Pertussis: recurrence in this last decade ?

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LE MICROBE DE LA COQUELUCHE

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Avec la planche XXVIII.

(Travail de l'Institut Pasteur de Bruxelles.)

Introduction

- Pertussis = kinkhoest = whooping cough = coqueluche
- Very contagious bacterial infection of the upper respiratory tract (*B. pertussis*, sometimes *B. parapertussis*)
- Droplet transmission < infected individuals (90% of susceptible household contacts will be contaminated)
- High lethality in children < 1 year old:
  - Developping countries: 1-3%
  - Developped countries: 1-2/1000
- WHO data:
  - 20 - 40 millions cases/year (90% in developping countries)
  - Mortality: 200 000 – 400 000 deaths/year

Clinical manifestations

- Classic (unvaccinated preschool child):
  - incubation period: 1-2 weeks
  - catarrhal stage: 7-10 days
    - mild upper respiratory tract symptoms
  - paroxysmal stage: 1- 4 weeks
    - characteristic cough, inspiratory whoop, → vomiting
  - convalescent stage: 4- 6 weeks → months
    - waning symptoms

Complications

- Respiratory:
  - asphyxia
  - broncho-alveolitis
  - bronchopneumonia, pneumothorax, bronchiectasis→ elderly (only scarce data)
- CNS:
  - encephalitis
  - convulsions, coma
  - intracranial haemorrhage
  - long-term disabilities (spastic paralysis)
- nutritional:
  - vomiting, dehydration… (developing countries)

Clinical manifestations: atypical disease

- Unimmunised infant < 6 months, preterm infant:
  - sudden infant death syndrome-SIDS
  - early apnoea, acute life threatening event-ALTE, bradycardia
  - respiratory failure→ PICU admission, oxygen suppl, feeding suppl, intubation, artificial ventilation
  - absence of whoop and cough

➔ fatality, unrecognised

Clinical manifestations: atypical disease

- Crowcroft et al. Arch Dis Child 2003; 88: 802-806

  Inclusion:
  - n=142 infants < 5 m, admission in PICU
  - resp failure – ALTE
  - systematically specimen collection for microbiology (incl *B pert*)

  Results:
  - 23% (n=33) pertussis confirmed (PCR, culture)
    - 33% co-infection with RSV
    - n=2 cases of fatality
- Conclusion:
  - severe pertussis is “atypical” and underdiagnosed
  - clinical diagnosis is difficult
  - RSV co-infection does not exclude pertussis and can aggravate clinical course

Clinical manifestations: atypical disease

- in older children, adolescents, adults

  ➔ atypical, asymptomatic, unrecognised

WHO definition: paroxysmal cough of ≥ 21 days

Person-to-person transmission in household contacts

- 28 index patients (age 3 m – 17 y, median 3.7 m) → 68 household contacts investigated → 25 culture and/or PCR positive persons (19 asymptomatic !)
- Age of positive contacts: 16 adults (27 – 59 y, m 31y) and 9 children (4 m – 9.5 y, m 2.3 y)
- symptoms:
  - 19/25 asymptomatic
  - 2/25 atypical, mild upper airway infection
  - 4/25 typical whooping cough
- Coupled isolates obtained from 10 families: always same PFGE, *prn* & *ptxS1* types

De Schutter et al. CID, 2003; 36:1391-6.

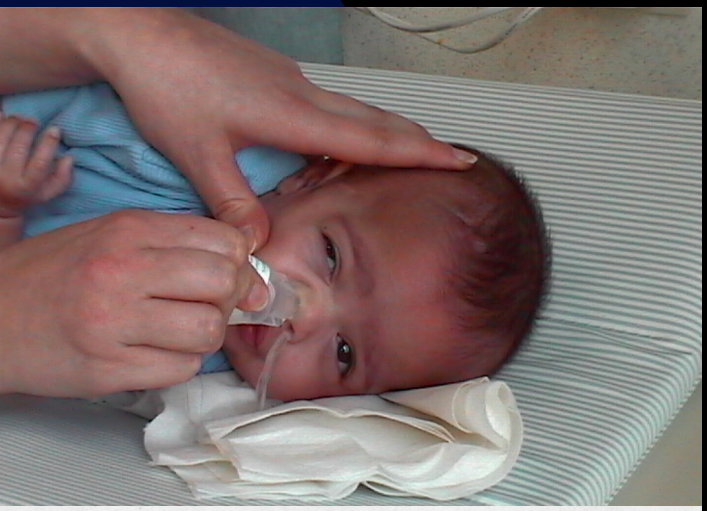
Clinical manifestations: summary

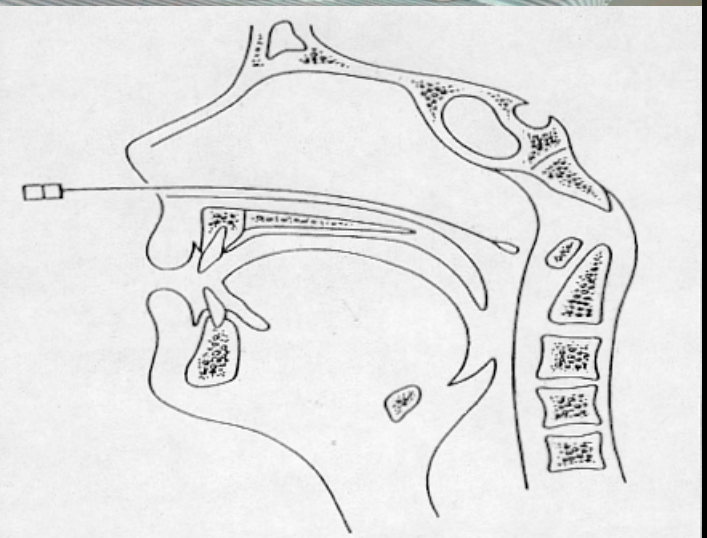
- Clinical manifestations depend on age, vaccination status, co-infection
- 3 categories must be considered:
  - 1. unvaccinated children between 6 months and 10 years with typical, classic symptoms of pertussis
  - 2. children> 10 years, adolescents, adults (vaccinated or not): atypical disease, even asymptomatic infection (but contagious)
  - 3. unvaccinated infants : life threatening events.
  - [elderly ??? no data, risk population ← excellent babysitters!]

Laboratory diagnosis of *Bordetella pertussis* infection

- Direct immunofluorescence: low sensitivity, variable specificity
- Culture: reference method, but low sensitivity ± 60 %
- Molecular detection: high sensitivity
- Serology: seroconversion considered as diagnostic, one-point very difficult to standardise

Collection, transport and storage of specimens

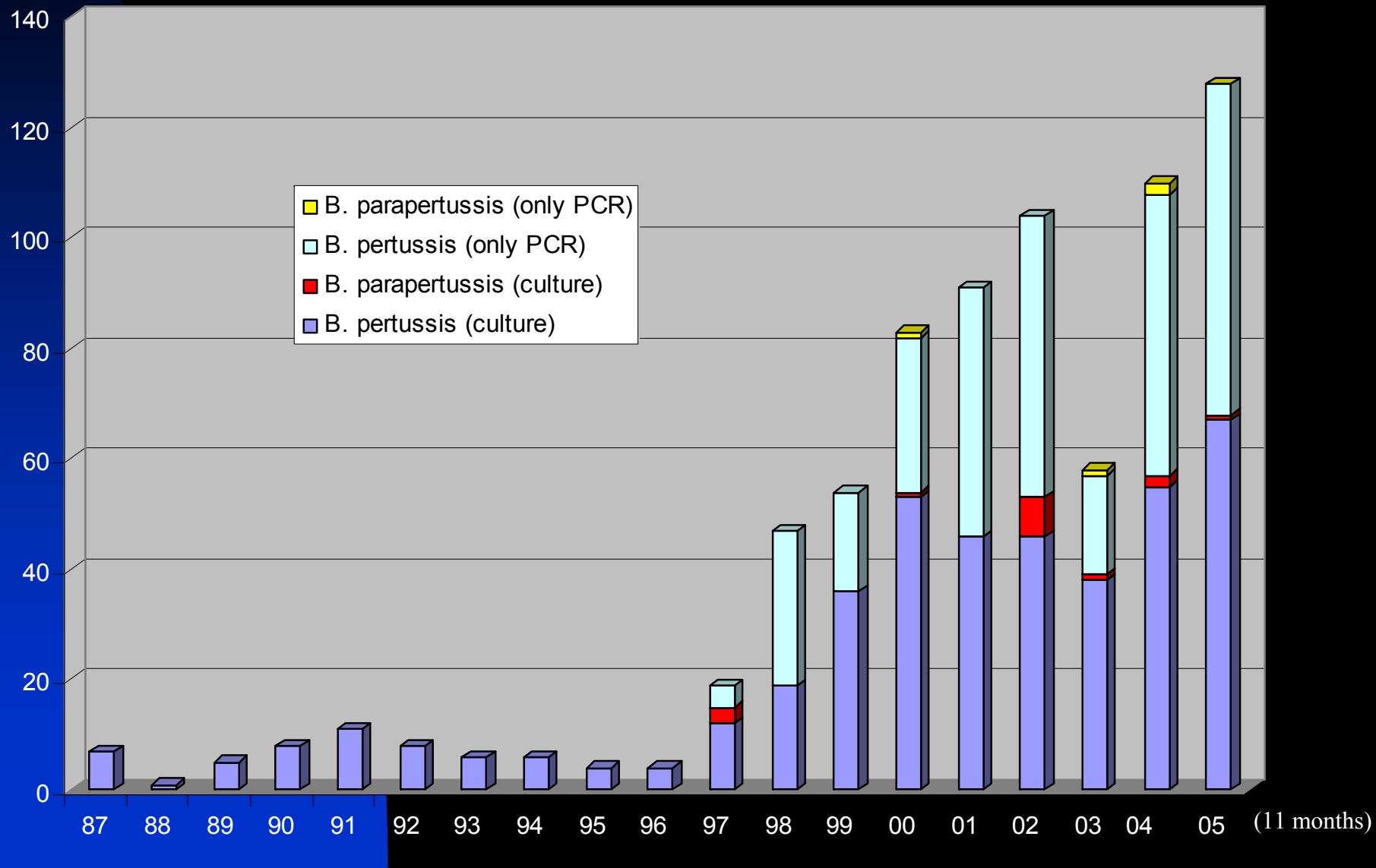




- Preferred specimens = nasofaryngeal aspirates (lavage) or posterior NP swabs (= pernasal swabs)
- Swabs: Dacron or rayon (no cotton for culture, no Ca alginate for PCR) on transport medium (Amies + charcoal or Stuart)
- Transport & storage: at 4°C if possible
- No « cough » plates !! (Mauritzen test)


bacteria
cilia
nonciliated cells

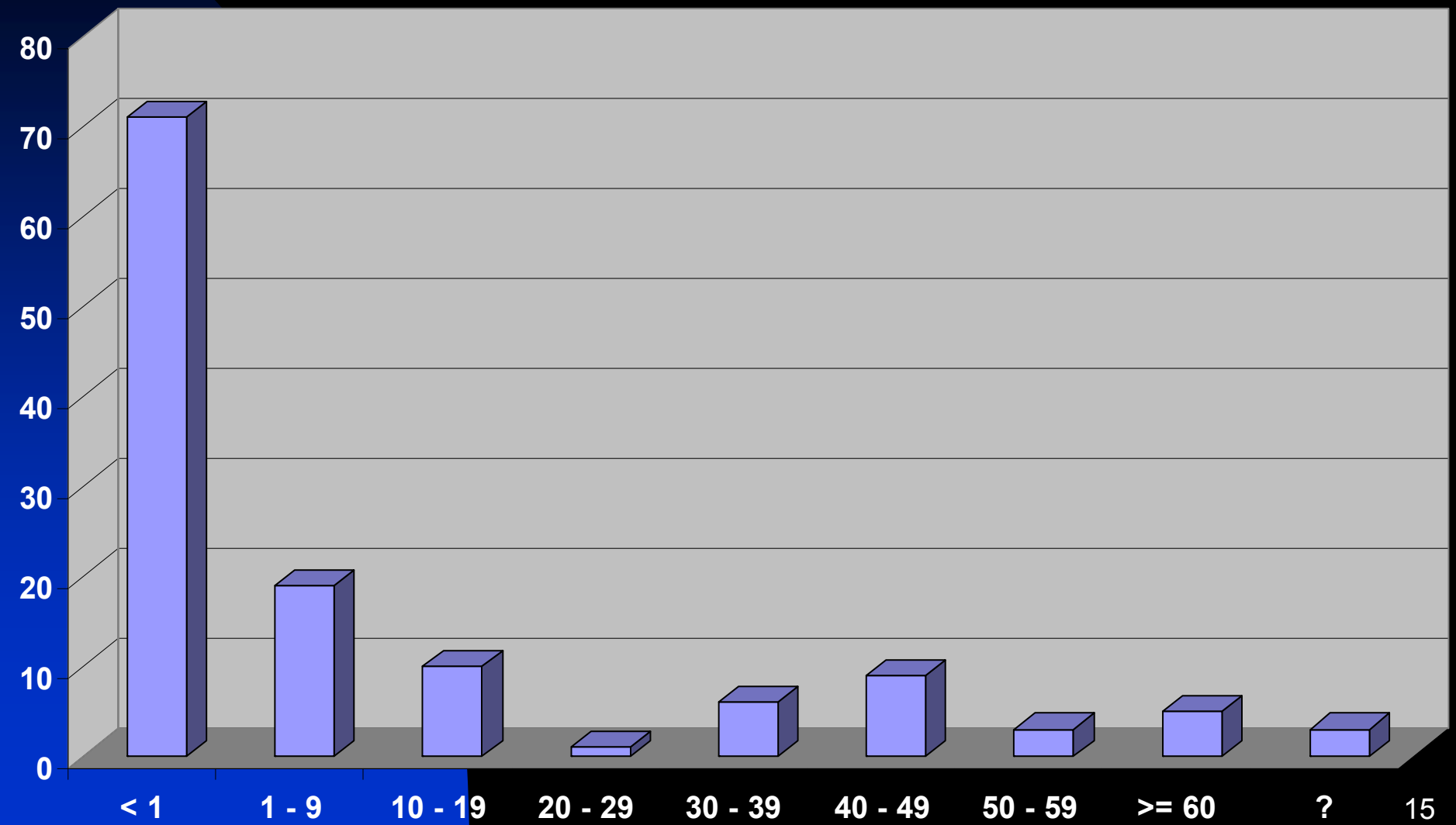
Evolution of reference lab-confirmed cases of pertussis 1987-2005



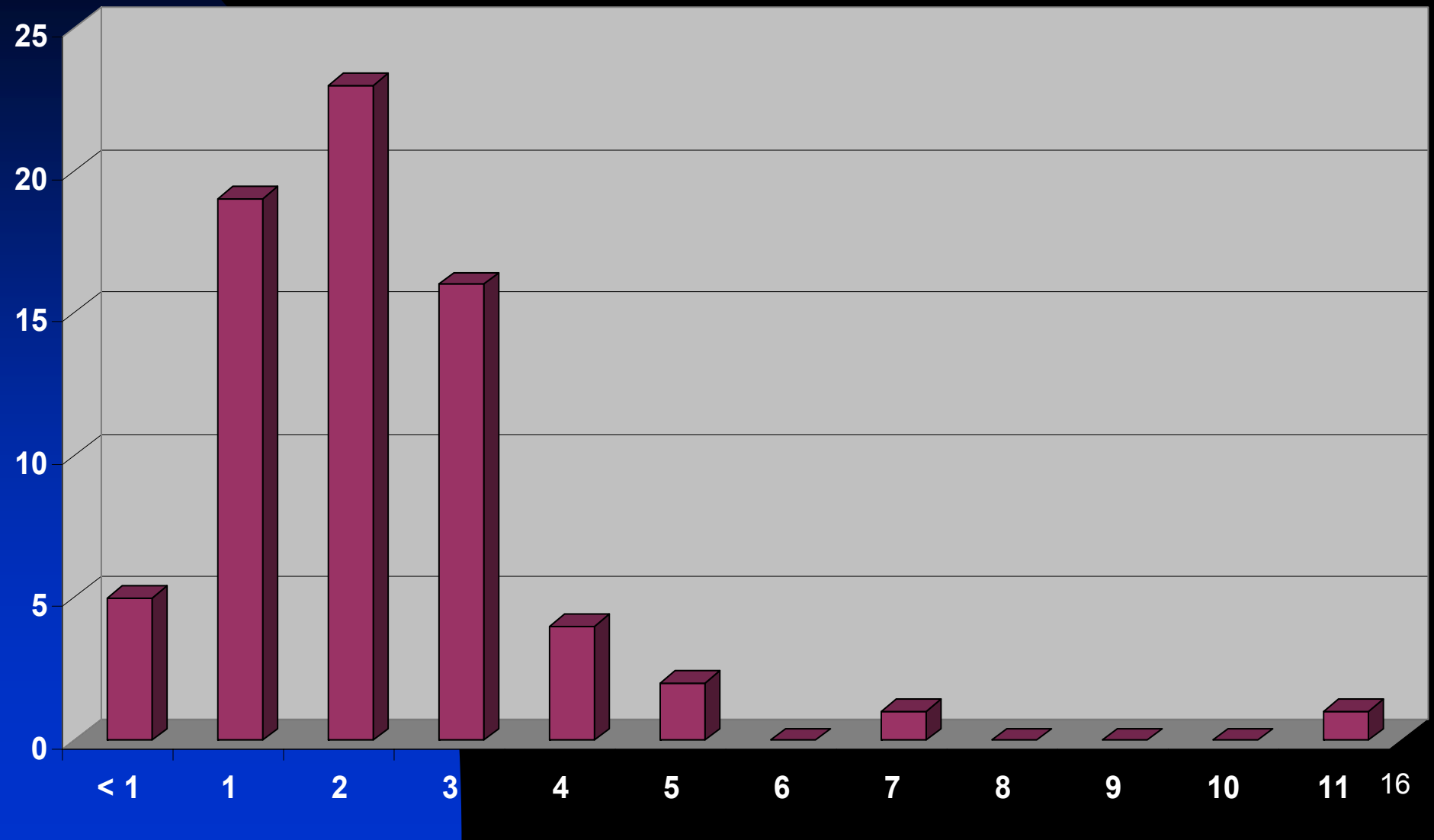
Reference laboratory for pertussis: data for 2005

- Culture and/or PCR: 126 *B. pertussis* &
  1 double infection *B. pertussis* + *B. parapertussis*
- Incidence = 1.3 cases/100 000 inhabitants
- Sex ratio: 48 M & 79 F
- Age distribution: 15 days – 77 years
  (median 4 months); 57% less than 1 year old
- Note: these data are only from the reference lab. Since 2005, the sentinel labs are asked to report *B. pertussis* infections and 159 cases were reported by the 44th week.
- See also yearly reports on IPH website:
  http://www.iph.fgov.be/epidemio/epien/index0000.htm

Age distribution of the 127 confirmed cases (2005)



Age distribution in months of cases less than 1 year old (2005)



Basisvaccinatieschema aanbevolen door de Hoge Gezondheidsraad (2005-2006)

LEEFTIJD[1] / VACCINS	2 MAAND	3 MAAND	4 MAAND	12 MAAND	13 MAAND	15 MAAND	18 MAAND	5-7 JAAR	10– 13 JAAR	14 – 16 JAAR
Poliomyelitis[2]	IPV	IPV	IPV		●	IPV	●	IPV		
Difterie- Tetanus- Kinkhoest[3]	DTPa	DTPa	DTPa		●	DTPa	●	DTPa		dT dTpa
Haemophilus influenzae type b[4]	Hib	Hib	Hib		●	Hib	●			
Hepatitis B[5]	HBV	HBV	HBV		●	HBV	●		HBV	
Mazelen Bof Rubella[6]				MBR_1	●			MBR_3	MBR_2	MBR_2
Meningokok C[7]				MenC	●					
Pneumokok[8]	Pn7V	Pn7V	Pn7V		●	Pn7V	●			

● Richtperiode waarbinnen gevaccineerd kan worden

Gecombineerd vaccin

Vaccinatietoestand nagaan en zo nodig aanvullen

EUVAC-NET data

Celentano et al. Resurgence of pertussis in Europe, Pediatr Infect Dis J 2005, 24:761-765

- Surveillance of measles and pertussis in 16 European countries: data for 1998-2002
- Based on (heterogeneous) country specific definition and surveillance methods
- Results:
  - Highest incidence in children < 1 year old
  - Increase in > 14 yrs age group of 115%
  - Highest incidence in Northern countries
  - 70% hospitalisation in children < 1 year
  - 32 deaths reported, 87% in children < 6 months of age

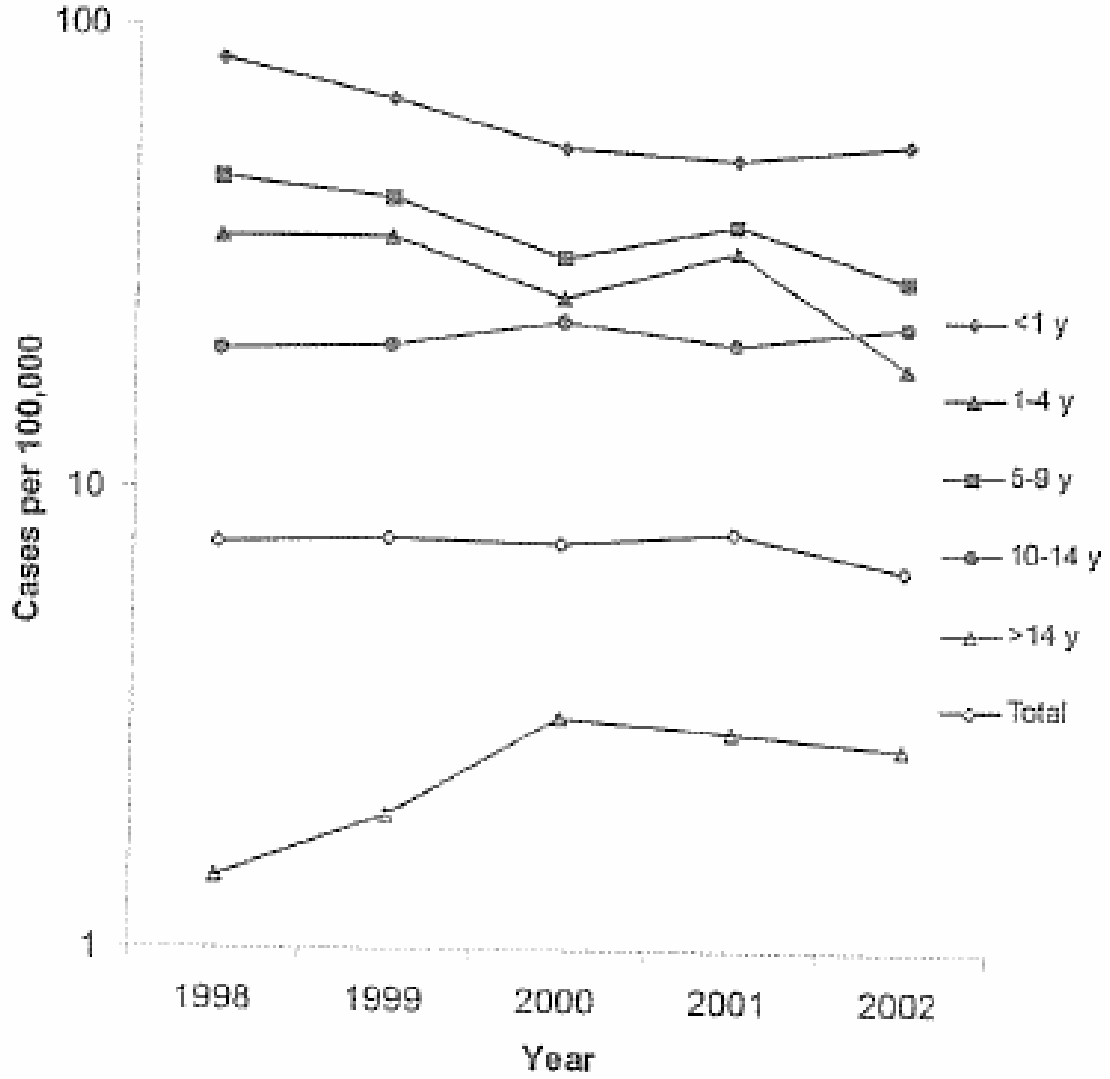
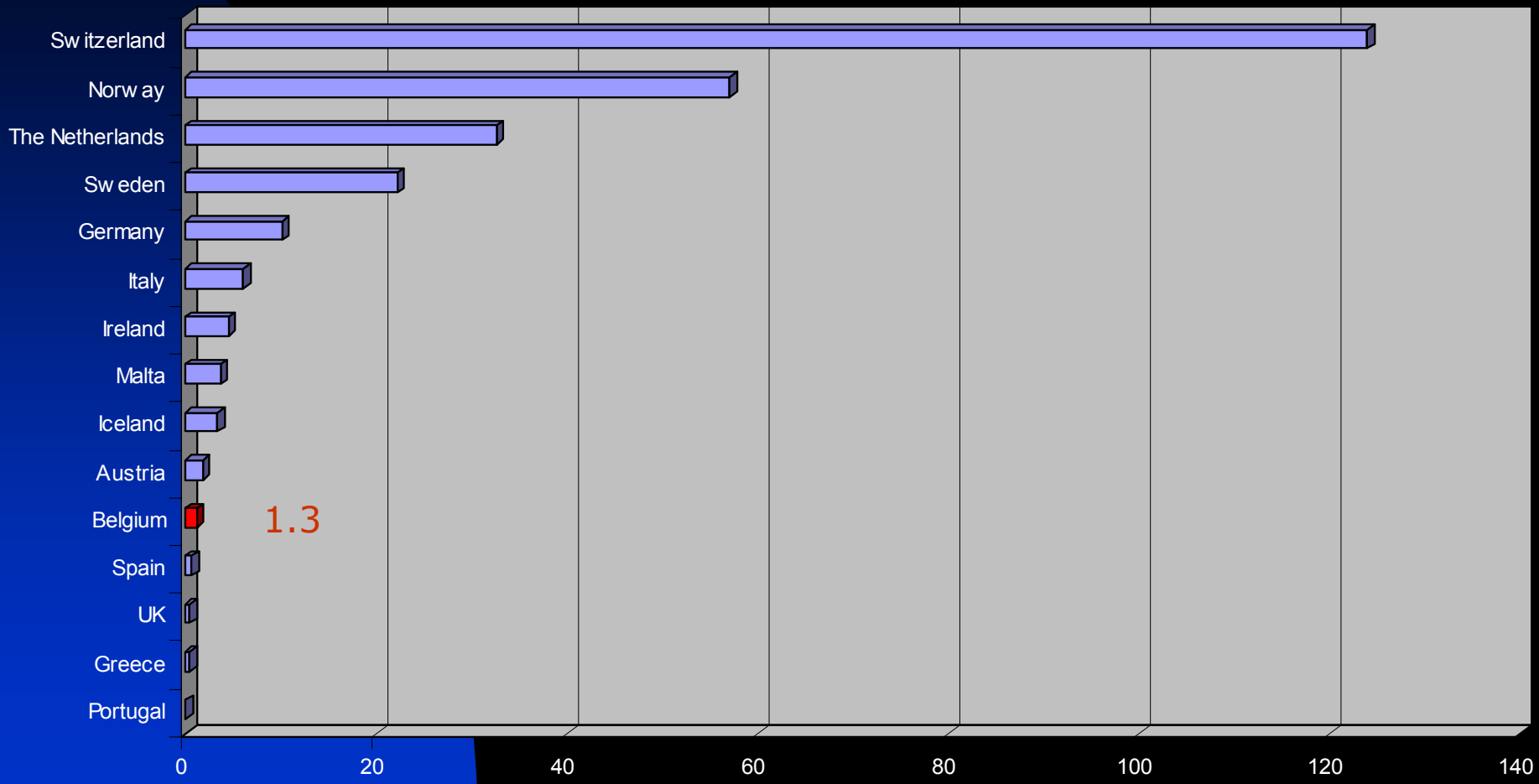


FIGURE 1. Number of pertussis cases per 100,000 population by age-group and year. Incidences are plotted on a logarithmic scale. The graph includes data from Germany, Greece, Iceland, Italy, Malta, Norway, Portugal, the Netherlands and England, Wales and Northern Ireland.

Incidence/10^5 inhabitants: total

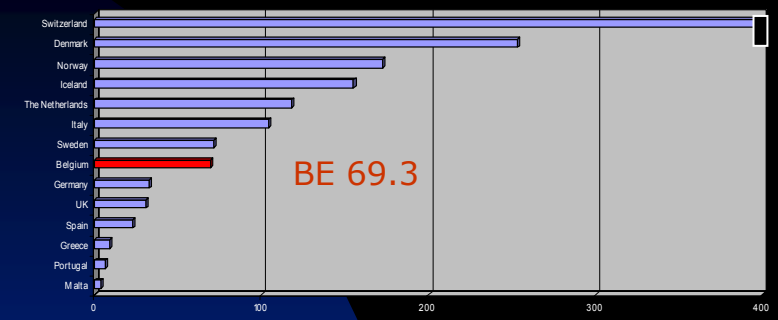
Comparison of EUVAC data 98-02 and reference lab 2005



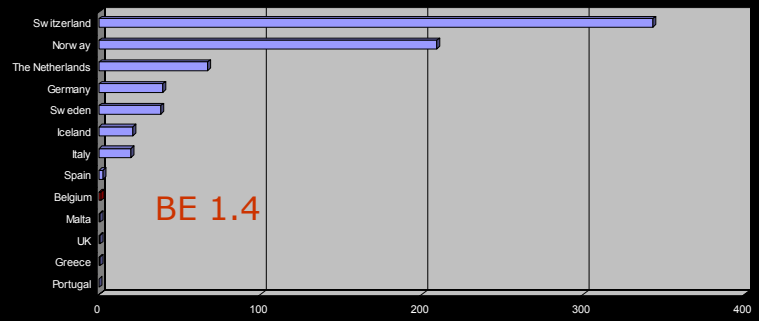
Incidence/10^5 inhabitants by age

Comparison of EUVAC data 98-02 and reference lab 2005

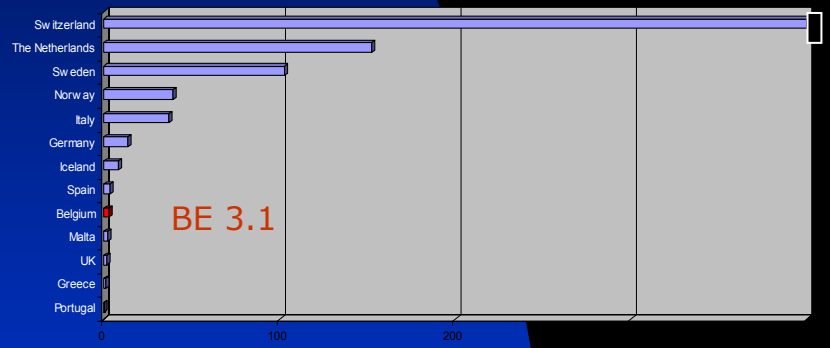
< 1 yr



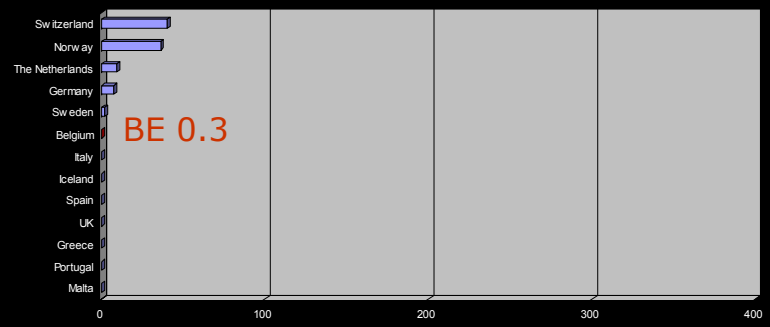
10 - 14 yr



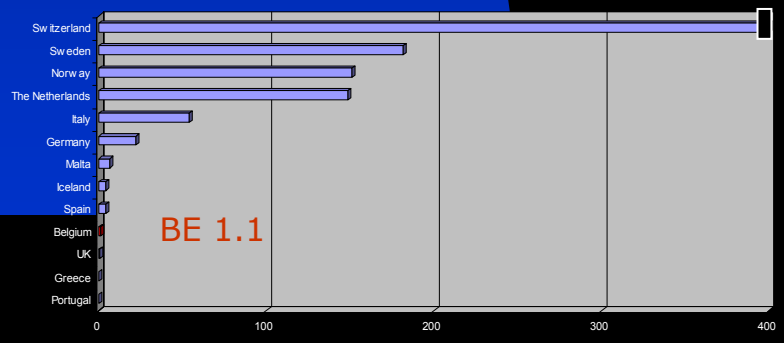
1 - 4 yr



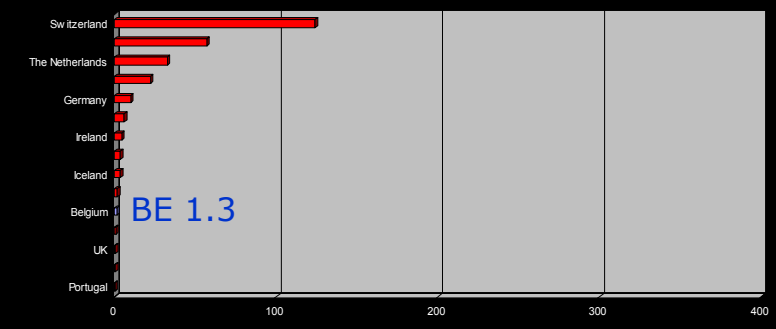
> 14 yr



5 - 9 yr



Total

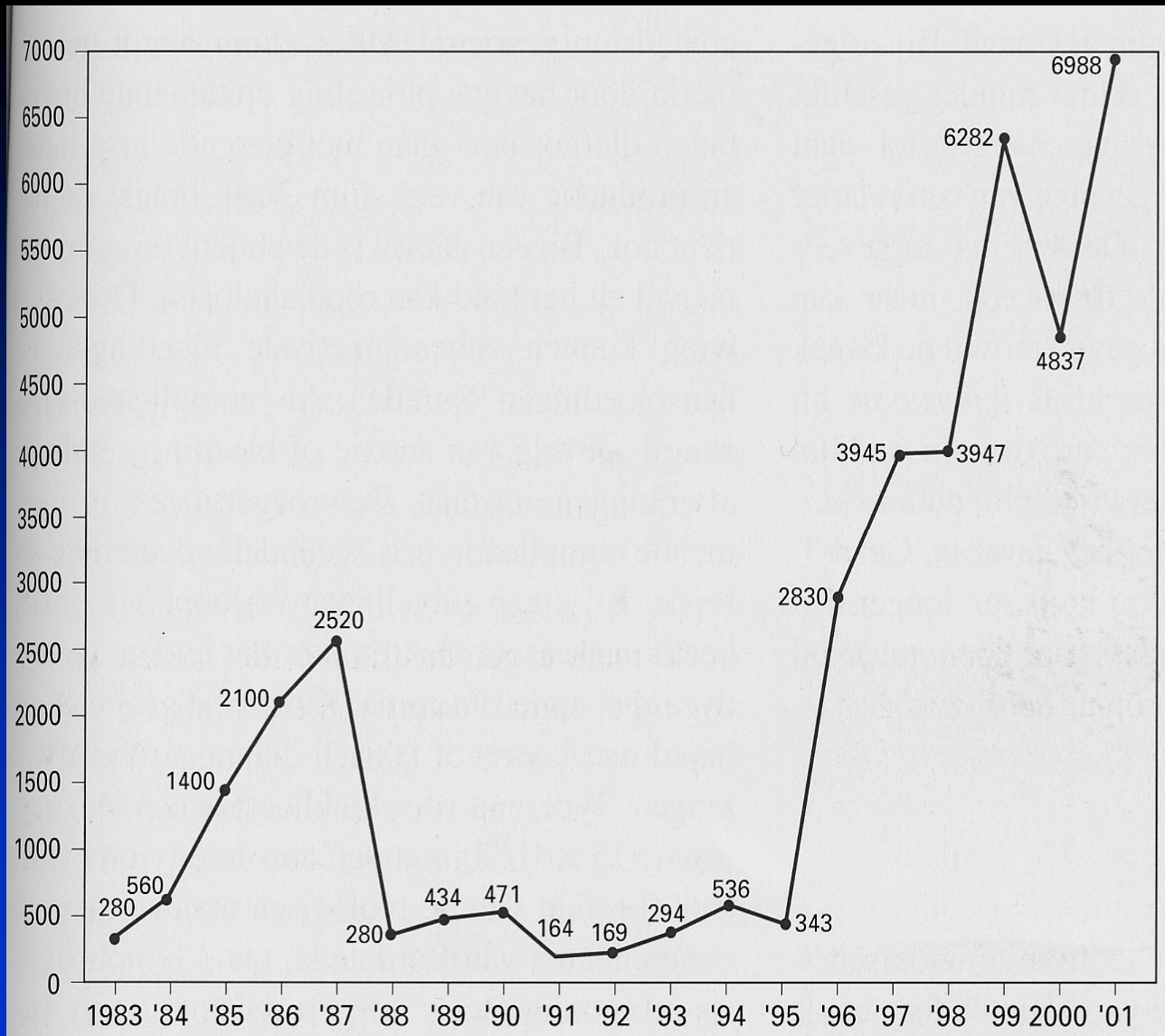


Changing epidemiology of pertussis

- Dramatic decline in incidence, morbidity and mortality after introduction of whole-cell vaccines in many countries in the 1940s and 1950s.
- Introduction of less reactogenic acellular vaccines (composed of up to 5 purified proteins) in Japan in the 1970s, in Europe and the USA in the 1990s and 2000s
- Age distribution of pertussis disease has been influenced by the implementation of general immunization:
  - unvaccinated populations: preschool children (3-6 years), with outbreaks occurring every 3 to 5 years
  - widespread vaccination →
    - redistribution of age-groups
    - change in clinical manifestations to a “less typical” clinical picture

Changing epidemiology (cont'd)

- However, pertussis remains endemic and re-emergence has been observed in several countries with high vaccination coverage:
  - Canada & The Netherlands: epidemics in children normally protected by vaccination (1-4 yrs old) → weak vaccine
  - France & UK: no major epidemics , but resurgence mostly in older age groups and unvaccinated children → waning vaccine-induced immunity & increased circulation of *B. pertussis* in these age groups in the absence of circulation in well vaccinated children → replacement of child-to-child transmission by parent-to-child transmission, with increased mortality rates in the very young (<4 months of age)



Figuur 3.5 *Aangiften wegens kinkhoest (duidelijk is het cyclische beloop te zien). (Bron: Inspectie voor Gezondheidszorg.)*

Changing epidemiology (cont'd)

- increasing incidence in adolescents and adults (and in infants) in our vaccinated populations
  - Strabel. JID 2001; 183: 1353
  - Jackson. CID 2000; 31: 3
  - Yih. JID 2000; 182: 1409
  - Rangananthan. Arch Dis Child 1999; 80: 297
- fatality is higher in young infants
  - Crowcroft. Arch Dis Child 2003;88: 802-806
  - Heininger. Pediatrics 2004; 114: 9-15
- some data on complications in elderly

Virulence factors

- Toxins: pertussis toxin, adenylate cyclase toxin, tracheal cytotoxin
- Adherence factors to ciliated epithelial cells: pertussis toxin, fimbriae, filamentous hemagglutinin, pertactin
- Others: dermatonecrosis toxin, lipopolysaccharide(endotoxin), tracheal colonisation factor

→ 2 to 5 factors included in « acellular vaccine »

Typing of virulence genes: 362 isolates from 1987 to 2004

- Four genes were typed:
  - *ptxS1* by real-time PCR + sequencing if not *ptxS1A*
  - *ptxS3* by real-time PCR
  - *tcfA* by sequencing
  - *prn* by real-time PCR + sequencing some varaiants

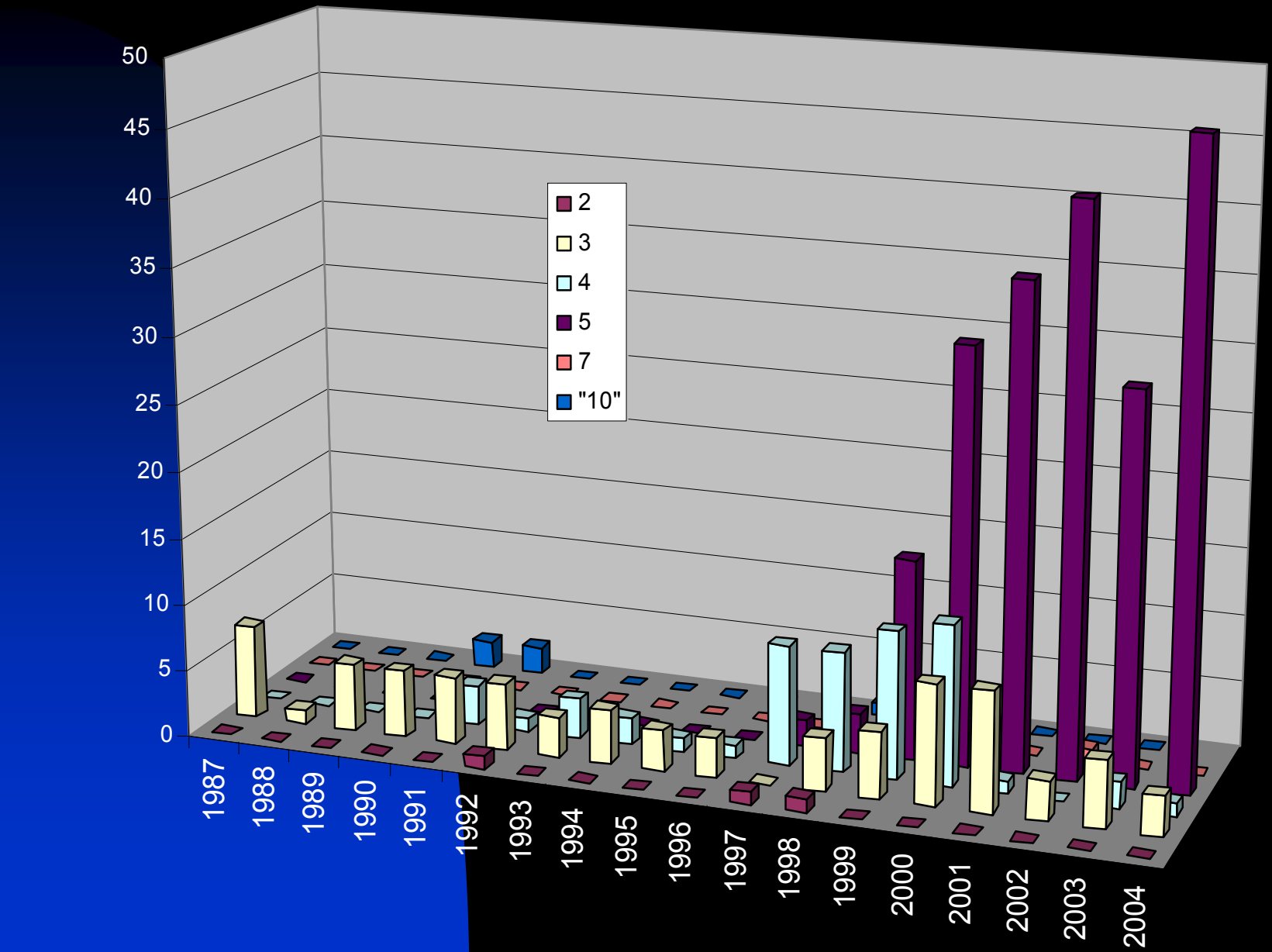
Adapted from Van Loo et al., JCM 2002, 40:1994-2001

See also Muyldermans et al., JCM 2004, 42:1614-19

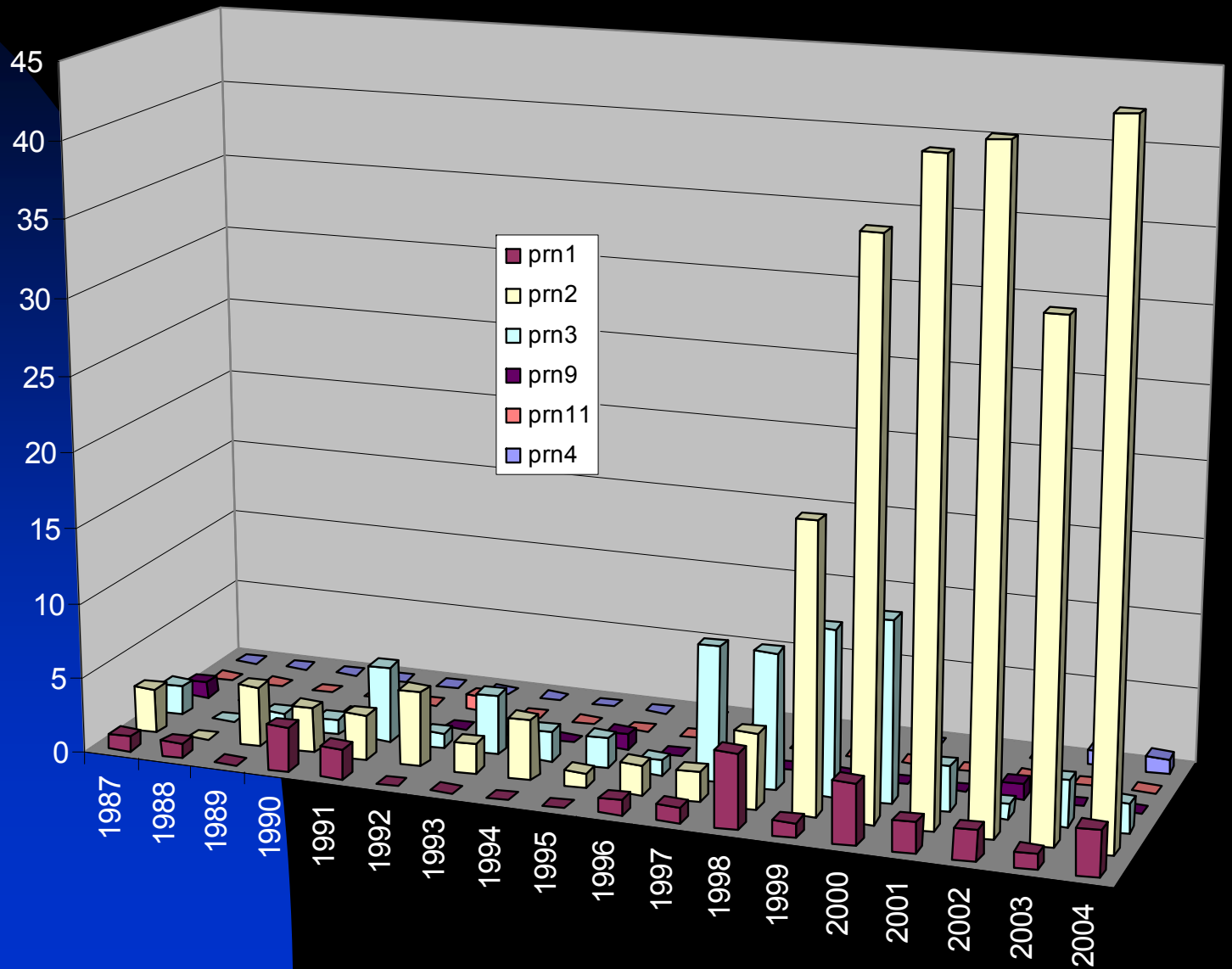
Typing of virulence genes: results

ptxS1	99% A 1% B	No evolution
ptxS3	59% B 41% A	*ptxS3B* ↑
tcfA	81% 2 16% 3	*tcfA3* appeared from 97 and disappeared after 2000 4 isolates without *tcfA* genes
MLST	59% 5 23% 3 16% 4	Type 3 predominant < 97 Type 4 important in years 98-2000 Type 5 predominant after 2000
prn	70% 2 19% 3 8% 1	Predominance of *prn2* since 1999

Evolution of MLST types from 97 to 04



Evolution of *prn* types from 97 to 04



Concluding remarks

- There is an increase in the number of reported cases in our country.
- However, it is not clear if this is a real pertussis increase or an effect of the new diagnostic tools, resulting in better sensitivity but also in increased awareness of clinicians.
- In Europe, a shift to older age groups and potential transmission to children too young to be protected by vaccination is observed.
- The predominance in Belgium of cases in very young children suggests B. pertussis circulates in older age groups without being diagnosed.

Concluding remarks (2)

- Polymorphism of B. pertussis was observed over time, but no direct link to vaccination programs has been noted to date. Epidemics observed in countries like The Netherlands can probably be explained by decreased vaccine efficacy.
- An adult formulation of dTap vaccine is available and the HGR/CSH recommends it in:
  - Adolescents and adults without complete history of vaccination
  - Adolescents and adults in general, especially if they are in contact with infants: young parents and close family contacts, personnel of pediatric units and child care centers.

Unsolved problems

- Lack of epidemiological data in adults and elderly with prolonged illness with cough due to insufficient diagnostic efforts
- Safety and immunogenicity of dTap in elderly and pregnant women
- dTap not recommended in persons who received T or dT < 5 yrs ago
- What might be the impact of adolescent and adult vaccination on epidemiology in infants too young to have completed vaccination ?

Thank you for your attention J. Bordet by P. Delvaux