PREVENTION OF INFANT DISEASE: IMMUNIZATION IN PREGNANT WOMEN AND ITS APPLICATION IN DEVELOPING COUNTRIES

Annecy ADVAC 15
May 21, 2014

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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)

Thanks to my sister-in-law
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

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.
# 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>

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

IMMUNIZATION DURING PREGNANCY: RECENT HISTORY

- Routine immunization during pregnancy with diphtheria, influenza and polio vaccines during 1950’s - 60’s
- Safety and benefit of polio vaccine during polio outbreaks (Finland, Israel), and meningococcal outbreaks (Brazil) between 1970 – 1990
- 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 vaccination
- 2012-2014 pertussis epidemic emphasized high risk of neonatal pertussis deaths
Examples of maternal immunization to be discussed:

- Diphtheria
- Tetanus
- Hib
- Influenza
- Pertussis, RSV

Not discussed:

- Group B Streptococcus
- Meningococcus
- CMV, HSV
More maternal Ab $\rightarrow$ 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>
<tr>
<td><strong>Vaccines in Development</strong></td>
<td></td>
<td></td>
</tr>
<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>
Elimination of Neonatal Tetanus


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.

PLACENTAL STRUCTURE:
Reduced Transfer of Tetanus Antibodies with Malaria

Cord/Maternal IgG ratio:

- No placental parasites: 0.82
- <35 parasites per 200 white cells: 0.23
- >35 parasites per 200 white cells: 0.18

Brair et al. Lancet 1994;343:208
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>
<th>Mother</th>
<th>Infant</th>
<th>% Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sacaton, AZ&lt;sup&gt;1&lt;/sup&gt;</td>
<td>20</td>
<td>11</td>
<td></td>
<td>73%</td>
</tr>
<tr>
<td>3&lt;sup&gt;rd&lt;/sup&gt; Trimester</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Houston, TX&lt;sup&gt;2&lt;/sup&gt;</td>
<td>78</td>
<td>47</td>
<td></td>
<td>60%</td>
</tr>
<tr>
<td>The Gambia&lt;sup&gt;3&lt;/sup&gt;</td>
<td>4</td>
<td>2</td>
<td></td>
<td>61%</td>
</tr>
</tbody>
</table>

<sup>1</sup> Santosham et al, PIDJ 2001;20:931;  <sup>2</sup> Englund et al JID 1995;  <sup>3</sup> Mulholland et al. JAMA 1996
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.

Options for Prevention: Influenza Vaccine

- Trivalent inactivated vaccine (TIV)
  - Approved for > 6 months of age
  - Only vaccine for pregnant women (recommended by CDC; not licensed by FDA for use during pregnancy)
  - At least 5 manufacturers in US
  - Single dose-thimerosal free and multidose vials available
  - Dose: 0.5 ml IM once early in season
- Adjuvanted inactivated influenza vaccine
  - MF59
  - AS03 – enhanced immunity; licensed in EU
  - Not studied prior to 2009 pandemic
- Live attenuated influenza vaccine
  - Not recommended for use in pregnancy
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

Photo thanks to my fellow
### Table 1

<table>
<thead>
<tr>
<th>Paper</th>
<th>Risk of hospitalization</th>
<th>Risk of ICU admission</th>
<th>Risk of death</th>
<th>Risk of severe disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>New South Wales Public Health Network</td>
<td>RR, 5.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>RR, 10.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANZIC</td>
<td>RR, 7.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Campbell et al&lt;sup&gt;123&lt;/sup&gt;</td>
<td>RR, 0.7 (0.4–1.2)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>RR, 1.1 (0.3–4.1)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>RR, 0.7 (0.4–1.3)</td>
<td></td>
</tr>
<tr>
<td>Creanga et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td>RR, 7.2&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>RR, 4.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Fuhrman et al&lt;sup&gt;62&lt;/sup&gt;</td>
<td>aOR, 0.3 (0.04–3.0)</td>
<td>aOR, 0.5 (0.2–0.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gérardin et al&lt;sup&gt;46&lt;/sup&gt;</td>
<td>RR, 0.4 (0–2.6)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hanslik et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>OR, 5.2 (4.0–6.9)</td>
<td>OR, 1.4 (0.3–4.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jamieson et al&lt;sup&gt;3&lt;/sup&gt;</td>
<td>RR, 4.3 (2.3–7.8)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kelly et al&lt;sup&gt;28&lt;/sup&gt;</td>
<td>RR, 5.2 (4.6–5.8)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>RR, 6.5 (4.8–8.8)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>RR, 1.4 (0.4–4.5)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Koegeenberg et al&lt;sup&gt;20&lt;/sup&gt;</td>
<td>OR, 1.13 (0.1–8.88)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oliveira et al&lt;sup&gt;81&lt;/sup&gt;</td>
<td>RR, 1.07 (0.82–1.41)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yang et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>OR, 0.8 (0.2–3.5)</td>
<td>OR, 0.4 (0.2–3.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zarychanski et al&lt;sup&gt;106&lt;/sup&gt;</td>
<td>OR, 3.64 (0.86–15.4)&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ANZIC, ANZIC Influenza Investigators and Australasian Maternity Outcomes Surveillance System; aOR, adjusted odds ratio; ICU, intensive care unit; OR, odds ratio; RR, relative risk.

<sup>a</sup> Compared to nonpregnant women of reproductive age; <sup>b</sup> Compared to general population; <sup>c</sup> This study reports increased odds that pregnant women would require ICU admission over that they would require only outpatient treatment.

<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 1990-2002</td>
<td>Maternal influenza season respiratory hospitalization (208)</td>
<td>No hospitalization (132,099)</td>
<td>Newborns of hospitalized cases were 90gm smaller, 40% more likely to be small for gestational age</td>
</tr>
<tr>
<td>Mendez-Figueroa AJOG 2011</td>
<td>USA 2009-10</td>
<td>Maternal ILI with lab confirmed pandemic H1N1 (15)</td>
<td>Maternal ILI with lab test negative (25)</td>
<td>Newborns exposed to influenza were 285gm smaller</td>
</tr>
<tr>
<td>Pierce BMJ 2011</td>
<td>UK 2009-2010</td>
<td>Pregnant women with Lab-confirmed hospitalization for pandemic H1N1 (256)</td>
<td>Historical comparison of pregnant women from 2005-2006 (1220)</td>
<td>Newborns exposed to influenza were 255 g smaller. Higher perinatal mortality and premature birth in exposed.</td>
</tr>
</tbody>
</table>
Risk of Fetal Death after Pandemic Influenza Virus Infection or Vaccination

Siri E. Håberg, M.D., Ph.D., Lill Trogstad, M.D., Ph.D., Nina Gunnes, Ph.D., Allen J. Wilcox, M.D., Ph.D., Håkon K. Gjessing, Ph.D., Sven Ove Samuelsen, Ph.D., Anders Skrondal, Ph.D., Inger Cappelen, Ph.D., Anders Engeland, Ph.D., Preben Avitsland, M.D., Steinar Madsen, M.D., Ingebjørg Buajordet, Ph.D., Kari Furu, Ph.D., Per Nafstad, M.D., Ph.D.,

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).

Table 2. Hazard Ratios for Fetal Death, According to Status Regarding Vaccination, Pregnancy during the Pandemic Wave, and a Clinical Diagnosis of Influenza.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Pregnancy-Days at Risk†</th>
<th>Hazard Ratio (95% CI) Without Adjustment</th>
<th>Hazard Ratio (95% CI) With Initial Adjustment‡</th>
<th>Hazard Ratio (95% CI) With Further Adjustment¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of days</td>
<td>18,970,404</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Vaccinated during pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>15,942,252</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>3,028,152</td>
<td>0.95 (0.74–1.21)</td>
<td>0.84 (0.64–1.10)</td>
<td>0.88 (0.66–1.17)</td>
</tr>
<tr>
<td>Pregnant during the pandemic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>10,422,035</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>8,548,369</td>
<td>1.15 (0.96–1.37)</td>
<td>1.21 (1.00–1.48)</td>
<td>1.26 (1.02–1.55)</td>
</tr>
<tr>
<td>Without an influenza diagnosis</td>
<td>8,221,514</td>
<td>1.11 (0.93–1.33)</td>
<td>1.18 (0.96–1.44)</td>
<td>1.23 (0.99–1.52)</td>
</tr>
<tr>
<td>With an influenza diagnosis</td>
<td>326,855</td>
<td>2.00 (1.20–3.32)</td>
<td>2.10 (1.27–3.49)</td>
<td>1.91 (1.07–3.41)</td>
</tr>
</tbody>
</table>
Influenza-associated Mortality and Hospitalizations Are High in the Youngest Children*

Influenza-associated deaths among US children, 2003-2004*

Neuzil et al. NEJM 2000;342:225-231;

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*

**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 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>-14.2 (-25.5 to -2.9)</td>
</tr>
<tr>
<td>Temperature &gt;38°C</td>
<td>33</td>
<td>19</td>
<td>-7.3 (-14.5 to -0.1)</td>
</tr>
<tr>
<td>Diarrheal disease</td>
<td>60</td>
<td>49</td>
<td>-5.9 (-16.4 to 4.5)</td>
</tr>
<tr>
<td>Clinic visit</td>
<td>25</td>
<td>19</td>
<td>-3.2 (-9.8 to 3.4)</td>
</tr>
</tbody>
</table>

*Zaman et al, NEJM 2008;359

**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.
Influenza Ab in Immunized Mothers and Babies over Time

Figure 1. Proportions of Immunized Mothers and Their Infants with Hemagglutination-Inhibition (HAI) Titer of 1:40 or Greater.

Data at birth are from cord-serum samples. Before immunization, the proportions with an HAI titer of 1:40 or greater were significantly (P<0.001) higher for A/Fujian (H3N2) than either of the other two strains, among mothers, and the proportions were significantly higher for A/Fujian (H3N2) than for A/New Caledonia (H1N1) at all other time points. The proportions with seroprotection were significantly lower for B/Hong Kong than for either of the other two strains at all time points after immunization. (Immunization occurred during the third trimester.) I bars indicate 95% confidence intervals.
### Maternal Influenza Immunization and Infant Outcomes

<table>
<thead>
<tr>
<th>Author</th>
<th>Site/ Dates</th>
<th>Design</th>
<th># VX</th>
<th># Control</th>
<th>Infant Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaman 2008</td>
<td>Bangladesh 2004-5</td>
<td>RC Vx Trial</td>
<td>172</td>
<td>168</td>
<td>↓ 36% ILI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓ 69% lab + flu</td>
</tr>
<tr>
<td>Poehling 2011</td>
<td>TN, OH, NY USA 2002-9</td>
<td>Case Control</td>
<td>151</td>
<td>1359</td>
<td>↓ 45-48% hospitalization</td>
</tr>
<tr>
<td>Eick 2011</td>
<td>Apache/ Najavo USA 2002-5</td>
<td>Prospective observational cohort</td>
<td>573</td>
<td>587</td>
<td>↓ 41% lab + flu</td>
</tr>
<tr>
<td>Benowitz 2010</td>
<td>CN/ USA 2000-9</td>
<td>Case-control</td>
<td>91</td>
<td>156</td>
<td>↓ 91.5% hospitalized flu+</td>
</tr>
</tbody>
</table>

J. Englund. Presentation to SAGE. April 2012.
Data from 3 studies of pregnant women who were either immunized or experienced influenza supports birthweight observations from Bangladesh:

<table>
<thead>
<tr>
<th>Author</th>
<th>Site</th>
<th>Design</th>
<th>Intervention</th>
<th>Control</th>
<th>Newborn Birth weight</th>
<th>% SGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steinhoff 2011</td>
<td>Bangladesh 2004-05</td>
<td>RC Trial</td>
<td>Flu vaccine 172</td>
<td>Spn vaccine 168</td>
<td>↑ 200g</td>
<td>↓ 34%</td>
</tr>
<tr>
<td>McNeill 2011</td>
<td>NS, Canada 1990-2002</td>
<td>Retrospective</td>
<td>“flu” adm 208</td>
<td>No adm 132,099</td>
<td>↑ 90gm</td>
<td>↓ 40%</td>
</tr>
<tr>
<td>S. Omer 2011</td>
<td>GA, USA 2004-06</td>
<td>Cohort analysis</td>
<td>Flu vaccine 578</td>
<td>No vaccine 3,748</td>
<td>___</td>
<td>↓ 70%</td>
</tr>
<tr>
<td>Anderson 2011</td>
<td>RI, USA 2009-10</td>
<td>Prospective cohort (pH₁N₁)</td>
<td>Lab flu 16</td>
<td>ILI, lab negative 25</td>
<td>↑ 285g</td>
<td>___</td>
</tr>
</tbody>
</table>
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.

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.
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 in 2\textsuperscript{nd} year, with thousands of pregnant women enrolled at each site.
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

Department of Health Recommendations
- From 1 October 2012
- Offer a single dose of Repevax® (dTaP/IPV) between 28-38 weeks pregnancy
- Offer in every pregnancy
- Outbreak response measure

http://www.nhs.uk/conditions/pregnancy-and-baby/pages/whooping-cough-vaccination-pregnant.aspx#So
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.

### 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>Single dose administered to pregnant women with crossover design</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Antepartum</td>
<td></td>
</tr>
<tr>
<td>Interventions</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><strong>Single dose administered to non-pregnant women</strong></td>
<td><strong>Tdap vaccine</strong></td>
</tr>
</tbody>
</table>

---

Munoz FM et al. JAMA 2014; 311:1760-9
RESULTS: Immunogenicity (GMC) Pertussis Antibodies in Mothers and Infants

*Munoz et al.
JAMA 2014

---

**Pertussis Toxin**

- Tdap Antepartum
- Tdap Postpartum
- *p-value < 0.01

**Filamentous Hemagglutinin**

**Pertactin**

**Fimbriae 2 and 3**

---
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>Tdap Antepartum/Placebo Postpartum (n = 31)</th>
<th>Placebo Antepartum/Tdap Postpartum (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pertussis Toxin</td>
<td>1.23 (1.03 to -1.47)</td>
<td>0.34 (0.29 to 0.41)*</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>
</tr>
<tr>
<td>Pertactin</td>
<td>1.19 (0.93 to 1.52)</td>
<td>0.31 (0.25 to 0.39)</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>
</tr>
<tr>
<td>Tetanus</td>
<td>1.36 (1.14 to 1.62)</td>
<td>0.27 (0.22 to 0.31)*</td>
</tr>
<tr>
<td>Diphtheria</td>
<td>1.26 (0.91 to 1.75)</td>
<td>0.28 (0.22 to 0.36)</td>
</tr>
</tbody>
</table>

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
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 (RSV is not susceptible to ampicillin!)

Nair et al Lancet 2011
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

RSV Vaccine Snapshot 2013

http://sites.path.org/vaccinedevelopment/files/2012/12/RSV_vaccine_landscape_snapshot.pdf
Legal Liability for Vaccine Manufacturers

- Background rates of major congenital anomalies, spontaneous abortions, and still births EVEN without vaccination are substantial.
- Temporal relationships, rather than causation, will be difficult to prove or disprove.
- Background of a litiginous society AND “medical terrorism” makes supporting studies difficult for manufacturers.
- Indemnification needed before companies will participate in production and testing.
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
Mt. Everest

Acknowledgements:

- Helen Chu, MD and Jane Kuypers PhD- Univ. Washington
- Kathy Neuzil, MD, MPH and Justin Ortiz, MD, MPH, MD – Univ.Washington & PATH
- Flor Munoz, MD and WP Glezen, MD- Baylor College of Medicine
- Mark Steinhoff, MD, James Tielsch, PhD, Joanne Katz – Nepal site (Cincinnati Children’s Hospital/ George Washington U/Johns Hopkins)
- Liz Milller, Helen Campbell– UK Health Protection Agency
- ClaireAnne Siegrist- SAGE enthusiast for maternal immunization

- Funding: NIAID, PATH, Thrasher, Bill and Melinda Gates Fndn.
Acknowledgements:
Women participating in our studies
Inhibition of Active Immune Response to Diphtheria Toxoid in Infants Based on Presence of Passive Antibody

BMJ 1954; pp 476-481
The Effect of Maternal Antibody on the Serologic Response and the Incidence of Adverse Reactions After Primary Immunization With Acellular and Whole-Cell Pertussis Vaccines Combined with Diphtheria and Tetanus Toxoids

Janet A. Englund, Edwin L. Anderson, George F. Reed, Michael D. Decker, Kathryn M. Edwards, Michael E. Pichichero, Mark C. Steinhoff, Margaret B. Rennels, Adamadia Deforest and Bruce D. Meade

*Pediatrics* 1995;96;580

**Figure A:** Pre vs post PT antibody in infants receiving DTaP vaccine (no effect of maternal Ab)

**Figure B.** Pre vs. post-PT antibody in infants receiving DTP Vaccine (Neg. effect of maternal Ab)
A COMPELLING CASE

• THERE IS COMPELLING DATA TO VACCINATE PREGNANT WOMEN TO PROTECT THE WOMAN AND HER INFANT

• Flu vaccines are safe and immunogenic

• WHY DON’T WE? In countries with physician malpractice concerns, are health care providers at risk by not promoting maternal flu vaccination?

• If you had a limited vaccine supply or health care budget, who would you immunize?
Vaccines Administered during Pregnancy in NIH Funded Trials, USA

- Capsular Polysaccharide of Hib
- Protein Conjugate-Polysaccharide of Hib
- 23 valent Pneumococcal Polysaccharide
- Group B Streptococcal polysaccharide and conjugate vaccines
- RSV-subunit vaccine (PFP-2)
- Pneumococcal conjugate vaccines
- Acellular pertussis vaccines

Today’s talk: Tetanus, influenza, RSV
RSV Is Predominant Cause of Community-Acquired Pneumonia in Children Ages 2Mo - 3Yr in Nepal

N = 2219 children
“Whereas reliance on supranational/regional data may be necessary for many countries to assess the overall epidemiological situation, individual national decisions on the use of influenza vaccines will be determined by national capacity and resources.”

“To this end, country-specific information about risk groups, disease burden and cost-effectiveness are important to aid national policy makers and health programme planners.”

# Guidelines for Vaccinating Pregnant Women

*Modified after:* Advisory Committee on Immunization Practices (ACIP)  
CDC, July 2012

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>May be used if benefits outweigh risks</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Recommended in some circumstances</td>
</tr>
<tr>
<td>Human Papillomavirus (HPV)</td>
<td>Not recommended</td>
</tr>
<tr>
<td>Influenza (Inactivated)</td>
<td>Recommended</td>
</tr>
<tr>
<td>MCV4, PCV 13, PPS23</td>
<td>Inadequate data for specific recommendation</td>
</tr>
<tr>
<td>IPV</td>
<td>May be used if needed</td>
</tr>
<tr>
<td>Td</td>
<td>Should be used if otherwise indicated</td>
</tr>
<tr>
<td>TdaP</td>
<td>Recommended</td>
</tr>
<tr>
<td>Varicella, LAIV, MMR, Zoster</td>
<td>Contraindicated</td>
</tr>
</tbody>
</table>

**Source:** Gruber M. Annecy maternal immunization meeting. 2012
Infants are protected from symptomatic influenza A virus infection by transplacentally acquired antibody (Puck 1980)

Passive maternal antibody to influenza:
- delays the onset of influenza disease
- decreased the severity of influenza disease (Reuman 1987)

Maternal immunization increases antibody transmission to the infant (Englund 1993)
Immunization of Women During Pregnancy is NOT New

• 1879: Maternal immunization with vaccinia conferred protection to smallpox in infants
• 1938: Maternal immunization with crude whole cell pertussis vaccine given multiple times conferred protection of infants to pertussis
• 1961: Maternal immunization with tetanus toxoid prevented maternal mortality as well as neonatal tetanus in New Guinea
Considerations for Vaccination During Pregnancy

- Disease burden in mothers and infants versus disease burden predominantly in infant or mother.
- Immunogenicity/effectiveness:
  - Immune response in mother.
  - Kinetics of antibody transfer.
  - Influence of maternal antibody on infant immune responses.
- Safety.
- Regulatory and legal considerations.
- Programmatic.
- Public perception/risk communication.
- Advocacy/demand creation.
- Financial.

Partially adapted from: ACIP. MMWR 2008; 57: 580 and Ortiz JR Vaccine 2012.
INFLUENZA DURING PREGNANCY

- 1918: ~50% mortality associated with infection during pregnancy with highest rates in later pregnancy*
- 1957: 50% of women of childbearing age who died of influenza were pregnant; 10% of all influenza deaths that season were in pregnant women (most in latter half of pregnancy)**
- 1970-1980’s: Case reports of complications—many in later stages of pregnancy, with high rates of resp. failure***
- 2009 H1N1 Pandemic: increased rates, severe outcomes in US, UK, Argentina, Australia****

*Harris. JAMA 1919;14:978;
***Neuzil et al Inf Dis Clin N Am 2001;15:123
****Jamieson Lancet 2009
Good evidence that infants are protected from symptomatic influenza by transplacentally acquired antibody:

- Undetectable flu antibody in cord blood of infants who are hospitalized with influenza\(^1\)
- Delayed onset and decreased severity of disease in infants with higher antibody levels \(^2\)

Maternal immunization increases the amount of antibody transmitted to infants\(^3\)

1. Puck et al, J Infect Dis 1980; 142:844-9;
Influenza is a serious disease in the youngest children

Influenza-associated deaths per 100,000 US children, 2003-4

Excess Hospitalizations of Influenza per 10,000 Children/Year By Age


Pandemic Influenza A (H1N1) : Age Specific Hospitalization Rates

Australia

Argentina

*The rates for pandemic (H1N1) 2009 are from 15 June to 21 August 2009 whereas the rates for seasonal influenza are averaged annual rates (i.e. for a full influenza season). Source: NETEPi database
EFFICACY: Maternal Immunization with Influenza in Low Resource Countries*

- **Study design:**
  - Randomized controlled trial carried out in Bangladesh, 2004-5.
  - 340 pregnant women received either inactivated influenza vaccine or pneumococcal polysaccharide vaccine (control) during 3rd trimester.
  - Women followed through pregnancy and women/babies through 6 M after birth.

- **Results:**
  - Maternal TIV decreased respiratory illness with fever:
    - 29% among infants;
    - 36% among their mothers.
  - Vaccine efficacy against laboratory-confirmed influenza among newborns was 63%.

- **Caveats:**
  - Small sample size
  - Laboratory testing not optimal
  - Not placebo-controlled

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*From the New England Journal of Medicine*

Effectiveness of Maternal Influenza Immunization in Mothers and Infants

K. Zaman, M.B., B.S., Ph.D., Eliza Roy, M.B., B.S., D.C.H.,
Shams E. Arifeen, M.B., B.S., Dr.P.H., Mahbubur Rahman, M.B., B.S., Ph.D.,
Rubhana Raqib, Ph.D., Emily Wilson, M.H.S., Saad B. Omer, M.B., B.S., Ph.D.,
Nigar S. Shahid, M.B., B.S., M.P.H., Robert E. Breiman, M.D.,
and Mark C. Steinhoff, M.D.

H1N1 2009 influenza virus infection during pregnancy in the USA

Denise J Jamieson, Margaret A Honein, Sonja A Rasmussen, Jennifer L Williams, David L Seward, Matthew S Biggerstaff, Stephen Lindstrom, Janice K Louie, Cara M Christ, Susan R Bohm, Vincent P Fonseca, Kathleen A Ritger, Daniel J Kuhles, Paula Eggers, Hollianne Bruce, Heidi A Davidson, Emily Lutterloh, Meghan L Harris, Colleen Burke, Noelle Cocoras, Lyn Finell, Kitty F MacFarlane, Bo Shu, Sonja J Olsen, and the Novel Influenza A (H1N1) Pregnancy Working Group*

• ~6% of deaths in US from pandemic (H1N1) 2009 Influenza are among pregnant women (based on 484 H1N1 deaths reported to CDC by August 21, 28 of whom were pregnant)

• Pregnant women ~1% of the general population
Transplacentally-acquired Influenza Vaccine-specific Antibody in US Infants*

Antibody to influenza A and B in infants following maternal immunization with TIV or TT (control)

*Englund et al, JID 1993;68:647
Maternal Influenza Vaccine Increases the Antibody Transferred To Infants *

Antibody to influenza A and B in mothers and their infants following maternal immunization with influenza vx or tetanus toxoid vx.

Safety of influenza vaccines in pregnancy (1)

- Influenza vaccination (TIV) is an essential element of prenatal care because pregnant women are at increased risk of serious illness due to influenza.

- Vaccination is recommended at any time in pregnancy, before and during the influenza season.

- No study to date has shown an adverse consequence of inactivated influenza vaccine in pregnant women or their offspring.

- Data from an observational cohort study in Canada and from a birth and infant health registry in the United States did not point to any safety concerns related to pandemic vaccines among women during gestation or their offspring. Several studies on the safety of pandemic vaccines among pregnant women are still being completed in other regions.

- GACVS has established a subgroup on safety during pregnancy issues that is reviewing safety issues related to the use of influenza vaccines during pregnancy and lactation.

ACOG Committee Opinion, Obstet Gynecol Vol16;No.4:1006,Oct.2010
GACVS advice: Safety of Influenza vaccines in pregnancy (3)

- 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 vaccines' benefits to women are often included in product labelling on pregnancy and lactation.

- Further action by GACVS (Dec 2011):
  - continue to monitor and report adverse events in pregnant women following the use of influenza vaccines
  - review relevant evidence
  - include methodological points for planning and analysis of clinical trials and post marketing studies.
NEPAL MATERNAL INFLUENZA IMMUNIZATION STUDY

Helen Teaching

Informed Consent

Pregnancy testing

Study Blood draw
Excess Hospitalization of Low Risk Women During Influenza and Non-Influenza Season

Adapted from Neuzil et al. Am J Epi 1998;148:1094
Zaman 2008: TIV in Bangladesh
- 25-45% clinical effectiveness against nonspecific criteria

Sheffield 2011: TIV given to pregnant women 2003-2004 (non-randomized)
- 2889 women received TIV; 1998 matched controls
- Decrease flu+ disease in women: 99% efficacy

Observational studies using administrative databases with mixed findings:
- Black 2004: no benefit to mother or child
<table>
<thead>
<tr>
<th><strong>RCT Endpoint</strong></th>
<th><strong>Nepal (Steinhoff)</strong></th>
<th><strong>Mali (Levine)</strong></th>
<th><strong>South Africa (Madhi)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Safety and efficacy in mothers and infants</td>
<td>Safety and efficacy in mothers and infants</td>
<td>Safety and efficacy in mothers (without HIV) and infants. Safety and immuno in mothers with HIV and infants.</td>
</tr>
<tr>
<td><strong>Years</strong></td>
<td>2010-2013</td>
<td>2011-13</td>
<td>2011-2013</td>
</tr>
<tr>
<td><strong>Sample Size</strong></td>
<td>3,000</td>
<td>5,440</td>
<td>HIV-:2,100 HIV+:180 (year 1)/ 789 (year 2)</td>
</tr>
<tr>
<td><strong>Vaccines</strong></td>
<td>Vaxigrip/placebo</td>
<td>Vaxigrip/Menactra</td>
<td>Vaxigrip/placebo</td>
</tr>
<tr>
<td><strong>Geography</strong></td>
<td>Rural</td>
<td>Urban</td>
<td>Urban</td>
</tr>
<tr>
<td><strong>Infant Mortality</strong></td>
<td>47/1,000 l-b</td>
<td>102/1,000 l-b</td>
<td>44/1,000 l-b</td>
</tr>
<tr>
<td><strong>HIV prevalence</strong></td>
<td>&lt;1%</td>
<td>2.3%</td>
<td>29%</td>
</tr>
<tr>
<td><strong>Climate/Influenza Seasonality</strong></td>
<td>Sub-tropical/Year Round</td>
<td>Tropical/Unknown</td>
<td>Temperate/ Seasonal</td>
</tr>
</tbody>
</table>

- Clinicaltrials.gov
Evaluation of Safety of Influenza Vaccination During Pregnancy

- No systematic review currently available
- 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: 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
recommending that the vaccine should not be administered during pregnancy unless there is definite risk of group A meningococcal disease, and lactating women should not be given the vaccine since it is not known whether it is excreted in breast milk. The Committee noted that this kind of precautionary statement has also been used for other inactivated vaccines, including other meningococcal conjugate vaccines, and is not based on any known risks to these groups. **Given the clear benefits of the vaccine, the increased risk of disease in the geographical area and past experiences using similar vaccines in comparable conditions, GACVS supported WHO’s technical guidance that MenAfriVac should be offered to pregnant and lactating women residing in the meningitis belt during any stage of pregnancy or lactation. . . .**
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Pregnant women</th>
<th>Non-pregnant</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hulka Obstet Gynecol 1964</td>
<td>Nonrandomized cohort; 2 doses whole virus</td>
<td>225</td>
<td>44</td>
<td>Similar pattern of rise and fall of influenza titers</td>
</tr>
<tr>
<td>Murray J Clin Micro 1979</td>
<td>Prospective cohort; ‘76 monovalent whole virus</td>
<td>26</td>
<td>18</td>
<td>No significant difference in GMT HAI antibody between pregnant and non-pregnant or by trimester</td>
</tr>
<tr>
<td>Sumaya 1976</td>
<td>Conven. sample, ‘76 monovalent whole virus</td>
<td>40</td>
<td></td>
<td>HAI antibody similar to nonpregnant adults in another trial.</td>
</tr>
<tr>
<td>Englund JID 1993</td>
<td>TIV in third trimester</td>
<td>13</td>
<td></td>
<td>All 13 seroconverted</td>
</tr>
<tr>
<td>Steinhoff NEJM 2010</td>
<td>TIV</td>
<td>311</td>
<td>0</td>
<td>Good immunogenicity in mothers with antibody persisting for up to 6 months in infants</td>
</tr>
<tr>
<td>Risk Factor</td>
<td>RR Hospitalization</td>
<td>RR Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------------</td>
<td>--------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>1.0 (0.8-1.1)</td>
<td>0.8 (0.7–1.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory Disease</td>
<td>3.3 (2.0–5.8)</td>
<td>7.8 (4.9–26.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>1.8 (1.2–2.6)</td>
<td>1.7 (1.5–2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.9 (0.5–1.7)</td>
<td>4.0 (3.1–6.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac Disease</td>
<td>2.0 (1.5–2.2)</td>
<td>9.2 (5.4–10.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Disease</td>
<td>4.4 (4.2–4.5)</td>
<td>22.7 (21.0–25.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver Disease</td>
<td>3.5 (3.2–15.7)</td>
<td>17.4 (11.6–28.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological Disease</td>
<td>1.1 (0.9–1.3)</td>
<td>13.1 (8.4–32.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune Compromised</td>
<td>24.3 (16.1–32.6)</td>
<td>27.7 (14.0–66.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>6.8 (4.5–12.3)</td>
<td>1.9 (0.0–2.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

### Neonatal Outcomes after Influenza Immunization During Pregnancy - Steinhoff et al. CMAJ 2012; 184:645

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control vaccine n = 166</th>
<th>Influenza vaccine n = 161</th>
<th>p value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, mean, g</td>
<td>3027</td>
<td>3117</td>
<td>0.09</td>
<td>–</td>
</tr>
<tr>
<td>Gestational age, mean, wk</td>
<td>39.4</td>
<td>39.5</td>
<td>0.6</td>
<td>–</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>63 (38.0)</td>
<td>45 (28.0)</td>
<td><strong>0.05</strong></td>
<td>0.63 (0.4–1.0)</td>
</tr>
<tr>
<td>Weighed less than &lt; 2500 g</td>
<td>13 (7.8)</td>
<td>1 (4.4)</td>
<td>0.2</td>
<td>0.53 (0.2–1.4)</td>
</tr>
<tr>
<td>Born before 37 weeks’ gestation</td>
<td>14 (8.4)</td>
<td>10 (6.2)</td>
<td>0.4</td>
<td>0.72 (0.3–1.7)</td>
</tr>
</tbody>
</table>

**Note:** CI = confidence interval, OR = odds ratio.
*Unless stated otherwise.

### Comments:

1) Secondary analysis
2) Control vaccine = pneumococcal vaccine
3) Increased impact in infant when flu virus circulating
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.
- Further action by GACVS (Dec 2011):
  - Continue to monitor and report adverse events in pregnant women following the use of influenza vaccine.
  - Review relevant evidence.
  - Include methodological points for planning and analysis of clinical trials and post-marketing studies.
  - GACVS meeting to discuss maternal immunization.
UPDATE ON SAFETY OF INFLUENZA VACCINES DURING PREGNANCY

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
## 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 clinical 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 received vx 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>Gisslser et al ESPID 2012</td>
<td></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></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 immunized with 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>
Infants are protected from symptomatic influenza A virus infection by transplacentally acquired antibody (Puck 1980)

Passive maternal antibody to influenza:
- delays the onset of influenza disease
- decreased the severity of influenza disease (Reuman 1987)

Maternal immunization increases antibody transmission to the infant (Englund 1993)
BIRTH ASSESSMENT and WEEKLY ASSESSMENTS

Birth Assessment

Weekly Assessment

Transport of specimens
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
Safety of maternal influenza immunization in controlled studies

- Many “older” studies reported but often not well controlled
- Over 100 pregnant women received 1976 swine influenza vaccine (A/New Jersey/8/76)\(^1-3\)
- Recent prospective\(^4\) and retrospective\(^5-6\) studies of safety of TIV during pregnancy
- No significant adverse reactions, including fever, local or systemic reactions, or fetal complications associated with flu vaccine in literature\(^7\)
- Canadian, European, US studies of influenza vaccine in healthy and HIV+ pregnant women with H1N1: good safety, immunogenicity
- At least 3 international field trials underway (S. Africa, Nepal, Nepal)

1. Sumaya CV et al. JID 1979;140:141-46
Is inactivated influenza vx vs. no intervention or non-influenza vx in pregnant women effective to prevent influenza infection and severe outcomes of infection in pregnant women?

- **Zaman 2008:**
  - Effectiveness against respiratory illness with fever was 36%, implying a significant reduction achieved by influenza vaccination of pregnant women.

- **Englund 1993:**
  - No information on vaccine efficacy in pregnant women and the impact on laboratory-confirmed influenza (Note: not studied).

- **Hulka 1964:**
  - No significant difference in effectiveness of influenza vaccine vs. other vaccine against MAARI.

**Excluded:** Decades of immunogenicity studies, observational studies, effectiveness studies in non-pregnant adults, outcomes including newborn influenza or birthweight.

*http://www.who.int/immunization/position_papers/influenza_grad_maternal_outcomes.pdf*
ACIP recommends that providers of prenatal care implement a Tdap immunization program for all pregnant women. Health-care personnel should administer a dose of Tdap during each pregnancy irrespective of the patient’s prior history of receiving Tdap. If not administered during pregnancy, Tdap should be administered immediately postpartum.

ACIP. October 24, 2012
EXAMPLE: Maternal Immunization to Prevent Infant RSV Disease

- Most urgent need for protection against RSV is during first months of life, when vaccines are poorly immunogenic.

- >75% of hospitalization for significant RSV disease occurs in full term, healthy infants.

- Clinical studies with RSV subunit vaccines show good immunogenicity and lack of reactogenicity in postpartum women.

- US government regulation (FDA): Teratogenicity of PFP vaccine in animal model required and performed prior to human trial.