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ACTUALIZACIÓN  
EN PEDIATRÍA  
ALAPE 2011**

# **MANAGEMENT OF MENINGITIS 2001**

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## **Declaración de potenciales conflictos de intereses**

**I have no potential conflicts of interest to declare**

# MANAGEMENT OF MENINGITIS 2011

- x Changing incidence rates
- x Factors affecting therapy and outcome
- x Adjunctive therapies
- x Impact of the conjugate vaccines
- x Other causes of CNS infection

# ETIOLOGIC AGENTS BY AGE GROUPS

## x Neonatal

- Group B & other streptococci
- *Escherichia coli* and other Gram negative enteric bacilli
- *Listeria monocytogenes*

## x Infants and younger children

- *Neisseria meningitidis*
- *Streptococcus pneumoniae*

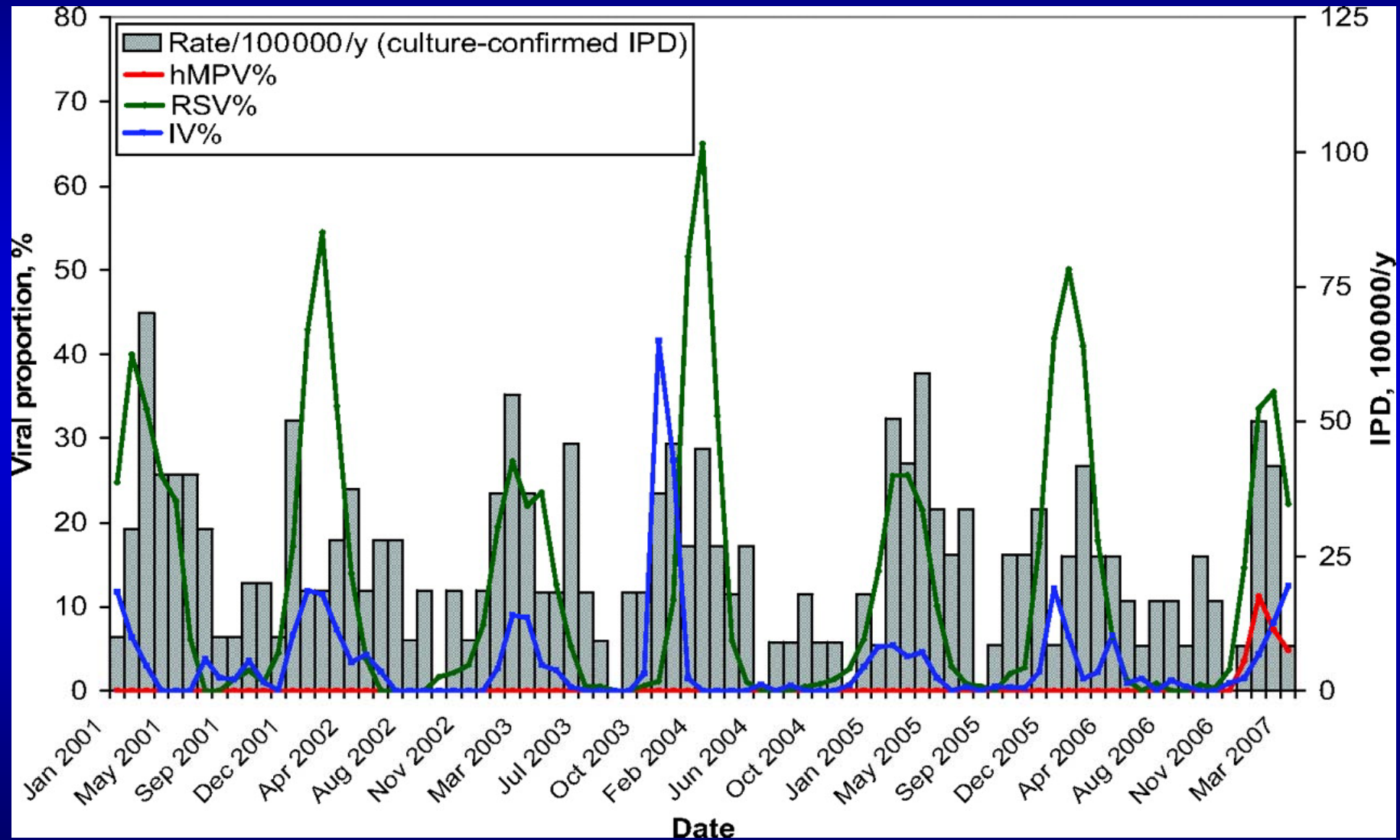
## x Older children – adults

- *Streptococcus pneumoniae*
- *Neisseria meningitidis*
- Others

## **PATHOGENESIS**

- X Bacterial colonization of the nasopharynx;  
viral co-infection**
- X Mucosal invasion with blood penetration**
- X Intravascular multiplication and  
penetration of the blood-brain barrier**
- X Subarachnoid space inflammation**
- X Induction of neuronal and auditory nerve  
damage resulting from inflammation**

# Respiratory Viral Infections and Invasive Pneumococcal Disease, Utah, 2001-2007\*



\* Pediatrics 2008;122:229

## Genetically Determined Susceptibility

- x Pathogen recognition receptors as part of the innate immune mechanisms
- x Expressed on antigen presenting and phagocytic cells in neural (astrocytes & microglia) and non-neural (macrophages & dendritic cells) tissues
- x SNPs in toll like receptors (TLRs) like TLR 9 (meningococci) and TLRs 2 & 4 (pneumococci and meningococci) can affect susceptibility and degree of inflammation.

## **PNEUMOCOCCAL MENINGITIS**

- x CFR 5-7% Long-term sequelae, 35% (hearing deficit 20%). No apparent differences among serotypes. CFR higher in HIV-infected children**
- x In Malawi, children treated with pen and chloro had higher CFR when there was resistance to either agent\***
- x For 2001-2004 rates decreased 66% in < 2 yo and 52% in 2-4 yo; in those > 65 yo, rates down 33%. Approx 1820 cases prevented by PCV7 in <5 yo\*\***

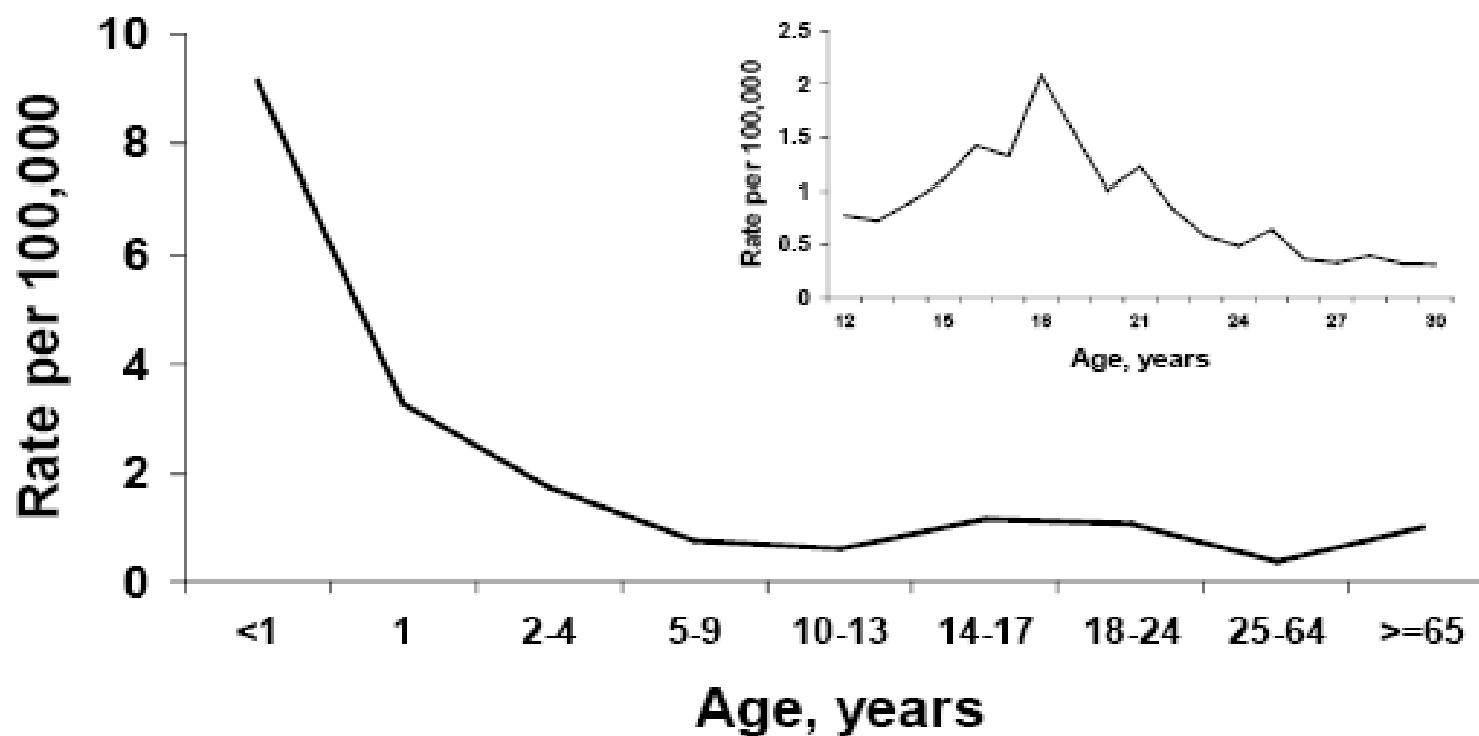
**\* Klugmann et al *Pediatr Infect Dis J* 2008;27:671**

**\*\*Tsai et al *Clin Infect Dis* 2008;46:1673**

## **MENINGOCOCCAL MENINGITIS**

- x Incidence is sporadic; small outbreaks can occur. Group B, C and in Y strains most common in US**
- x CFR is +/- 5%, worse in outbreaks. Long-term morbidity is +/- 10%**
- x Incidence highest in infancy and in late adolescence**
- x Serogroup X strain caused outbreaks in Burkina Faso and Niger and W135 in S Africa**

Figure. U.S. rates of meningococcal disease by age, 1991-2002\*



\* Active Bacterial Core surveillance data

Source: CDC. Prevention and control of meningococcal disease. MMWR 2005;54(RR-7):1-21

## **Factors Affecting Antibiotic Therapy for Meningitis**

- x Lack of antibodies and complement in CSF**
- x Very high titers of bacteria in CSF**
- x Poor CSF penetration of many antibiotics**
- x Resistance of meningeal pathogens, especially in developing countries (e.g. pen and chloro)**
- x Dosage regimens must be based on robust PK/PD data from animals models  $\hat{U}$  humans (many FDA approved drugs have not been adequately studied)**

## Criteria for Diagnosing Bacterial Meningitis\*

- x **Indices applied:** 1. Positive CSF Gram stain; 2. CSF ANC >1000 cells/ $\mu$ l; 3. CSF protein >80 mg/dl; 4. Peripheral ANC >10,000 cells/ $\mu$ l and 5. Seizure before or at admission.
- x Based on 3295 children with pleocytosis, the sensitivity was 98% and specificity was 62%. However, **NPV was 99.9% if no risk factors**

\***Pediatr Emerg Care 2009; 29:112**

# TREATMENT OF NEONATAL MENINGITIS

## INITIAL EMPIRIC REGIMENS

<b>Early onset</b>	<b>Ampicillin + aminoglycoside or cefotaxime</b>
<b>Late onset</b>	<b>Term. infant same as above</b>
<b>LBW/preterm</b>	<b>Antistaphylococcal + amikacin or cephalosporin</b>

## WHEN ETIOLOGY IS KNOWN

<b>Group B strep</b>	<b>Ampicillin</b>	<b>+/-</b>	<b>aminoglycoside</b>
<b>Coliforms</b>	<b>Cefotaxime</b>	<b>+/-</b>	<b>aminoglycoside</b>
<b>Pseudomonas</b>	<b>Ceftazidime</b>	<b>+/-</b>	<b>aminoglycoside</b>
<b>Listeria</b>	<b>Ampicillin</b>	<b>+/-</b>	<b>aminoglycoside</b>

## MANAGEMENT OF NON-NEONATAL MENINGITIS

- x Vancomycin (60-80 mg/kg/d) initially & CTX or CTR until results of culture and susceptibility testing available (resistant pneumococci continue to cause disease after PCV7)
- x Quinolones penetrate well and are effective for selected patients
- x Role of linezolid and daptomycin is unknown for MRSA CNS infections (nafcillin for MSSA)
- x Future role of ceftaroline?

# DURATION OF TREATMENT FOR UNCOMPLICATED BACTERIAL MENINGITIS\*

## NEONATES

GBS and other strep.	≥ 14 d
Gram neg. enterics	≥ 21 d
<i>Listeria</i>	10 d

## INFANTS AND CHILDREN

Meningococcus	4 d
<i>Haemophilus</i>	7-10 d
Pneumococcus	≥ 10 d

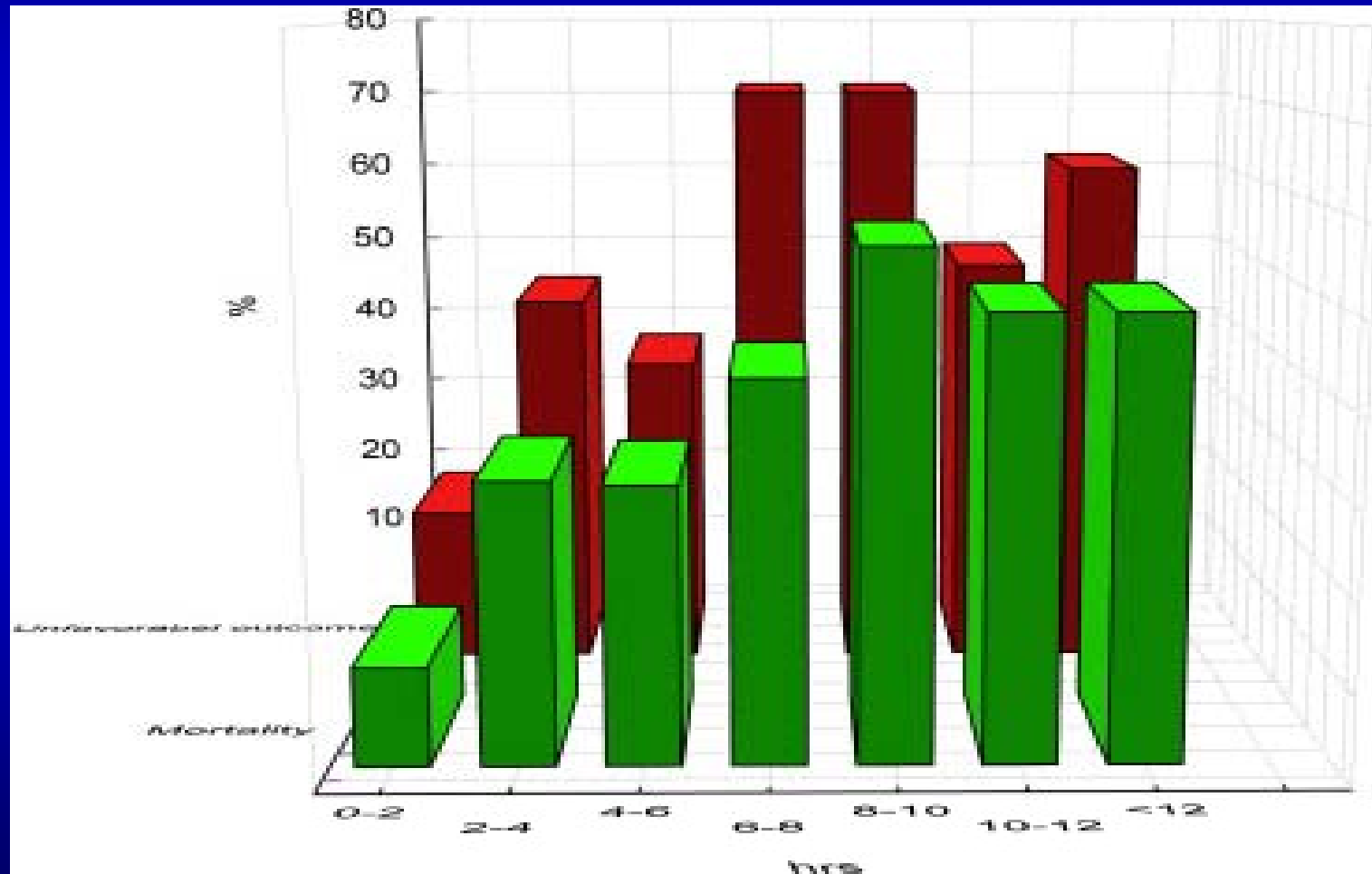
\* More an art than a science; studies indicate that outcome is similar with 4-7 vs 10-14 days of Rx

## **FACTORS INFLUENCING OUTCOME FROM MENINGITIS**

- x Age**
- x Duration of meningitis before diagnosis**
- x Glasgow coma score on admission**
- x HIV status and bacterial etiology**
- x Concentration of bacteria or bacterial products in CSF at diagnosis**
- x WBC and glucose values in CSF**
- x Time to sterilization of CSF cultures**

## Mortality and Unfavorable Outcome Related to Treatment Delay in Bacterial meningitis\*

Delay was 1 h 39 min in children and 2 h in adults



\*J Infect 2008;57:449

## **“Killing Bacteria Softly”\***

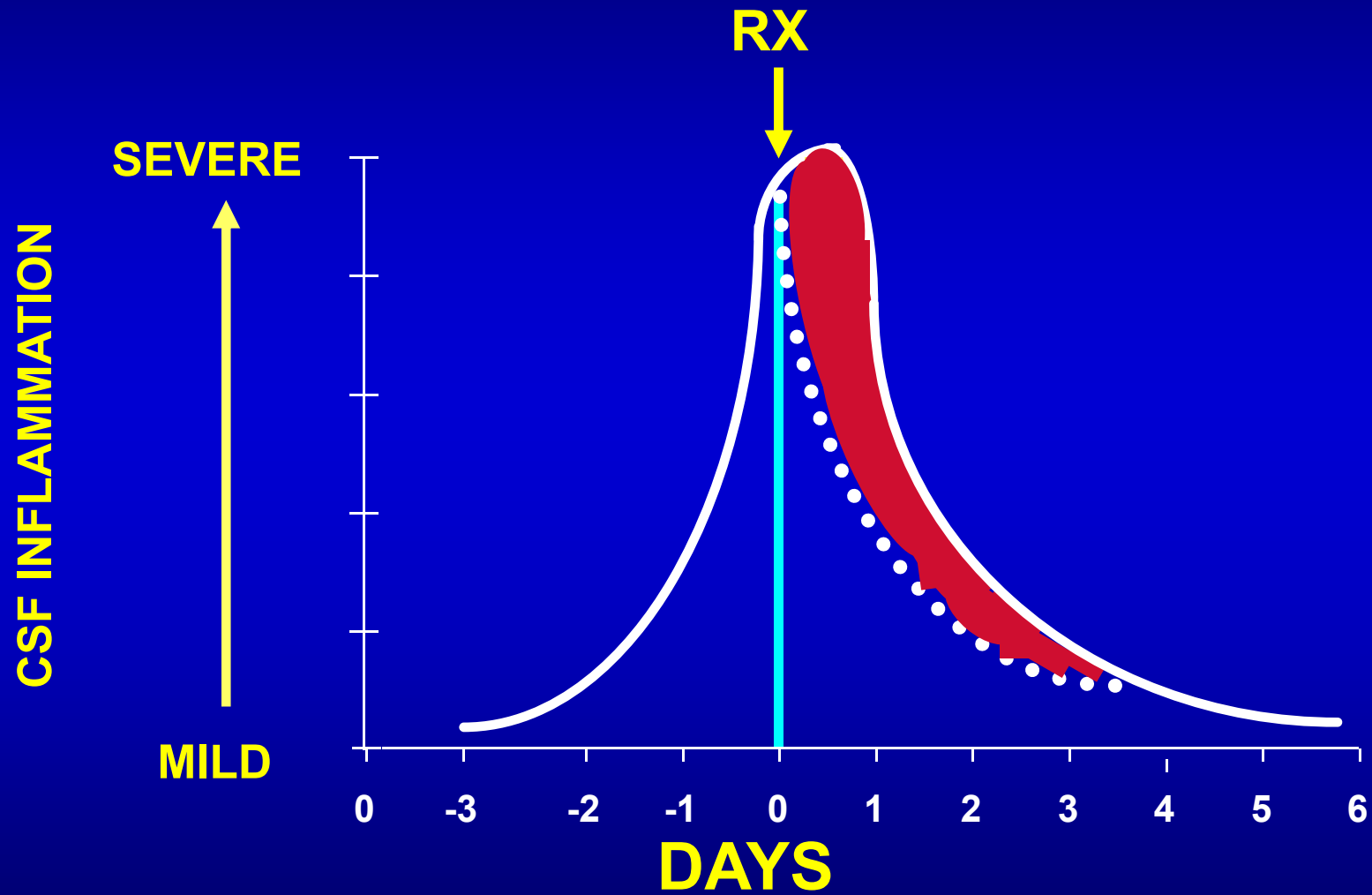
- x Many antibiotics (e.g. CTR) cause disruption of bacterial cell walls & membranes resulting in release of inflammatory mediators into the CSF**
- x Rifampin given before CTR resulted in less mediator released and less brain damage vs CTR alone in the pneumococcal rabbit meningitis model**
- x Is this clinically applicable?**

**\*Crit Care Med 2009;37:2253 & 2317**

## DEXAMETHASONE THERAPY FOR MENINGITIS

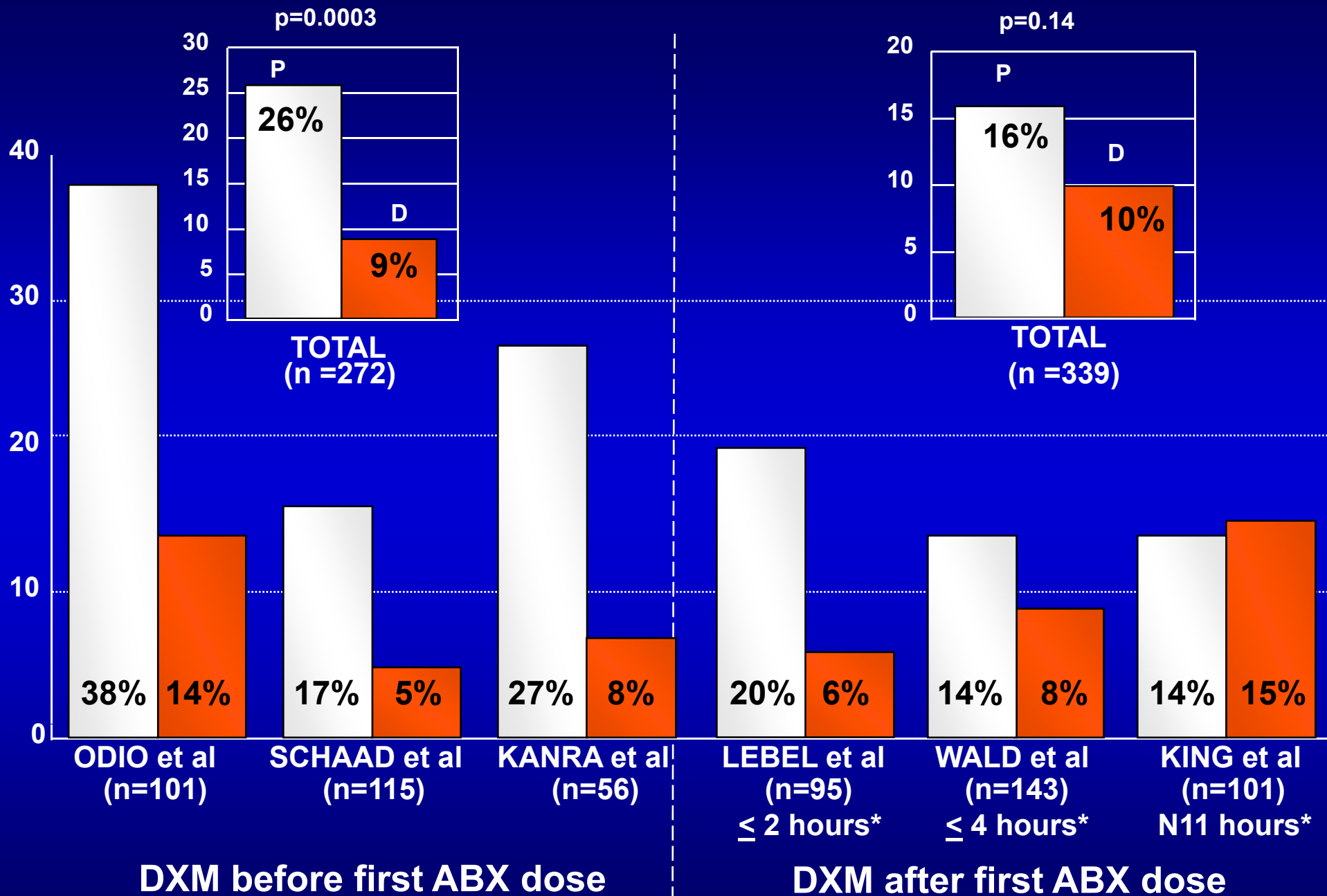
- x Regimen: 0.6 - 0.8 mg/kg daily in 2 or 3 divided doses for 2(or 4) days
- x First dose should be given **before or at the time** of the first parenteral antibiotic dose to impact **secondary inflammatory response** (> 12 hrs is too late)
- x Proven effectiveness in *Haemophilus* meningitis and likely effective for *S. pneumoniae* meningitis

# MENINGEAL INFLAMMATORY RESPONSE IN BACTERIAL MENINGITIS



RX: ANTIBIOTIC ———  
DEXAMETHASONE AND ANTIBIOTIC - - - -

**% PATIENTS WITH LONG-TERM SEQUELAE**



\* Time DXM given after first parenteral ABX dose

## **DXM vs Glycerol in Bacterial meningitis\***

- x 654 children studied in 10 LA centers**
- x Fewer severe neurologic sequelae were seen in those receiving glycerol (OR 0.31; 0.31- 0.76) or glycerol + dxm (0.39; 0.17-0.93) vs placebo**
- x A favorable effect of dxm was seen only for severe neurologic and hearing outcomes in those with H influenzae meningitis**
- x Provocative study that requires confirmation in children before prescribed routinely<sup>^</sup>**

**\* Clin Infect Dis 2007;45:1287; ^ Clin Infect Dis 2007;45:1287**

## “Glycerol in Bacterial Meningitis: One Strike and Out”\*

- x 265 Malawi adults with bacterial meningitis given glycerol or placebo and all got ceftriaxone
- x Interim analysis after 100 patients showed CFR of **63% vs 49% (p=0.003)** and convulsions in **50% vs 31% (p=0.002)** for glycerol vs placebo, respectively
- x Adjusted OR of dying: 2.4 (1.3-4.2,p=0.003) in glycerol-treated patients
- x Glycerol therapy can **not** be recommended for treatment of meningitis.

## **Clinical Predictors of Hearing Loss in Children with Bacterial Meningitis\***

- x 171 identified; 41 (31%) had at least a unilateral, mild hearing loss (36% S pn, 24% N men)**
- x Predictors included length of hospitalization, seizures, increase CSF protein & decrease CSF glucose, especially for pneumococcal meningitis**
- x Relatively little change on follow up audiometry**

**\*Arch Otolaryngol Head Neck Surg 2006:132:941**

## **Effect of bacterial meningitis during infancy on educational achievement in adolescence\***

- x Case-control study of 461 teenagers with past meningitis and 289 age-matched controls**
- x 8% of cases in special education vs no controls**
- x 25% of cases vs 6.6% of controls failed to pass any of their educational achievement exams in 5 key subject areas at 16 yrs of age**
- x At 5 yrs cases who were neurologically WNL did no better at 16yrs than did those with disabilities**

**\*De louvois, J et al Arch Dis Child 2007;92:959**

## **Long-Term Sequelae of Bacterial Meningitis\***

- ❖ **Worldwide literature review from Jan 1970- Jan 2010**
- ❖ **Of 1433 survivors who were evaluated, most at 10 years or longer after discharge, 705 (49%) had  $\geq 1$  sequelae**
  - 45% had behavioral and/or intellectual disorders**
  - 14% had neurological deficits**
  - 7% had abnormal hearing**
- ❖ **Conclusions: Outcome varies by etiology, age, area of world and availability of medical care**

**\*Chandran et al PIDJ 2011; 30: 3**

# PREVENTION OF MENINGITIS

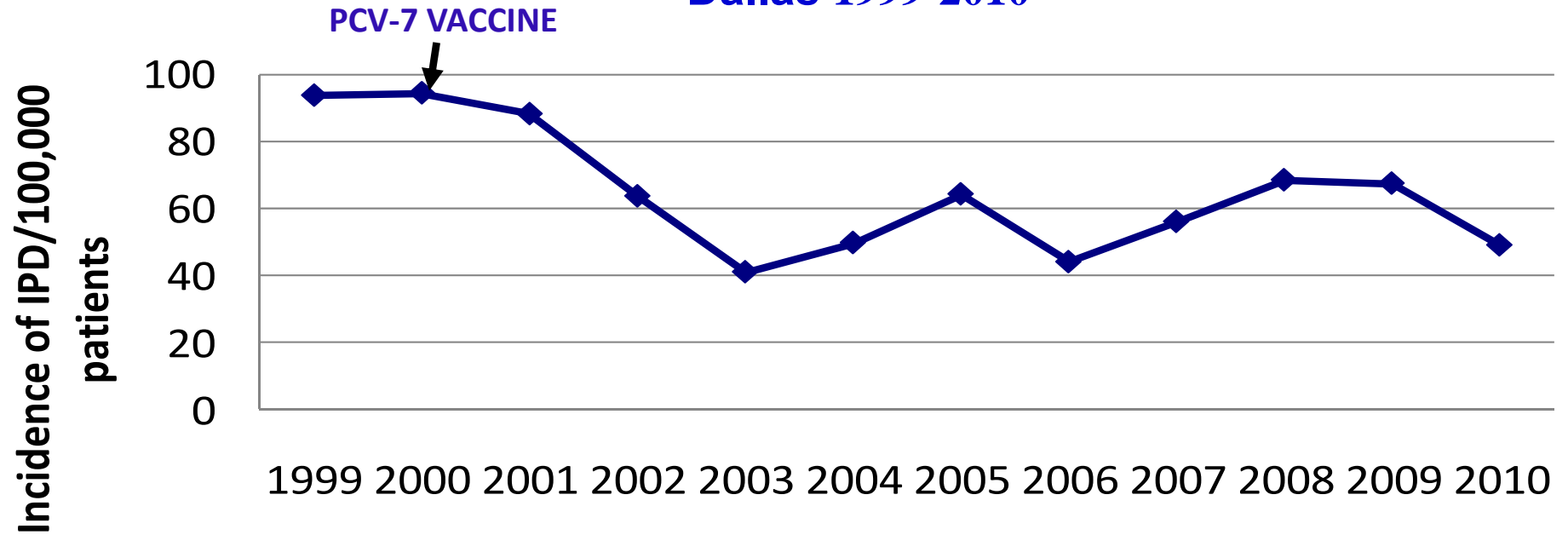
## Vaccination (conjugate vaccines)

- *Haemophilus* (> 99% effective)
- **Pneumococcal (> 95% effective)**
- Meningococcal C (>90% effective, UK)

## Chemoprophylaxis

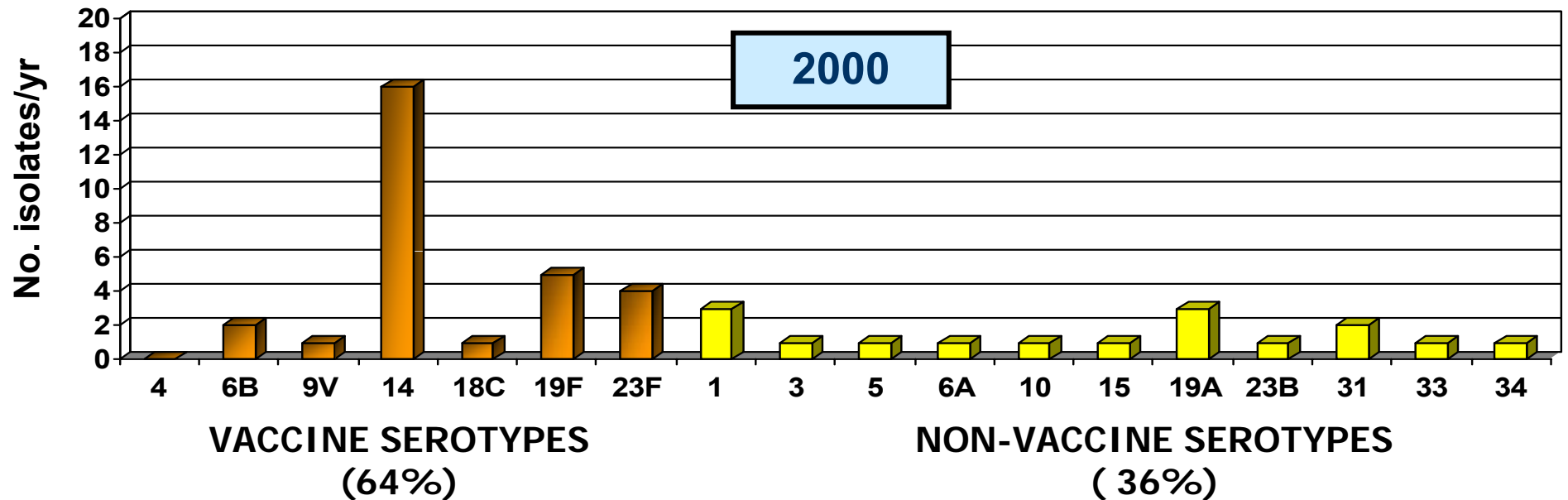
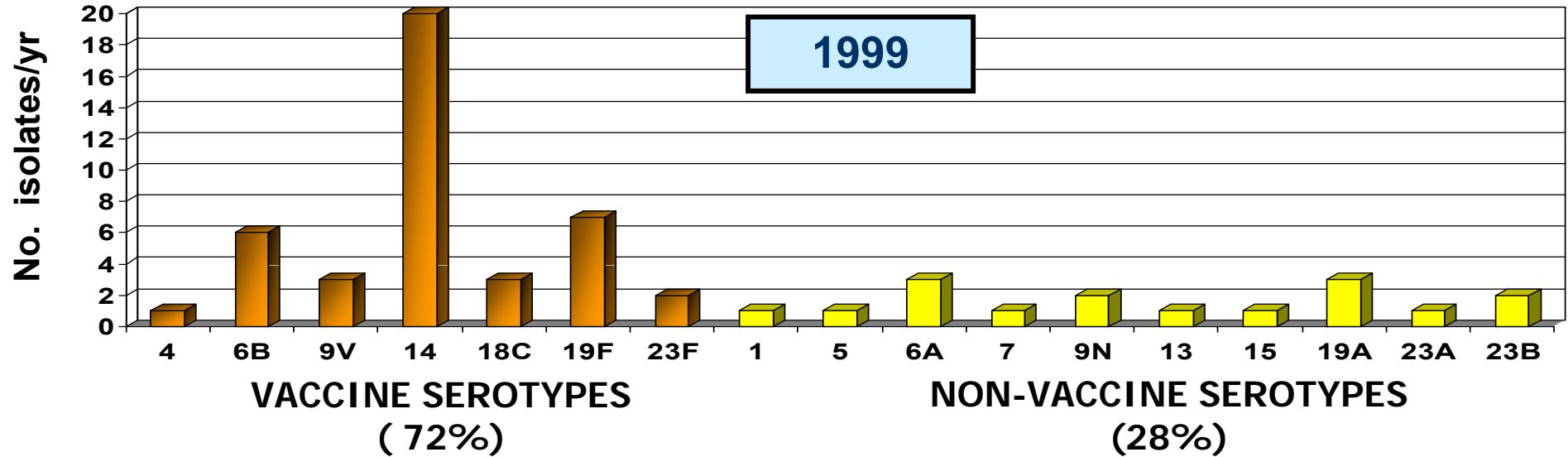
- Intrapartum penicillin- GBS (=/- 60% effective)
- Rifampin, CTR or FQ for *Haemophilus* and meningococcal infections(? FQ resistance)

## INCIDENCE OF PNEUMOCOCCAL MENINGITIS AT CMC Dallas 1999-2010

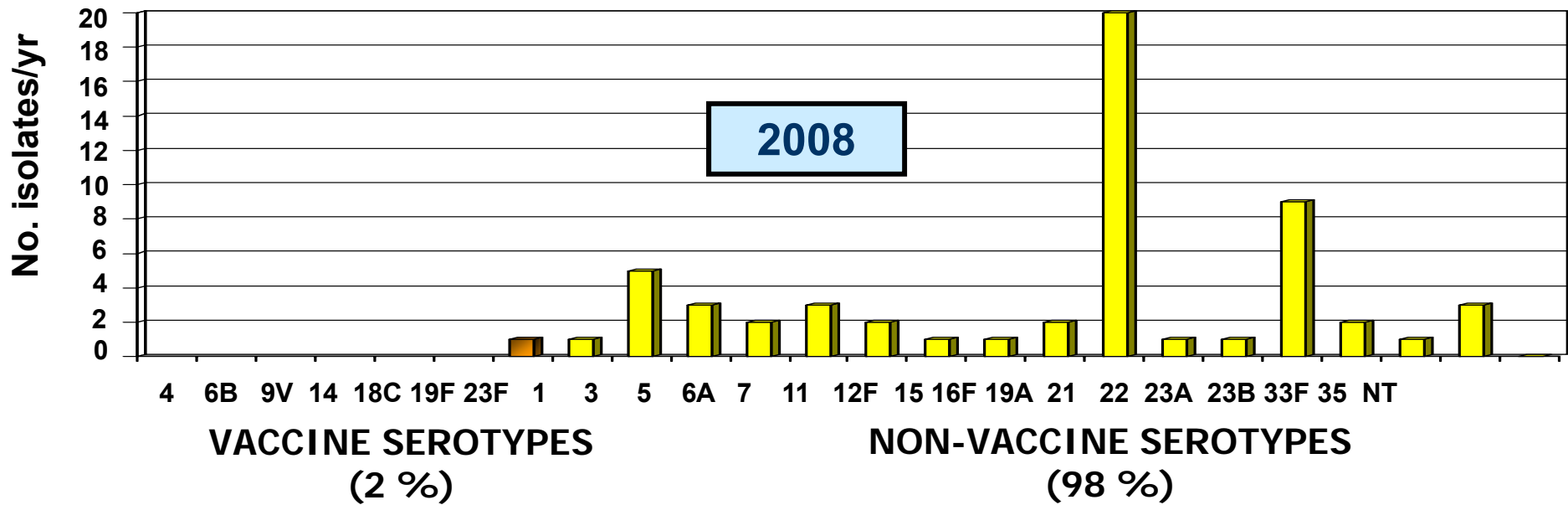
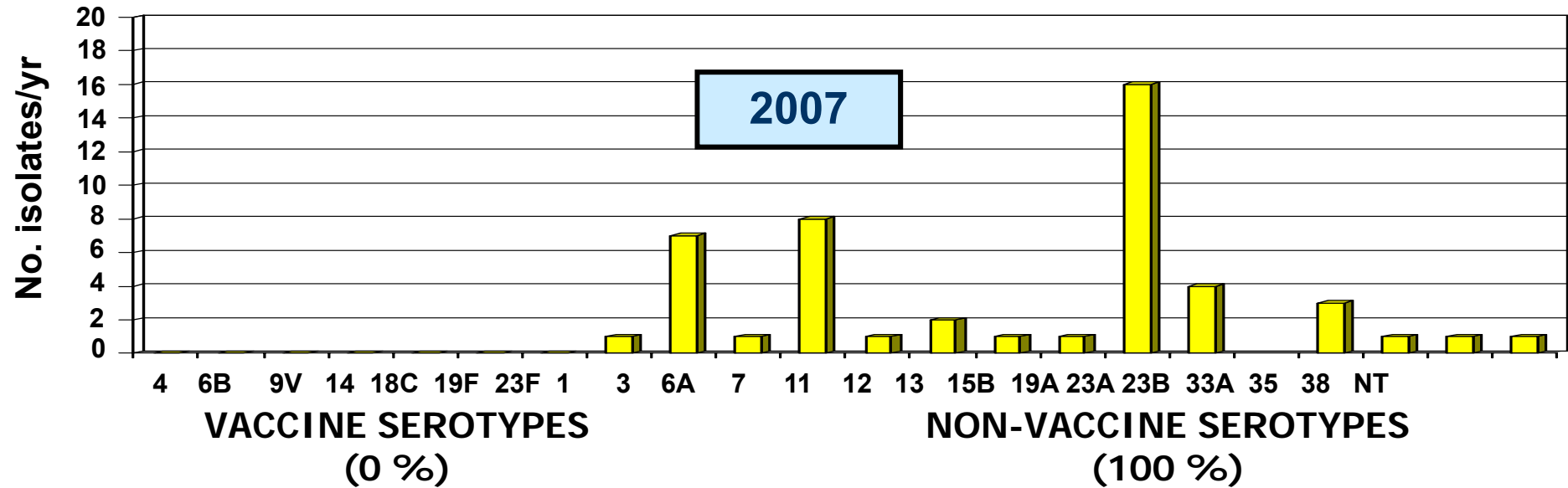


\* Denominator = ER admissions + Inpatient admissions by unique medical record number

# PCV7 vs. Non-PCV7 Serotypes



# PCV7 vs. Non-PCV7 Serotypes





# ASEPTIC MENINGITIS

- x Many etiologies
- x Far more frequent than bacterial meningitis
- x Enteroviruses account for +/- 90% of cases
- x Long-term outcome is usually good
- x Can be difficult to distinguish aseptic from bacterial meningitis in young infants
- x Diagnosis made by PCR

# ASEPTIC MENINGITIS: ETIOLOGIES\*

- x **Enteroviruses**
- x **Herpes simplex**
- x **HIV**
- x **EBV**
- x **Influenza viruses, including H1N1**
- x **Arboviruses**
- x **Others: CMV, toxoplasmosis, mumps, LCM**

\* ***Excludes Mycobacterium tuberculosis, Borellia and Bartonella***

## California Encephalitis Project 1998-2000\*

- x 334 patients with encephalitis studied using PCR, serologies and cultures for 15 possible etiologies
- x Confirmed/probable **infectious** causes, 42 (**13%**): viral, 31 cases (9%); bacteria, 9 (3%); parasitic, 2 (1%) Possible infectious causes, 41 (**12%**)
- x **Non-infectious** causes: 32 (**10%**)
- x Etiology unexplained in two-thirds of cases

\*Clin Infect Dis 2003; 36:731

## Conclusions

- x Bacterial meningitis is a serious problem, especially in the developing world
- x There is a need for new antibacterial agents
- x Conjugate vaccines will continue to reduce the incidence of disease
- x Aseptic meningitis is far more common
- x Etiology of encephalitis is often unknown



# **Importance of History for Diagnosis of Aseptic Meningitis**

- x Exposure to infected contacts, tick or mosquitoes**
- x Epidemiologic considerations**
- x Travel**
- x Animal bites or scratches**
- x Recent immunizations**
- x Medications**

## DELAYED CSF STERILIZATION AND OUTCOME IN BACTERIAL MENINGITIS\*

- x Pos. cultures at 18 – 48h: 8% (2 – 23%)
- x Higher rates of neurologic abnormalities at discharge (45% vs 19%) and at F/U (41% vs 13%), including mod – profound hearing impairment (35% vs 15%). Data apply mainly for *H influenzae* meningitis
- x Bacteriologic eradication is one measure of antibiotic success (surrogate endpoint)

\* **Lebel & McCracken Pediatrics 1989;83:161 (data derived from 4 studies)**

## **Dxm Therapy for Meningitis in 435 Vietnamese Adolescents and Adults\***

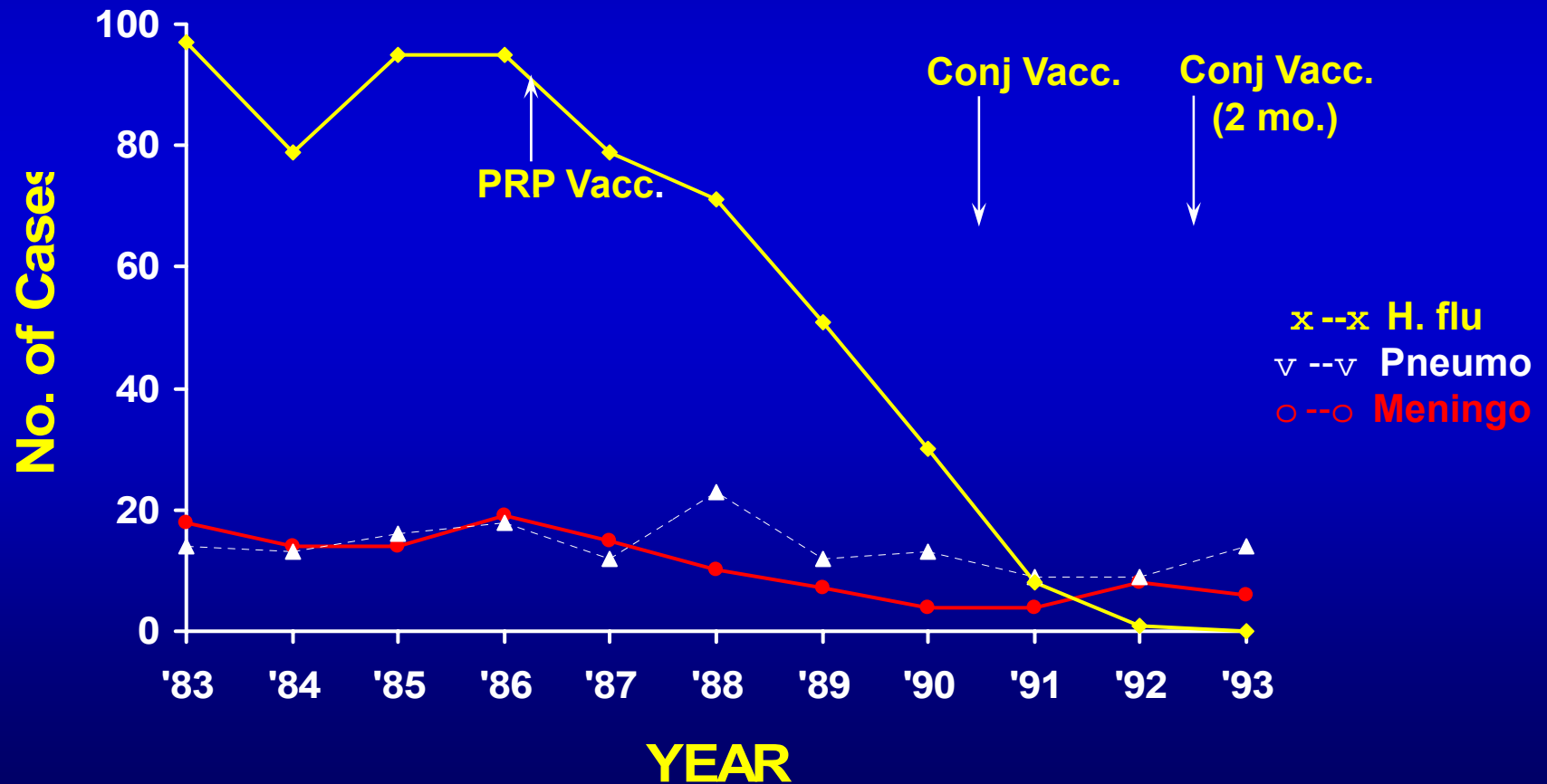
- x 300 patients with documented bacterial meningitis randomized to Dxm or placebo**
- x Risk of death reduced at 1 month (RR: 0.43; 95%CI 0.2- 0.9)**
- x Risk of death or disability reduced at 6 months ( OR: 0.56; 95% CI 0.32- 0.98)**

**\*NEJM 2007; 357:2431**

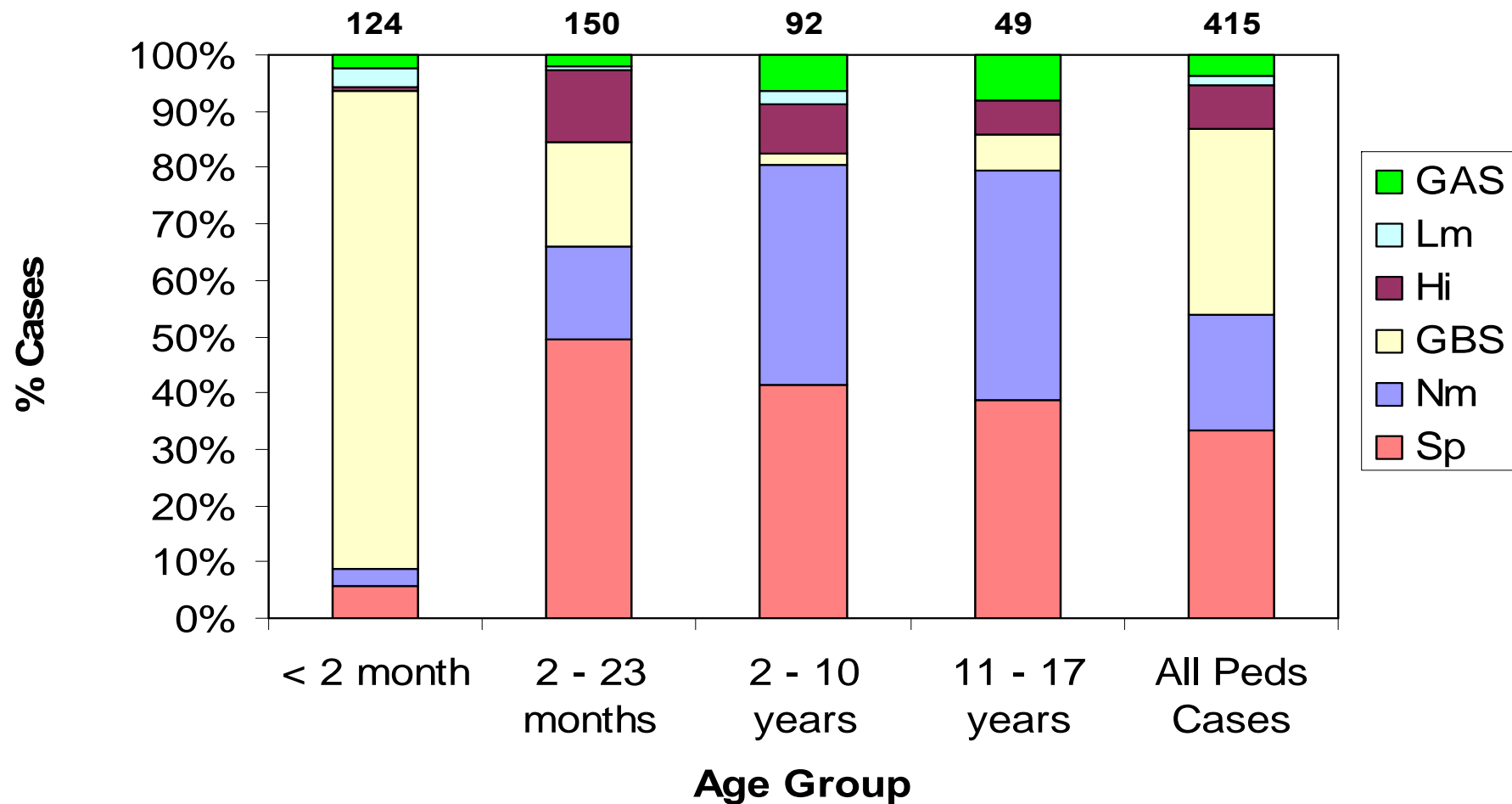
# BACTERIAL MENINGITIS CHILDREN'S MEDICAL CENTER, DALLAS

Total Cases of Meningitis

151 124 141 174 119 121 86 58 27 29 44



# Etiology of Bacterial Meningitis in Pediatrics ABC Surveillance, CDC 2003-2005\*



\*M. Thigpen, CDC

# **DXM for *Streptococcus suis* Meningitis**

## **Subset analysis of meningitis in adults in Vietnam\***

- x 151 patients treated with CTR and either DXM or placebo for 4 days**
- x Severe deafness (>80 dB loss) assoc directly with age >50 yrs & carrying the *epf* gene and inversely with DXM therapy (OR, 0.23; 0.06-0.78)**
- x >80 dB loss at discharge was 15.5% vs 33.3% and at 6 month F/U, 9.8% vs 21.7% favoring DXM therapy**

**\* Clin Infect Dis 2008;46:659**

# **Bilateral Hearing Impairment in 374 Children with Bacterial Meningitis**

## **(Subanalysis of Latin American data\*)**

- x Admission Glasgow Coma Score of < 15 predicted hearing loss at >40, 60 and 80 dB ORs of 1.18-1.19 (95% CI 1.01-1.34)**
- x Age was inversely correlated with mild-mod loss**
- x “Neither dexamethasone or glycerol alone or the combination of the 2 agents prevented hearing impairment (measured at 80, 60, or 40 dB), regardless of the causative organism or timing of adjunctive therapy”\***

**\*Heikki Peltola: unpublished data**

## **Long-term Outcome of Pneumococcal meningitis\***

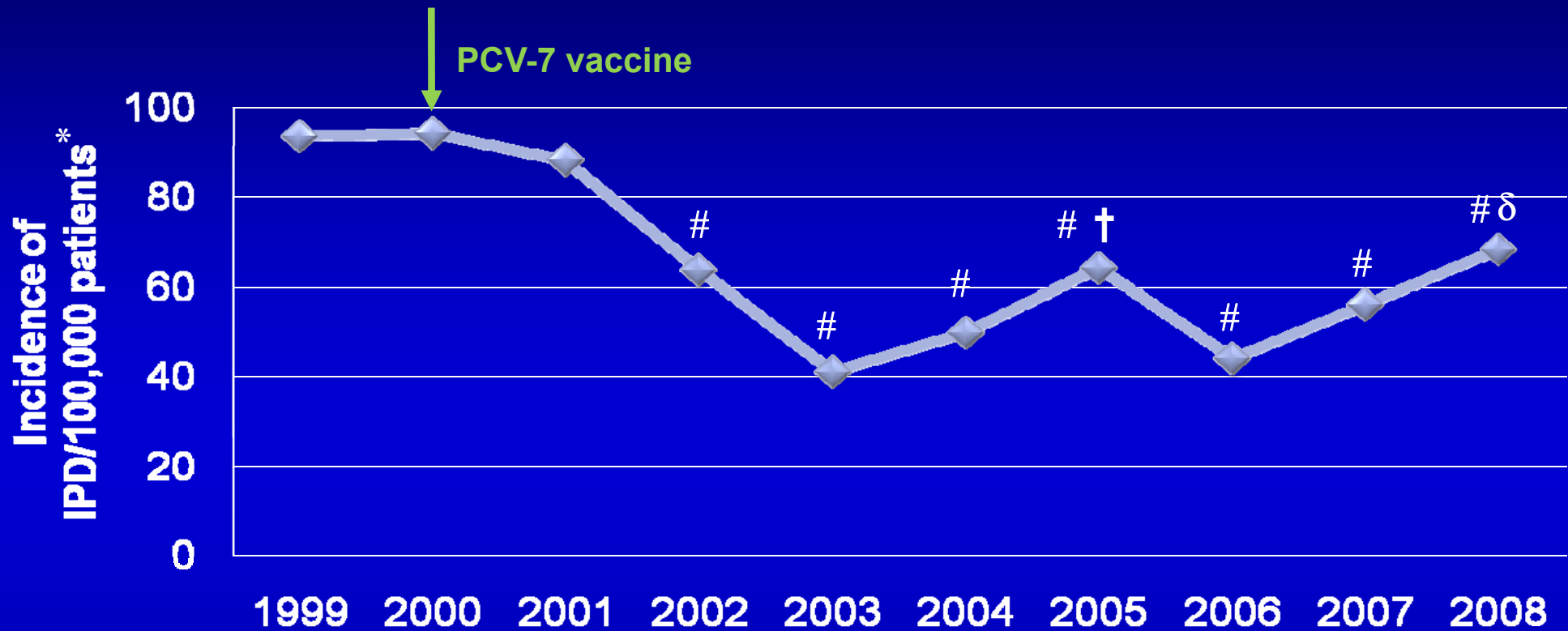
- x Population-based, case-control study in 2 areas of UK; 97 cases <14 yrs; 93 controls were sibs or neighbors; neuropsychologic and hearing testing performed**
- x Hearing impairment in 14% of cases (1% controls)**
- x Patients had significantly lower IQ scores, total quality of life, school & psychosocial functioning, and psychologic difficulties**
- x Conclusions: Pneumococcal meningitis is associated with major sequelae**

## Changing Epidemiology of Pneumococcal Meningitis after PCV7 Introduction\*

- x Annualized rate of meningitis hospitalizations per 100,000 admissions( 1994-9 vs 2000-4):
  - <2 year old: 7.7 to 2.6 (↓66%)
  - 2-4 year olds: 0.9 to 0.5 (↓52%)
  - >65 years: 1.2 to 0.8 (↓35%)
- x The rates dropped for meningococcal meningitis during these 2 periods: 54%, 47% and 23%

\*Clin Infect Dis 2008;46:1164 from Nationwide Inpatient Sample database

## Incidence of IPD at CMCD 1999-2008



\* Denominator = ER admissions + Inpatient admissions by unique medical record number

#  $P < 0.05$  Incidence IPD compared with 1999-2000

†  $P = 0.048$  Incidence IPD in 2003 VS 2005

δ  $P = 0.038$  Incidence IPD in 2006 VS 2008

Cochran-Armitage Trend Test for trend analysis,  $p < 0.001$

# Pneumococcal Meningitis at CMCD 1999-2008

