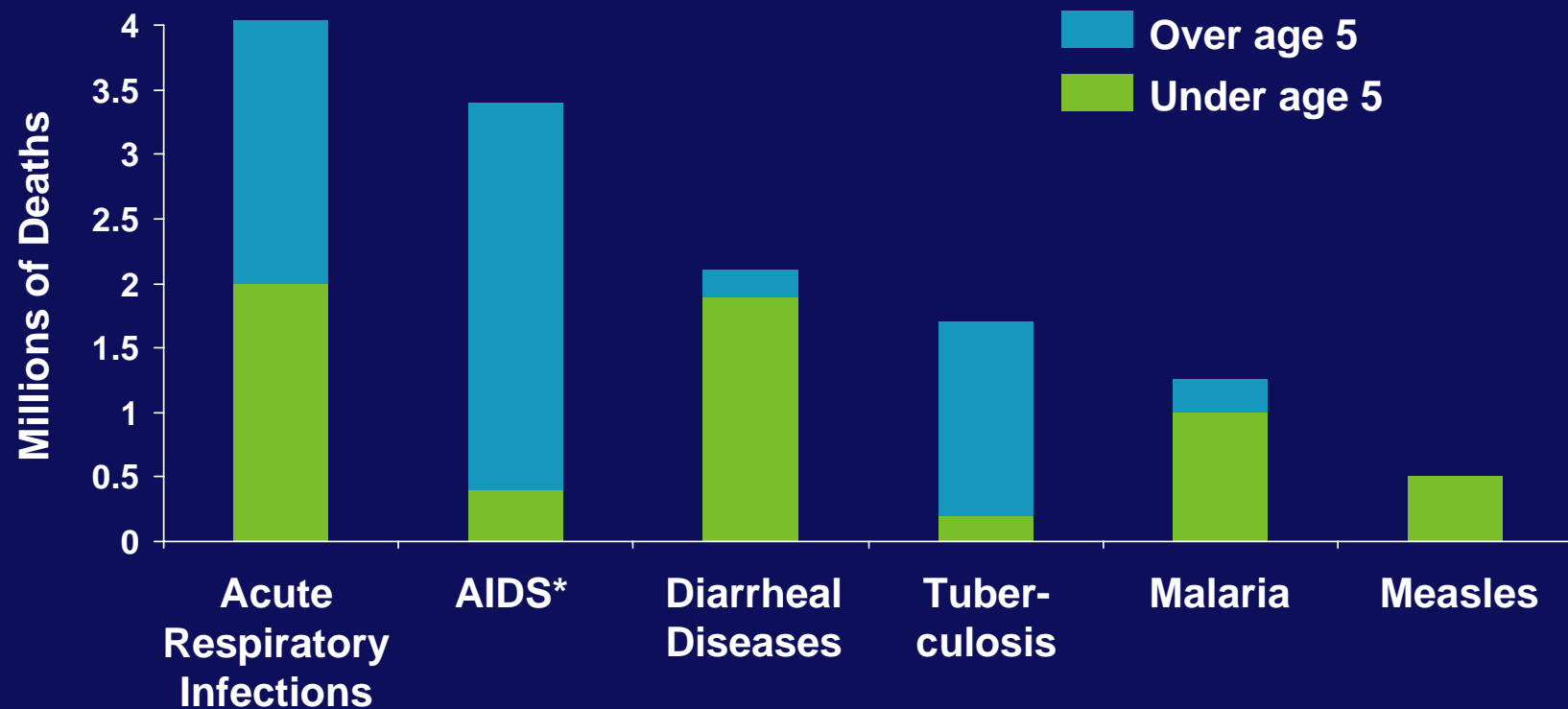




# Risk Factors for Antibiotic Resistance

Keith P. Klugman, MD, PhD

# Acute Respiratory Infections: The Leading Infectious Cause of Death



\*HIV-positive people who have died with tuberculosis have been included among AIDS deaths.

Estimates for adults, 2002; children < 5 years of age, 2000-2003; World Health Report, 2004-2005.

# Factors Influencing the Selection of Antibiotic-Resistant Pneumococci

- **Age**
- **Site of specimen**
- **Hospitalization**
- Antibiotic use
  - National, individual
  - Dose and duration of therapy
  - Therapy with cross-reacting molecule
- Day care
- Clonal spread
- HIV
- Mechanisms of resistance
- Conjugate vaccine

# Risk Factors for Penicillin-Resistant Pneumococcal Infections

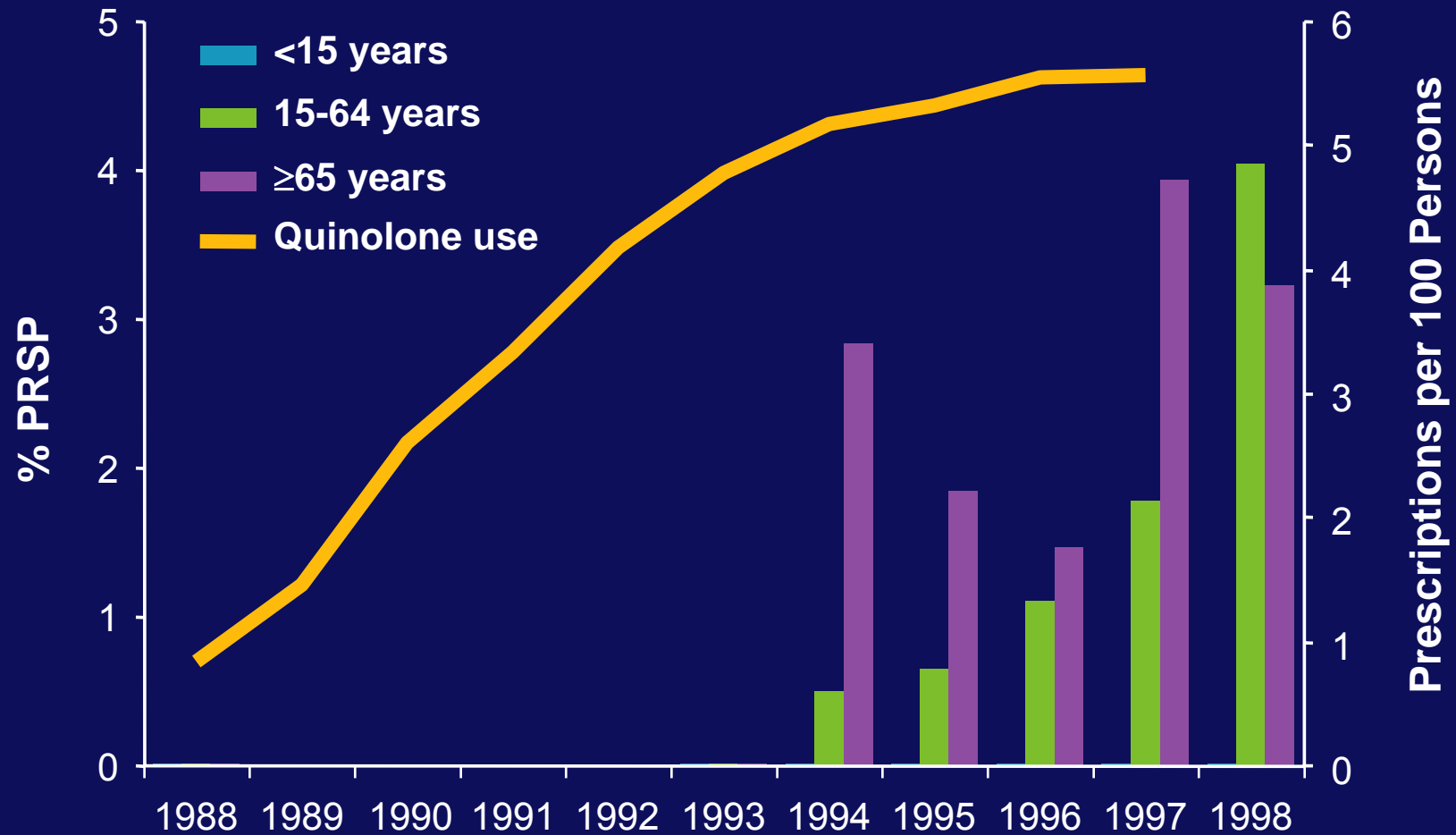
- French retrospective study on 10,350 isolates

Risk Factor	Odds Ratio
Age <15 years	2.01
Isolation from URT	2.36
Isolation from sinus and middle ear	1.63
HIV infection	2.01
$\beta$ -lactam R <sub>x</sub> in prev. 6 months	1.99
Nosocomial acquisition	2.12

URT = upper respiratory tract.

Bedos JP, et al. *Clin Infect Dis.* 1996;22:63-72.

# Fluoroquinolone Use and PRSP, Canada, 1988-1998



PRSP = penicillin-resistant *Streptococcus pneumoniae*.

Chen DK, et al. *N Engl J Med*. 1999;341:233-239.

## Risk Factors for Acquisition of Levofloxacin-Resistant Pneumococci in Hong Kong

- Nosocomial origin – OR 16.2 (95% CI 2.1-122.2)  
 $P = 0.007$
- Exposure to an FQ in past 12 months – OR 10.7 (95% CI 1.6-71.2)  
 $P = 0.01$
- Presence of COPD – OR 10.3 (95% CI 1.6-66.2)  
 $P = 0.01$
- Residence in a nursing home – OR 7.4 (95% CI 1.5-35.1)  $P = 0.01$

OR = odds ratio; FQ = fluoroquinolone; COPD = chronic obstructive pulmonary disease.

Ho PL, et al. *Clin Infect Dis.* 2001;32:701-707.

# Residence in a Long-Term Care Facility as a Risk for Fluoroquinolone Resistance, USA

- Patients admitted to hospital with pneumococcal bacteremia from long-term care facilities had higher rates of FQ resistance than did age-matched controls admitted from the community
- Cipro, levo  $\geq 4$ , gati  $\geq 2$

FQ	LTCF % R	Community % R	P Value
Cipro	8.7	2.2	<0.01
Levo	4.2	0.4	<0.01
Gati	3.5	0.3	<0.01

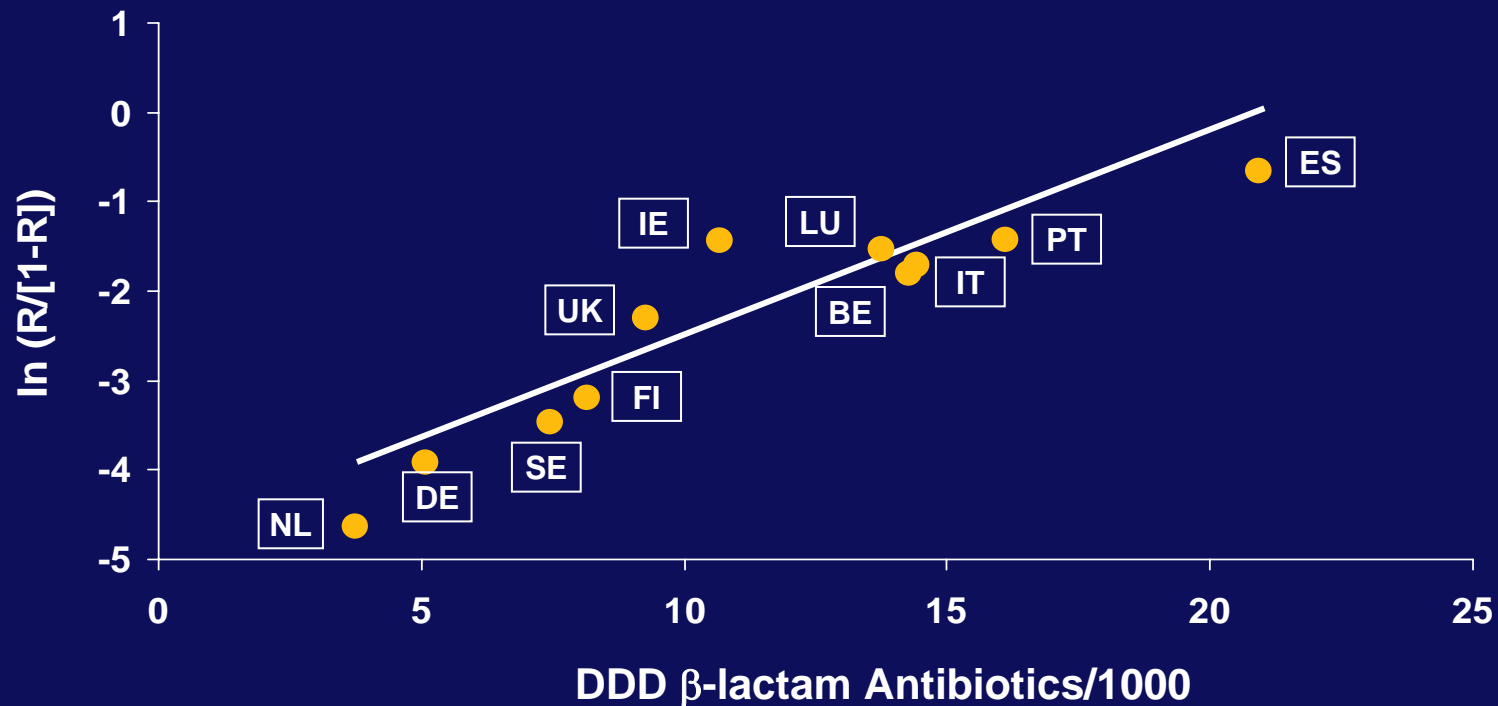
# FQ Resistance in Kids – A Warning From Africa?

- To date only a single report of FQ-resistant *Pneumococcus* from a child (apparent nosocomial transmission in a tuberculosis hospital in South Africa): von Gottberg A, et al. *Pediatr Infect Dis J.* 2003;22:1020-1021
- Ongoing surveillance of blood isolates of the *Pneumococcus* in adults and children in South Africa susceptibility testing was performed through July 2005 on 14,204 isolates. Of these only 14 (0.1%) were FQ-resistant, increasing from 0.05% in 2001 to 0.3% in 2005
- If this were the USA, none would be expected to be from children – 12/14 were children
- All HIV-infected, 9 known to be receiving treatment for tuberculosis and all 12 resistant also to rifampin (12/12 (100%) vs 254/5911 (4%),  $P < 0.001$ )
- Risk is exposure to hospitals where children are given FQ for multidrug-resistant tuberculosis

# Factors Influencing the Selection of Antibiotic-Resistant *Pneumococci*

- Age
- Site of specimen
- Hospitalization
- **Antibiotic use**
  - **National, individual**
  - **Dose and duration of therapy**
  - Therapy with cross-reacting molecule
- Day care
- Clonal spread
- HIV
- Mechanisms of resistance
- Conjugate vaccine

# Association of Antibiotic Use With Resistance in the *Pneumococcus*

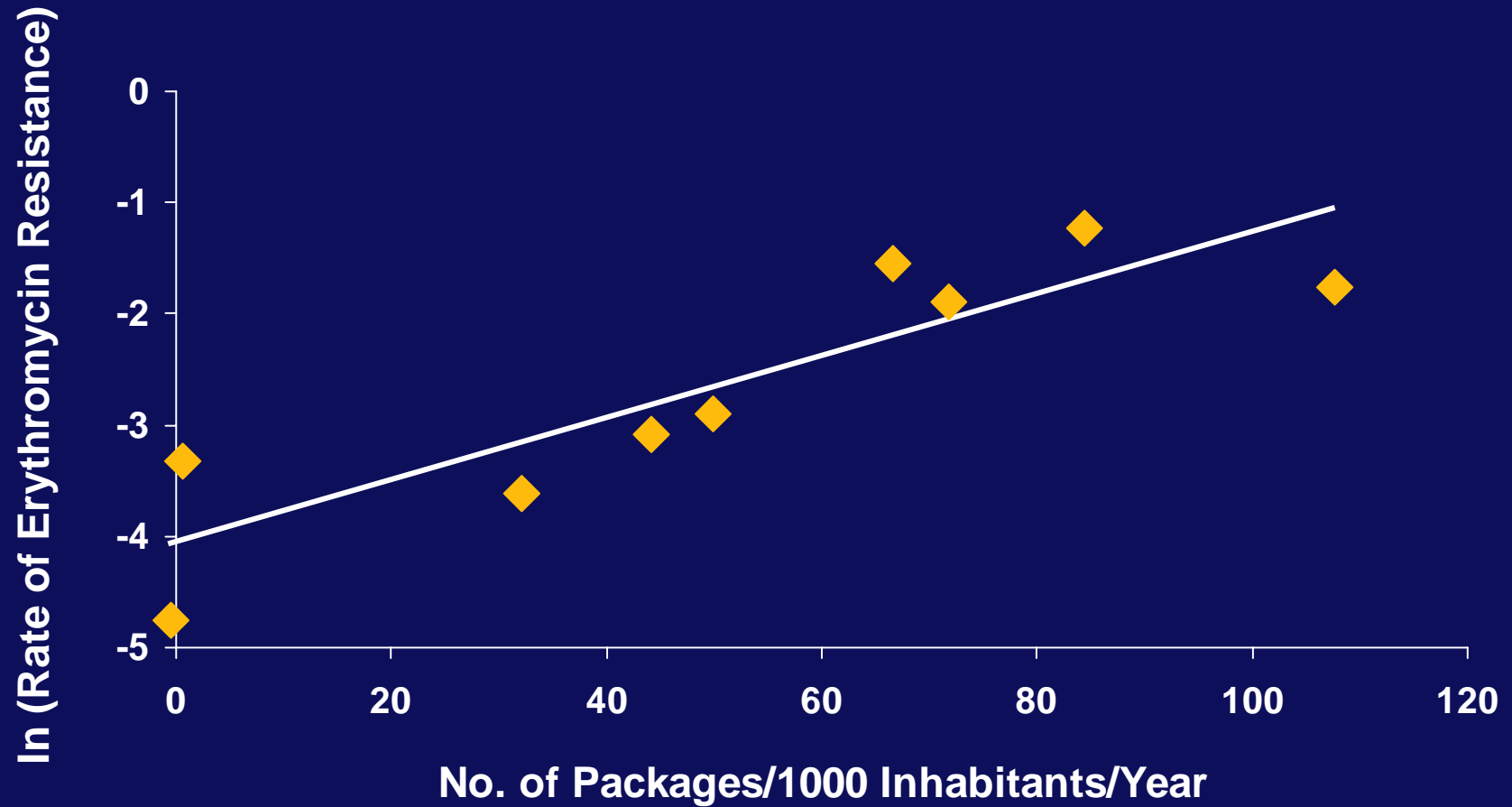


The log odds of resistance to penicillin among invasive isolates of *Streptococcus pneumoniae* (PNISP;  $\ln(R/[1-R])$ ) is regressed against outpatient sales of  $\beta$ -lactam antibiotics in 11 European countries

DDD = defined daily doses.

Bronzwaer S, et al. *Emerg Infect Dis.* 2002;8:278-282.

# Azithromycin Use vs Macrolide Resistance in Portugal



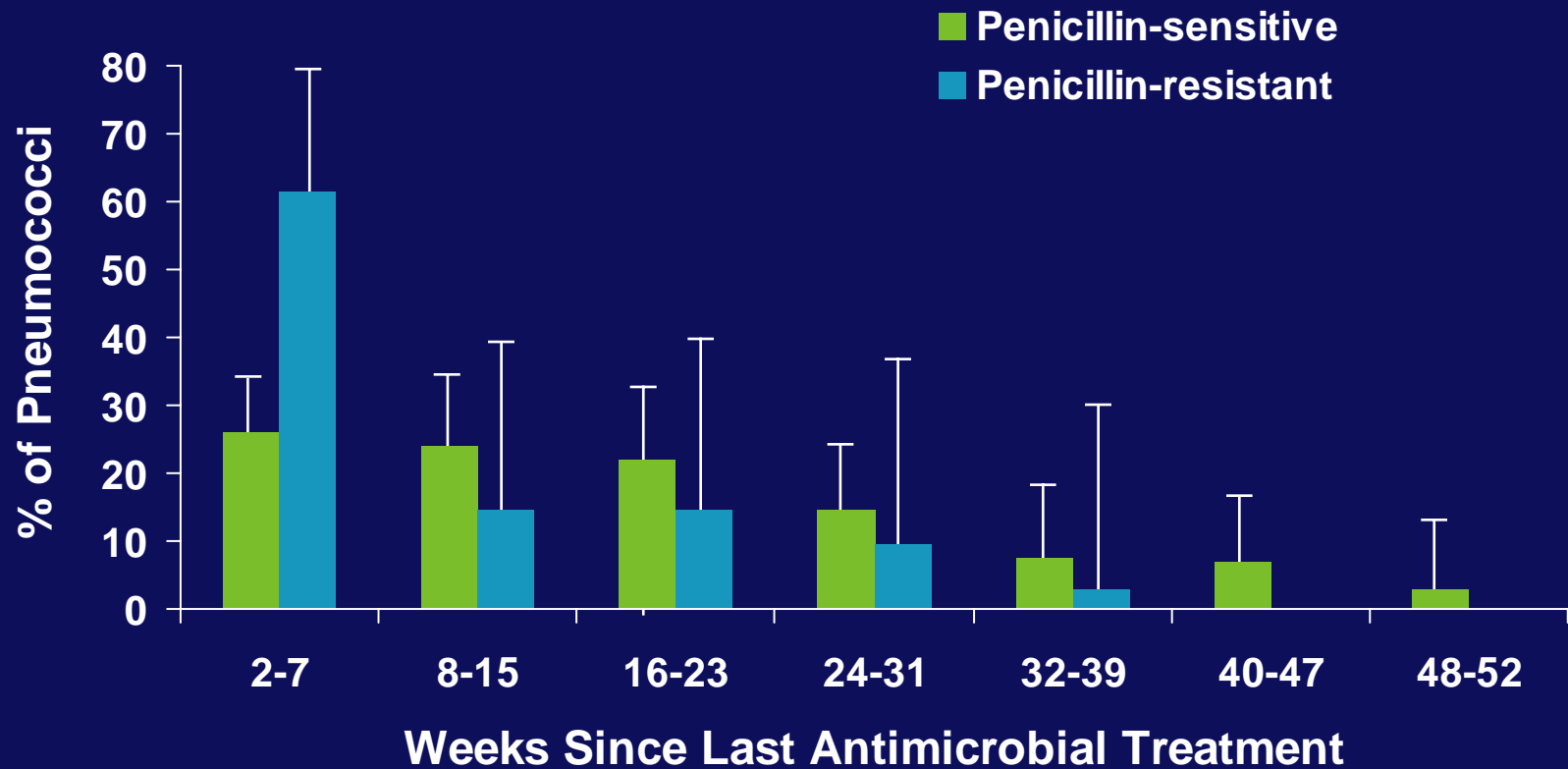
## Differences in Antibiotic Use and Resistance, Germany and France

Variable	France	Germany
Penicillin resistance	53	7
Macrolide resistance	47	4
No. office visits for common cold/1000 population	253	19
No. prescriptions/100 office visits for common cold	48.7	7.7
Prescriptions for common cold/1000 population*	123	1

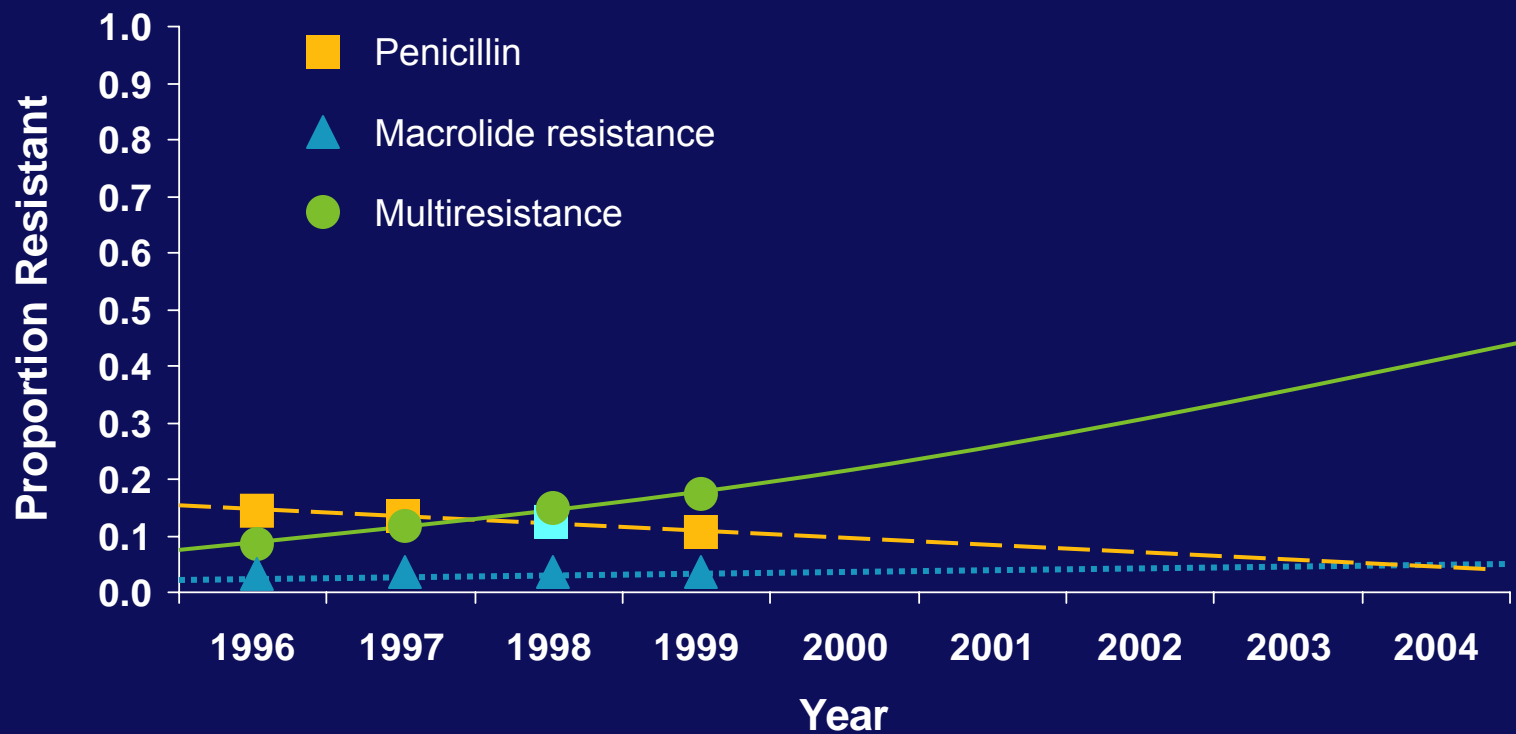
\*Calculated from figures above.

Harbarth S, et al. *Emerg Infect Dis.* 2002;8:1460-1467.

# Percentages of Penicillin-Sensitive and Penicillin-Resistant Pneumococci



# Model Predicting the Emergence of Dual Resistance in USA



# Selection of Resistant Pneumococci by High-Dose, Short-Duration Amoxicillin R<sub>x</sub>

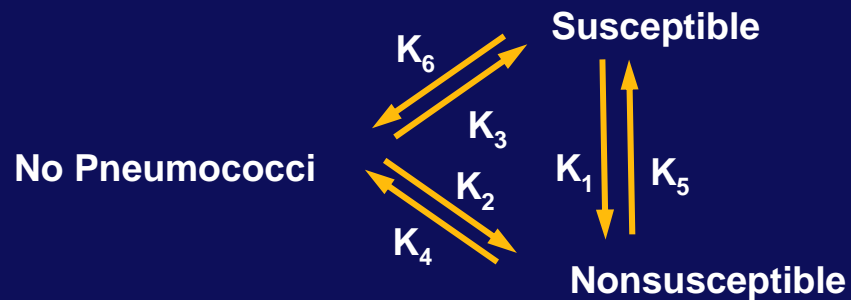
## Relative Risk of PRSP in Carriers

High dose vs low dose	0.78 (0.65-0.95)	<i>P</i> = 0.01
Day 28 vs day 0 high dose	1.22 (1.02-1.48)	<i>P</i> = 0.03
Day 28 vs day 0 low dose	1.60 (1.36-1.89)	<i>P</i> <0.001

# Factors Influencing the Selection of Antibiotic-Resistant *Pneumococci*

- Age
- Site of specimen
- Hospitalization
- Antibiotic use
  - National, individual
  - Dose and duration of therapy
  - **Therapy with cross-reacting molecule**
- Day care
- Clonal spread
- HIV
- Mechanisms of resistance
- Conjugate vaccine

# Impact of Fansidar Therapy for Malaria on Cotrimoxazole Resistance in the *Pneumococcus*

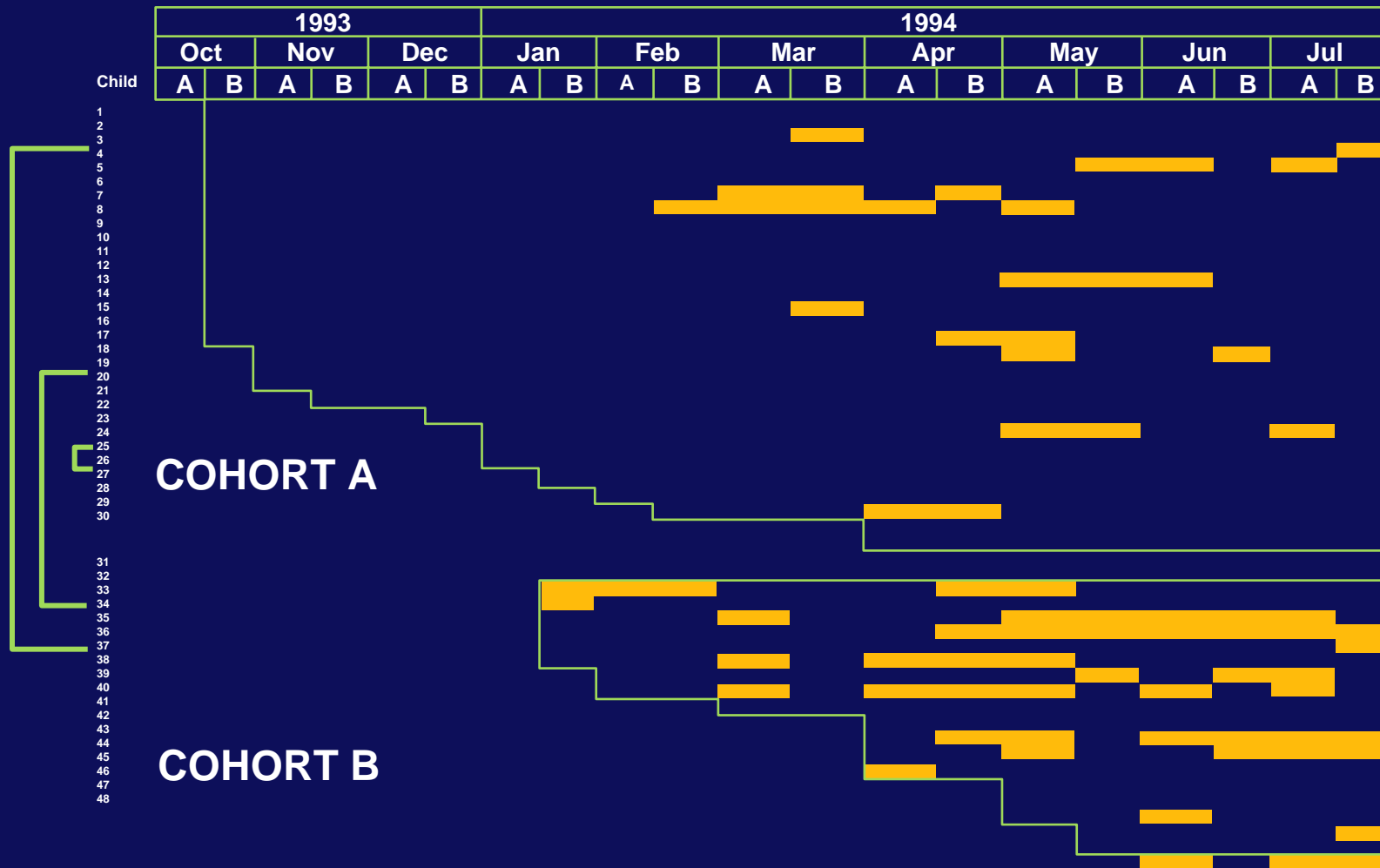


Transition Rate Between Initial Visit and 1-Week Visit		
	K1	
No treatment	6/50	(12%)
Cotrimoxazole	29/69	(42%)
Fansidar	29/96	(30%)

Transition Rate Between Initial Visit and 1-Week Visit		
	K1	
No treatment	2/24	(8%)
Cotrimoxazole	9/40	(23%)
Fansidar	28/73	(38%)

# Factors Influencing the Selection of Antibiotic-Resistant Pneumococci

- Age
- Site of specimen
- Hospitalization
- Antibiotic use
  - National, individual
  - Dose and duration of therapy
  - Therapy with cross-reacting molecule
- **Day care**
- **Clonal spread**
- HIV
- Mechanisms of resistance
- Conjugate vaccine



■ Isolation of *S. pneumoniae* 23F, intermediately susceptible to penicillin and resistant to trimethoprim-sulfamethoxazole

□ Siblings

Yagupsky P, et al. *J Infect Dis.* 1998;177:1003-1012.

# Multivariate Analysis of Risk Factors for Penicillin-Resistant Invasive *S. pneumoniae* Infections (52 Penicillin-Resistant Cases, 280 Control Subjects)

Age Group	Covariate	Adjusted OR *	95% CI
2-59 months	Recent day-care attendance	3.79	1.85-7.77
	At least one recent course of antibiotics	3.08	1.28-7.40
	At least one recent ear infection	2.38	1.05-5.42

\*Adjusted for age.

Levine OS, et al. *Pediatrics*. 1999;103:e28.

## Family Transmission of Resistant Strains

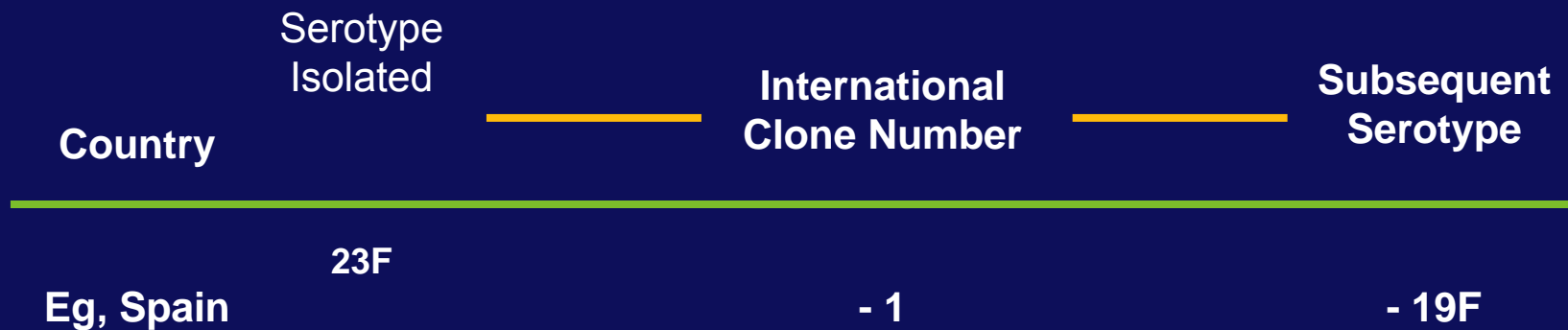
- In a multivariate model of risk factors for the acquisition of resistant (pen and/or erythro and/or TMP/SMX) pneumococcal carriage in children in Utah, US, the significant risk factors were
  - Cephalosporin use in previous 4 months  
OR **2.7**    95% CI 1.1-6.6     $P = 0.035$
  - Sibling carrying a resistant strain  
OR **7.5**    95% CI 0.7-20.7     $P < 0.001$

# Clonal Spread of *S. pneumoniae* 23F



# Pneumococcal Molecular Epidemiology Network of the IUMS

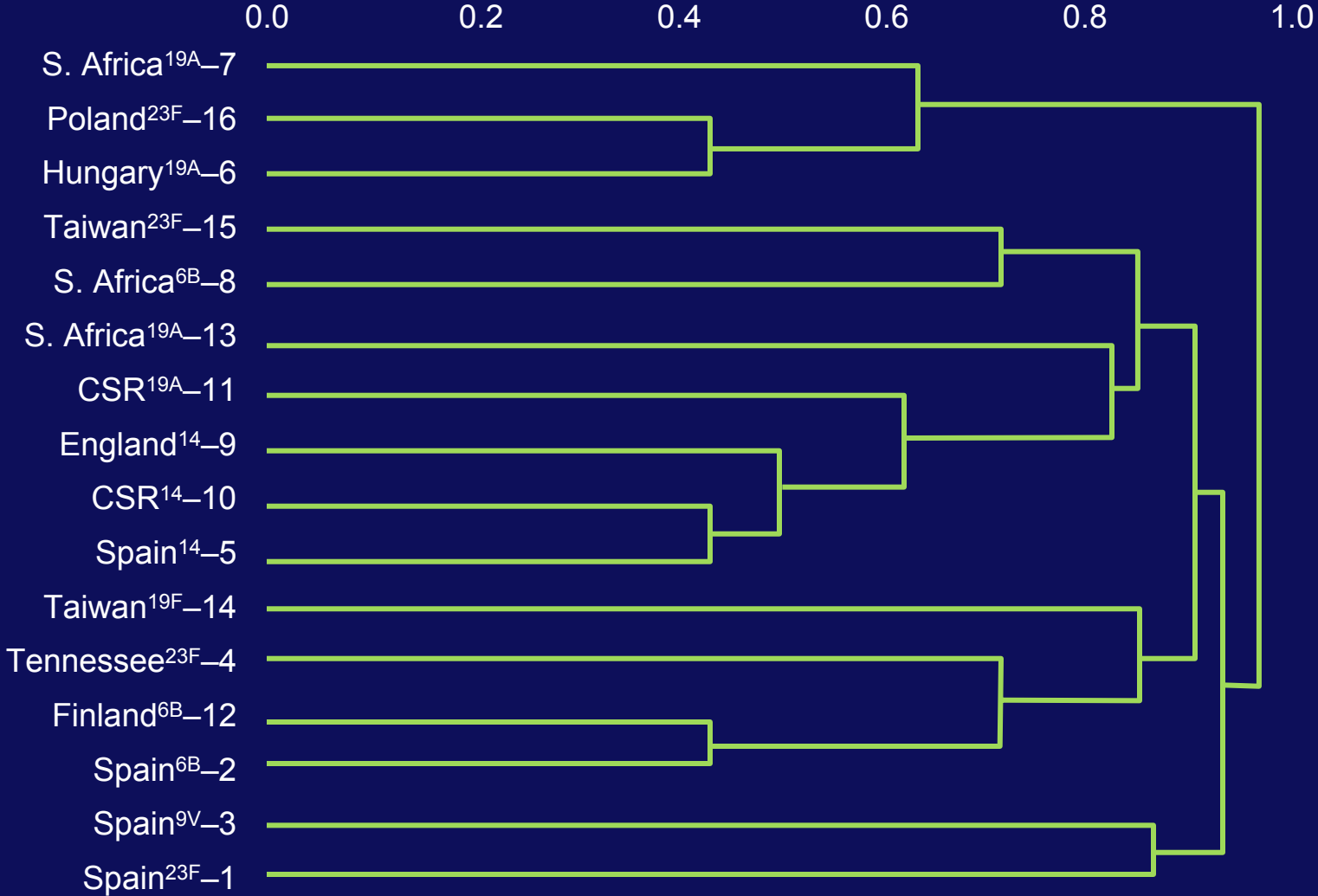
## Nomenclature



IUMS = International Union of Microbiological Societies.

McGee L, et al. *J Clin Microbiol.* 2001;39:2565-2571.

# Linkage Distance



# Clones of Penicillin-Resistant *Pneumococci* in the US

<b>Spain<sup>23F</sup>-1 – 14,19</b>	127/328	38.7%
<b>Spain<sup>9V</sup>-3 – 14,19</b>	40/328	12.2%
Eight other clones	112/328	34.1%
The above ten clones	<b>279/328</b>	<b>85.0%</b>

# Clonality of Highly Penicillin-Resistant *Pneumococci* in the US

<b>Spain<sup>23F</sup>-1</b>	123/672	18.3%
<b>Spain<sup>9V</sup>-3</b>	96/672	14.3%
PFGE type 3	65/672	9.7%
<b>Spain<sup>6B</sup>-2</b>	44/672	6.5%
PFGE type 5	42/672	6.3%
<b>Tennessee<sup>23F</sup>-4</b>	33/672	4.9%
PFGE types 7-10	95/672	14.1%
<b>Taiwan<sup>19F</sup>-14</b>	11/672	1.6%
PFGE types 12,13	15/672	2.2%
12 clones	<b>524/672</b>	<b>78.0%</b>

PFGE = pulsed-field gel electrophoresis.

Richter SS, et al. *Clin Infect Dis*. 2002;34:330-339.

# Clones of Penicillin-Resistant *Pneumococci* in the US

<b>Spain<sup>23F</sup>-1 – 19</b>	23/144	16%
<b>Spain<sup>6B</sup>- 2</b>	4/144	3%
<b>Spain<sup>9V</sup>-3 – 9A,14</b>	40/144	28%
<b>Tennessee<sup>23F</sup>-4</b>	19/144	13%
<b>England<sup>14</sup>-9</b>	31/144	22%
Three other clones	17/144	12%
The above eight clones	<b>134/144</b>	<b>93%</b>

# Increase in FQ Resistance in the *Pneumococcus* in Hong Kong

- Two studies of sequential clinical isolates from 6 hospitals in Hong Kong – 1998 and 2000
- Levo MIC  $\geq 4$   $\mu\text{g/mL}$  –  $\uparrow$  from 5.5% to 13.3%
- In penicillin-resistant strains –  $\uparrow$  9.2% to 27.3%
- Risk factors were
  - Patients  $\geq 65$  y – 17.1% vs 9.1% (18-64 y) ( $P < 0.001$ )
  - Adults with COPD – 24.6% vs 9.3% ( $P = 0.01$ )
- All FQ-resistant strains are a clone of Spain<sup>23F</sup>-1 resistant to penicillin (MIC 2-4  $\mu\text{g/mL}$ ) and cefotaxime (MIC 1-4  $\mu\text{g/mL}$ )

# Factors Influencing the Selection of Antibiotic-Resistant *Pneumococci*

- Age
- Site of specimen
- Hospitalization
- Antibiotic use
  - National, individual
  - Dose and duration of therapy
  - Therapy with cross-reacting molecule
- Day care
- Clonal spread
- **HIV**
- Mechanisms of resistance
- Conjugate vaccine

# Impact of HIV on Penicillin Resistance in the *Pneumococcus*

Age	HIV+	HIV-
Adults	19/100 (19%)	11/259 (4%)
Children	24/45 (53%)	16/53 (30%)

## Emerging Problem

- Cotrimoxazole-resistant (and multiply-resistant) pneumococcal infections are more common in HIV-infected children and adults on prophylaxis with the drug

## Gender as a Risk Factor for Antibiotic Resistance: Independent Risk Factors in a Multivariate Model for Pneumococcal Bacteremia in Women

Variable	Odds Ratio	95% CI
Pediatric serotype	1.59	1.18-2.15
<b>Penicillin resistance</b>	1.65	1.06-2.59
HIV seropositive	1.85	1.26-2.71
Ages 18-39 vs $\geq 40$ years	1.72	1.25-2.36

# Factors Influencing the Selection of Antibiotic-Resistant *Pneumococci*

- Age
- Site of specimen
- Hospitalization
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  - Therapy with cross-reacting molecule
- Day care
- Clonal spread
- HIV
- **Mechanisms of resistance**
- Conjugate vaccine

# Amino Acid Substitutions in Sensitive and Resistant DHFRs

	NCCLS 69419E	14	20	60	65	70	74	77	78	81	91	92	94	100	111	135	147	149
<b>SENSITIVE</b>		E	E	K	I	P	I	V	A	Q	Q	D	E	I	P	L	F	A
	92				V							A						
	119											A			A			
	120		D									A						
	124											A						
<b>RESISTANT</b>																		
P1			D	Q		S				H		A		L	S	F		
P2	D		D			S	L			H	H	A	D	L		F	S	T
P3			D	Q				A	V			A		L		F		

Single-base mutation conferring resistance suggests rapid selection

DHFR = dihydrofolate reductase.

Adrian PV, Klugman KP. *Antimicrob Agents Chemother.* 1997;41:2406-2413.

# Factors Influencing the Selection of Antibiotic-Resistant *Pneumococci*

- Age
- Site of specimen
- Hospitalization
- Antibiotic use
  - National, individual
  - Dose and duration of therapy
  - Therapy with cross-reacting molecule
- Day care
- Clonal spread
- HIV
- Mechanisms of resistance
- **Conjugate vaccine**

# Impact of 9-Valent Conjugate Vaccine on Carriage of Antibiotic-Resistant *Pneumococci*

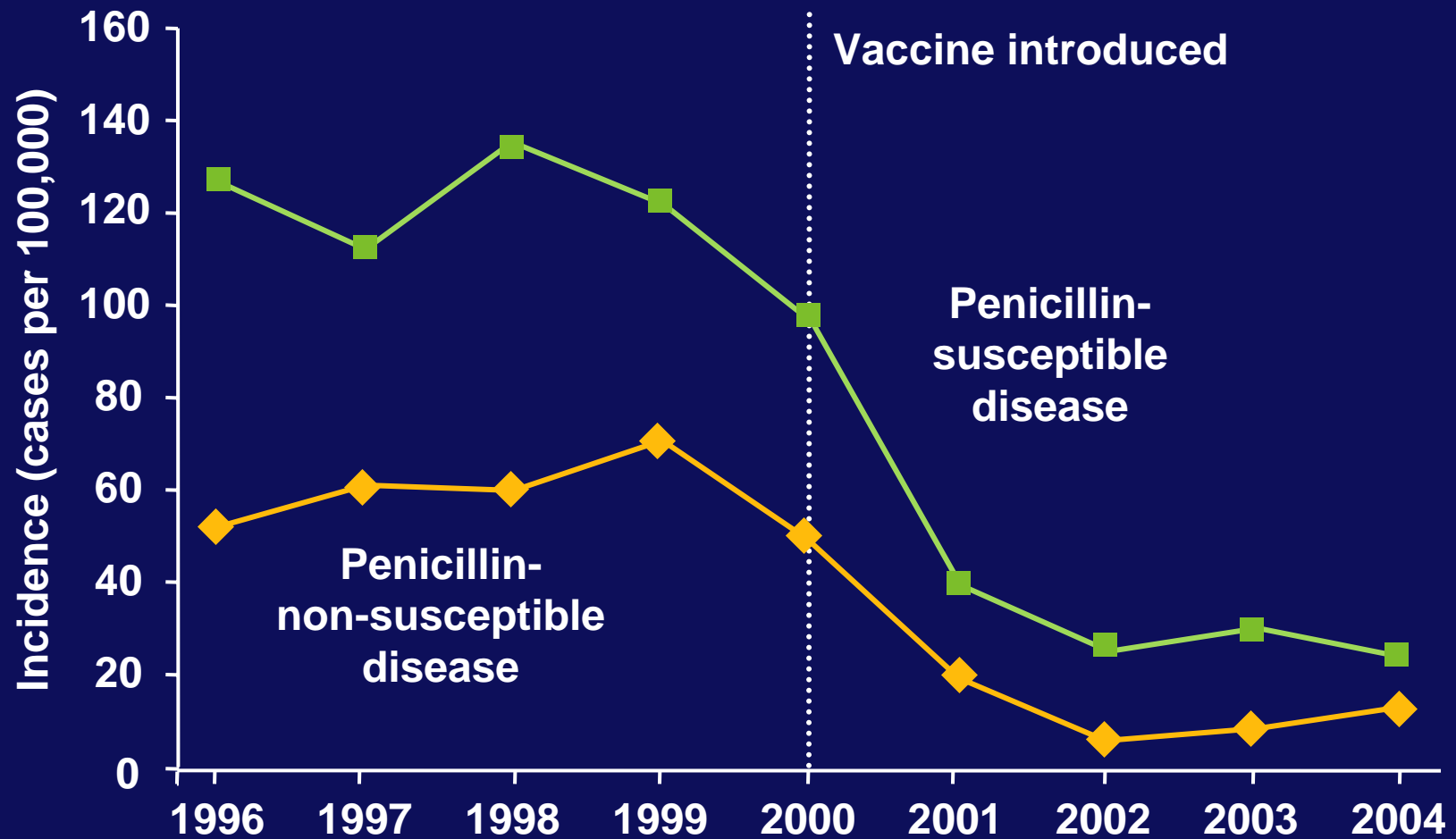
Antibiotic Resistance	Vaccines (%) (n = 130)	Controls (%) (n = 145)	P Value
Penicillin	27 (21)	60 (41)	0.0002
Chloramphenicol	2 (2)	5 (3)	—
Tetracycline	14 (11)	13 (9)	—
Erythromycin	8 (6)	6 (4)	—
Clindamycin	7 (5)	4 (3)	—
Rifampicin	2 (2)	1 (1)	—
Cotrimoxazole	30 (23)	51 (35)	0.003
Any of the above	59 (45)	90 (62)	0.005

# Vaccine Efficacy – Resistance to Antibiotics – All Children – ITT

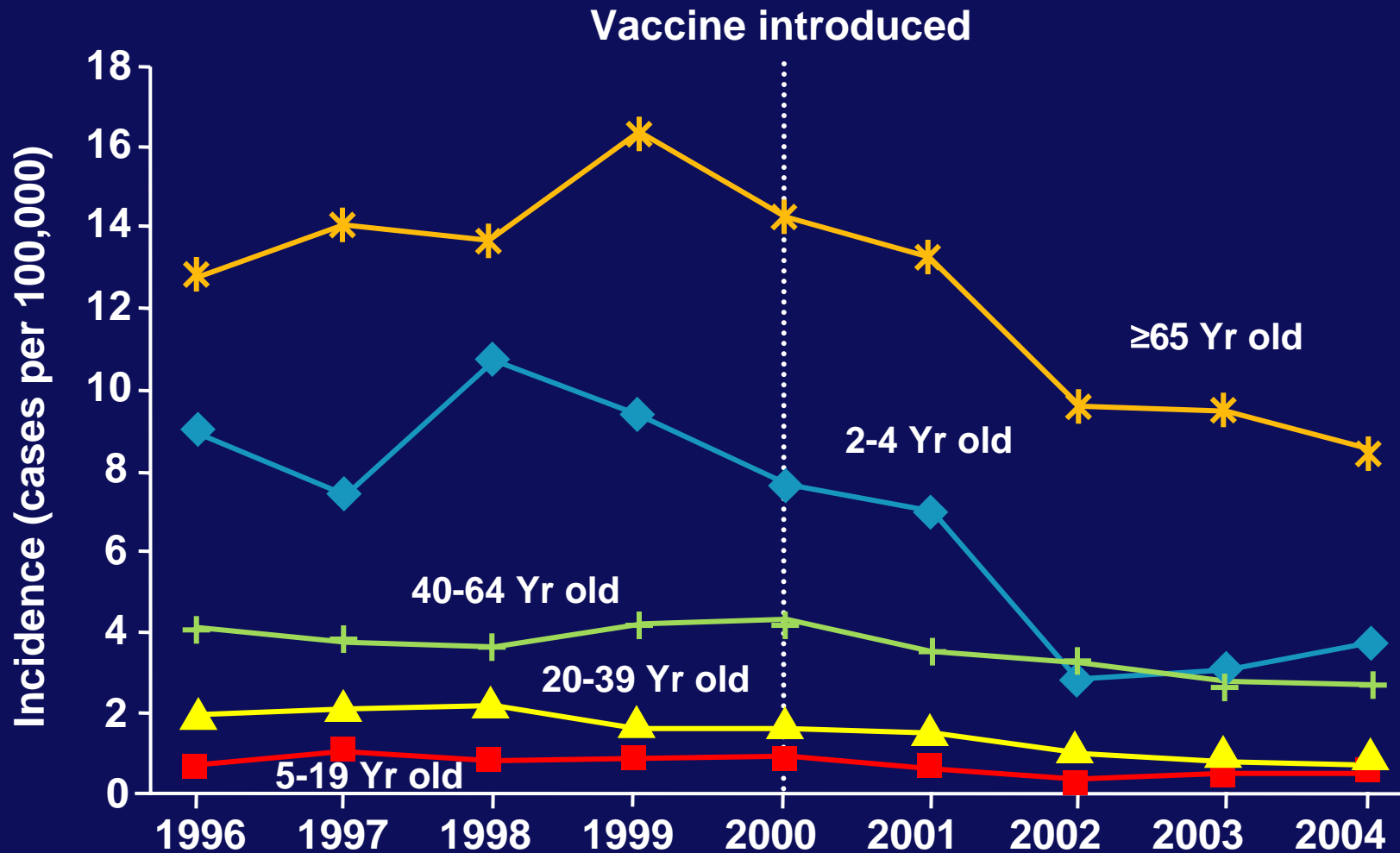
	Cases in Control Group	Cases in Vaccine Group	Vaccine Efficacy (VE)	95% CI
Penicillin	21	7	67	19-88
Cotrimoxazole	32	14	56	16-78
Any	39	17	56	21-77

In the cotrimoxazole group, 29 and 13 are HIV<sup>+</sup> (VE 55%).

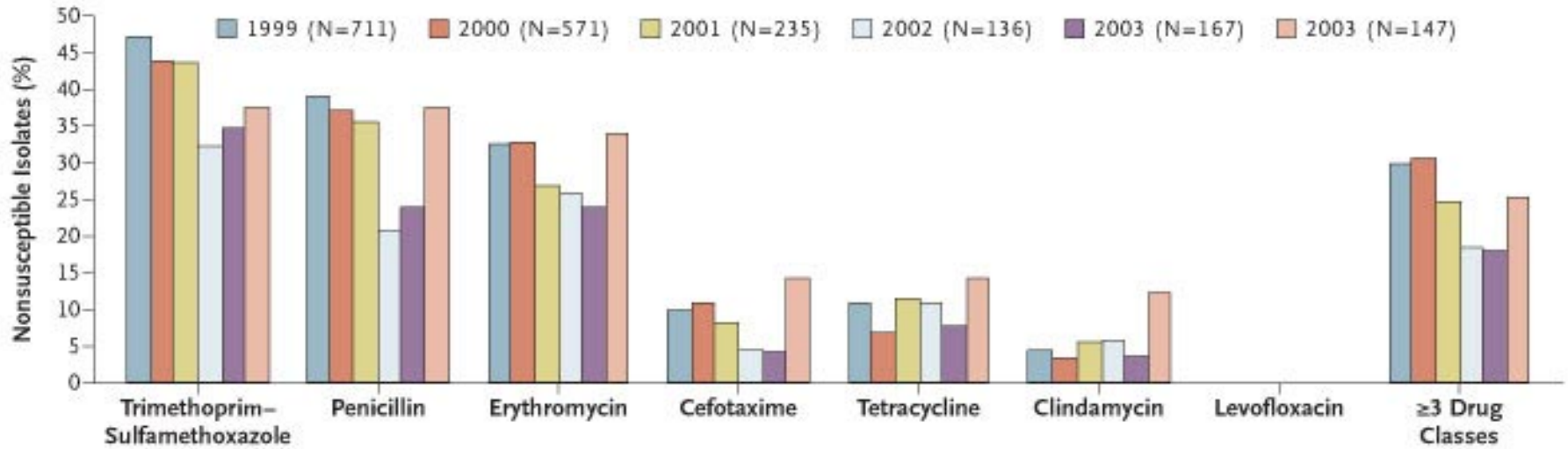
## Children <2 Years of Age



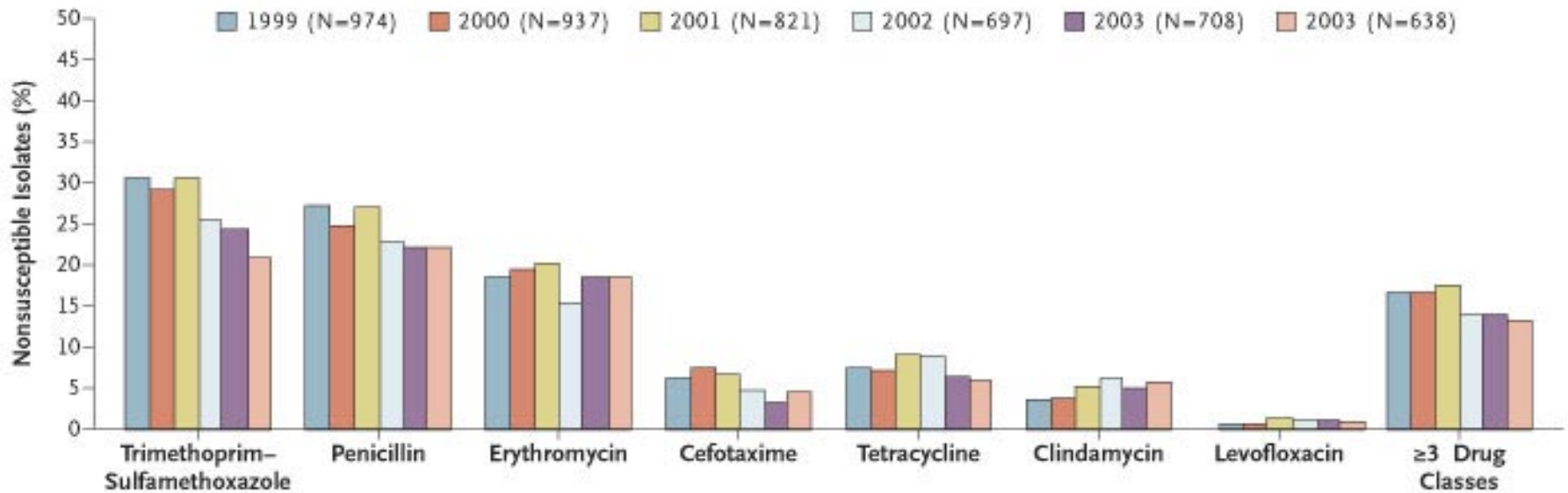
# >2 Years of Age



**A <2 Yr Old**



**B ≥65 Yr Old**

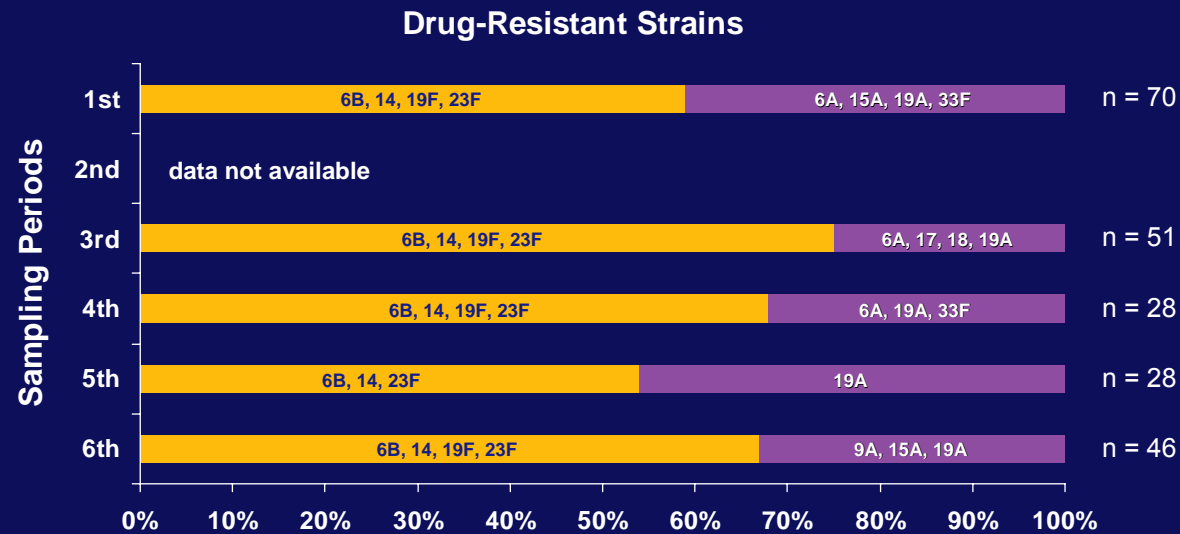
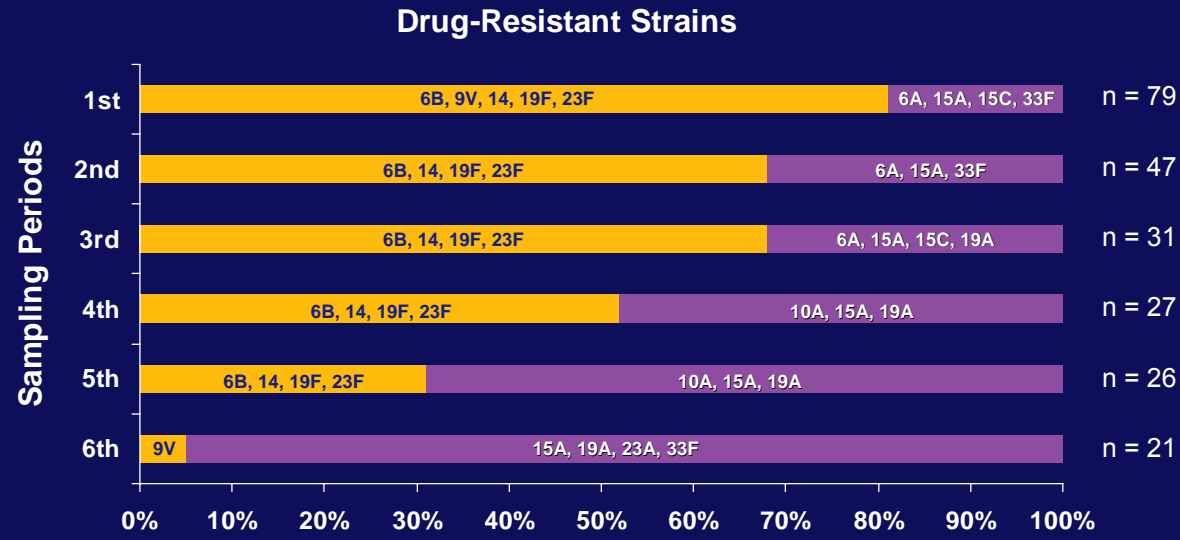


## Antibiotic Resistance Remains Common in URT Isolates in the Vaccine Era

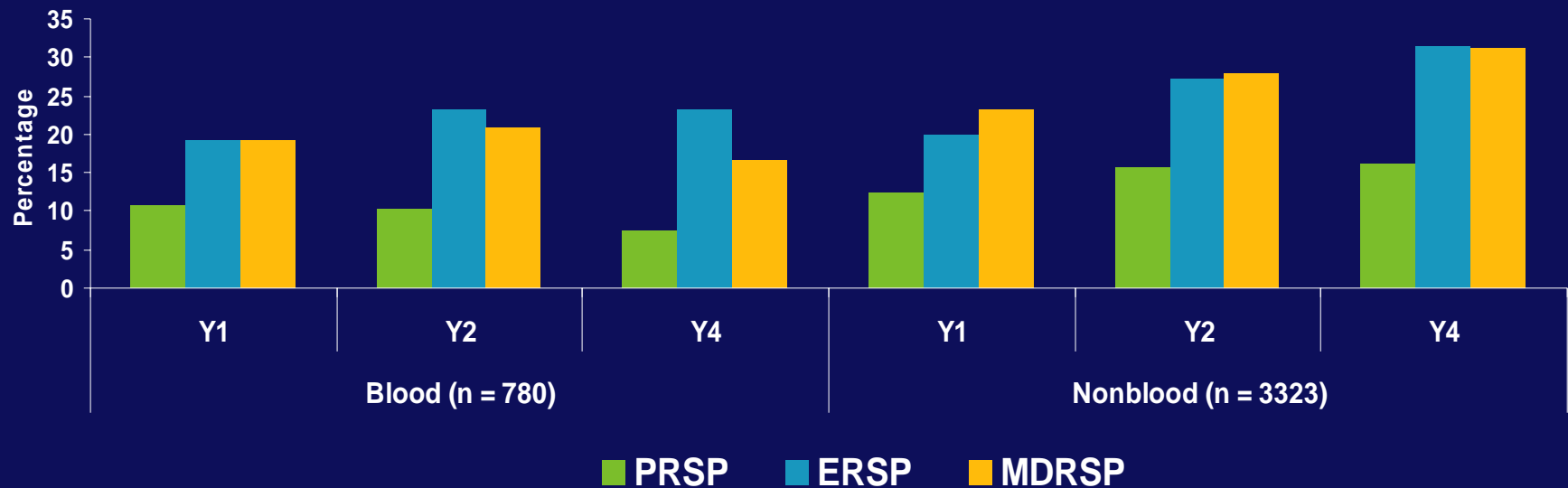
- Rates of resistance in NP carriage studies in Boston show evidence of replacement, but also no reduction in antimicrobial resistance associated mainly with serotypes 19A and 19F<sup>1</sup>
- In Alaska, NP surveillance reveals reduced COT resistance associated with little selective pressure, but no drop in pen resistance associated with increased resistance in 19F<sup>2</sup>
- In Kentucky, although pneumococci decreased in MEF, antibiotic resistance did not<sup>3</sup>

1. Pelton SI, et al. *Pediatr Infect Dis J.* 2004;23:1015-1022; 2. Moore MR, et al. *J Infect Dis.* 2004;190:2031-2038; 3. Block SL, et al. *Pediatr Infect Dis J.* 2004;23:829-833.

# Day Care in Portugal



# Serotypes Not Represented in PCV7 (N = 4112)



Farrell JJ, et al. Presented at: 45th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); December 16-19, 2005; Washington, DC.

## Future Prospects

- Strategies to reduce antimicrobial use in order to decrease resistance are complicated by multiple resistance
- Pneumococcal conjugate vaccines have been shown to interrupt the transmission of multiply-resistant strains that belong to vaccine serotypes, but resistance is emerging in nonvaccine types