Neonatal vaccination against Pertussis: an industry perspective

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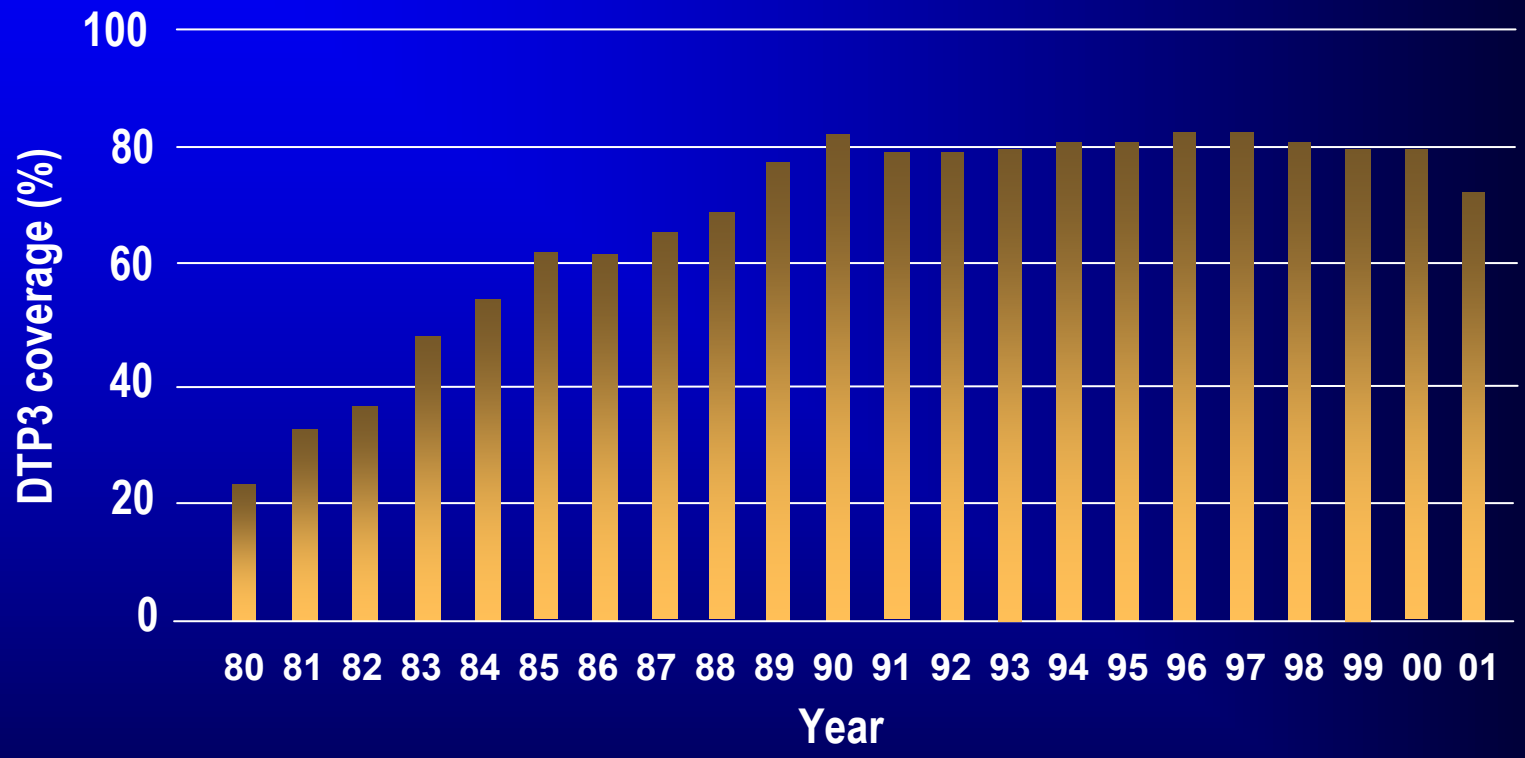
Presentation outline

- $DT_{(a)}P$ cornerstone of infant vaccination
- the pertussis GAP
- GSK aP: composition
  - clinical and preclinical data
  - clinical development in neonates
- aP at birth: business risk
- Conclusions

DTP3 – worldwide infant coverage 1980–2001



WHO 2003

GSK DTaP-based pediatric combinations

DTaP : Diphtheria/ Tetanus/ PT, FHA, Pertactin
Hib : Lyophilized PRP-T conjugate
HBV : Recombinant HBsAg
IPV : Inactivated enhanced-potency poliomyelitis

DTaP	DTaP / Hib
DTaP - HBV	DTaP - HBV / Hib
DTaP - IPV	DTaP - IPV / Hib
DTaP - HBV - IPV	DTaP - HBV - IPV / Hib
Pediarix™	**Infanrix hexa™**

⇒ flexibility to accommodate evolving local vaccination practices

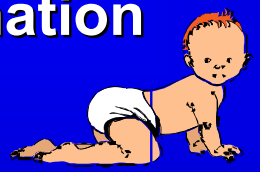
GSK DTaP-based combinations: safety profile up to 31 December 2003

	AEs	SAEs	SAEs/AEs(%)
• Infanrix™ - licensed in 1994, - > 73.5 mio doses	3044	628	20.6
• Infanrix™ Combos - > 37.2 mio doses	3385	698	20.6
• Infanrix™ hexa - licensed in 2000, - > 5.6 mio doses	804	207	25.7

Source: GSK data on file

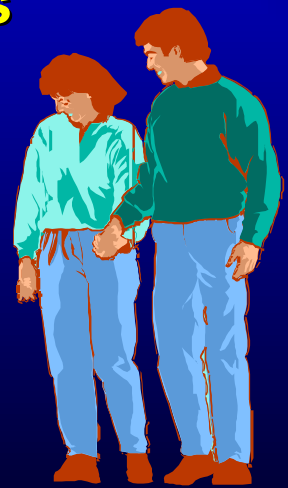
The Pertussis Gap

Primary vaccination



Booster vaccination at 16–18 months and 4-6 y of age

Non-vaccinated or partially vaccinated infants: at risk of complications



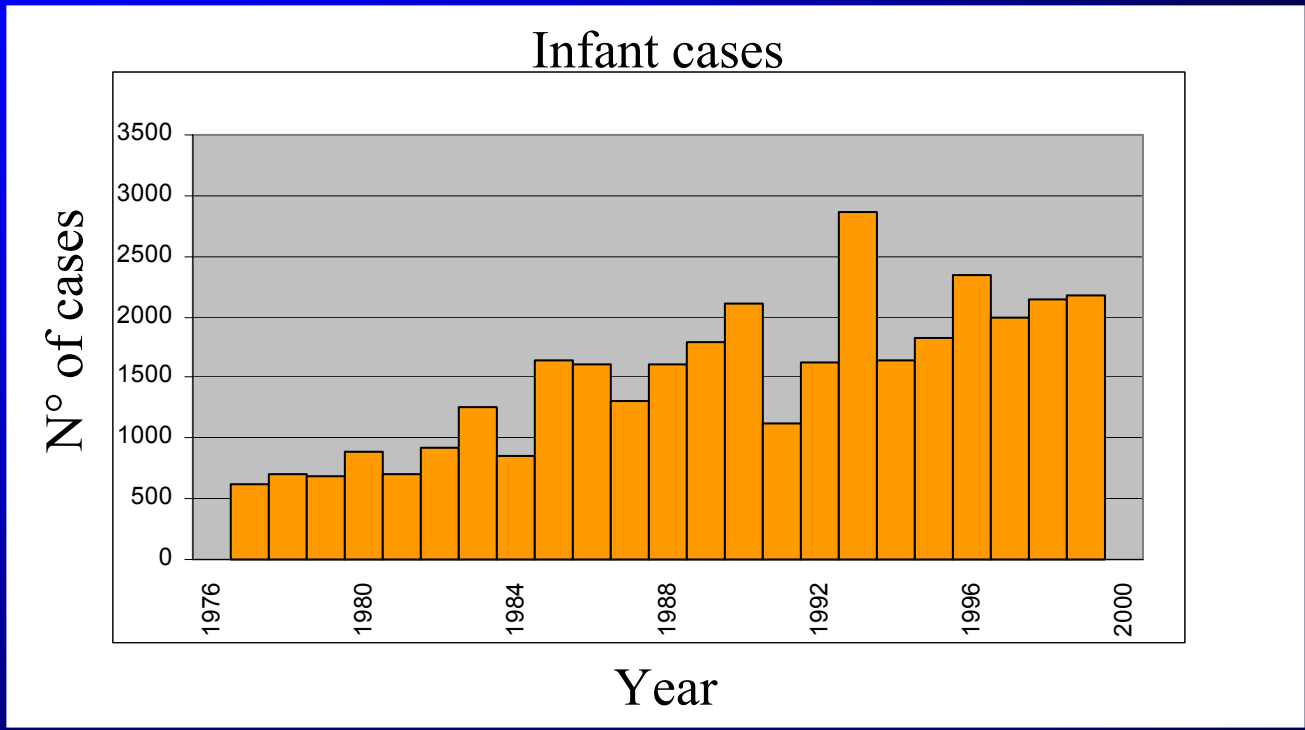
No vaccinal booster; immunity wanes over time: disease burden

Adults serve as reservoirs of infection

Based on Baron S et al. Pediatr Infect Dis J 1998;17:412–8

GlaxoSmithKline

True increase in infant pertussis: US, 1977-1999



- especially < 4 months of age
- resulting in excess hospitalisations and deaths

Source: Tanaka M. et al, JAMA. 2003; 290: 2968-2975

GSK Biologicals' aP vaccine

- Composition / 0.5ml dose:

		compared to Infanrix
– detoxified PT	25µg	25µg
– FHA	25µg	25µg
– Pertactin	8µg	8µg
– preservative	free	2.5mg 2 - PE
– adjuvant	0.5mg Al salts	
		DT

- Licensed in a limited number of countries (e.g. Australia, Sweden, Italy)

GSK Bio aP: supportive clinical data

- aP in adolescents (Germany): n = 48
  - 10-18 y of age, DTPw primed
  - one aP booster dose (commercial Td given one month earlier)

  ⇒ vaccine response ranged from 97.5 to 97.7 %

  ⇒ redness ≥ 50 mm: 4.3 %, swelling ≥ 50 mm: 2.2 %

  fever ≥ 39.1°C: 0.0%

- aP in children (Sweden): n = 200
  - 2-5 y of age, DT primed
  - 3 aP priming doses (0-2-4 and 0-2-8 mth schedule)

  ⇒ vaccine responses ranged from 98.8 to 100 %

  ⇒ redness > 20 mm: 13.0 - 17.1 %, swelling > 20 mm: 6.0 - 9.2 %

  fever > 39.5°C: 1.0 - 1.0 %

GSK Bio data on file

GSK Bio DTaP: supportive clinical data

- DTaP in pre-term infants (Spain): n = 185
  - pre-terms of < 37 weeks of gestation compared to ≥ 37 weeks
  - DTaP IPV HBV Hib (Infanrix hexa) at 2, 4, 6 mths of age

  ⇒ response to pertussis Ags ranged from 98.9 to 100%

  seroprotection for D, T, Polio: 100%
  for HBV: 93.4 and 95.2%
  for Hib (≥0.15µg/ml): 92.5 and 97.8%

  ⇒ solicited symptoms (4 days follow-up)

  local pain: 35.1 and 35.9% most frequent symptom
  1.1 and 2.2% grade "3"
  fever > 39.5°C 0.0%

Omenaca F et al; ICAAC 2003 (Late breaker L-186a)

GSK Bio aP: pivotal pre-clinical data (1)

Model:
- validated neonatal mice model (Roduit et al. 2002)
- 7 day old BALB/C mice mimicking human neonate
- 0.25 of a human dose

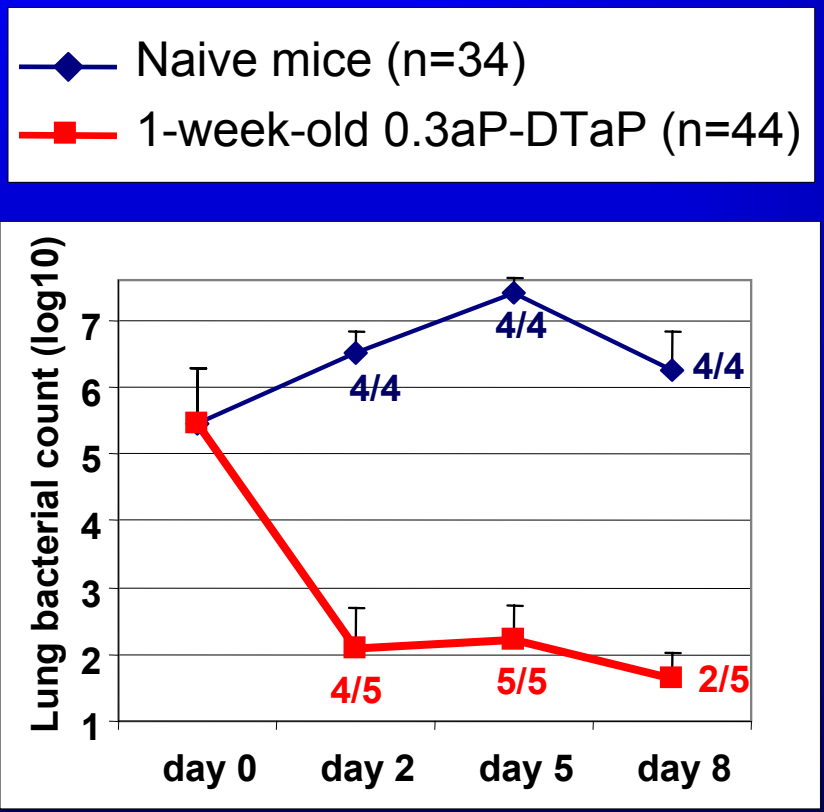
Design:
- 1 neonatal dose of 0.3 aP followed by 1 dose DTaP (Infanrix™) 3 weeks later
- aerosol challenge on day 35

Objective: Does neonatal immunisation prime for significant protection at the time of a subsequent dose of DTaP

Study conducted by C.A. Siegrist, Geneva, 2003

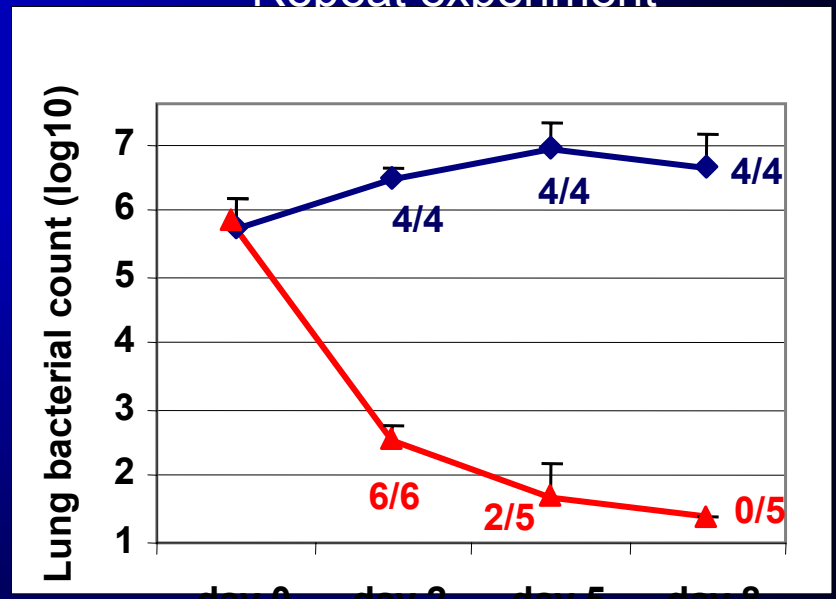
GSK Bio aP: pivotal pre-clinical data (2)

Results: the 0.3 aP neonatal dose primed for secondary responses to DTaP that are as immunogenic and protective as those elicited with 2 doses of DTaP



AUC/AUC max
1 week 0.3aP-DTaP 0.37

Repeat experiment



AUC/AUC max
1 week 0.3aP-DTaP 0.36

Data generated by C.A. Siegrist, Geneva, 2003

Considerations regarding aP at birth

- programmatically feasible: BCG, Polio, Hepatitis B
- acellular pertussis based vaccines pave the way:
  - basic technical and clinical developments done
  - well tolerated, also in pre-term infants
  - first choice for infants in many industrialised countries
  - reduced antigen formulation (dTap) for boosters postchildhood
- encouraging pre-clinical (mouse model) and preliminary clinical data

aP at birth: proof of concept clinical study

- Objective: explore indicators of early protection
- Design: Single aP birth dose followed by 3 doses of Infanrix™ hexa at 2, 4 and 6 mths of age
- Endpoints:
  - any serological evidence of immune tolerance (post dose III)
  - indications of anamnestic response:
    - serology post DTaP dose I
    - CMI
    - avidity

aP at birth: clinical development issues

- Demonstrate early protection in absence of serological correlate
- size of the specific safety database against extensive background experience with aP-based vaccines
- aP and/or aP-HBV ?

aP at birth: business risk

- **Investments**
  - production capacity
    - facility
    - Q & A
    - establishment license
  - clinical / regulatory requirements
    - proof of concept
    - immunogenicity
    - reactogenicity
    - evidence of protection
    - safety
  - further line extension: aP - HBV ?

- **Return**
  - vaccine price
  - uptake
  - Recommendation !!

RISK !

Neonatal vaccination against pertussis: Conclusions

- A neonatal strategy for vaccination against pertussis is programmatically feasible
- Complementary to vaccination of adolescents, adults (cocooning)
- Technical development completed
- POC clinical trial underway: accelerated protection ?
- Economical viability depends on uptake = need for UMV recommendation to cover business risk