be home, so she decided she best do something.
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- ClaireAnne Siegrist – SAGE enthusiast for maternal immunization

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