

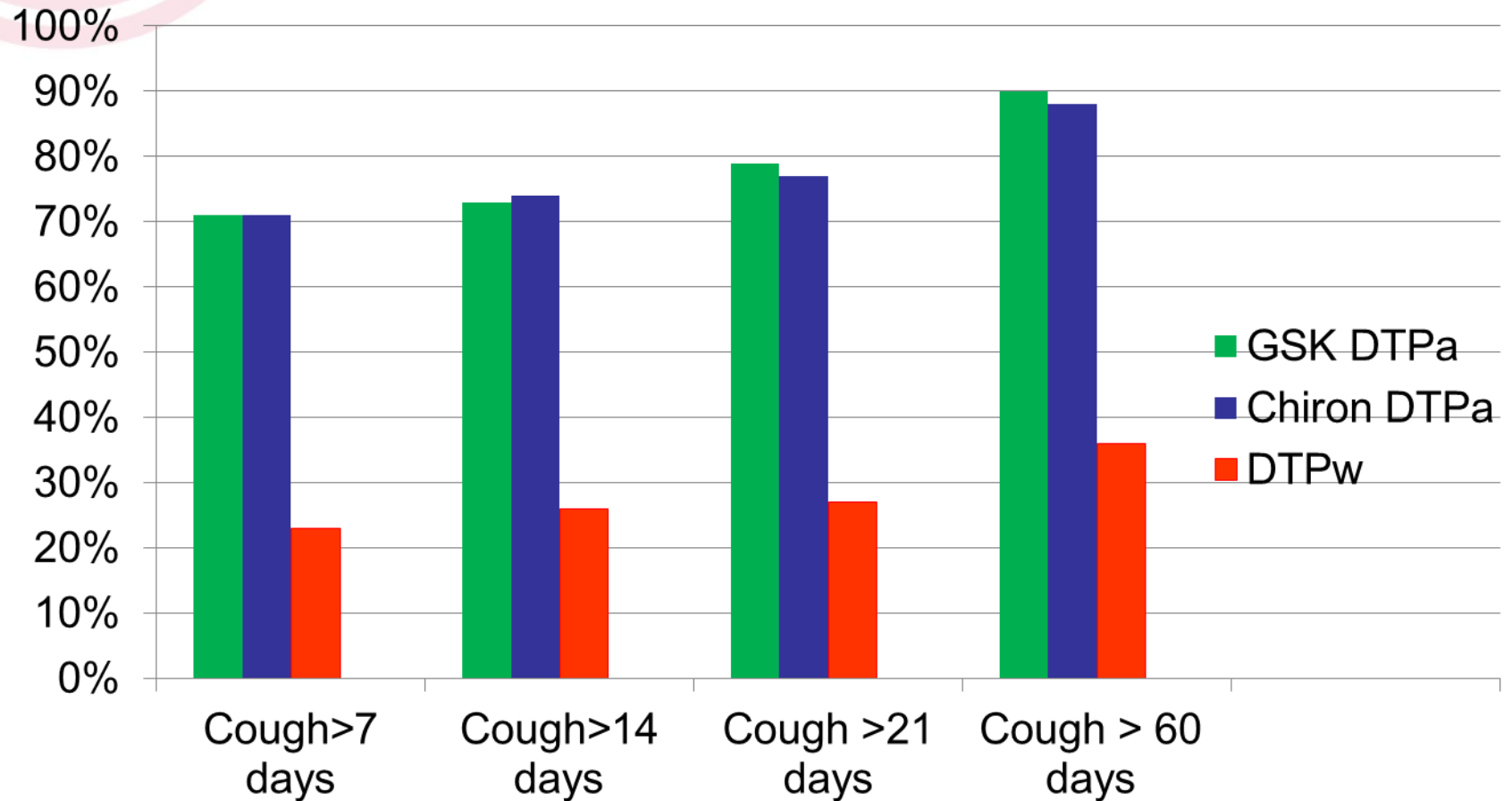
Serologic correlates of protection from pertussis vaccines

Peter McIntyre
**National Centre for Immunisation Research
and Surveillance - Sydney**

Lessons from pertussis vaccine trials

**Evidence for relative efficacy against
less severe disease**

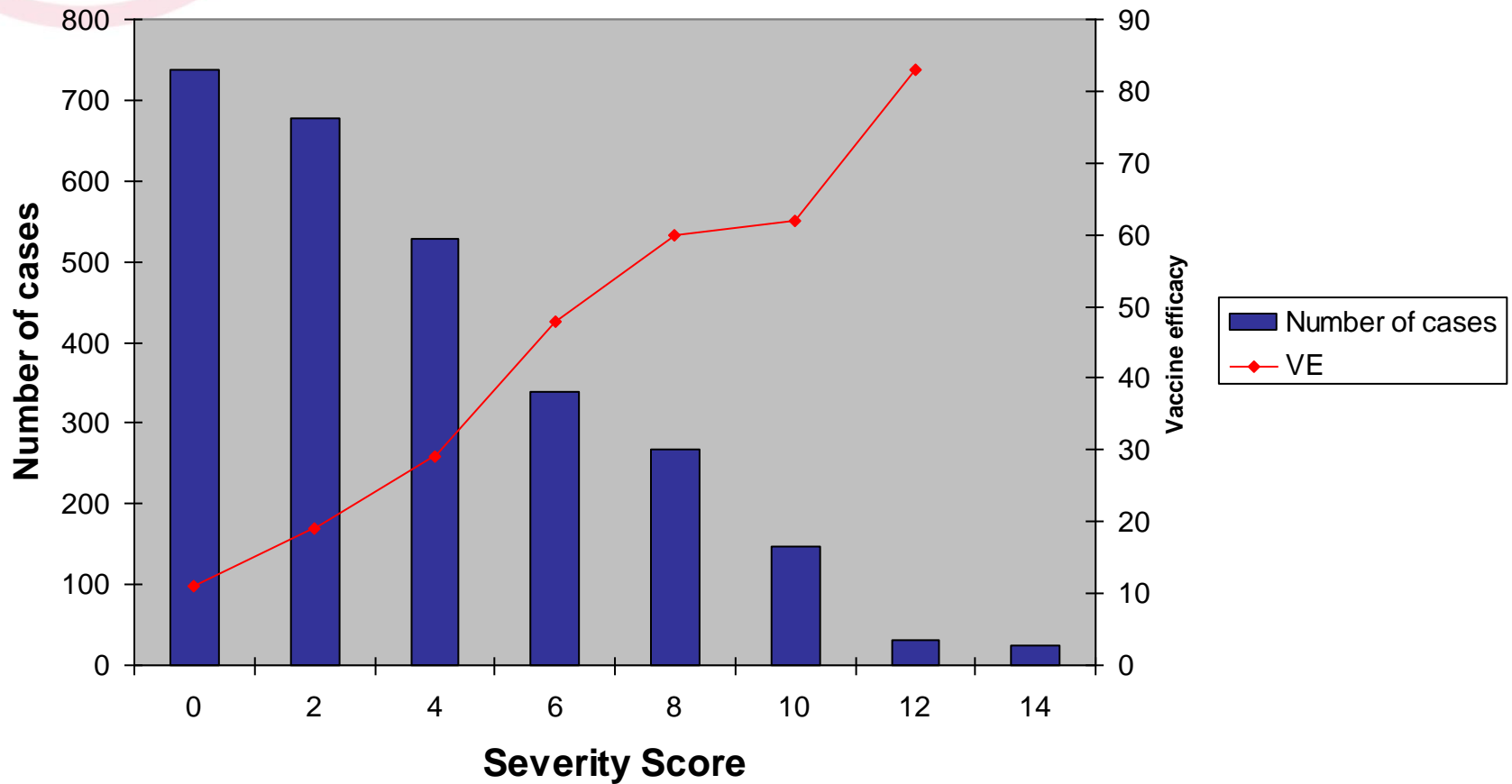
Efficacy of vaccines in Italian trial against increasing duration of cough



Greco et al NEJM 1996; 334: 341

Vaccine efficacy in relation to disease severity score

Senegal trial N=834 cases¹



1. Prezosi Clin Inf Diseases 2003; 37: 772

Swedish vaccine trials

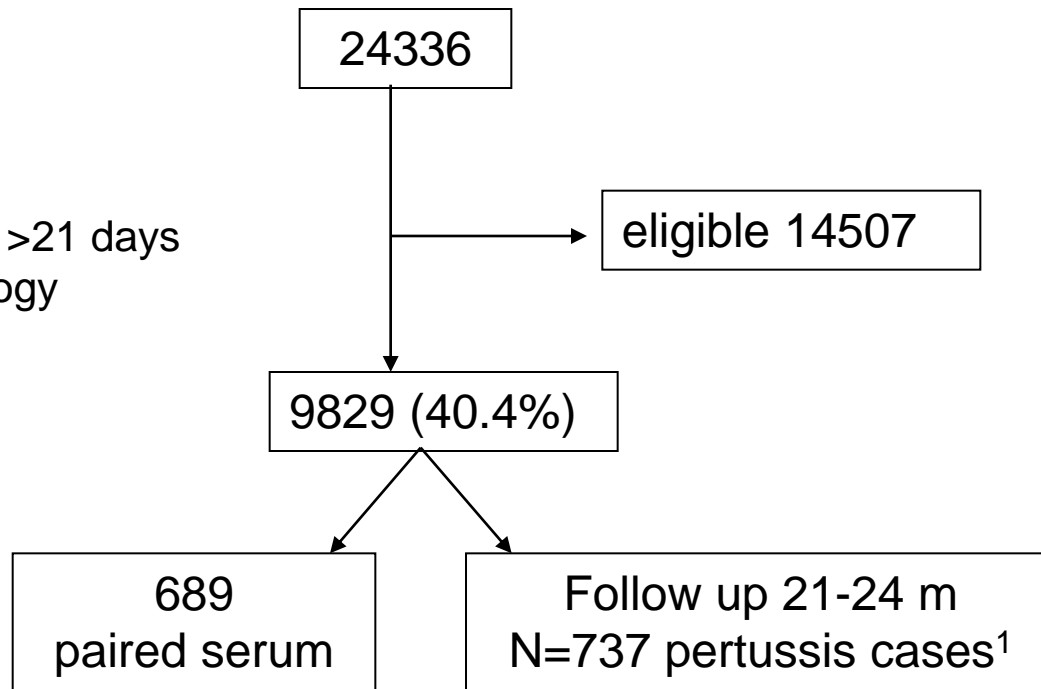
Sweden II - 2,4,6 schedule, poor DTPw

Sweden III – 3,5,12 schedule, good DTPw

Sweden II - Gustafson, NEJM 1996; 334-349

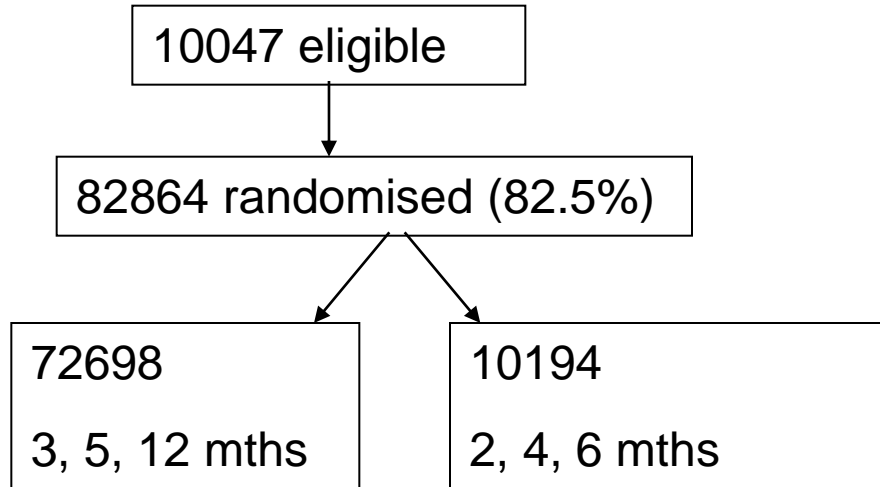
- 3 vaccines
 - Connaught WC
 - Connaught 5C (10 μ g PT, 3 μ g PRN)
 - GSK 2C
 - DT
- Pertussis epidemic during trial period
- Active follow-up:
 - Nurse contacted household every 6-8 weeks and parents asked to report
 - Standard clinical data
 - Nasopharyngeal aspirates
 - Paired serum

1. Case definition = >21 days
cough + cult or serology



| | 2C | 5C | WC | DT |
|---|----------------|----------------|----------------|---------------|
| Incidence per 10 ⁵ post 3 d (culture pos %) | 3200 (56%) | 1200 (42%) | 4000 (59%) | 7800 (73%) |
| VE 21 d cough (post 3 d) (95% CI) | 59% (51-66) | 85% (81-88) | 48% (37-56) | - |
| VE any cough (95%CI) | 42% (32-51) | 78% (73-82) | 41% (30-51) | - |

Sweden III Trial – Olin et al Lancet 1997;350;1569



| | | |
|--------------------|-------|------|
| GSK 2 component | 18145 | 2552 |
| Chiron 3 component | 18184 | 2544 |
| Canada 5 component | 18196 | 2551 |
| UK whole cell | 18173 | 2547 |

Vaccine efficacy – Sweden III trial

N = 72655 Follow up period = 22 months
4 pertussis vaccine groups, no DT arm

Outcomes

1. *Culture confirmed*

- all post dose 3
 - with ≥ 21 days paroxysmal cough
 - with any cough
- all post dose 1
 - with ≥ 21 days paroxysmal cough
 - all between dose 2 and 3

2. *Not culture confirmed*

- all parent reported whooping cough parent stated 'certain'

Pertussis cases by case definition – Sweden III

| | 3 Component N= 17679 | 5 Component N=17686 | Whole Cell N=17453 |
|--|-------------------------|----------------------------------|-----------------------|
| Number with cough of any duration (≥ 21 days) | | | |
| 3 doses | N=49 (21) | N=27 (13) | N=19 (15) |
| Incidence of all culture + /10⁵ (≥ 21 days) | | | |
| 3 doses | 155 (67) | 85 (50) | 61 (48) |
| RR (any cough) | 2.6 (1.5-4.3) | 1.4 (0.8-2.5)¹ | 1.0 |
| Incidence of all culture + / 10⁵ between dose 2 and 3 (>21 days) | | | |
| | 353 (210) | 152 (95) | 181 (67) |
| RR 1.0 (2C vaccine) | 0.5 (0.4-0.8) | 0.2 (0.1-0.4) | 0.3 (0.2-0.5) |

RR for 3C vs 5C = 1.8 (95% CI 1.1 to 2.9)

Serologic correlates

Household contact studies

Household contact studies post vaccine trials - Sweden and Germany

- Needed for interpretation:
 - Antibody levels obtained pre-exposure
 - Antibody levels obtained within a short time post exposure
- Challenges:
- Different vaccines
 - different antigenic components
 - different combinations of antibody results
- Limited eligible subjects
 - power to compare outcomes

Levels of anti-pertussis antibodies related to protection after household exposure to *Bordetella pertussis*

Jann Storsaeter*†, Hans O. Hallander†, Lennart Gustafsson† and Patrick Olin†

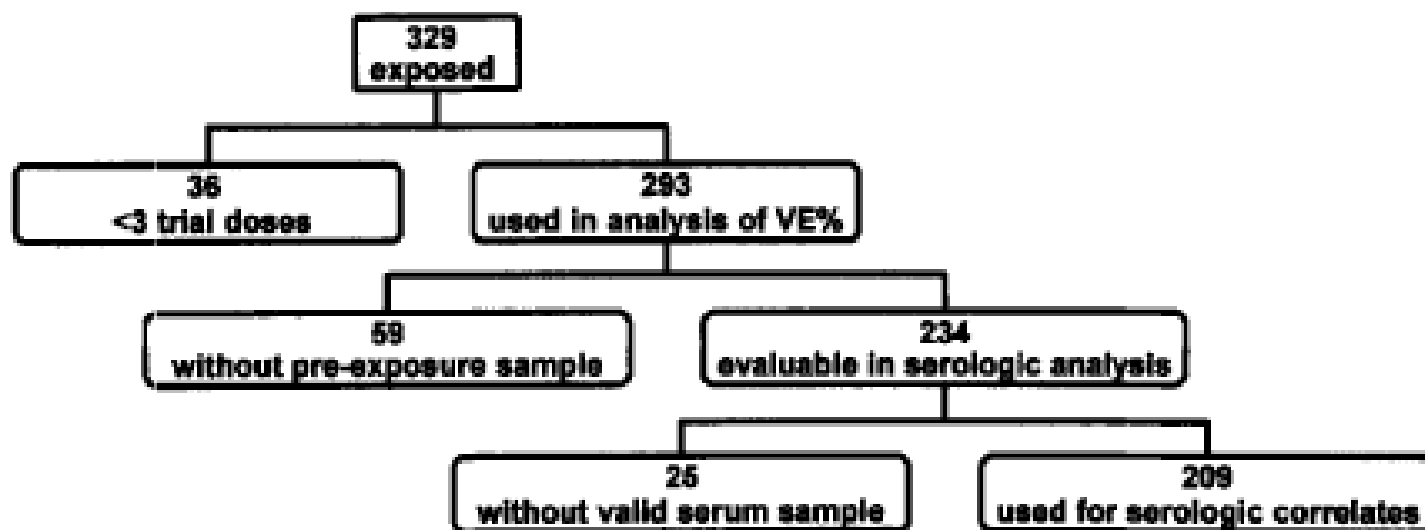


Figure 1 Study children exposed to *B. pertussis* in the household.

Household contact study in Sweden: WHO “typical” pertussis

Table 2. Attack rate of pertussis according to the World Health Organization definition, ≥ 21 days of paroxysmal cough, and corresponding estimates of vaccine efficiency in the Sweden 1 trial household exposure.

| Anti-PT | Fimbriae | 69 kDa, pertactin | No. exposed | No. cases | Attack rate, % | Vaccine efficacy, % | 95% CI |
|------------|----------|-------------------|-------------|-----------|----------------|---------------------|--------|
| H/L | H | H | 49 | 5 | 10 | 85 | 65–94 |
| H/L | L | H | 6 | 1 | 17 | 75 | 0–96 |
| H/L | H | L | 16 | 3 | 19 | 72 | 22–90 |
| H | L | L | 33 | 12 | 36 | 46 | 14–66 |
| DTP groups | | | | | | | |
| L | L | L | 40 | 27 | 68 | — | — |
| DT group | | | | | | | |
| L | L | L | 65 | 44 | 68 | — | — |

NOTE. D, diphtheria; H, high preexposure antibody levels; H/L, antibody levels independent of high or low levels (as defined in text); L, low preexposure antibody levels; P, pertussis; PT, pertussis toxin; T, tetanus. Data from [8].

Household contact study in Sweden: Any cough, laboratory-confirmed

Table 3. Attack rate of *Bordetella pertussis* with ≥ 1 day of cough and corresponding estimates of vaccine efficacy in Sweden 1 trial household exposure.

| Anti-PT | Fimbriae | 69 kDa, pertactin | No. exposed | No. cases | Attack rate, % | Vaccine efficacy, % | 95% CI |
|------------|----------|-------------------|-------------|-----------|----------------|---------------------|--------|
| H/L | H | H | 49 | 14 | 29 | 67 | 49–79 |
| H/L | L | H | 6 | 4 | 67 | 24 | 0–57 |
| H/L | H | L | 16 | 11 | 69 | 22 | 0–44 |
| H | L | L | 33 | 28 | 85 | 3 | — |
| DTP groups | | | | | | | |
| L | L | L | 40 | 35 | 88 | — | — |
| DT groups | | | | | | | |
| L | L | L | 65 | 57 | 88 | — | — |

NOTE. D, diphtheria; H, high preexposure antibody levels; H/L, antibody levels independent of high or low levels (as defined in text); L, low preexposure antibody levels; P, pertussis; PT, pertussis toxin; T, tetanus. Data from [8].

Low levels of antipertussis antibodies plus lack of history of pertussis correlate with susceptibility after household exposure to *Bordetella pertussis*

Jann Storsaeter*, Hans O. Hallander, Lennart Gustafsson, Patrick Olin

Swedish Institute for Infectious Disease Control, Solna, Sweden

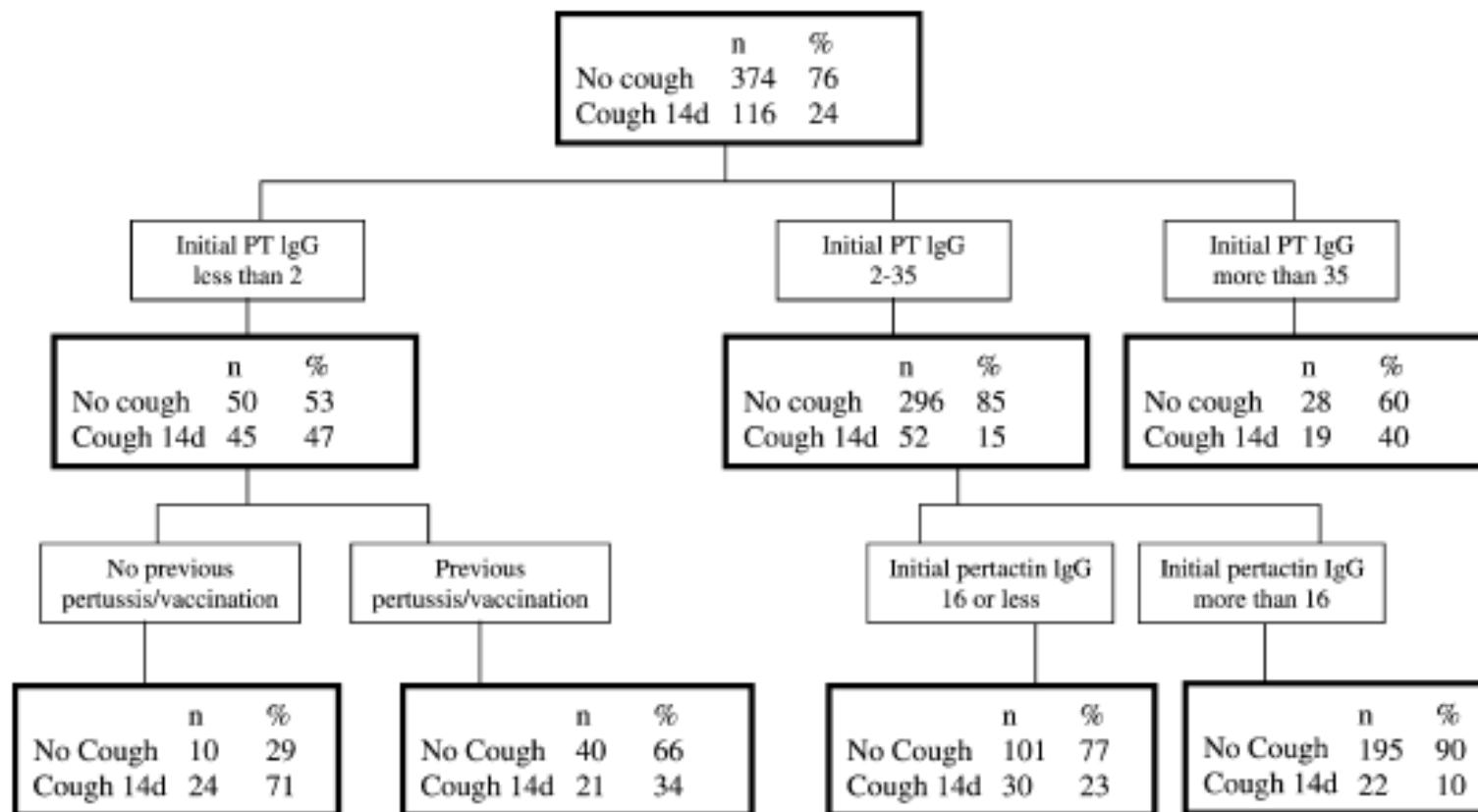
Table 2
Duration of cough in primary cases (study infants) and number of exposed household members by vaccine group and age

| Primary cases among study infants | | | Exposed household members | | |
|-----------------------------------|--------|-------------------------------------|----------------------------|-----------|------------|
| Vaccine group | Number | Duration of cough (mean \pm S.D.) | Adults born 1978 or before | Children | All |
| DTPa2 | 58 | 45.0 \pm 22.8 | 116 (76%) | 36 (24%) | 152 (100%) |
| DTPa5 | 19 | 46.5 \pm 44.0 | 34 (77%) | 10 (23%) | 44 (100%) |
| DTPwc | 59 | 66.5 \pm 31.4 | 115 (72%) | 44 (28%) | 159 (100%) |
| DT | 181 | 69.6 \pm 36.8 | 343 (76%) | 110 (24%) | 453 (100%) |
| All | 317 | 63.1 \pm 36.8 | 608 (75%) | 200 (25%) | 808 (100%) |

Low levels of antipertussis antibodies plus lack of history of pertussis correlate with susceptibility after household exposure to *Bordetella pertussis*

Jann Storsaeter*, Hans O. Hallander, Lennart Gustafsson, Patrick Olin

Swedish Institute for Infectious Disease Control, Solna, Sweden



Antibody response patterns to pertussis in vaccinated and unvaccinated children

Re-analysis of household contact study data

- **Post pertussis infection:**
 1. PT only vaccine
 - blunted response to FHA c.f. PT+FHA
 2. PT+FHA vaccine
 - blunted response to PRN and Fim
 3. DT vaccine
 - Lower responses to all vaccine antigens

Conclusions from household contact studies

- There are correlations
- Lack of PT antibody is single most important factor
 - Especially for severe disease
 - PT wanes rapidly post 3 dose infant schedule
 - Correlation with whole cell vaccine efficacy less clear
- Pertactin antibody and Fimbrial antibodies
 - Correlate with agglutinogens
 - Important against less severe disease
- Combinations of antibody have synergistic effects

Serologic correlates – summary

- Agreement on important factors
 - Antibody combinations
 - PT, Pertactin and Fimbriae
 - Case definition
- Uncertainties
 - Thresholds
 - by combination
 - by case definition
 - Case definition and transmission
 - Importance of Fim as independent factor

Re-introduction of pertussis vaccination – the Swedish experience¹

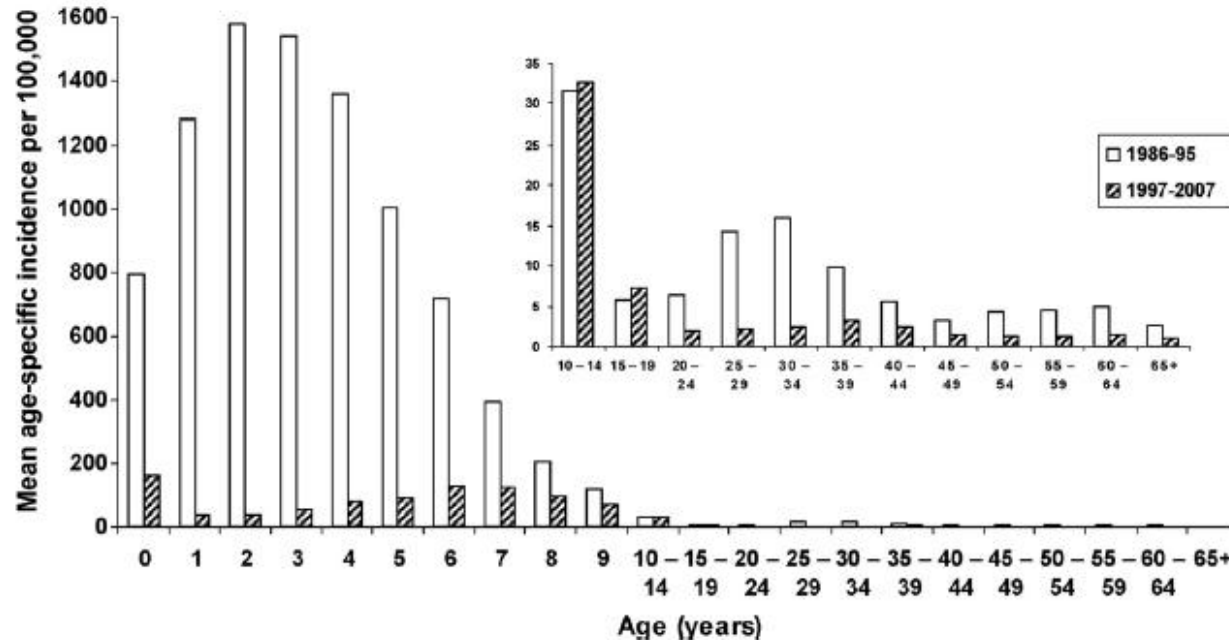
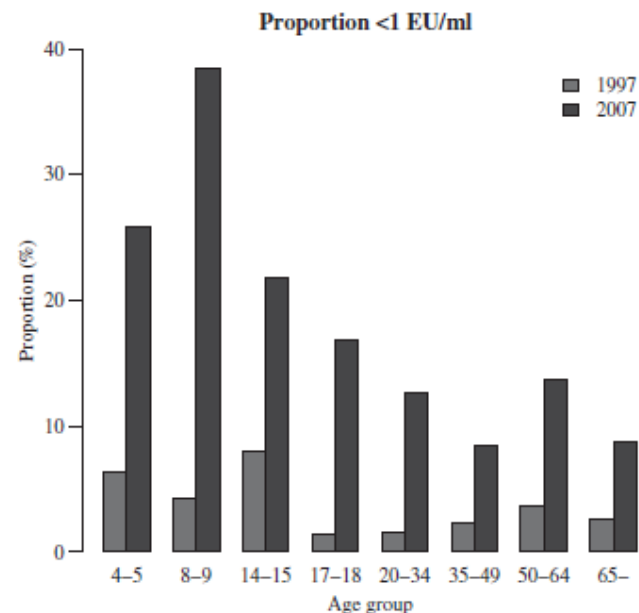
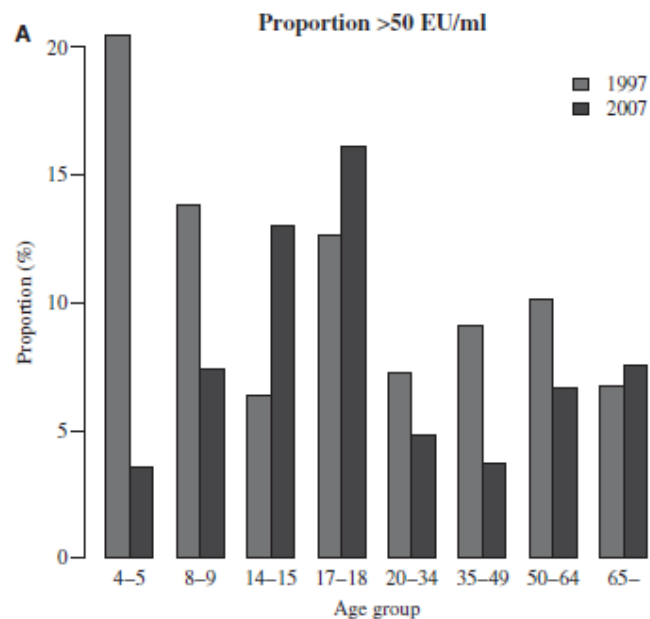


Fig. 2. Age-specific incidence of laboratory-confirmed pertussis in Sweden during 10 calendar years before and 11 calendar years after introduction of pertussis vaccination (using aP-containing vaccines) into the general vaccination programme in 1996 (mean incidence rates per 100,000 population 1986–1995 and 1997–2007). An enlarged version of the bar chart for the age groups 10 years and above is shown in the insert [2].

1. Carlsson and Trollfors Vaccine 2009

Seroprevalence of pertussis antitoxin (anti-PT) in Sweden before and 10 years after the introduction of a universal childhood pertussis vaccination program

HANS O. HALLANDER, MIKAEL ANDERSSON, LENNART GUSTAFSSON, MARGARETHA
LJUNGMAN and EVA NETTERLID



Summary

- Immunity to pertussis is **multifactorial**
- Clearest evidence is for **susceptibility related to low antibody levels**
- **More than one antibody** is important
- **More evidence** on serologic correlates is needed
 - ? Challenge studies
- **Hypothesis: Hierachy of immunity**
 - Post symptomatic infection
 - Whole cell vaccines: highest vs lowest efficacy
 - Acellular vaccines: more vs less components