Vaccines including Tdap in pregnancy

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Faculty of Medicine

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Disclosures

- Received research grants from Pfizer, Merck, VBI Vaccines
- All funds paid to institution
- No personal payments

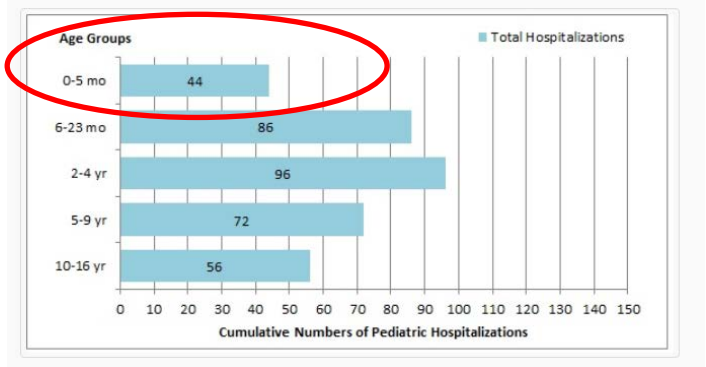
Objectives

- Describe the means by which maternal immunization provides additional protection to both the mother and the infant against vaccine preventable diseases

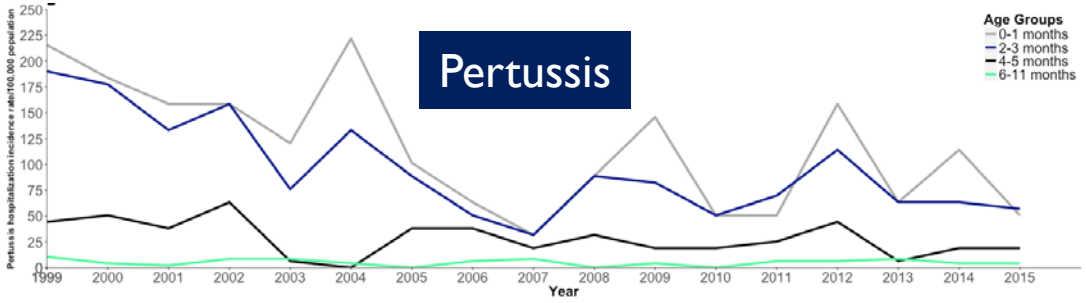
- Consider the role of the various providers in the delivery of maternal immunization programs to achieve high uptake

The challenge of protecting infants

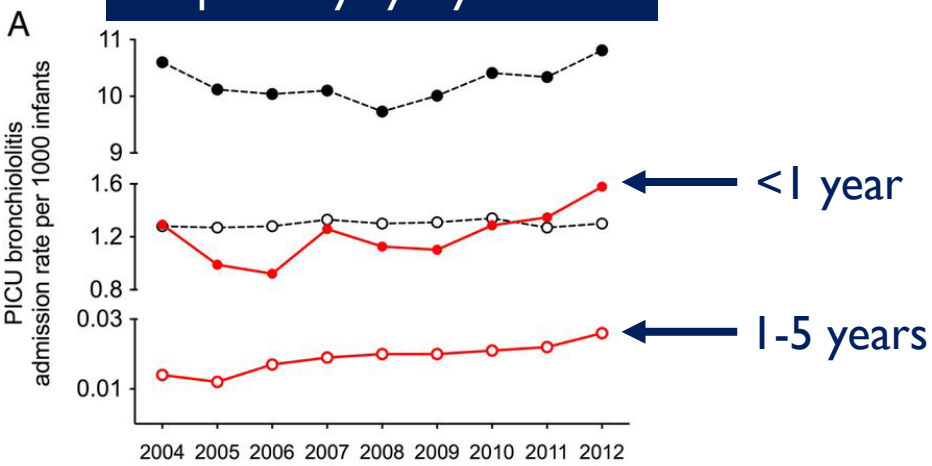
Influenza



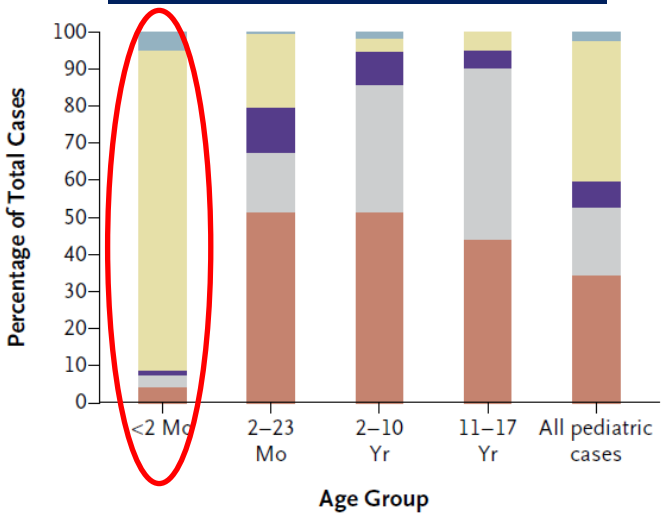
Pertussis



Respiratory syncytial virus



Group B Streptococcus



Green et al. Arch Dis Child 2016; Thigpen et al. NEJM 2011
PHAC FluWatch Report 26th January, 2018
Abu Raya et al (submitted for publication)

Every pathogen is different

	Pertussis	Influenza	Group B streptococcus	Respiratory syncytial virus
Maternal disease risk	+	+++	++	+
Infant mortality	++	+	+++	++
Infant disease frequency	+ (cyclic*)	++	+	+++
Disease seasonality	✓	✓	×	✓
Microbial diversity	+	++	++	+
Licensed vaccine available	✓	✓	×	×
Maternal booster response expected†	✓	Partial‡	Not assumed	✓
Passive protection of infant	✓	✓	✓	✓
Maternal to cord antibody ratio	1·1–1·9	0·7–1·0	0·7–0·8	1·0
Antibody half-life (days)	36–40	40–50	30–44	36–79
Infant vaccination	✓	≥6 months	×	(✓)§
Correlate of protection	×	Partial¶	×	×
Functional immunoassay	×	✓	||	✓
Competing control option	×	×	✓**	✓††

+=low. ++=medium. +++=high. *Increased disease incidence usually occurs every 3–4 years. †Via previous vaccination or infection. ‡Previous vaccination or infection will lead to partial protection due to virus evolution. §Monoclonal antibody administered to high-risk infants during respiratory syncytial virus season. ¶Correlates of protection based on haemagglutinin inhibition assay or microneutralisation titres have not been validated in young infants and are not based on maternal immunisation. ||Bacterial killing in an opsonophagocytic assay has been suggested as a possible correlate of protection. **Intrapartum antibiotic prophylaxis has reduced the incidence of early onset group B streptococcus neonatal sepsis. ††Monoclonal antibodies administered to high risk infants during respiratory syncytial virus season reduces rates of hospital admission.

Table: Targets of maternal immunisation

Marchant, Sadarangani et al.
Lancet Inf Dis 2017

UBC BC Children's Hospital Research Institute

Influenza *vs.* pertussis

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Pregnancy as a risk factor for severe outcomes from influenza virus infection: A systematic review and meta-analysis of observational studies

Dominik Mertz [a,b,c,d], Johanna Geraci [e], Judi Winkup [b], Bradford D. Gessner [f], Justin R. Ortiz [g], Mark Loeb [b,c,d,*]

- 152 studies
- Individual level data on >300,000 subjects
- ↑ hospitalization in pregnant women with influenza

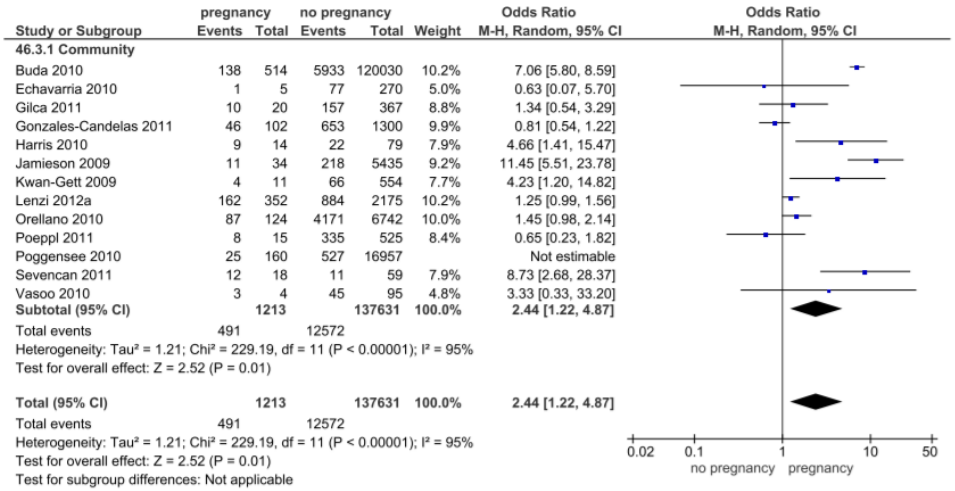
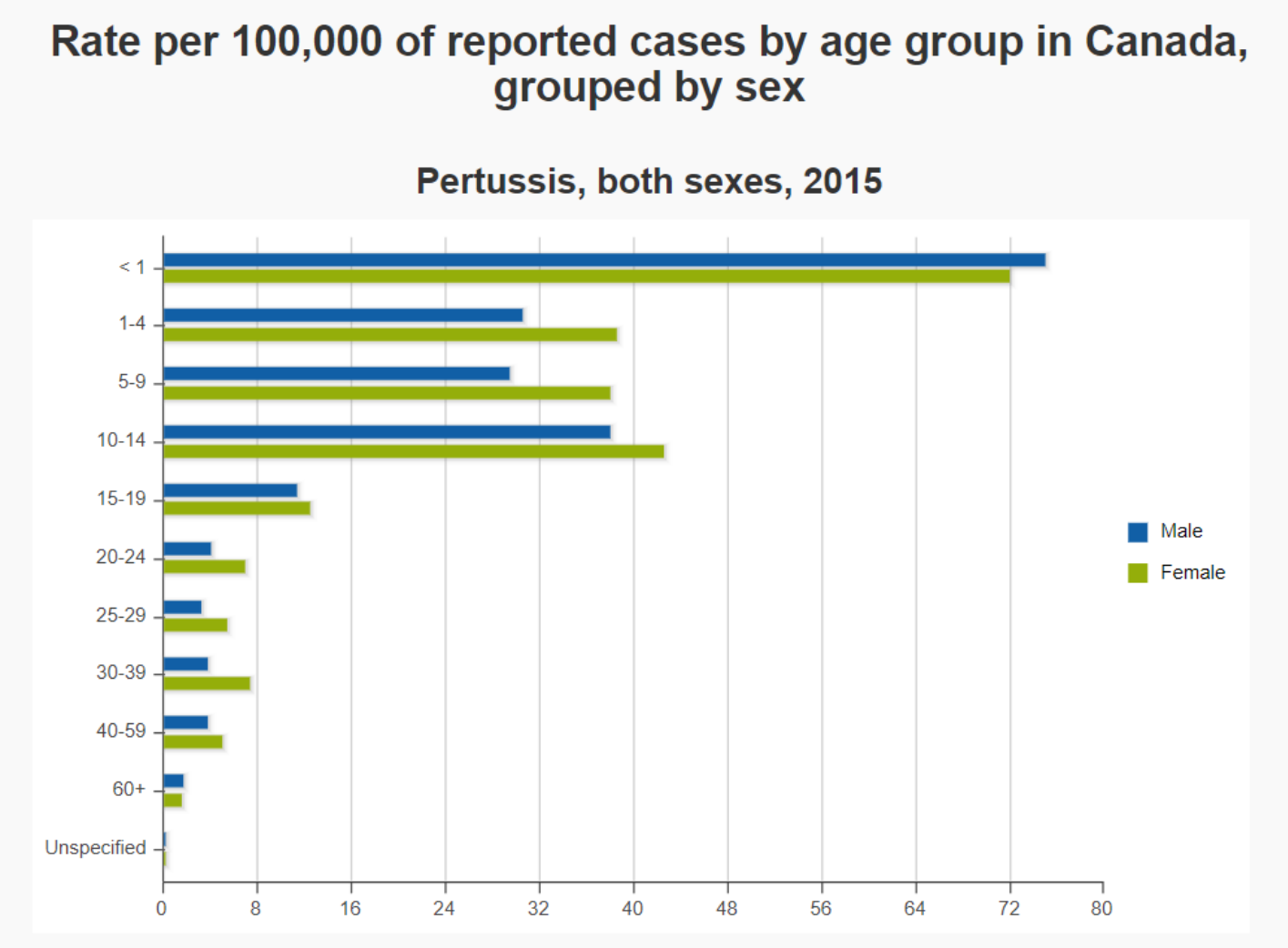


Fig. 3. Forest plot for pregancy as a risk factor for hospitalization following influenza.

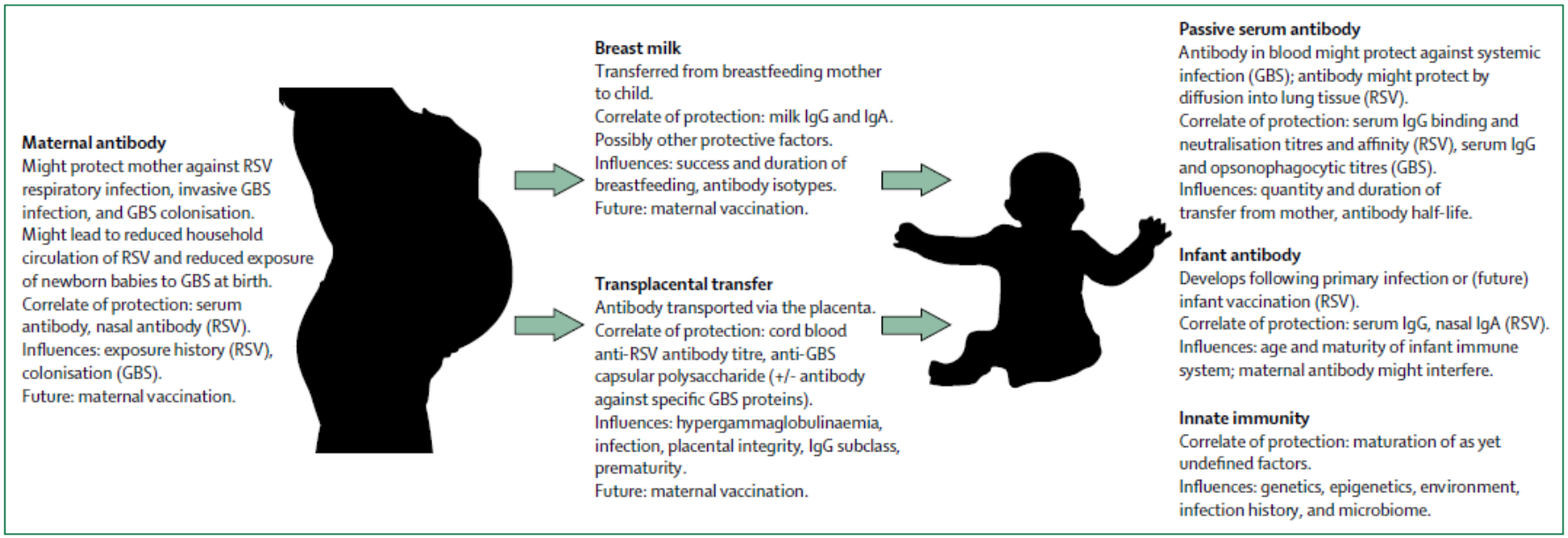
Influenza *vs.* pertussis



PHAC. Notifiable diseases online (http://diseases.canada.ca/notifiable/charts?c=abs)

Protection via immunization in pregnancy

- Transfer of IgG antibody across the placenta
- Transfer of breast milk factors
- Reduction of carriage/disease in mother
  - ↓ transmission to infant (e.g. GBS, pertussis)



Heath et al. Lancet Inf Dis 2017

Goals of immunization in pregnancy

- Temporary protection of the young infant against
  - Severe illness and Death
- Via
  - Passive transplacental transfer of maternal IgG
  - Transfer of breast milk immune factors
  - Reduction of carriage/disease in the mother
  - ?Induction of immune responses in the fetus
- Until
  - High risk period has elapsed (e.g. GBS) and/or
  - Infant immunization provides protection (e.g. pertussis)
- Without adverse effect on infant immunity

The ideal vaccine for pregnancy

- Safe to mother and fetus
- Induces high titer of IgG antibody
- Allows sufficient placental transfer of IgG to infant
- Provides sufficient duration of protection
- No impairment of infant response to immunization

Safety of vaccines in pregnancy

- Influenza
- Mixed evidence suggesting reduced risk of adverse birth outcomes
- Tdap

- Mainly retrospective observational studies
- No evidence of harm

Outcome	OR/RR/IRR (point estimate range)
Preterm birth (<37 weeks gestation)	0.47 to 1.50
Small for gestational age (<10th percentile)	0.65 to 1.00
Stillbirth	0.36 to 0.85
Neonatal death	0.16 to 1.00
Low birth weight	0.76 to 1.20
Congenital anomalies	0.20 to 0.91

We need more data

Vaccine 34 (2016) 6038–6046

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

ELSEVIER

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2015; **24**: 361–367
Published online 12 February 2015 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3754

ORIGINAL REPORT

Adverse event following immunization surveillance systems for pregnant women and their infants: a systematic review

Christine Cassidy[1], Noni E. MacDonald[2,3], Audrey Steenbeek[1,3] and Karina A. Top[2,3,4]*

[1] *School of Nursing, Faculty of Health Professions, Dalhousie University, Halifax, Nova Scotia, Canada*
[2] *Department of Paediatrics, Dalhousie University, Halifax, Nova Scotia, Canada*
[3] *Canadian Center for Vaccinology, IWK Health Centre, Halifax, Nova Scotia, Canada*
[4] *Department of Community Health and Epidemiology, Dalhousie University, Halifax, Nova Scotia, Canada*

Neonatal infections: Case definition and guidelines for data collection, analysis, and presentation of immunisation safety data☆

Stefania Vergnano[a], Jim Buttery[b], Ben Cailes[a], Ravichandran Chandrasekaran[c], Elena Chiappini[d], Ebiere Clark[e], Clare Cutland[f], Solange Dourado de Andrade[g], Alejandra Esteves-Jaramillo[h], Javier Ruiz Guinazu[i], Chrissie Jones[a], Beate Kampmann[j,k], Jay King[h], Sonali Kochhar[l], Noni Macdonald[m], Alexandra Mangili[n], Reinaldo de Menezes Martins[o], César Velasco Muñoz[p], Michael Padula[q], Flor M. Muñoz[r], James Oleske[s], Melvin Sanicas[t], Elizabeth Schlaudecker[u], Hans Spiegel[v], Maja Subelj[w], Lakshmi Sukumaran[x], Beckie N. Tagbo[y], Karina A. Top[m], Dat Tran[z], Paul T. Heath[a,*], The Brighton Collaboration Neonatal Infections Working Group[1]

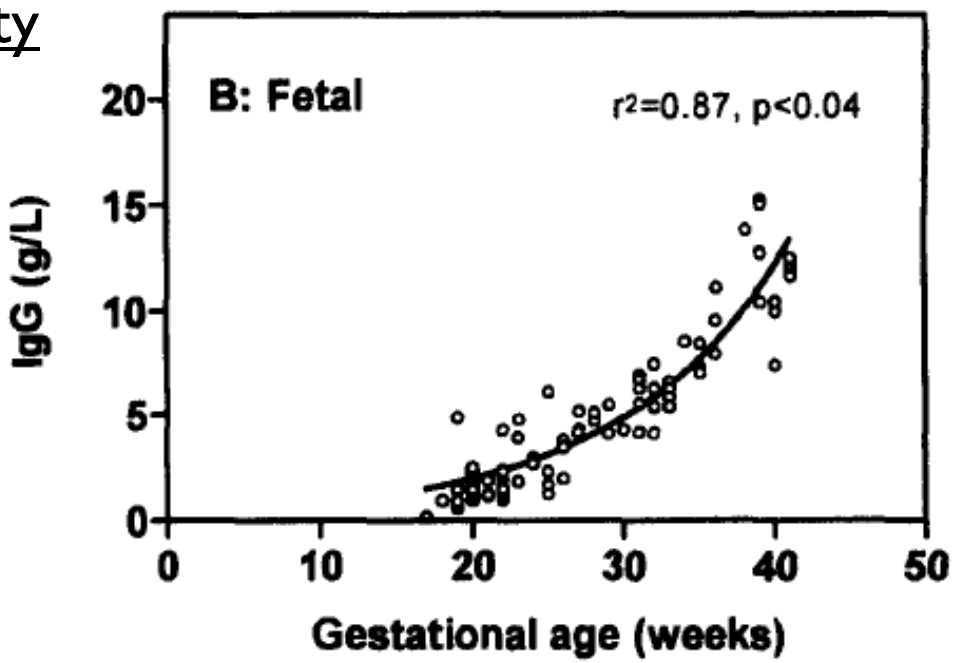
Do pregnant women respond to vaccines?

- Many immunologic changes occur during pregnancy
- Few controlled studies pregnant *vs.* non-pregnant
  - Influenza: variable results
  - Tdap, TT: no difference
  - Hepatitis B, pertussis, yellow fever: lower immunogenicity, no clinical effect
- Responses generally similar to non-pregnant women
- Conflicting data on stage of pregnancy and response
- Risks/benefits of early *vs.* later immunization
- Eliciting primary *vs.* booster responses?

When is the best time to immunize?

- Influenza – early to protect mother and infant

- Tdap?
  - Antibody <u>quantity</u>

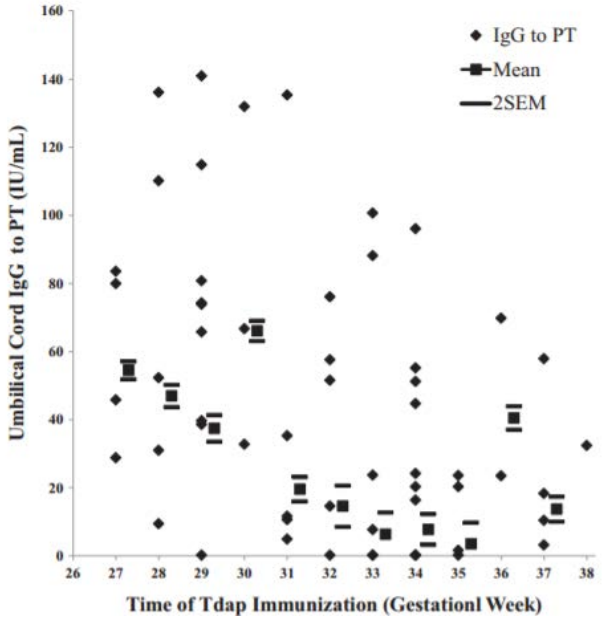


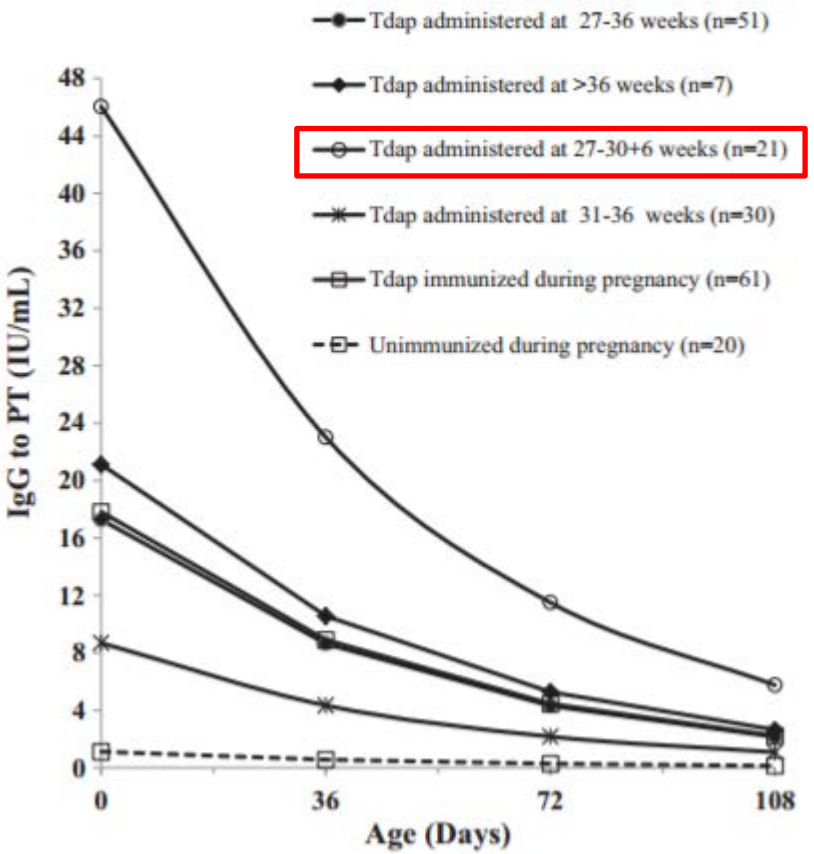
Malek et al. Am J Rep Imm (1996)

When is the best time to immunize?

- Influenza – early to protect mother and infant

- Tdap?
  - Antibody <u>quantity</u>



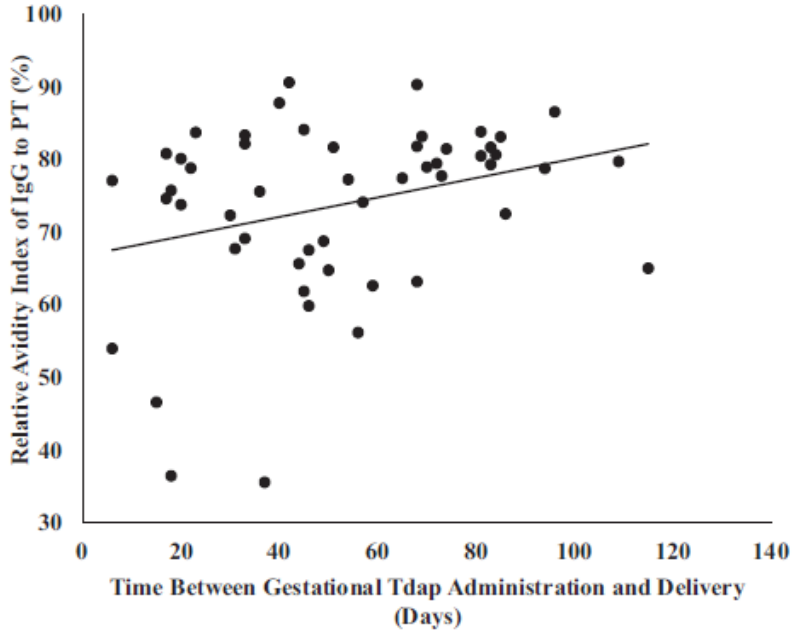


Abu Raya et al. Vaccine (2014)

When is the best time to immunize?

- Influenza – early to protect mother and infant

- Tdap?
  - Antibody quality



Abu Raya et al. Vaccine (2015)

When is the best time to immunize?

- Influenza – early to protect mother and infant
- Tdap?

The role of breast milk factors

- Strong correlation between breast feeding and reduction in infection-associated infant mortality
- Lack of data in context of immunization in pregnancy

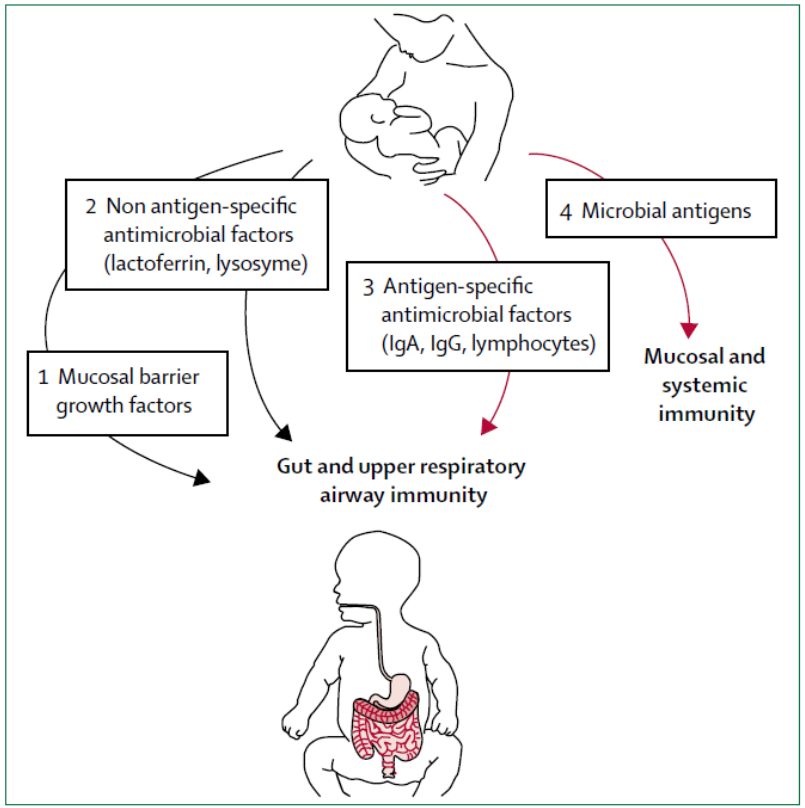


Figure 2: Transfer of maternal immunity through breastfeeding

Marchant, Sadarangani et al.
Lancet Inf Dis (2017)

Breast milk factors modified by immunization

- Secretory IgA antibodies
  - Increased after immunization in pregnancy
    - Influenza, pertussis, RSV, pneumococcus, meningococcus
  - Mucosal only or systemic effects?
  - Possible inhibition of infant mucosal vaccines

- Breast milk IgG antibodies
  - Transported from serum + produced locally
  - ~10% of IgA concentration
  - Increased after immunization in pregnancy
    - RSV, pneumococcus
  - Role unclear

Modification of infant responses?

JAMA Pediatrics | Original Investigation

The Influence of Maternally Derived Antibody and Infant Age at Vaccination on Infant Vaccine Responses
An Individual Participant Meta-analysis

Merryn Voysey, MSc; Dominic F. Kelly, PhD; Thomas R. Fanshawe, PhD; Manish Sadarangani, DPhil; Katherine L. O'Brien, PhD; Rafael Perera, PhD; Andrew J. Pollard, PhD

Figure 1. Influence of Age at First Vaccination and Preexisting Antibody Concentration Prior to Vaccination and on Antibody Concentration After the Third Priming Dose

Antigen	No. of Participants	GMR (95% CI)
Diphtheria	4897	
Maternal IgG (per 2-fold increase)		0.76 (0.74-0.77)
Age at first vaccination (per month older)		1.26 (1.18-1.35)
Tetanus	4188	
Maternal IgG (per 2-fold increase)		0.87 (0.86-0.88)
Age at first vaccination (per month older)		1.10 (1.04-1.17)
Pertussis		
PT	4941	
Maternal IgG (per 2-fold increase)		0.89 (0.87-0.90)
Age at first vaccination (per month older)		1.15 (1.10-1.20)
FHA	4952	
Maternal IgG (per 2-fold increase)		0.89 (0.88-0.90)
Age at first vaccination (per month older)		1.22 (1.16-1.28)
PRN	4778	
Maternal IgG (per 2-fold increase)		0.78 (0.77-0.80)
Age at first vaccination (per month older)		1.22 (1.14-1.29)
PRP	3369	
Maternal IgG (per 2-fold increase)		0.97 (0.94-1.00)
Age at first vaccination (per month older)		1.71 (1.52-1.92)
Polio 1	1699	
Maternal IgG (per 2-fold increase)		0.80 (0.78-0.83)
Age at first vaccination (per month older)		1.33 (1.13-1.57)
Polio 2	1699	
Maternal IgG (per 2-fold increase)		0.72 (0.69-0.74)
Age at first vaccination (per month older)		1.29 (1.09-1.53)
Polio 3	1699	
Maternal IgG (per 2-fold increase)		0.78 (0.75-0.82)
Age at first vaccination (per month older)		1.28 (1.08-1.51)
Hep B	1180	
Maternal IgG (per 2-fold increase)		0.89 (0.85-0.94)
Age at first vaccination (per month older)		1.28 (1.04-1.59)
Men C	1082	
Maternal IgG (per 2-fold increase)		0.90 (0.82-0.98)
Age at first vaccination (per month older)		1.07 (0.73-1.58)

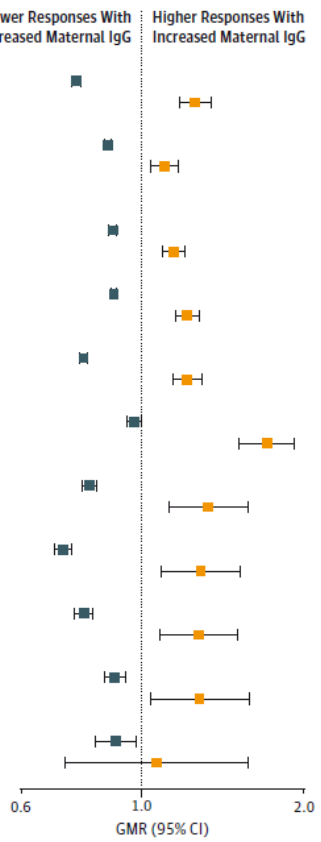
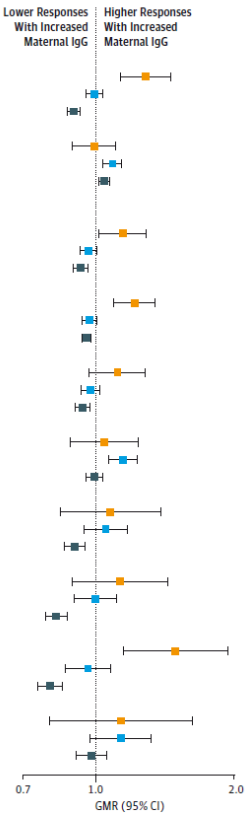


Figure 3. Influence of Age on Antibody Concentrations in Nonpneumococcal Vaccine Antigens

Antigen	No. of Participants	GMR (95% CI)
Diphtheria	2051	
Age at first vaccination (per month older)		1.28 (1.13-1.46)
Age at booster vaccination (per month older)		0.99 (0.95-1.04)
Maternal IgG (per 2-fold increase)		0.90 (0.87-0.92)
Tetanus	1732	
Age at first vaccination (per month older)		0.99 (0.89-1.10)
Age at booster vaccination (per month older)		1.09 (1.04-1.14)
Maternal IgG (per 2-fold increase)		1.05 (1.02-1.07)
Pertussis		
PT	2079	
Age at first vaccination (per month older)		1.15 (1.02-1.28)
Age at booster vaccination (per month older)		0.97 (0.93-1.01)
Maternal IgG (per 2-fold increase)		0.93 (0.89-0.96)
FHA	2412	
Age at first vaccination (per month older)		1.21 (1.09-1.34)
Age at booster vaccination (per month older)		0.97 (0.94-1.00)
Maternal IgG (per 2-fold increase)		0.96 (0.93-0.98)
PRN	2124	
Age at first vaccination (per month older)		1.11 (0.97-1.28)
Age at booster vaccination (per month older)		0.98 (0.93-1.02)
Maternal IgG (per 2-fold increase)		0.94 (0.90-0.97)
PRP	2044	
Age at first vaccination (per month older)		1.04 (0.88-1.23)
Age at booster vaccination (per month older)		1.15 (1.07-1.23)
Maternal IgG (per 2-fold increase)		0.99 (0.95-1.04)
Polio 1	488	
Age at first vaccination (per month older)		1.08 (0.84-1.38)
Age at booster vaccination (per month older)		1.05 (0.94-1.17)
Maternal IgG (per 2-fold increase)		0.90 (0.86-0.95)
Polio 2	484	
Age at first vaccination (per month older)		1.13 (0.89-1.43)
Age at booster vaccination (per month older)		1.00 (0.90-1.11)
Maternal IgG (per 2-fold increase)		0.82 (0.78-0.87)
Polio 3	464	
Age at first vaccination (per month older)		1.49 (1.15-1.93)
Age at booster vaccination (per month older)		0.96 (0.86-1.08)
Maternal IgG (per 2-fold increase)		0.80 (0.75-0.84)
Hepatitis B	558	
Age at first vaccination (per month older)		1.14 (0.80-1.62)
Age at booster vaccination (per month older)		1.13 (0.97-1.32)
Maternal IgG (per 2-fold increase)		0.98 (0.91-1.06)



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Knowledge, attitudes, perceptions

Qualitative Meta-Analysis: General Article

Qualitative Health Research
2016, Vol. 26(3) 411–425

DOI: 10.1177/1049732315573207
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"Nature Does Things Well, Why Should We Interfere?": Vaccine Hesitancy Among Mothers

Eve Dubé[1], Maryline Vivion[2], Chantal Sauvageau[2], Arnaud Gagneur[3], Raymonde Gagnon[4], and Maryse Guay[5]

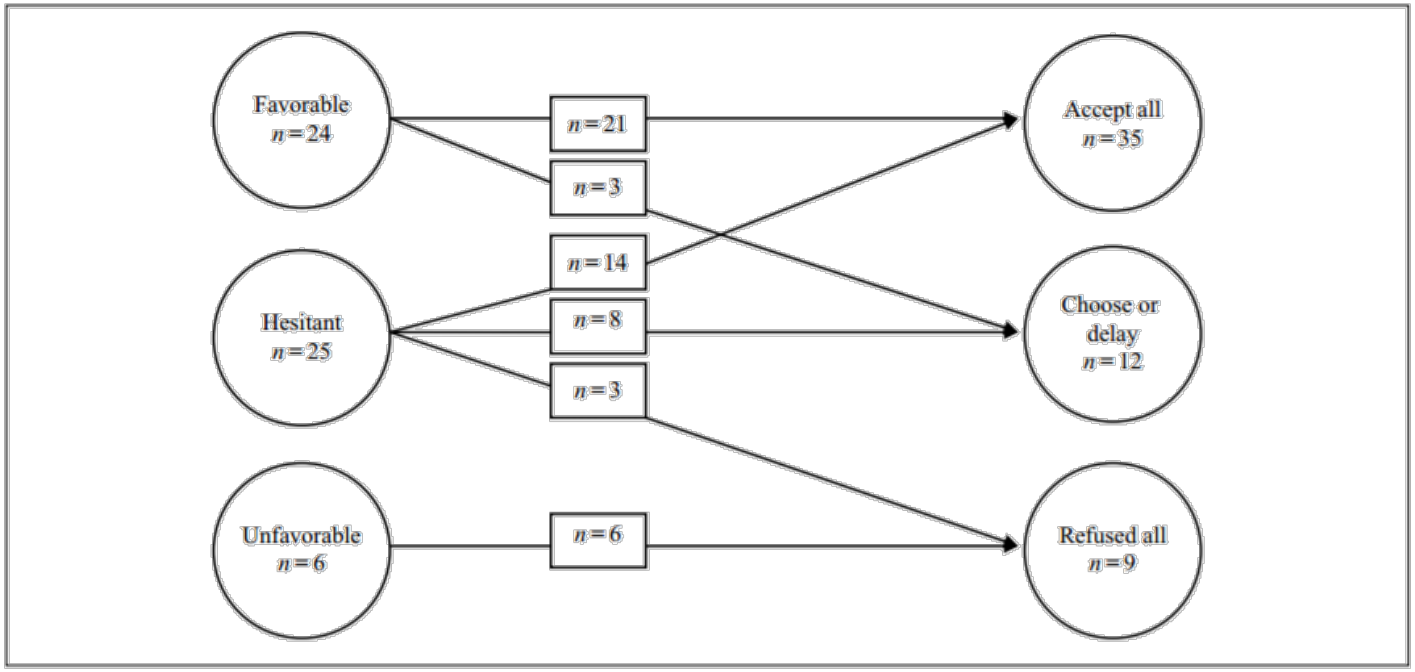

Figure 1. Mothers' attitudes at first interview and mothers' decision at second interview.

Knowledge, attitudes, perceptions

Qualitative Meta-Analysis: General Article

"Nature Does Things Well, Why Should We Interfere?": Vaccine Hesitancy Among Mothers

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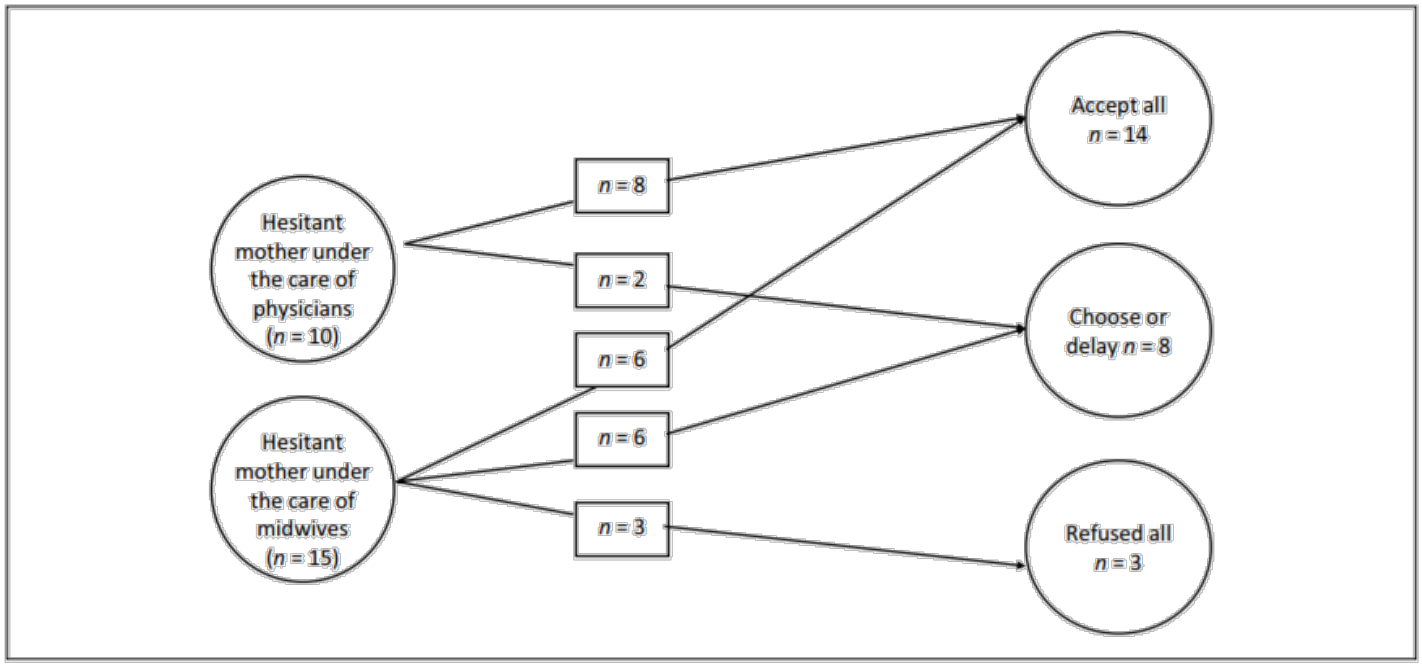

Figure 2. Vaccine-hesitant mothers' decisions and type of care.

Knowledge, attitudes, perceptions

Qualitative Meta-Analysis: General Article

Qualitative Health Research
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"Nature Does Things Well, Why Should We Interfere?": Vaccine Hesitancy Among Mothers

Eve Dubé[1], Maryline Vivion[2], Chantal Sauvageau[2], Arnaud Gagneur[3], Raymonde Gagnon[4], and Maryse Guay[5]

Table 2. Main Factors Influencing Mothers' Decision About Vaccination.

To accept all vaccines following the recommended schedule	• To protect the child from catching VPD, fear of VPD • Anticipated regret if the child catches a VPD • Because it is the "normal thing to do," vaccination as a social norm • Pressure to vaccinate (from family, spouse, friends, etc.) • Trust in health professionals' recommendation • Because the child is at particular risk of VPD (i.e., older siblings, will go to day care, etc.) • To protect others, to prevent the spread of VPD in the community
To refuse one or more vaccines and/or to delay vaccination	• As a "trade-off" position between refusing all and accepting all vaccines • Disease perceived as mild (mostly for rotavirus vaccine) • Fear of adverse events (to refuse some vaccines)/fear of diseases (to accept some vaccines) • Because it is a new vaccine (mostly for rotavirus vaccine) • Feeling of guilt/pressure to vaccinate (to accept some—all vaccines with a delayed schedule or not) • Bad experience with vaccination for the child/for others in the social network • Fear of multiple injections at the same visit • Advice/information on "alternative vaccination schedule"
To refuse all vaccines	• Perception that vaccines are unsafe and ineffective • Preference for natural immunity • Perception that risk associated with vaccination is higher than risk of VPD • Preference for other modes of protection (e.g., homeopathic vaccines)

Note. VPD = vaccine-preventable diseases.

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Influenza vaccine and uptake

- Flu vaccine during pregnancy recommended since 2007

- Uptake among pregnant women is <<< target of 80%
  - Nova Scotia: 16% seasonal vaccine post-pandemic
    - *vs.* 64% during pandemic
  - Alberta: 31% seasonal vaccine *vs.* 70% during pandemic
  - Quebec: 10% seasonal *vs.* 76% pandemic

Legge et al. CMAJ 2014
Gracie et al. J Obstet Gynaecol Can 2011
Fabry et al. Vaccine 2011

The UK pertussis problem – a case study

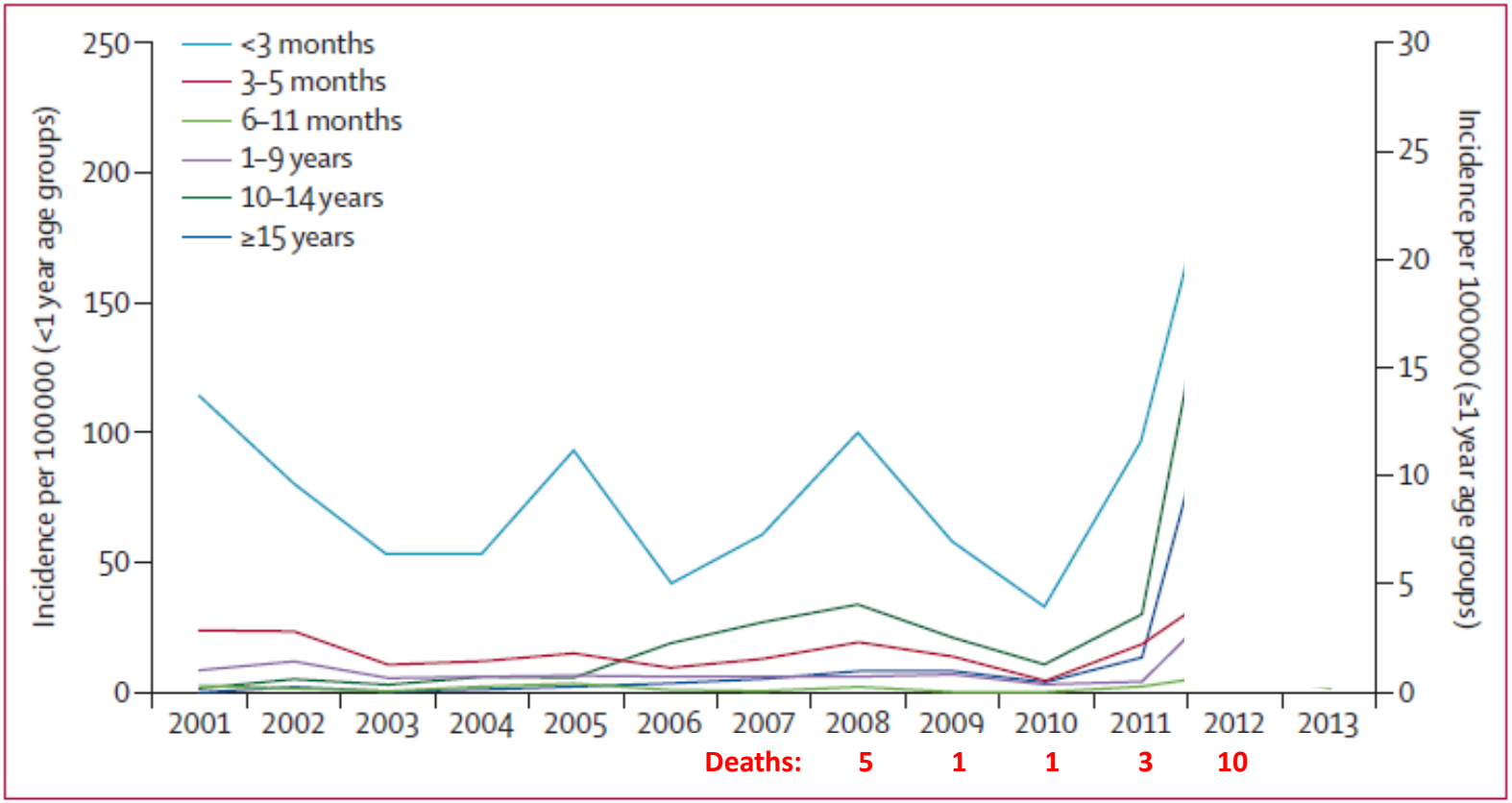


Figure 2: Annual incidence of laboratory-confirmed cases of pertussis by age group
Figure shows incidence from 2001 to 2013 in England only.

Amirthalingam et al. Lancet (2014)

What happened next?

- Urgent review by UK Joint Committee on Vaccination and Immunisation

- Sep 2012: Introduction of maternal immunization
  - "Temporary" program (outbreak response situation)
  - No need for evidence of cost-effectiveness (for 5 years)
  - dTaP/IPV to all women at 28-38 weeks pregnancy

Vaccine uptake

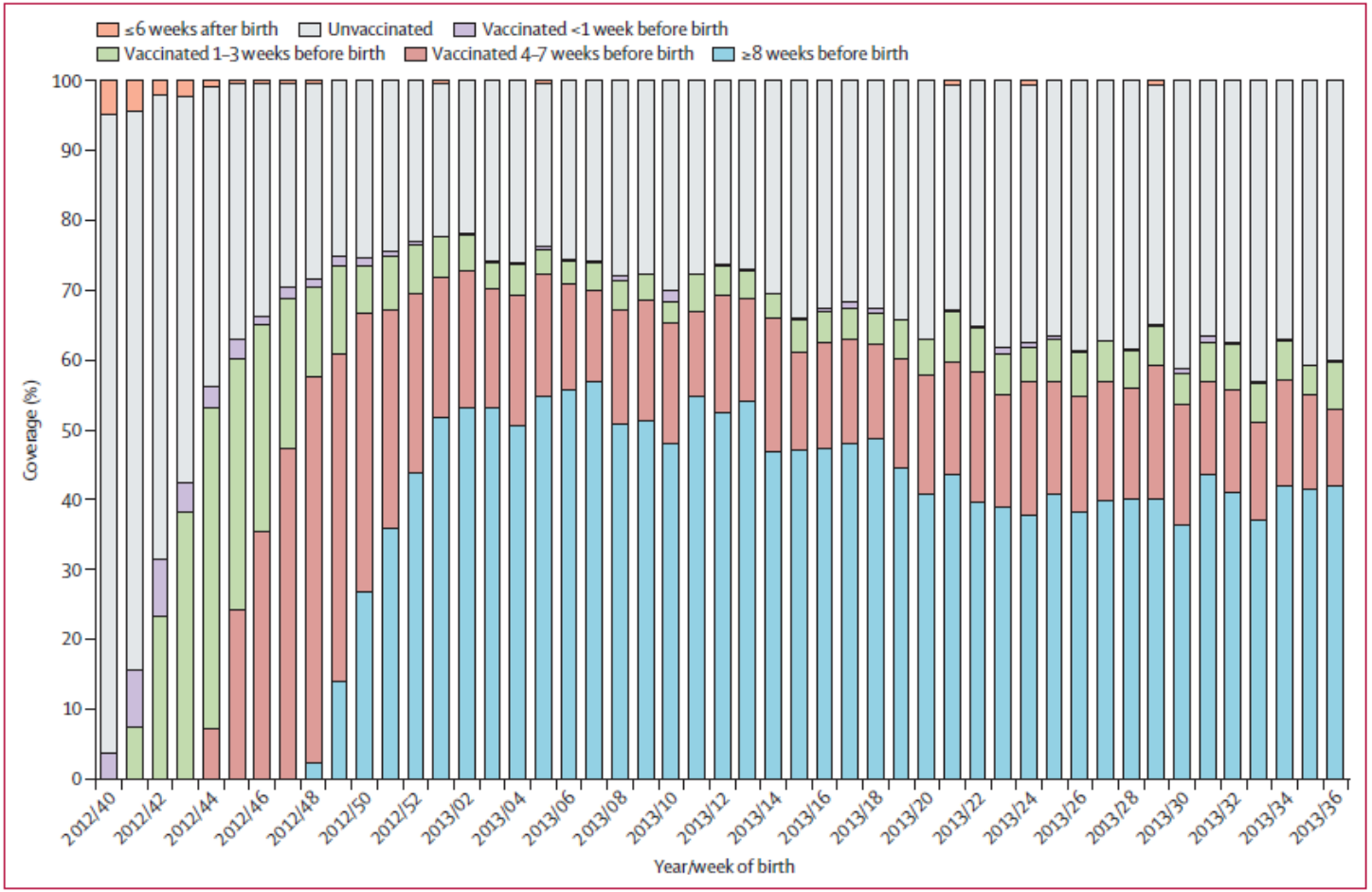


Figure 1: **Estimated maternal vaccine coverage by week of birth**
Figure shows coverage from week 40, 2012, to week 36, 2013. Figure based on data provided by the Clinical Practice Research Datalink.

Amirthalingam et al. Lancet (2014)

Vaccine impact – 1st analysis

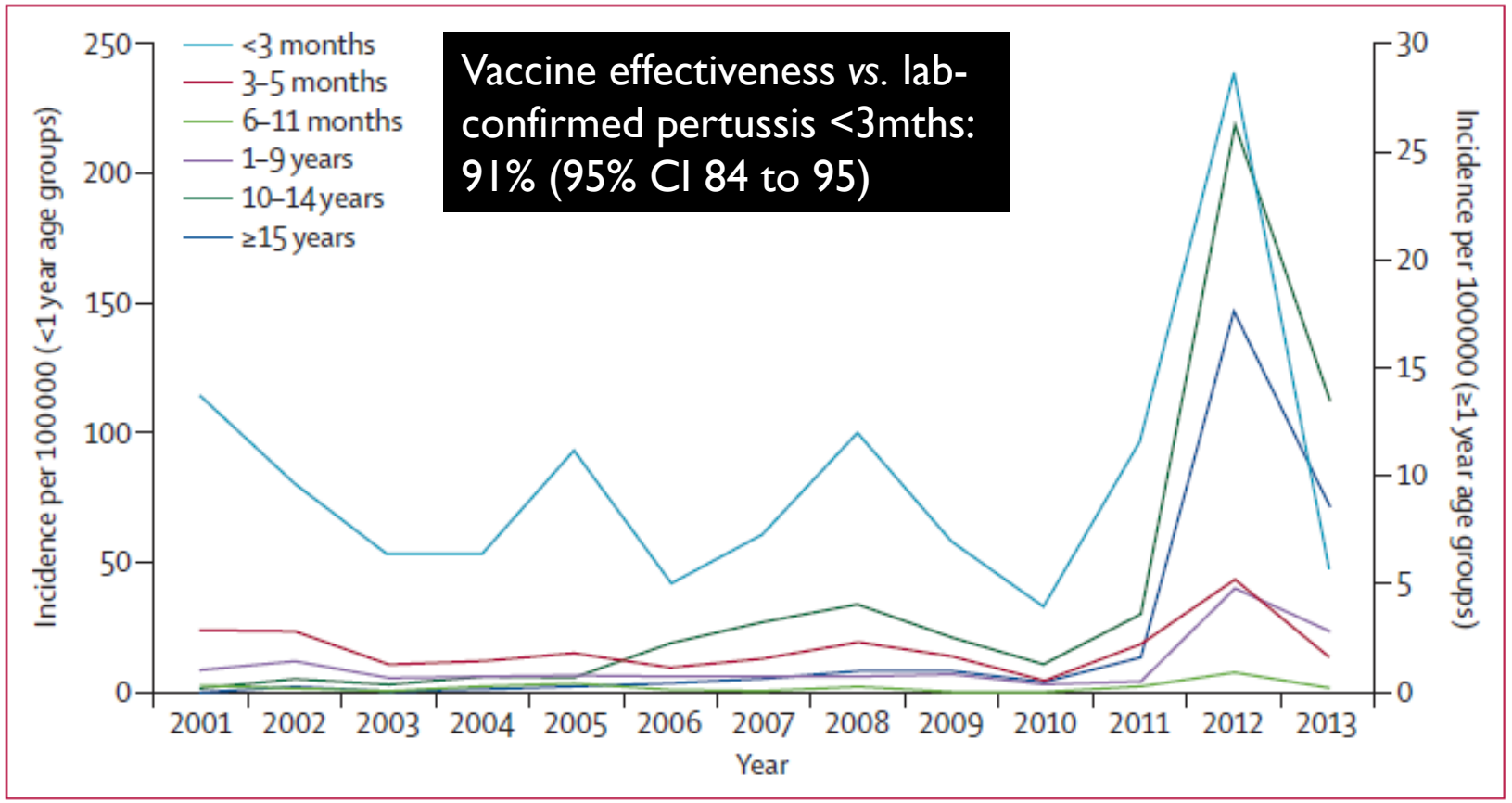


Figure 2: **Annual incidence of laboratory-confirmed cases of pertussis by age group**
Figure shows incidence from 2001 to 2013 in England only.

Amirthalingam et al. Lancet (2014)

Vaccine impact – later analyses

- Separate case-control study to assess effectiveness
  - Infants aged <8 weeks; 58 cases, 55 controls
  - Vaccine effectiveness 93%

  Dabrera et al. Clin Inf Dis (2015)

- No safety concerns in >20,000 immunized women

  Donegan et al. BMJ (2014)

- Cost-effectiveness?
  - "highly dependent on future incidence which is uncertain"

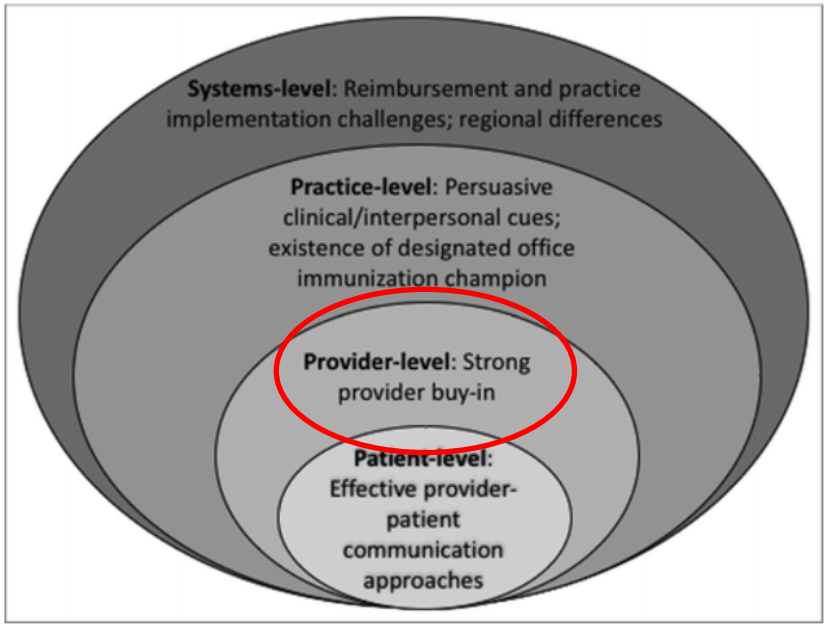
  Van Hoek et al. J Inf (2016)

- After 3 years
  - Vaccine uptake ~50-60%
  - Vaccine effectiveness (<3 mths): 91%

  Amirthalingam et al. Clin Inf Dis (2016)

Who should deliver maternal immunization programs?

- Public health clinics
- Pharmacists
  - Immunization expertise
  - Additional visits



Frew et al. Hum Vac Imm 2018

- Midwives
- Obstetricians
  - Regular contact with pregnant women
  - Philosophy to avoid all unnecessary medications
  - Multiple barriers to administering vaccines

- Family physicians?

Maternity care provider barriers

MacDougall & Halperin.
Hum Vac Imm 2016

- Lack of knowledge
- Misconceptions about disease risk
- Concerns about vaccine safety & efficacy
- Need for vaccination during pregnancy
- Lack of studies done in pregnant women
- Patient refusal
- Lack of time
- Concern about liability & blame
- Ambiguous guidelines
- Uncertainty about who bears responsibility
- Inability to track vaccination status
- Vaccination not part of typical practice

Maternity care provider facilitators

MacDougall & Halperin.
Hum Vac Imm 2016

- Positive attitude toward vaccination
- Concern about seriousness of influenza
- Belief in safety and efficacy of vaccines
- Older providers
- Vaccinated providers
- Multispecialty groups
- Engaged with influenza program
- Existence of national recommendations

Moving forward – likely a mixed model

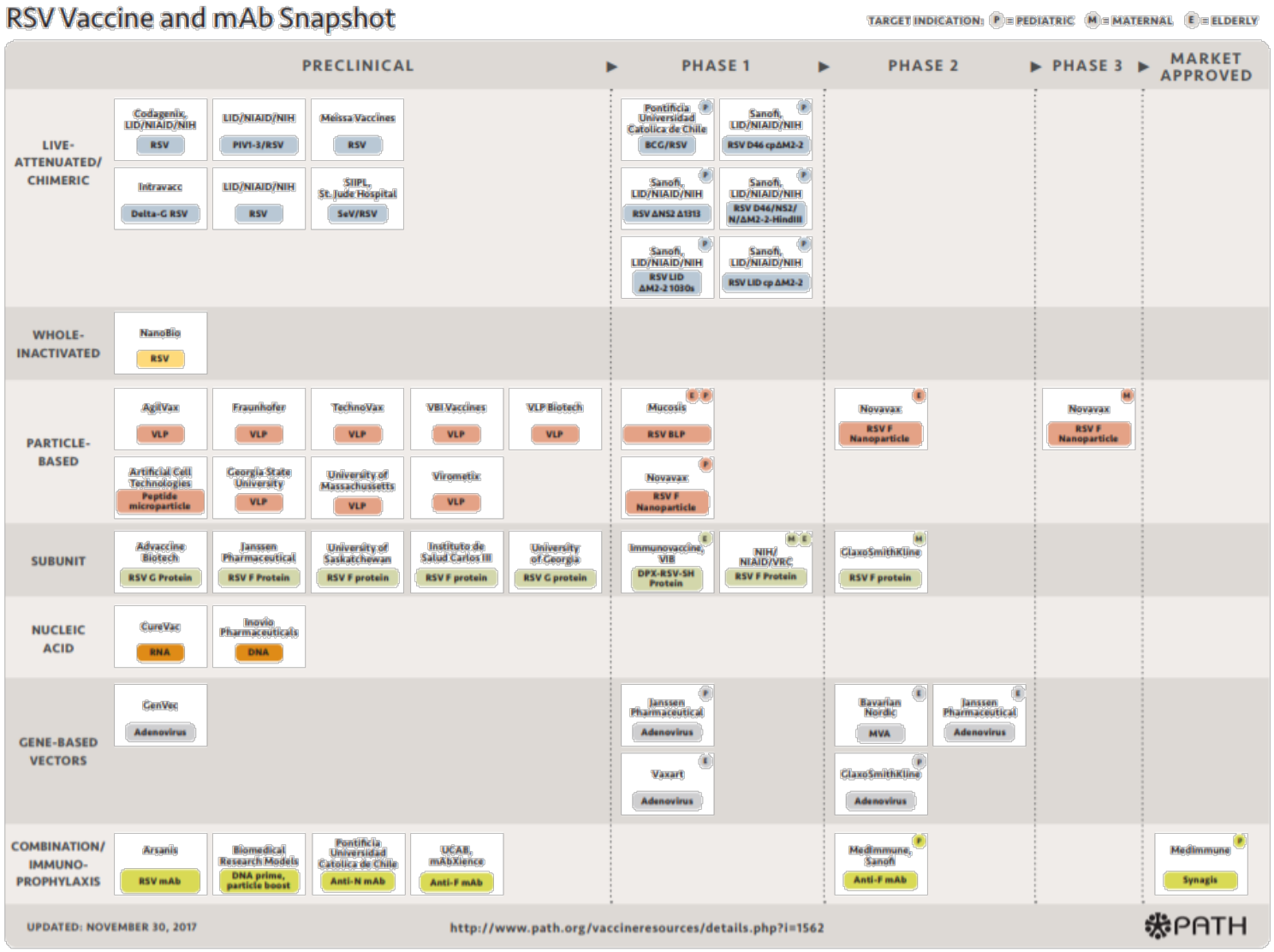
- Enhanced communication strategy
- Understanding factors contributing to hesitancy
- Timely updates to maternity care providers
- Immunization needs to be integrated into standard maternity care
- Formal maternal immunization strategy
  - Evidence-based guidelines
- Support for maternity care providers
  - Education and training
  - Immunization competency
- Avoiding missed opportunities

Avoiding the Dutch situation

"The Dutch National Institute for Public Health is currently investigating how to arrange this vaccination for pregnant women."

"Women can be vaccinated by their family doctor…not all practices offer the vaccination…or go to the Public Health Service"

The future will be busy…



Concluding remarks

- Immunization in pregnancy is highly effective in protecting pregnant women and young infants against vaccine preventable disease

- Influenza currently recommended
- Tdap to come

- Vaccine uptake in this pregnant women is low

- Comprehensive delivery will be a challenge

Thank you

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