Current situation of pertussis in 2006

Nicole Guiso
Institut Pasteur, Paris, France

Vaccines

Today, millions of lifes are saved because of vaccination against tetanos, diphteria, whooping cough, polio, haemophilus, hepatitis, measles, mumps, rubella, tuberculosis… vaccines

However, only small pox is eradicted, poliomyelitis and measles are on the way of eradication, diphteria can be controled but other vaccine preventable diseases are neither eradicated nor controled

Exemple: Pertussis

Pertussis

- Strictly respiratory human disease
- Disease that is not strictly restricted to children. It is dramatic for a newborn or an infant but can also be very severe for an adult or an elderly
- The causal agent is a bacterium: *Bordetella pertussis*

Why speaking about pertussis?

Because

→ pertussis is still not controled in countries where an efficacious pertussis vaccine is used since several decades

→ new pertussis vaccines are on the market

What are the pertussis vaccines available?

1. Whole cell pertussis vaccines or wP

2. Subunit or acellular pertussis vaccines or aP

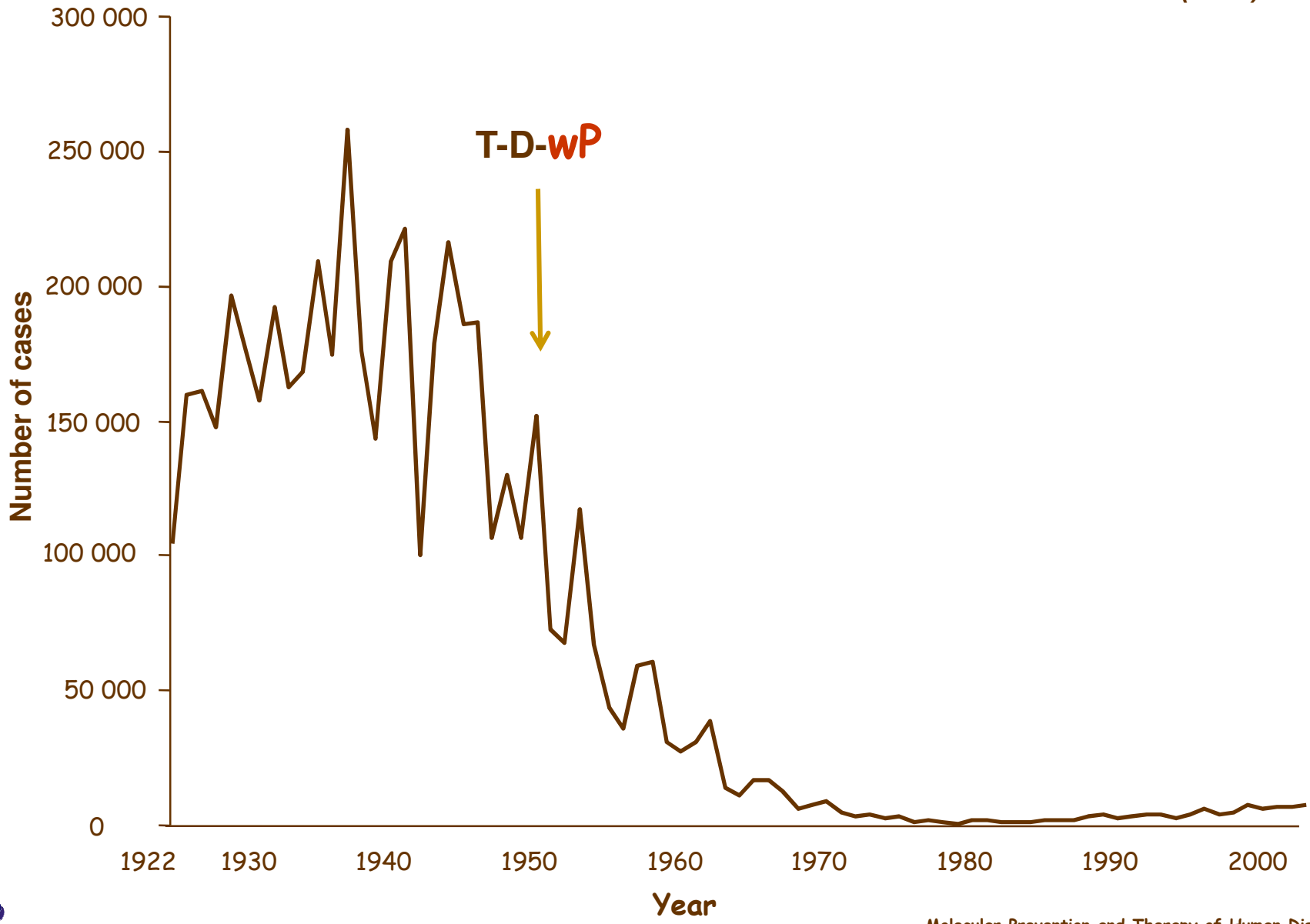
Whole cell pertussis vaccines

1. which are composed of bacterial suspensions inactivated by heat, are

efficacious

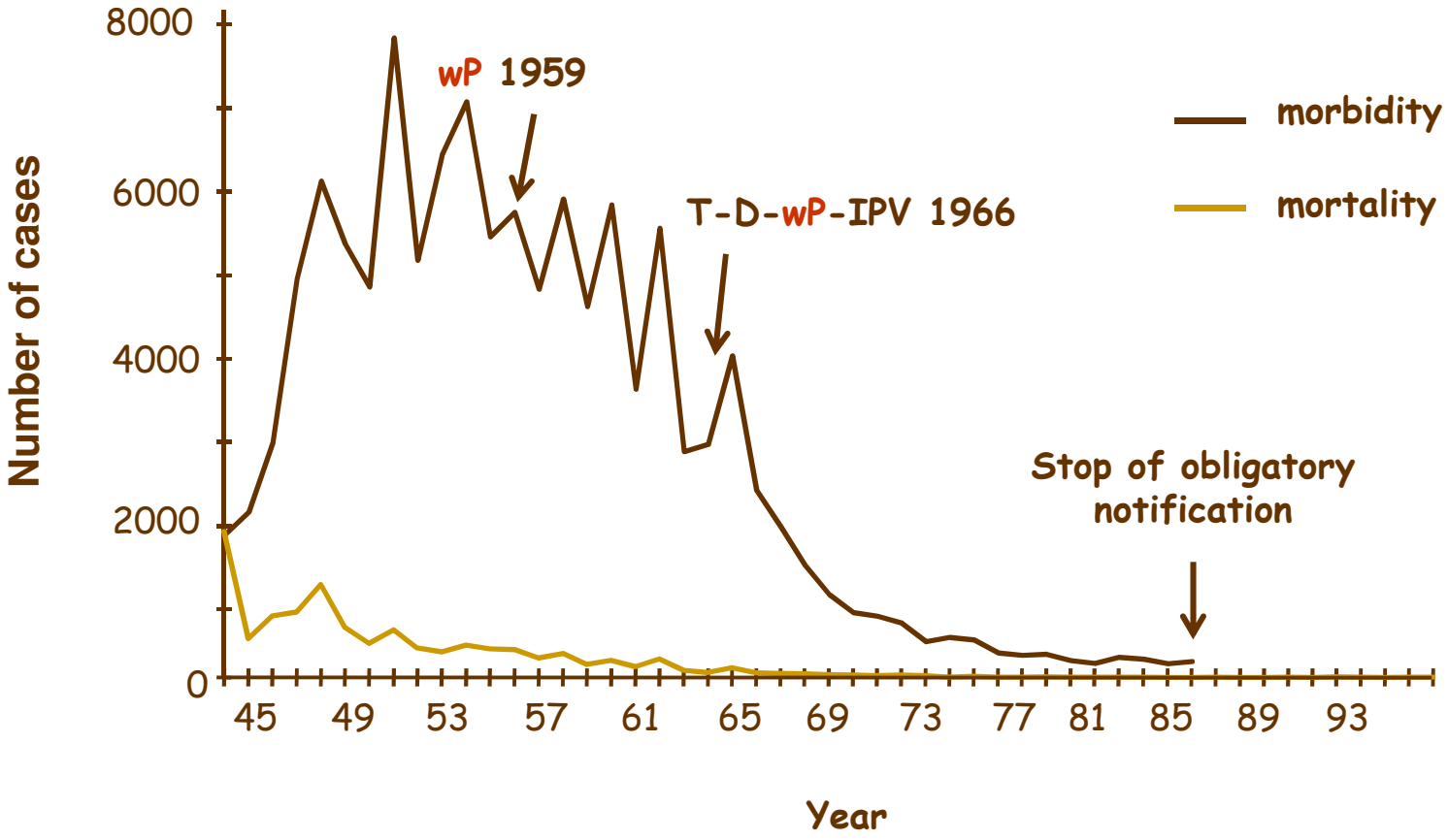
Whole cell pertussis Vaccines in the US

(CDC)



Whole cell pertussis vaccines in France

- Primo-vaccination : 2-3-4 months
- Booster : 16-18 months

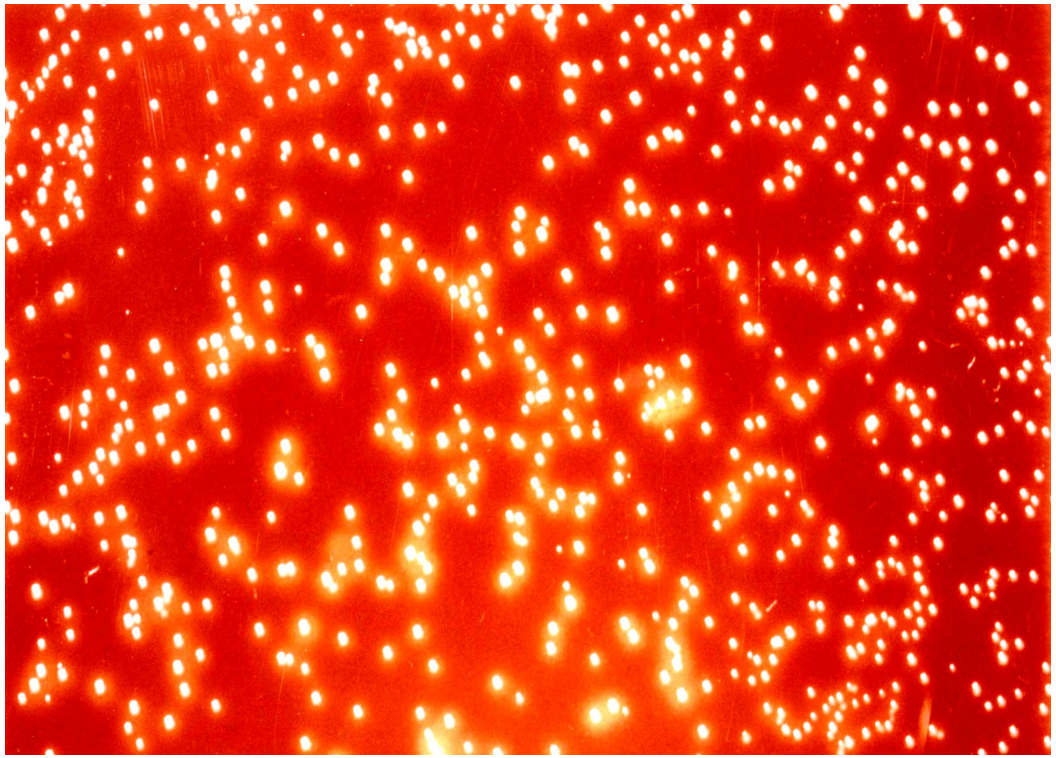


Whole cell pertussis vaccines

1. which are composed of bacterial supensions inactivated by heat, are

- efficacious
- difficult to produce in a reproducible manner

Bordetella pertussis



is a bacterium identified in 1900 by Jules Bordet and Octave Gengou but isolated only in 1906 because of the development of a medium containing potatoes extract and rabbit blood.

Jules Bordet
1870-1961

Whole cell pertussis vaccines

1. which are composed of bacterial supensions inactivated by heat, are

- efficacious
- difficult to produce in a reproducible manner
- reactogenic

Reactogenicity of whole cell pertussis vaccines

• Redness	16.4%
• Swelling	22.4%
• Moderate pain	25.9%
• Important pain	14.3%
• Fever <38.4°C	44.5%
• Fever 38.5°C à 38.9°C	12.4%
• Fever >39°C	3.5%

Sudden death ? No

Irreversible encephalopathy ? No

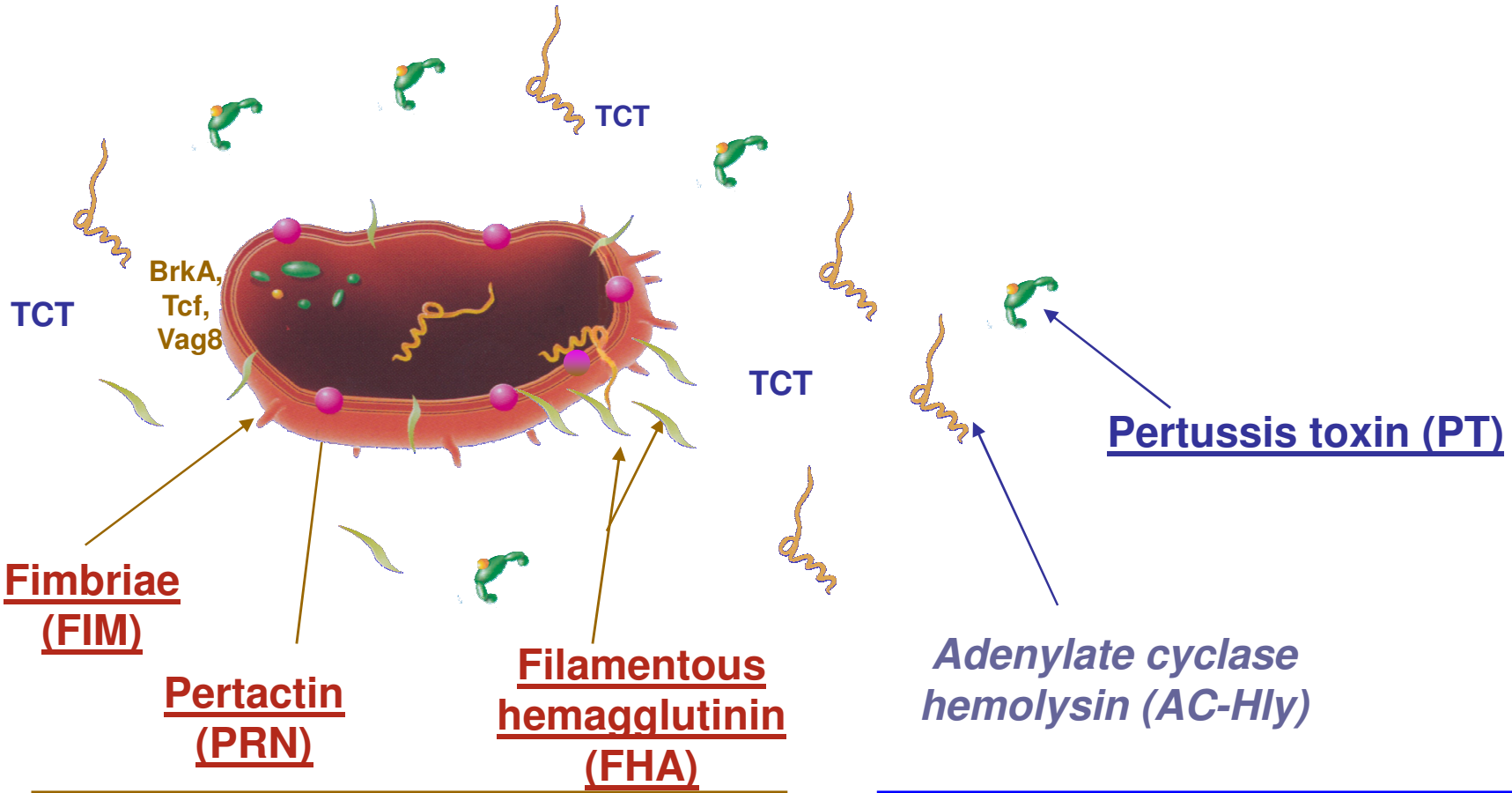
Edwards and Decker. Pertussis Vaccine, 2004

Acellular pertussis vaccines

2. which are composed of purified inactivated bacterial proteins are

easier to produce in a reproducible manner

Bordetella pertussis virulence determinants



Adhesins: adhesion => multiplication and colonisation of respiratory tract

Toxins: local and systemic cytopathogenic effects

Acellular pertussis vaccines

All aP vaccines contain detoxified PT with

one adhesin (FHA): aP-2

or two adhesins (FHA+PRN): aP-3

or four adhesins (FHA+PRN+FIM2+FIM3): aP-5

Acellular pertussis vaccines

2. which are composed of purified inactivated bacterial proteins are

→ easier to produce in a reproducible manner

→ better tolerated by infants

Reactogenicity of whole cell and acellular pertussis vaccines

	wP (n= 371) en %	aP (n=1818) en %
Redness	16.4	3.3
Swelling	22.4	4.2
Moderated pain	25.9	6.5
Important pain	14.3	0.4
Fever<38.4°C	44.5	20.8
Fever 38.5°C à 38.9°C	12.4	2.5
Fever > 39°C	3.5	0.9

Edwards and Decker. Pertussis Vaccine, 2004

Acellular pertussis vaccines

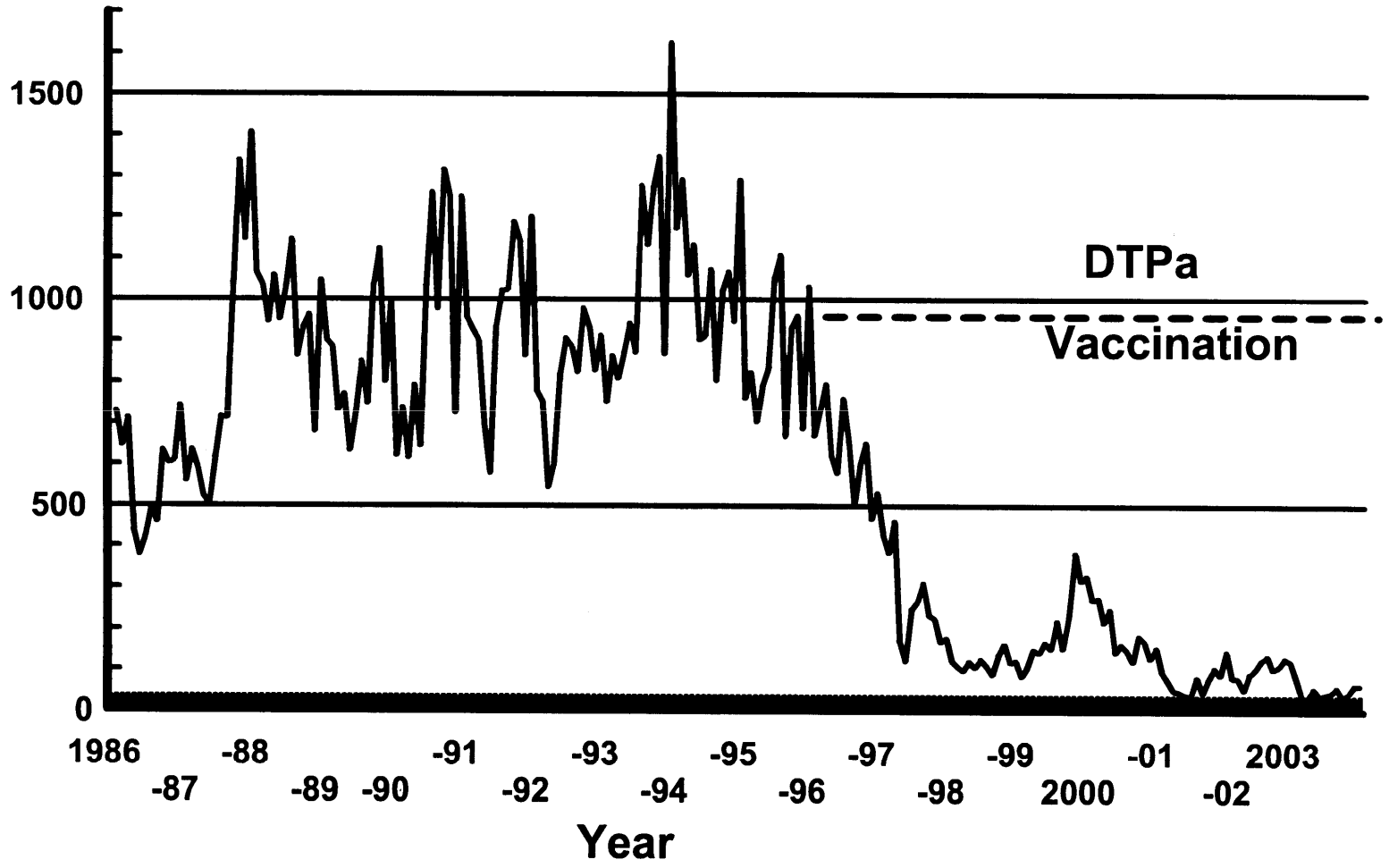
2. which are composed of purified inactivated bacterial proteins are

- ➡ easier to produce in a reproducible manner
- ➡ better tolerated by infants
- ➡ efficacious

Acellular pertussis vaccines

- were shown to be efficacious during clinical trials (1990-1995)
- are shown to be efficacious after their generalized use

Acellular pertussis vaccines in Sweden



Is pertussis controled in vaccinated populations?

→ wP vaccination induced a 95% decrease of mortality and mobidity!!

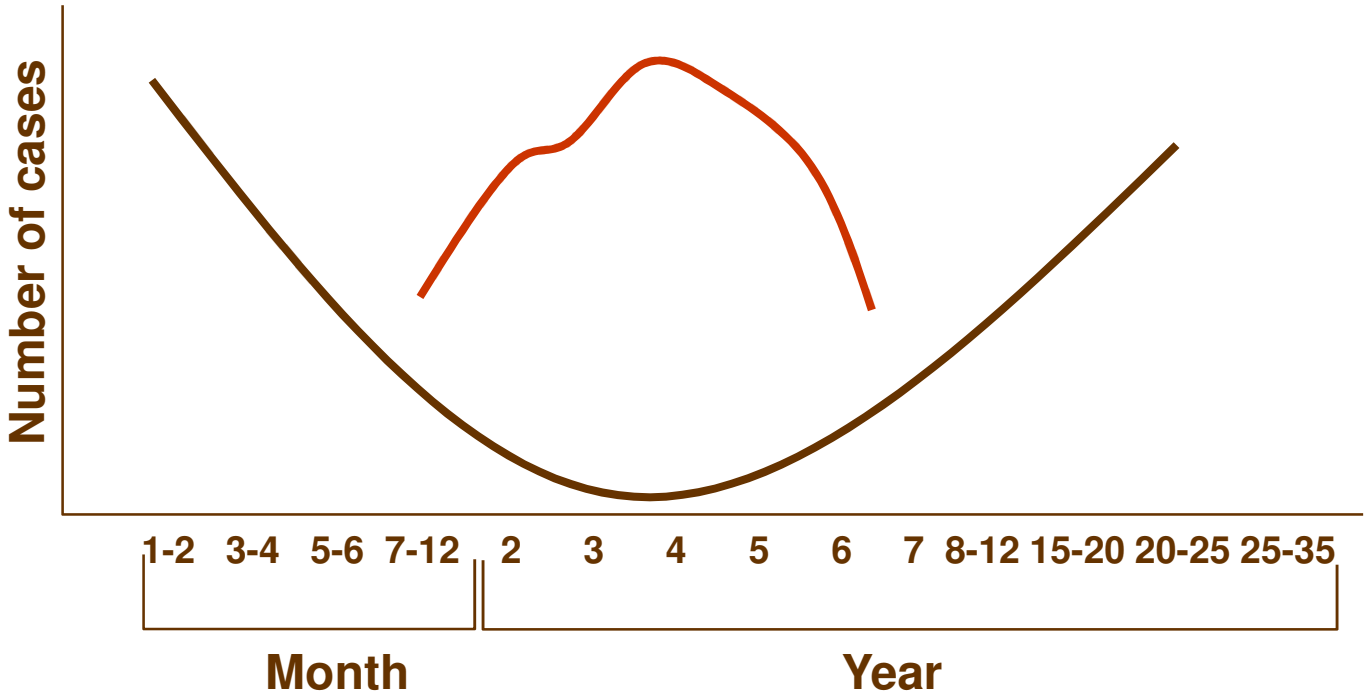
but

→ detection of adolescents and adults cases is more and more frequent indicating a change in the transmission of the disease as compared to pre-vaccinal era

Pertussis in a vaccinated country vs a non vaccinated country

Low vaccine coverage

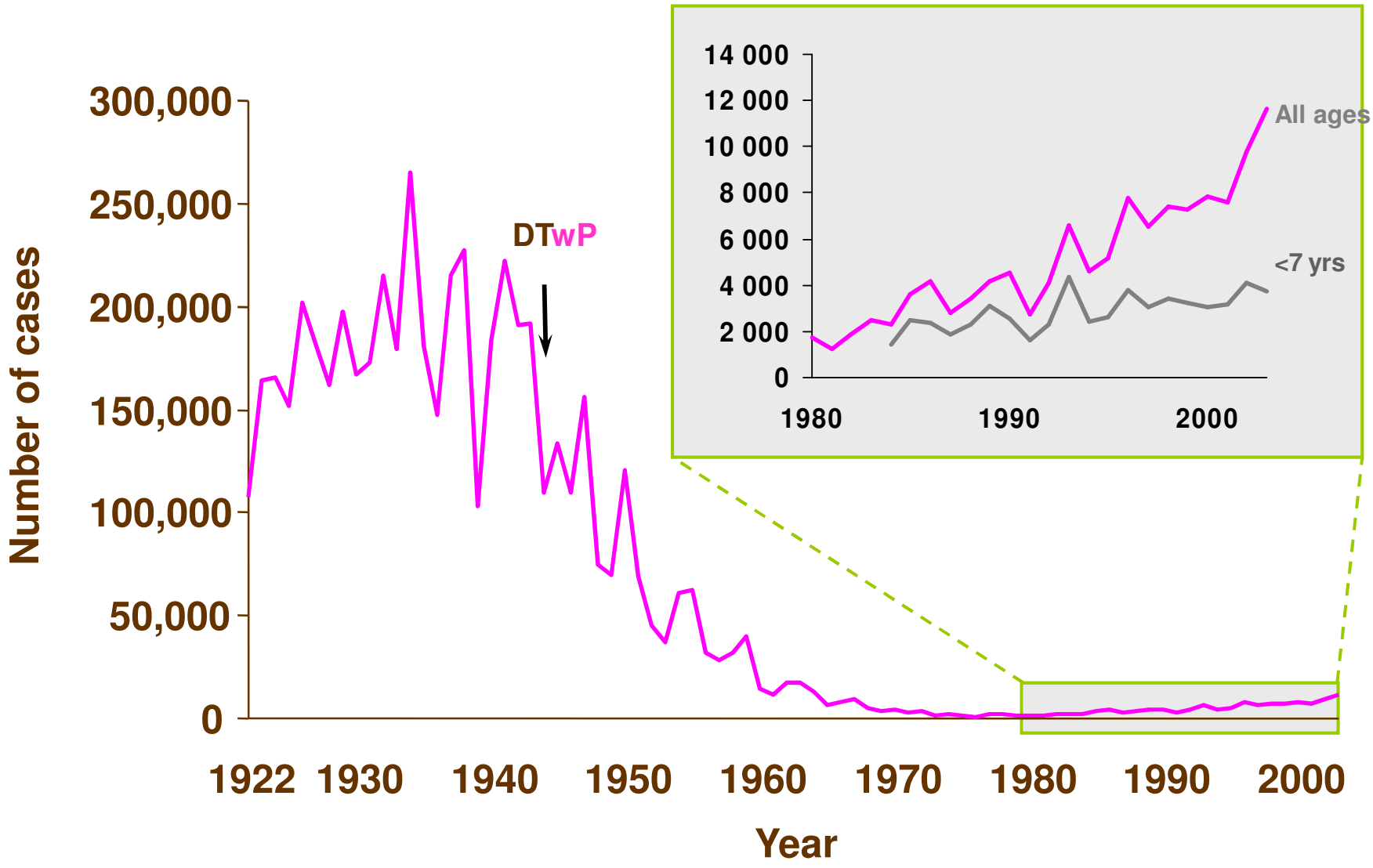
*High morbidity and mortality in infants
*Regular asymptomatic contacts throughout life
*Unknown epidemiology in adults



High vaccine coverage

*Low morbidity and mortality in infants
*Few asymptomatic contacts throughout life
*Increase in susceptible adolescents and adults

Reported Pertussis Cases U.S., 1922-2003



Proportion of pertussis in different vaccinated populations

- Mink *et al.*, 1994 (US):
  - > 18 years 25%
- Senzillet *et al.*, 2001 (Canada):
  - 12-19 years 33%
  - 20-29 years 19%
  - 40-59 years 19%
  - > 60 years 16%
- Gilberg *et al.*, 2002 (France):
  - > 18 years 32%

Increased reporting of the disease in vaccinated populations

Why?

- increased recognition of the disease in adolescents and adults?
- waning of vaccine induced immunity?
- decrease of vaccine effectiveness due to an antigenic shift of the *B. pertussis* population?

Increased recognition of the disease

Population	Reported incidence	Estimated incidence	Ref
USA, adolescents	4	71	Yih *et al.*, 2000
USA, adults	0.8	507	Strebel *et al.*, 2001
UK, adults	4	330	Miller *et al.*, 2000
France, adults	Nd	508	Gilberg *et al.*, 2002

Needs of biological diagnosis:
Culture, PCR, Serology

Waning of immunity

- Neither vaccine-acquired nor naturally acquired immunity is life-long
- Exact duration of naturally acquired immunity is undetermined and varies depending of the herd immunity and the level of circulation of the bacteria. In highly vaccinated populations it is around 10-15 years
- Protective immunity provided by whole-cell vaccine appears to persist for at least 6–8 years after vaccination (four doses)

Herd immunity should be improved by addition of booster vaccination

Did forty years of intensive vaccination with wP vaccine induce an evolution of the bacterial population?

The answer to this question necessitates :

- analysis and comparison of clinical isolates collected before and after introduction of vaccination in the region of interest
- analysis of the epidemiology of the disease in the same region

How to analyse Bordetella pertussis polymorphism?

Using typing techniques analysing **proteins** such as:

Multi-Locus Enzyme Electrophoresis (MLEE)

Using typing techniques analysing **portions of the genome** such as:

Restriction Fragment Length Polymorphism (RFLP)
Multi-Locus Sequence Typing (MLST)
Multiple Antigen Sequence Typing (MAST)
Multiple-Locus-Variable-number tandem repeat Analysis (MLVA)

Using typing techniques analysing the **whole genome** such as:

Pulsed-Field Gel Electrophoresis of Genomic DNA (PFGE)
Microarrays

Polymorphism of Bordetella pertussis

- is very limited
- isolates circulating in the world are very similar whatever the vaccine calendar

However, isolates circulating before vaccination and vaccine strains can be differentiated from isolates circulating now, by some typing techniques

Van Amersfoorth *et al.* J. Clin. Microbiol. 2005
Caro *et al.* J. Clin. Microbiol. 2005

Polymorphism of Bordetella pertussis

- Temporal analysis of *B. pertussis* evolution suggests that there is a temporal decrease in genetic diversity with clonal expansion. This decrease is accompanied by gene loss rather than gene acquisition
- However, *B. pertussis* has the capacity to generate variation by rearranging its chromosome and altering gene expression rather than modifying proteins

Brinig *et al.* J. Bact 2006
Cumming *et al.* J. Bact. 2006
Caro et *al.* submitted

Polymorphism of Bordetella pertussis

- Despite differences there is no evidence that there is a threat. First data concerning duration of immunity of aP vaccines indicate that it is similar to efficacious wP vaccines in countries where a temporal change of the isolates was observed

However, surveillance must continue

Pertussis in France

- 1990-1993: Development of biological diagnosis (Culture, PCR and serology) and a study performed in one pediatric hospital
- 1993-1994: National hospital based study (22 pediatric hospitals,epidemiologists of the Ministery of Health and Institut Pasteur)
  - ➢ Increase of the number of infants hospitalized due to pertussis, contaminated by an adult or an adolescent in the household

Biologicals 1993, 21:5-7, PIDJ 1998, 17:442-418

1998: France is the first country to introduce a booster at 11-13 years of age with aP vaccines (2 or 3 components)

Pertussis in France

- **1999-2000:** Study in the Paris area (125 general practitioners and Institut Pasteur) to evaluate the proportion of pertussis in adults older than 18 years of age and coughing more than 7 days and less than 30 days

  - Estimated incidence in adults: **507/100,000**

J. Infect. Dis. 2002, 186:415-418

- **2002:** Nosocomial infection in a big hospital

  - **91 patients including 77 health care workers, 12 patients and 2 members of the families of patients**

Infect. Cont. Hosp. Ep 2004, 2005

2004: Introduction of a booster for health care workers in contact with newborns as well as for young adults and persons at risk (such as pregnant women or elderly) with combined **ap** vaccines (3 or 5 components)

Vaccine schedules in the world

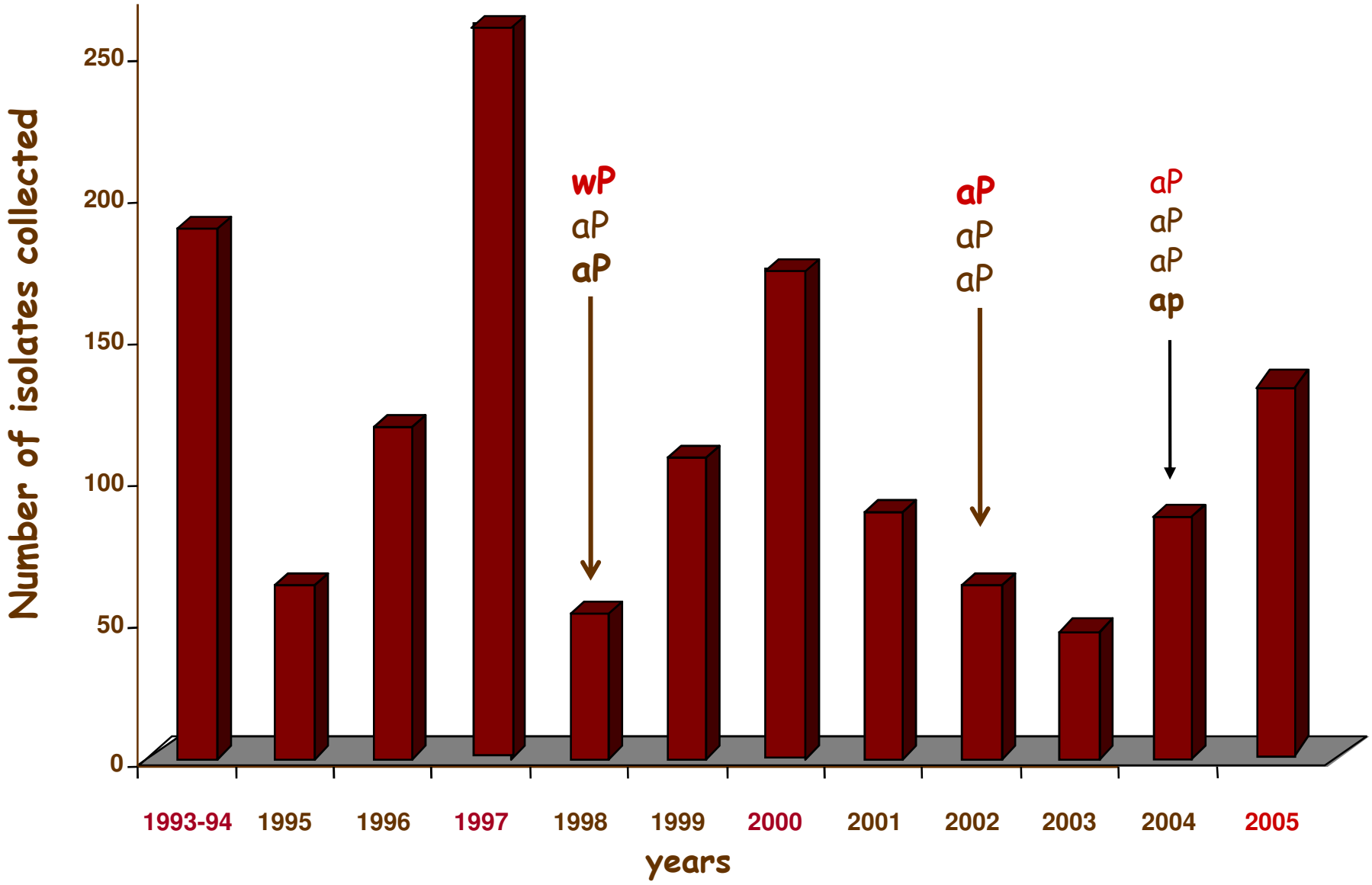
Country	Primo-vaccination	Booster 1	Booster 2	Booster 3	Boosters n
FRANCE	2-3-4$_m$ aP	16-18$_m$ aP	11-13$_a$ aP	Young Parents, Health care workers	
GERMANY	3-4-5$_m$ aP	11-14$_m$ aP	10-18$_y$ aP	Young Parents Health care workers	
AUSTRALIA	2-4-6$_m$ aP	18$_m$ aP	4-6$_y$ aP	Young Parents Health care workers	All adults ap
CANADA	2-4-6$_m$ aP	18$_m$ aP	4-6$_y$ aP	15-17a aP	
BELGIUM	2-3-4$_m$ aP	15-18$_m$ aP	3-7$_y$ aP	14-16a aP	
BRASIL	2-4-6$_m$ aP	15$_m$ aP	4-6$_y$ aP	Health care workers in discussion ap	
SPAIN	2-4-6$_m$ wP/aP	15-18$_m$ aP	6$_a$ aP	Adolescents in discussion	
USA	2-4-6$_m$ aP	15-18$_m$ aP	4-6$_a$ aP	All adolescents aP	All adults ap
FINLAND	3-4-5$_m$ aP	20-24$_m$ aP	4-6$_y$ aP		
ISRAEL	2-4-6$_m$ aP	12$_m$ wP	7-14$_a$ aP		
The NETHERLANDS UNITED KINGDOM	2-3-4$_m$ wP/aP 2-4-6$_m$ aP	11$_m$ wP/aP	4-6$_y$ aP 4-6$_y$ aP		

Pertussis in France

How to analyse impacts of vaccine and schedule changes?

- Hospital based surveillance (43 pediatric hospitals): RENACOQ net since 1996
- Pediatric surveillance (126 pediatricians): ACTIV net since 2002

Pertussis in France: RENACOQ surveillance



Pertussis in France

RENACOQ surveillance

	1996	1997	1998	1999	2000	2001	2002	2003	2004
N° of cases	339	588	270	335	415	190	82	68	93
Age < 3m.	32%	33 %	40 %	34 %	43 %	41 %	48 %	56 %	78 %
Cases/100,000	214	400	220	260	478	278	150	115	272
Estimated hosp.	-	1571	763	764	1145	538	250	250	300
Deaths	2	5	1	3	9	3	0	4	1
Contaminators	177	264	118	152	179	96	39	31	66
Parents	36%	42 %	48 %	45 %	46 %	50 %	44 %	65 %	66 %
Siblings	34%	36 %	26 %	31 %	35 %	20 %	26 %	10 %	18 %
Contact cases	30%	21 %	26 %	24 %	18 %	25 %	26 %	25 %	16 %

Conclusion

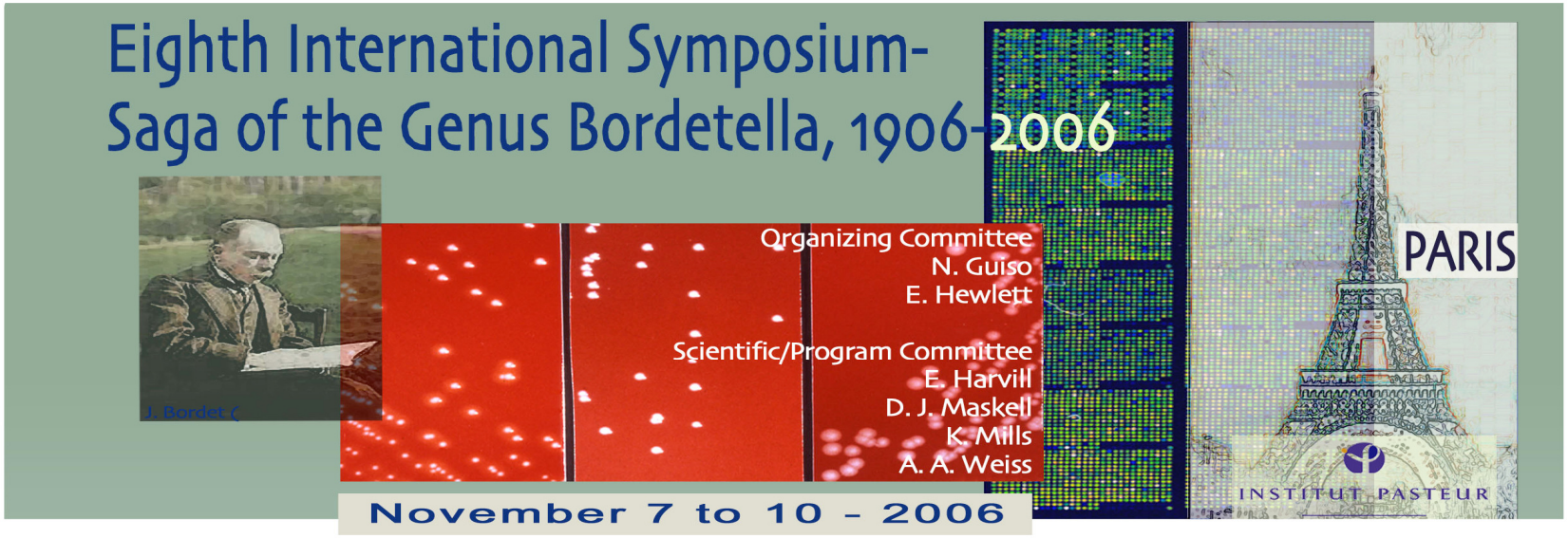
- **Ideal strategy:**
  - Universal vaccination against pertussis at regular intervals throughout life

- **First steps in this strategy:**
  - Reinforce current immunization schedules
  - Adolescents
  - Parents
  - Childcare workers
  - Healthcare workers
  - Adults at risk of severe pertussis disease (elderly)

Ped. Infect. Dis.J., 2005

Conclusion

- Surveillance of vaccine preventable diseases needs a tight collaboration between
  - Clinicians
  - Microbiologists
  - Epidemiologists
  - Public health authorities
  - Manufacturers



An international symposium on Bordetellae will be held November 7-10, 2006, at the Institut Pasteur, Paris, France. This meeting is a continuation of the series of international symposia on pertussis, which has been expanded to include research on all Bordetellae. This year, 2006, is the 100th anniversary of the isolation of *Bordetella pertussis* by Bordet and Gengou. The program will focus on the history, genetics, biology, pathogenesis and control of infections caused by these species and will consist of oral and poster presentations. Further information (on registration, housing and program) will be provided on a website at the Institut Pasteur. www.pasteur.fr/infosci/conf/sb/8thBordetellae