Vaccination to Reduce Antimicrobial Resistance

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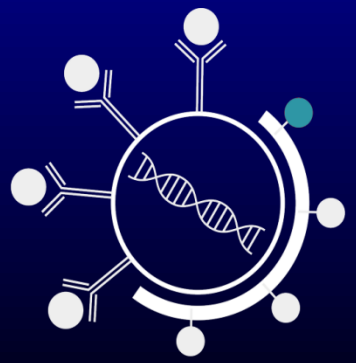


RMPRU
respiratory & meningeal pathogens research unit

COI

- K. P. Klugman, Pfizer Vaccines Role(s): Research Relationship, Scientific Advisor (Review Panel or Advisory Committee), Speaker's Bureau, Received: Research Support, Speaker Honorarium. GSK Biologicals Role(s): Scientific Advisor (Review Panel or Advisory Committee), Received: Consulting Fee. Merck Role(s): Scientific Advisor (Review Panel or Advisory Committee), Received: Consulting Fee. Bayer Role(s): Scientific Advisor (Review Panel or Advisory Committee), Received: Consulting Fee. Astellas Role(s): Scientific Advisor (Review Panel or Advisory Committee), Received: Consulting Fee. sanofi Role(s): Scientific Advisor (Review Panel or Advisory Committee), Received: Consulting Fee

Scope

- Two classes of vaccines may reduce bacterial resistance
- Bacterial vaccines that may or may not have been demonstrated to impact on resistance
- Viral vaccines that may reduce bacterial resistance by reducing bacterial transmission and / or by reducing antimicrobial prescribing

Bacterial Vaccines That May Reduce Resistance by Reducing Burden of Disease of Resistant Pathogens

- BCG
- Pertussis
- Hib
- Typhoid
- Cholera

A **Viral** Vaccine for Resistance

- Influenza vaccine
- By reducing episodes of otitis media flu vaccines may reduce antimicrobial use and by inference therefore resistance - LAIV may be more effective in reducing otitis than TIV – Block et al, PIDJ, 2011, 30, 203 – 7 (85% vs placebo and 54% vs TIV)
- TIV for pregnant women reduces respiratory infections in their infants in Bangladesh (Zaman et al, NEJM, 2008, 358, 1555-64), and Navajo (Eick et al, Arch Pediatr Adolesc Med, 2011, 165, 104 – 111)

Impact of Pneumococcal Conjugate Vaccine on Resistance

- Evidence of efficacy and effectiveness
- Impact of replacement and continuing selective pressure from antimicrobial use

Competing Selection

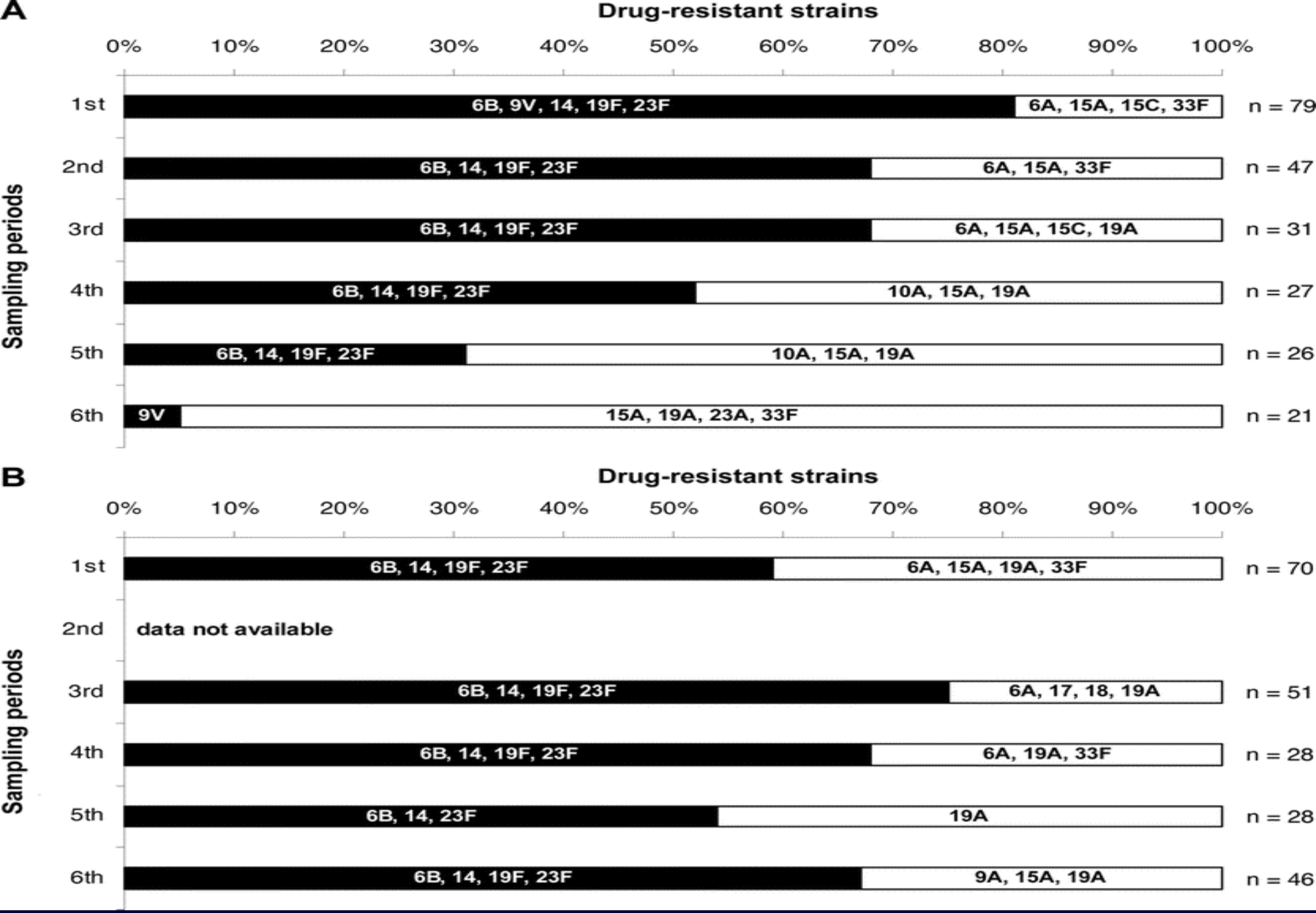
- A new vaccine given to children successfully eliminates 7 of 93 strains including 90% of antibiotic resistant strains in vaccinated children, but also reduces resistance in adults by interruption of transmission of vaccine type strains
- Antibiotic use continues to select resistance in the remaining 86 strains
- Do replacement strains emerge and will they be antibiotic – resistant ?

Vaccine efficacy – resistance to antibiotics – all children - ITT

	Cases in control group	Cases in vaccine group	Vaccine efficacy	95% confidence interval
Penicillin	21	7	67	19 - 88
Cotrimoxazole	32	14	56	16 – 78
Any	39	17	56	21 - 77

Klugman et al, 2003, NEJM, 349,1341-8

In the cotrimoxazole group
29 and 13 are HIV +ve – VE 55%



Day care in Portugal Frazao et al, PIDJ, 2005, 24, 243 - 52

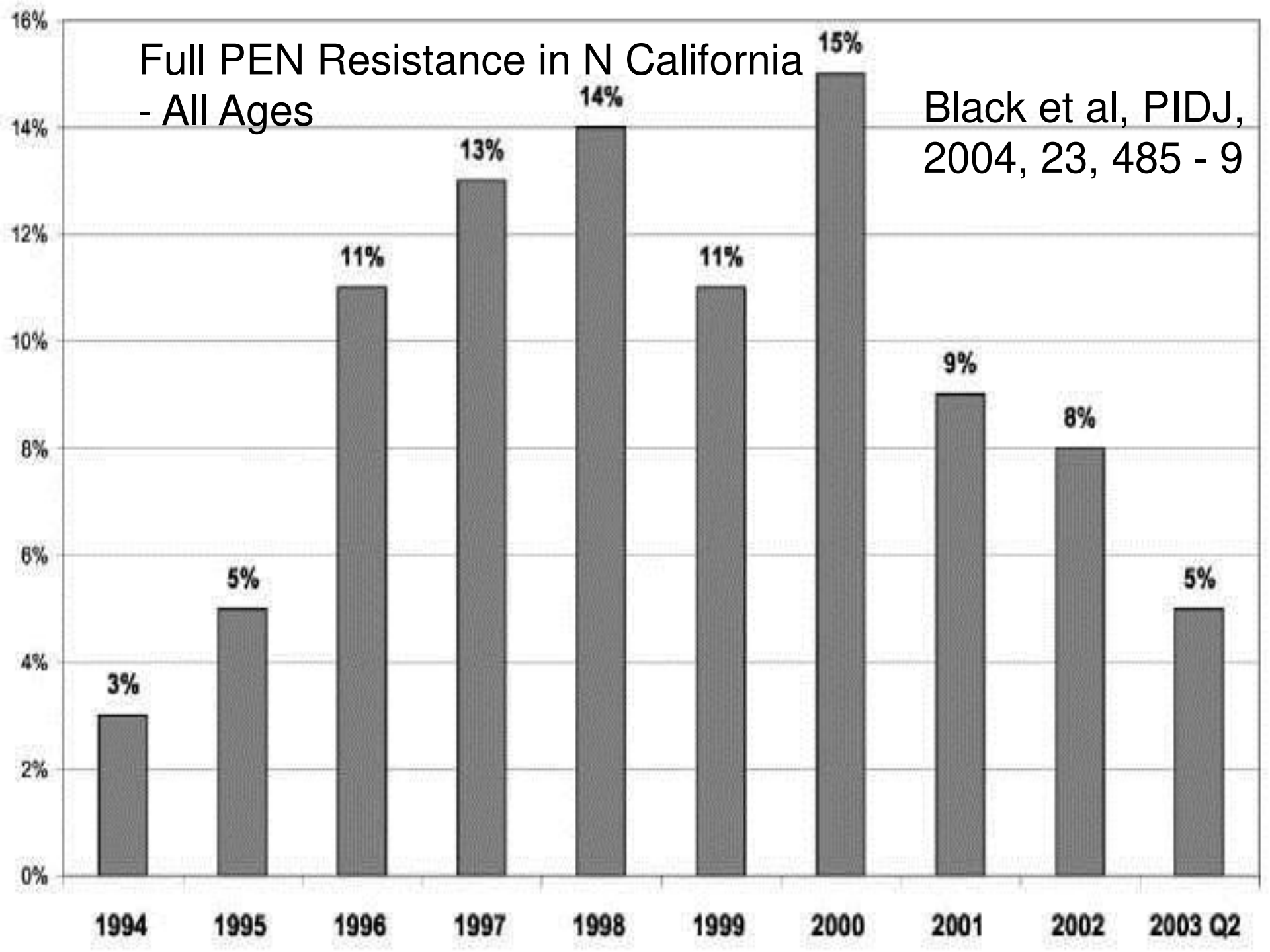
Reduction in Antibiotic Use

"PCV reduced antibiotic prescriptions by 5.4% (CI 4.0 to 6.7%) in all follow-up starting at Dose 1 and by 5.7% (CI 4.2 to 7.2%) after the primary series in children followed "per protocol."

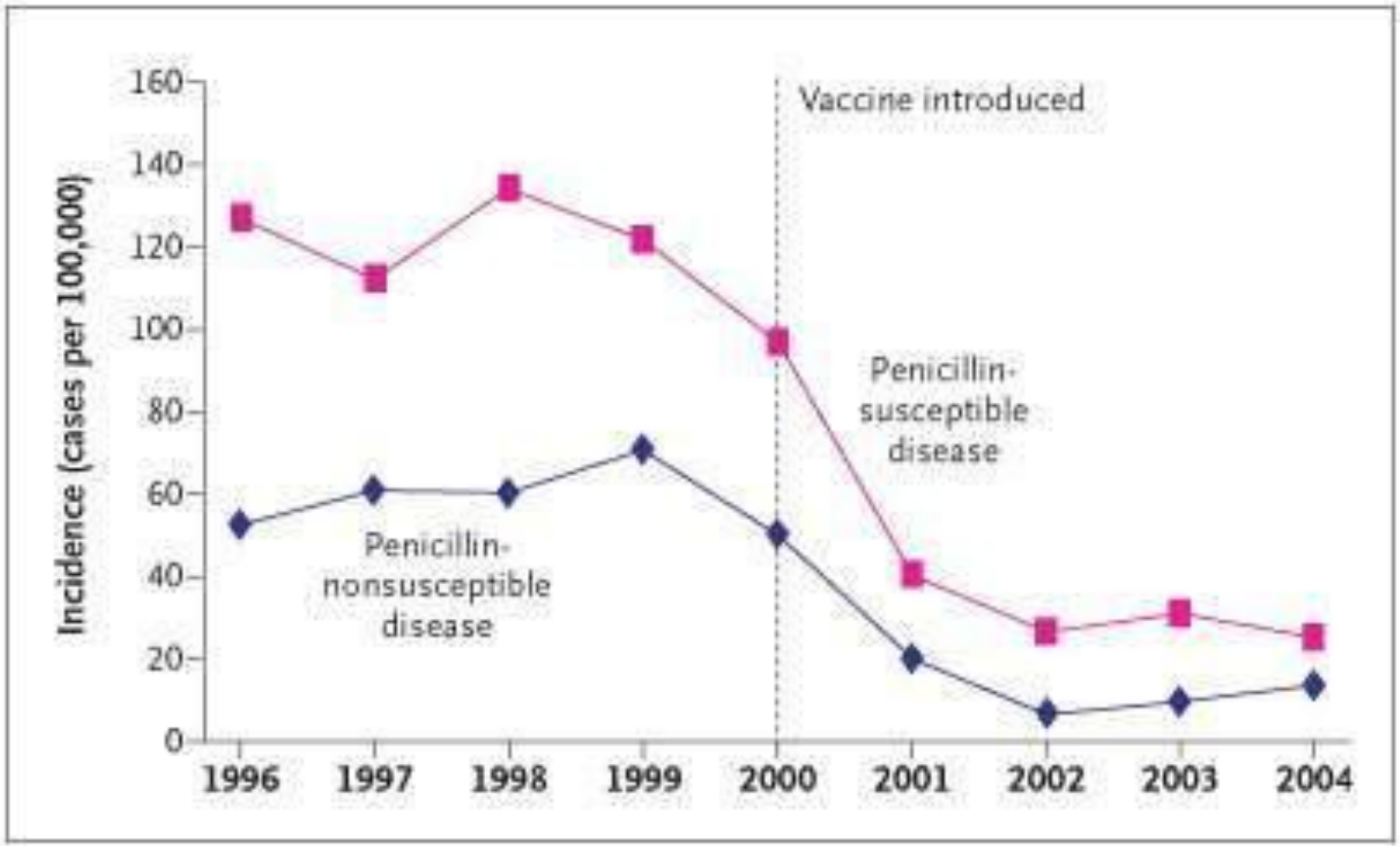
PCV reduced the subset of "second line" antibiotics by 12.6% (CI 9.6 to 15.6%) in all follow-up time and by 13.3% (CI 9.9 to 16.5%) in per protocol follow-up.

"From Dose 1 to age 3.5 years, PCV prevented a total of 35 antibiotic prescriptions per 100 children vaccinated per protocol."

Fireman et al, PIDJ 2003; 22:10-16

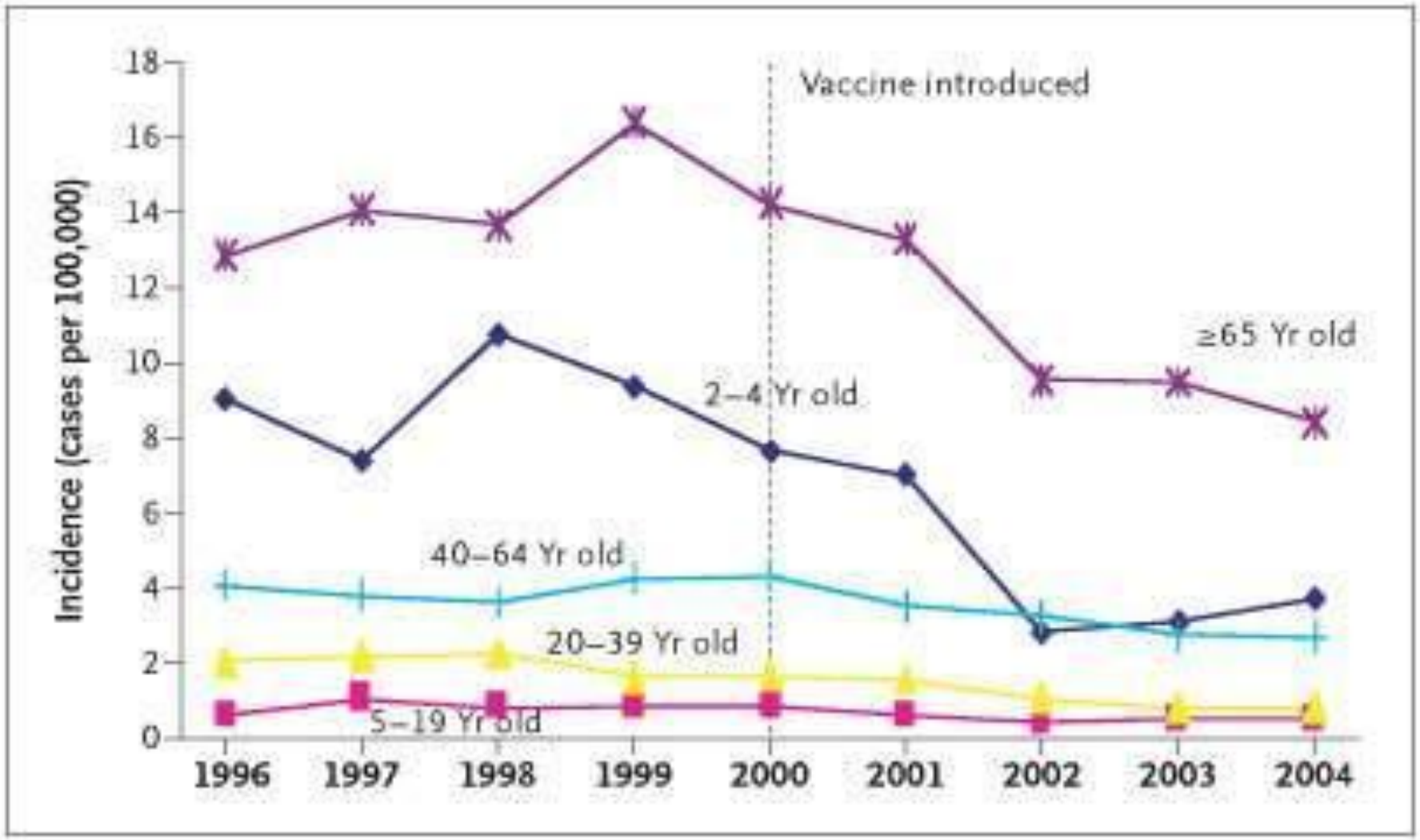

Full PEN Resistance in N California - All Ages
Black et al, PIDJ, 2004, 23, 485 - 9
16%
14%
12%
10%
8%
6%
4%
2%
0%
3%
5%
11%
13%
14%
11%
15%
9%
8%
5%
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003 Q2

Children Less Than Two Years of Age



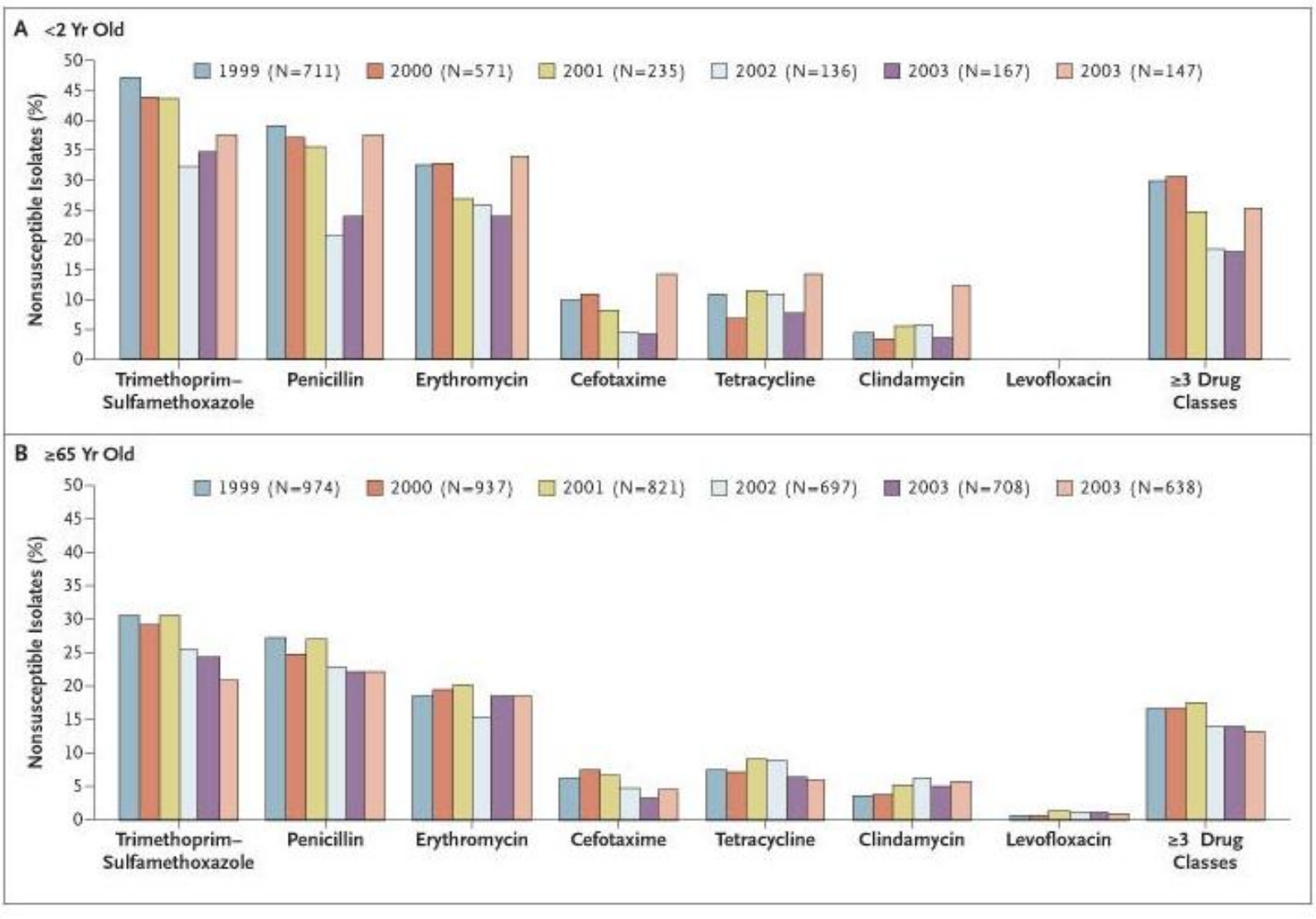
Kyaw et al, NEJM, 2006,354,1455-63

Penicillin Resistance Children Over Two and Adults



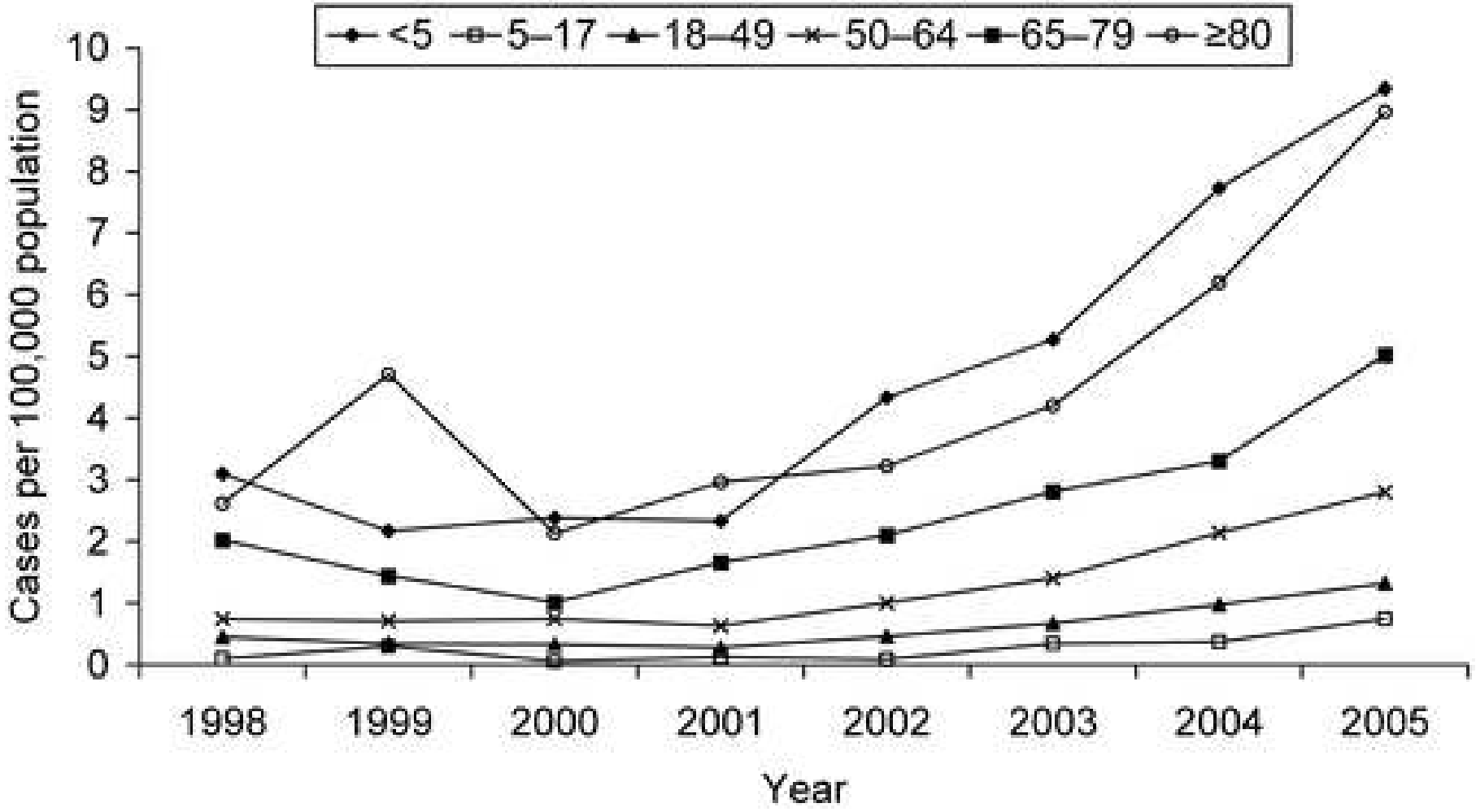
Kyaw et al, NEJM, 2006,354,1455-63

Effect of introduction of PCV-7 on drug-resistant *S. pneumoniae*



Kyaw *et al. N Engl J Med*. 2006; **354**:1455–63

Serotype 19A



Moore et al, JID, 2008, 197(7):1016–1027

Serotype 19A

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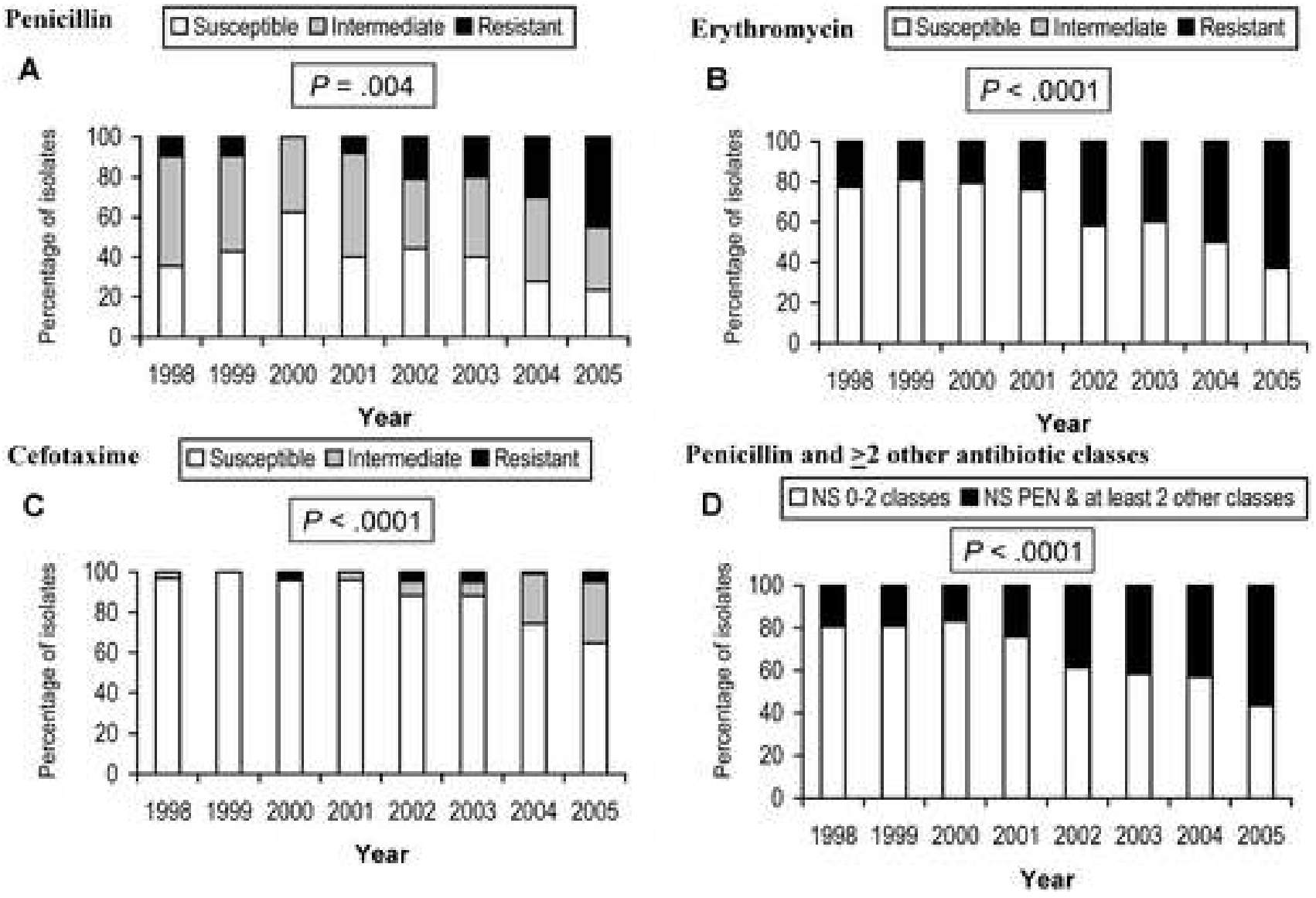
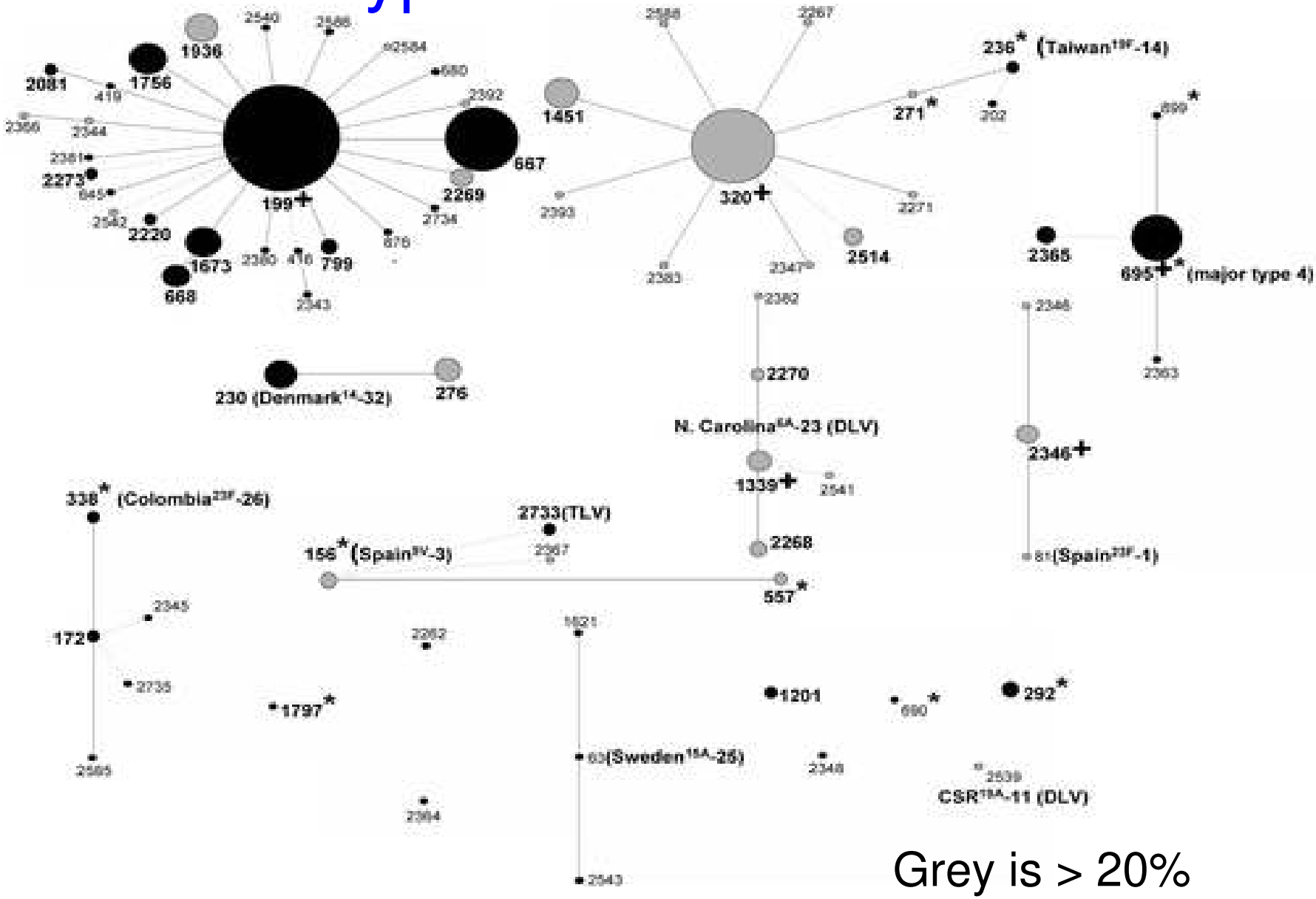


Moore et al, JID, 2008, 197(7):1016–1027

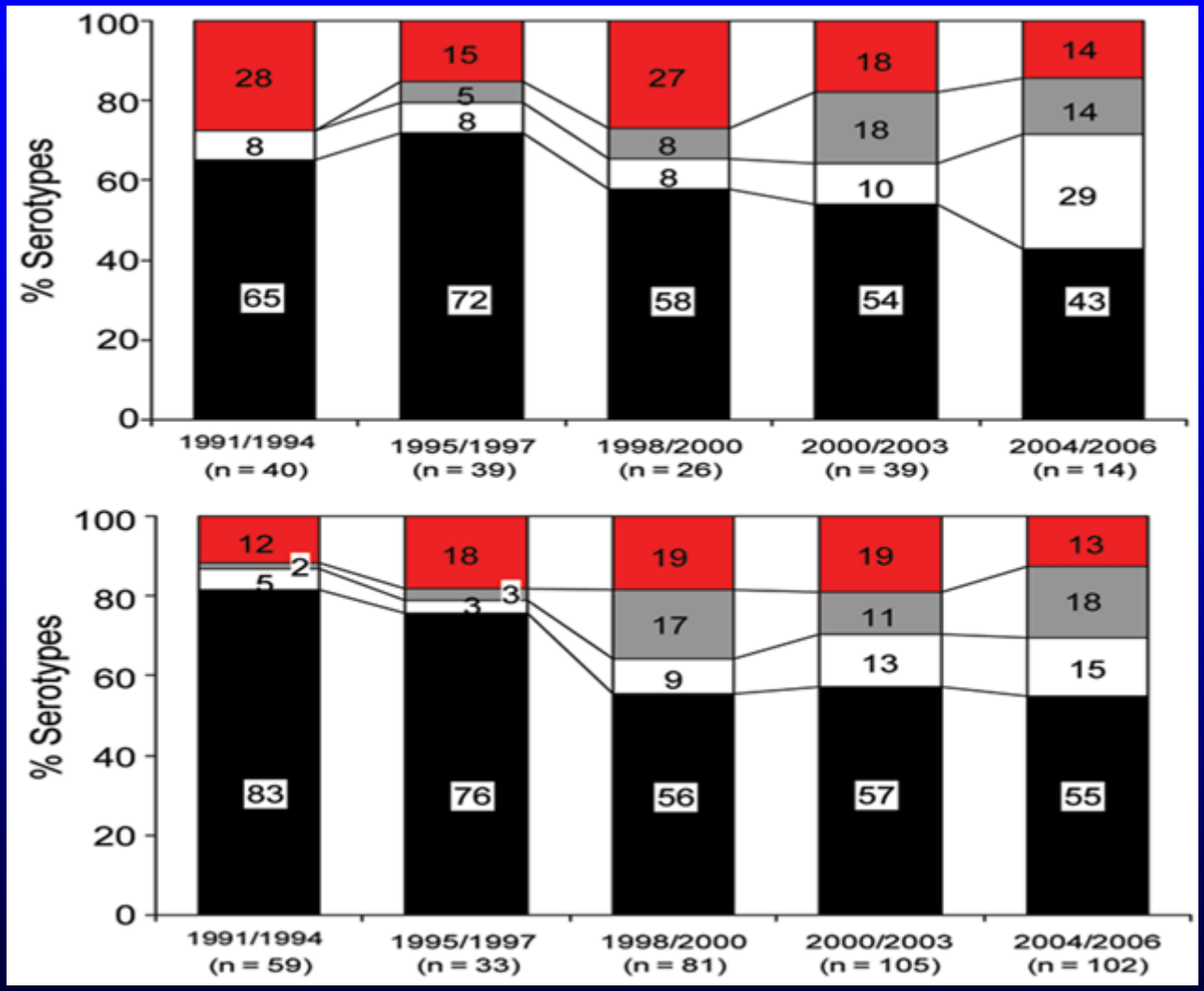
Serotype 19A



Grey is > 20%
Pen > 1ug/ml

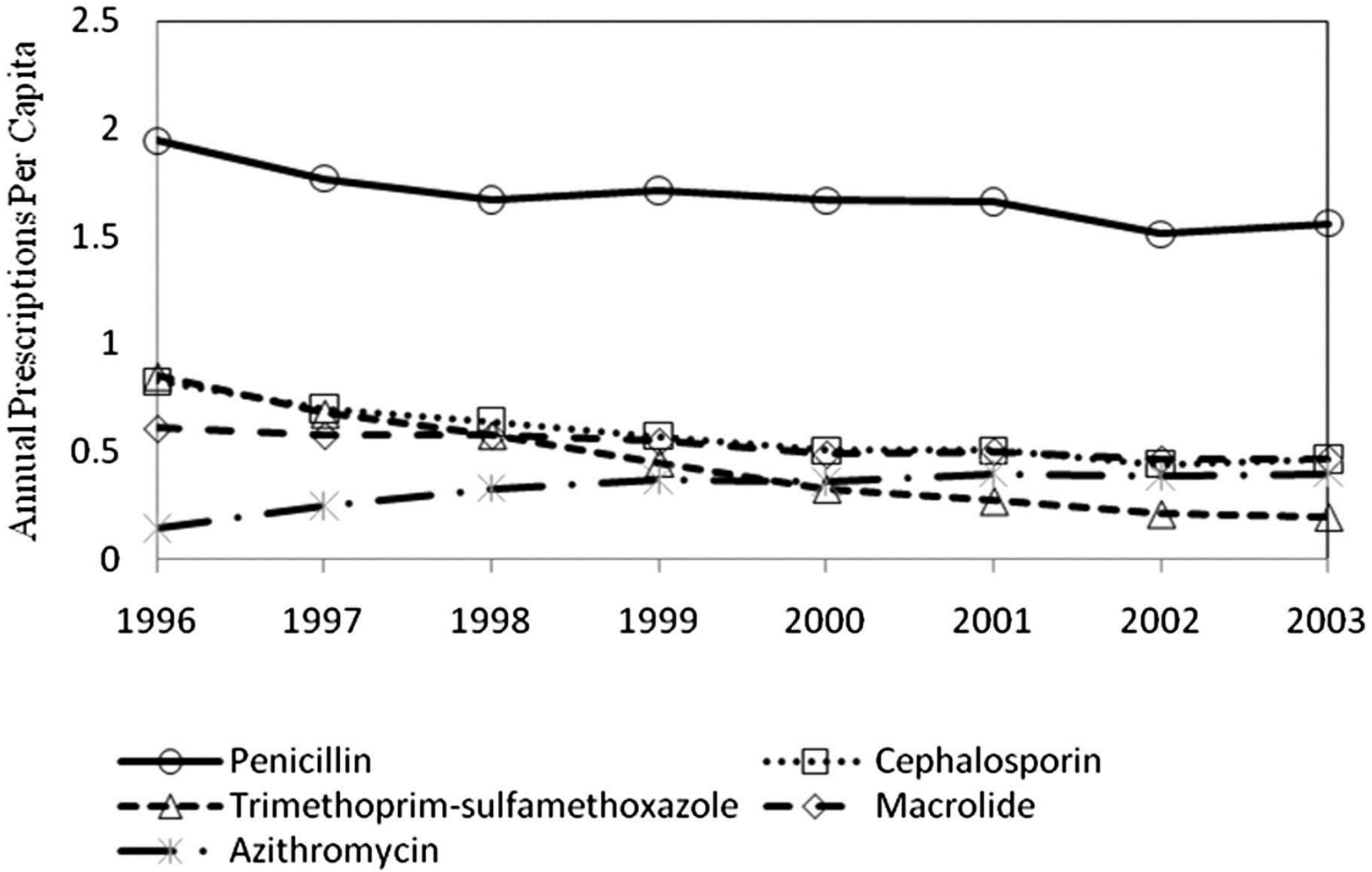
Moore et al, JID, 2008, 197(7):1016–1027

Expansion of 19A without PCV in invasive and non-invasive strains



Choi *et al. EID*, 2008; **14**: 275–281

Outpatient antibiotic prescription rates for children ≤5 years of age, 1996–2003.



Hicks L A et al. Clin Infect Dis. 2011;53:631-639

Clinical Infectious Diseases

Table 2. A Comparison of the Proportion of Strain 19A Invasive Pneumococcal Disease (IPD) Among IPD Isolates in Active Bacterial Core Surveillance Sites With High and Low Antibiotic Prescription Rates, 1996–2003

Serotype 19A IPD	Parameter	1996–1999[a] (n = 11,264)[b]	2000–2003[b] (n = 10,811)[b]	1996–2003[b] (n = 22,075)[b]
Penicillin prescriptions				
Proportion, %	High-prescribing sites	3.2	5.7	4.5
	Low-prescribing sites	3.0	5.3	4.1
	P	.32	>.99	.47
Logistic regression	Point estimate (β_1)	0.049	0.08	0.10
	OR (exp β_1), (95% CI)	1.05 (0.84–1.31)	1.08 (.91–1.28)	1.10 (.97–1.26)
	P	.67	.38	.15
Cephalosporin prescriptions				
Proportion, %	High-prescribing sites	3.4	6.8	4.9
	Low-prescribing sites	2.6	4.2	3.5
	P	.32	.03	.03
Logistic regression	Point estimate (β_1)	0.26	0.51	0.36
	OR (exp β_1), (95% CI)	1.30 (1.04–1.62)	1.67 (1.41–1.98)	1.43 (1.25–1.64)
	P	.02	<.001	<.001
Macrolide prescriptions				
Proportion, %	High-prescribing sites	3.4	6.8	4.9
	Low-prescribing sites	2.6	4.2	3.5
	P	.32	.03	.03
Logistic regression	Point estimate (β_1)	0.26	0.51	0.36
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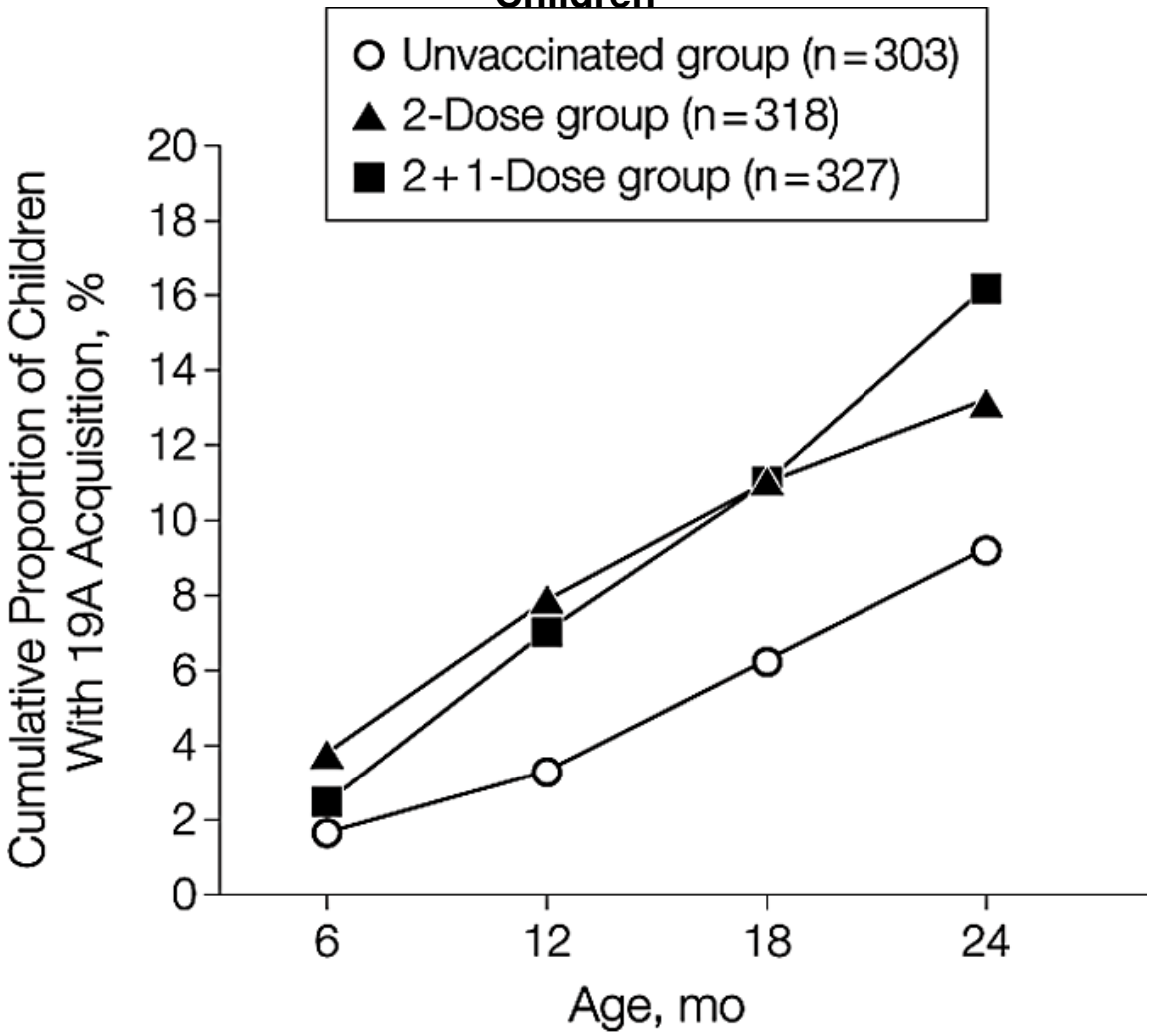
	P	.02	<.001	<.001
Trimethoprim-sulfamethoxazole prescriptions				
Proportion, %	High-prescribing sites	3.2	5.7	4.5
	Low-prescribing sites	3.0	5.3	4.1
	P	.32	>.99	.47
Logistic regression	Point estimate (β_1)	0.049	0.08	0.10
	OR (exp β_1), (95% CI)	1.05 (.84–1.31)	1.08 (.91–1.28)	1.10 (.97–1.26)
	P	.67	.38	.15

Figure 2. Cumulative Proportions of Children With New Acquisition of Serotype 19A After Finishing Primary Series of 7-Valent Pneumococcal Conjugate Vaccine vs Unvaccinated Children



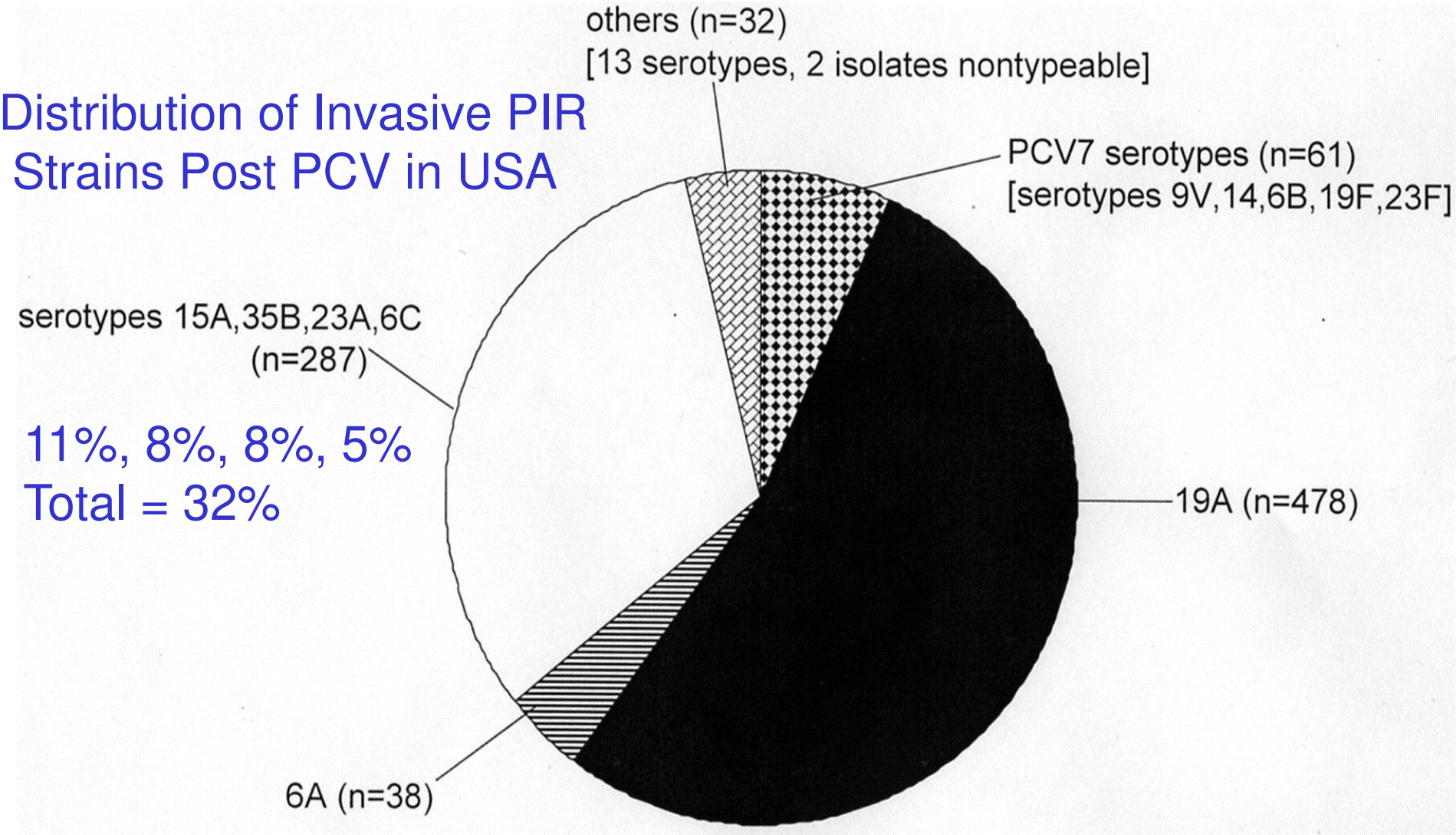
van Gils, E. J. M. et al. JAMA 2010;304:1099-1106

Relationship Between antibiotic Use and PCV in Reduction of NP Resistance in Children with AOM

- Prospective French study of Pen R carriage following PCV introduction
- Vaccine and NO antibiotic last 3 months: 4.6%
- Vaccine and HAD antibiotic last 3 months: 8.6%
- NO vaccine and NO antibiotic last 3 months: 10.3%
- No vaccine and HAD antibiotic last 3 months: 16.2%
- P for trend = 0.0001

Cohen R et al, PIDJ, 2006, 25, 1001-7

Distribution of Invasive PIR Strains Post PCV in USA



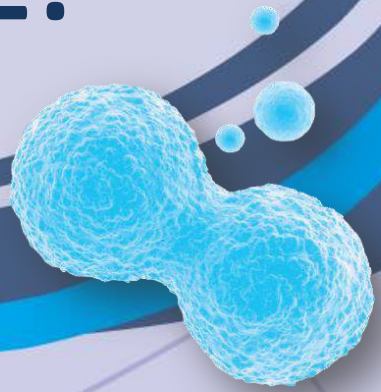
11%, 8%, 8%, 5%
Total = 32%

Gertz et al, JID, 2010, 201, 770 5

Conclusions

- PCV has reduced the burden of antibiotic resistant pneumococcal disease, particularly among invasive infections in the USA
- Replacement disease has eroded some of these gains by the selection of resistance in replacement strains
- Serotype 19A has emerged as a major cause of IPD in many countries – both antibiotic selection and vaccination may select these highly resistant clones
- Resistance is also emerging in types 6C, 15A, 23A and 35B

See you at ISPPD-8 2012!



ISPPD-8

8TH International Symposium on Pneumococci and Pneumococcal Diseases

Iguaçu Falls, Brazil

March 11-15, 2012

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