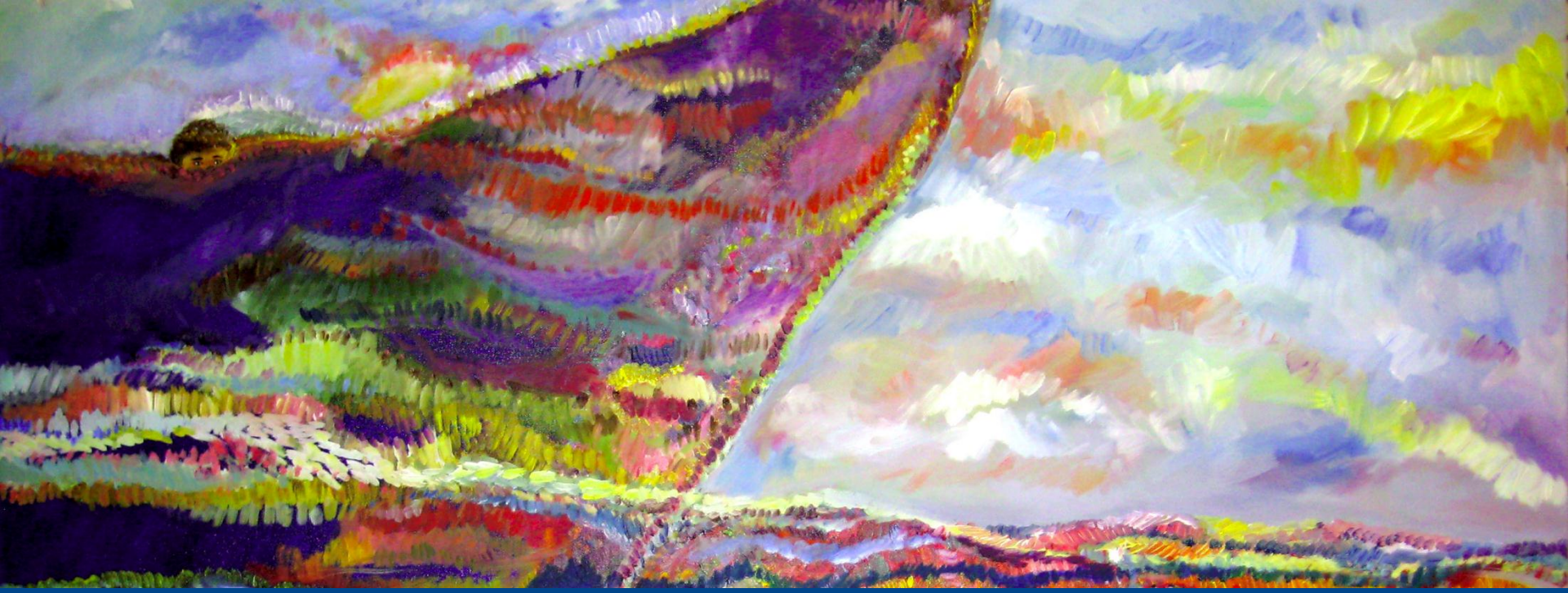


Pertussis vaccines: a partial success story

Jennifer Jacons, *Stowaway*
Jennifer is a New York based artist living with Type 1 diabetes.

Jan Poolman

Vice President | Infectious Diseases & Vaccines | November 2015

Infectious Diseases and Vaccines

janssen | PHARMACEUTICAL COMPANIES OF Johnson&Johnson

Reduction of global burden of pertussis

- It is estimated that without vaccination there would be >1.3 million pertussis related deaths globally in 2001
- Estimates from WHO suggest that, in 2013:
  - Around 63,000 deaths in children < 5 years of age
- Facts and data from USA : pre-vaccination 5000 deaths/yr mostly pediatric ; 2014 : 9 deaths, 7 in < 3 mths of age

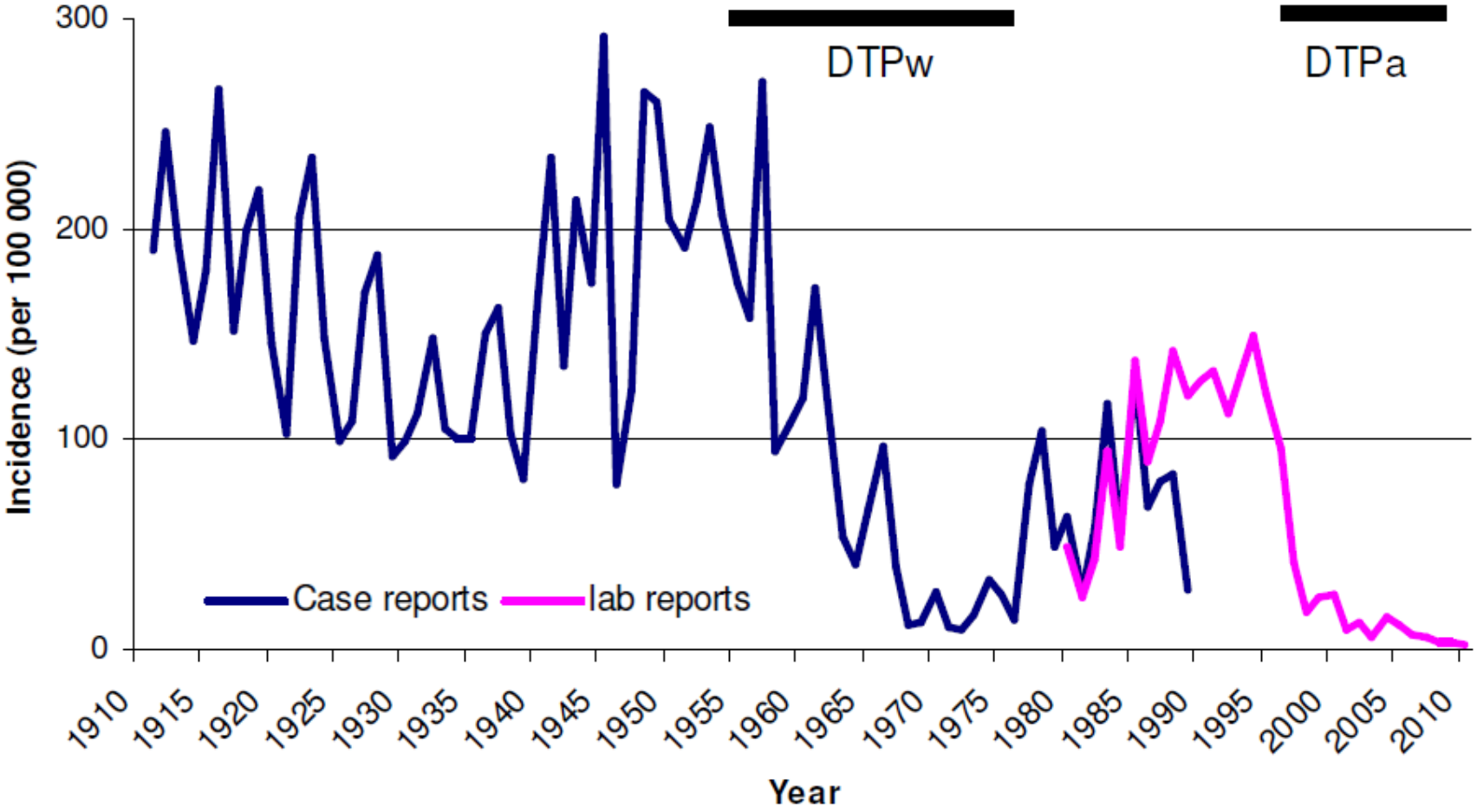
This qualifies as a partial success story

Bob Dylan 1965 :
"There is no success like failure, but failure is no success at all"

Source: http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/pert.pdf; WHO Pertussis vaccines: WHO position paper 2015

Vaccines protect: Swedish example

Overall incidence of laboratory reported pertussis over time



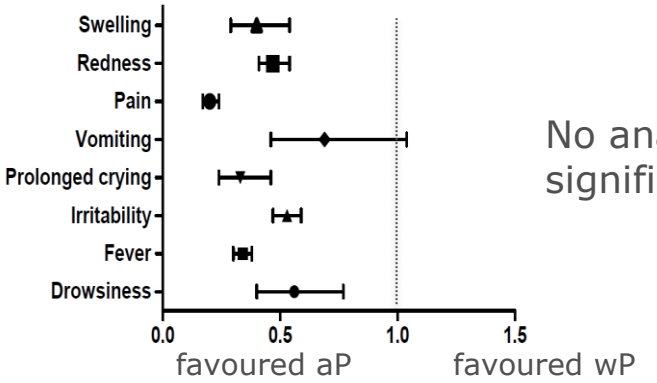
Source: Swedish Institute for Communicable Disease Control (Smittskyddsinstitutet). Article number: 2011-18-1. Case reports from general practitioners until mid 1980:s and according to the communicable disease act from 1997, lab-reports from 1980

Why did high income countries stop wP?
Reactogenicity, neurological illness, vaccine encephalopathy

Observations:
Numerous reported cases of neurologic damage following wP

However:
- Comparisons with unvaccinated subjects were not available
- Alternative causes were rarely studied
- No link demonstrated between vaccination and neurological illness

Less side effects associated with aP vaccines over wP:



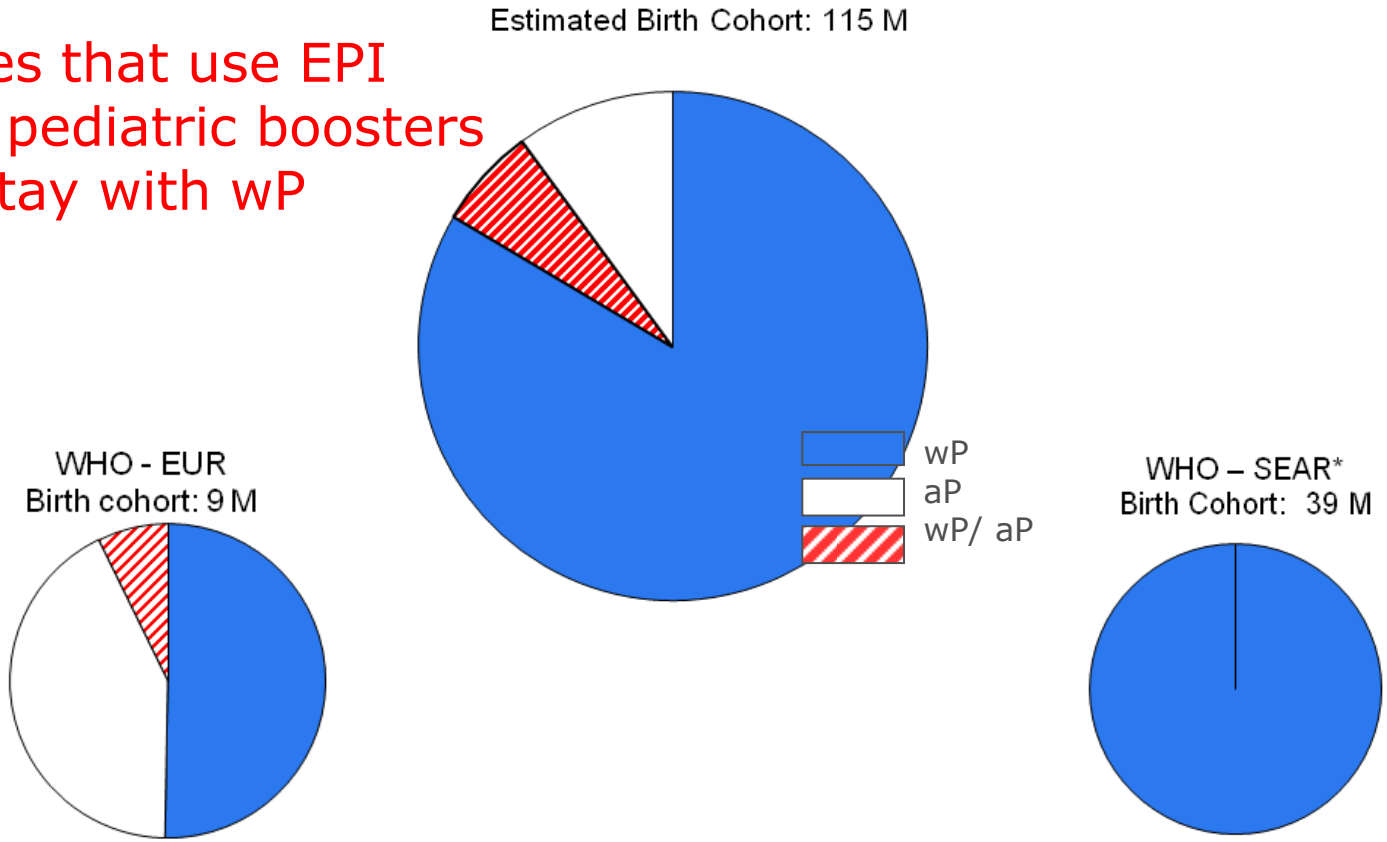
No analysis of any endpoint resulted in a RR that significantly favoured whole-cell vaccines*

Source: Moore D, et al. PIDJ 2004; Mattoo S, et al. Clin Micro Rev 2005; *Zhang L, et al. Cochrane Database of Systematic Reviews 2014

Current worldwide use of wP and aP

Annually 115 million children worldwide receive a DTP vaccine

Countries that use EPI without pediatric boosters better stay with wP

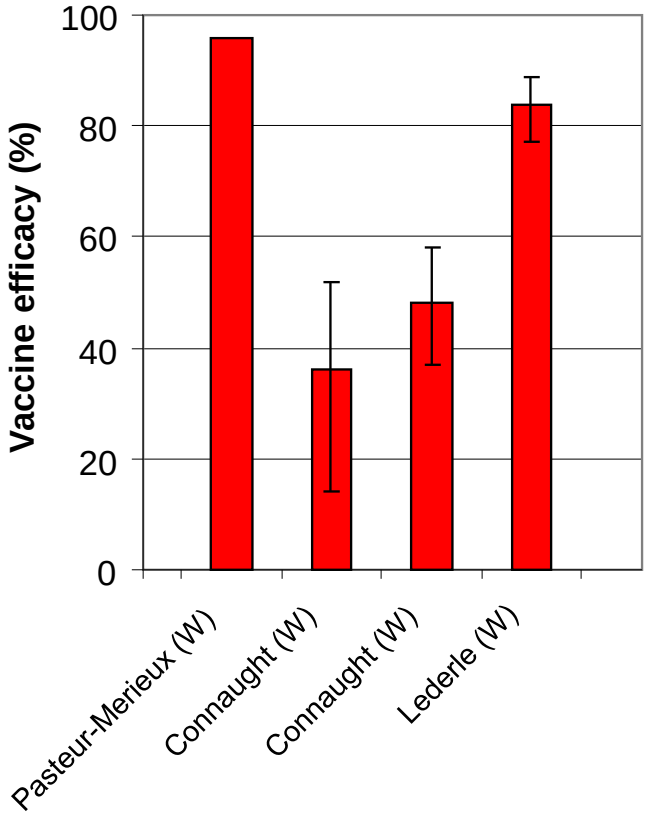


DTwPHBV-Hib vaccines are the cornerstone of Global Immunization programs

Source: WHO/UNICEF Joint Reporting Form (2010); 2008 population/birth rates NationMaster.com; WHO/UNICEF coverage estimates 2014 revision, July 2015, * South East Asian Region

Differences in clinical efficacy of wP vaccines

Presumed manufacturing issues?

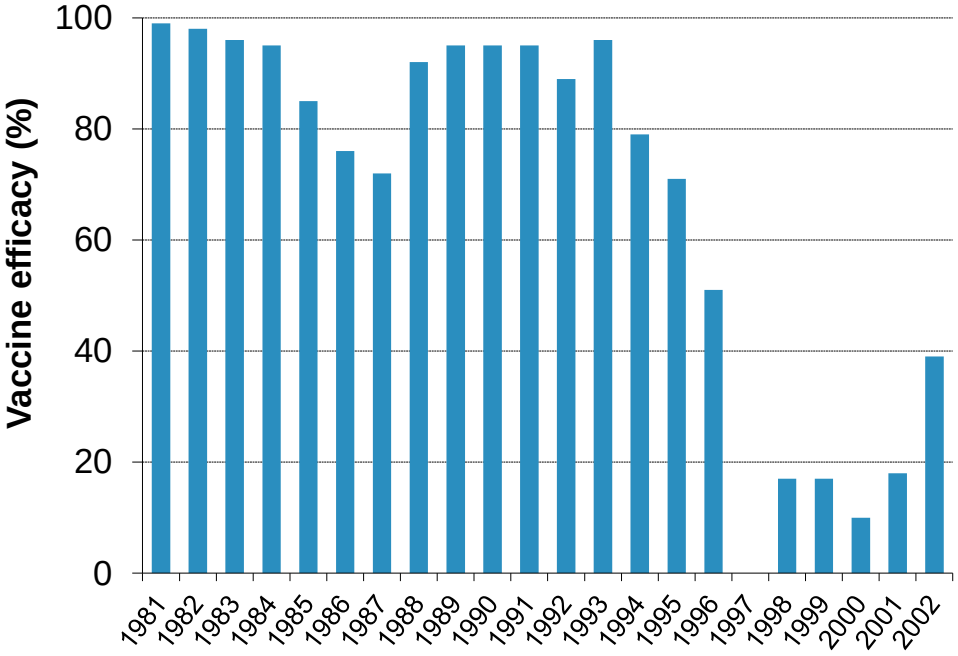


Explanations:

- Mutations in circulating strains
- Weak vaccine: different in production/seed lots
- Shift to ptxS1A and prn2

Source: Zhang L, et al. Cochrane Database of Systematic Reviews 2014

Dutch wP vaccine in the late 90's: wP vaccine efficacy going down

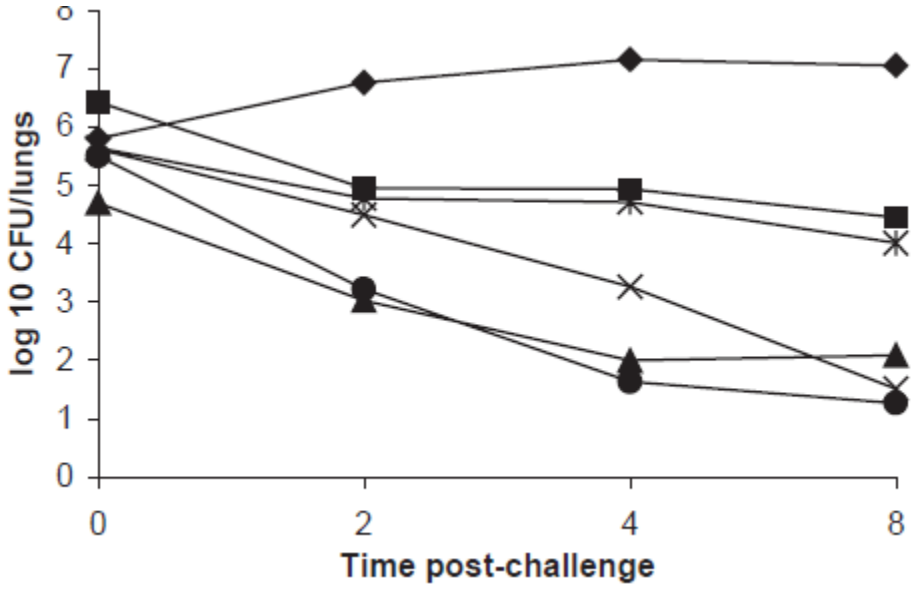


Possible explanations

- Switch to an avirulent Bvg-negative phenotype?
- *B. pertussis* phenotype controlled by BvgAS two-component signal transduction system

Source: Health Council of the Netherlands. Vaccination against pertussis 2004; publication no. 2004/04E Accessed on November 3, 2015 @ http://www.gezondheidsraad.nl/sites/default/files/engreport.pdf

Mouse intranasal challenge test correlates with vaccine efficacy



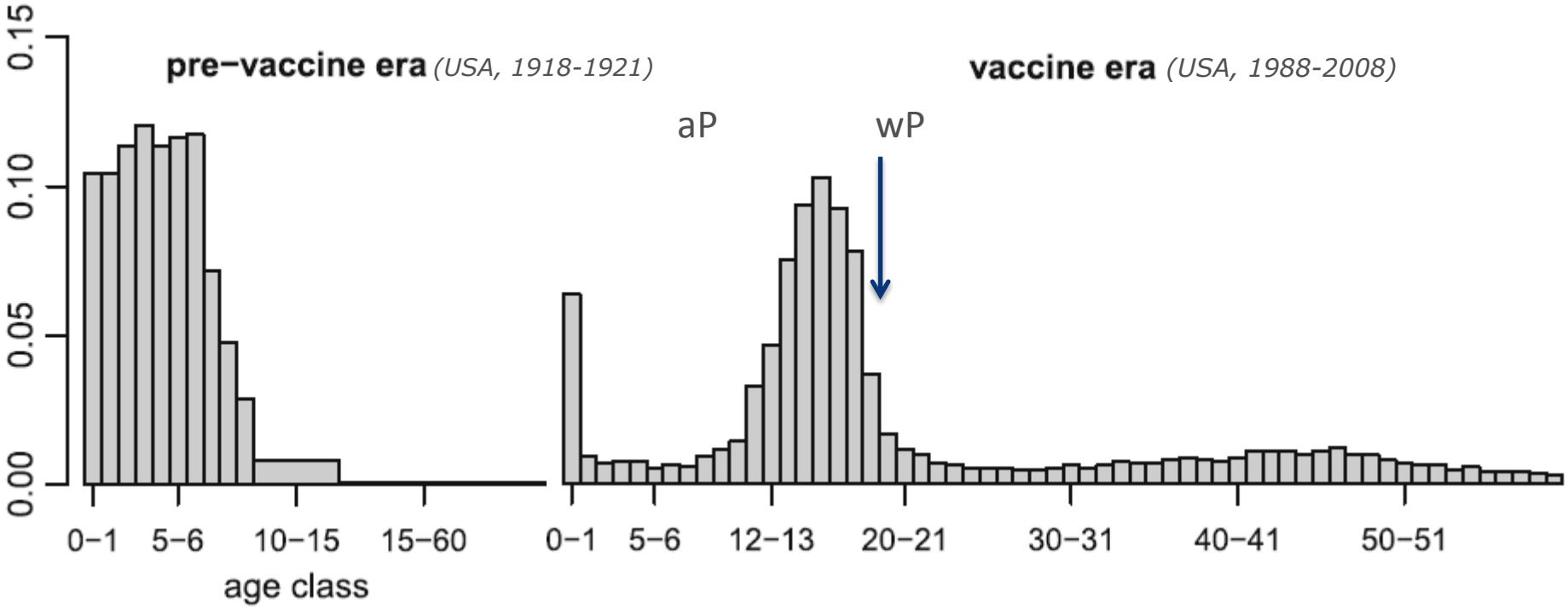
Mouse Model	Clinical Trials
Control	
aP2 - GSK	59%
wP - Connaught	36 to 48%
aP3 - GSK	84-89%
wP - Behring	98%
wP - Wellcome	>90%

Mouse lung clearance test would be valuable in addition to Kendrick test

Source: Godfroid F, Int J Med Micr. 2004

Vaccines have changed pertussis epidemiology

Age related shift in pertussis disease
Among adolescents high incidences are found



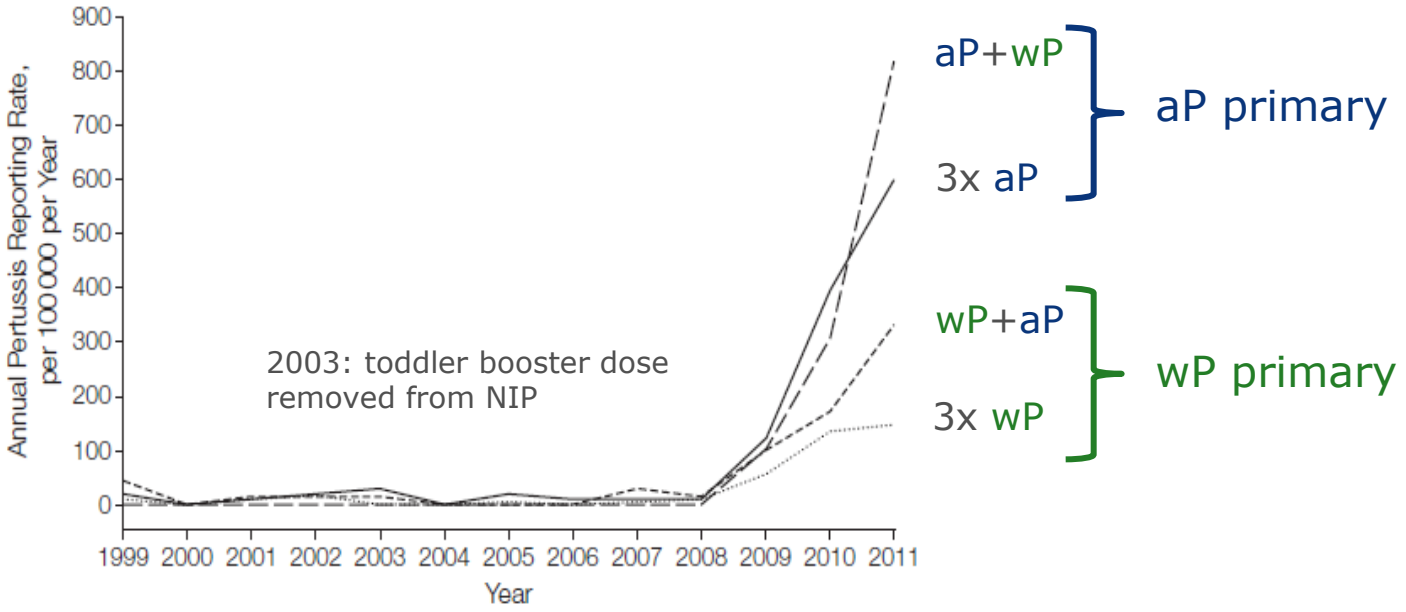
- High disease burden between 0-8 years of life
- High disease burden in infants too young to be (fully) vaccinated
- Short duration of protection of aP vaccines: disease peak in teenagers

Source: Lavine J, et al. PNAS 2011

Shorter duration of protection after priming with aP versus wP could explain age-shifts

Australian

Figure. Pertussis Reporting Rates Between 1999 and 2011 by Primary Course of Pertussis Vaccination for Children Born in 1998



DTaP indicates diphtheria-tetanus-acellular pertussis; DTwP, diphtheria-tetanus-whole cell pertussis.

Source: Sheridan S, et al. JAMA 2012

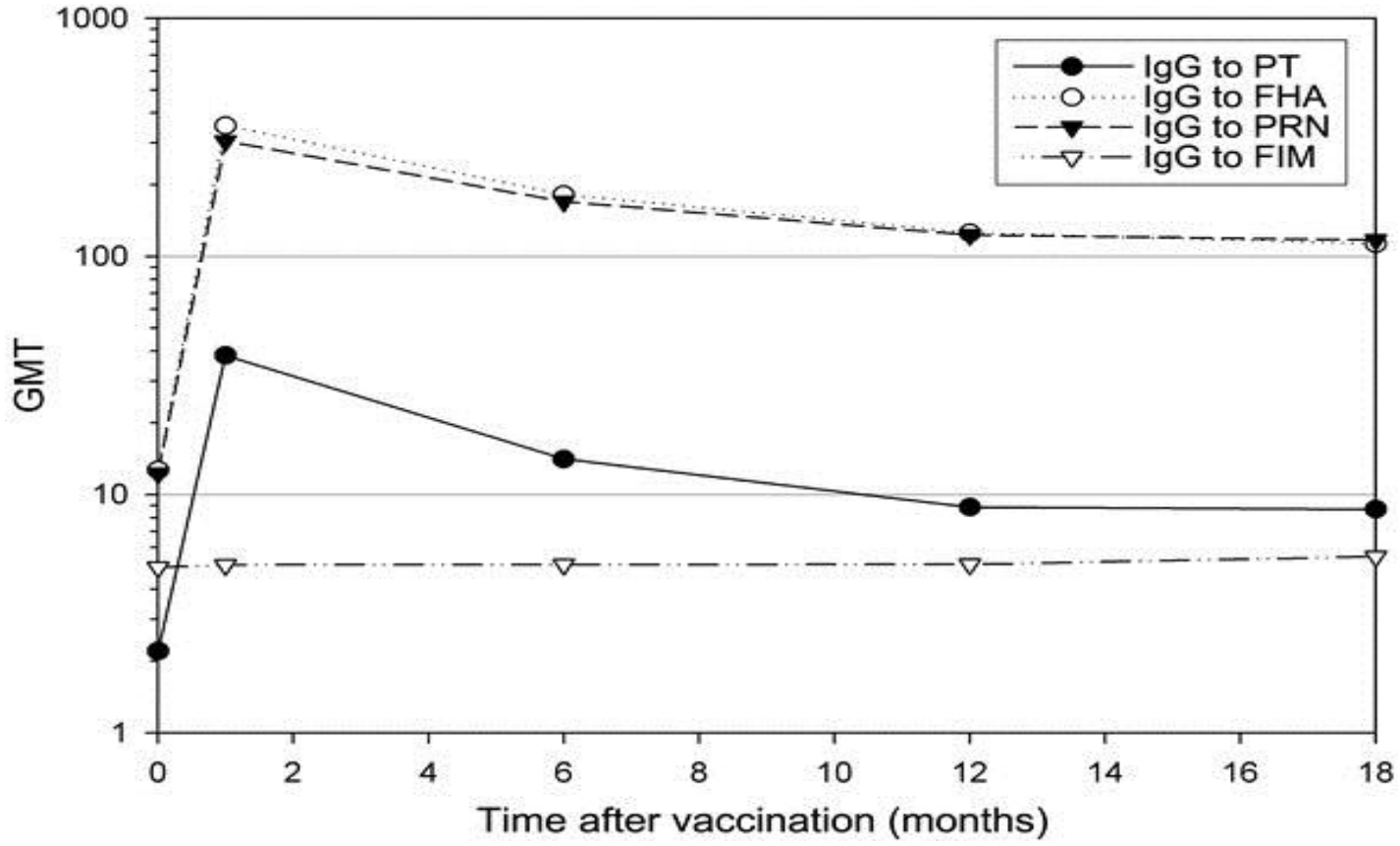
Possible explanations? Multifactorial!

To pick four :

1. Shorter duration of protection of aP vaccines :
2. Short duration of anti-PT
3. *B. pertussis* isolates lacking pertactin production
4. Different impact of aP on transmission of *B.pertussis*

Antibodies against pertussis toxin wane fast

Pressure on PRN escape?



Source: Le T, et al. JID 2004

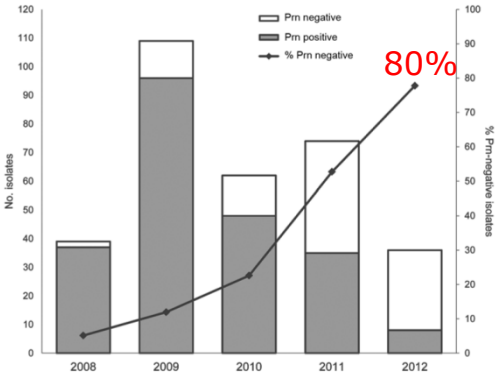
Currently between 3 to 85% of isolates is PRN-deficient

USA, 2011-2013

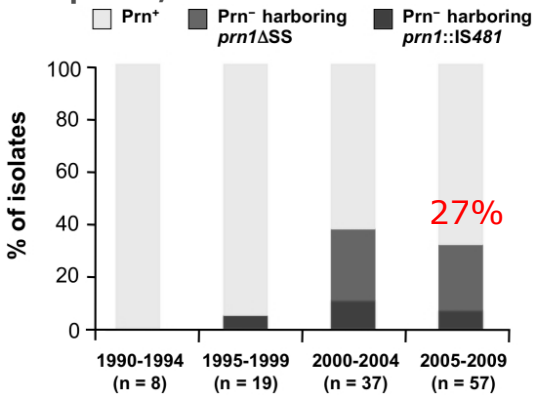
Table 1. Number of *Bordetella pertussis* Isolates Collected Between May 2011 and February 2013

State Submitting Isolate	Pertactin Protein Deficient, No. (%)	Pertactin Protein Produced, No. (%)	Total
Colorado	6 (67)	3 (33)	9
Connecticut	13 (81)	3 (19)	16
Minnesota	83 (95)	4 (5)	87
New Mexico	4 (100)	0 (0)	4
New York	51 (94)	3 (6)	54
Oregon	68 (79)	18 (21)	86
Vermont	235 (92)	20 (8)	255
Washington	180 (74)	62 (26)	242
Total	85%	113 (15)	753

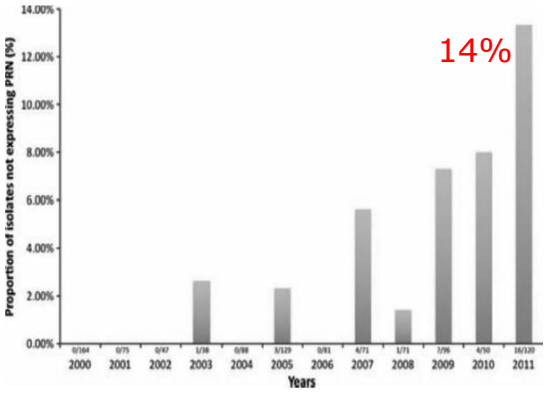
Australia, 2008-2012



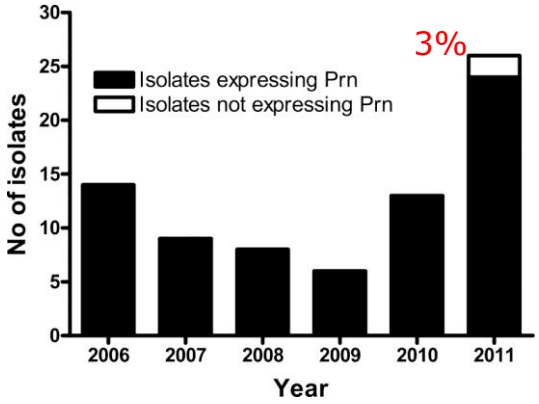
Japan, 1990-2009



France, 2000-2011



Finland, 2006-2011



Source: Martin S, et al. JID 2015; Lam C, et al. Emer Inf Dis 2014; Otsuka N, et al. PLoS One 2012; Hegerle N, et al. Clin Microbiol Infect. 2012; Barkoff A, et al. Clin. Vaccine Immunol 2012

2 to 3 times higher odds of having pertussis disease by PRN-neg. strain when vaccinated

Vaccine Receipt	Pertactin Protein Deficient	Pertactin Protein Produced	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Vaccinated: ≥1 dose	462	65	3.2 (1.9–5.3)	2.2 (1.3–4.0)
Unvaccinated	65	29	Referent	Referent
Vaccinated: Up-to-date, according to schedule and >1 y of age	248	26	3.7 (1.9–7.1)	2.7 (1.2–6.1)
Unvaccinated and >1 y of age	52	20	Referent	Referent

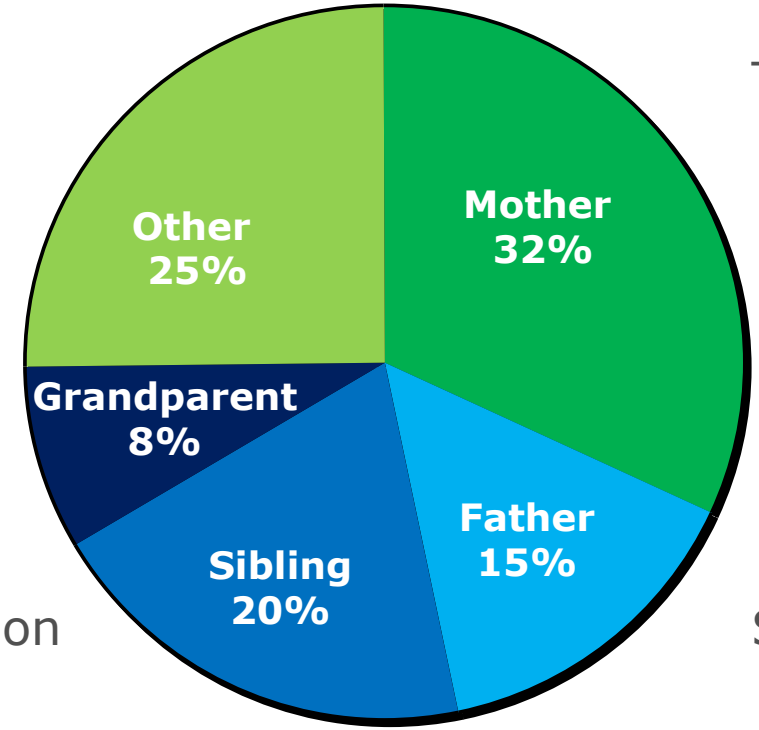
Important remark: No correlation observed between PRN-neg. and disease symptoms

Source: Martin S, et al. CID 2015; Bodilis H, et al. Emer Inf Dis 2013

Sources of pertussis transmission

Neonates are most vulnerable

Toddler immunization



Increased transmission
aP > wP ?

Subclinical infections

Source of infant pertussis

Source: Bisgard K, et al. PIDJ. 2004

wP vaccinated seem less susceptible

Different impact of wP on subclinical infections and transmission?

Pa primed children had higher rates of reported pertussis during a USA outbreak

Table 1. Pertussis among Children in Oregon, According to Type of First Dose of Pertussis Vaccine.*

	First Pertussis Vaccine†		Pertussis Cases‡		Incidence per 100,000		Risk Ratio (95% CI)§
	Acellular	Whole Cell	Acellular	Whole Cell	Acellular	Whole Cell	
Any pertussis vaccination¶	164,885	31,074	315	31	191.0	99.8	1.91 (1.32–2.77)
3 pertussis vaccinations in first yr of life	120,712	24,569	243	23	201.3	93.6	2.15 (1.40–3.30)
≥5 pertussis vaccinations starting before 1 yr of age	111,965	22,093	190	18	169.7	81.5	2.08 (1.28–3.38)
≥5 pertussis vaccinations starting before 1 yr of age, and disease at age ≥10 yr	113,502	22,229	130	10	114.5	45.0	2.55 (1.34–4.84)
≥5 pertussis vaccinations starting before 1 yr of age, with Tdap at age ≥10 yr	86,105	16,800	65	5	75.5	29.8	2.54 (1.02–6.36)
Any receipt of Tdap	106,893	17,889	85	6	79.5	33.5	2.37 (1.04–5.42)

Source: Liko J, et al. NEJM 2013

Ultimate goal: induce long-lasting protection, without reactogenicity such as with DTwP

Short-term aP improvements with known protective antigens:

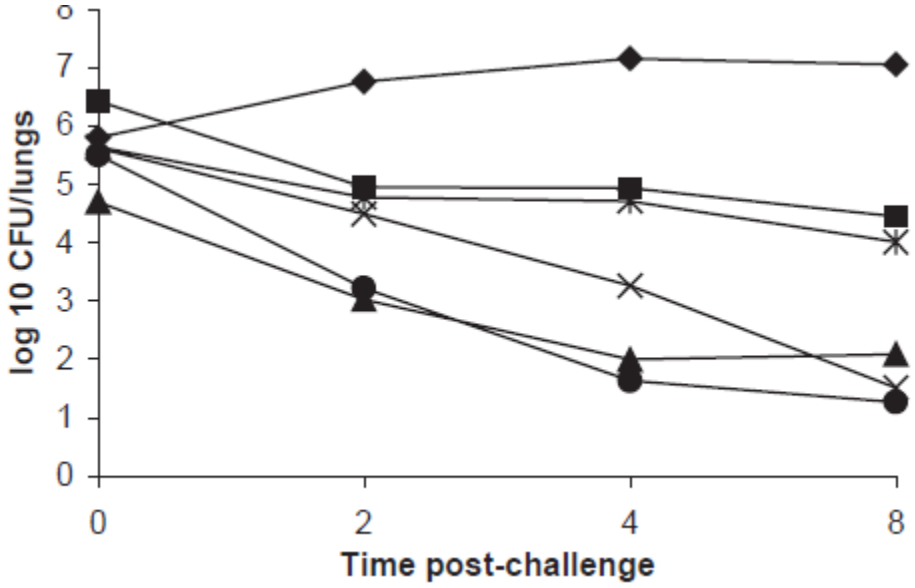
1. PT immunogenicity (by genetically detoxified PT)
2. Effectiveness against PRN- strains (by increasing/adding FIM)
3. Introduce maternal vaccination

Long-term improvements:

4. New antigens, incl[illegible]uated wP
5. Adjuvantia
6. New del[illegible]y systems

Will not be discussed

Mouse intranasal challenge test correlates with vaccine efficacy



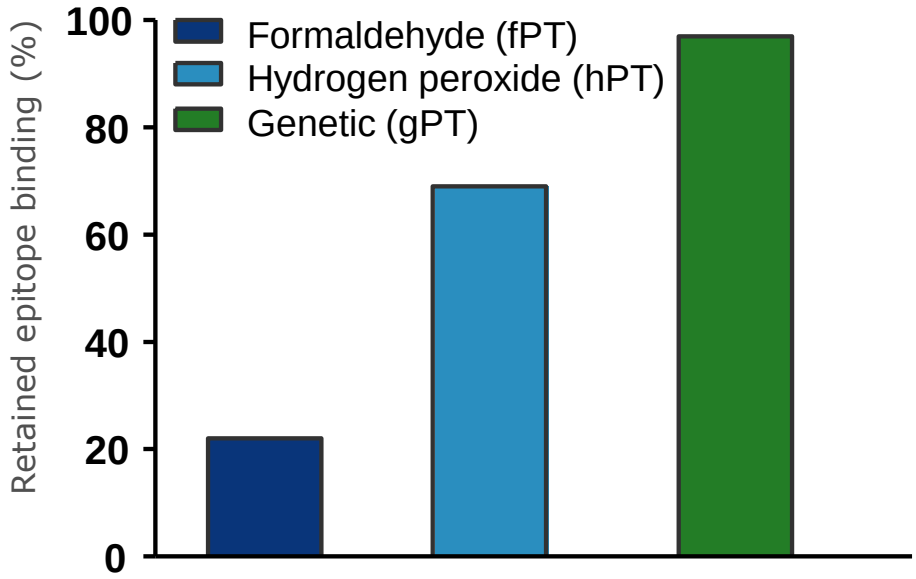
Mouse Model	Clinical Trials
Control	
aP2 - GSK	59%
wP - Connaught	36 to 48%
aP3 - GSK	84-89%
wP - Behring	98%
wP - Wellcome	>90%

Mouse model measures nonlethal colonization , not a disease endpoint : disfavours anti-PT immunity

Source: Godfroid F, Int J Med Micr. 2004

Chemical PT detoxification reduces immunogenicity first short-term improvement : mutant PT

Epitope-binding patterns of several PT MAbs varied considerably and were dependent on the detoxification procedure



fPT - PT treated with formaldehyde at a final protein/formalin ratio (wt/wt) of 0.3 and 0.03 were prepared as described by Nencioni

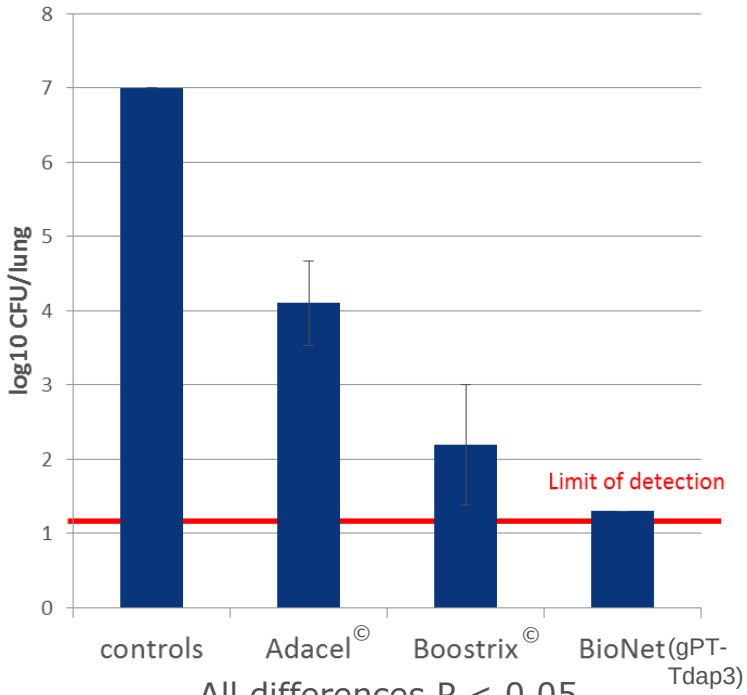
hPT - Hydrogen peroxide-detoxified PT: North American Vaccines

gPT - Genetically detoxified PT (PT-9K/129G): Sclavo Research Center

Source: Ibsen P. Vaccine 1996

Variation in vaccine efficacy: combination of PT quantity and quality

Vaccine efficacy 1/10 HD
Mouse intranasal challenge (WHO 18323)



All differences P < 0.05

High dose PT is associated with a 38% lower incidence of *B. pertussis* (IRR = 0.62)

Tdap History Characteristic	Adjusted[a] IRR (95% CI)
Tdap brand	
Adacel	Reference
Boostrix	0.62 (.52–.74)
Unspecified *	1.07 (.88–1.31)
DTaP	0.41 (.10–1.64)

*Unspecified = unspecfied brandname

Source: Koepke R, et al. JID 2014; Janssen lab notebook BN-6, BN-7, BN-8; from lungs of 9 week old mice vaccinated with 1/10 human dose 4 and 7 weeks of age. Cave: PT concentration Adacel©, Boostrix© and gPT (BioNet Ltd.), respectively 2.5, 8 and 5 µg/hd

Detoxification method also suggestive of improved immunogenicity in adults

Indirect comparison from three RCTs in adults

	hPT SSI TdaP	fPT Boostrix®	fPT Adacel®	gPT BioNet
	Study 1 (n=802)	Study 2 (n=2,284)		Study 3* (n=20)
Post-vaccination				
Anti-PT response rate (%)	92.0	77.2	47.1	94.4
GMC anti-PT (IU/mL)	121.8	63.6	32.2	268.5

Source: Thierry-Carstensen B, et al. Vaccine 2012; Blatter M, et al. Vaccine 2009; * Personal communication, PhI study; Differences in PT concentration between SSI TdaP, Adacel®, Boostrix® and gPT (BioNet Ltd.), respectively 20µg, 2.5 µg, 8 µg and 5 µg

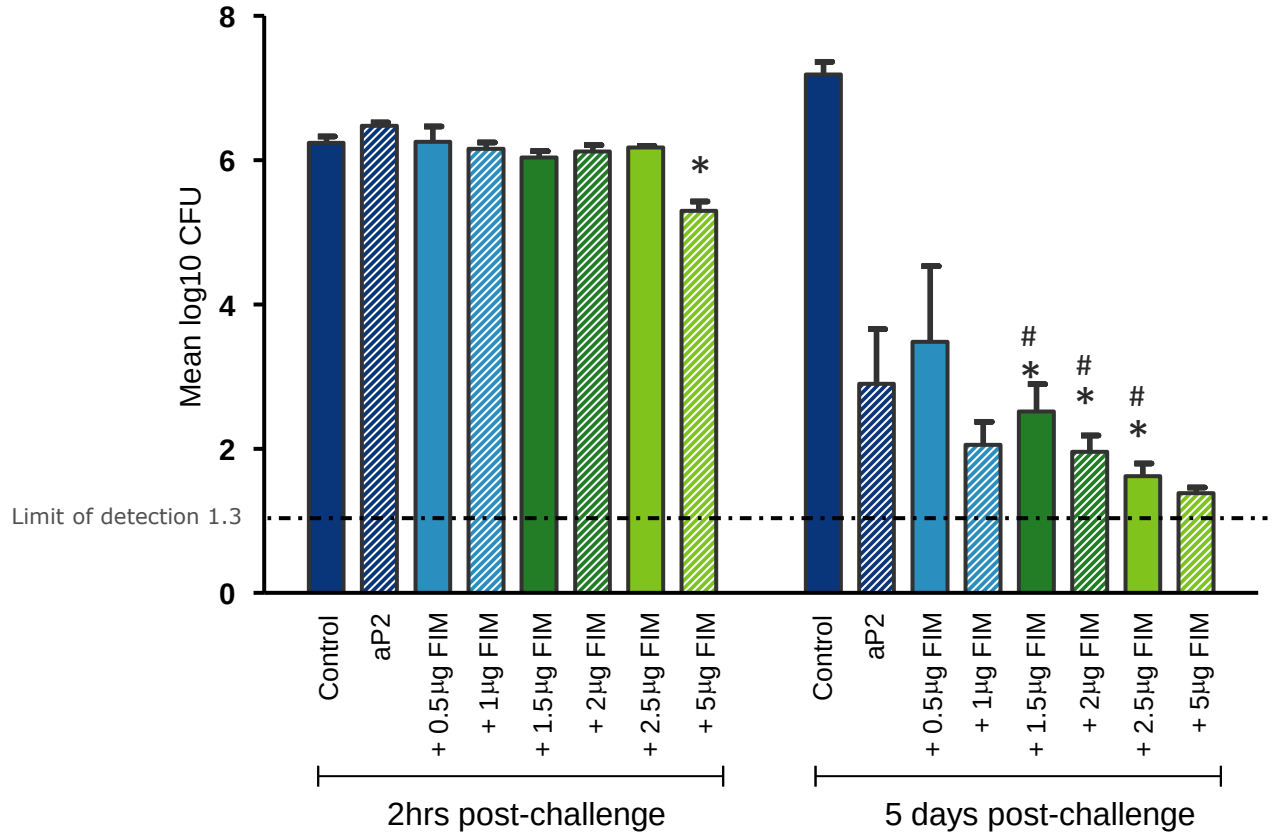
Pertussis in Denmark: No major ourbreaks

- Mono-component 40µg H_2O_2-PT-vaccine used in pediatric schedule at 3, 5 and 12 months since 1997
- Last pertussis epidemic year was 2002 with an incidence of 36/100,000
- Pre-school booster since 2003, peak incidence from 5-7yrs to adolescents
- Other explanations for the low incidence of pertussis related to testing and surveillance methods cannot be ruled out

Source: Thierry-Carstensen B, et al. Vaccine 2012; Biggelaar A, et al. 2015 (Submitted for publication)

Second short-term improvement increase levels of FIM

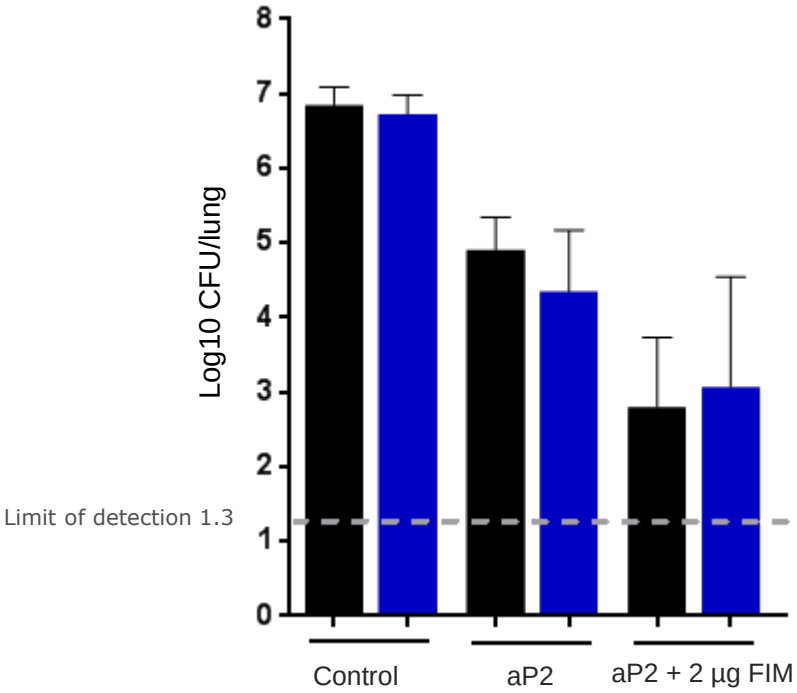
A high level of FIM significantly increases vaccine efficacy in mouse nasopharyngeal challenge model



Challenge: PRN- I195 strain
* Statistically significant vs DTaP2 alone
# Statistically significant vs DTaP2+0,5µg

Source: WO2014/135651 A1 Janssen NB24779 p160; Mice vaccinated at 4 and 7 weeks with at 1/10 hd DTaP2 = Pentavac®; containing 25 µg/hd PT and 25 µg/hd FHA

FIM2/3 improves DTaP2 vaccine efficacy for both FIM2 and FIM3 challenge strains



Challenge: FIM2 (**black**) or FIM3 (**blue**) expressing *B. pertussis* strain

Source: [REF]; from 9 week old mice 5 days post-challenge after vaccination with 1/25 hd of DTaP2 (= Pentavac®; 25 µg/hd PT and 25 µg/hd FHA) with the addition of an increasing amount of FIM at 4 and 7 weeks of age

Third short-term improvement implementation of maternal aP

UK experience: Maternal immunization is safe and effective when given in the 3rd trimester

Safety: No evidence of increased risk of adverse events related to pregnancy

Event*	Vaccinated v historical unvaccinated controls: No (%) events — Vaccinated women (n=6185)	Matched unvaccinated women (n=18 523)	Incidence rate ratio (95% CI)
Stillbirth	12 (0.19)	42 (0.23)	0.85 (0.45 to 1.61)
Neonatal death (within 7 days)	2 (0.03)	6 (0.03)	1.00 (0.20 to 4.95)
Pre-eclampsia/eclampsia	22 (0.36)	54 (0.29)	1.22 (0.74 to 2.01)
Placenta praevia	2 (0.03)	15 (0.08)	0.40 (0.09 to 1.75)
Intrauterine growth retardation/low birth weight/weight <2500 g	126 (2.04)	311 (1.68)	1.20 (0.98 to 1.48)
Caesarean section	1238 (20.02)	3748 (20.22)	0.99 (0.93 to 1.06)
Premature labour (without delivery)	5 (0.08)	21 (0.11)	0.71 (0.27 to 1.89)
Postpartum haemorrhage	59 (0.95)	181 (0.98)	0.98 (0.73 to 1.31)

Effectiveness of maternal pertussis vaccine by infant age at onset and timing of 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)

Source: Donegan K, et al. BMJ 2014; Amirthalingam G, et al. Lancet ID 2014

Summary

Changing epidemiology

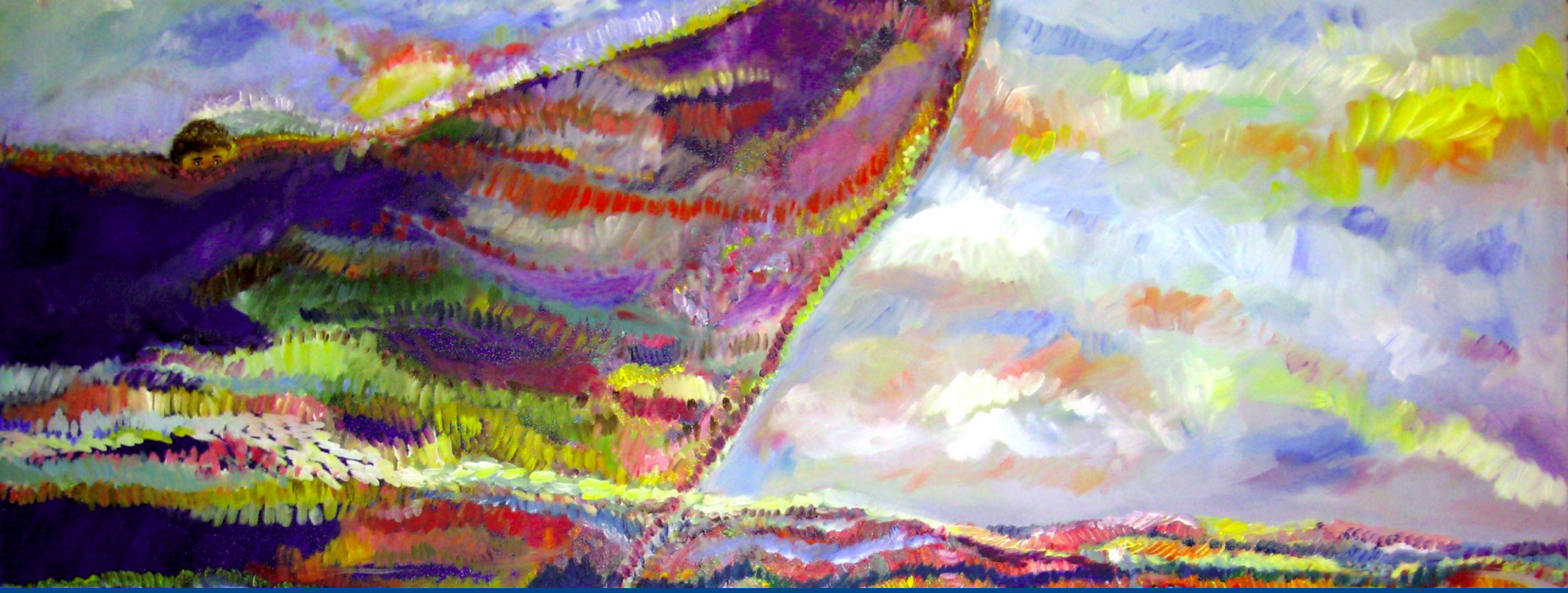
- Increase in pertussis
- Shift in age groups with high disease burden

Challenges with aP and wP

- PRN- negative strains
- Antibodies against detoxified PT wane fast
- Current Tdap short-lived protection
- Not all wP-vaccines are equally efficacious

Short-term improvements

- Better PT: genetically detoxified PT
- Address PRN- strains: High level of FIM
- Protect neonates: Maternal immunization



Thank you

Jennifer Jacons, *Stowaway*
Jennifer is a New York based artist living with Type 1 diabetes.

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