Disclosure

• No conflict of interest to declare
Acknowledgements

• Dr. Deborah Money
• Dr. Vanessa Poliquin
• Dr. Chelsea Elwood
• Dr. Reka Gustafson
Objectives

• To review principles of Immunization in pregnancy

• To review specific vaccines that are indicated and contraindicated in the perinatal period

• Influenza and Pertussis
Vaccination as Preventive Medicine.

Routine Immunizations Led to the Eradication of...

**Smallpox** (vaccine in 1798)
- 20th Century: An estimated 300+ million deaths
- Eradicated by 1979

**Polio** (vaccine in 1955)
- 20th Century: Paralyzed or killed more than 500 million people
- Eradicated by 1988 in the U.S. and Western Hemisphere*

* Eradication of polio has run into major setbacks with recent outbreaks in Somalia and Syria, which points to the importance of continued vaccinations.

Because of Immunizations for Deadly Disease:
- Worldwide 2 to 3 million deaths prevented annually.
Maternal Benefit

- Susceptibility
- Vaccine efficacy
- Engaged in care
- Can immunize pre, during post pregnancy

Benefit for Fetus/Neonate

- Immune system is immature and relatively ineffective
- Active immunization unsuccessful in newborns (except Hepatitis B)
- No protection until first vaccine series
Vaccine Safety

Maternal Safety

- No increase in adverse reactions to vaccines
- No increased risk of pregnancy complications associated with vaccinations
- Large RCTs examining the efficacy and safety of vaccine use in pregnancy limited
- VAERS

Safety for Fetus/Neonate

- No known embryotoxicity or teratogenicity with approved vaccines
- Even live attenuated viruses – although theoretical concern – have no proven adverse events in fetus from vaccination
- VAERS
How does this work?

- Maternal Ab passively transferred to infant after 17-20 wks GA
- All subclasses of IgG are readily transferred
- Passive & active transport of IgG = 20-200% maternal blood levels
- Half life ~ 4 weeks with detectable levels of passive maternal antibody in neonate for 6-12 months
Types of Vaccines

- Live, attenuated
- Inactivated
- Subunit
- Toxoid
- Conjugate
- DNA
- Recombinant vector

What can be offered in pregnancy??
## Non-Live Vaccine Summary in Pregnancy

### Non-Live

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Risk/Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis A</td>
<td>Low theoretical risk</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>No apparent fetal risk</td>
</tr>
<tr>
<td>Pneumococcus</td>
<td>Indicated in high-risk patients</td>
</tr>
<tr>
<td>Meningococcus</td>
<td>Safe and efficacious in pregnancy</td>
</tr>
<tr>
<td>Cholera</td>
<td>No data on safety</td>
</tr>
<tr>
<td>Plague</td>
<td>No data on safety</td>
</tr>
<tr>
<td>Typhoid</td>
<td>No data on safety</td>
</tr>
<tr>
<td>Some preparations are live</td>
<td></td>
</tr>
<tr>
<td>Diphtheria/tetanus</td>
<td>No evidence of teratogenicity</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>No data on safety</td>
</tr>
<tr>
<td>(inactivated Japanese encephalitis vaccine)</td>
<td></td>
</tr>
</tbody>
</table>

**Appropriate in the presence of medical indication**

- Vaccines recommended for pregnant women at risk
- No safety data available, but no adverse effects reported; high-risk patients should therefore be vaccinated
- Vaccine to be administered using same guidelines as for non-pregnant patients
- To be used if high-risk situation only (e.g., outbreak)
- Vaccination to be considered only if benefits outweigh risk
- To be considered only in high-risk cases (e.g., travel to endemic areas)
- Susceptible women to be vaccinated as per general guidelines for non-pregnant patients
- Not to be given routinely in pregnancy, as theoretical risk exists
- Consider only if travel where risk exposure is high (benefit > risk)
Recommended Vaccines for Women of Reproductive Age

- Diptheria, Tetanus, Pertussis
- Hepatitis A, Hepatitis B
- HPV
- Influenza
- Measles, mumps, rubella
- Meningococcus
- Polio
- Varicella

Recommended Vaccines in Pregnancy

- **Influenza** (November-April)
- Consideration for:
  - Hepatitis B
  - TdAP
  - Polio
  - Pneumococcal
  - Meningococcal
  - Travel vaccines where required

- PHAC 2016
# Live Vaccine Summary in Pregnancy

## SOGC Guideline

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Indication for use in pregnancy</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Live</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles</td>
<td>Contraindicated</td>
<td>No known fetal effects, but theoretical increased risk of preterm labour</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and low birthweight with live vaccine</td>
</tr>
<tr>
<td>Mumps</td>
<td>Contraindicated</td>
<td>As above—see text</td>
</tr>
<tr>
<td>Rubella</td>
<td>Contraindicated</td>
<td>As above—see text</td>
</tr>
<tr>
<td>Varicella</td>
<td>Contraindicated</td>
<td>No known fetal effects. Not reason for termination</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Varicella zoster immunoglobulin to be considered if pregnant woman</td>
</tr>
<tr>
<td></td>
<td></td>
<td>exposed to virus</td>
</tr>
<tr>
<td>Poliomyelitis Sabin/ Salk</td>
<td>To be considered in high-risk situations (inactivated preparation)</td>
<td>Consider if pregnant woman needs immediate protection (high-risk situation/travel) No known fetal effects</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Generally contraindicated unless high-risk situation</td>
<td>No data on fetal safety, although fetuses exposed have not demonstrated complications Not a reason for pregnancy termination If travel to high-risk endemic area unavoidable, suggest vaccination</td>
</tr>
<tr>
<td>Influenza</td>
<td>Indicated in pregnancy, primarily for protection at &gt; 20 weeks when risk is greatest</td>
<td>No adverse effects in over 2000 fetuses exposed Influenza may be associated with greater morbidity in pregnancy, so immunization recommended</td>
</tr>
<tr>
<td>Rabies</td>
<td>No indication of fetal anomalies</td>
<td>Risks from inadequate treatment significant Pregnancy not contraindication to post-exposure prophylaxis</td>
</tr>
<tr>
<td>Vaccinia</td>
<td>Contraindicated</td>
<td>Has been reported to cause fetal infection</td>
</tr>
</tbody>
</table>
Influenza

- Among the top 10 leading causes of death in Canada
- Every season → 10% of pregnant women diagnosed with influenza
  - ↑ hospitalization
    - 1 per 1000 pregnant women
  - ↑ cardiopulmonary complications
  - ↑ death
    - H1N1 → 5% of deaths occurred in pregnant women (1% of the population)

Influenza

- Pregnancy complications associated with maternal influenza infection
  - ↑ Spontaneous abortion
  - ↑ Stillbirth and neonatal death
  - ↑ Preterm birth
  - ↑ Low birth weight infants

2016 Trivalent Inactivated Influenza Vaccine (TIIV) for Adults

- Fluviral
- Agriflu
- Both contain
  - A/California/7/2009 (H1N1)
  - A/Hong Kong/4801/2014 (H3N2)
  - B/Vaccine types available for flu
- Egg Allergy: even with anaphylaxis, can safely receive all influenza vaccines
Influenza vaccine- ‘twofer’

- Recommended for all pregnant women
  - 15% vaccination rate pre-H1N1
  - 37-42% vaccination rate during H1N1
  - Variable rates since H1N1 (10-40%)
- Primarily indicated for maternal benefits
  - 30-50% reduction if febrile influenza-like illness
- Infant benefits → important consideration
  - Infants <6 months have the highest rate of pediatric influenza hospitalizations
  - No influenza vaccines are licensed for this vulnerable age-group

Vaccine effectiveness = 63% (95% CI 5-85)

Conclusion: 5 pregnant women would need to be vaccinated to prevent a single case of respiratory illness+fever in a mother or infant.
Pertussis

- Pertussis (whooping cough) highly infectious respiratory illness - *Bordetella pertussis* – respiratory failure
- Disproportionately affects newborns, vast majority of deaths occurring in those aged less than three months.
- Unvaccinated older children and adults – reservoirs
- Infant vaccine schedule 2,4,6 months
- Rely on maternal transplacental IgG > breastmilk IgG
Bordetella pertussis

- One of the **top 10 causes of childhood mortality**
  - 294,000 pediatric deaths per year, globally
- Disproportionate burden of mortality and morbidity
  - **86%** of pertussis-related deaths in **infants <4 months**

<table>
<thead>
<tr>
<th>Review of pertussis admissions in Manitoba (n=42) between 2007-2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion &lt;1.5y</td>
</tr>
<tr>
<td>Admitted to ICU</td>
</tr>
<tr>
<td>Required supplemental O2</td>
</tr>
<tr>
<td>Required intubation and ventilation</td>
</tr>
<tr>
<td>Mean length of intubation</td>
</tr>
<tr>
<td>(IQR 2-7d)</td>
</tr>
<tr>
<td>Death</td>
</tr>
</tbody>
</table>

Incidence of laboratory-confirmed pertussis by age group, England and Wales, 1998–2012
Bordetella pertussis in Canada: 2012

- 7x increase in national incidence
  - 4800 cases nationally
  - 104 hospitalizations (2-fold increase)
  - 3 deaths (otherwise healthy)

- Several Canadian jurisdictions

- Incidence highest in infants
  - 72.2 cases per 100,000 among infants <4 mo
### Maternal vaccination

**TABLE 1**

Newborn antibody levels stratified whether mothers Tdap

<table>
<thead>
<tr>
<th>Outcome Antibodies</th>
<th>Mother did not receive Tdap, mean (SEM) n = 52</th>
<th>Mother received Tdap, mean (SEM) n = 52</th>
<th>P value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria</td>
<td>0.571 (0.157)</td>
<td>1.970 (0.291)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Tetanus</td>
<td>4.237 (1.381)</td>
<td>9.015 (0.981)</td>
<td>.004</td>
</tr>
<tr>
<td>PT</td>
<td>11.010 (1.796)</td>
<td>28.220 (2.768)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>FHA</td>
<td>26.830 (4.022)</td>
<td>104.15 (21.664)</td>
<td>.002</td>
</tr>
<tr>
<td>PRN</td>
<td>24.700 (5.765)</td>
<td>333.01 (56.435)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>FIM 2/3</td>
<td>82.83 (14.585)</td>
<td>1198.99 (189.937)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

<sup>FHA</sup>, filamentous hemagglutinin; <sup>FIM</sup>, fimbriae; <sup>PRN</sup>, pertactin; <sup>PT</sup>, pertussis toxin; <sup>Tdap</sup>, tetanus, reduced diphtheria, and acellular pertussis antigens vaccine.

<sup>a</sup> Significant at .05 level.

Timing of TdaP in pregnancy

Concentration and avidity of IgG to PT were significantly higher in women immunized 27-30 weeks of pregnancy.

Current Canadian recommendations (2014)

- All individuals receive one dose of Tdap in adulthood
- Vaccine is safe and immunogenic in pregnant women
- Effectiveness to prevent severe disease in newborns is not well established
- Given present epidemiology, universal vaccination in pregnancy is NOT recommended
  - Depending on regional epidemiology, Tdap may be offered during pertussis outbreaks to pregnant women >26 weeks irrespective of their immunization history

Conclusions

- Pregnancy presents an opportunity to engage women in vaccination

- Potential for both maternal and fetal/neonatal benefit

- Influenza vaccine during pregnancy is safe and recommended in flu season

- Tdap during pregnancy is safe and can be offered
  - Local outbreaks
  - When booster is required
Conclusions

- This issue is not going away
  - GBS vaccine trials
  - CMV vaccine trials
  - ZIKV vaccine development

- Ethical considerations when there is no maternal benefit
Thimerosal

- Ethyl Mercury derivative
- Used in manufacture and preservation of vaccines (multidose vials)
- Prevents microbial growth

- Influenza vaccines
- Well controlled studies do NOT link thimerosal with autism
- Autism rates have increased since thimerosal has been removed from more vaccines