

Vaccines for ***Streptococcus pneumoniae***

5th ESCMID School

Santander June 2006

Dr. José María Marimón. Hospital Donostia. Donostia-San Sebastián, Spain

Pneumococcal disease

Pneumonia
Invasive disease

Pneumococcal disease: a major health threat

- *Streptococcus pneumoniae* is the leading bacterial cause of infection worldwide:
 - asymptomatic colonisation
 - common infections (otitis media, ...)
 - life-threatening infections (sepsis, meningitis, ...)
- Despite the introduction of antimicrobial drugs over the past few decades it remains a significant threat to health

Types of infection

non-invasive

- otitis (25-50%)
- sinusitis
- recurrent bronchitis

invasive

- pneumonia
- sepsis
- meningitis



Pneumococcal pneumonia

Ten leading causes of death, developed and developing regions, Version 2 estimates, 2000

Developed countries	% of total deaths	Developing countries	% of total deaths
1 Ischaemic heart disease	23.3%	1 Ischaemic heart disease	9.2%
2 Cerebrovascular disease	13.4%	2 Cerebrovascular disease	8.4%
3 Trachea, bronchus, lung cancers	4.4%	3 Lower respiratory infections	7.9%
4 Lower respiratory infections	3.6%	4 Perinatal conditions	6.0%
5 COPD	3.2%	5 HIV/AIDS	6.0%
6 Colon and rectum cancers	2.3%	6 COPD	5.2%
7 Self-inflicted injuries	1.8%	7 Diarrhoeal diseases	4.6%
8 Diabetes mellitus	1.7%	8 Tuberculosis	3.6%
9 Stomach cancer	1.7%	9 Malaria	2.7%
10 Hypertensive heart disease	1.7%	10 Road traffic accidents	2.4%

PNEUMONIA

HIGH MORTALITY

1st CAUSE OF DEATH OF INFECTIOUS DISEASES

In 2002: 2,1 millions of deaths due to pneumococcal pneumonia, which 1,5 in children under age of five

PNEUMOCOCCAL PNEUMONIA MORTALITY

8%-10%

Overall healthy young adults (non bacteriemic) < 1%

Bacteriemic pneumonia: 15%-20%

High-risk groups: 50%

Elderly > 70 years: 30%-40%

Young adults (<45 years): <8%

Pneumococcal invasive disease

Deaths due to vaccine-preventable diseases

Estimated number of deaths in all age groups from diseases currently recommended by the World Health Organization

- Measles: 610 000
- Hepatitis B: 600 000
- *Haemophilus influenzae* type b (Hib): 386 000
- Pertussis: 294 000
- Tetanus: 213 000
- Other (polio, diphtheria, yellow fever): 36 000^b

Other vaccines not included in WHO recommendations

- Pneumococcal disease: 1 612 000, of which 716 000 under age five
- Meningococcal disease: 26 000, of which 10 000 under age five
- Rotavirus: 449 000, of which 402 000 under age five

Burden of the disease

WHO: nearly 1 million children die annually of pneumococcal disease worldwide

Europe and United States

(annual rates per 100.000 population)

Pneumonia: 100 cases

Bacteraemia: 15-19 cases

Meningitis: 1-2 cases

Incidence of pneumococcal invasive disease in Spain

- **Invasive infection:** (before heptavalent conjugate vaccine)

6.4-10.5 cases/100,000 population

30- 50 cases/ 100,000 children aged < 2 years

Differences in rates:

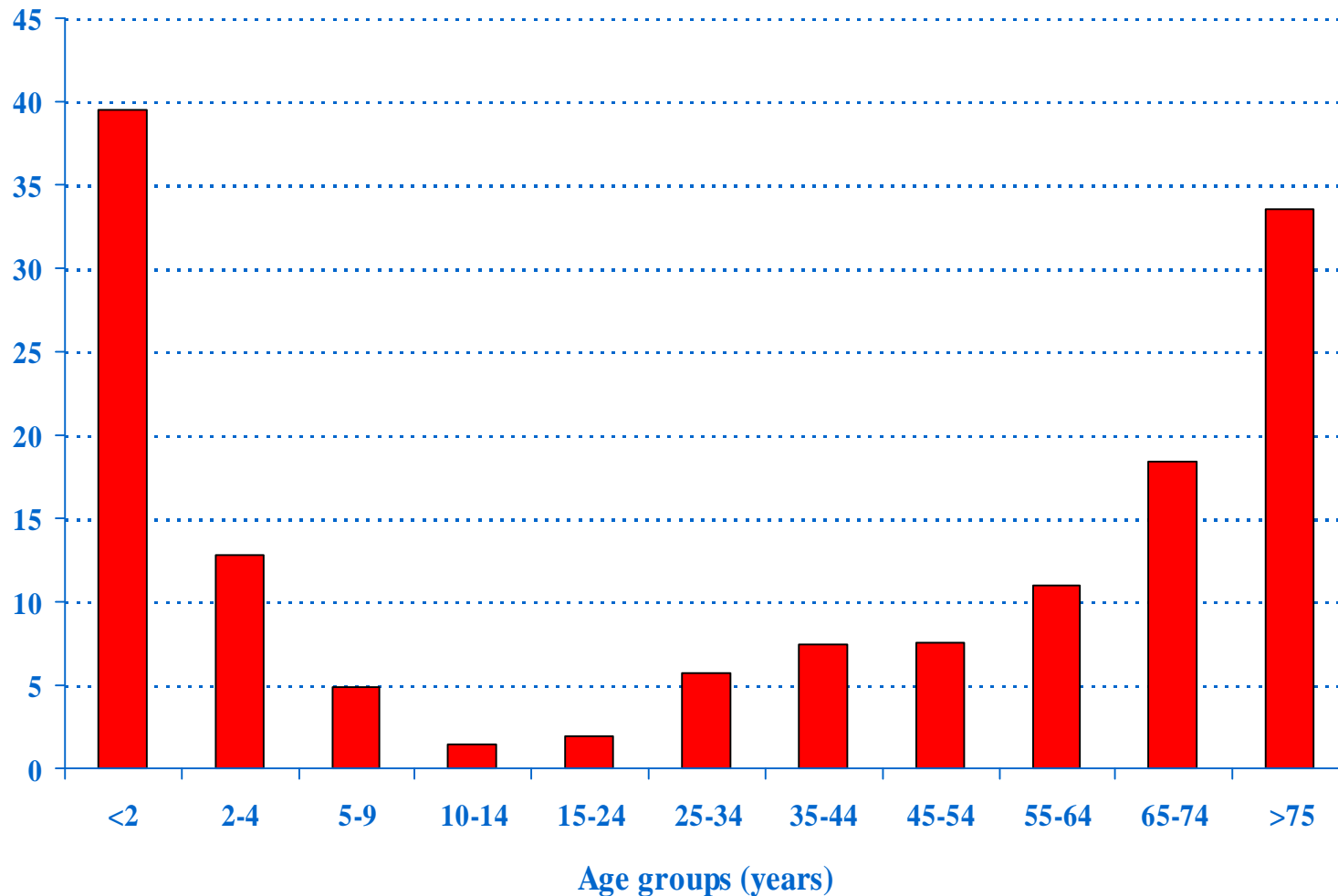
Blood culture performance

Health-care variations

- **Meningitis <2 years:** **6.7 - 15.5 cases/100.000 children**

Incidence of pneumococcal invasive disease by ages Gipuzkoa, Spain 1985-2005

Annual rate of PID per
100,000



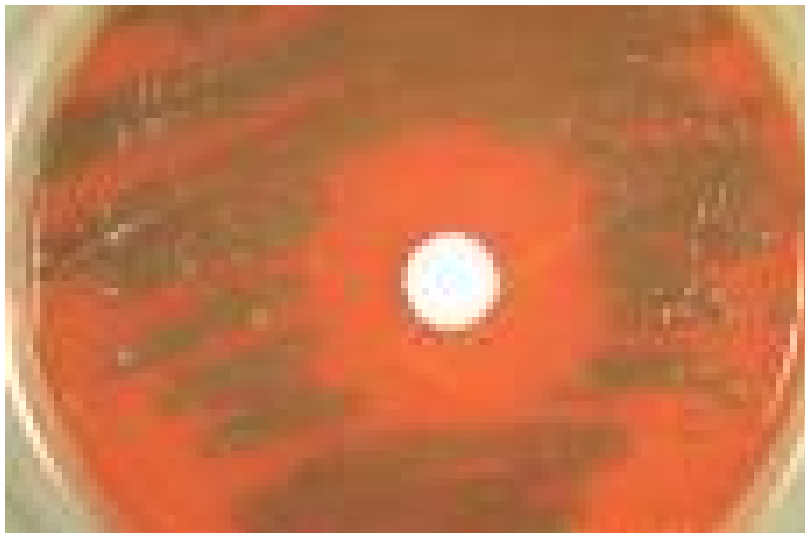
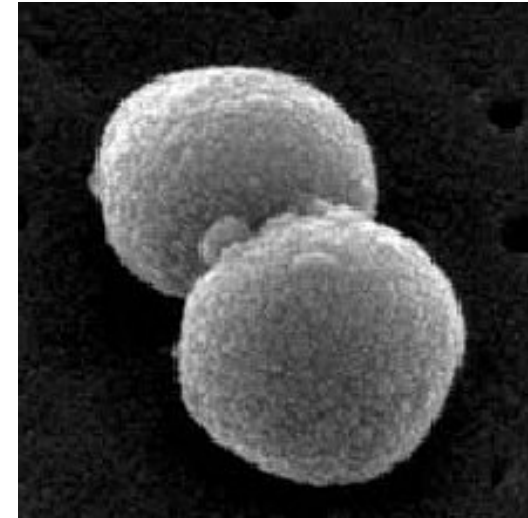
Streptococcus pneumoniae

Characteristics. The capsule
Epidemiological aspects

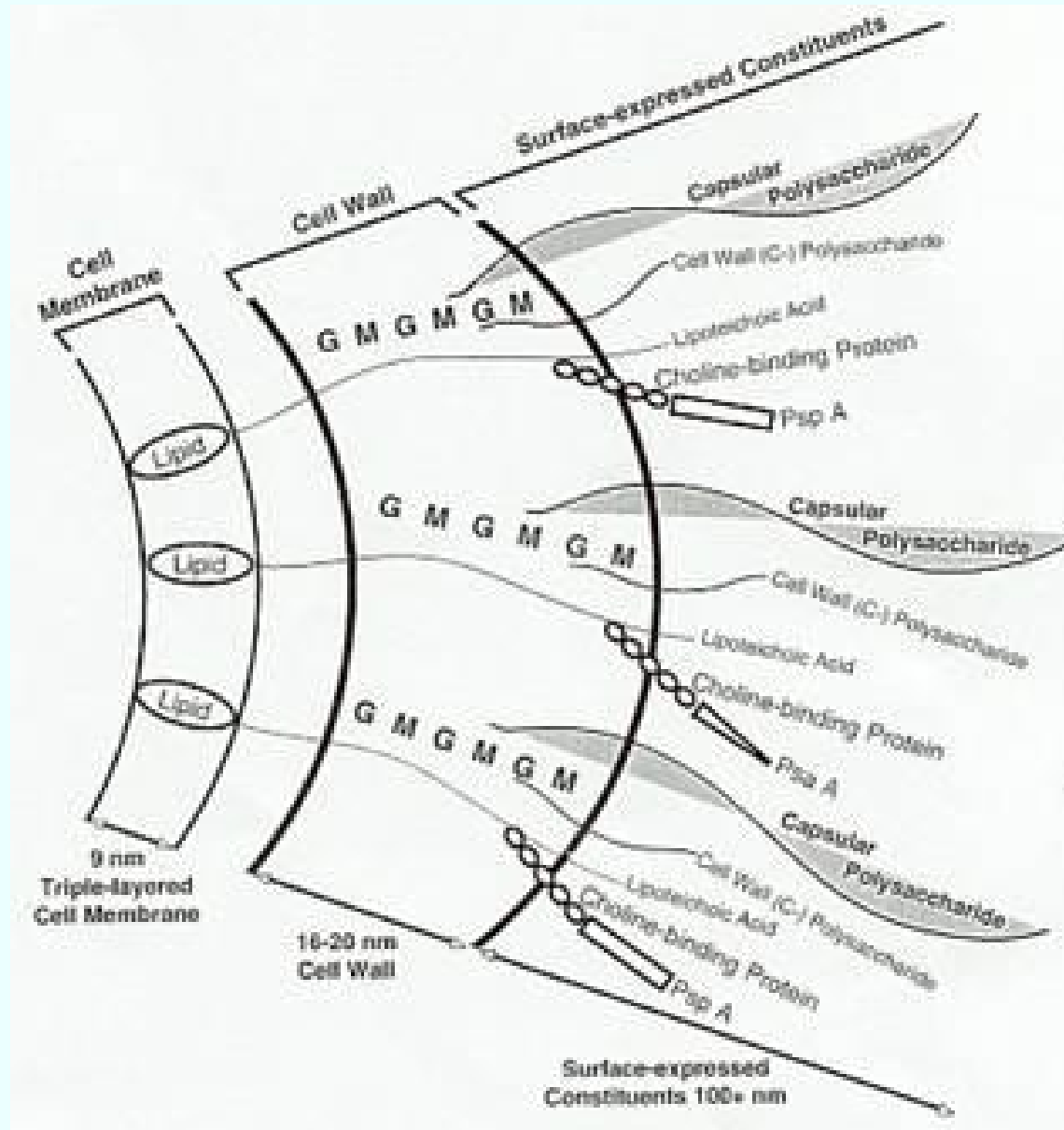
Streptococcus pneumoniae

Microbiology

- Gram-positive diplococci
- Growth requirements
- α -haemolytic on blood-agar
- Capsulated

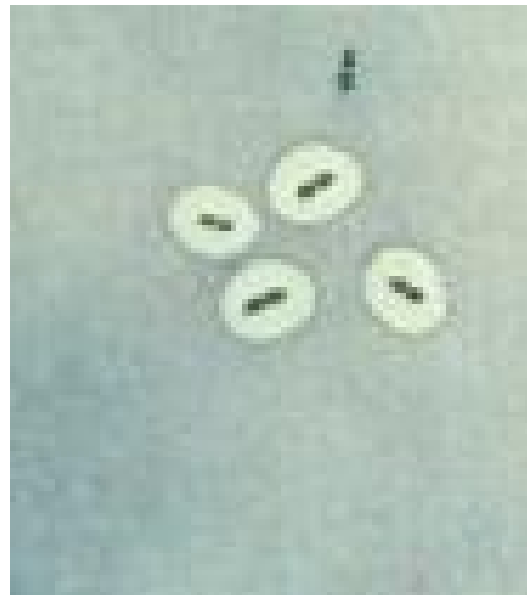


Pneumococcal cell surface



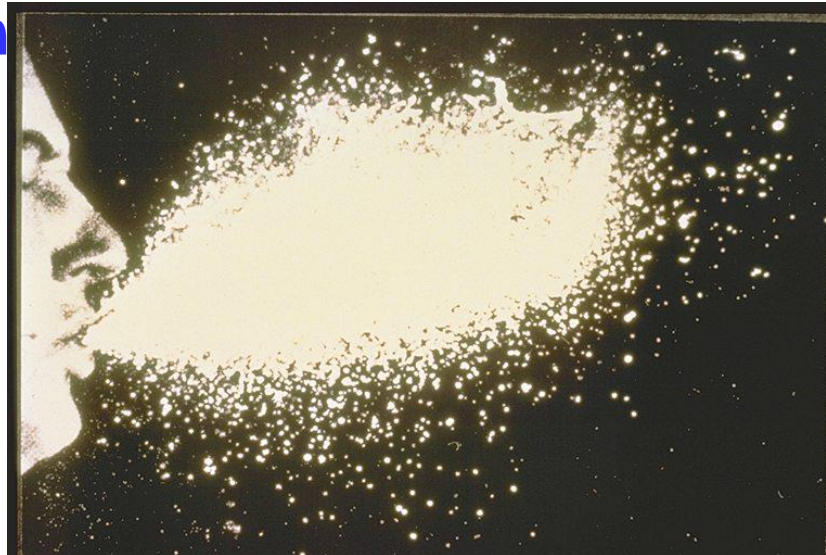
The capsule

- # Composition: polysaccharide
- # Virulence factor: avoiding phagocytosis
- # Induce type-specific immune response
- # More than 90 different serotypes

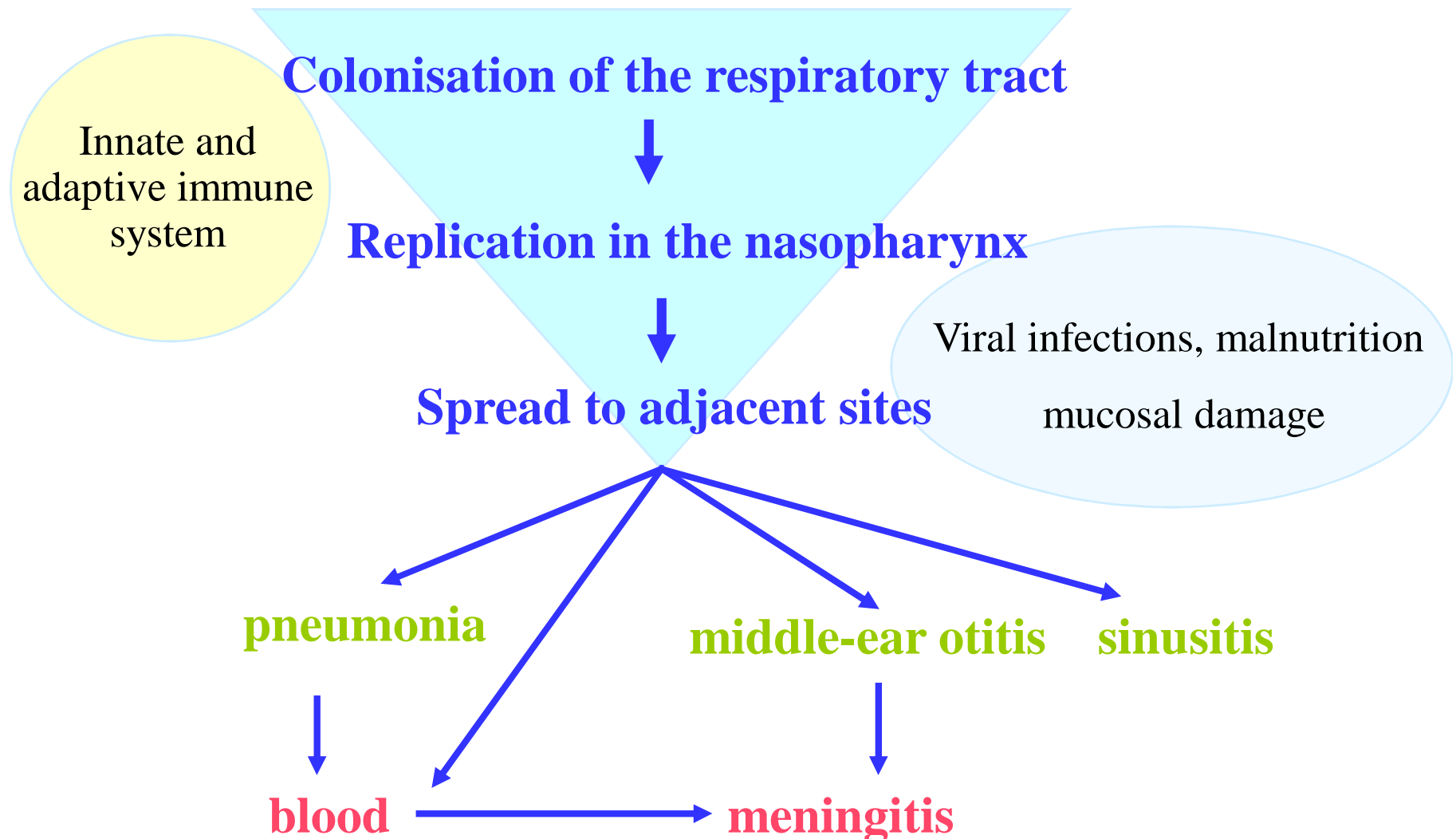


Pneumococcus: colonisation and transmission

- Exclusively a human pathogen, part of the normal microbial flora of the upper respiratory tract
- Transmission: by droplet secretions
- Temporal pattern: winter-early spring
- Communicability: Unknown. Probably as long as organism in respiratory secretion



Pathogenesis: the route to infection



Vaccines

Introduction

Pneumococcal vaccines

Components of the Classical Vaccines

■ **IMMUNIZATING AGENT**

■ **FLUID CONTAINING:**

Disinfectant

Antibiotics

Stabiliser

■ **ADYUVANT (SOMETIMES)**

Immunizing agents

- **VACCINES**

(against the effects of the infection: anti-adhesins, ...)

- **TOXOIDS**

(against the toxin)

- **IMMUNOGLOBINS**

- **Naturally (placenta)**

- **Artificially**

Modern history: capsular vaccines (polysaccharide or oligosaccharide)

■ *pneumococci*

- 1946: 6-valent
- 1977: 14-valent
- **1984: 23-valent**

■ *meningococci A*

- 1974: A
- 1975: C; A+C
- 1982: A+C+W-135+Y

■ **1985: *Haemophilus influenzae b***

Modern history: conjugate vaccines

■ *Haemophilus influenzae* b:1987

- Haemophilus b Conjugate Vaccine (Diphtheria CRM197 Protein Conjugate)
- Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)
- Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate)
- Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate) & Hepatitis B Vaccine (Recombinant)

■ *meningococci* A: 1999

- Meningococcal Polysaccharide (Serogroups A, C, Y and W-135) Diphtheria Toxoid Conjugate Vaccine
- Meningococcal Polysaccharide Vaccine, Groups A, C, Y and W-135 Combined

■ *pneumococci* : 2000

- Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM197 Protein)

Immunity

- Cell wall constituents & pneumolysin:
 - inflammatory response
- Anti-capsular antibodies:
 - serotype-specific
 - in adults: protective against pneumococcal infections
 - in <2 years and advanced immunological impairments:
not protective levels
 - do not induce immunological memory

Pneumococcal vaccines

- Protective immunity is conferred by **anti-capsular** type-specific antibodies
- Antibodies against pneumococcal **surface proteins** confer protection in animal models. In humans this role is to be determined

Currently licensed in Europe: 2 types of pneumococcal vaccines

Old 23-valent Pneumococcal Polysaccharide Vaccine (PPV23)

New 7-valent Pneumococcal Conjugated Vaccine (PCV7)

23-valent Pneumococcal Polysaccharide Vaccine PPV23

- 25 µg of purified capsular polysaccharide antigen serotypes:
1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 10A, 11A, 12F, 14,
15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F
- Covers 85-90% of invasive pneumococcal disease
- Relatively good antibody responses (60–70%) following a single intramuscular/subcutaneous immunization in most healthy adults

PPV23

Negative aspects

- immune response mediocre in children <2 years and in immunocompromised individuals (HIV/AIDS)
- does not induce immunological memory which is required for subsequent booster responses

PPV23 recommendations

- For healthy adults ≥ 65 years of age, particularly those living in institutions
 - Based on data from **observational studies**:
significant protective effect against IPD, but not pneumonia
 - Based on data from **randomised controlled trials**:
failed to show a beneficial effect of the vaccine
- Persons ≥ 2 years at higher risk of PID (asplenic, immunocompromised, ...)

7-valent Pneumococcal Conjugated Vaccine

PCV7

- **Seven *S. pneumoniae* capsular polysaccharide antigens, conjugated to nontoxic diphtheria toxin (cross-reactive material, CRM(197))**
- **CRM(197): inert but immunogenic variant of diphtheria toxoid also used as a carrier molecule in one *H.influenzae* type b conjugate vaccine**

PCV7. Characteristics

- higher antibody levels and a more efficient immune response in infants
- significant immunological memory
- >90% effective against invasive disease
- less effective against other forms of the disease (non-invasive pneumonia, otitis media, ...)

PCV7. Effectiveness

(Wyeth Lab. Prevnar[®], USA or Prevenar[®], Europe)

- serotypes 4, 6B, 9V, 14, 18C, 19F, 23F
- serotypes included: most prevalent in invasive diseases and antibiotic resistance

potential coverage of serotypes causing PID:

85% for the USA

70-75% for Europe

≈ 65% for Latin America

≈ 50% for Asia

PPV7. Efficacy in invasive disease Pre-licensed study

Northern Carolina Kaiser Permanent Trial

- **37,816 children enrolled & 4 doses of vaccine or control**
- **efficacy against vaccine serotype disease: 97.4% (19F)**
- **efficacy against all serotypes IPD: 89.1%**

Black S, *et al.* Efficacy, safety and immunogenicity of the heptavalent pneumococcal conjugate vaccine in children. *Pediatric Infect Dis J.* 2000;19:187-195

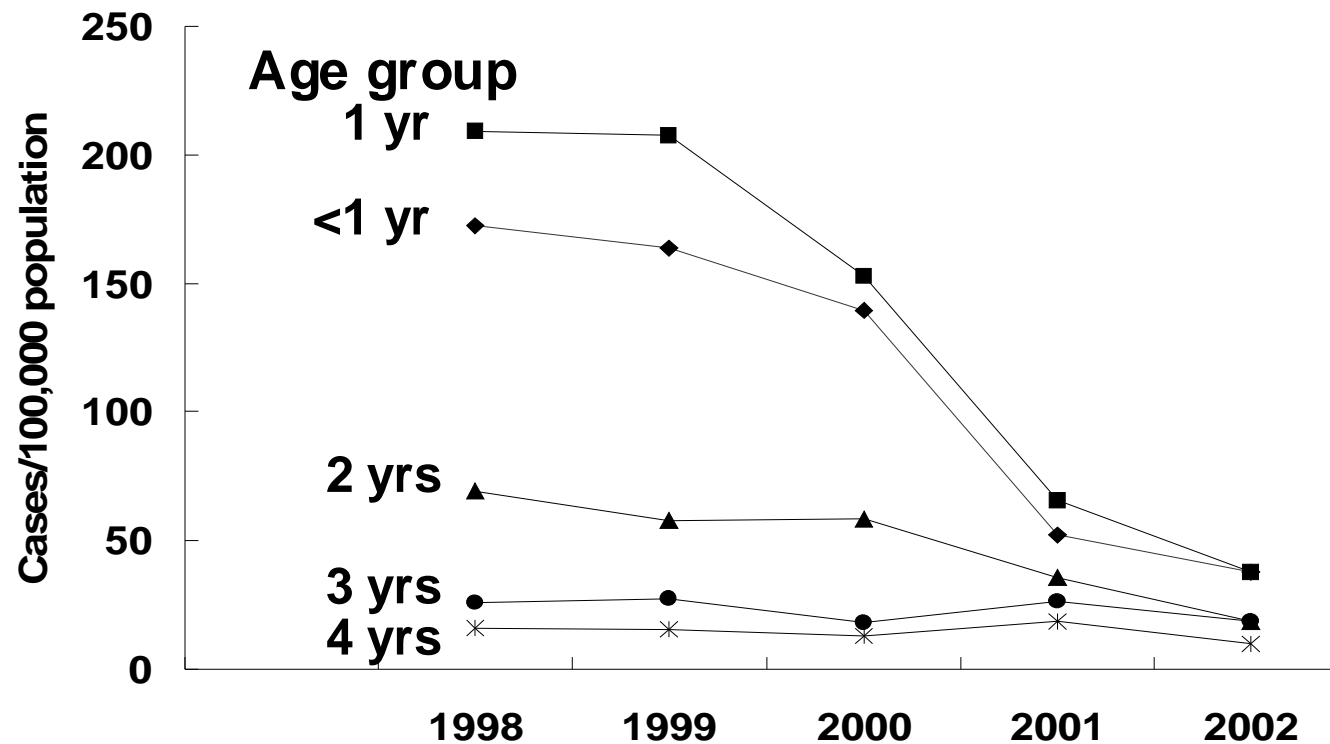
PPV7. Efficacy in invasive disease

Post-licensed study

- Rate IPD in < 1 year:
from 73.8 cases/100 000 pre-vaccine to 0.0 in 2002-2003
- Rate IPD in < 2 years:
from 91.3 to 0.0 in 2002-2003

Black S, *et al.* Post-licensure surveillance for pneumococcal invasive disease after use of heptavalent pneumococcal conjugate vaccine in Northern California Kaiser Permanente.
Pediatr Infect Dis J. 2004;23:485-489.

Invasive Pneumococcal Disease by Age and Year— Children <5 Years, 1998-2002*



*2003 data are preliminary.

Source: Active Bacterial Core Surveillance/EIP Network

PPV7. Efficacy in non-invasive disease

- **Pneumonia:**
reduction about 20%
 - **Acute otitis media:**
reduction about 6% -7%
-

PCV7. Indirect effects

Nasopharyngeal carriage suppression

Creation of “herd immunity” reducing bacterial transmission in the community and thus protecting unvaccinated individuals

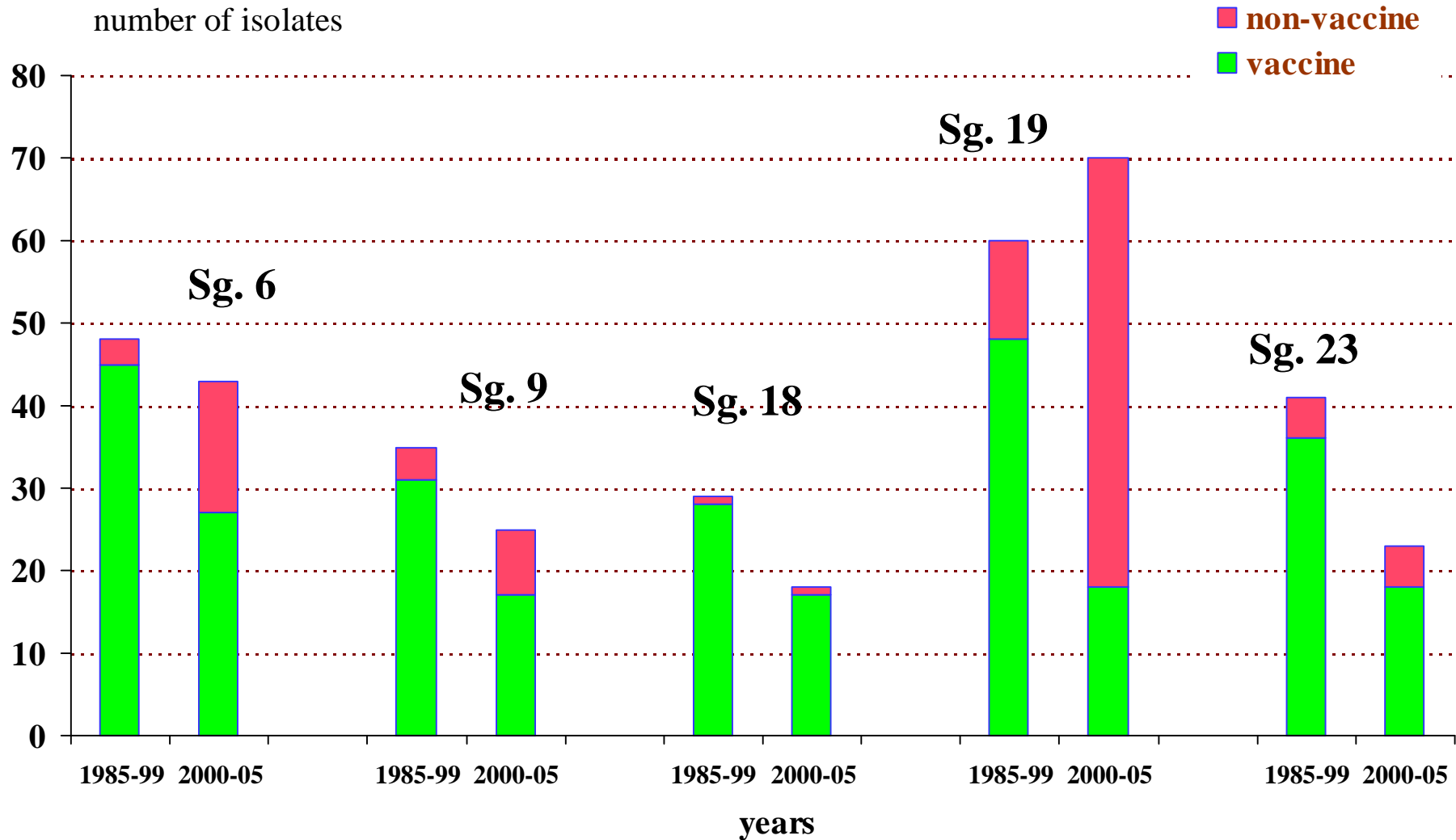
(herd immunity: benefit that unvaccinated subjects receive from those vaccinated)

PPV7. Unwanted effects

- **“Replacement” of strains:**
increased prevalence of colonisation and disease by non-vaccine strains and/or other bacteria

 - **Not cross-immunity between related serotypes**
-

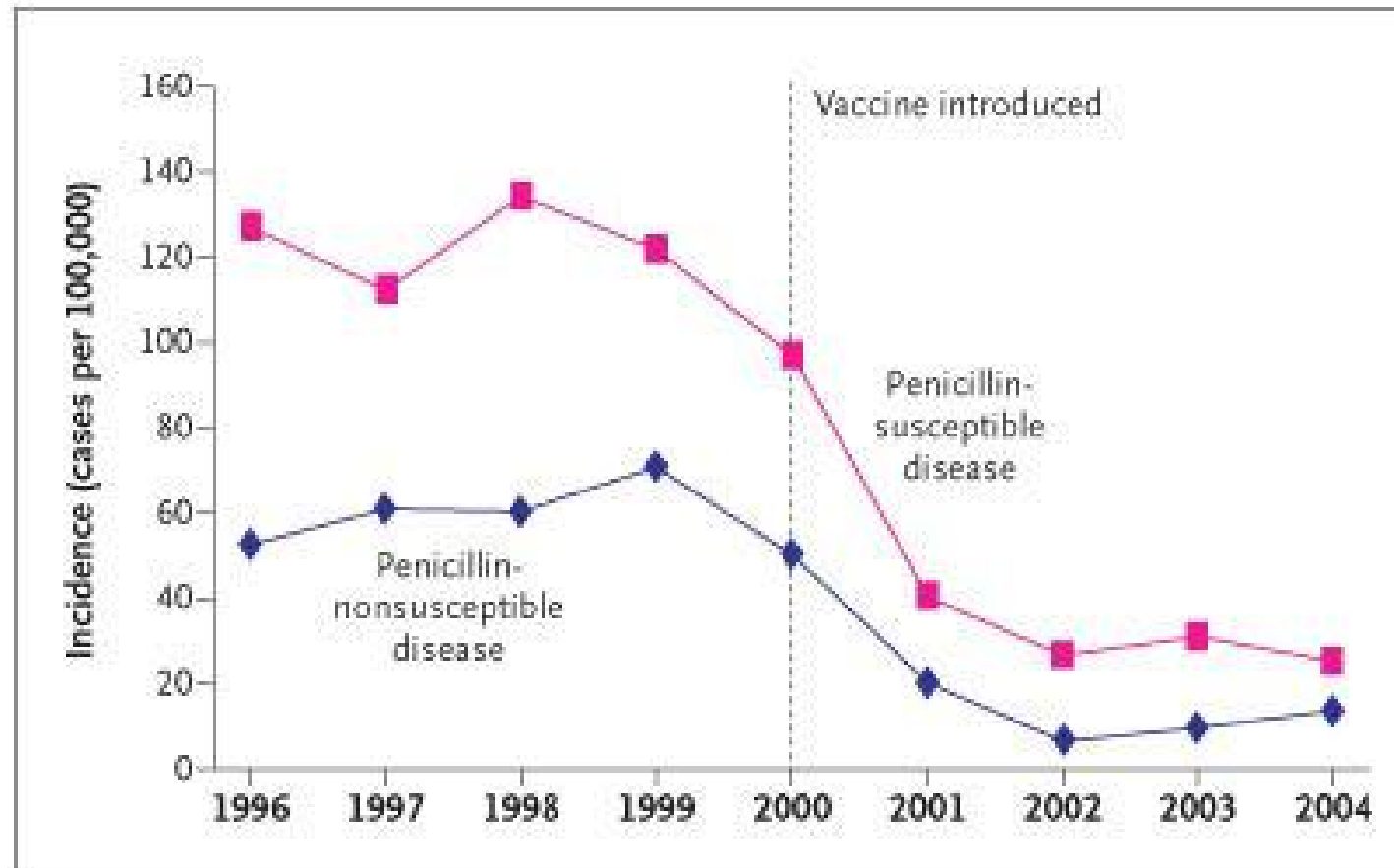
PPV7. Serotypes responsible for invasive disease Gipuzkoa, Spain 1985-2005



PPV7. Effects on antimicrobial resistance

- **Reduced rates** of infection and colonisation by antibiotic-resistant strains (included in the PCV7)
 - **Increase** in non-vaccine serotypes: types 15 and 19A (antibiotic resistant)
-

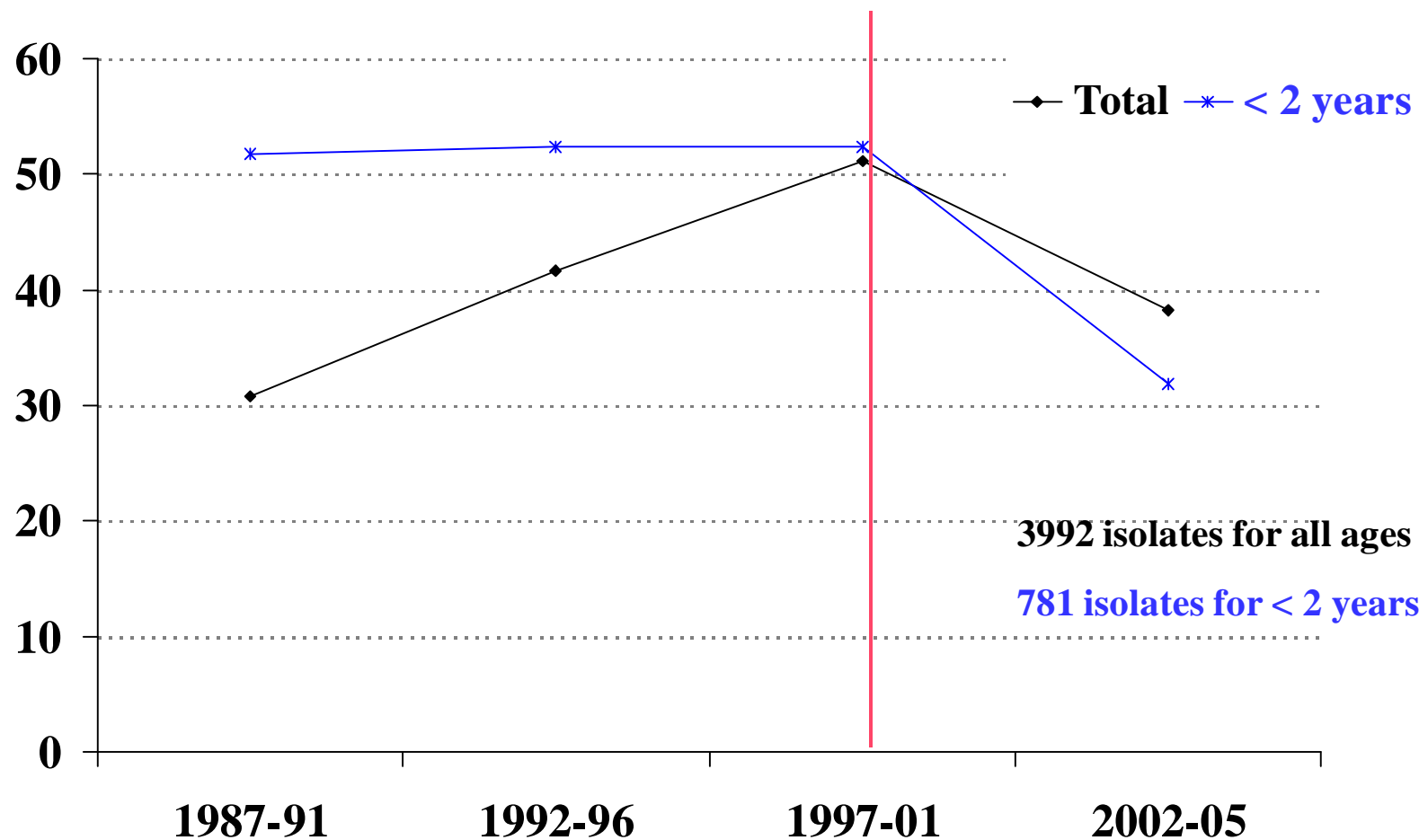
Annual Incidence of Invasive Disease Caused by Penicillin-Susceptible and Penicillin-Nonsusceptible Pneumococci among Children under Two Years of Age, 1996 to 2004 .



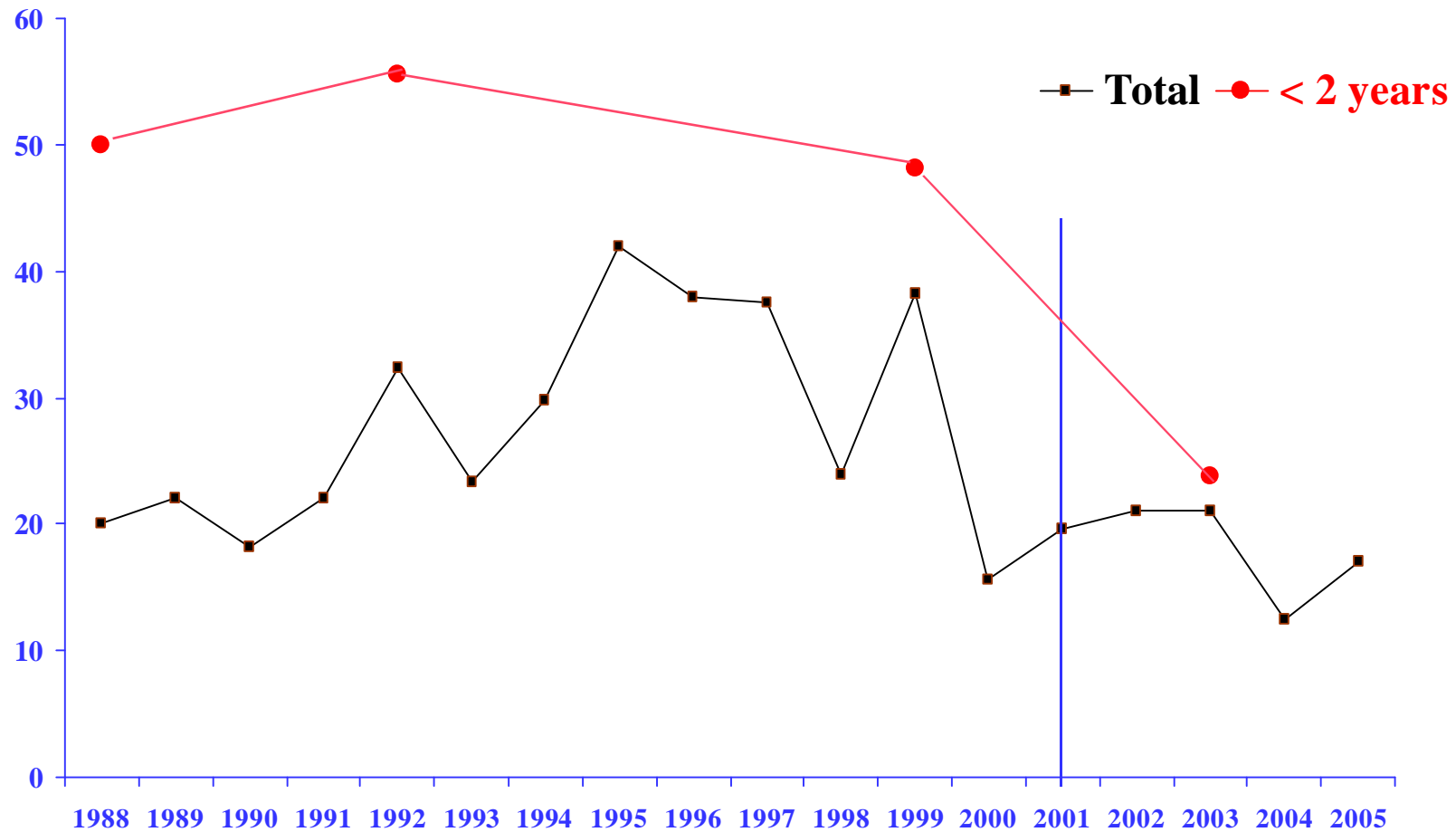
Population under surveillance ranged from 14.3 million to 16.9 million, including \approx 500,000 children <2 years of age.

Kyaw MH, et al. Active Bacterial Core Surveillance of the Emerging Infections Program Network.
N Engl J Med. 2006; 354:1455-63.

Percentage of penicillin non-susceptible isolates (all sites). Gipuzkoa, 1987-2005



Percentage of penicillin non-susceptible isolates from invasive disease. Gipuzkoa, 1987-2005



PCV7. Safety and schedule

- **2, 4, 6 months, booster 12-14 months**
- **Possible interference with other conjugate vaccines (meningococcal) when administered together**

- **Safe**
- **Adverse reactions: fever**

Other conjugate vaccines PCV9

9-valent vaccine:

Serotypes: 4, 6B, 9V, 14, 18C, 19F, 23F + 1 and 5

conjugated with CRM197

Efficacy in children < 2 years*:

HIV (-): 77%-83%

HIV (+): 65%

***against invasive pneumococcal disease due to serotypes included in the vaccine**

Klugman KP *et al.* A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *N Engl J Med* 2003; 349: 1341–8.

Cutts F *et al.* Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomized, double-blind, placebo-controlled trial. *Lancet* 2005; 365:1139-46.

Other conjugate vaccines PCV11

- 11-valent vaccines: 7-valent plus serotypes 1, 3, 5, and 7F

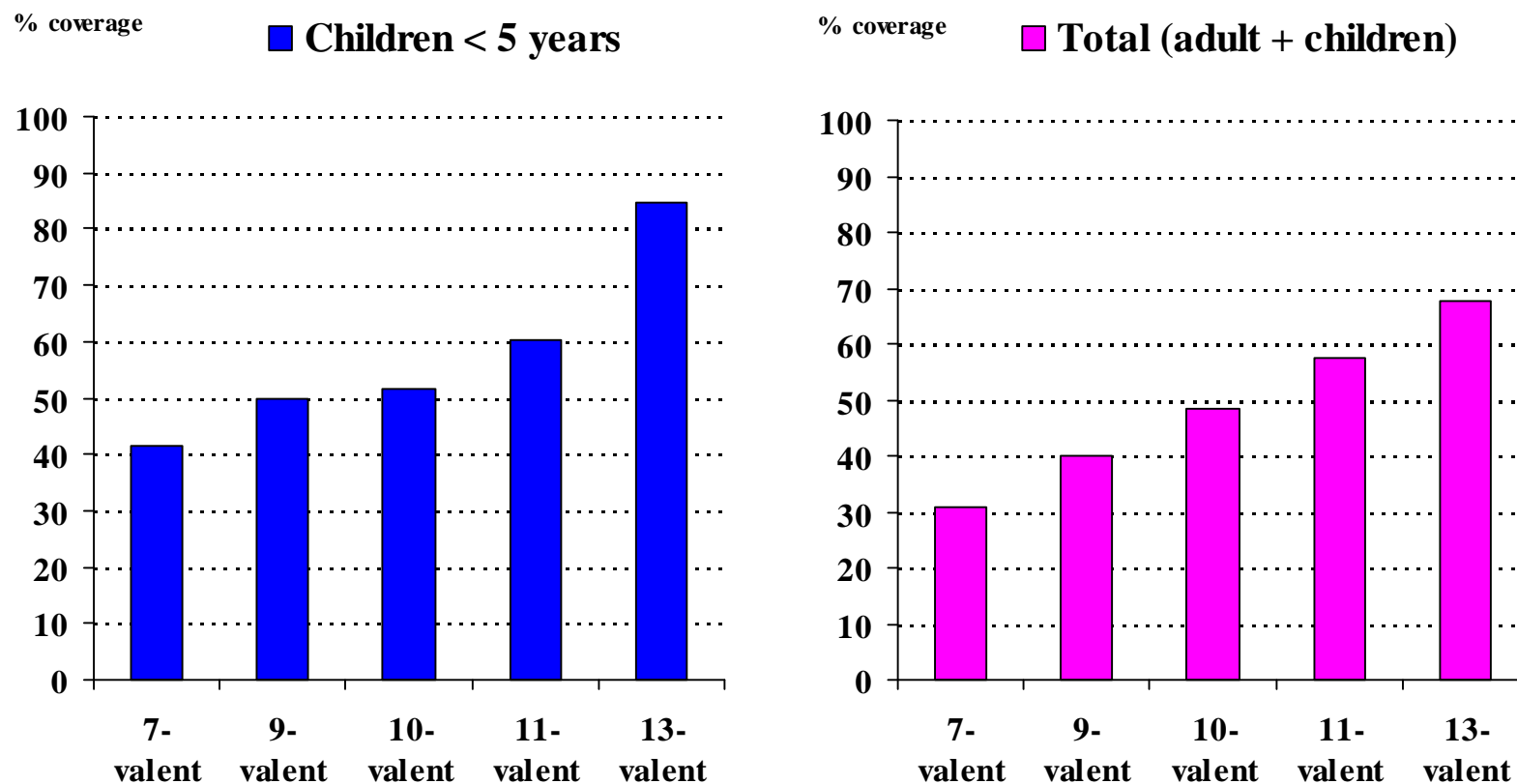
serotypes 1, 4, 5, 7F, 9V, 19F, and 23F conjugated to tetanus protein; and serotypes 3, 6B, 14, and 18C conjugated to diphtheria toxoid

- Immunogenic and safe in infants
- Antibodies showed opsonophagocytic activity against st.4, 6B, 14, 19F, and 23F

Nurkka A, *et al.* Immunogenicity and safety of the eleven valent pneumococcal polysaccharide-protein D conjugate vaccine in infants. *Pediatr Infect Dis J.* 2004; 23:1008-14.

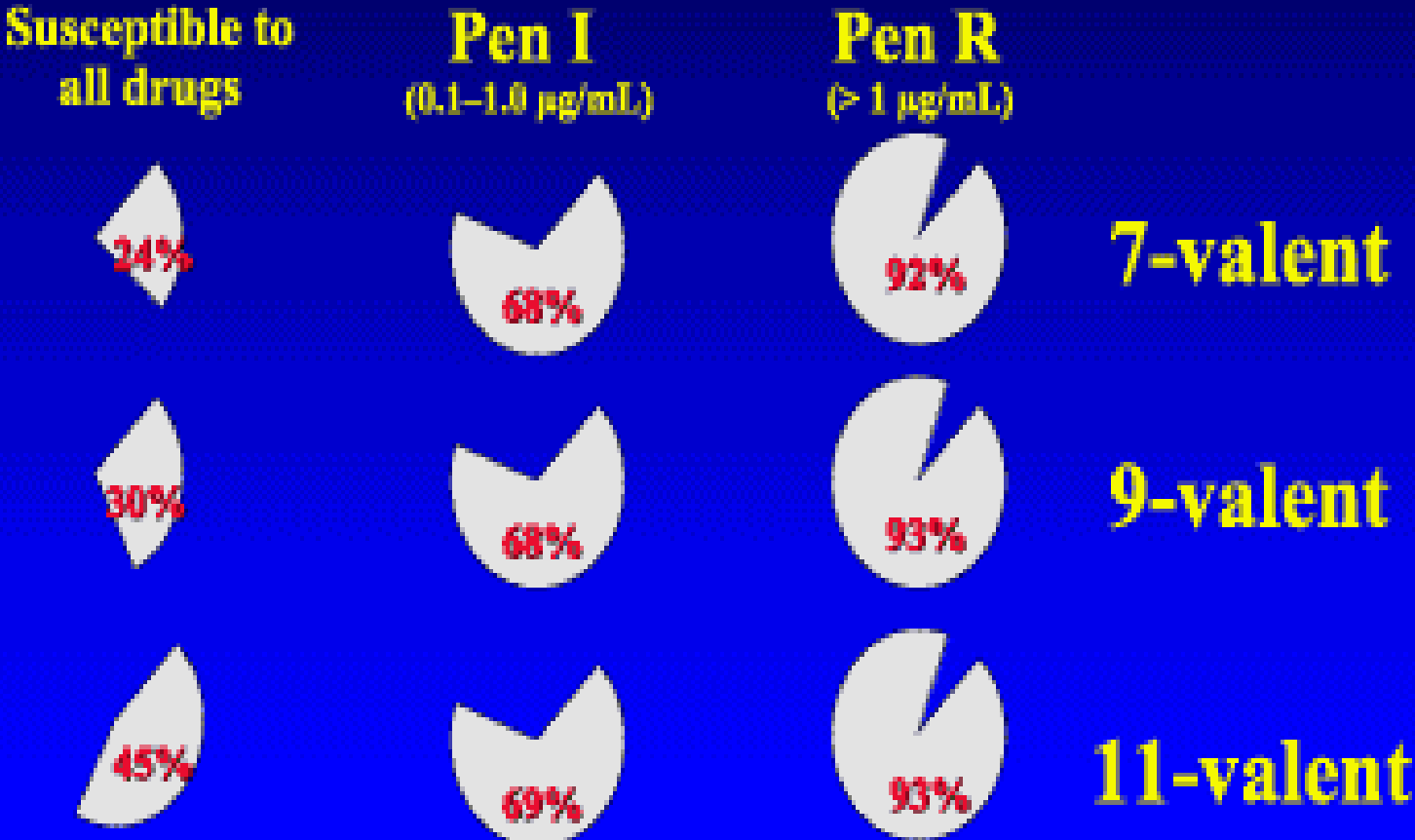
Lucero MG *et al.* Similar antibody concentrations in Filipino infants at age 9 months, after 1 or 3 doses of an adjuvanted, 11-valent pneumococcal diphtheria/tetanus-conjugated vaccine: a randomized controlled trial. *J Infect Dis.* 2004; 189: 2077-84.

Estimated vaccine coverage for the different pneumococcal vaccines according to serotypes causing invasive disease in Gipuzkoa, 2000-05



9-valent (hepta + 1, 5)
10-valent (hepta + 3, 5, 7F)
11-valent (hepta + 1, 3, 5, 7F)
13-valent (hepta + 1, 3, 5, 6A, 7F, 19A)

Coverage by 7-, 9-, and 11-Valent Vaccines*



* 821 MEF isolates.

Dagan R et al. J Infect Dis. 2000;181:1332-1339.

Other non-polysaccharide vaccines

- Proteins: pneumolysin
 - pneumococcal surface protein A (PspA)
 - pneumococcal surface adhesin (PsaA)
- Provide protective immunity against a larger number of *S. pneumoniae* serotypes
- Circumvent the complexity of manufacture of conjugate vaccines

Vaccines for *S. pneumoniae*

Conclusions

- **PPV23:**

good spectrum, low protective immunity in high-risk population

- **PCV7:**

lower spectrum, better protective immunity
replacement of serotypes causing PID

- **Newer PCV and protein vaccines:**

higher coverages and immunogenic
