Immunization before, during and after pregnancy

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Objectives

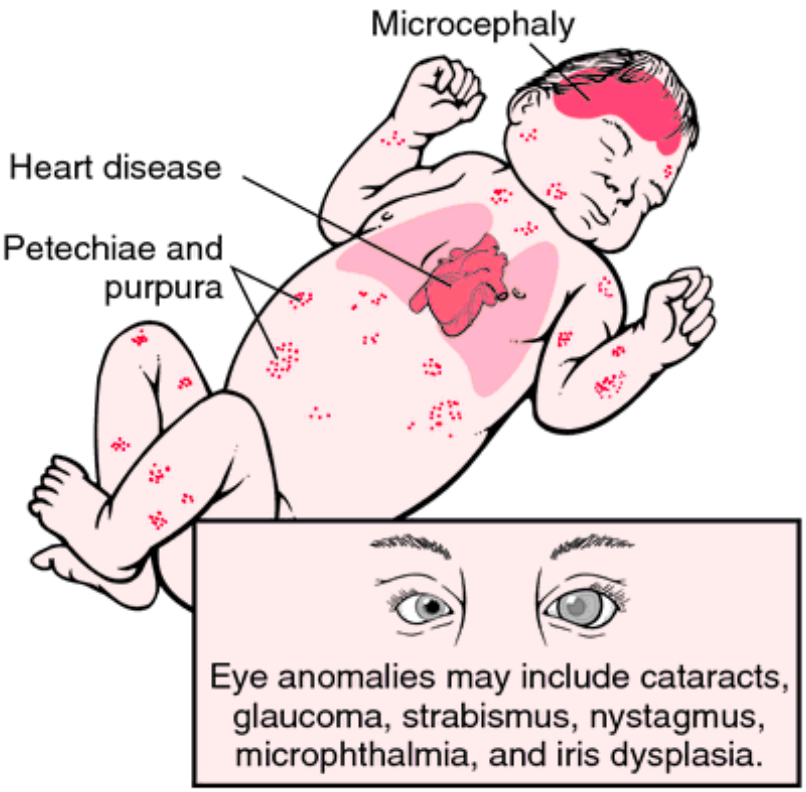
- Review determination of immune status against rubella
- Explore the existing evidence around maternal vaccination strategies for the seasonal influenza and pertussis
- List current recommendations for maternal immunization
- Recognize instances in which pneumococcal and hepatitis vaccinations are indicated during pregnancy

Immunizations in anticipation of conception and post-partum

Maternal vaccination for maternal, fetal and newborn protection: Rubella and Varicella

Rubella

- Vaccine-preventable disease
- Rubella in the mom → mild and self-limited
- Rubella in the fetus → congenital rubella syndrome (CRS)
  - 85% risk if infection at <8wk GA
  - Sensorineural deafness
  - Cardiac defects (PDA)
  - Ophthalmic defects (cataracts)
  - Developmental delay
  - etc.



Rubella vaccination

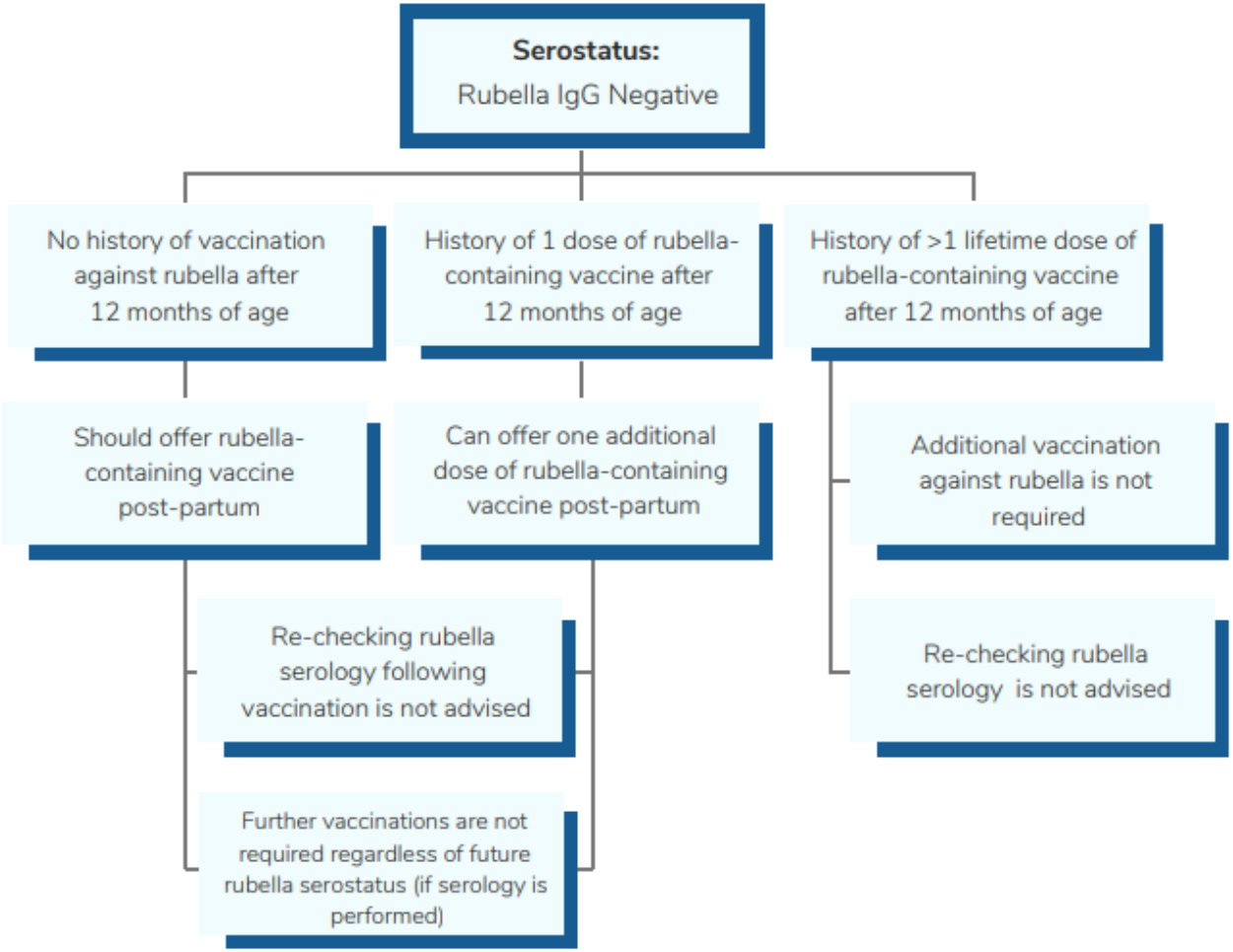
- No tx for maternal exposure to rubella → prevention through immunization
  - Majority of women in Canada are immune
  - Routine childhood vaccination
- Immunity:
  - Presence of rubella IgG
  - Documented history of immunization
- Vaccine NOT recommended in pregnancy
  - Live vaccine
  - Ideal topic to discuss pre-conception

Management of seronegative women

- 1-10% of a vaccinated population will appear seronegative on testing for rubella immunity
  - Depending on the sensitivity of test used
- Majority of seronegative women are in fact immune to rubella
  - Based on immune response to booster
- Persistent seronegativity after documented vaccination → do NOT require re-vaccination

Zealley (1982) *BMJ*, 284:382-384.
Mortimer (1981) *J Hyg 87*:131-132.

Suggested algorithm for determining need for rubella-containing vaccine



Varicella (chicken pox) in pregnancy

Maternal effects

- Flu-like illness
- Crops of maculopapules
- Pneumonitis → 5-10% pregnant women
  - Cigarette smoking
  - >100 skin lesions
- Mortality
  - More common in T3
  - ↑ age ↑ mortality

Fetal/newborn effects

- **Congenital varicella syndrome = embryopathy**
  - Chorioretinitis
  - Cerebral cortical atrophy
  - Hydronephrosis
  - Cutaneous and bony lesions
- **Neonatal varicella syndrome = no embryopathy**
  - Fulminant neonatal infection
  - **5d antepartum → 2d PP**

If varicella susceptible → vaccinate >4 weeks prior to attempting conception

- Most individuals born in Canada are immune to varicella
  - Natural infection
  - Childhood vaccination
- Can typically ascertain immunity on history
- Consider serologic screening if:
  - No history of vaccination or natural infection
  - Immigrants are most likely to be seronegative, especially if:
    - From tropical climate
    - Short time since arrival to Canada
    - Low SES
    - Rural area

Cadieux (2015) *J Immigrant Minority Health* DOI 10.1007/s10903-015-0313-y.

Immunizations during pregnancy

Maternal vaccination for maternal, fetal and newborn protection: Flu and Tdap

Influenza

- Every season → **10% of pregnant women diagnosed with influenza**
  - ↑ hospitalization
  - ↑ 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 from maternal influenza infection
  - ↑ Spontaneous abortion
  - ↑ Stillbirth and neonatal death
  - ↑ Preterm birth
  - ↑ Low birth weight infants

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

Influenza vaccine

- **Recommended for all pregnant women**
- Primarily indicated for maternal benefits
- 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

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

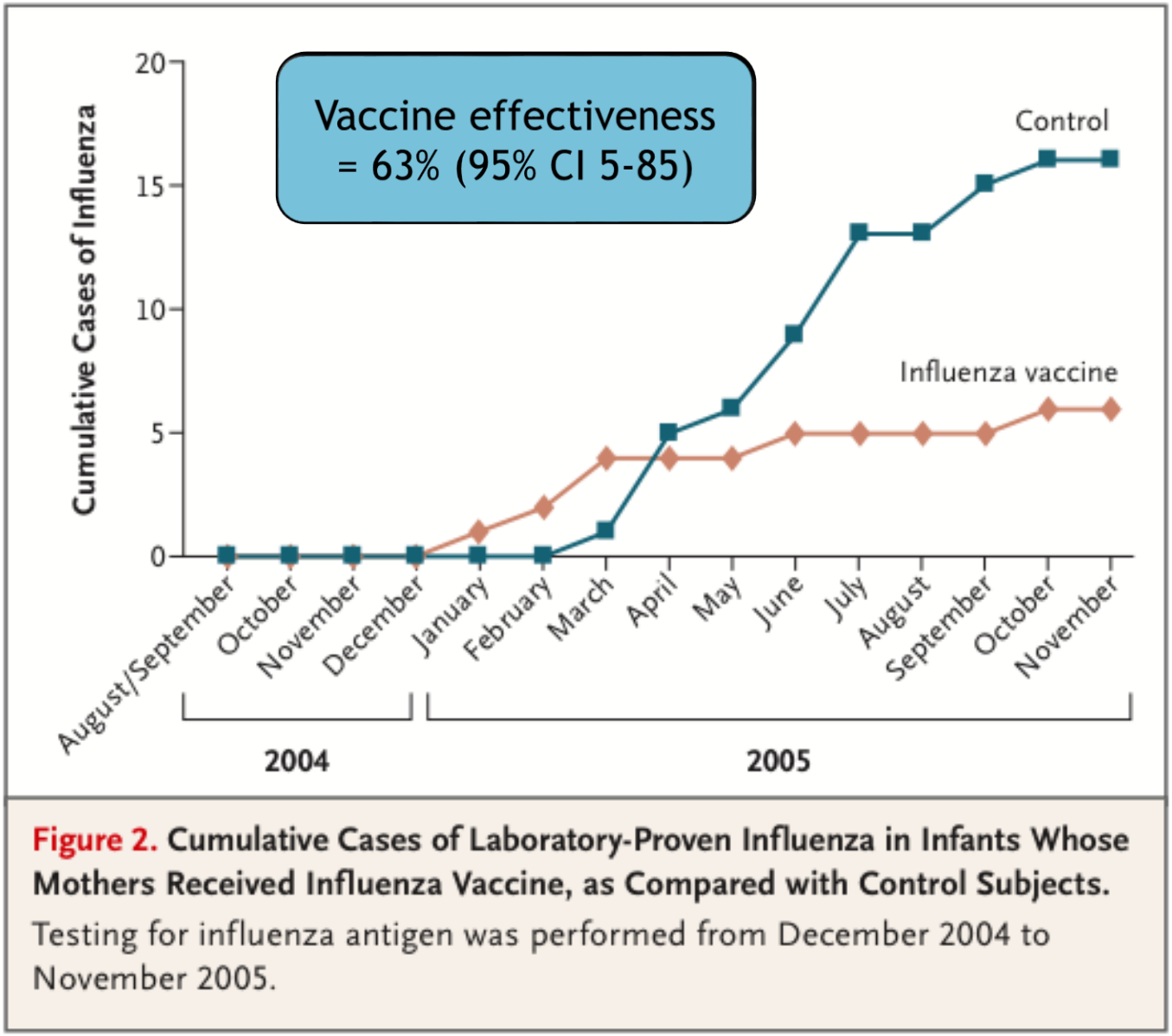


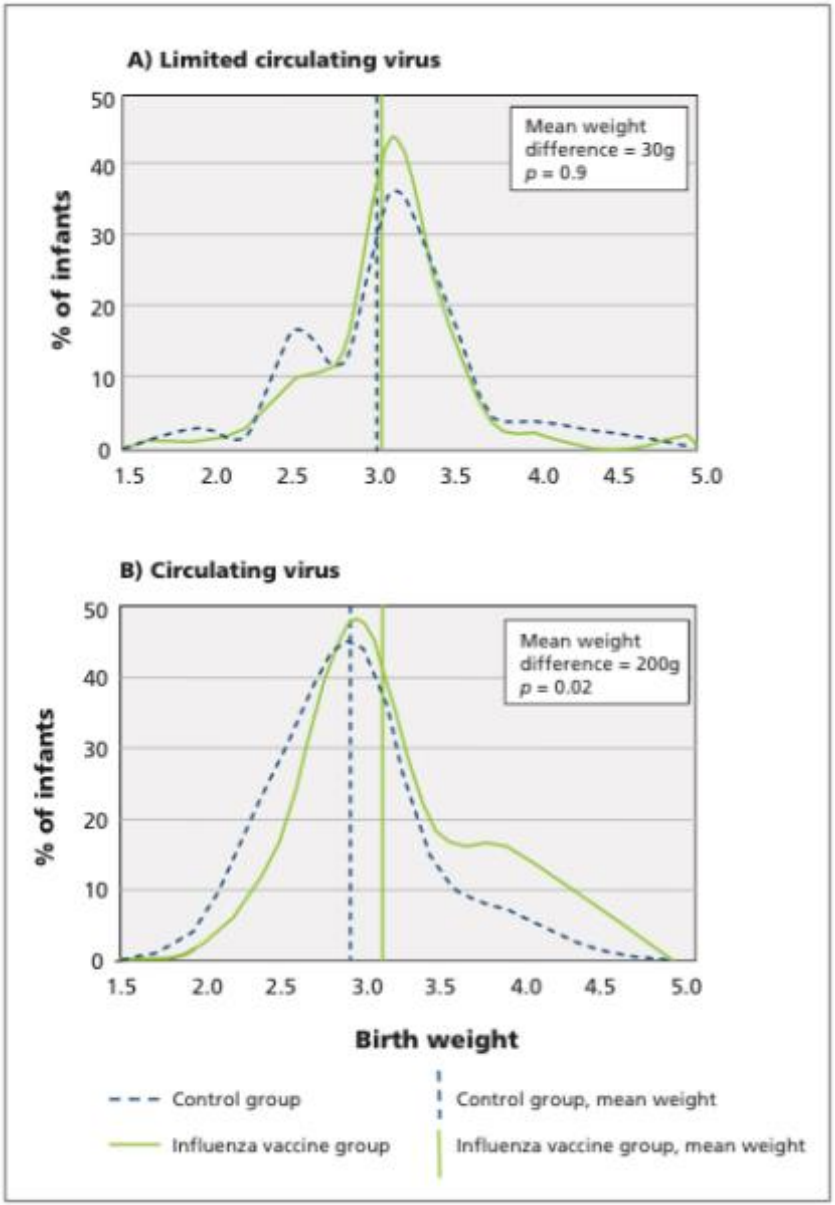
Figure 2. Cumulative Cases of Laboratory-Proven Influenza in Infants Whose Mothers Received Influenza Vaccine, as Compared with Control Subjects.

Testing for influenza antigen was performed from December 2004 to November 2005.

Mother'sGift Project

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

	SGA Infants		p-value
	Controls	Influenza vaccine	
Limited circulating virus	34.3%	29.1%	p=0.4
Circulating virus	44.8%	25.9%	P=0.03



Steinhoff et al (2012) *CMAJ*, 184(6):645-.

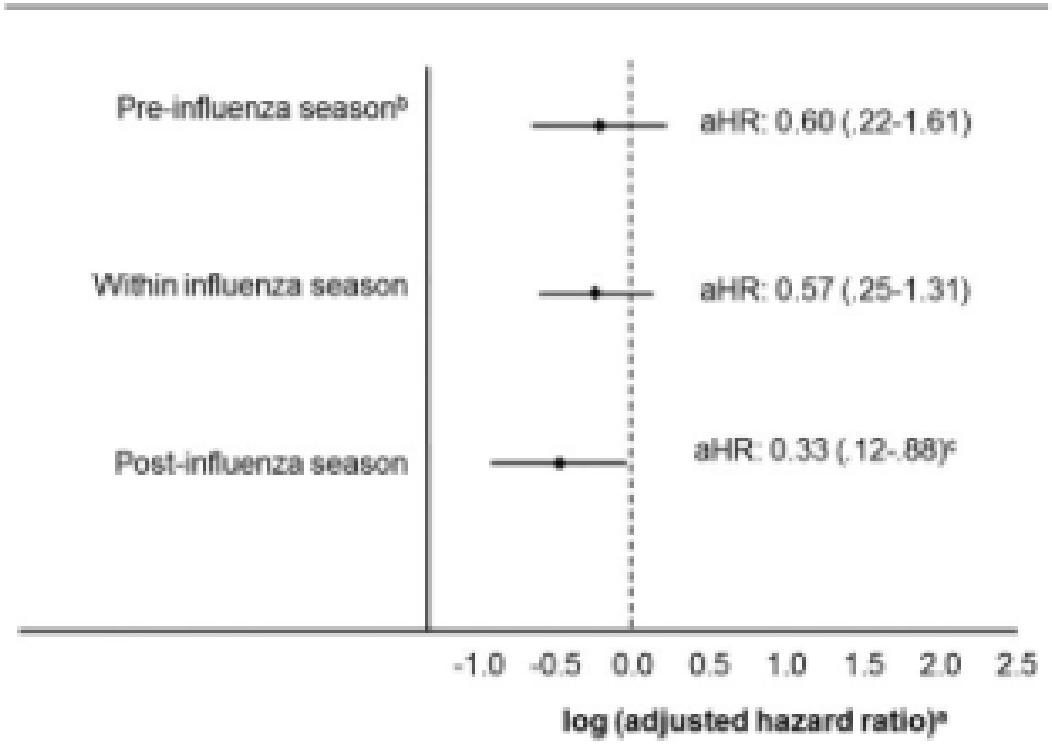
In a Canadian context…

Table 3: Association between neonatal outcomes among singleton liveborn infants (n = 11 293) and mother's receipt of seasonal influenza vaccine during pregnancy

Outcome	Maternal vaccination status; no. (%) of infants		Effect of vaccine (v. no vaccine)	
	No vaccine n = 9437*	Vaccine n = 1856*	Unadjusted OR (95% CI)	Adjusted OR† (95% CI)
Preterm birth (< 37 wk)	617 (6.5)	92 (5.0)	0.75 (0.60–0.93)	0.75 (0.60–0.94)
Low birth weight (< 2500 g)	461 (4.9)	65 (3.5)	0.71 (0.54–0.92)	0.73 (0.56–0.95)
Low birth weight at term	160 (1.7)	26 (1.4)	0.82 (0.54–1.25)	0.85 (0.56–1.29)
Small-for-gestational age (< 10th percentile)	749 (8.0)	138 (7.5)	0.93 (0.77–1.12)	0.96 (0.79–1.16)
Composite neonatal morbidity variable‡	441 (4.7)	95 (5.1)	1.10 (0.88–1.38)	1.06 (0.85–1.34)

Note: CI = confidence interval, OR = odds ratio.
*Numbers exclude infants whose mothers had missing values for adjustment covariates in the model.
†Adjusted for maternal age, high-risk status, smoking during pregnancy, marital status, parity and location of residence.
‡Includes neonatal death, asphyxia, sepsis, low Apgar score at 5 min, moderate or severe respiratory distress syndrome, intraventricular hemorrhage and acute necrotizing enterecolitis.

Legge et al. *CMAJ*, 2014; 186(4):E157.



51% reduction in rate of stillbirth among women who received the influenza vaccine

Regan et al (2016) *CID*, 62(7): online ahead of print.

Safety of Influenza Vaccine in Pregnancy

- **Active studies** of influenza immunization → no evidence of harm to mother or fetus
  - Overall sample size small, esp. in 1st trimester
- Passive surveillance of influenza immunization → no evidence of harm to mother or fetus
  - Decades of use
  - >100,00 pregnant Canadian women
  - >488,000 pregnant European women
  - Both adjuvanted, unadjuvanted and pH1N1 vaccines
- Live attenuated Influenza vaccine (FluMist®) not recommended → theoretical risk

NACI (2016) Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2016-2017. PHAC, Feb 2014.

Antepartum Influenza Vaccine

- Safe to administered during pregnancy
- Evidence supporting antenatal vaccination strategy to protect:
  - Maternal health
  - Fetal health
  - Incidence of influenza in infants <6 mo.
- More incentive to ↑ rate of influenza vaccination during pregnancy

2016-2017 NACI Recommendations

- Recommended for **all pregnant women**
- Adults and children with chronic medical conditions
- People residing in a nursing or chronic care homes
- People ≥ 65 years of age
- Children 6-59 months
- Aboriginal Peoples

Bordetella pertussis

- Respiratory pathogen
- Very young infants (<4 months) bear the highest burden of morbidity and mortality
  - **>70%** of pertussis-related hospital admissions
  - **>85%** of pertussis-related deaths

Bordetella pertussis

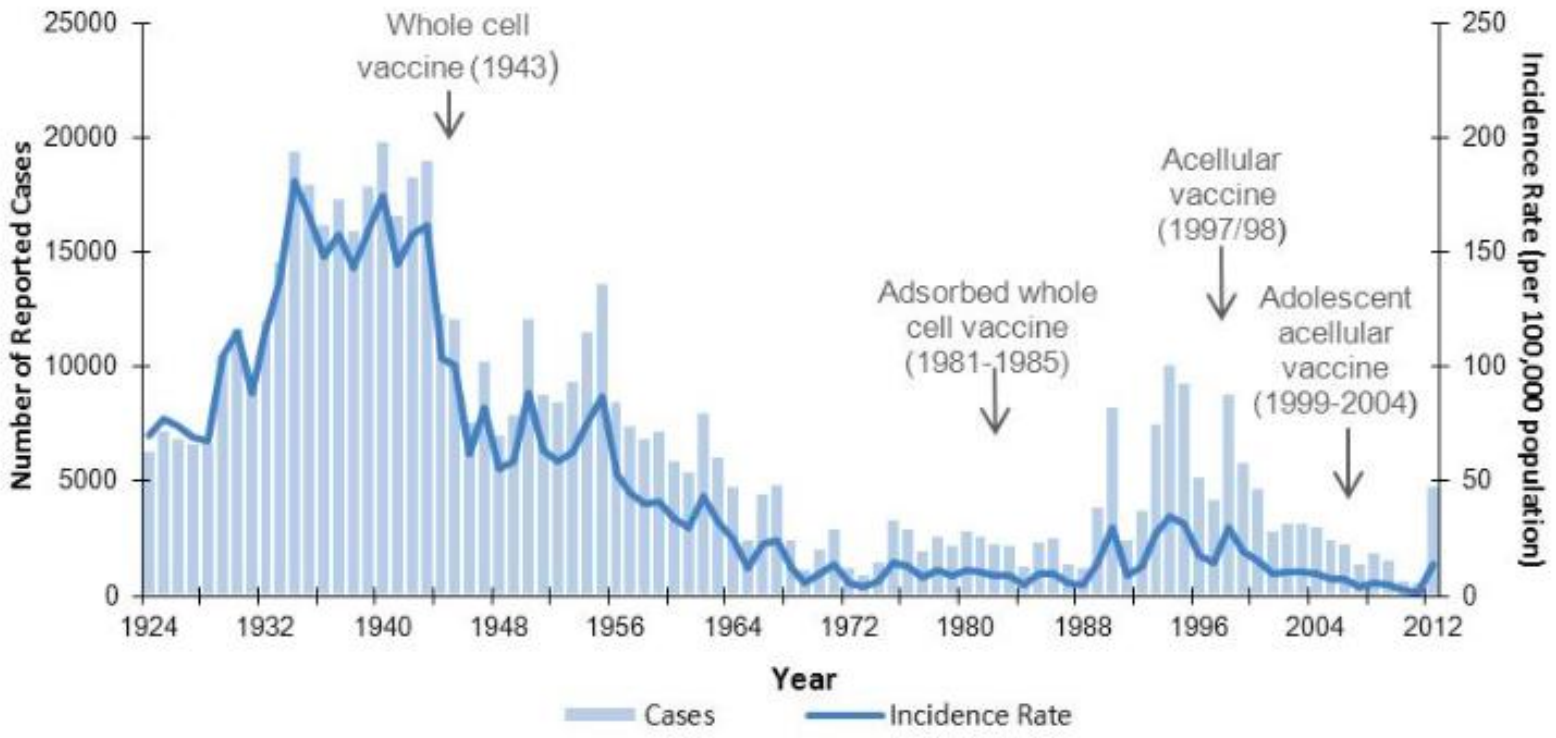
- One of the **top 10 causes of childhood mortality**
  - 294,000 pediatric deaths per year, globally
- Disproportionate burden of mortality and morbidity
  - **86%** of pertussis-related deaths in **infants <4 months**

Review of perussis 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%

Wengiel M and Fanella S (2013) *Can J Infect Dis Med Microbiol*, 24(3):162-163.

Epidemiology of pertussis in Canada during the 20th and 21st centuries

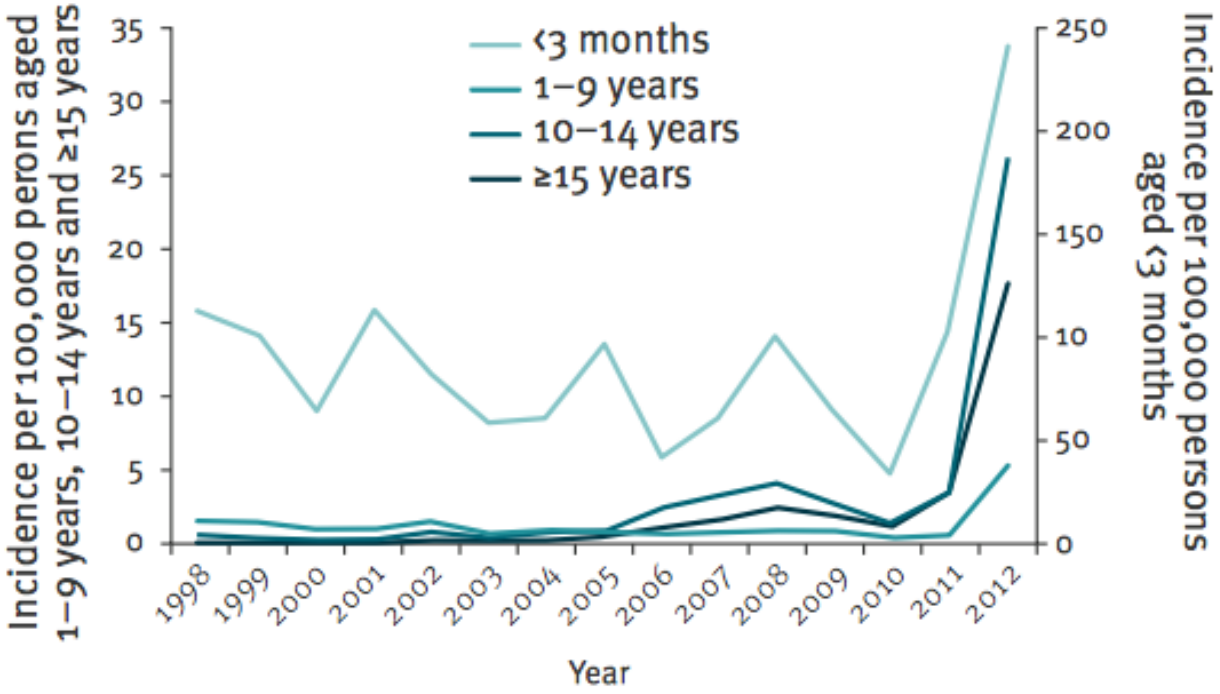
Figure 1. Reported cases and incidence rate (per 100,000 population) of pertussis in Canada by year, 1924 to 2012



NACI (2018) Update on Immunization in Pregnancy with Tdap vaccine. *PHAC*.

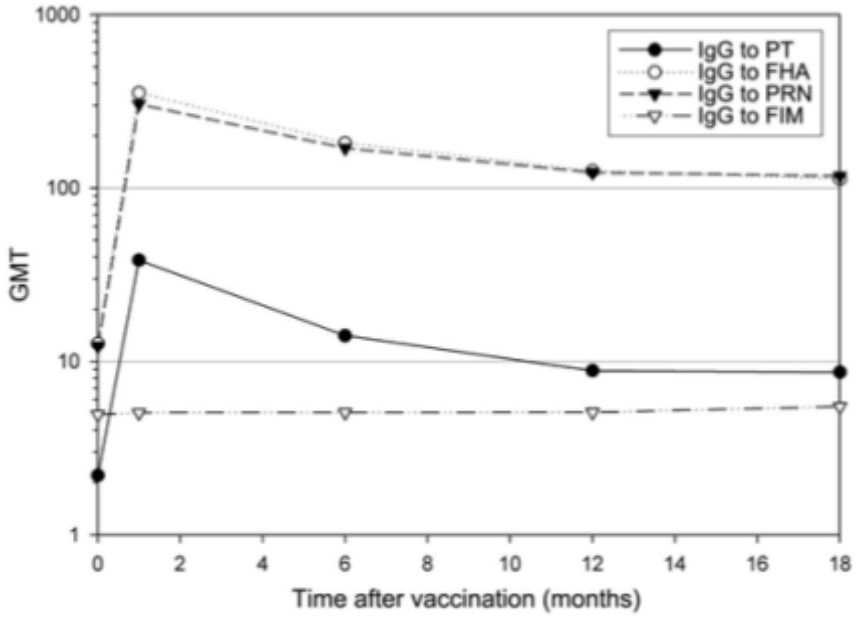
Rising incidence noted in multiple jurisdictions: 2011-2012

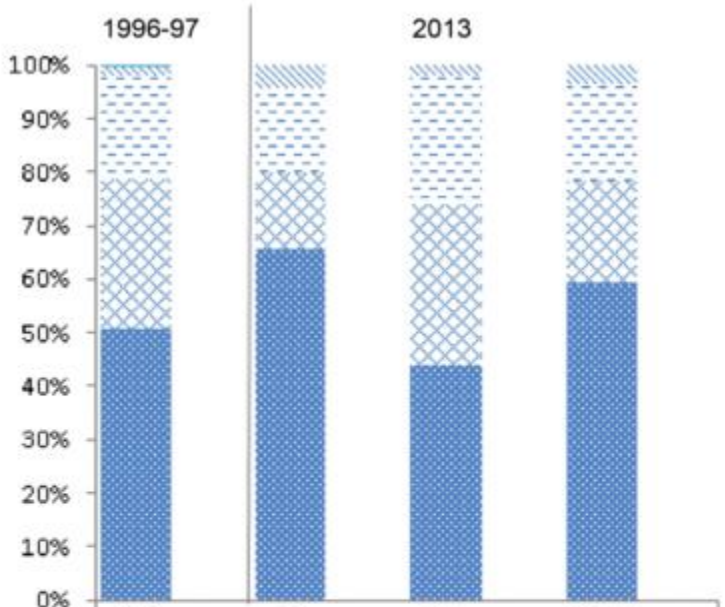
Incidence of laboratory-confirmed pertussis by age group, England and Wales, 1998–2012



Amirthalingam (2013) Euro Surveillance 18:pii=20587

Waning immunity to pertussis





	BC		FH		HA		Total	
	n	%	n	%	n	%	n	%
125+ EU/ml	1	0.5	0	0	0	0	0	0.0
63-124 EU/ml	3	1.5	5	4.2	1	2.0	6	3.6
20-62 EU/ml	39	19.5	19	16.0	12	24.0	31	18.3
10-19 EU/ml	56	28.0	17	14.3	15	30.0	32	18.9
Undetectable†	101	50.5	78	65.5	22	44.0	100	59.2

†Undetectable level was deemed to be <10 EU/mL, based on assay detection limits.

Bigham et al. (2014) Vaccine, 32: 6493-6498.

Adolescent and adult pertussis vaccines

Vaccine Ingredients	Adacel®, Sanofi[42]	Boostrix®, GSK[43]
Pertussis Toxin (PT, µg)	2.5	8
Pertussis filamentous hemagglutinin (FHA, µg)	5	8
Pertussis pertactin (PRN, µg)	3	2.5
Pertussis fimbriae (FIM 2/3, µg)	5	-
Diphtheria Antigen (Lf µg)	2	2.5
Tetanus Antigen (Lf, µg)	5	5
Aluminum Adjuvant (mg)	1.5	0.5
Other ingredients	2-phenoxyethanol, water	sodium chloride, water
Trace Amounts	formaldehyde, glutaraldehyde	

NACI recommends that every effort be made to ensure that every adult gets at least one adult dose of a pertussis containing vaccine.

9.3%

NACI (2018) Update on Immunization in Pregnancy with Tetanus Toxoid, Reduced Diphtheria Toxoid, Reduced Acellular Pertussis (Tdap) vaccine. *PHAC*.

Adults as the source of infection

Infections in adults are common.

- **Unvaccinated** adolescents and adults
- **Remotely** vaccinated adolescents and adults
- Adult cases are not suspected, detected or reported

Household contacts are the major source of infection.

Either Parent	**52-58%**
Sibling	16-43%
Non-household contact	4-22%

Wiley et al (2013) Vaccine 13:618-625

Cocoon strategy

- Logistically challenging
- Resource intensive
- Inefficient

Infant Outcome	Number Needed to Vaccinate
Hospitalization	10,000-20,000
ICU Admission	60,000-100,000
Death	>1,000,000

Skowronski DM et al (2012) CID, 54(3):318-327.

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.

Efficacy of Maternal Vaccination

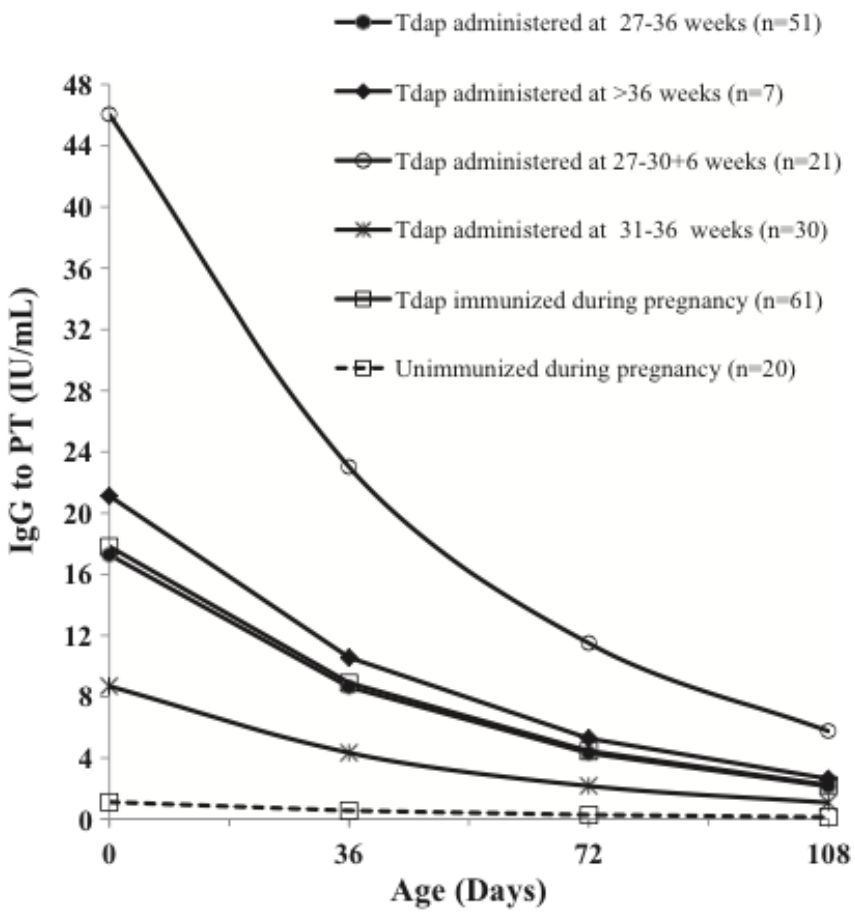
	Percentage of cases vaccinated	Average matched coverage*†	Vaccine effectiveness‡
Infants <3 months of age			
Vaccination at least 7 days before birth	15% (12/82)§	62%	91% (84 to 95)
Vaccination at least 7 days before birth with coverage reduced by a relative 20%	15% (12/82)§	49%	84% (71 to 93)
Infants <3 months of age by timing of maternal immunisation			
Vaccination at least 28 days before birth	14% (10/69)¶	63%	91% (83 to 95)
Vaccination 7–27 days before birth	3% (2/72)‖	19%	91% (70 to 96)
Vaccination 0–6 days before or 1–13 days after birth	3% (2/68)**	5%	38% (−95 to 80)
Infants <2 months of age			
Vaccination at least 7 days before birth	15% (11/71)	61%	90% (82 to 95)
Vaccination at least 7 days before birth with coverage reduced by a relative 20%	15% (11/71)	49%	82% (67 to 90)

Amirthalingam et al (2014) Lancet, 384:1521-1528.

Antepartum vs. Postpartum Vaccination

- Retrospective cohort study of 74, 504 women who delivered in California and received Tdap:
  - Antepartum → 42,941 (58%)
  - Postpartum → 31,563 (42%)
- Outcome of interest → pertussis in infants <12 months
- Results → 119 infants with pertussis (1.6 cases per 1000)
  - Vaccine effectiveness of 85% (95% CI, 33-98%) for prevention of pertussis in infants <8 week
  - Ideal timing was maternal vaccination at 27-36 weeks GA

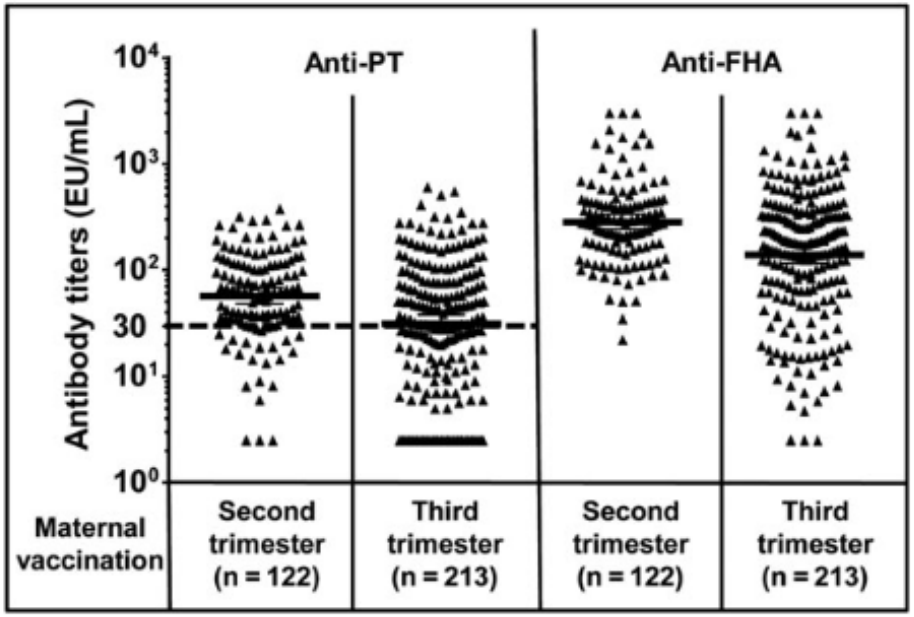
Timing of Tdap in pregnancy



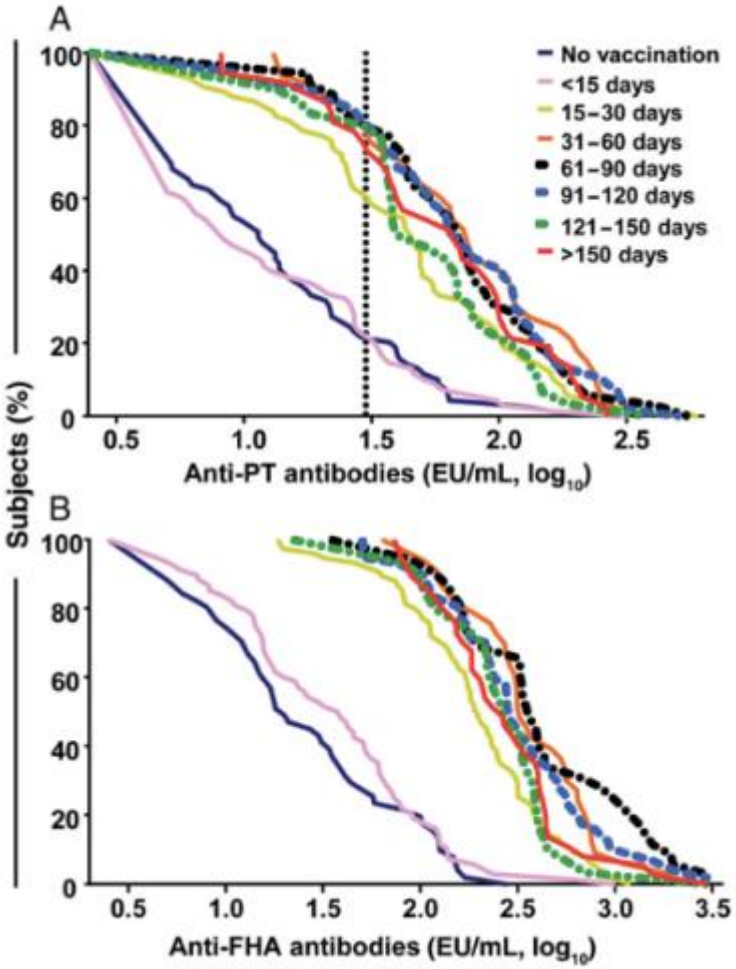
Concentration and **avidity** of IgG to PT were significantly higher in women immunized **27-30**[6]

Abu Raya (2014) Vaccine 32:5787-5793.

Timing of Tdap in pregnancy

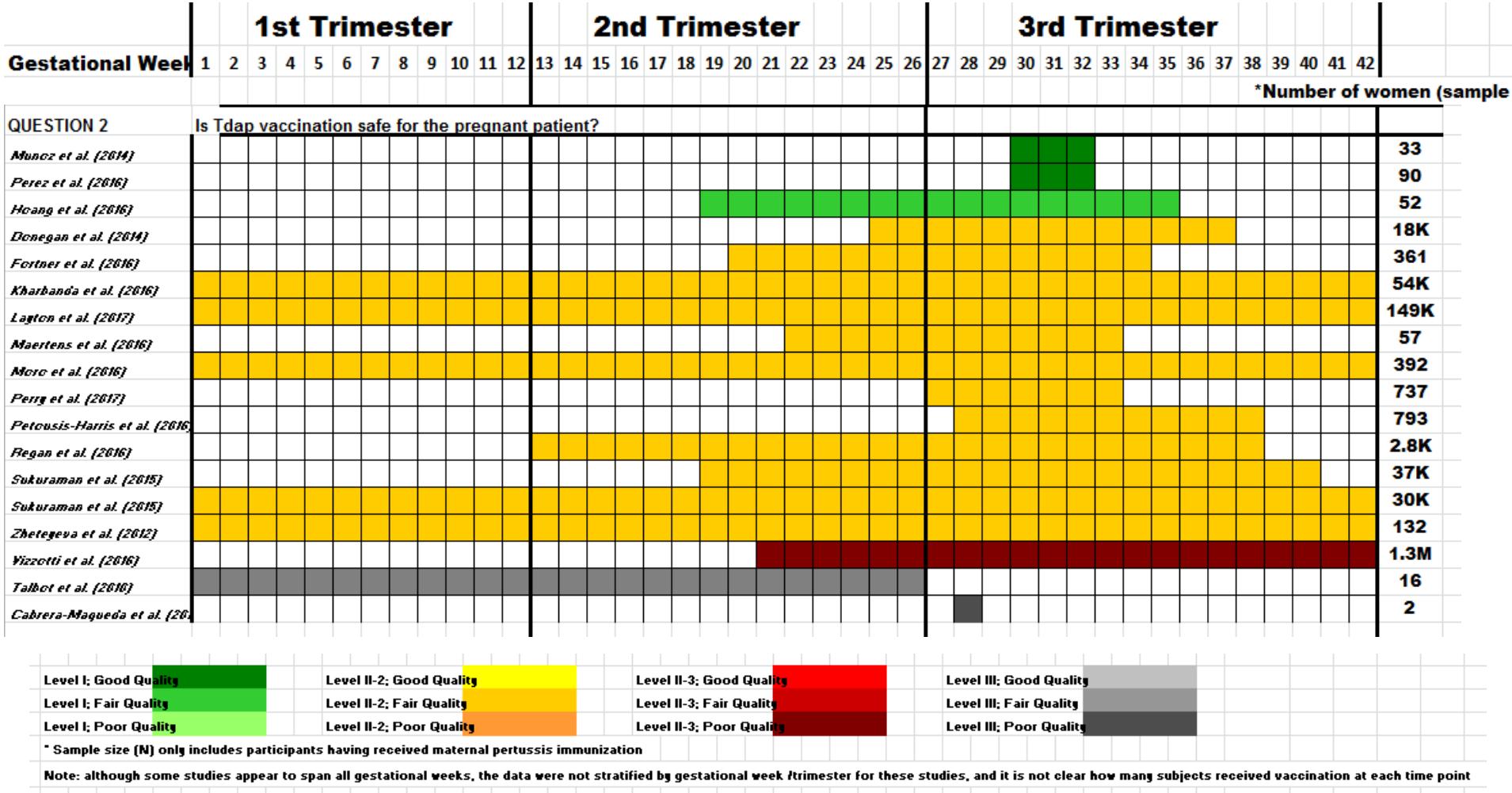


"Best" timing is several weeks **remote from delivery**



Eberhardt (2016) CID 62(7):829-36.

Is Tdap safe for pregnant women?



Samuel Duchesne-Belanger, Mathew Tunis, Oliver Baclic, Eliana Castillo

2018 Recommendations about Tdap in pregnancy

2018 NACI Recommendation

Recommendation: NACI recommends that immunization with Tdap vaccine should be offered in every pregnancy, irrespective of previous Tdap immunization history (Strong NACI Recommendation). NACI concludes that there is good evidence to recommend immunization (Grade A Evidence)

2018 SOGC Recommendation

All pregnant women should be offered the diphtheria, tetanus toxoid and acellular pertussis vaccine during the second or third trimester, preferably between 21-32 weeks gestation, regardless of their immunization history.

Many other vaccinations may be appropriate during pregnancy

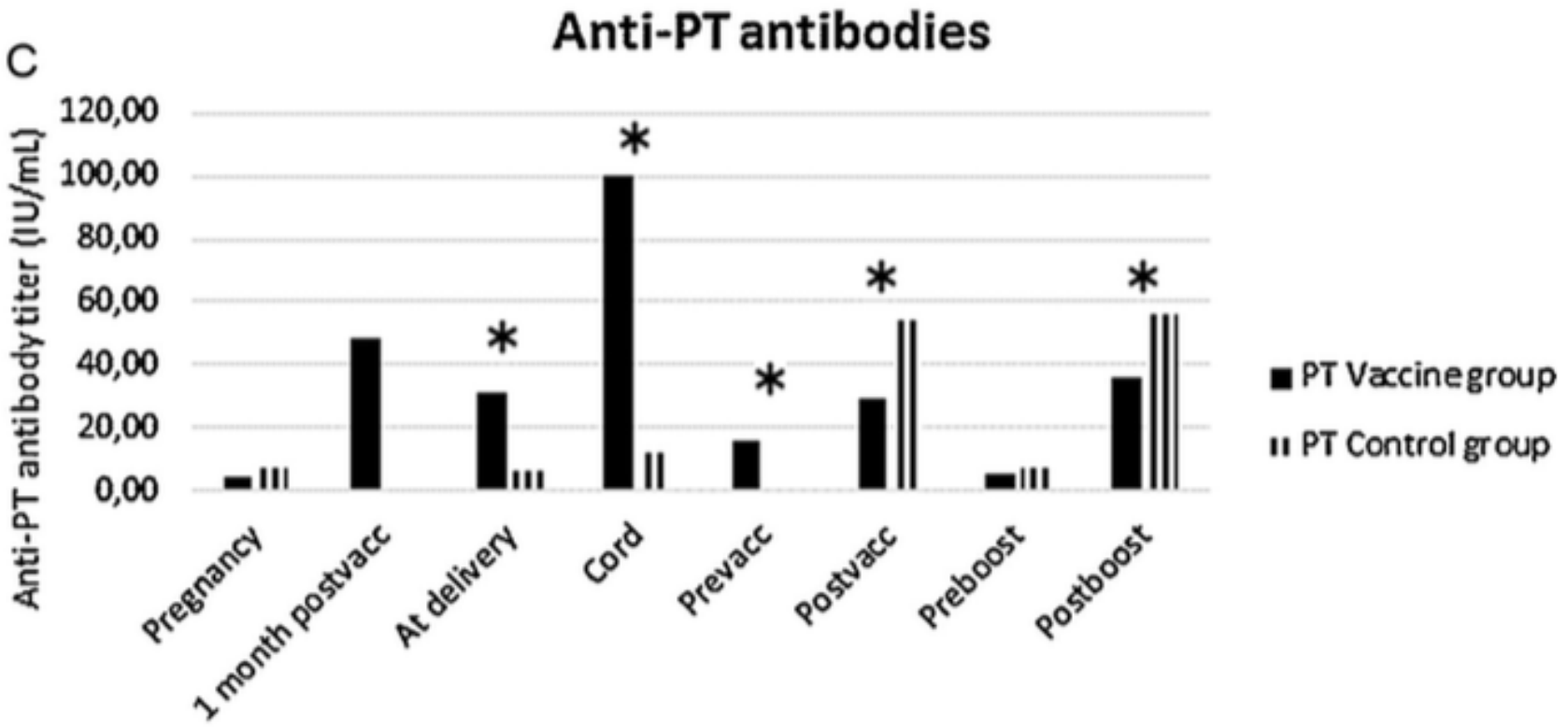
- As a general rule, inactivated vaccinations are safe to give in pregnancy and live vaccine should be avoided.
- Hepatitis B vaccine
  - Susceptible to HBV and risk factors (personal or employment) for HBV exposure
- Pneumococcal vaccinations
  - For pregnant women with medical comorbidities putting them at risk of invasive pneumococcal disease
- Travel vaccinations
  - Evaluated case-by-case +/- in collaboration with a travel medicine specialist

Summary

- Many vaccines can be safely administered during pregnancy
- Immunization during pregnancy has the potential to protect the mother, fetus and the newborn infant
- The seasonal influenza vaccination and acellular pertussis vaccinations are recommended for every pregnant woman and should become part of routine obstetrical care

Supplemental Slides

Concept of immune-blunting



Maertens (2016) Vaccine, http://dx.doi.org/10.1016/j.vaccine.2016.04.066.
Maertens (2016) Vaccine 34:142-150

Pertussis: Numbers for Ontario

	Cases	Hospitalizations	Death
2017	584	33	1
2016	463	30	0
2015	700	36	0

Data Source: Public Health Ontario

Cost effectiveness data

Cocooning Strategy

Infant Outcome	Number needed to vaccinate
Hospitalization	10,000-20,000
ICU Admission	60,000-100,000
Death	>1,000,000

Maternal Vaccination Strategy

Infant Outcome	Number needed to vaccinate
Hospitalization	1331
ICU Admission	
Death	200,000

Van Bellingham (2019) Human Vaccine Imunotherapeutics 10.1080/21645515.2018.1474315.
Skowronski DM et al (2012) CID, 54(3):318-327.

Vaccine Hesitancy and Pregnancy

Julie van Schalkwyk MD MSc FRCSC

Associate Professor, Department of Obstetrics and Gynecology

University of British Columbia

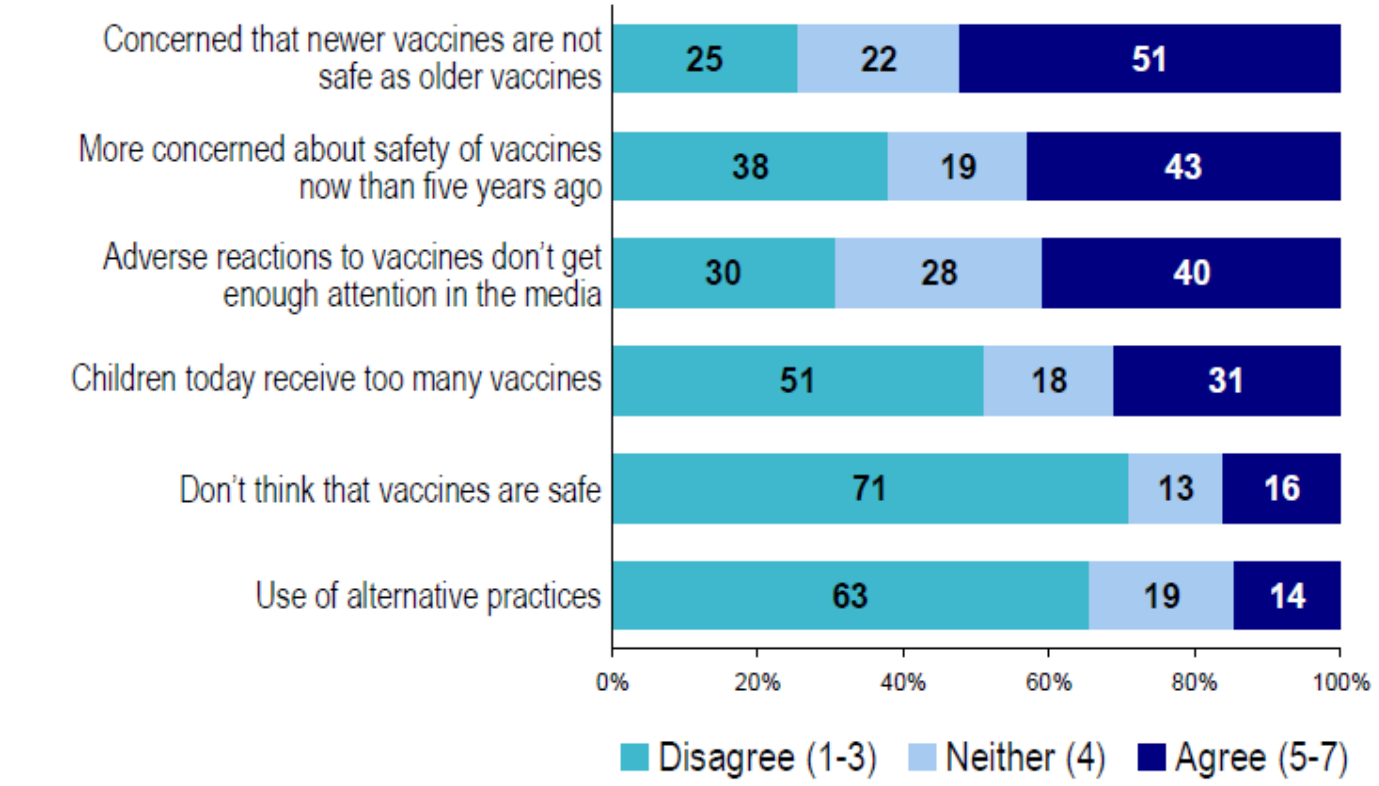
Objectives

- To define vaccine hesitancy
- To present determinants of vaccine hesitancy
- To review strategies to address vaccine hesitancy

The problem

Concerns about Vaccine Safety

"To what extent do you agree with the following statements?"



EKOS Research Associates Inc.

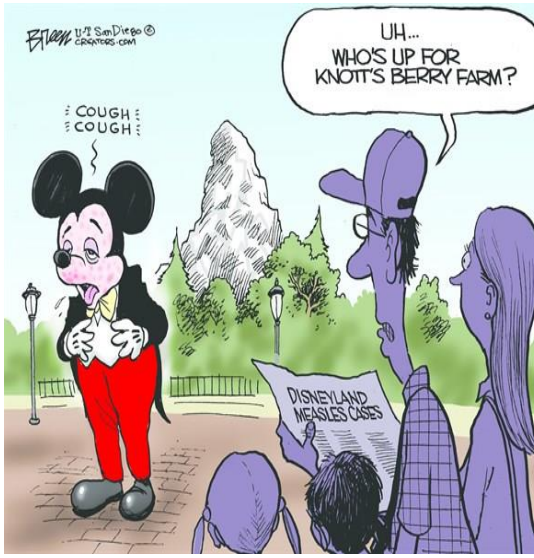
n=1247-1285

Vaccine Safety Survey, 2011

Definition of Vaccine Hesitancy

- ***Vaccine Hesitancy***
  - Refers to delay in acceptance or refusal of vaccines ***despite availability of vaccine services (WHO)***
  - **Complex and context specific** varying across ***time***, ***place*** and ***vaccine***

- Reluctance to receive recommended vaccination because of concerns and doubts about vaccines that may or may not lead to delayed vaccination or refusal of one, many or all vaccines.
  - Dube et al., PLoS One 2016



Vaccine Hesitancy

- As old as vaccination. Since Jenner first scraped cow-pox blisters & inoculated people
- **Vaccine refusal:**
  - Associated with outbreaks
    - Pertussis in the UK, US and Japan
    - Measles in USA, Canada, France
  - Associated with deaths
    - 2 due to **diphtheria** in EU
    - 10 due to **measles** 2008-11 France
    - 8 **whooping cough** 2017 US/Canada

Anti-vaccine cartoon, *The Punch,* 1802.
Opponents of smallpox vaccination showed vaccinees developing bovine features

Vaccine Hesitancy

"Despite exhaustive scientific evidence that immunizations are amongst the safest and most cost-effective public health measure, achievement and maintenance of high levels of immunization coverage has remained a challenge."

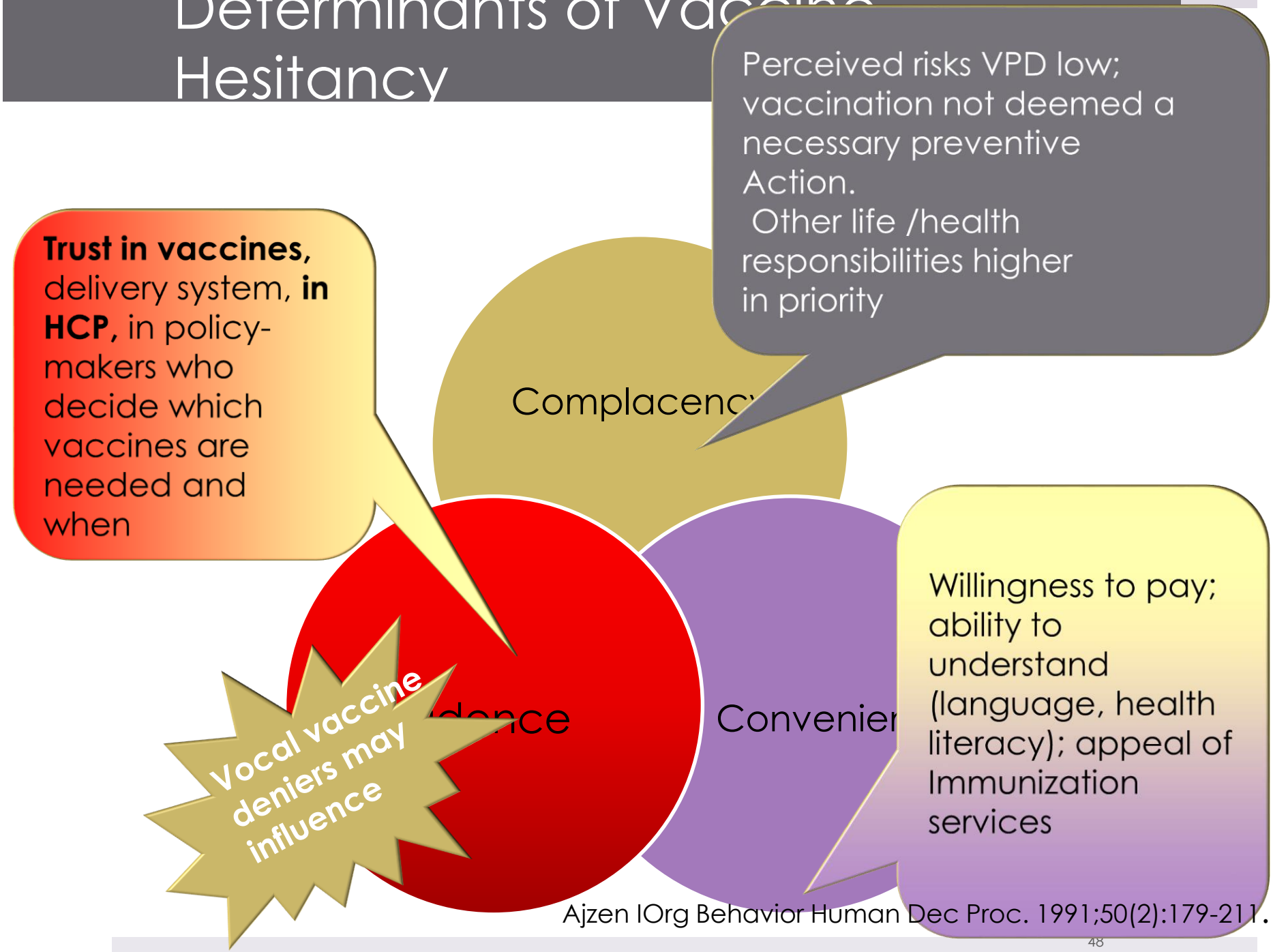
Survey of Parents on Key Issues Related to Immunization, 2011

Vaccine Hesitancy

- Influenced by such factors as
  - **Complacency**
  - **Convenience**
  - **Confidence**

SAGE working group on Vaccine Safety Vaccine 2015; 33(34):4161-4

Determinants of Vaccine Hesitancy



Ajzen IOrg Behavior Human Dec Proc. 1991;50(2):179-211.

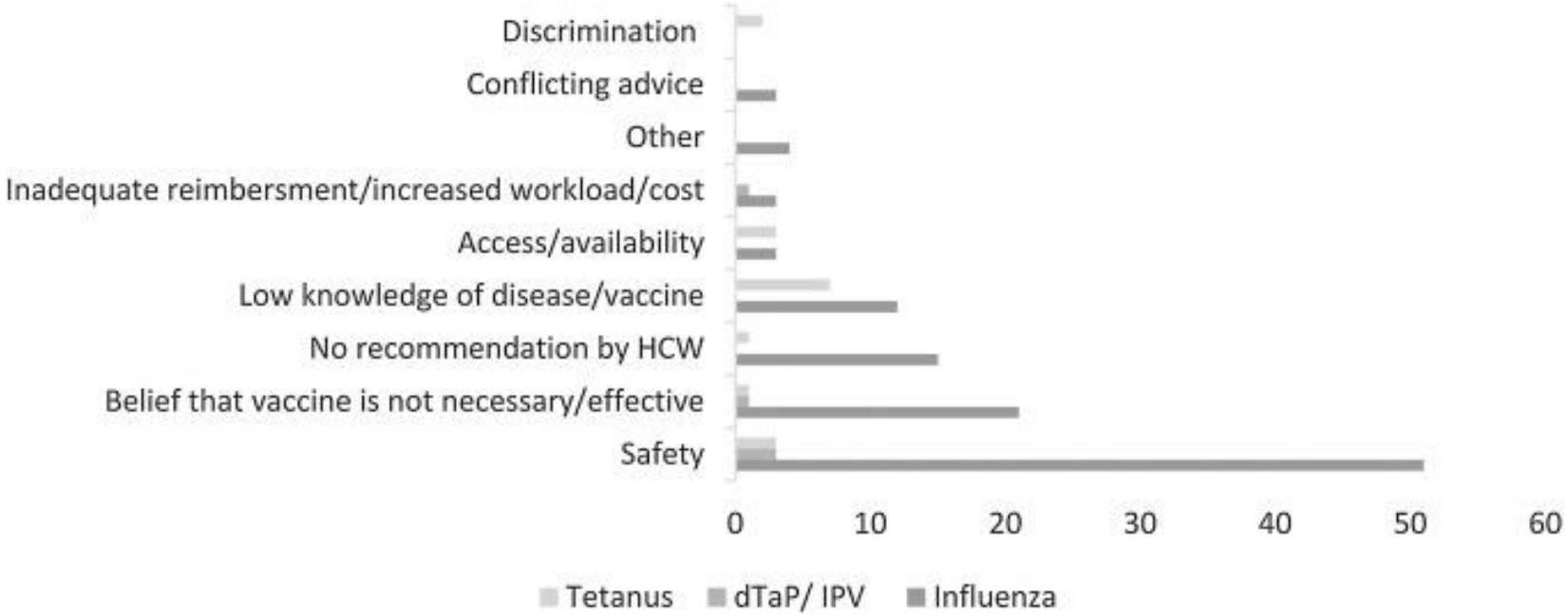
Vaccine hesitancy in Canada

- 1.5% of children never vaccinated
- 70% parents worried about vaccine side effects
- 37% believe the vaccines can cause the same disease it is supposed to prevent
- Small percentage believe alternative/homeopathic/chiropractic practices can eliminate the need for vaccinations

Canadian National Immunization Coverage Survey 2013

Vaccine hesitancy in pregnancy

- Barriers to vaccination are complex, vary by population and context



- Understanding factors influencing vaccination acceptance during pregnancy: A literature review. Wilson et al., Vaccine 2015

Vaccine hesitancy in pregnancy

- Survey of 1184 pregnant women in Australia
- First time mothers have more vaccine concerns (49%) and are less likely to vaccinate their children (27% undecided).
- 46% received influenza and 82% pertussis vaccination.
- 66% all mothers felt they received sufficient information on vaccination in pregnancy
- Danchin et al Vaccine 2018

Vaccine hesitancy in pregnancy

- 325 unvaccinated pregnant women surveyed
- 73-81% felt flu and pertussis would be serious for them and 87-92% felt serious for infant
- Despite this only 34 and 44% planned maternal vaccination for influenza and pertussis respectively
- 46% had concerns about vaccine safety
- Evidence-based vaccine promotion emphasizing safety needed.
  - Chamberlain et al., PLoS current 2015

A Systematic Review of Barriers to Vaccination During Pregnancy in the Canadian Context

Vanessa Poliquin, MD[1,*], Devon Greyson, PhD, MLIS[2,3], Eliana Castillo, MHSc, MD[4,5]

17 studies
Patient and provider knowledge important facilitator for vaccination

Vaccine endorsement by prenatal care provider and clear messaging of safety for fetus motivators for uptake

Urgent need for strategies to improve uptake of vaccination in pregnancy

JOGC 2018

Determinants of vaccine uptake or hesitancy in pregnancy

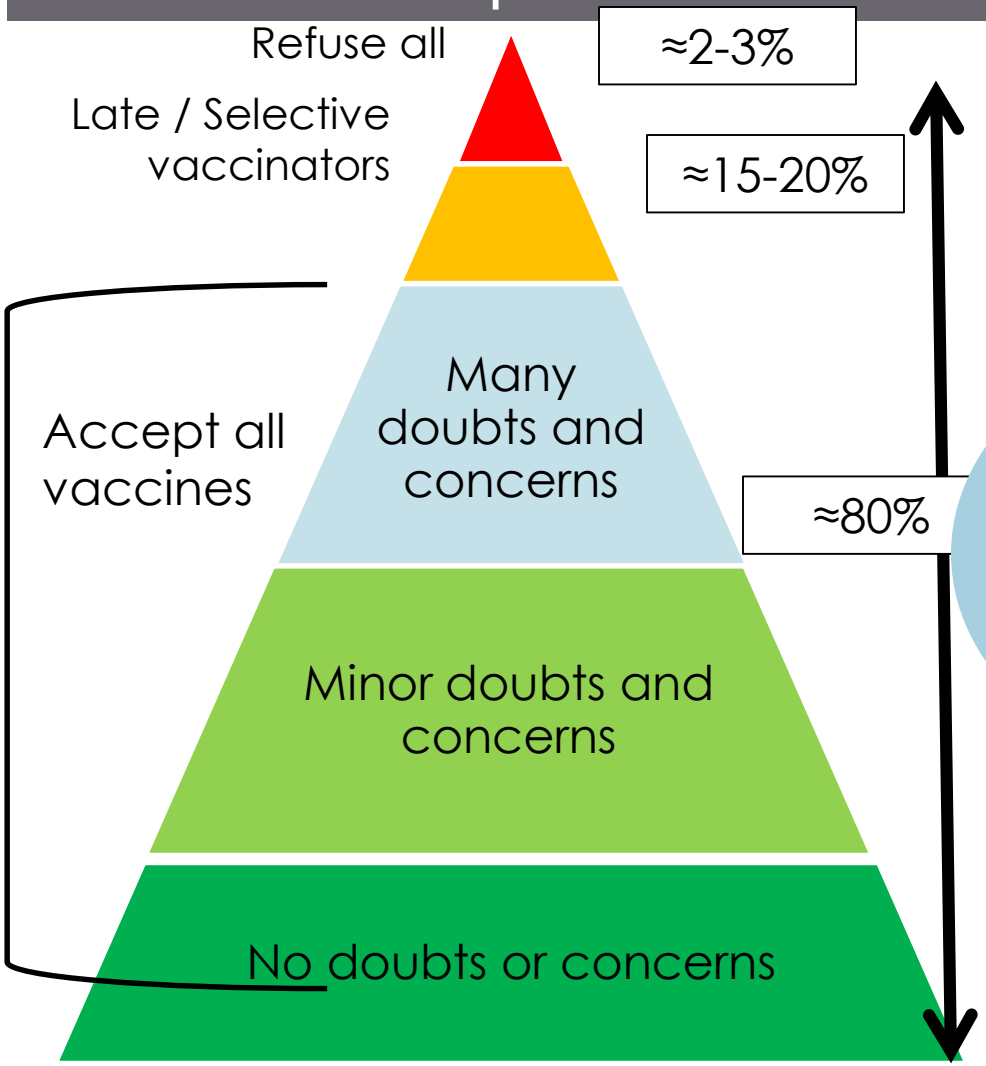
- Acceptance
  - Older maternal age
  - Higher income
  - Increased education
  - Presence of medical comorbidities
  - Prenatal care by family doctor
  - Clear vaccine info provided by a trusted source

Hesitancy/Rejection

- Younger maternal age
- Low income
- Fewer prenatal care visits prior to 32 weeks gestation
- Safety concerns
- Prenatal care by OBGYN
- Lack of knowledge about risk
- Past negative experience with HCP, medical system and/or vaccines

Yuen and Tarrant, Vaccine 32(36), 2014

The Continuum of Vaccine Acceptance



The Refusers
- Strong-willed and committed against vaccines
- Natural approach to health
- Religious/moral considerations

vaccines
- Actively seeking information
- Conflicting feelings on who to trust
- Influenced by social networks

The Acceptors
-Consider vaccines important
-Consider vaccines safe
- Trust their HCP,
- Influenced by social norm

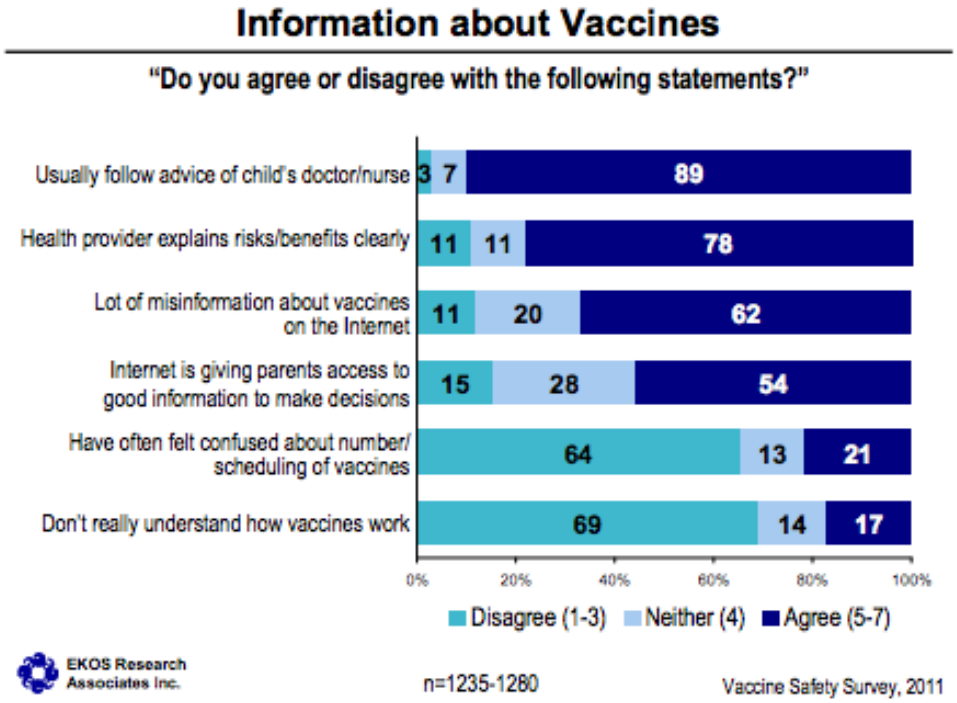
Benin et al, Pediatrics. 2006: 117(5):1532-41
Leask et al., BMC Pediatrics 2012:12:154

Confidence: Vaccine uptake/refusal determinants

- Past experiences with health and vaccination services
  - Past encounters with HCP/medical system
  - Fear of needles / pain
  - Adverse events (real or perceived)
- Trust in health system and healthcare providers
  - Recommendations from HCP
  - Trust and communication with HCP
  - Trust/Distrust of the medical community
  - Trust/Distrust of the pharmaceutical industry

Dube and MacDonald Lancet ID 2016.

Providers Important Information Source



Providers can influence vaccination hesitancy

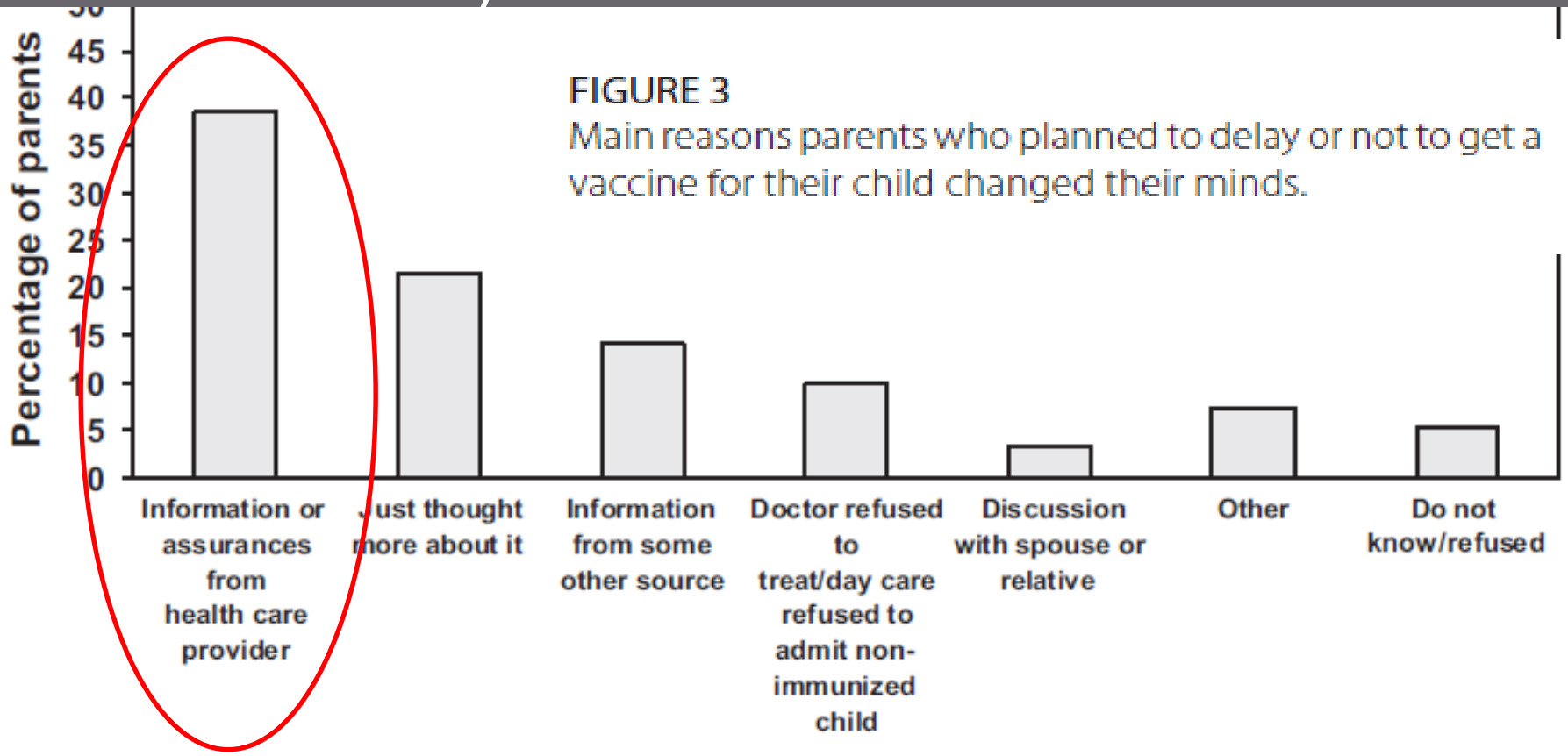
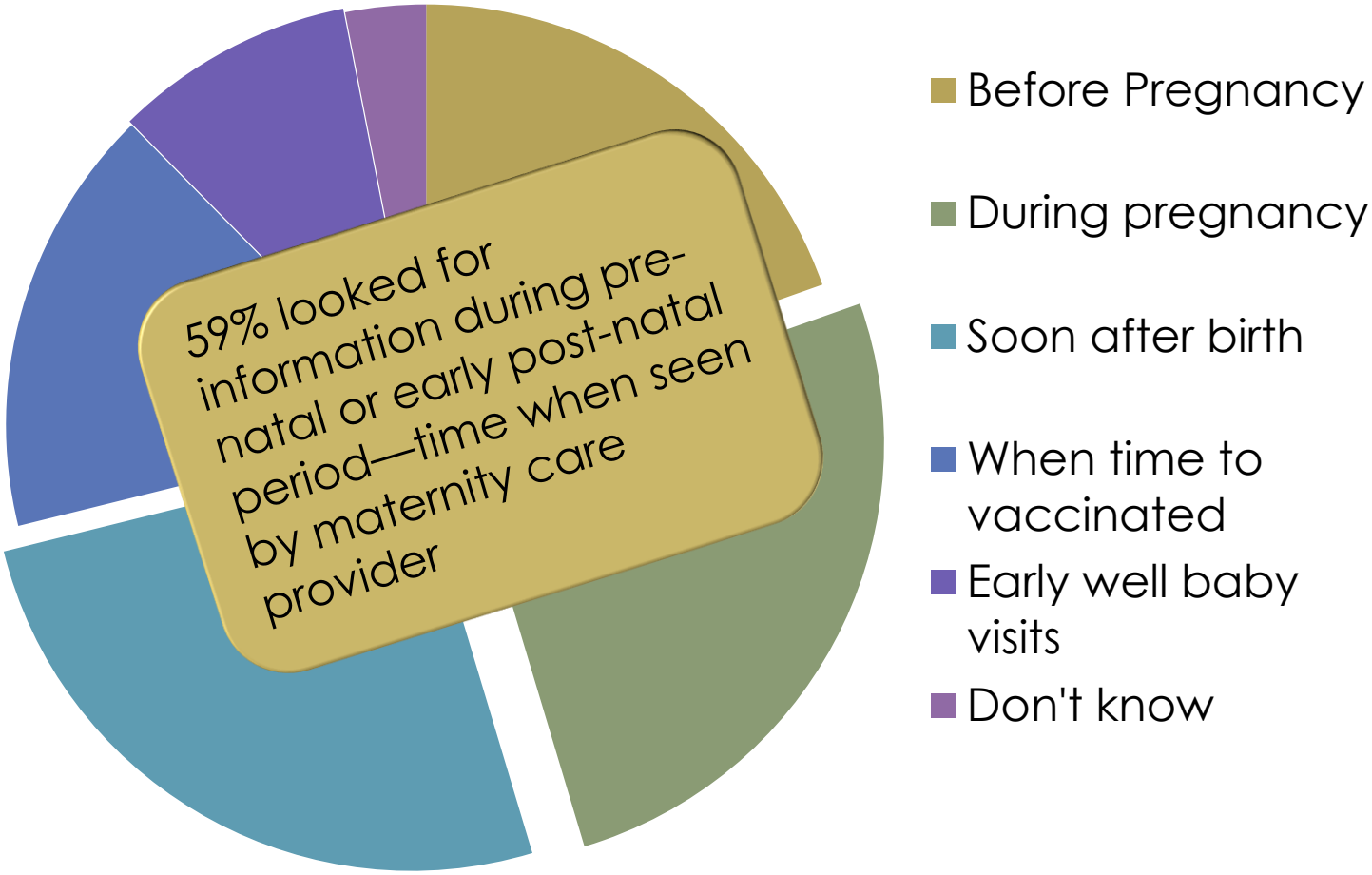


FIGURE 3
Main reasons parents who planned to delay or not to get a vaccine for their child changed their minds.

When parents/pregnant women looked for child vaccine info



Ekos Research 2011. Vaccine Safety Survey.
http://www.ekospolitics.com/articles/0719.pdf

Chief Public Health Officer Statement Dr. Theresa Tam

- March 12, 2019
- "Some parents have come to fear the prevention more than the disease".
- "Support parents as they tease apart fact from fiction".
- "How we talk to parents who have questions about vaccines can have a direct effect on improving their confidence and supporting them in getting their children vaccinated".

6 Approaches to Enhance Vaccine Acceptance/Address Hesitancy

- At individual HCP Level

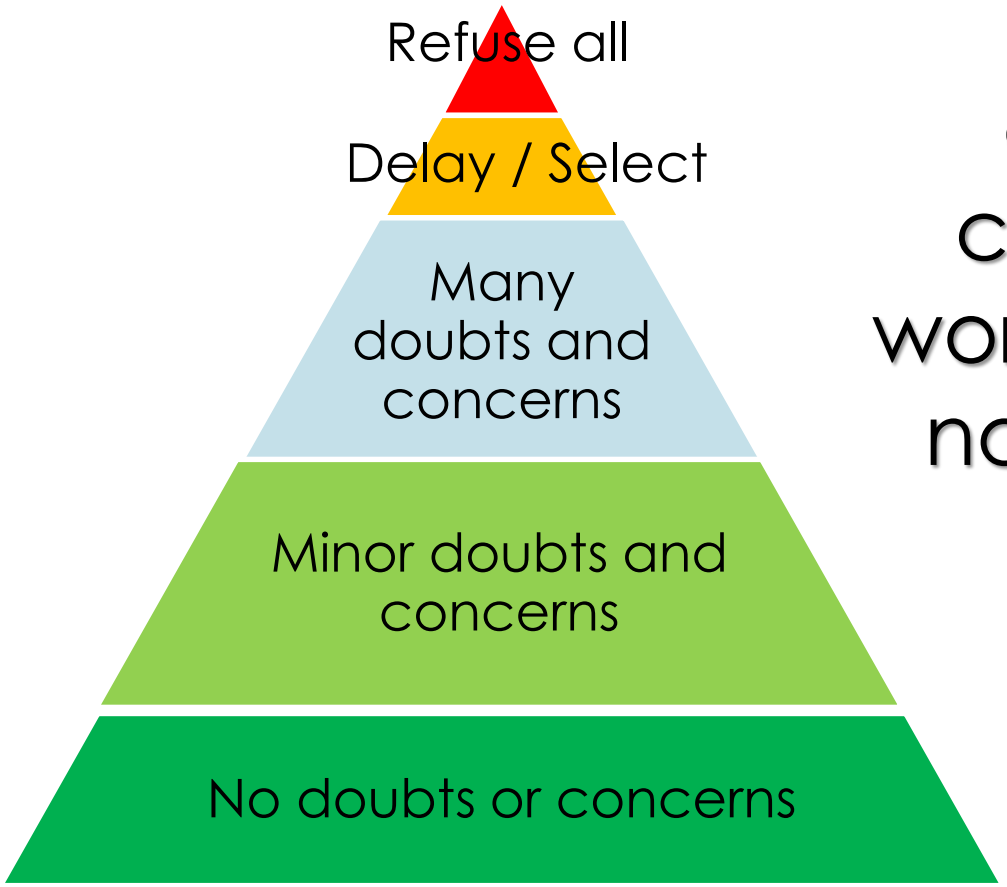
1. HCP recommendation #1 reason for vaccine acceptance
2. Use effective patient discussion techniques
3. Use clear language
4. Reinforce role community immunity/circle of protection (herd immunity): as relates to unborn child & newborn
5. Maintain trust: Don't dismiss from practice
6. Address pain at immunization

What YOU can do:

- EDUCATE YOURSELF so you can confidently educate expectant mothers
- LISTEN
- Make no assumptions
- Identify questions and concerns
- Extra attention and information sharing with hesitant mothers (whether or not they vaccinate)
- Tailor your advice
- Acknowledge that while HCPs are trusted sources, some mothers/mothers-to-be will want to verify info

Conclusion

- All parents want to do what's best for their child



Vaccination acceptance = continuum, what works for some might not work for others

Remember

- You are one of the MOST trusted sources of information for your pregnant patients/clients

- Your recommendation can change behavior and result in healthier pregnancies, children and societies

Acknowledgements and Ongoing Research

Dr. Julie Bettinger

- Ongoing research: maternity care provider study for ob/gyn, family dr, nurses and midwives to understand YOUR views about vaccination
  - for more information: http://vaccineevaluationcenter.ca/ or juliebettinger@bcchr.ubc.ca

Internet resources for patients

- https://immunize.ca/
- https://www.pregnancyinfo.ca/
- https://www.caringforkids.cps.ca/
- https://www.canada.ca/en/public-health/services/provincial-territorial-immunization-information.html Federal govt. site with links to vaccine information by province and territory

https://www.pregnancyinfo.ca/

HCP across Canada can take Immunization courses for free-details at: http://www.bccdc.ca/health-professionals/education-development/immunization-courses