Maternal Vaccination: Protecting Mothers and Babies

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Alaska MCH & Immunization Conference
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NEONATES AND YOUNG INFANTS ARE AT HIGH RISK FROM INFECTIOUS DISEASES

- Neonates are uniquely at risk for many 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 and should have the right to make informed consent for themselves and their unborn child (although this is country and culture-specific)
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.

See Back Page, MOOSE

Ashley Switzer shot a moose while she was 8½ months pregnant.
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 due to decreased clearance
- Decreased cell mediated immunity: relatively minor but can predispose to listeria, TB, toxoplasmosis, etc.
- Decrease in concentration of IgG (hemodilution)
- No significant alteration in antibody responses to vaccines or infections

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.
### Health Service Coverage Among Pregnant Women

#### MDG 5
**Antenatal care coverage (%) 2000-2009**

<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>
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<tr>
<td>High income</td>
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</tr>
<tr>
<td>Global</td>
<td>78</td>
<td>48</td>
</tr>
</tbody>
</table>

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: perhaps RSV?)

Not discussed:

- Group B Streptococcus
- Meningococcus
- CMV, HSV

UK poster 1950
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
- Currently, diphtheria disease is prevented with vaccine
- Treatment in 1920’s was antitoxin which worked OK (neither vaccine nor antibiotics invented yet)
- Alaska outbreak with shortage of antitoxin – 2 children died in Jan. 1925
- Balto and Gunnar Kaasen delivered vaccine to Nome saving lives of many people (but nonetheless, 3 children died during the outbreak)
More maternal Ab $\Rightarrow$ Less infant Ab after infant immunization
<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>
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

Highlands, New Guinea
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>
Elimination of Neonatal Tetanus

1989 WHO & 1990 World Summit for Children made declarations for the global elimination of neonatal tetanus by 1995... 2000...2005...2010....*

Reported Neonatal Tetanus Cases, 1990-2011

1990: 25,293 reported NT cases (no data for 39 countries)

2011: 4213 reported NT cases (no data for 26 countries)

Source: WHO/IVB database, 2012
194 WHO Member States. Data as of August 2012
Date of slide: 1 October 2012.
34 Countries eliminated MNT between 2000 & 2013
*(Plus 18 States out of 35 in India, Ethiopia all except Somali region and 29 provinces out of 33 in Indonesia) leaving 25 countries yet to eliminate MNT

Data Source: WHO/UNICEF database, May 2014

WHO Member States

Map production: Immunization Vaccines and Biologicals, (IVB), World Health Organization

Date of Slide: 12 May 2014

The definitions and terms shown and the designates 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 borders. Coloured areas on maps represent approximate border areas for which there may not be legal agreement.
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.

Decreased Antibody Titers in Uninfected, HIV-exposed vs Healthy HIV-unexposed Infants at Birth*

IMMUNIZATION DURING RATHER THAN PRIOR TO PREGNANCY HAS ADVANTAGES

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></td>
</tr>
<tr>
<td>Sacaton, AZ(^1)</td>
<td>20</td>
</tr>
<tr>
<td>3(^{rd}) Trimester</td>
<td></td>
</tr>
<tr>
<td>Houston, TX(^2)</td>
<td>78</td>
</tr>
<tr>
<td>The Gambia(^3)</td>
<td>4</td>
</tr>
</tbody>
</table>

\(^1\) Santosham et al, PIDJ 2001; 20:931; \(^2\) Englund et al JID 1995; \(^3\) Mulholland et al. JAMA 1996
Influenza Disease During Pregnancy

Influenza infection in pregnant women:

• Increased severity during 3rd trimester
• Increased severity with pre-existing conditions
• Increased severity with new influenza strain
• Impacts the fetus
## 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*
<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>
There were 117,347 eligible pregnancies in Norway from 2009 through 2010. Fetal mortality was 4.9 deaths per 1000 births. During the pandemic, 54% of pregnant women in their second or third trimester were vaccinated. Vaccination during pregnancy substantially reduced the risk of an influenza diagnosis (adjusted hazard ratio, 0.30; 95% confidence interval [CI], 0.25 to 0.34). Among pregnant women with a clinical diagnosis of influenza, the risk of fetal death was increased (adjusted hazard ratio, 1.91; 95% CI, 1.07 to 3.41). The risk of fetal death was reduced with vaccination during pregnancy, although this reduction was not significant (adjusted hazard ratio, 0.88; 95% CI, 0.66 to 1.17).
Safety of influenza vaccines in pregnancy

- Data available includes
  - 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**

- Data available supports safety of vaccination of pregnant women with inactivated influenza vaccine, with potential to benefit both mother and infant.
  (Maternal Influenza Immunization Convening London, June 2011)

* Limitations: Design and statistical power (N)
** 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/causality; 3. Confounders; 4. Insufficient power
Maternal Immunization with Influenza Vaccine Protects Mothers and Babies Against Influenza*

Effectiveness of Maternal Influenza Immunization in Mothers and Infants


Babies born to mothers who received TIV

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
Influenza-specific Antibody After Maternal Immunization in Mothers and Babies*

Increased birth weight in babies born to TIV-immunized mothers support results of Bangladesh study.

Data from 3 studies of pregnant women who were either immunized or experienced influenza supports birthweight observations from Bangladesh:

Author

285g
• 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.

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.

Clinical Studies of Maternal Influenza Immunization Underway

• Ongoing clinical studies of influenza in pregnant women may help answer questions regarding effectiveness, safety, and benefits in outcomes.

• EXAMPLE: Prospective, randomized clinical studies of TIV in pregnant women sponsored by Gates Fndn underway in Mali, Nepal, and South Africa now completed, with thousands of pregnant women enrolled at each site and followed during flu season.
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 Teurnicht, Ph.D., Justin R. Ortiz, M.D., Marietjie Venter, Ph.D., Avy Violari, M.D., Kathleen M. Neuzil, M.D., Eric A. Simões, M.D., Keith D. Klugman, M.D., Dh D., and Marta C.

Table 4. Efficacy of IV3 Vaccination in Mothers and Infants until 24 Weeks after Birth, Intention-to-Treat Population.†

<table>
<thead>
<tr>
<th>Efficacy End Point</th>
<th>IV3 (N = 1026)</th>
<th>HIV-Uninfected Cohort (N = 1023)</th>
<th>Vaccine Efficacy</th>
<th>P Value</th>
<th>IV3 (N = 100)</th>
<th>HIV-Uninfected Cohort (N = 88)</th>
<th>Vaccine Efficacy</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td></td>
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</tr>
<tr>
<td>RT-PCR-confirmed influenza — no. (%); (95% CI)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>With inclusion of B/Yamagata</td>
<td>19 (1.9); (1.1 to 2.9)†</td>
<td>37 (3.6); (2.6 to 5.0)‡‡</td>
<td>48.8 (11.6 to 70.4)</td>
<td>0.01</td>
<td>5 (5.0); (1.6 to 11.3)§</td>
<td>6 (6.8); (2.5 to 14.3)§§</td>
<td>26.7 (-132.0 to 76.8)</td>
<td>0.60</td>
</tr>
<tr>
<td>With exclusion of B/Yamagata</td>
<td>13 (1.3); (0.7 to 2.2)</td>
<td>25 (2.4); (1.6 to 3.6)</td>
<td>48.2 (-0.8 to 73.3)</td>
<td>0.05</td>
<td>4 (4.0); (1.1 to 9.9)</td>
<td>3 (3.4); (0.7 to 9.6)</td>
<td>14.8 (-270.4 to 80.4)</td>
<td>0.57</td>
</tr>
<tr>
<td>Influenza-like illness — no. (%); (95% CI)</td>
<td>595 (58.0); (54.9 to 61.0)</td>
<td>584 (57.1); (54.0 to 60.1)</td>
<td>-1.6 (-9.4 to 5.7)</td>
<td>0.68</td>
<td>66 (66.0); (55.8 to 75.2)</td>
<td>57 (64.8); (53.9 to 74.7)</td>
<td>-1.9 (-25.5 to 17.3)</td>
<td>0.86</td>
</tr>
<tr>
<td>Any respiratory illness — no. (%); (95% CI)</td>
<td>706 (68.8); (65.9 to 71.6)</td>
<td>697 (68.1); (63.2 to 71.0)</td>
<td>-1.0 (-7.1 to 4.8)</td>
<td>0.74</td>
<td>76 (76.0); (66.4 to 84.0)</td>
<td>70 (79.5); (69.6 to 87.4)</td>
<td>4.5 (-11.3 to 18.0)</td>
<td>0.56</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>RT-PCR confirmed influenza — no. (%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With inclusion of B/Yamagata</td>
<td>19 (1.8); (1.1 to 2.8)¶</td>
<td>38 (3.6); (2.6 to 4.9)¶</td>
<td>50.4 (14.5 to 71.2)</td>
<td>0.010</td>
<td>7 (7.0); (2.9 to 13.9)</td>
<td>16 (17.0); (10.1 to 26.2)</td>
<td>57.7 (0.2 to 82.1)</td>
<td>0.05</td>
</tr>
<tr>
<td>With exclusion of B/Yamagata</td>
<td>19 (1.8); (1.1 to 2.8)</td>
<td>35 (3.3); (2.3 to 4.6)</td>
<td>46.1 (6.4 to 69.0)</td>
<td>0.03</td>
<td>7 (7.0); (2.9 to 13.9)</td>
<td>13 (1.3); (7.6 to 22.5)</td>
<td>48.2 (-27.0 to 78.8)</td>
<td>0.15</td>
</tr>
<tr>
<td>Influenza-like illness — no. (%)</td>
<td>175 (16.5); (14.3 to 18.8)</td>
<td>181 (17.2); (14.9 to 19.6)</td>
<td>4.0 (-16.0 to 20.6)</td>
<td>0.67</td>
<td>24 (24.0); (16.0 to 33.6)</td>
<td>27 (28.7); (19.9 to 39.0)</td>
<td>-0.07 (-63.7 to 38.8)</td>
<td>0.99</td>
</tr>
<tr>
<td>Any respiratory illness — no. (%)</td>
<td>674 (63.5); (60.5 to 66.4)</td>
<td>687 (65.2); (62.2 to 68.1)</td>
<td>2.6 (-3.7 to 8.6)</td>
<td>0.41</td>
<td>72 (72.0); (62.1 to 80.5)</td>
<td>73 (77.7); (67.9 to 85.6)</td>
<td>5.2 (-12.2 to 19.8)</td>
<td>0.54</td>
</tr>
</tbody>
</table>
Neonatal Pertussis: CXR at admission
June 28, age 1 month
CXR shortly before death on ECMO, age 2 months on July 27
Annual incidence by State, 2011*

*2011 data are provisional. Incidence is per 100,000 population
Source: CDC National Notifiable Disease Surveillance System, 2011
CDC Wonder Population Estimates (Vintage 2009)
Annual Pertussis Incidence by State, 2012*

Incidence 5.2 (n=16,181)

*2012 data are provisional and reflect data reported through July 5, 2012. Incidence is per 100,000 population.
Pertussis cases by age — United States, 2012

Vaccine Type Received*

<table>
<thead>
<tr>
<th>Vaccine Type Received*</th>
<th>Acellular Only</th>
<th>Transition Period</th>
<th>Whole Cell and Acellular</th>
</tr>
</thead>
</table>
Diphtheria and Tetanus: Antibody GMCs up to 10 Years After Td and Tdap (Adacel)

Adults (n=644)

- Tdap (Study 1)
- Tdap (Study 3)
- Td (Study 3)

=Diptheria

GMT (IU/mL)

Pre 1 Month 1 Year 3 Years 5 Years 10 Years

Tetanus

GMT (IU/mL)

Pre 1 Month 1 Year 3 Years 5 Years 10 Years

= 0.10 IU/mL; seroprotection ≥0.10 IU/mL

Get Vaccinated Against Whooping Cough While Pregnant – USA – ACIP: 2013*

Pregnant women should get a whooping cough vaccine since vaccines are the best way to prevent this disease. There are 2 different whooping cough vaccines for different age groups:

- Tdap: for everyone 11 years and older, including pregnant women
- DTaP: for children 2 months through 6 years of age

Whooping cough vaccine is recommended during each of your pregnancies

- The best time to get the shot is your 27th through 36th week of pregnancy.

Maximizing the Vaccination Program

- Sustaining DTaP coverage
- Increasing Tdap coverage
- Vaccinating to protect infants
## Safety and Immunogenicity of Tetanus Diphtheria and Acellular Pertussis (Tdap) Immunization During Pregnancy in Mothers and Infants: A Randomized Clinical Trial

Flor M. Munoz, MD; Nanette H. Bond, PAC; Maurizio Maccato, MD; Phillip Pinell, MD; Hunter A. Hammill, MD; Geeta K. Swamy, MD; Emmanuel B. Walter, MD; Lisa A. Jackson, MD; Janet A. Englund, MD; Morven S. Edwards, MD; C. Mary Healy, MD; Carey R. Petrie, PhD; Jennifer Ferreira, ScM; Johannes B. Goll, MS; Carol J. Baker, MD

### Table

<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>

Single dose administered to pregnant women with crossover design.
RESULTS: Immunogenicity (GMC) Pertussis Antibodies in Mothers and Infants*

*Munoz et al JAMA 2014
Transplacental Transmission of PT Ab: US* vs Nepal**

### Table 5. Transplacental Transfer of Antibodies (Ratio of Infant Cord Blood Antibodies to Maternal Antibodies) and Antibody Concentrations in Infants at 2 Months of Age Compared With Concentrations at Birth (Ratio of Infant 2-Month Antibodies to Cord Blood Antibodies)

<table>
<thead>
<tr>
<th>Vaccine Antigen</th>
<th>Ratio (95% CI)</th>
<th>Infant Antibodies at 2 Mo to Cord Blood Antibodies at Delivery</th>
<th>Infant Antibodies at Maternal Antibodies at Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tdap Antepartum/Placebo Postpartum</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 31)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pertussis Toxin</td>
<td>1.23 (1.03 to 1.47)</td>
<td>0.34 (0.29 to 0.41)</td>
<td>1.54 (1.15 to 2.05)</td>
</tr>
<tr>
<td>Filamentous hemagglutinin</td>
<td>1.27 (1.13 to 1.42)</td>
<td>0.42 (0.36 to 0.49)</td>
<td>1.15 (0.74 to 1.76)</td>
</tr>
<tr>
<td>Pertactin</td>
<td>1.19 (0.93 to 1.52)</td>
<td>0.31 (0.25 to 0.39)</td>
<td>1.19 (0.98 to 1.44)</td>
</tr>
<tr>
<td>Fimbriae 2 and 3</td>
<td>1.26 (1.02 to 1.55)</td>
<td>0.26 (0.20 to 0.32)</td>
<td>1.49 (1.27 to 1.73)</td>
</tr>
<tr>
<td>Tetanus</td>
<td>1.36 (1.14 to 1.62)</td>
<td>0.27 (0.22 to 0.31)</td>
<td>1.19 (1.02 to 1.40)</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>1.26 (0.91 to 1.75)</td>
<td>0.28 (0.22 to 0.36)</td>
<td>1.28 (0.91 to 1.79)</td>
</tr>
</tbody>
</table>

| **Placebo Antepartum/Tdap Postpartum** |               |                                                               |                                                     |
| (n = 14)         |               |                                                               |                                                     |
| Pertussis Toxin | 1.15 (0.74 to 1.76) | 0.32 (0.19 to 0.53)                                            | 0.40 (0.29 to 0.56)                                  |
| Filamentous hemagglutinin | 1.15 (0.74 to 1.76) | 0.32 (0.19 to 0.53)                                            | 0.40 (0.29 to 0.56)                                  |
| Pertactin       | 1.19 (0.98 to 1.44) | 0.42 (0.29 to 0.60)                                            | 0.42 (0.29 to 0.60)                                  |
| Fimbriae 2 and 3 | 1.49 (1.27 to 1.73) | 0.25 (0.19 to 0.33)                                            | 0.42 (0.29 to 0.60)                                  |
| Tetanus         | 1.19 (1.02 to 1.40) | 0.38 (0.26 to 0.57)                                            | 0.42 (0.29 to 0.60)                                  |
| Diphtheria      | 1.28 (0.91 to 1.79) | 0.28 (0.22 to 0.36)                                            | 0.42 (0.29 to 0.60)                                  |

Nepal cord: maternal PT Ab transfer = 1.35 [95% CI, 1.04 – 1.28] **

US vaccinated mothers:
- cord: maternal PT transfer = 1.23 [95% CI 1.03-1.47]

US unvaccinated mothers:
- cord: maternal PT transfer = 1.54 [95% CI 1.15-2.05]

*Munoz et al JAMA 2014; ** Mergler PAS 2014 Abstract, Vancouver BC
Infant Pertussis: A serious outbreak in the UK, 2012-2014

In 2012: 235 babies <12 weeks of age diagnosed with pertussis; in 2013 with maternal Tdap in ~60% pregnant women: 79% drop in infant cases

In 2012: 14 babies died; in 2013-3 babies died of pertussis and none born to immunized mothers

http://www.nhs.uk/conditions/pregnancy-and-baby/pages/whooping-cough-vaccination-pregnant.aspx#So
2012: Serious Pertussis outbreak in UK, with

Oct. 2012: Pregnant women vx 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.

~70% rate of maternal TdapIPV uptake over time

Reduction in Pertussis cases

Mat Vx begun

Lancet 2014
Effectiveness of Maternal Tdap Vaccination in the UK, 2012-3*

- 82 confirmed pertussis infant cases in infants < 3 Months from Oct. 1, 2012-Sept. 3, 2013 born to 26,684 mothers with average vaccine coverage of 64%.

- VE was 91% (CI 84-95) for infants < 3 months of age

- VE was 90% (95% CI 82-95) for infants < 2 months of age
Burden of RSV Disease Worldwide

- Pneumonia is leading single cause of mortality in children < 5 years

- Emerging data indicate clinical importance of RSV in children worldwide:
  - Studies have detected RSV and demonstrated high burden of disease worldwide regardless of climate, socioeconomic burden
  - More disease at an earlier age documented in crowded setting, lower socioeconomic status.
  - Increased concern about antibiotic resistance and the proper use of antibiotics in children

Nair et al Lancet 2011
RSV: Most Common Symptomatic Virus in Children in Alaska

1994-2004: 10% of RSV hospitalizations in children <1 month.
50% of RSV hospitalizations in children <6 months.
79% of RSV hospitalizations in children <12 months.
97% of RSV hospitalizations in children <24 months.
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

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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
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- ClaireAnne Siegrist - SAGE enthusiast for maternal immunization
- Funding: NIAID, PATH, Thrasher, Bill and Melinda Gates Fndn.