Pertussis vaccination during pregnancy: immunological effects in pregnant women, young infants and breast milk composition

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No conflict of interest

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Examples of existing recommendations in pregnancy

ACIP (CDC), USA, August 2011

Tdap in pregnant women:

- during the third or late second trimester
- alternatively, immediately postpartum

UPDATE Oct 2012: every pregnancy and 27-36 weeks

Department of Health, UK, October 2012

Tdap(IPV) in pregnant women:

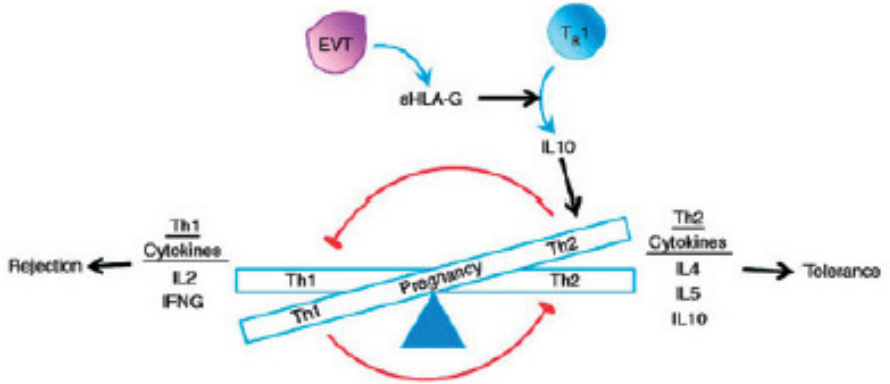
- within weeks 28 to 32 of pregnancy
- women with repeat pregnancies during each pregnancy

Superior Health Council, Belgium, July 2013

Tdap in pregnant women:

- every pregnancy between 24-32 weeks of gestation
- free and on the spot availability since July 2014

1. Immunological effects in pregnant women



a) Prostagen

- Stimulation of Th2-type response
- Less production of inflammatory cytokines

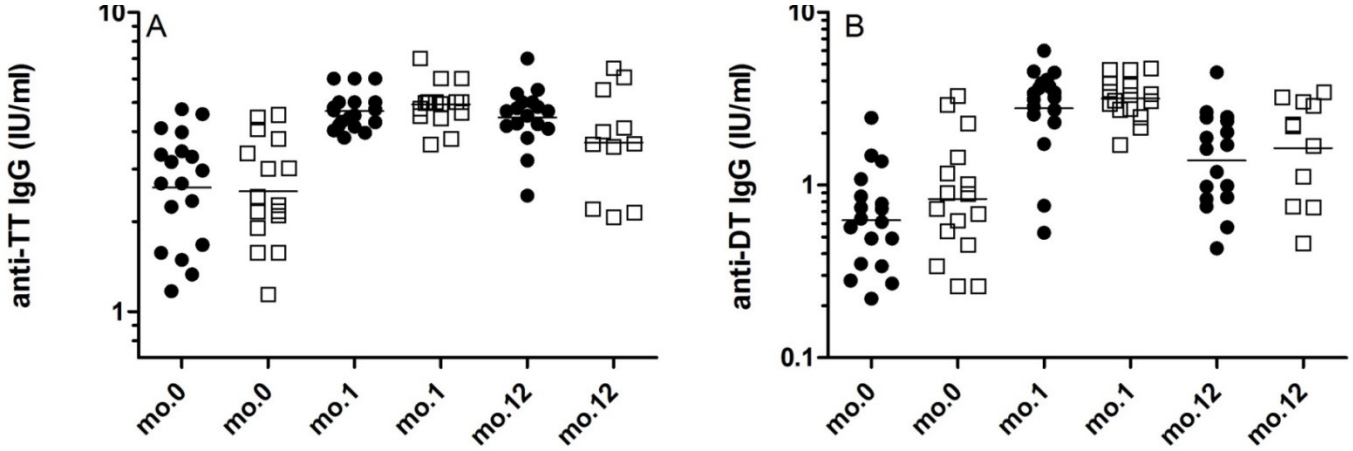
→Decrease of possible negative allogenic reactions Chen SJ et al. 2014

b) Increase oestrogen

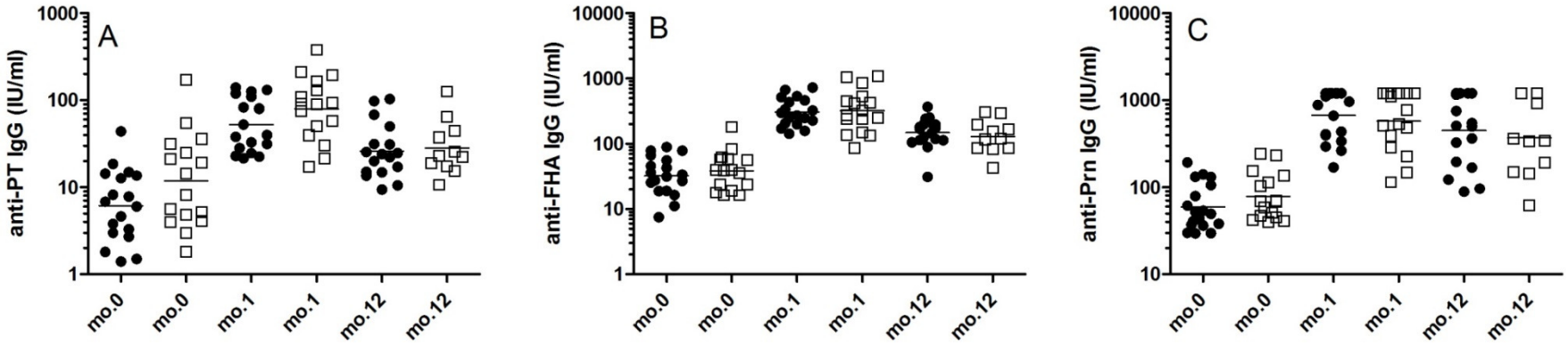
- At first: peripheral B-cells ↓
  → Possible goal: less auto-reactivity
- Later stadium:
  Improvement of B-cell maturation and antibody production

Faucette et al. Human Reproduction Update 2014.

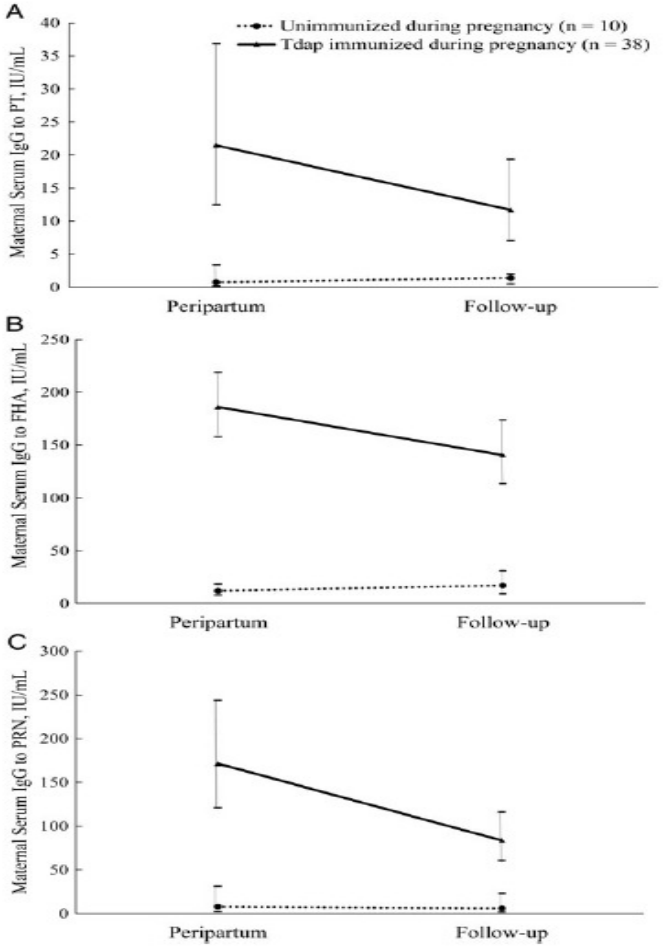
Effect of 'pregnancy' on humoral immune responses



• Pregnant □ Control

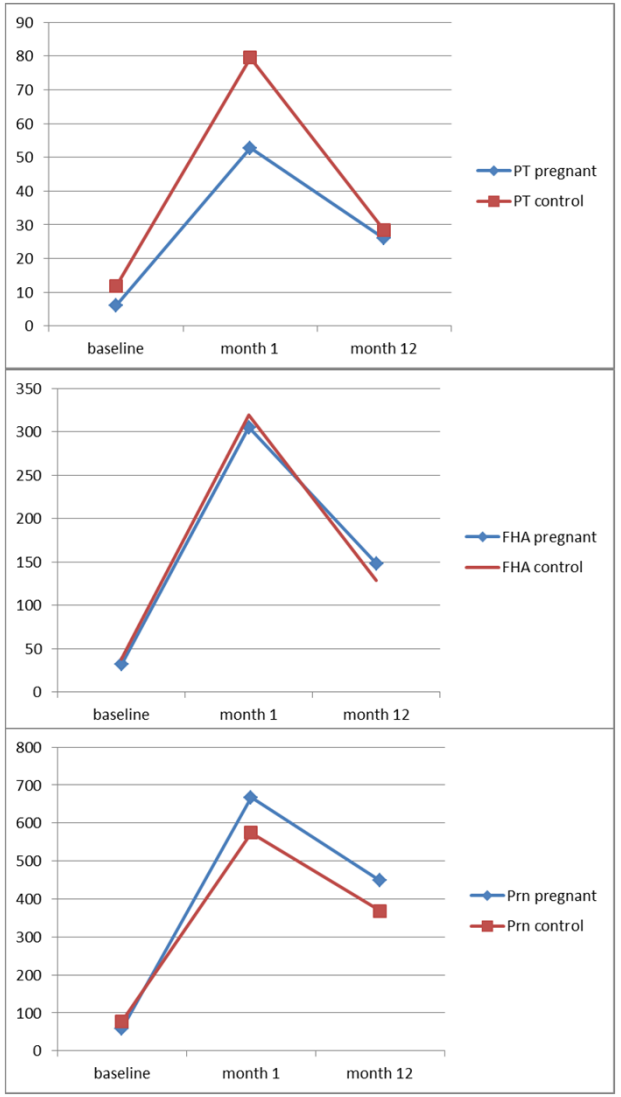


Huygen et al Vaccine 2015



Abu Raya JID 2015

Decline anti-PT/ FHA/ Prn IgG in women (9-15 months)



Huygen et al Vaccine 2015

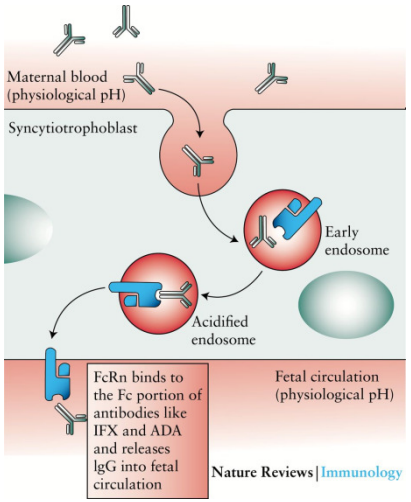
Decline anti-PT/ FHA/Prn IgG in women (12 months)

2) Immunological effects in infants

1/ Susceptibility gap

- Transplacental transport of pertussis antibodies is adequate, preferential transport of IgG towards the foetus

- Koller and Farr Nature 1966
- Gall et al AJOG 2011
- Ercan et al vaccine 2013 (premature born infants receive less anti-PTIgG)
- Healy JID 2004
- Munoz Jama 2014
- Hardy fairbanks PIDJ 2013
- Abu Raya CID 2014
- Maertens Vaccine 2015



- No correlate of protection known:
  - Is the titer of maternal antibodies high enough to offer protection?
  - How long do these antibodies persist?

2/ Persistence of the maternal pertussis antibodies

Table 2. Levels of IgG to pertussis antigens, in maternal delivery, cord, and infant serum.

Antigen	Geometric mean concentration (95% CI) [range], ELISA units/mL		
	Maternal delivery serum[a]	Cord serum[b]	Infant serum[c]
Pertussis toxin	2.4 (1.9–3.1) [1–33]	4.1 (3–5.5) [1–114]	1.4 (1.2–1.7) [1–17]
Filamentous hemagglutinin	6.9 (5–9.5) [1.5–137]	12.3 (8.8–17.3) [1.5–377]	3.0 (2.3–3.8) [1.5–62]
Fimbrial proteins	13.0 (9.2–18.5) [2.5–869]	20.4 (14–29.6) [2.5–1261]	5.8 (4.5–7.4) [2.5–123]

NOTE. CI, confidence interval.

[a] Obtained from mothers intrapartum.

[b] Obtained from umbilical cords at the time of delivery.

[c] Obtained from infants at 2 months of age.

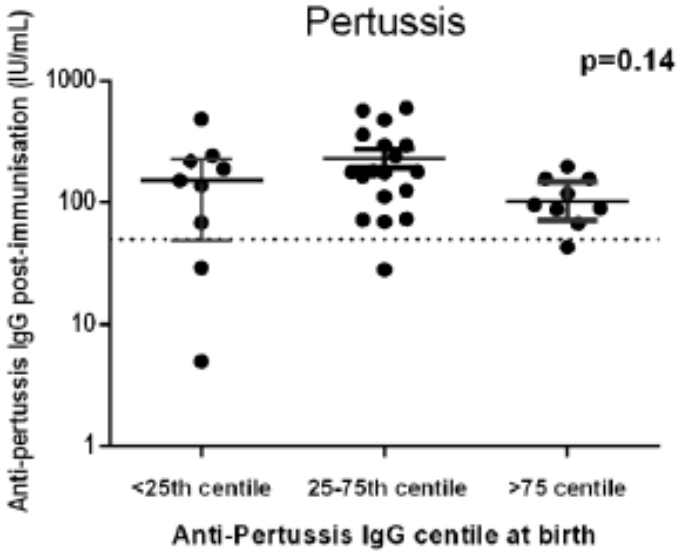
2 months, N=64

Healy JID 2004

3/ Interference/ blunting by maternal antibodies

- Interference of maternal antibodies has been described with infant immune responses to wP vaccines (Sako W TW Jama 1945; Provenzano NEJM 1965; *Englund JA*, Pediatrics 1995)

- Blunting by high titers of maternal antibodies for tetanus and pneumococcal responses, yet not for aP responses (p0.14) (Jones et al Vaccine 2014)



RCT USA: prospective double blind placebo controlled

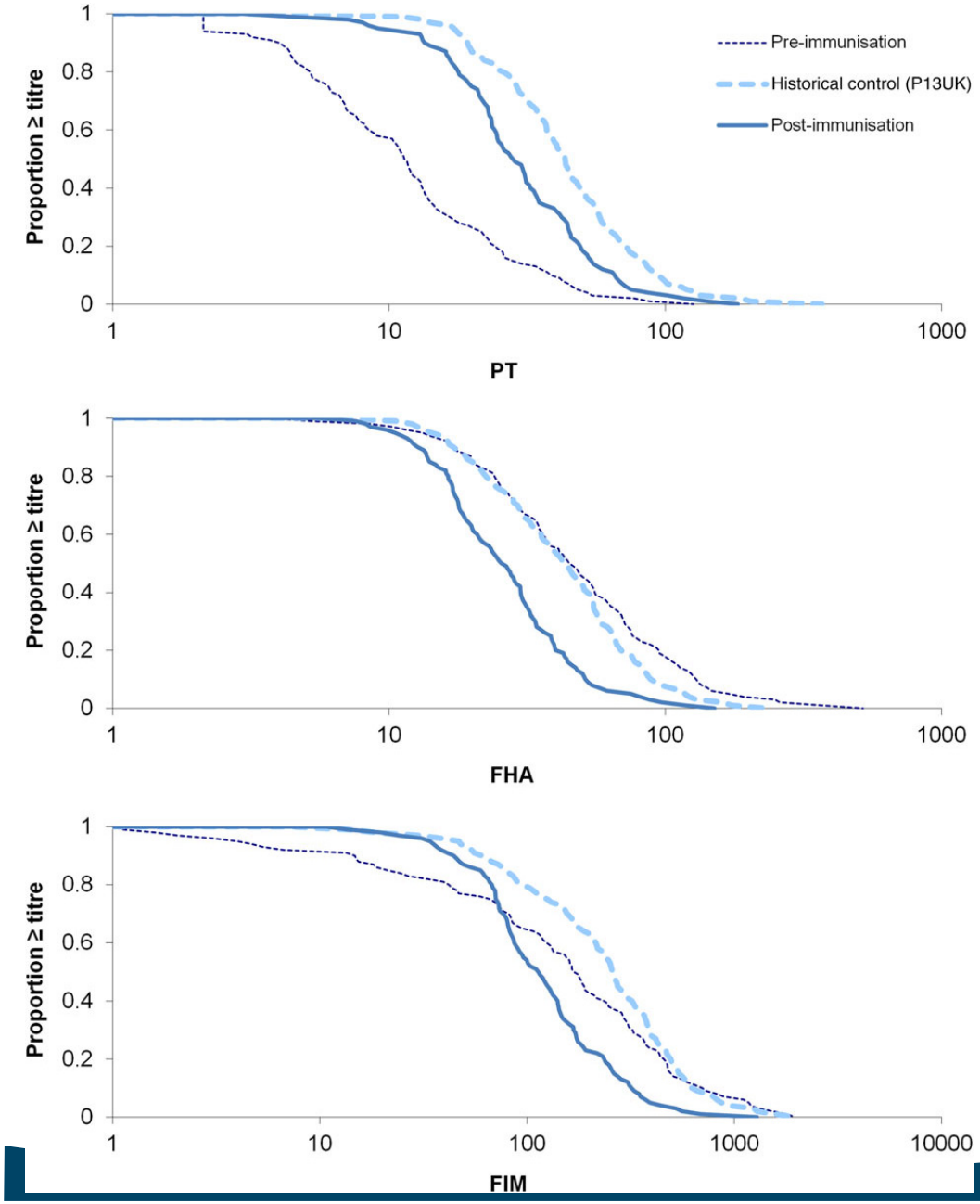
Characteristic	Women		
	Pregnant		
	Tdap Antepartum/Placebo Postpartum (n = 33)	Placebo Antepartum/Tdap Postpartum (n = 15)	Nonpregnant Tdap (n = 32)

Table 4. Geometric Mean Concentration of Antibodies to Tdap Vaccine Antigens in Sera From Mothers and Infants, and Nonpregnant Women, by Study Group and Time of Sample Collection

Antigen[a]/ Study Group	GMC (95% CI)							
	Pregnant and Nonpregnant Women				Infants			
	Prior to Immunization[b]	4 wk After Antepartum Tdap or Placebo[b]	At Delivery	2 Mo After Delivery	At Birth (Cord Blood)	Months 2	Months 7	Months 13
Pertussis toxin, EU/mL								
Antepartum[c]	7.9 (4.9-12.6)	56.5 (40.0-79.9)	51.0 (37.1-70.1)[f]	53.1 (39.4-71.7)[f]	68.8 (52.1-90.8)[f]	20.6 (14.4-29.6)[f]	64.9 (53.8-78.3)	80.1 (57.3-112.1)
Postpartum[d]	9.6 (5.2-17.6)	10.2 (5.6-18.7)	9.1 (4.6-17.8)	66.4 (42.2-104.8)	14.0 (7.3-26.9)	5.3 (3.0-9.4)	96.6 (56.7-164.6)	83.9 (50.0-140.8)
Nonpregnant	17.6 (12.5-24.7)	90.9 (69.1-119.7)						

Muñoz et al JAMA 2014

Study UK: prospective, historically controlled study



Pre- iMap: at 2 months before primary immunisation
Post-iMap: at 5 months (one month after primary immunisation)
Post P13-UK: at 5 months for historical cohort of infants whose mothers did not receive pertussis vaccine in pregnancy
IMAP cohort: N= 141 infants
Historical control: N= 203 infants

Conclusion: high pre-immunization antibody concentrations, but blunting of subsequent responses to pertussis toxin

Ladhani et al CID 2015

Table 2. Geometric Mean Concentrations and Proportions Above the Protective Thresholds for Diphtheria, Tetanus, Hib, and 13 Pneumococcal Serotypes After Primary Immunization in Infants Whose Mothers Were Given a Pertussis-containing Vaccine in the Third Trimester Compared With Infants in the Historical Cohort Whose Mothers Did Not Receive a Pertussis-containing Vaccine During Pregnancy

Vaccine Antigen	iMAP N	Geometric Mean (95% CI)	% >Threshold[a] (95% CI)	Historic Control N	Geometric Mean (95% CI)	% >Threshold[a] (95% CI)	Geometric Mean Fold Ratio[b] (iMap/control)	*P* Value for Fold Ratio
Diphtheria toxin	131	0.55 (.47–.63)	97.7 (93.5–99.5)	204	1.00 (.89–1.12)	100 (98.2–199)	0.55 (0.46–0.66)	<.001
Tetanus toxin	131	1.36 (1.24–1.50)	100 (97.2–100)	204	1.11 (.99–1.25)	100 (98.2–100)	1.24 (1.05–1.46)	.011
Hib	131	4.92 (3.71–6.51)	96.2 (91.3–98.7)	205	2.17 (1.71–2.77)	90.7 (85/9–94.3)	2.30 (1.59–3.34)	<.001
Pneumococcal serotype								
1	127	1.35 (1.18–1.54)	95.3 (90.0–98.2)	234	1.84 (1.63–2.07)	96.2 (92.8–98.2)	0.74 (0.61–0.89)	.001
3	124	0.56 (.51–.63)	76.6 (68.2–83.7)	231	1.65 (1.49–1.82)	97.4 (94.4–99.0)	0.34 (0.29–0.40)	<.001
4	127	1.08 (.96–1.22)	96.1 (91.1–98.7)	235	1.55 (1.41–1.70)	97.0 (94.0–98.9)	0.70 (0.60–0.82)	<.001
5	126	0.57 (.50–.65)	73.8 (65.2–81.2)	235	0.96 (.87–1.08)	88.5 (83.7–92.3)	0.59 (0.50–0.70)	<.001
6A	126	0.90 (.75–1.07)	81.0 (73.0–87.4)	234	1.56 (1.35–1.80)	89.3 (84.6–93.0)	0.58 (0.46–0.73)	<.001
6B	126	0.36 (.31–.42)	45.2 (36.4–54.3)	232	0.32 (.29–.36)	38.7 (32.4–45.4)	1.11 (0.92–1.33)	.28
7F	126	2.04 (1.80–2.32)	97.6 (93.2–99.5)	235	2.63 (2.37–2.93)	98.3 (95.7–99.5)	0.78 (0.65–0.93)	.005
9V	125	0.72 (.61–.85)	75.2 (66.7–82.5)	234	0.93 (.83–1.04)	87.6 (82.7–91.5)	0.78 (0.64–0.95)	.014
14	127	4.76 (3.94–5.76)	98.4 (94.4–99.8)	233	5.28 (4.54–6.13)	97.9 (95.1–99.3)	0.90 (0.71–1.15)	.41
18C	126	1.08 (.92–1.26)	90.5 (84.0–95.0)	235	1.19 (1.06–1.34)	89.4 (84.7–93.0)	0.91 (0.74–1.11)	.35
19A	126	1.27 (1.06–1.51)	87.3 (80.2–92.6)	234	1.56 (1.38–1.77)	94.9 (91.2–97.3)	0.81 (0.66–1.01)	.058
19F	126	4.01 (3.48–4.64)	100 (97.1–100)	234	4.57 (4.04–5.16)	99.6 (97.6–100)	0.88 (0.73–1.07)	.21
23F	124	0.64 (.54–.78)	64.5 (55.4–72.9)	234	0.69 (.60–.79)	68.8 (62.4–74.7)	0.94 (0.74–1.19)	.61

Effect on other components of infant vaccination schedule

- CRM conjugated vaccines: less good responses
- MCC-TT and Hib-TT enhanced response

Ladhani et al CID 2015

RCT Belgium: prospective randomised controlled study

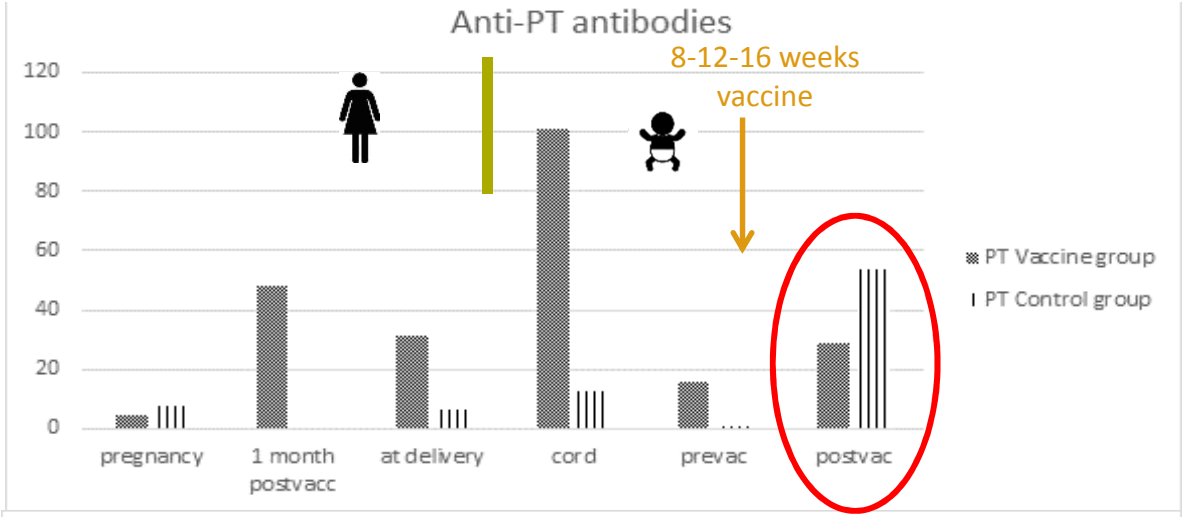
Design

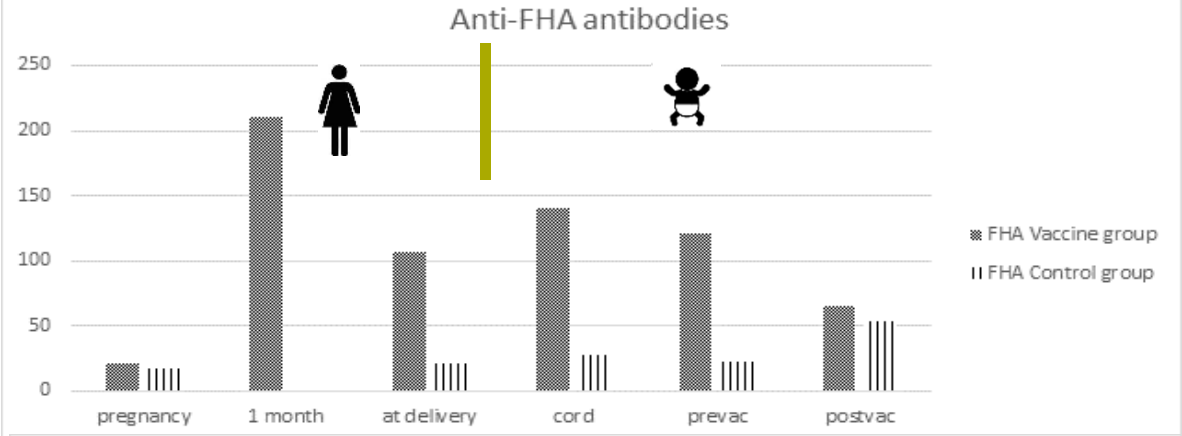
- VACCINE GROUP: Boostrix®
- CONTROL GROUP: no pertussis containing vaccine for at least 10 years
- Children vaccinated with Infanrix hexa according to the standard Belgian vaccination schedule

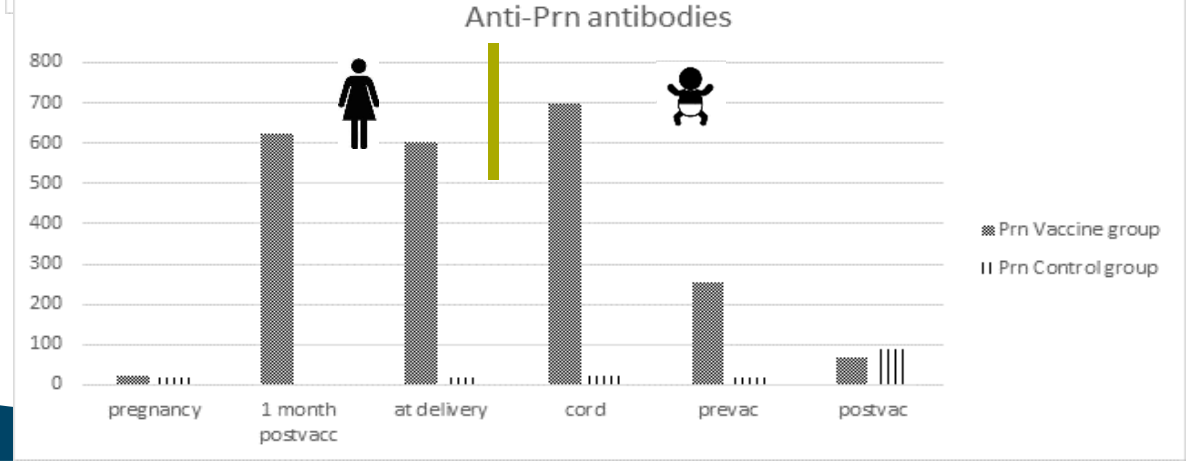
Laboratory tests (also the Vietnam study)

- ELISA: IgG against
  - pertussis toxin (PT) (Virion Serion),
  - filamentous Haemmaglutinin (FHA), pertactin (PRN), Tetanus Toxoid (TT) and Diphtheria Toxoid (DT) (Euroimmune)
- Anti-PT antibodies validated in a subsample at Dalhousie University

Maertens & Leuridan et al, Vaccine 2015, accepted







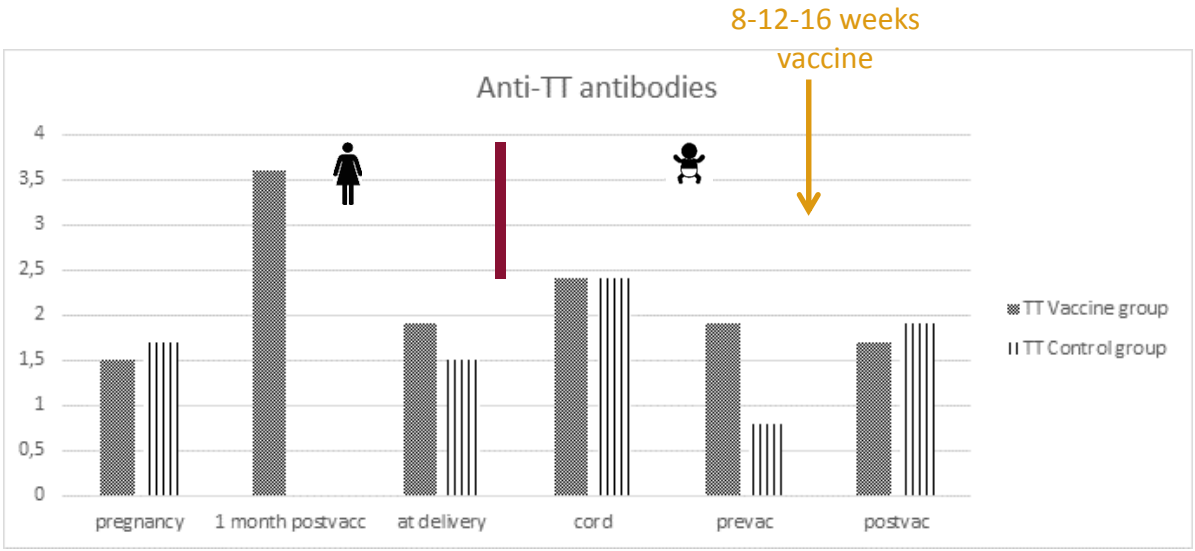
Vaccine group (Boostrix): N= 57 women, 55 infants

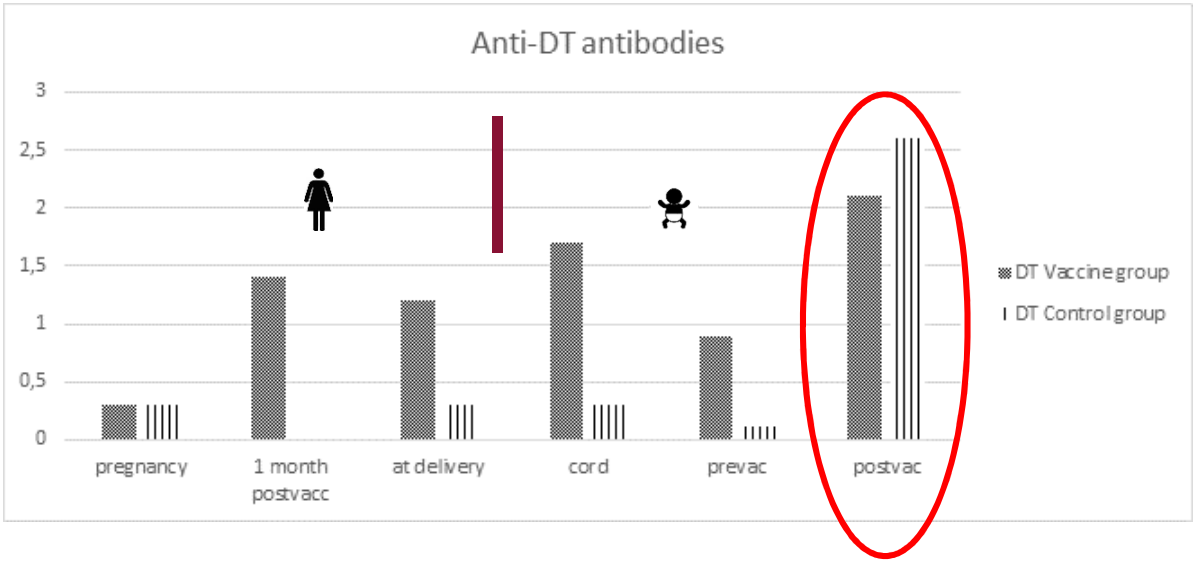
Control group (no vaccine): N=42 women, 26 infants

Infants received Infanrix hexa

significant

Maertens & Leuridan et al, Vaccine 2015, accepted





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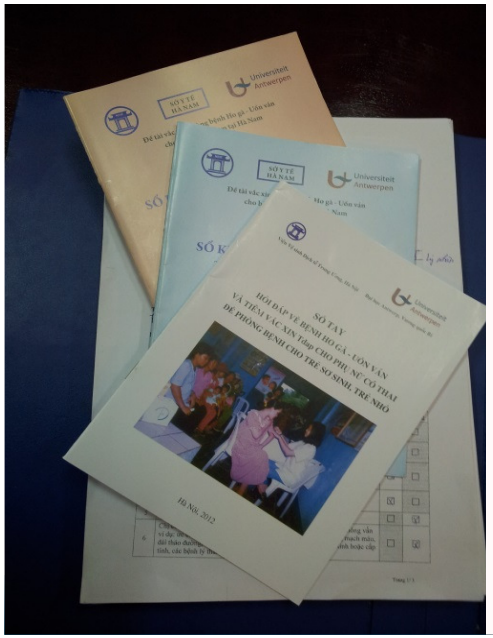
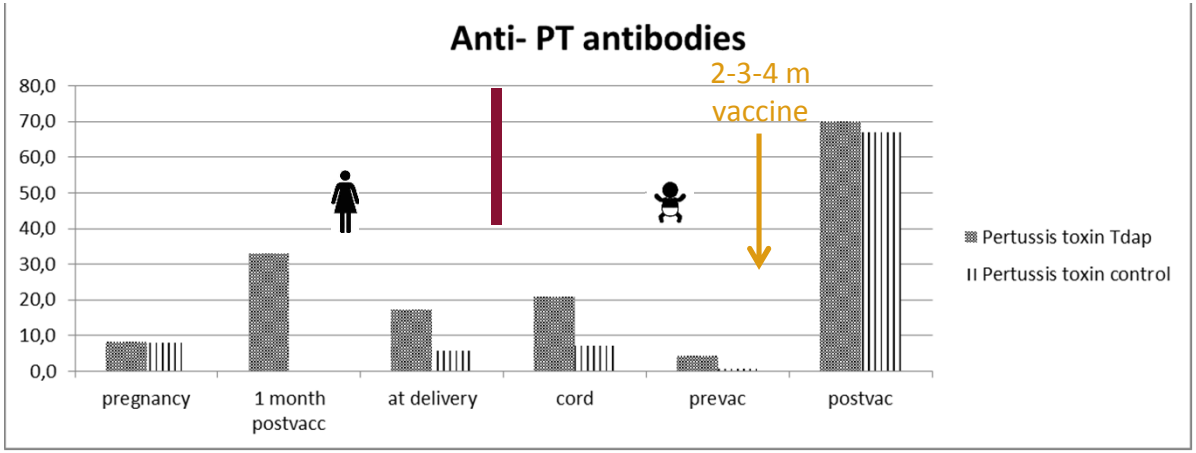
Maertens & Leuridan et al, accepted, Vaccine

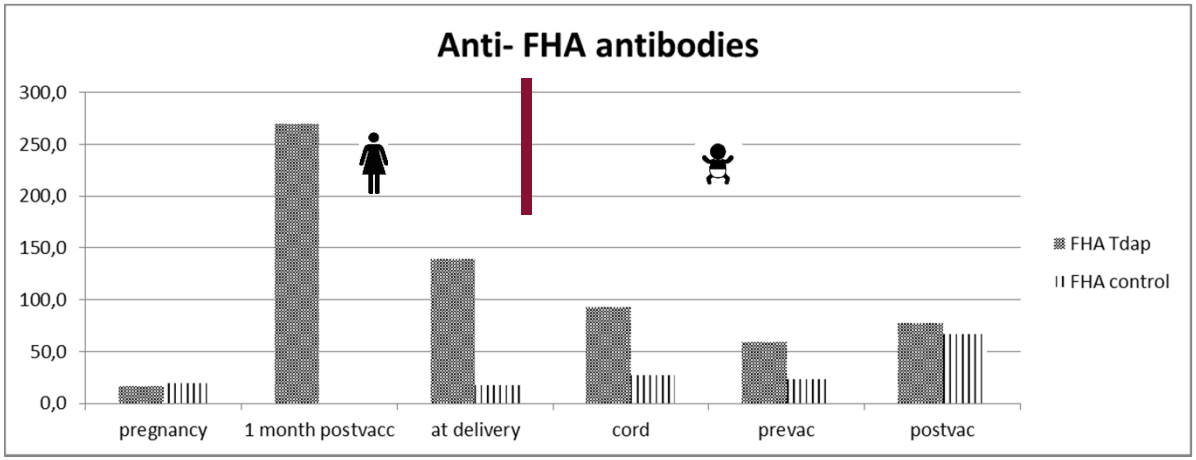
RCT Vietnam: prospective randomised controlled study

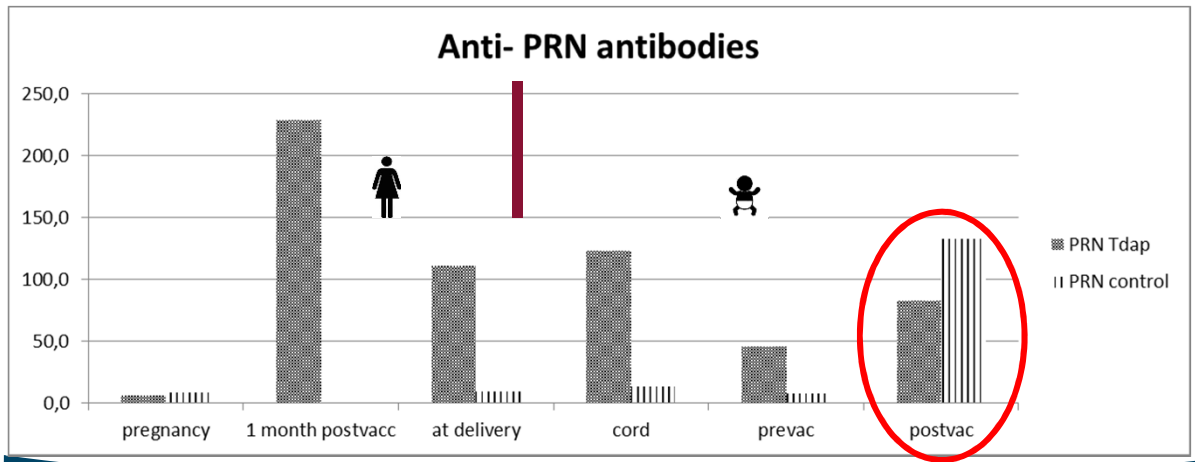
Dr Hoang Thi Thu Ha, Dr Hong, Dr Trung Dac Nguyen, Dr Vu Ngoc Ha, Prof Dr Dang Duc Anh
National Institute Hygiene and Epidemiology, Hanoi, Vietnam

and the team in Antwerp









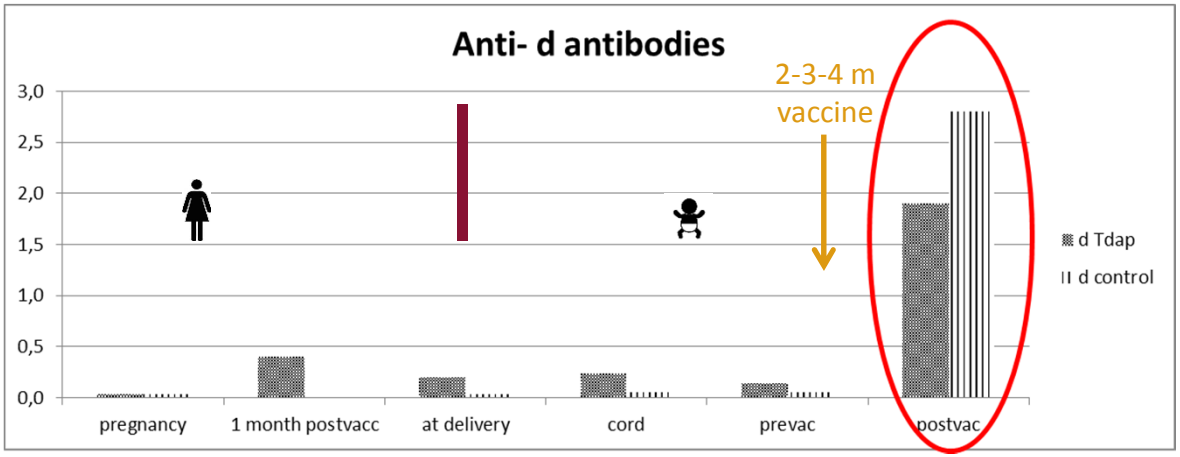
Vaccine group (Adacel): N= 52 women, 51 infants

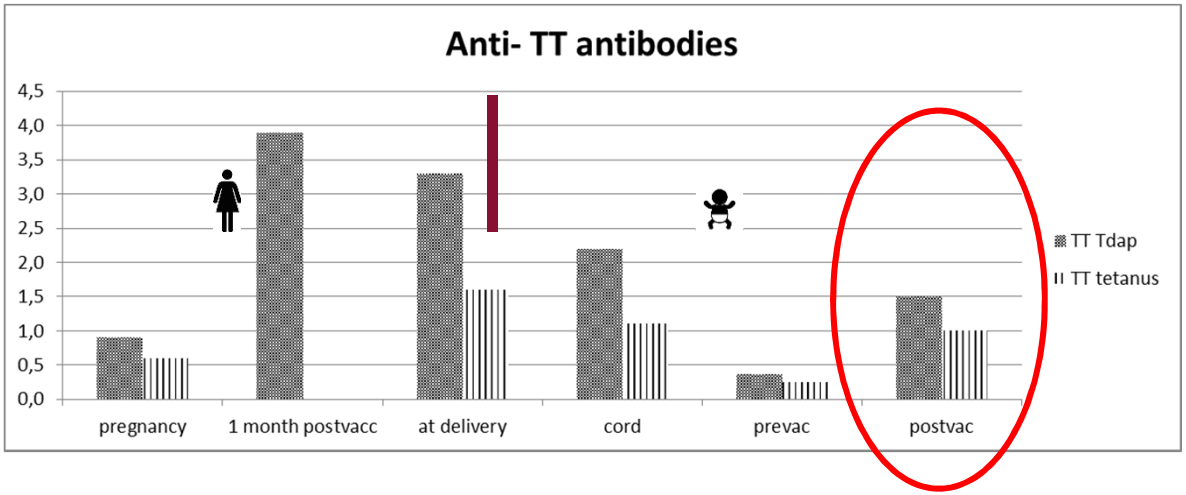
Control group (TTvac): N=51 women, 48 infants

Infants received Infanrix hexa

Hoang & Leuridan et al, Vaccine 2015, online proof available

significant





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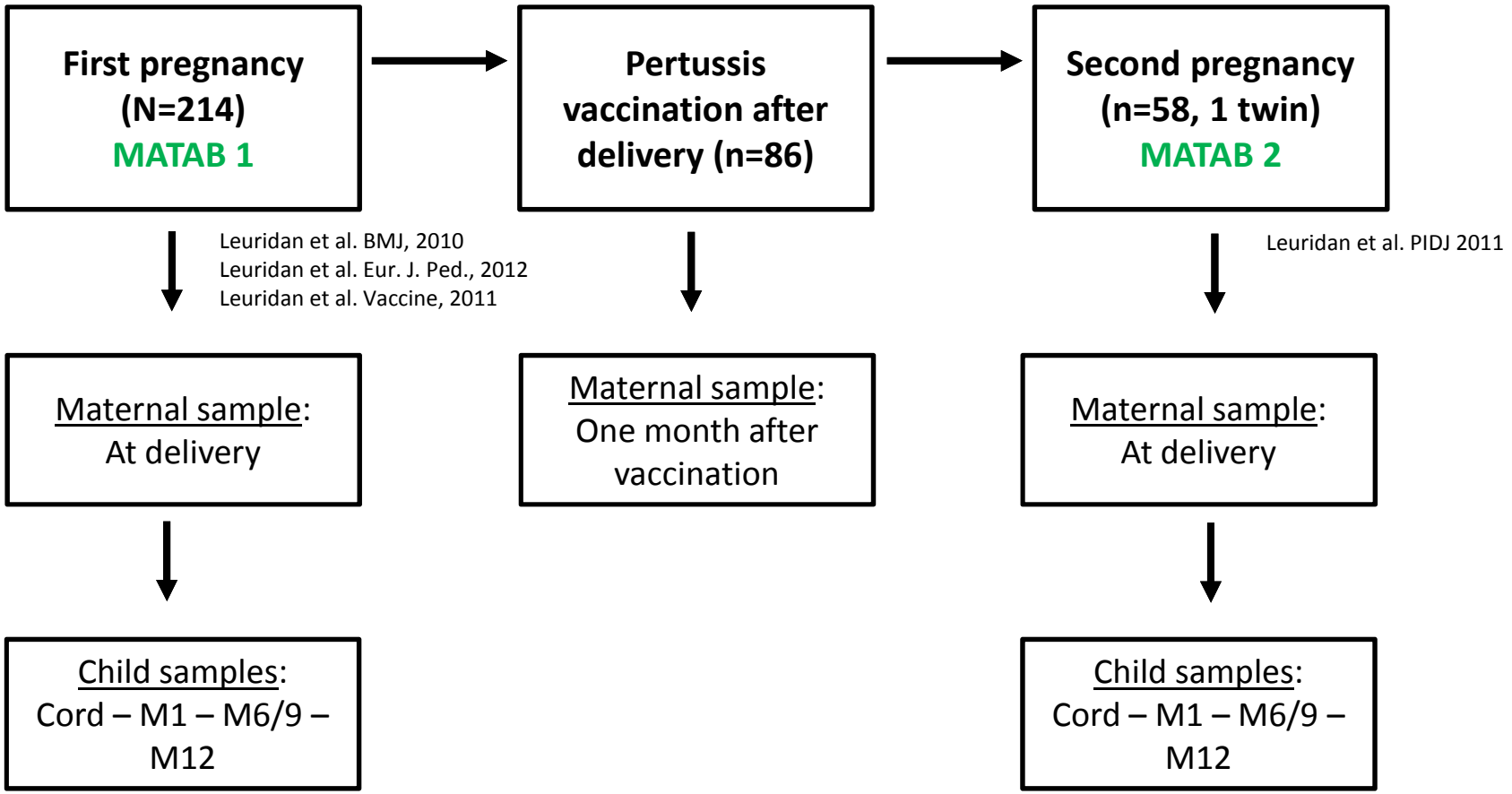
Hoang & Leuridan et al, Vaccine, online proof available

Reasons for differences BE-VN:

- Different brand of vaccine in pregnancy
- Different population (might have been first dose in women)

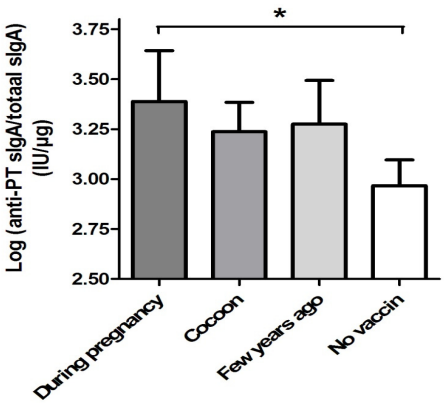
significant

Belgium: pre-pregnancy study (confidential results)



3. Effect in breast milk

- Protective effect of pertussis sIgA in human breast milk: up to 50% neutralisation of pertussis toxin in mice (Quinello C Scand J Immunol 2010)
- Significant effect of vaccination during pregnancy or cocoon vaccination at 8 weeks postpartum (De Schutter et al PIDJ, 2015)
- Significant effect during 2 weeks for anti-PT, yet not for anti-FHA sIgA (Abu Raya Vaccine, 2014)



8 weeks

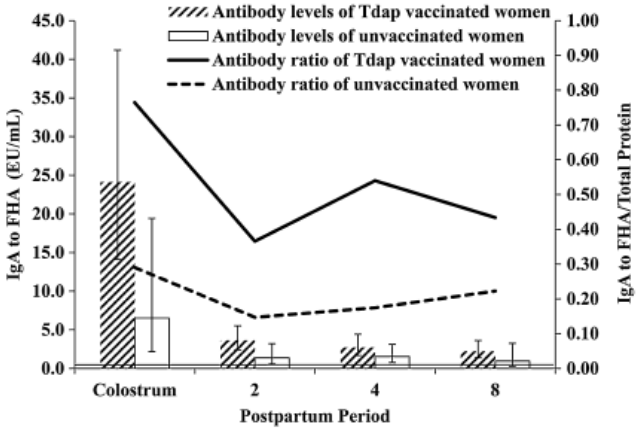


Fig. 2. Breast milk immunoglobulin A (IgA) to filamentous haemagglutinin (FHA) and its ratio to total protein of postpartum women vaccinated with tetanus–diphtheria–acellular pertussis (Tdap) during late pregnancy and unvaccinated postpartum women at sequential time intervals (weeks). Antibody levels are represented as geometric mean concentrations + 95% confidence interval. Horizontal line represents the lower limit of IgA to FHA detection (0.2 ELISA Unit per milliliter (EU/mL)). Antibody ratios are represented as geometric mean.

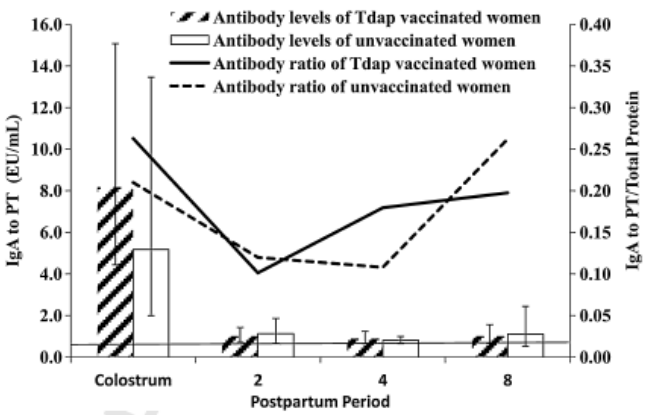
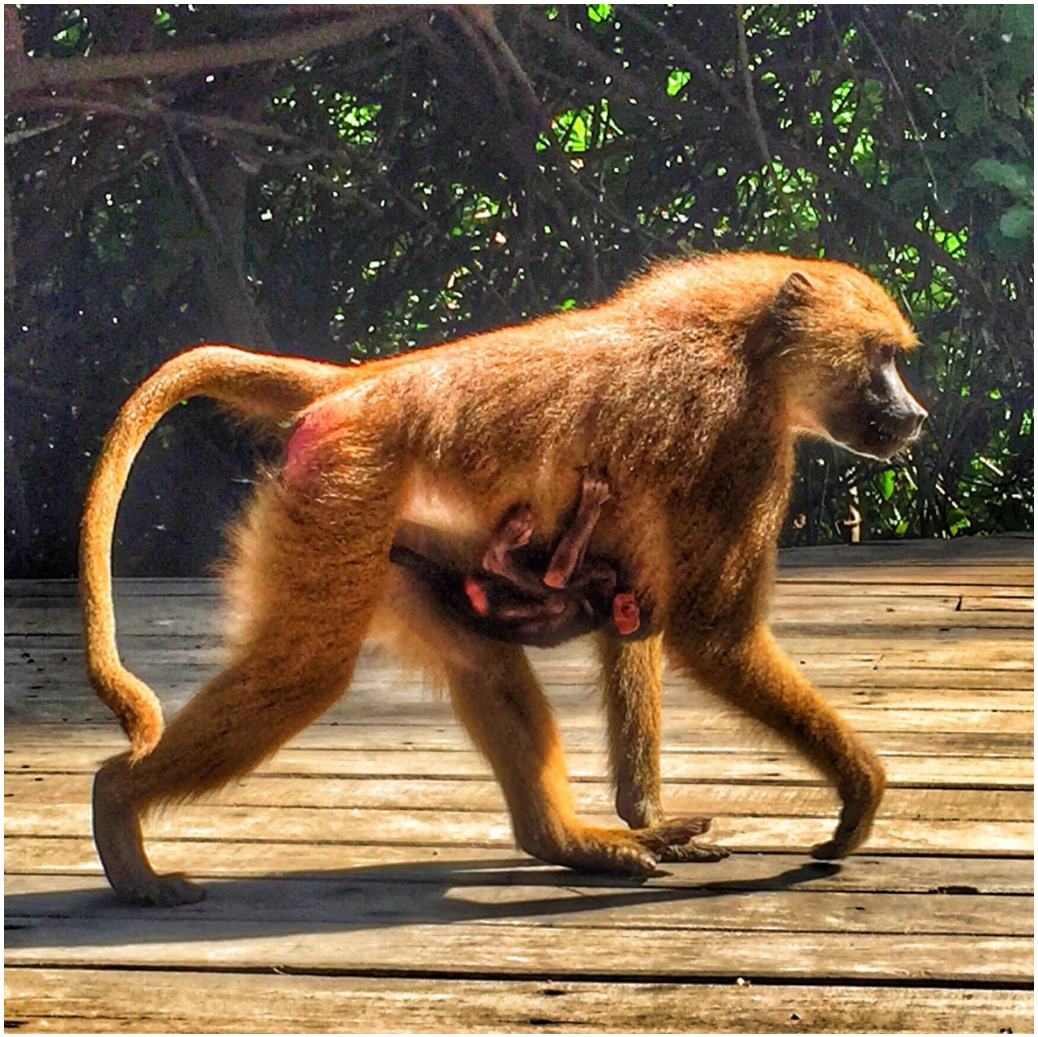


Fig. 1. Breast milk immunoglobulin A (IgA) to pertussis toxin (PT) and its ratio to total protein of postpartum women vaccinated with tetanus–diphtheria–acellular pertussis (Tdap) during late pregnancy and unvaccinated postpartum women at sequential time intervals (weeks). Antibody levels are represented as geometric mean concentrations in ELISA Unit per milliliter (EU/mL) + 95% confidence interval. The horizontal line represents the lower limit of IgA to PT detection (0.7 EU/mL). Antibody ratios are represented as geometric mean.



Challenges in research on pertussis vaccination in pregnancy

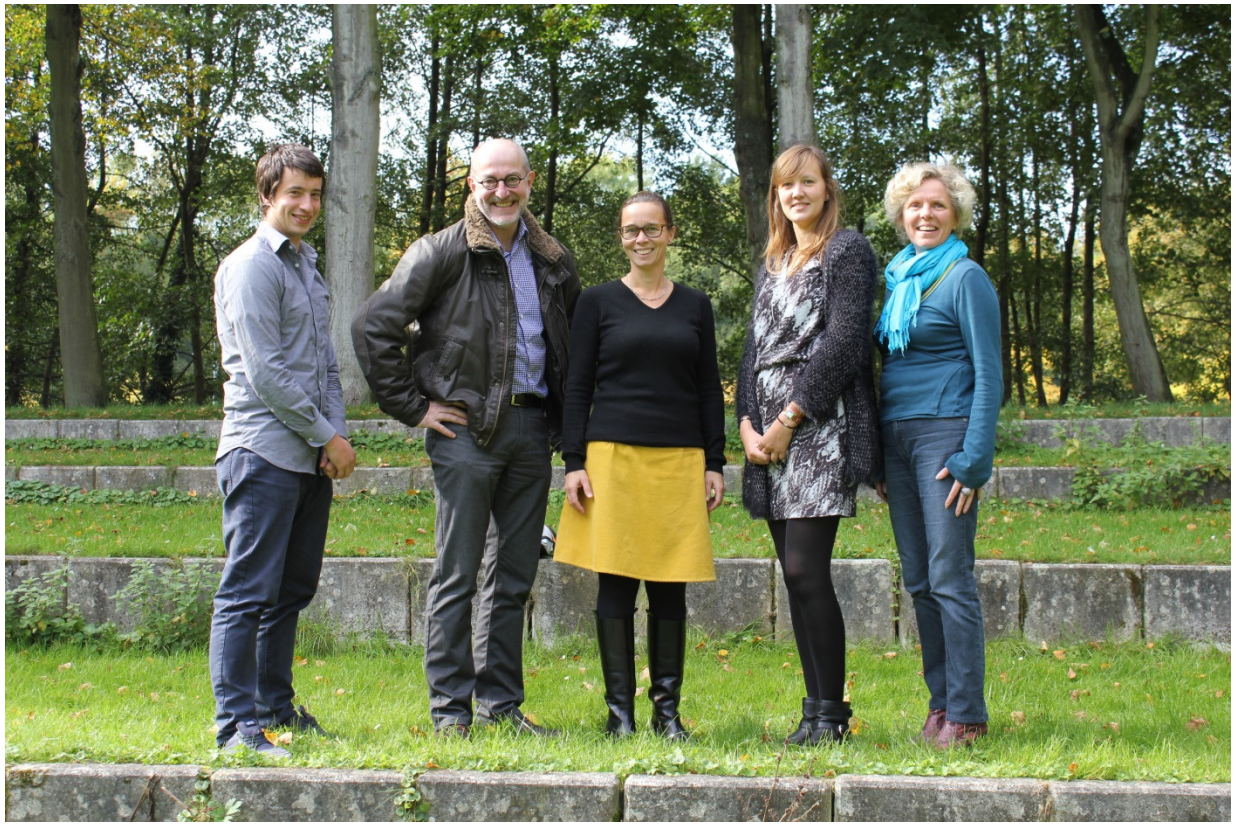
- Correlate of protection/ biomarker
- wP – aP use in infants combined with maternal vaccination (Thailand study, Thrasher funding)
- Need for other vaccines and/ or strategies? (e.g. neonatal vaccination)
- Interference with pertussis and other disease-specific infant immune responses
- Necessity of repeat boosters/ time frame(mathematical modelling)?

Conclusion

- Adequate humoral immune response during pregnancy
- Tdap vaccination during pregnancy offers increased antibody titers at birth, lasting at least until the infant's first vaccination

  → Closure of the susceptibility gap for infection
- Indications for interference/ blunting, possibly in between vaccine doses, and on other components of the infant vaccination schedule
- Effect on cellular immune responses in infants: more research needed
- Effect on breastmilk composition: more research needed

Thank you for your attention



The Antwerp ‘Matab’ team:

Wouter (PhD student), **Pierre** (Head of the Department),

Elke (Assistant Professor), **Kirsten** (PhD student) and **Aline** (Senior study nurse)

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All participating women and their lovely children

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Fonds Wetenschappelijk Onderzoek
Research Foundation – Flanders

vliruos
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