

IMMUNIZATION IN PREGNANCY

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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....

STOP 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



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Benefit for Fetus/Neonate

- Immune system is immature and relatively ineffective
- Active immunization unsuccessful in newborn (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

Hepatitis A	Low theoretical risk	Appropriate in the presence of medical indication
Hepatitis B	No apparent fetal risk	Vaccine recommended for pregnant women at risk
Pneumococcus	Indicated in high-risk patients	No safety data available, but no adverse effects reported; high-risk patients should therefore be vaccinated
Meningococcus	Safe and efficacious in pregnancy	Vaccine to be administered using same guidelines as for non-pregnant patients
Cholera	No data on safety	To be used if high-risk situation only (e.g., outbreak)
Plague	No data on safety	Vaccination to be considered only if benefits outweigh risk
Typhoid	No data on safety	To be considered only in high-risk cases (e.g., travel to endemic areas)
Some preparations are live		
Diphtheria/tetanus	No evidence of teratogenicity	Susceptible women to be vaccinated as per general guidelines for non-pregnant patients
Japanese encephalitis (inactivated Japanese encephalitis vaccine)	No data on safety	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

- Diphteria, 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

Live Vaccine Summary in Pregnancy

SOGC Guideline

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

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)

Swamy GK, Heine RP (2015) *Obstet Gynecol*, 125:212-26.
Pierce et al. (2011) *BMJ*, 342:d3214.

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 (TIV) for Adults

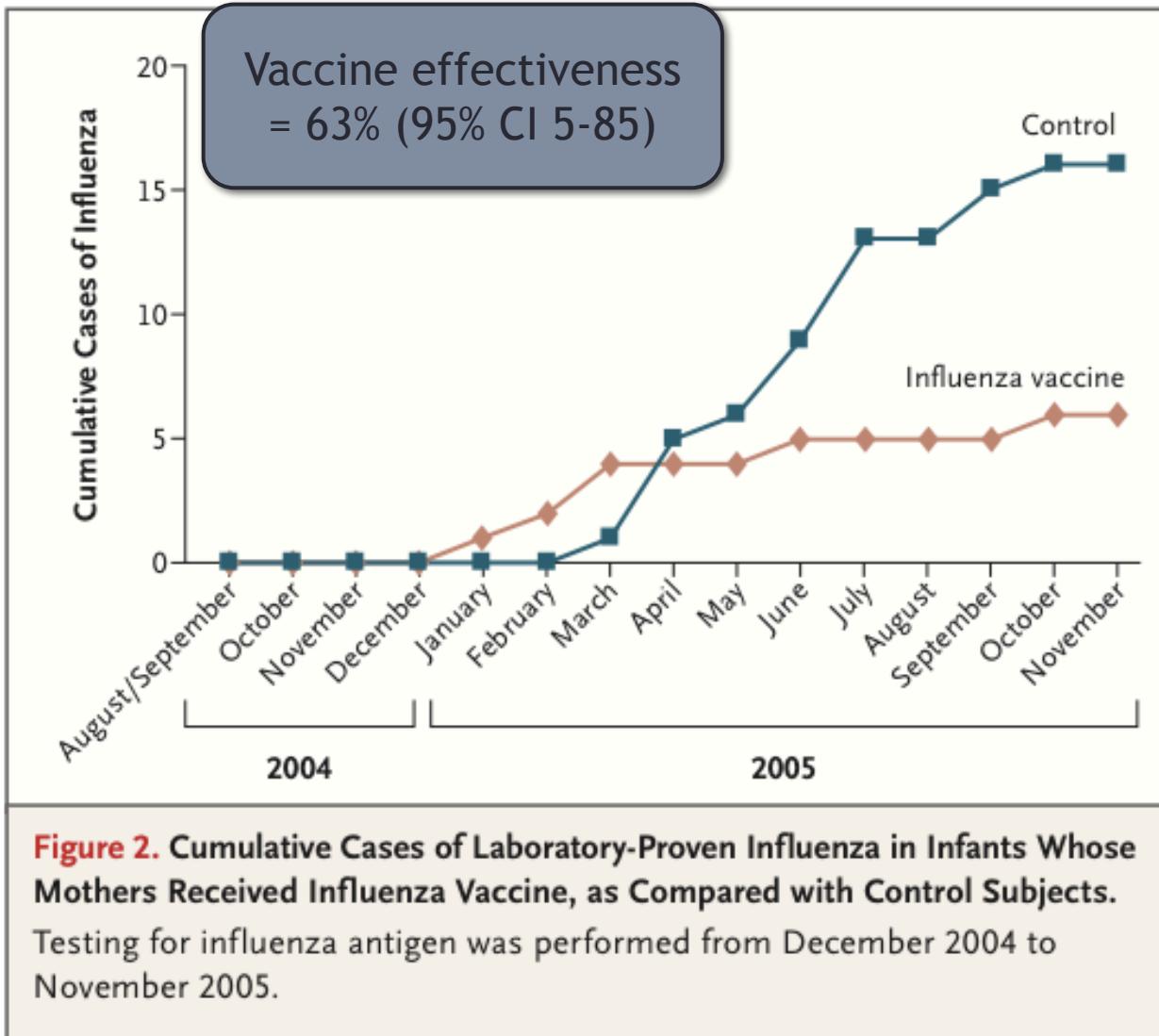
- Fluviral
- Agriflu
- Both contain
 - A/California/7/2009 (H1N1)
 - A/Hong Kong/4801/2014 (H3N2)
 - B/Vaccine types available for flu
- Egg Allergy: even with anaphylaxis, can safely receive all influenza vaccines

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

Regem (2016) CID: publication ahead of print.
Poehling (2011) AJOG, doi: 10.1016/j.ajog.2011.02.042
Gorman (2012) Vaccine, 31:213-218
Liu (2012) Can J Public Health, 103(5):e353-e538

Mother's Gift Project



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

Zaman et al (2008) NEJM, 359:1555-64.

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

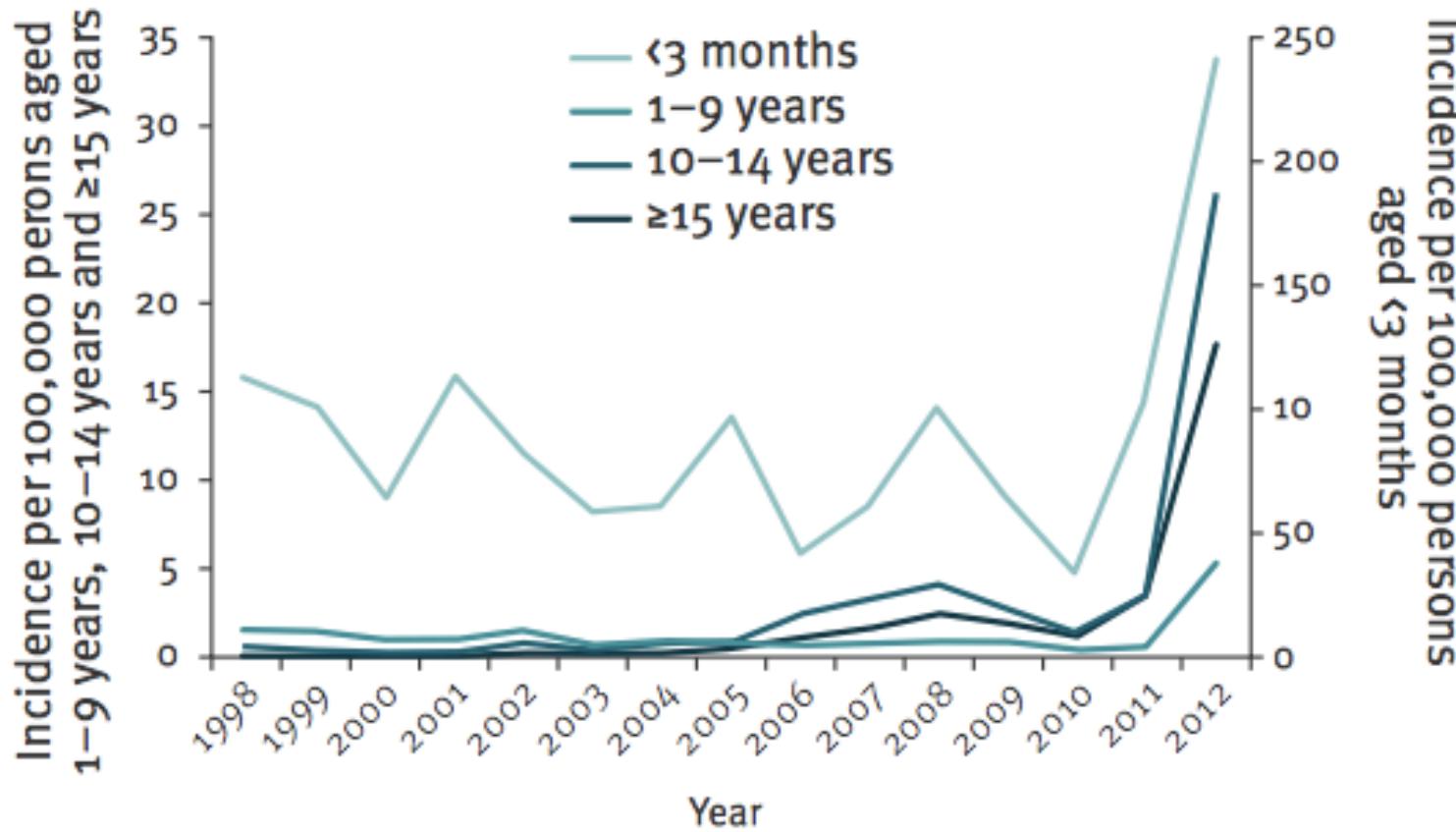
Bordetella pertussis

- 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**

Review of pertussis admissions in Manitoba (n=42) between 2007-2011

Proportion <1.5y	100%
Admitted to ICU	33%
Required supplemental O2	60%
Required intubation and ventilation	26%
Mean length of intubation	6.3d (IQR 2-7d)
Death	0%

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

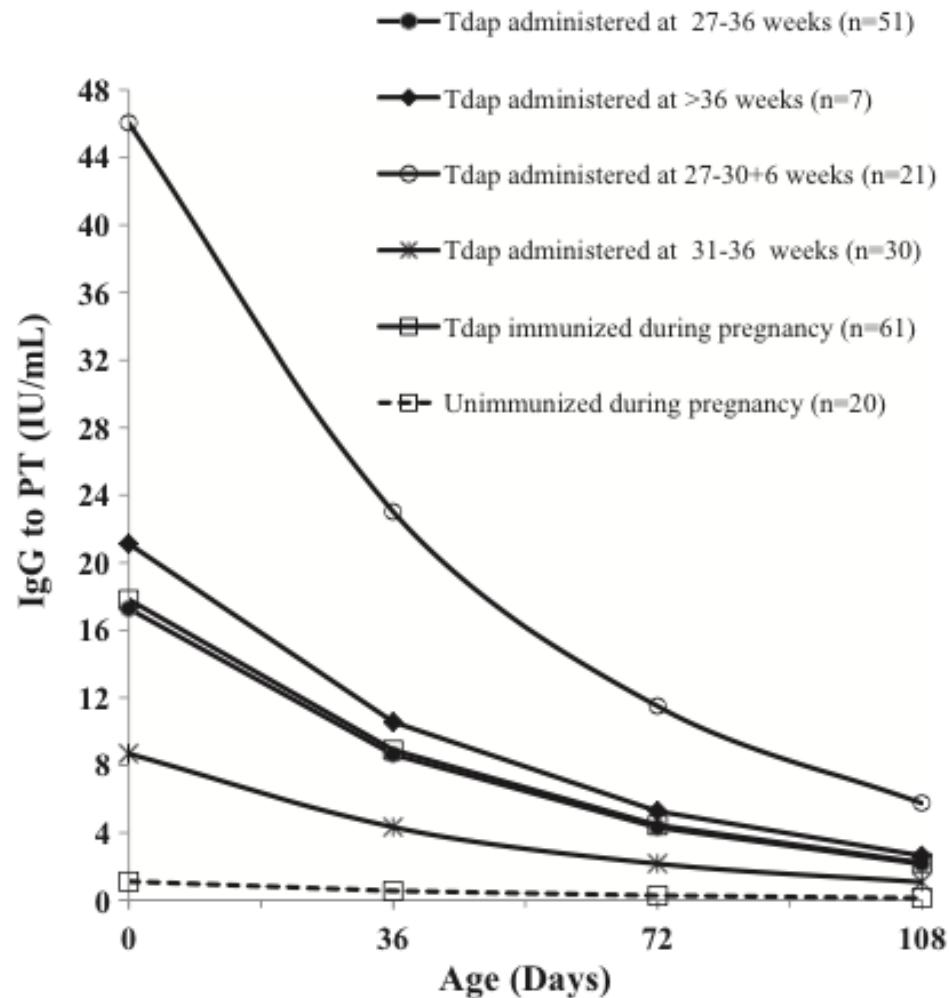
Outcome Antibodies	Mother did not receive Tdap, mean (SEM) n = 52	Mother received Tdap, mean (SEM) n = 52	P value ^a
Diphtheria	0.571 (0.157)	1.970 (0.291)	< .001
Tetanus	4.237 (1.381)	9.015 (0.981)	.004
PT	11.010 (1.796)	28.220 (2.768)	< .001
FHA	26.830 (4.022)	104.15 (21.664)	.002
PRN	24.700 (5.765)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

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

^a Significant at .05 level.

Gall. Effect of maternal immunization with Tdap. Am J Obstet Gynecol 2011.

Timing of TdaP in pregnancy



Concentration and avidity of IgG to PT were significantly higher in women immunized 27-30⁶

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