Pertussis vaccination in pregnancy: from research to practice

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No conflict of interest to declare

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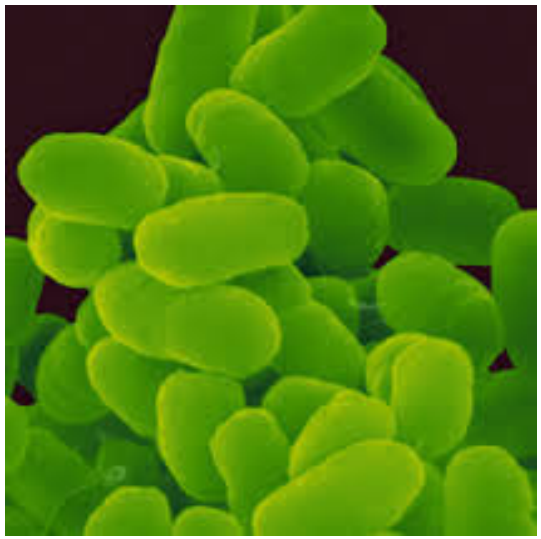
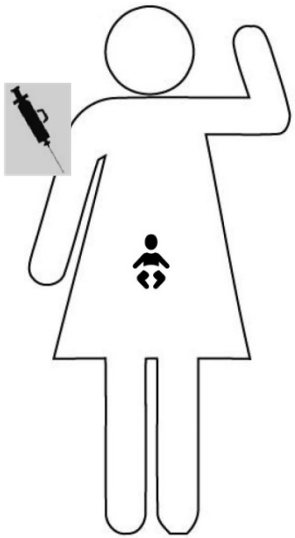
Outline of the talk

1. **General introduction**
   a) Vaccination in pregnancy: general background
   b) Epidemiology pertussis (relevant to maternal immunisation)
   c) Existing recommendations
2. Specific aspects
   a) Safety
   b) Immunogenicity
   c) Effectiveness
   d) Interference/blunting



1a) Vaccination in pregnancy: general background



From Taboo to Indication

Before: avoid vaccination during pregnancy

Trend: mother and (unborn) child have the right on protection

To: research on vaccination during pregnancy

And: indications for vaccination during pregnancy

BUT not a new concept

- 1879: vaccinia virus vaccination in pregnancy: protection
- 1938: wP vaccine in pregnancy: protection
- 1961: tetanus toxoid

General rules

Risk of infection: epidemiological or individual (preventive measures)

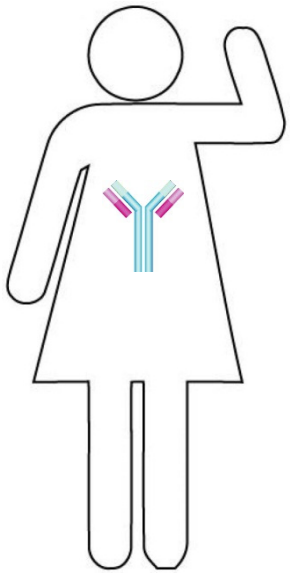
Risk attached to vaccination of a pregnant woman = theoretical risk or real risk.
Advantages of vaccination usually outweigh the potential risk of a side effect.

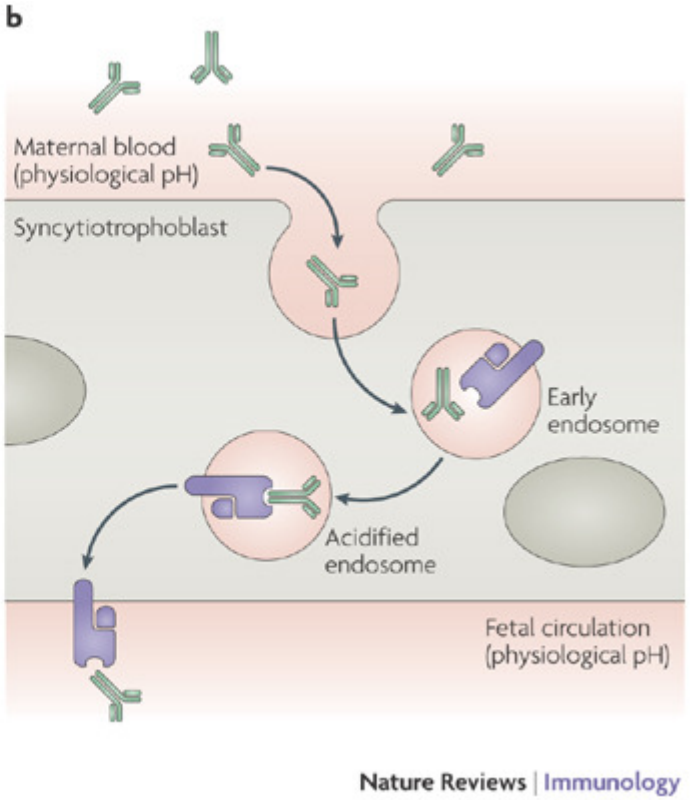
Vaccines containing **inactivated** material do not appear to be harmful to foetus or pregnant women.

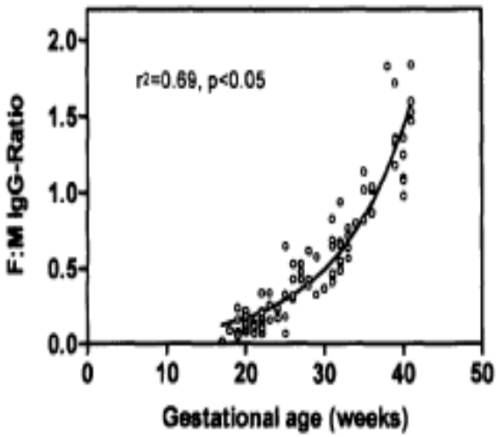
Attenuated vaccines are contra-indicated in pregnant women.

Immune response of a pregnant woman = equally adequate as a non-pregnant woman for vaccine response; BUT less adequate for response to infection!

Determinants of the amount of maternal antibodies in infants







(Malek 1996)

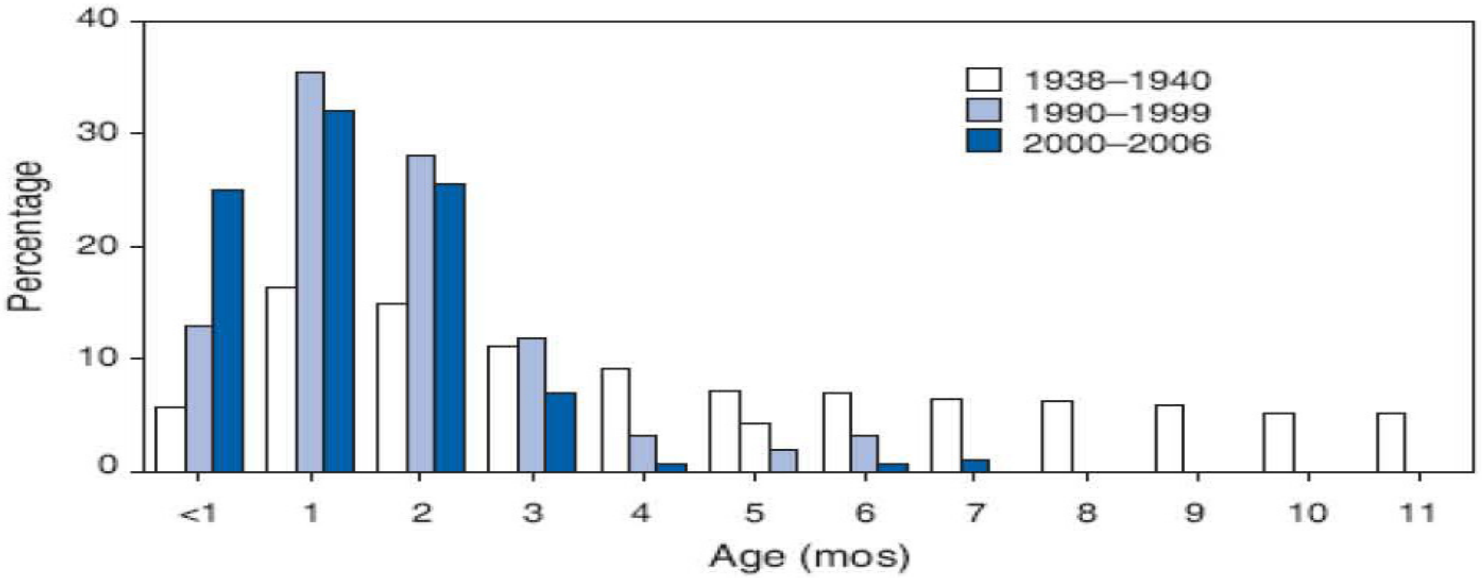
Maternal titer

Placenta:
FcRn Receptor

Gestational age:
(Pre)maturity

1b) Epidemiology of pertussis

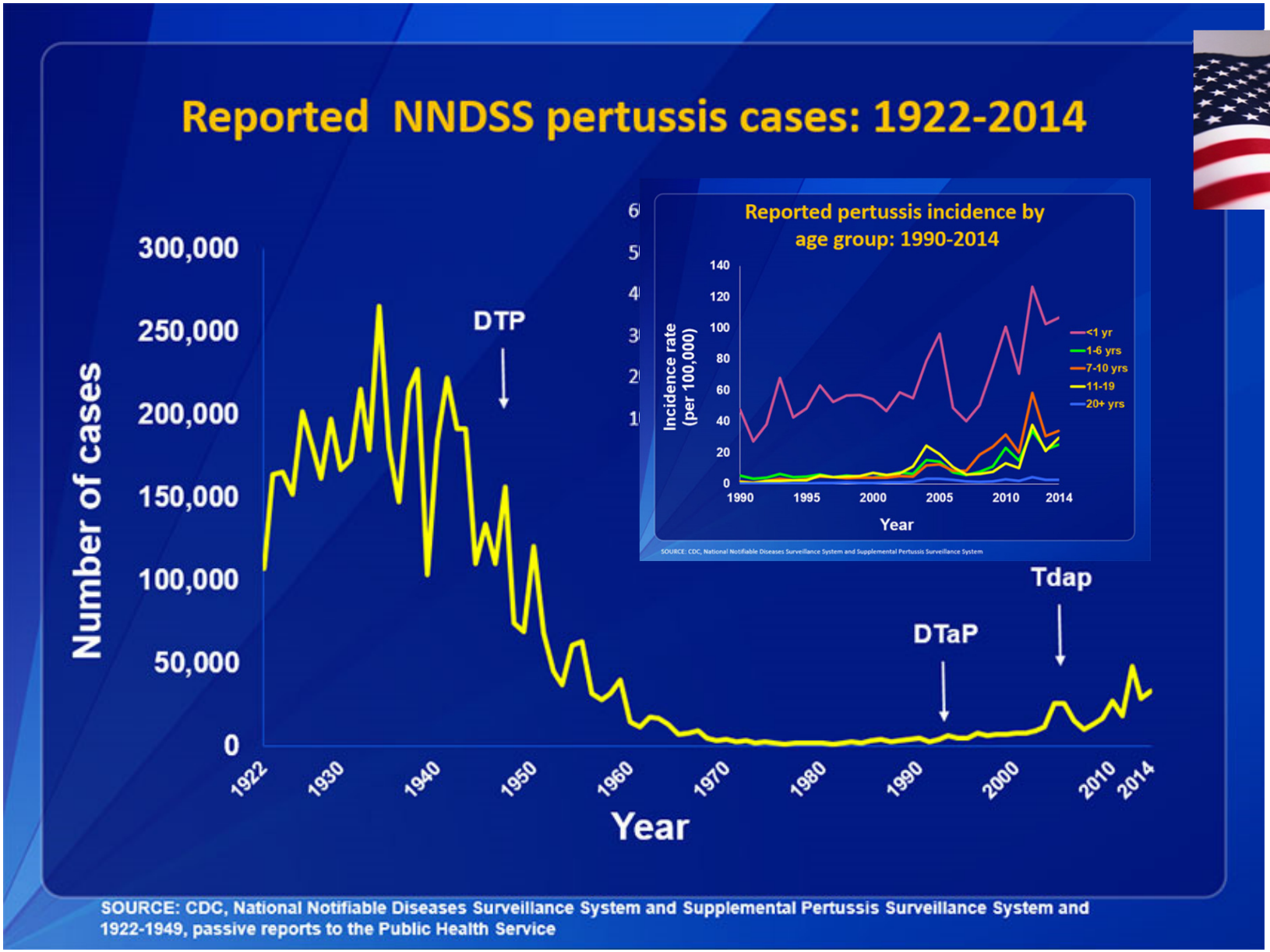
FIGURE 1. Proportion of reported infant pertussis deaths, by age — United States, 1938–1940,* 1990–1999,† and 2000–2006§



* **Source:** Sako W, Treuting WL, Witt DB, Nichamin SJ. Early immunization against pertussis with alum precipitated vaccine. JAMA 1945;127:379–84. N = 7,123 reported infant pertussis deaths.

† **Source:** Vitek CR, Pascual FB, Baughman AL, Murphy TV. Increase in deaths from pertussis among young infants in the United States in the 1990s. Pediatr Infect Dis J 2003; 22:628–34. N = 93 reported infant pertussis deaths.

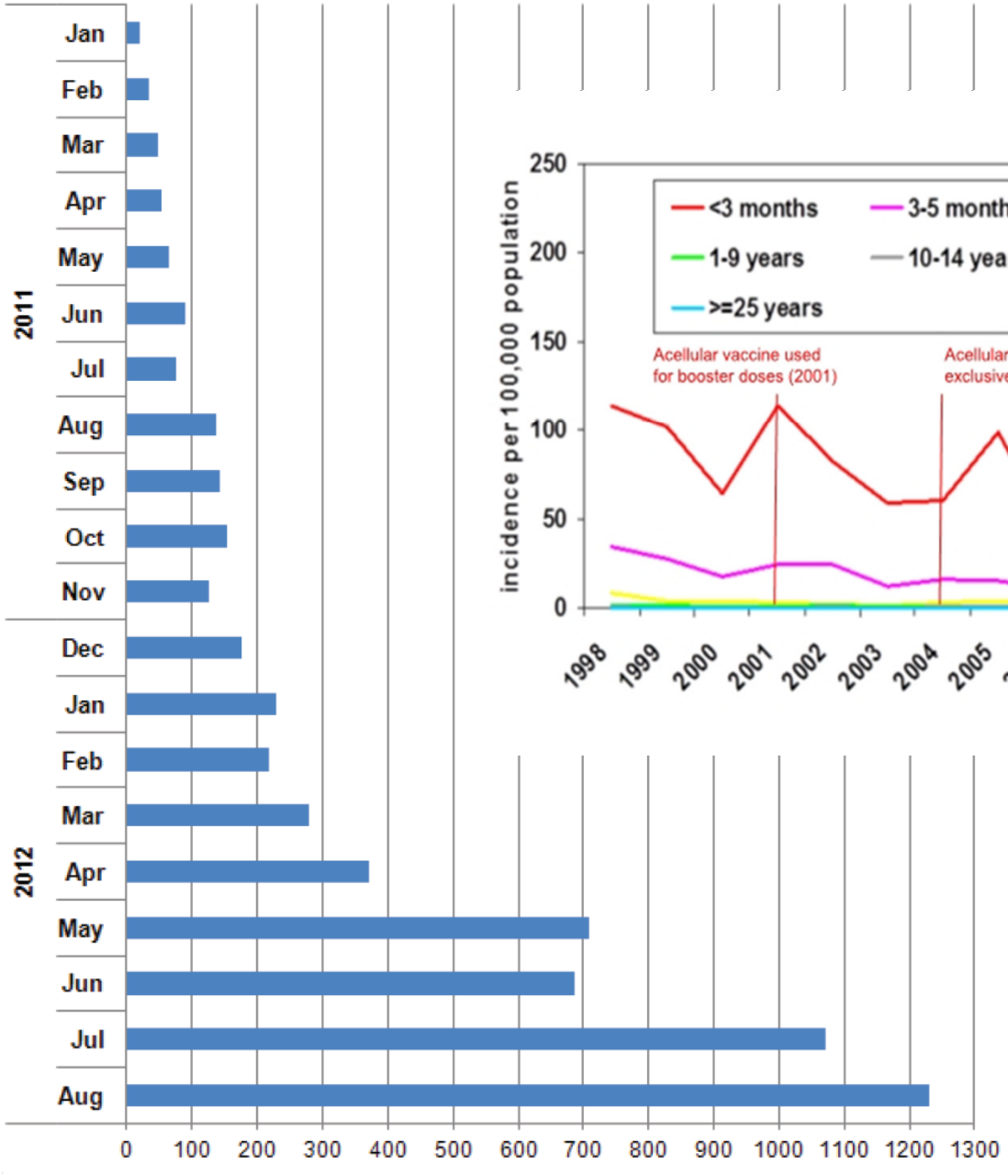
§ **Source:** CDC, unpublished data, 2007. N = 145 reported infant pertussis deaths.

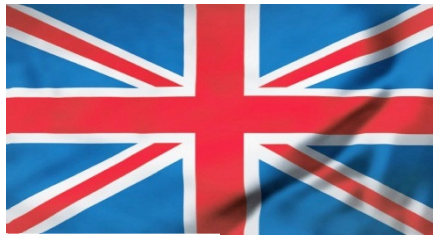


CDC data

Resurgence 8 years after aP introduction

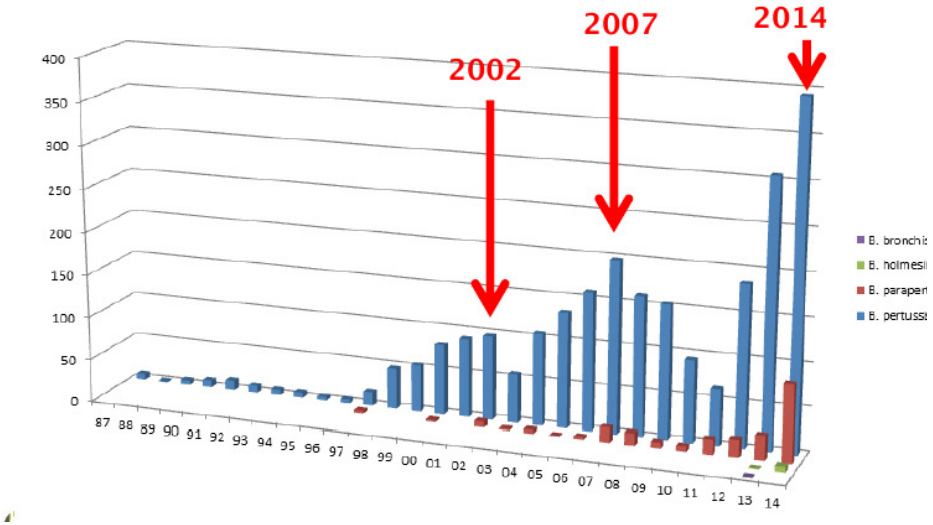
Figure 1. Provisional number of confirmed cases of pertussis, England and Wales, 2011 and 2012 by month





9 infants died in the first 8 months of 2012, 14 in total in 2012

Cyclus installation? An outbreak/5 to 7 years?



National Reference Laboratory for Pertussis

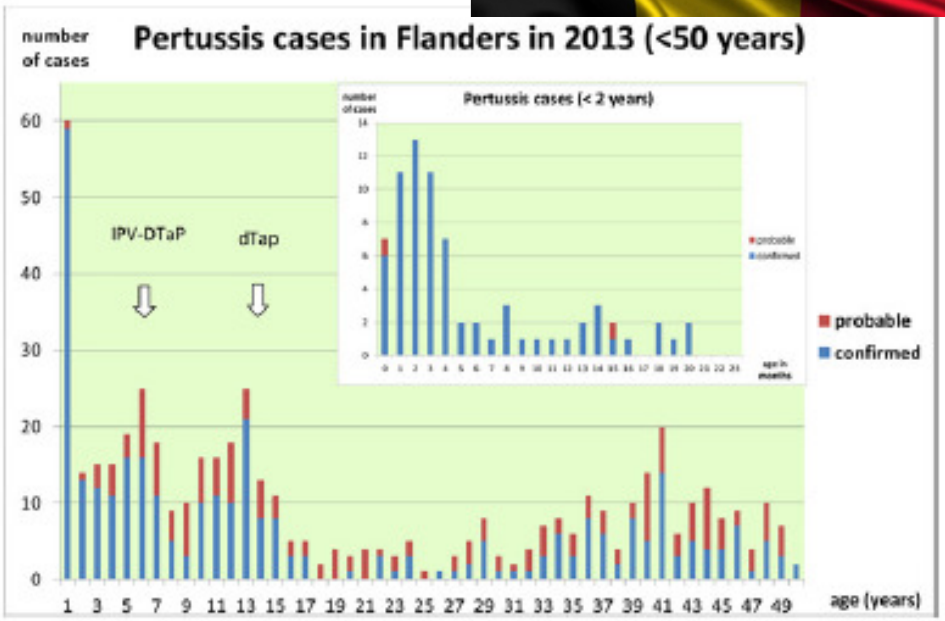
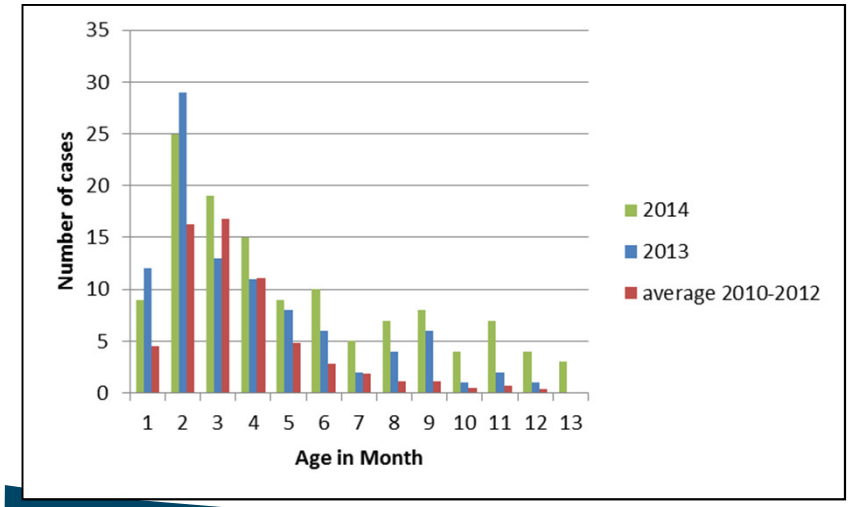


Figure 2: Age distribution of notified pertussis cases in 2013



Sabbe M. Jaarrapport 2014, WIV, Brussel. 2015. D/2015/2505/05.

1c) Existing recommendations in pregnancy

ACIP (CDC), USA, Augustus 2011

Use of Tdap in pregnant women

- for pregnant women who previously have not received Tdap
- **should administer Tdap during pregnancy, preferably during the third or late second trimester***. Alternatively, if not administered during pregnancy, Tdap should be administered immediately postpartum

Reason: burden of disease

UPDATE Oct 2012: **every** pregnancy

http://www.cdc.gov/vaccines/recs/provisional/default.htm

http://www.acog.org/~/media/Committee%20Opinions/Committee%20on%20Obstetric%20Practice/co521.pdf?dmc=1&ts=20120307T1535482729

Department of Health, UK, October 2012

Use of Tdap(IPV) in pregnant women.

- Immunisation within weeks 28 to 32 of pregnancy
- The committee considered that women with **repeat pregnancies** should be offered immunisation during **each** pregnancy as this would ensure maximal transplacental transfer of antibody.

- http://www.dh.gov.uk/health/2012/09/whooping-cough-information/
- **Reason:** most infant cases of pertussis continue to be below six weeks of age with a higher incidence in infants aged under three months than at any other point in over a decade; **nine confirmed deaths in infants under one year of age** have been reported up to week 39 in 2012, **all of whom were unvaccinated**

HGR-CSS: Belgium pertussis vaccination policy

Infants: 3 doses at 8-12-16 weeks + booster dose at 15 months (aP)

Children: 1 dose at 4-6 years (aP)

Adolescents: 1 dose at 14-16 years (since 2009) (aP)

Adults: 1 dose dTpa:

- For adults who did not receive the booster at 14-16 years
- **Pregnant women every pregnancy between 24-32 weeks of gestation (since 2013)**
- Adults in regular contact with infants (< 12 months)
  - Future parents
  - Grandparents
  - Personel in nurseries
  - Heatlh care personel

Hoge Gezondheidsraad
Conseil Supérieur de la Santé

vaccinnet

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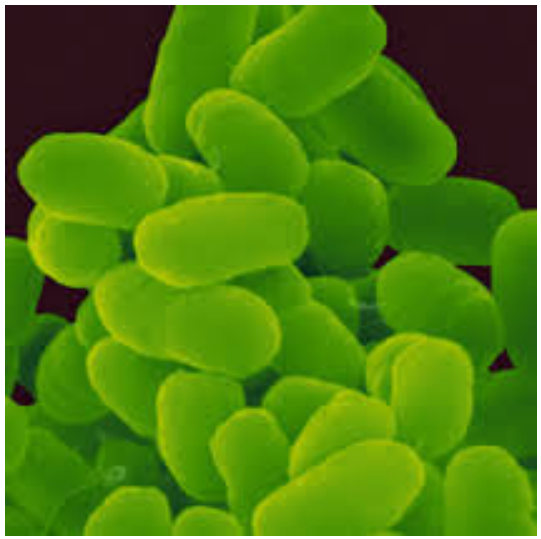


2a) Safety

UK:

- N= 17.560 women: FU until 28 days post vaccination
- N= 6.185 women: FU until 44 weeks post-last day menstruation
- Risk assessment: stillbirth, maternal or neonatal death, (pre-) eclampsia, haemorrhage, fetal distress, uterine rupture, placenta (vasa) praevia, C section, low birth weight, neonatal kidney failure, other severe diseases

> This study found no evidence of an increased risk of any of the extensive predefined list of adverse events related to pregnancy. In particular, there was no evidence of an increased risk of stillbirth.

Donegan BMJ 2014

US, 2 California VSD sites (Tdap): Kharbanda Jama 2014

- Risk assessment: sga, prematurity, hypertensive disorders, chorioamnionitis
- N= 123.494 vrouwen
- RR chorioamnionitis 1.19
- 50% confirmed after revision of charts; no preterm birth association

VAERS chorioamnionitis (Tdap): Datwani Vaccine 2015

- Chorioamnionitis was found to be uncommonly reported, representing 1% (N=31) of pregnancy reports to VAERS
- No clear risk factor

Review (general): Keller Stanlowski Vaccine 2014

- No evidence for increased risk
- Benefit> risk
- Importance of background incidence rates
- Surveillance necessary

2b) Immunogenicity

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.

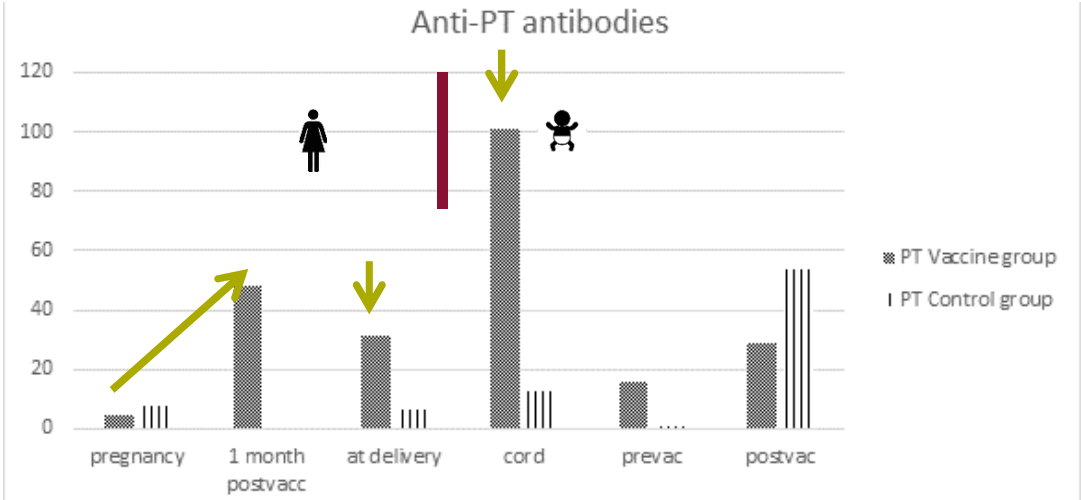
Gall. Effect of maternal immunization with Tdap. Am J Obstet Gynecol 2011.

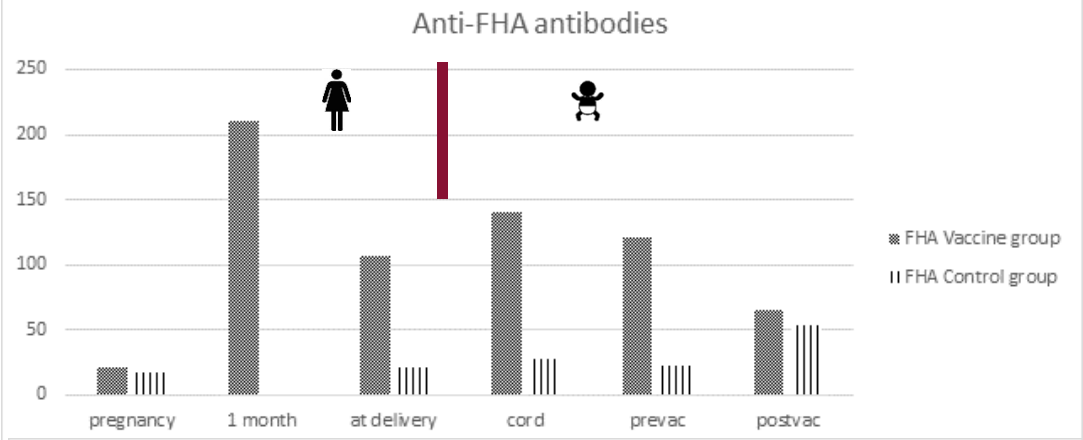
Characteristic	Women		
	Pregnant		
	Tdap Antepartum/Placebo Postpartum (n = 33)	Placebo Antepartum/Tdap Postpartum (n = 15)	Nonpregnant Tdap (n = 32)

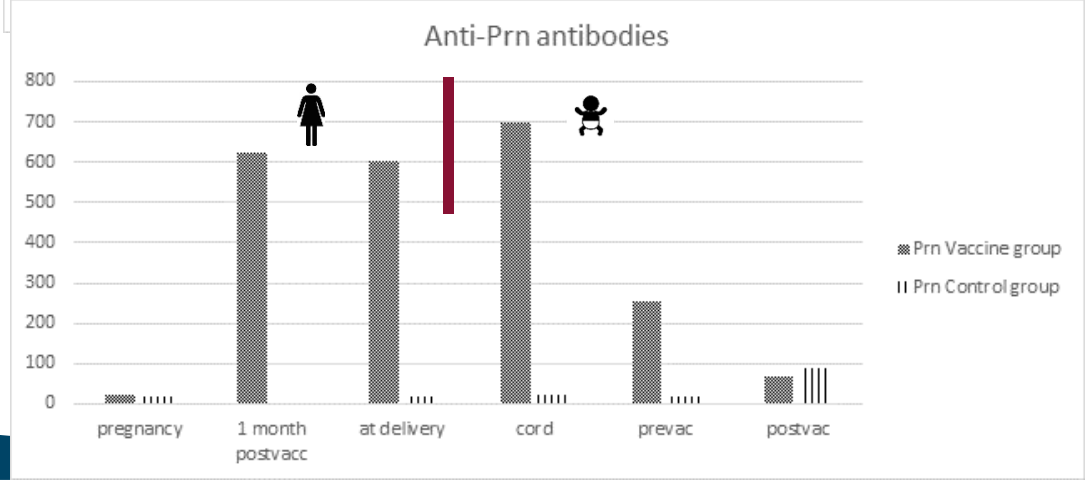
Table 4. Geometric Mean Concentration of Antibodies to Tdap Vaccine Antigens in Sera From Mothers and Infants, and Nonpregnant Women, by Study Group and Time of Sample Collection

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	7	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







Prospective study

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

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

Infants received Infanrix hexa

Maertens & Leuridan et al, Vaccine 2015

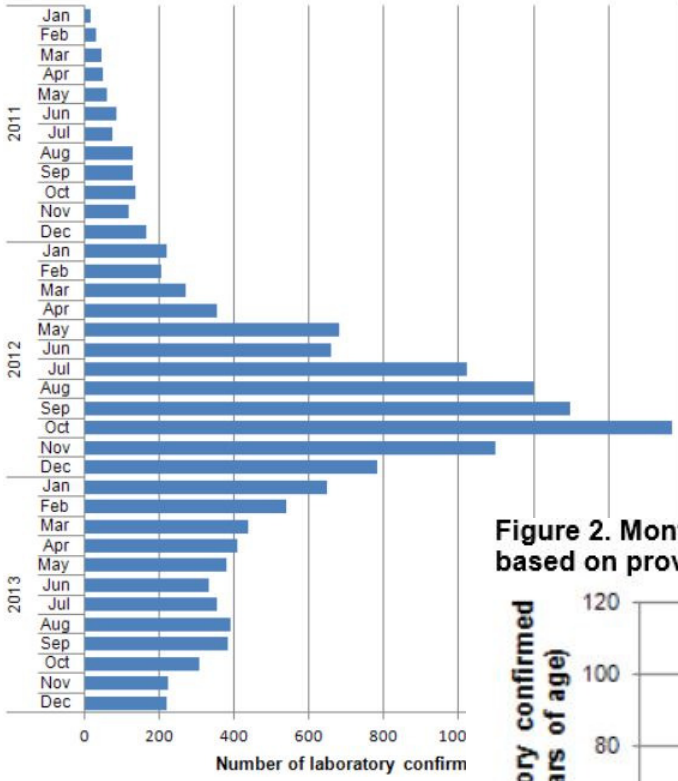
2c) Effectiveness

Historical data on maternal PT vaccination with wP vaccines

Study	Year	No	Vaccine /Doses	Safety	Effectiveness
Lichty	1938	42	3 wP	Arm pain	Not reported
Cohen/ Mishulow	1941-1946	~170	6 wP	Arm pain, lump, no adverse pregnancy outcomes	0/8 immunized and 3/6 unimmunized exposed infants developed pertussis
Kendrick	1945	57	3 wP	Not reported	Not reported
Adams	1947	16	3 wP	Not reported	Not reported
Cohen	1951	106	3 wP	Mild injection site; no adverse pregnancy outcomes	0/2 exposured infants of immunized women developed pertussis

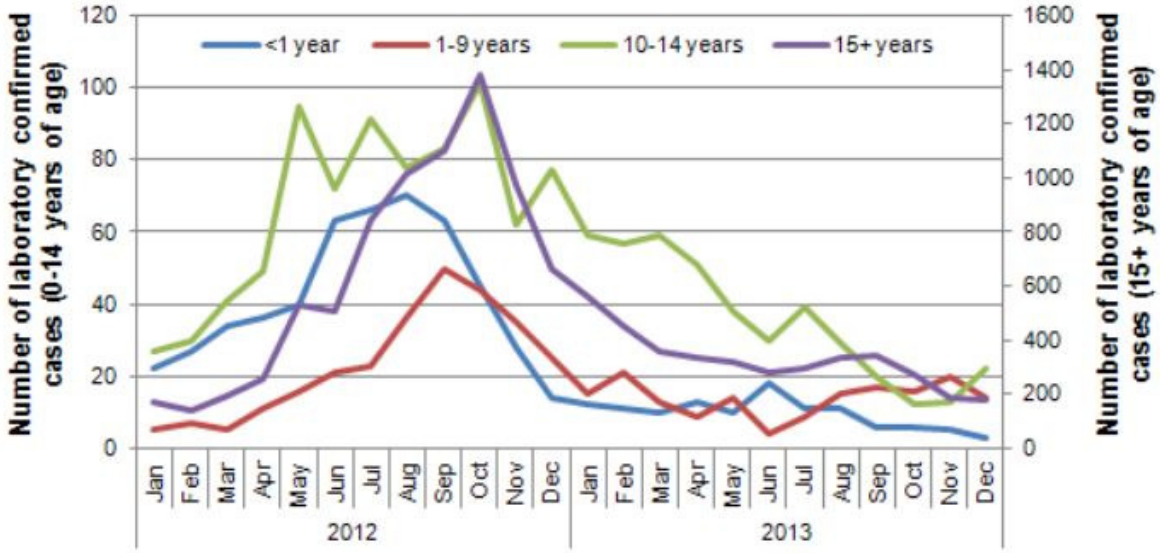
UK experiences

Figure 1. Provisional number of confirmed cases of pertussis in England, by month: Jan 2011 to Dec 2013

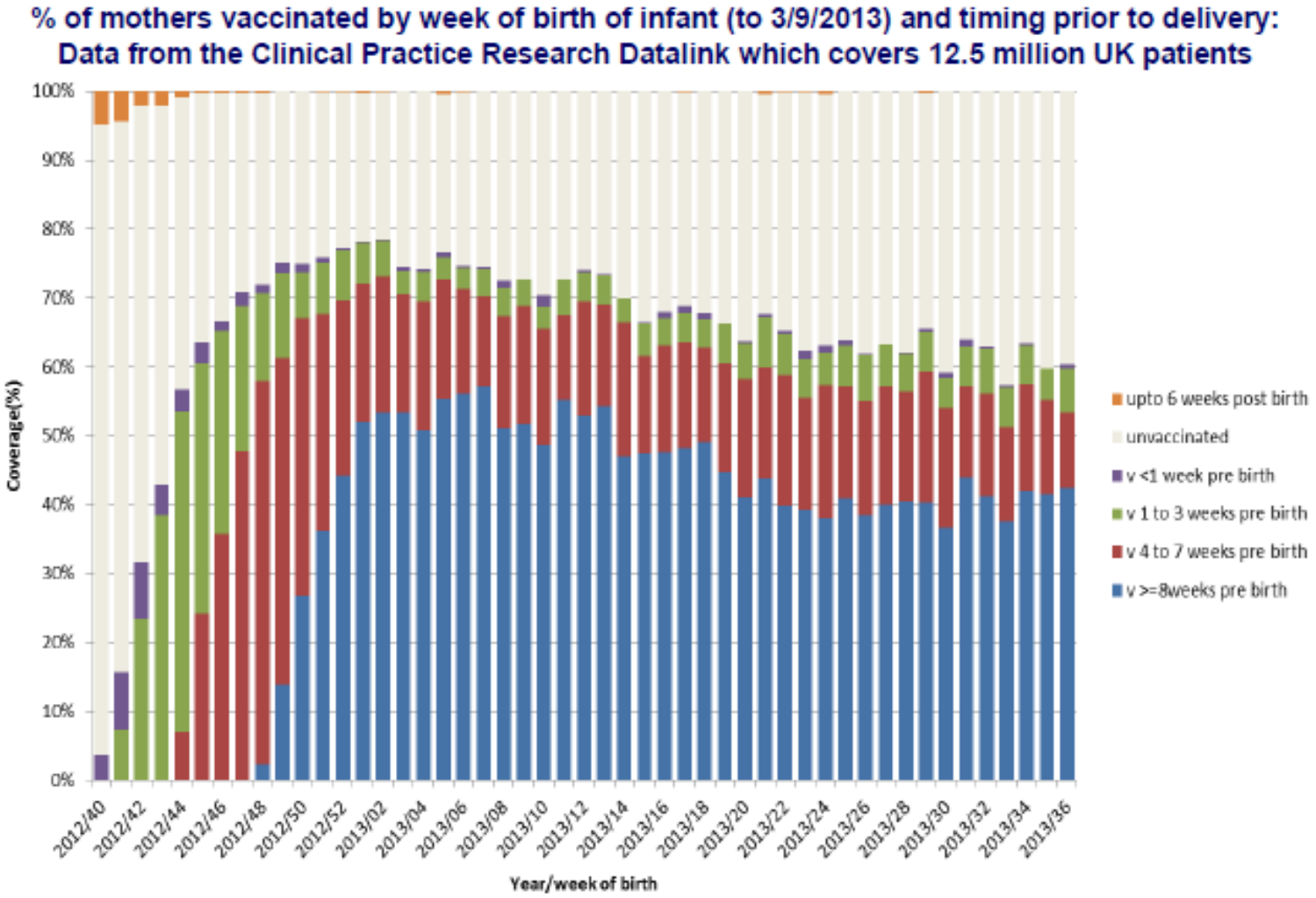


Pertussis vaccination pregnancy: Start oct 2012: 43,7%
Feb 2013: 59,6%

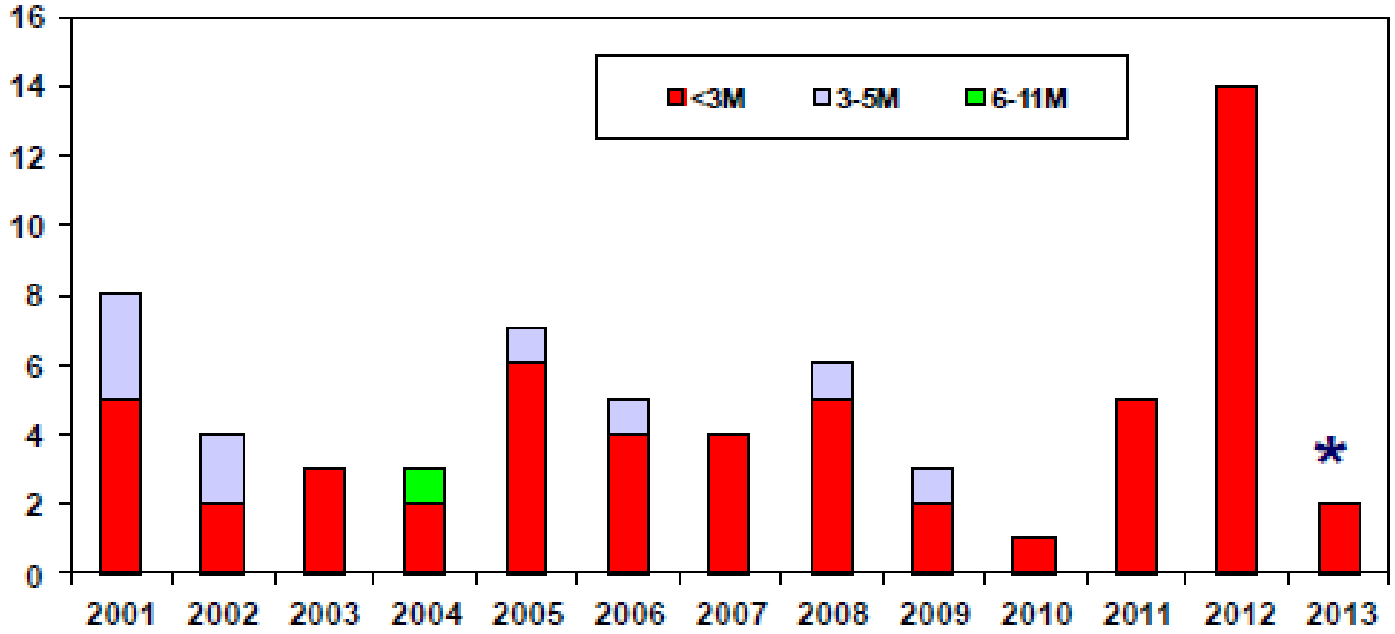
Figure 2. Monthly distribution of laboratory confirmed cases in 2012 and 2013, England, by age group based on provisional data



Coverage of the strategy in UK



Reconciled deaths from pertussis in infants, England only



Sources: lab confirmed cases, certified deaths, Hospital episode statistics, GP registration details
* Both with unvaccinated mothers

World Health Organization

http://www.who.int/immunization/sage/meetings/2014/april/3_SAGE_April_Pertussis_Miller_Strategies.pdf?ua=1

Effectiveness on hospitalisation, caused by pertussis disease among young infants

Timing of maternal immunisation	VE (95% CI)
At least 7 days before birth	91% (84% to 95 %)
At least 28 days before birth	91% (83% to 95%)
7 to 27 days before birth	91% (70% to 96%)
0-6 days before or 1-13 days after birth	38% (-95% to 80%)

Amirthalingam et al Lancet 2015

	2008	2009	2010	2011	2012	2013	% change 2013 vs 2012 (95% CI)	% change 2013 vs 2011 (95% CI)
<1 month	24 (3·4%)	16 (2·9%)	6 (2·0%)	16 (2·5%)	43 (0·7%)	10 (0·3%)	−77% (−90 to −53)	−38% (−75 to 46)
1 month	67 (9·5%)	43 (7·7%)	22 (7·2%)	57 (9·1%)	161 (2·7%)	37 (1·0%)	−77% (−84 to −67)	−35% (−58 to 0)
2 months	58 (8·3%)	29 (5·2%)	15 (4·9%)	45 (7·2%)	124 (2·1%)	25 (0·7%)	−80% (−87 to −69)	−44% (−67 to 7)
3–5 months	33 (4·7%)	20 (3·6%)	6 (2·0%)	21 (3·3%)	62 (1·0%)	22 (0·6%)	−65% (−79 to −41)	5% (−45 to 100)
6–11 months	8 (1·1%)	3 (0·5%)	3 (1·0%)	7 (1·1%)	22 (0·4%)	7 (0·2%)	−68% (−89 to −23)	0% (−70 to 234)
1–4 years	21 (3·0%)	19 (3·4%)	7 (2·3%)	10 (1·6%)	58 (1·0%)	41 (1·1%)	−29% (−54 to 7)	310% (102 to 818)
5–19 years	184 (26·2%)	121 (21·8%)	59 (19·4%)	124 (19·7%)	1128 (19·1%)	669 (17·6%)	−41% (−46 to −35)	440% (345 to 559)
≥20 years	307 (43·7%)	304 (54·8%)	186 (61·2%)	349 (55·5%)	4311 (73·0%)	2984 (78·6%)	−31% (−34 to −27)	755% (665 to 860)
Total number of cases	702	555	304	629	5909	3795	−36% (−38 to −33)	503% (454 to 557)
Reported deaths*	5 (CFR 3·4%)	1 (CFR 1·1%)	1 (CFR 2·3%)	3 (CFR 2·5%)	10 (CFR 3·0%)	2 (CFR 2·8%)	..	..

Table shows total number of laboratory-confirmed cases of pertussis in January to September (inclusive) for 2008–13 in England. Data are number of cases in each age group and percentage of total cases in that year. CFR refers to deaths as a percentage of all cases in infants younger than 3 months. CFR=case fatality rate. *Deaths reconciled from hospital admissions data, follow-up of laboratory-confirmed cases, and death certification.

Table 1: **Laboratory-confirmed cases by age group**

	2008	2009	2010	2011	2012	2013	% change 2013 vs 2012 (95% CI)	% change 2013 vs 2011 (95% CI)
<1 month	31 (9·2%)	24 (10·3%)	10 (8·3%)	25 (10·1%)	73 (11·3%)	18 (6·5%)	−75% (−86 to −58)	−28% (−73 to 37)
1 month	112 (33·1%)	80 (34·5%)	38 (31·4%)	99 (40·1%)	209 (32·3%)	68 (24·7%)	−67% (−76 to −57)	−31% (−50 to −6)
2 months	85 (25·1%)	47 (20·3%)	26 (21·5%)	59 (23·9%)	158 (24·4%)	54 (19·6%)	−66% (−75 to −53)	−8% (−38 to 35)
3–5 months	55 (16·3%)	44 (19·0%)	21 (17·4%)	26 (10·5%)	108 (16·7%)	54 (19·6%)	−50% (−65 to −30)	108% (28 to 246)
6–11 months	22 (6·5%)	10 (4·3%)	7 (5·8%)	11 (4·5%)	30 (4·6%)	11 (4·0%)	−63% (−83 to −25)	0% (−61 to 154)
1–4 years	18 (5·3%)	16 (6·9%)	9 (7·4%)	9 (3·6%)	29 (4·5%)	21 (7·6%)	−28% (−61 to 31)	133% (2 to 479)
5–19 years	11 (3·3%)	7 (3·0%)	5 (4·1%)	7 (2·8%)	23 (3·5%)	12 (4·4%)	−48% (−76 to 9)	71% (−38 to 414)
20+ years	4 (1·2%)	4 (1·7%)	5 (4·1%)	11 (4·5%)	18 (2·8%)	37 (13·5%)	106% (14 to 284)	236% (68 to 631)
Total	338	232	121	247	648	275	−58% (−63 to −37)	11% (−7 to 33)

Table shows total number of hospital admissions for pertussis in January to September (inclusive) for 2008–13 in England. Data are number of admissions in each age group and percentage of total pertussis admissions in that year.

Table 2: **Hospital admissions by age group**

Amirthalingam et al Lancet 2014

	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 Lancet 2015

Animal model: baboons

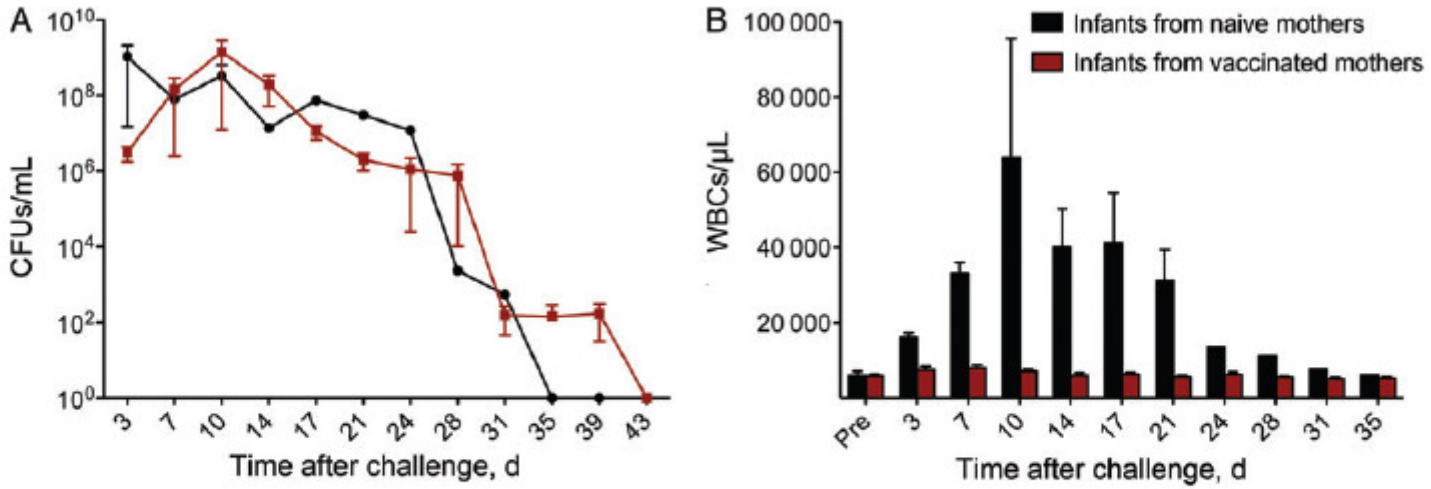


Figure 3. Maternal vaccination prevents leukocytosis but not colonization. Infant baboons were born to mothers that were vaccinated with the tetanus, diphtheria, acellular pertussis priming series and boosted during the third trimester (n = 7) or to unvaccinated mothers (n = 2). All animals were directly challenged with *Bordetella pertussis* at 5–6 weeks of age. *A*, Colonization was monitored by quantifying *B. pertussis* colony-forming units (CFUs) per milliliter in biweekly nasopharyngeal washes, with a limit of detection of 10 CFUs/mL. *B*, The mean circulating white blood cell (WBC) counts before and after challenge are shown for each group of animals (n = 2 per group). ***P* < .01 versus preinfection values from the same group.

Warfel et al JID March 2014

2d) Interference/ blunting

Effect of maternal antibodies in infants

- Passive protection
- Hamper humoral immune response on vaccination (life attenuated vaccines- wP vaccine…)
  - maternal antibody/vaccine antigen ratio: sufficient B cell vaccine epitopes free for binding by infant B cells

    (Siegrist, 1998)
  - maternal antibodies trigger a regulatory mechanism of B cell responses

    (Kim, 2011)

→Timing first dose of vaccination

(Leuridan, Vaccine, 2007)

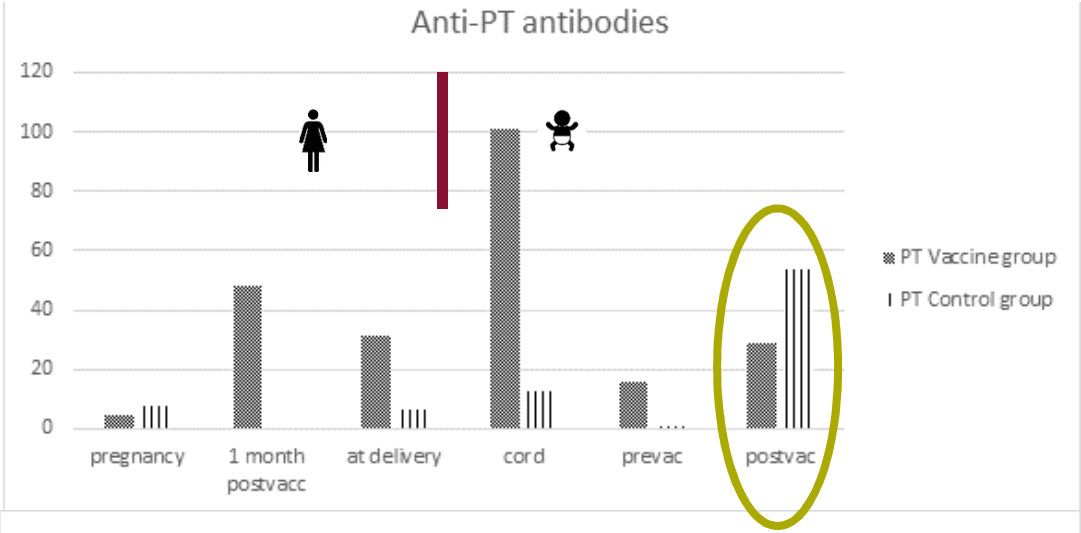
RCT, USA

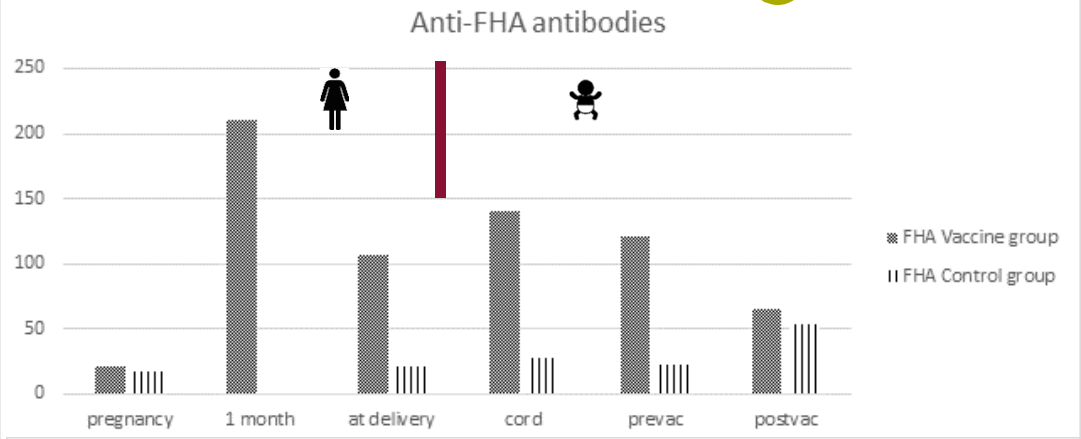
(Muñoz et al JAMA 2014)

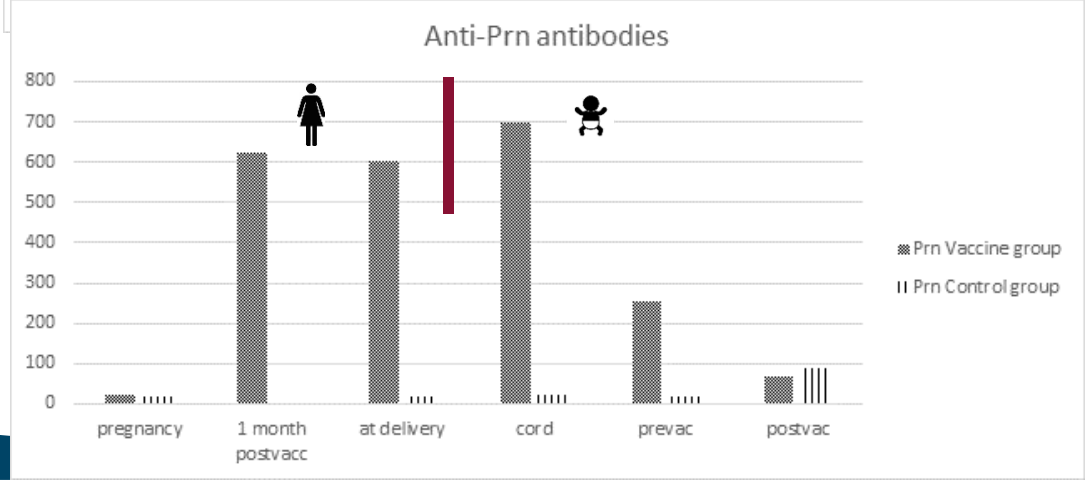
Characteristic	Women		
	Pregnant		
	Tdap Antepartum/Placebo Postpartum (n = 33)	Placebo Antepartum/Tdap Postpartum (n = 15)	Nonpregnant Tdap (n = 32)

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)						







Prospective study Belgium

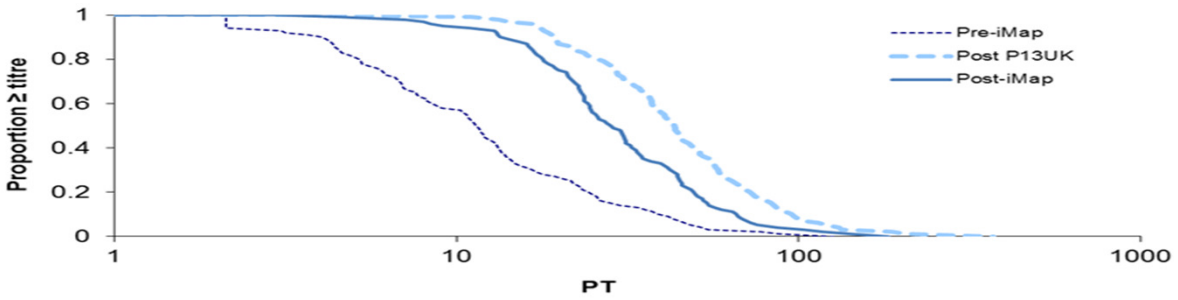
Vaccine group (Boostrix): N= 57 women, 55 infants

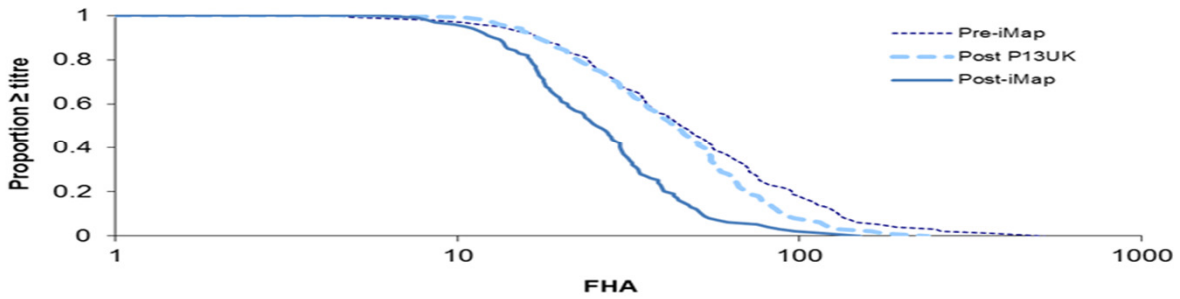
Control group (no vaccine): N=42 women, 26 infants

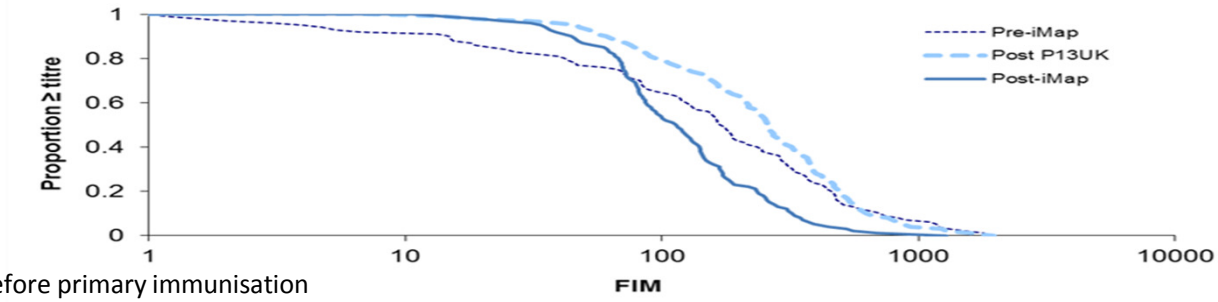
Infants received Infanrix hexa

Maertens & Leuridan et al, Vaccine 2015

UK data on interference







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

Ladhani CID 2015

Conclusion

- Good humoral immune response during pregnancy
- Vaccination during pregnancy offers increased antibody titers at birth
- Increased antibody titers last at least until the infant's first vaccination
  - Closure of the susceptibility gap for infection
- Children in control group higher antibody titers (PT, PRN, DT, TT) after a priming series, but follow up is reassuring (USA) and ongoing in BE
  - Possible interference, as observed by Munoz et al, Leuridan et al and Ladhani et al.

Challenges in research on pertussis vaccination in pregnancy

- Repeat boosters necessary/ time frame?
- Correlate of protection/ biomarker
- wP – aP use in infants and maternal vaccination?
- Need for other vaccines or strategies (neonatal vaccination); making maternal vaccination during pregnancy unnecessary?
- Interference with pertussis and other infant immune responses
- RCT in pregnant women

Thank you for your attention

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