Global drug Resistance: The Case of *Streptococcus pneumoniae*

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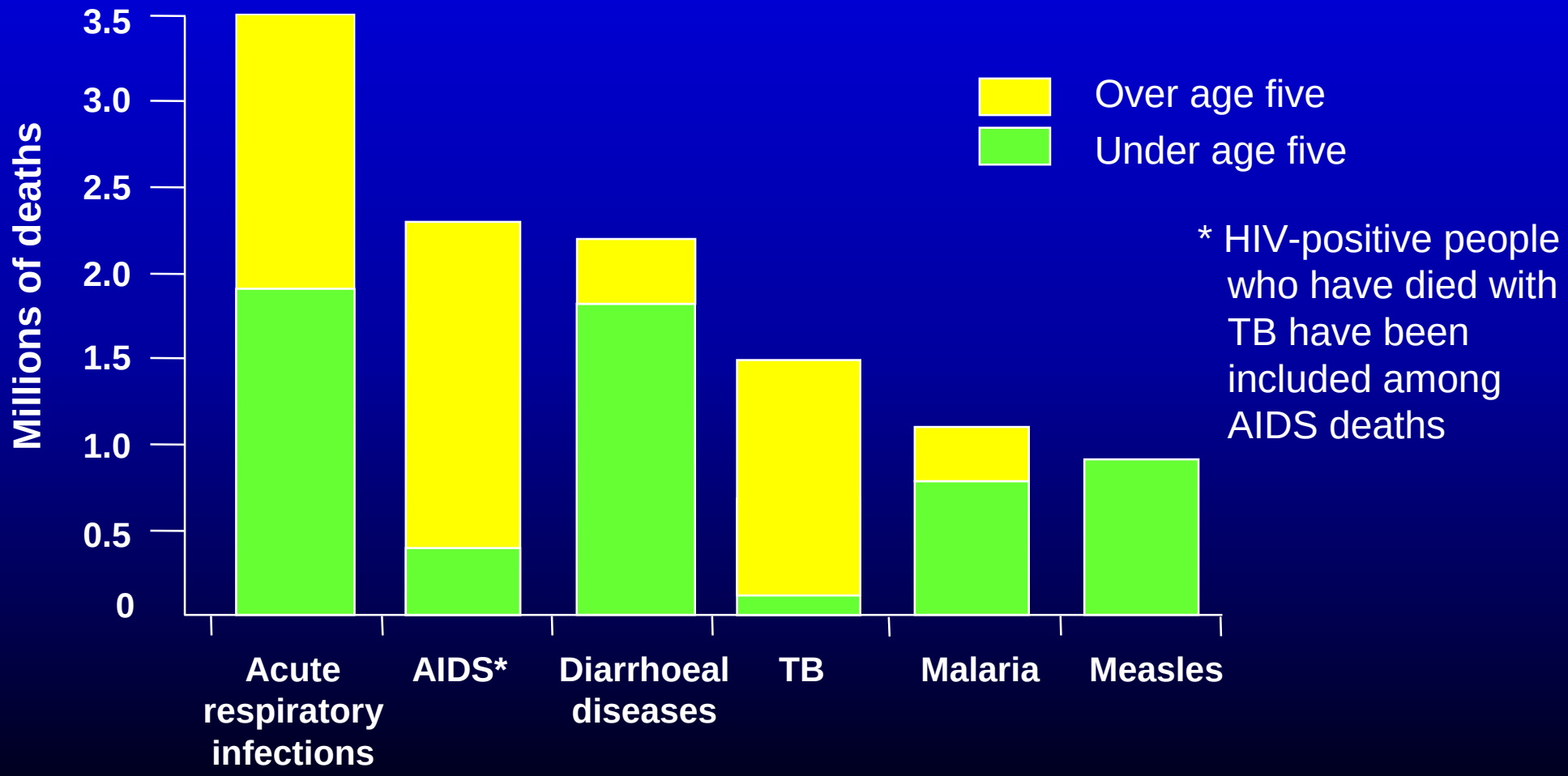
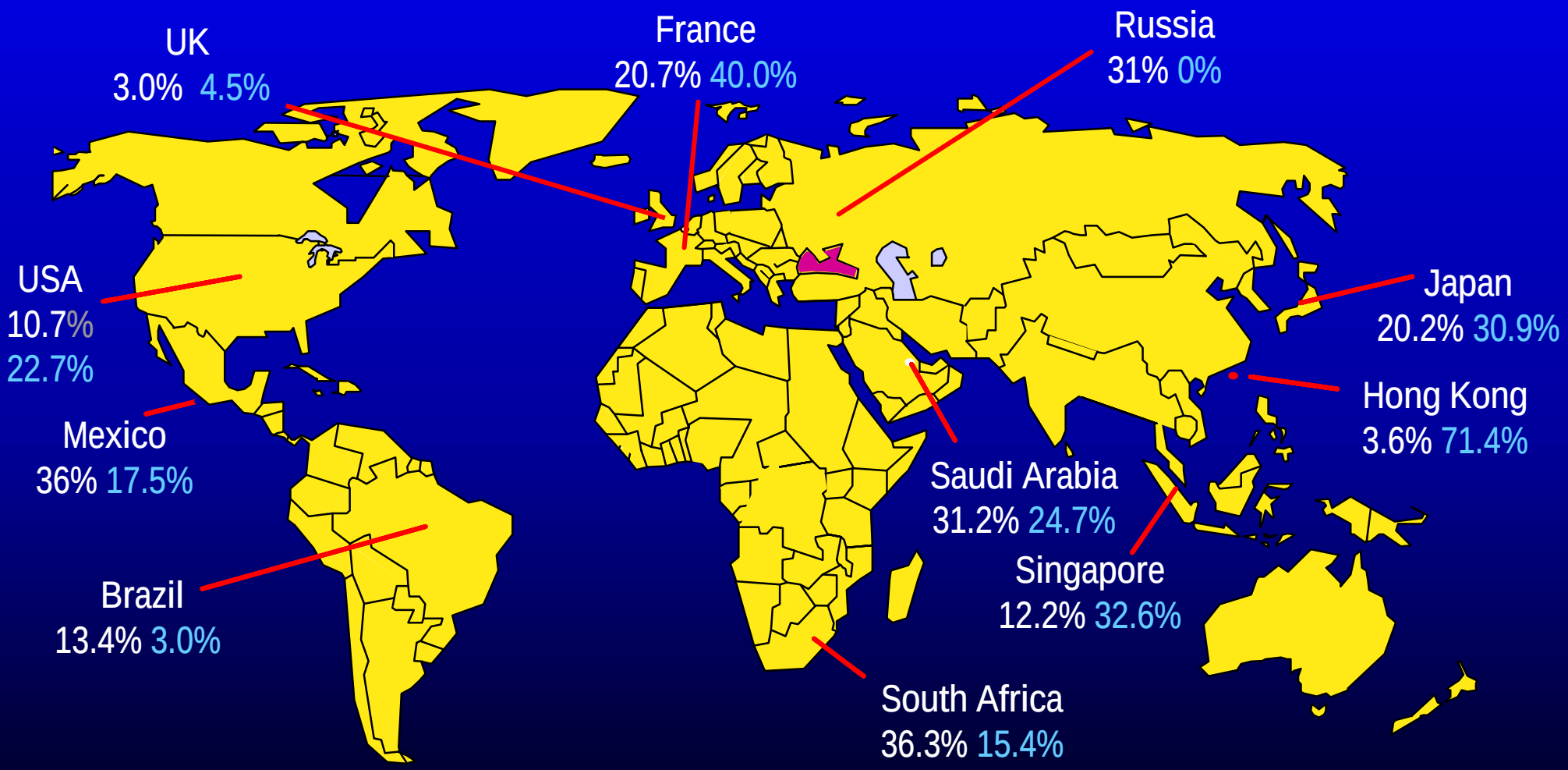
Acute respiratory infections – the leading cause of death in under 5s



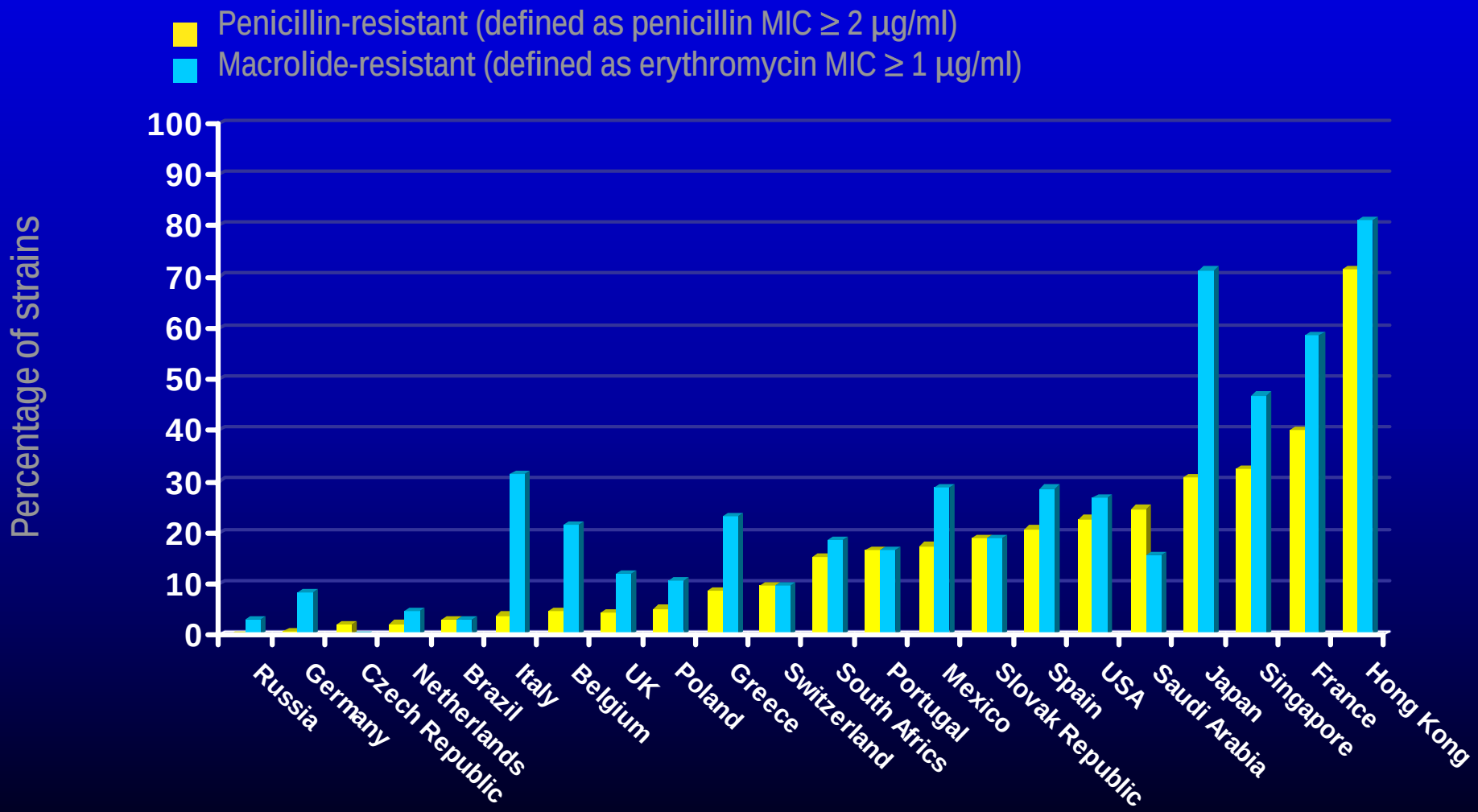
World Health Organization 1999

Global overview of pneumococcal penicillin resistance



Alexander Project data 2000

Prevalence of penicillin- and macrolide-resistant *S. pneumoniae*



Alexander Project data 2000

Factors Influencing the Selection of Antibiotic - Resistant Pneumococci

- Age
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- HIV
- Mechanisms of resistance
- Conjugate vaccine

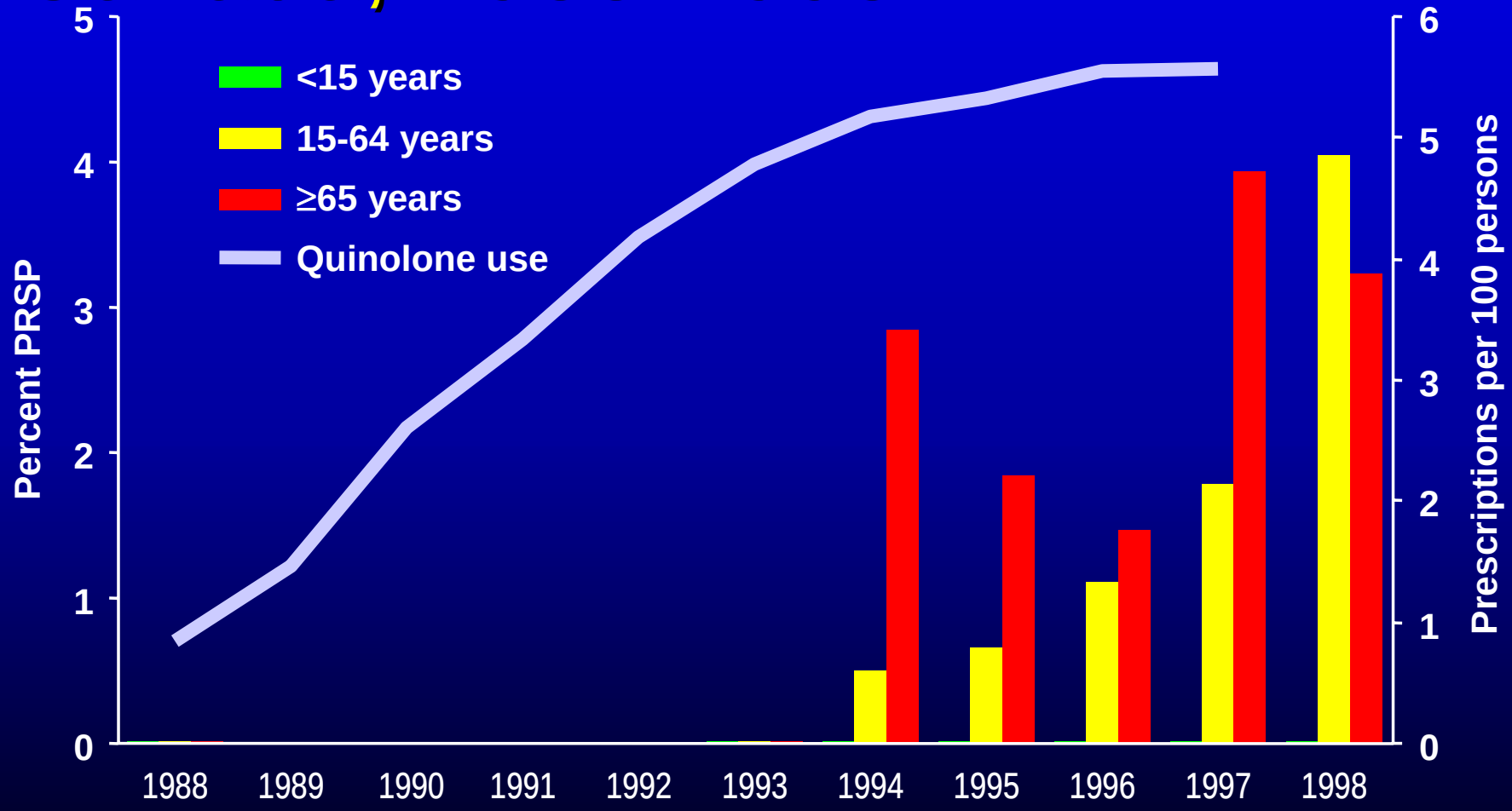
Risk Factors for Penicillin-Resistant Pneumococcal Infections

- 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
β-lactam R_x in prev.6 months	1.99
Nosocomial acquisition	2.12

Bedos et al, CID, 1996

Fluoroquinolone Use and PRSP Canada, 1988-1998



Chen et al, NEJM, 1999, 341, 233-9

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Risk Factors for Drug Resistant Pneumococcal Carriage

Multi-resistant type 14 strain in a hospital in Topolcany, Slovakia

- Hospitalization carriage — 33% vs O.P. 0.8%
- Prior hospitalization incidence — 68% vs 23%
- Previous antibiotics incidence — 78% vs 38%
- Hospital stay — carriage on admission 0%

carriage day	2- 7	13%
" "	8-14	16%
" "	15-21	29%
" "	>21	35%

Reichler et al, JID, 1996

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 a 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

Ho et al, CID, 2001, 32, 701-7

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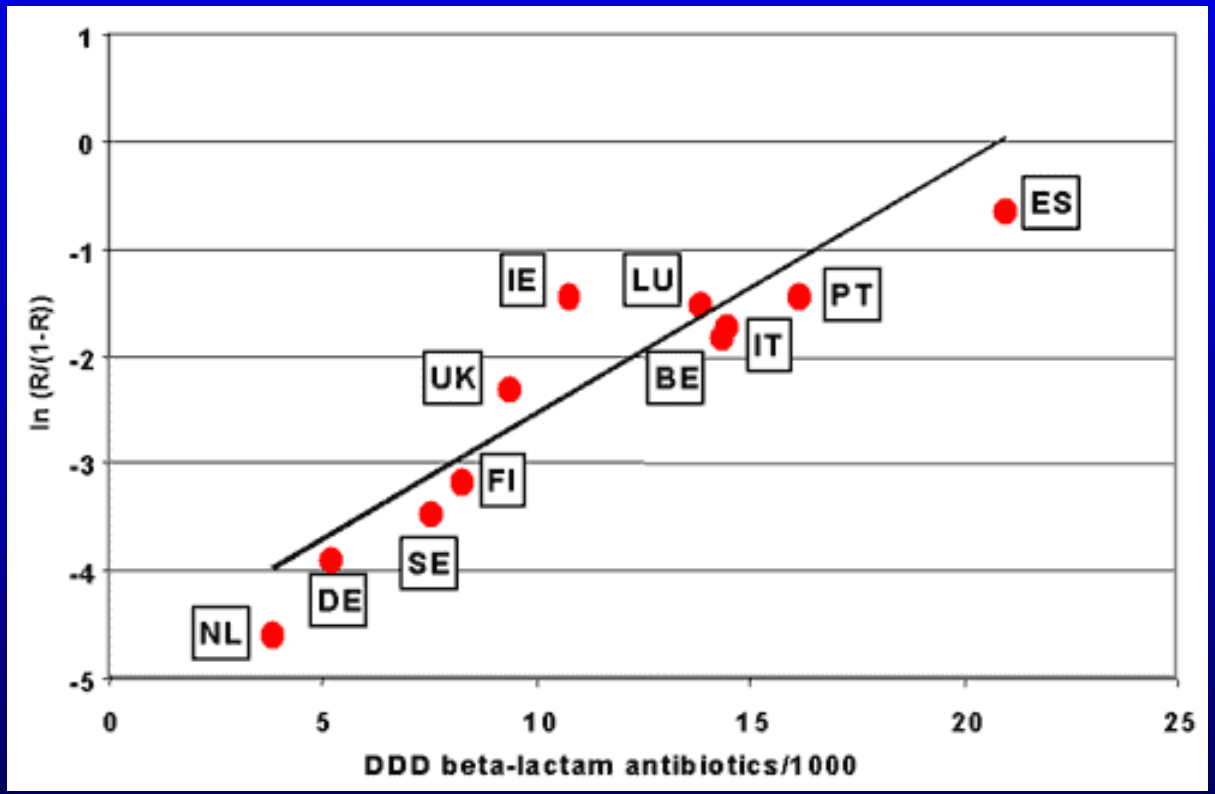
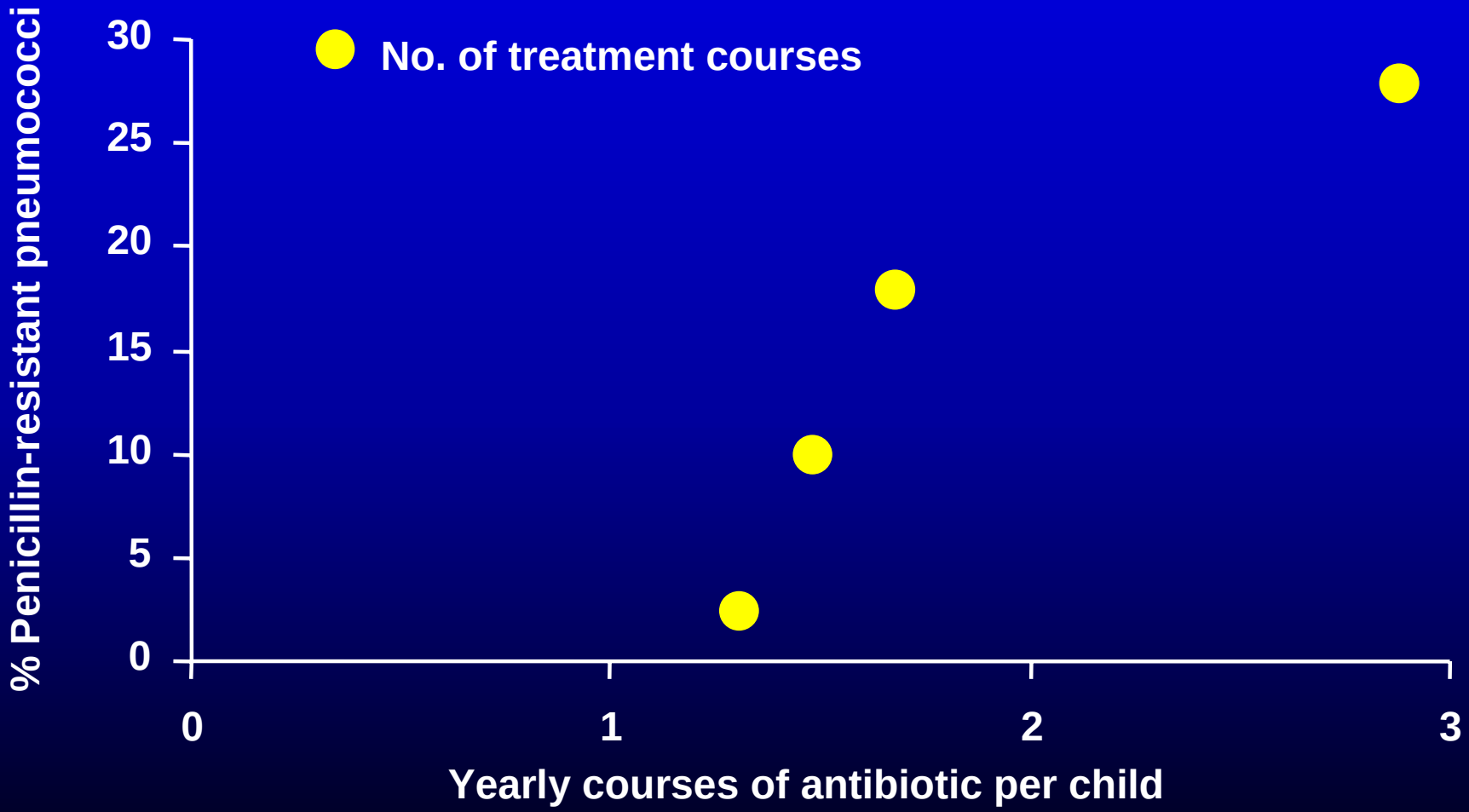
Association of Antibiotic Use with Resistance in the Pneumococcus



The logodds of resistance to penicillin among invasive isolates of *Streptoccus pneumoniae* (PNSP; ln(R/[1-R])) is regressed against outpatient sales of beta-lactam antibiotics in 11 European countries

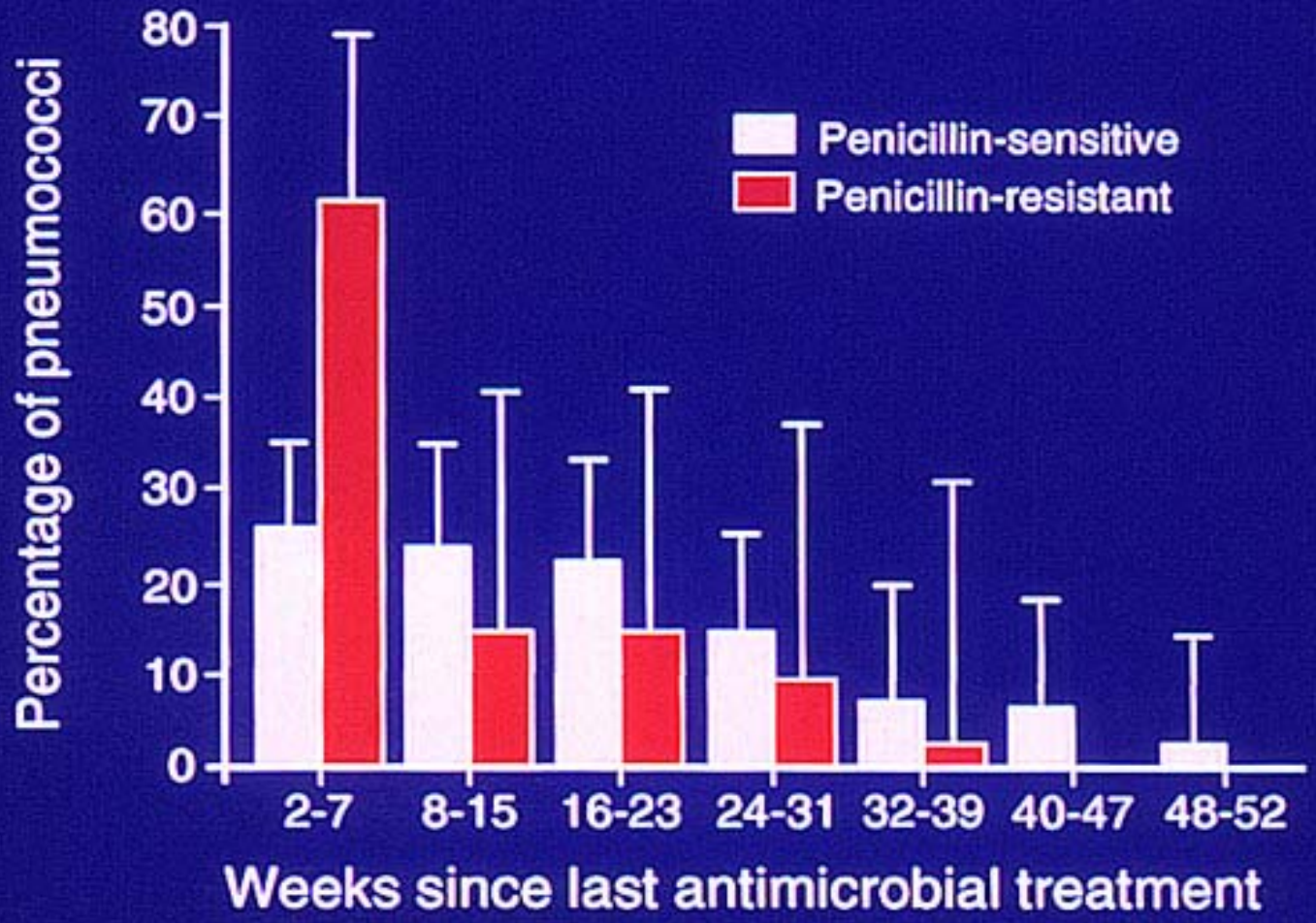
Bronzwaer et al, EID, March, 2002.

Association Between Antibiotic – Resistant Pneumococcal Carriage Rate and Regional Antibiotic Consumption: Iceland



Arason, 1996.

Percentages of penicillin-sensitive and penicillin-resistant pneumococci



Arason et al, BMJ, 1996

Impact of Azithromycin on Pneumococcal Carriage and Resistance in Aboriginal Children

Single dose 20 mg/kg

	Pre-treatment	Post-treatment		
		2-3 weeks	2 months	6 months
Carriage rate	54/79(68%)	11/38(29%)	29/37(78%)	34/39/(87%)
Azithromycin-resistance	1/54 (1.9%)	6/11(54.5%)	10/29(34.5%)	2/34(5.9%)
Azith resistant Serotypes I0F, 23A,45	1/79(1.3%)	16/75(21.3%)		2/32(6%)

Leach et al. CID. 199

Influence of Antibiotic Class on Pen Resistant Pneumo Carriage

Antibiotic	Number of cases	Courses in last 12 mos	Odds ratio	95% CI	p value
None	16	-	1.0	-	-
β-lactam	111	1 or 2	6.75	1.8–25	<0.001
	54	≥ 3	6.00	1.4–25	0.013
Co-trimoxazole	54	1 or 2	7.22	1.7–30	<0.001
	42	≥ 3	13.14	3.1–55	<0.001
Erythromycin	11	1 or 2	8.56	1.1–64	0.03
	12	≥ 3	12.16	1.9–75	0.007

The odds for co-trimoxazole and erythromycin being associated with PRP carriage were twice that for β-lactams in association with 3 or more antimicrobial courses

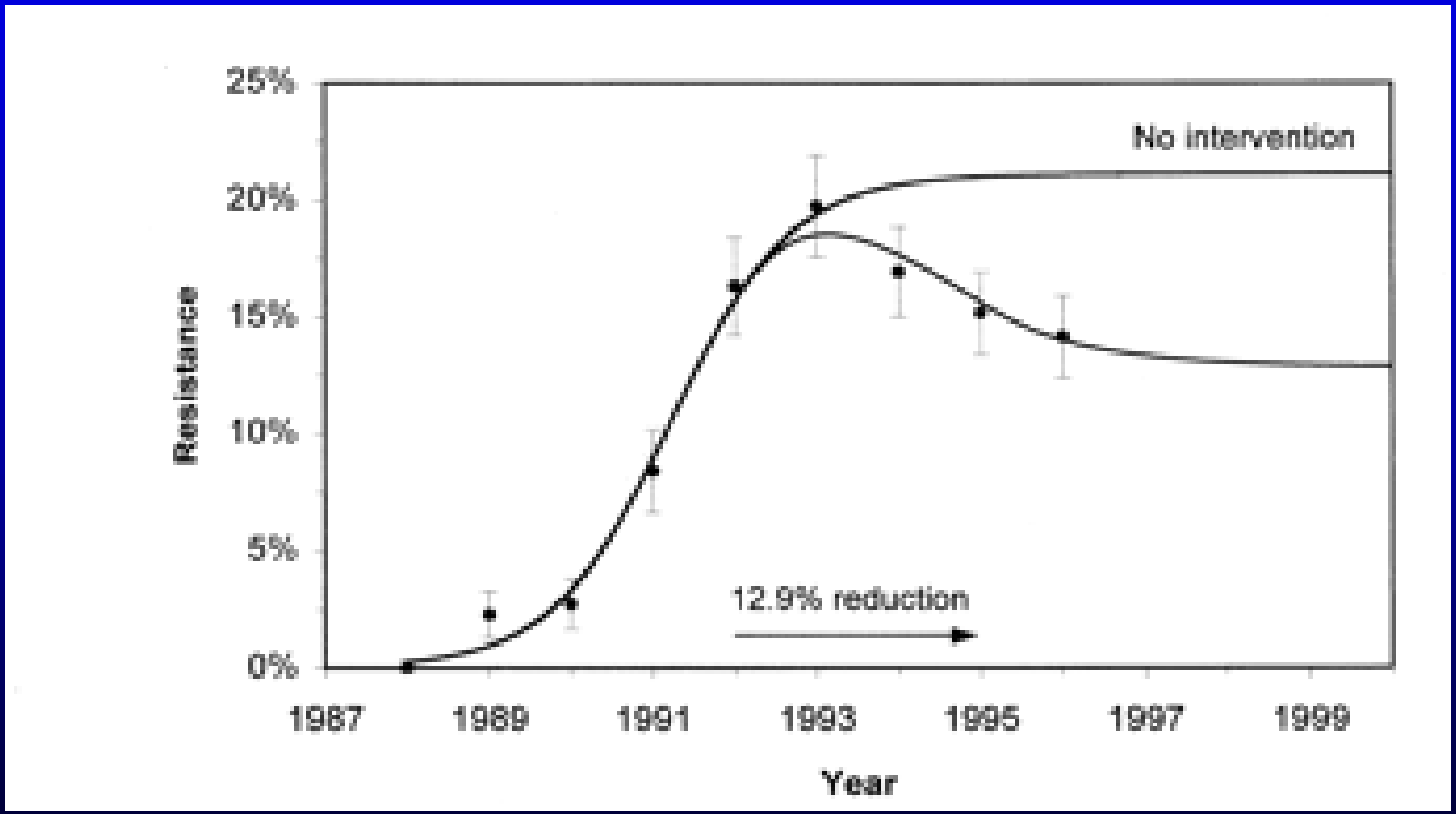
Arason et al, BMJ, 1996.

Impact of Reduction of Antibiotic Consumption on PRP Carriage

- Incidence of PNSP (penicillin non-susceptible) peaked in 1992 (19.8%): declined to 13% in 1997
- Predominant type 6B multi-resistant clone (Spanish-Icelandic)
- From 1990 β-lactam consumption was not reduced BUT: trimethoprim sulfamethoxazole (TMP/SXT) and erythromycin use was reduced by 30%

Arason et al, BMJ, 1996.

Impact of reduction in macrolide and cotrimoxazole Usage on penicillin – resistant pneumococci in Iceland



Austin DJ, Kristinsson KG, Anderson RM
Proc Natl Acad Sci U S A 1999 ;96:1152-6

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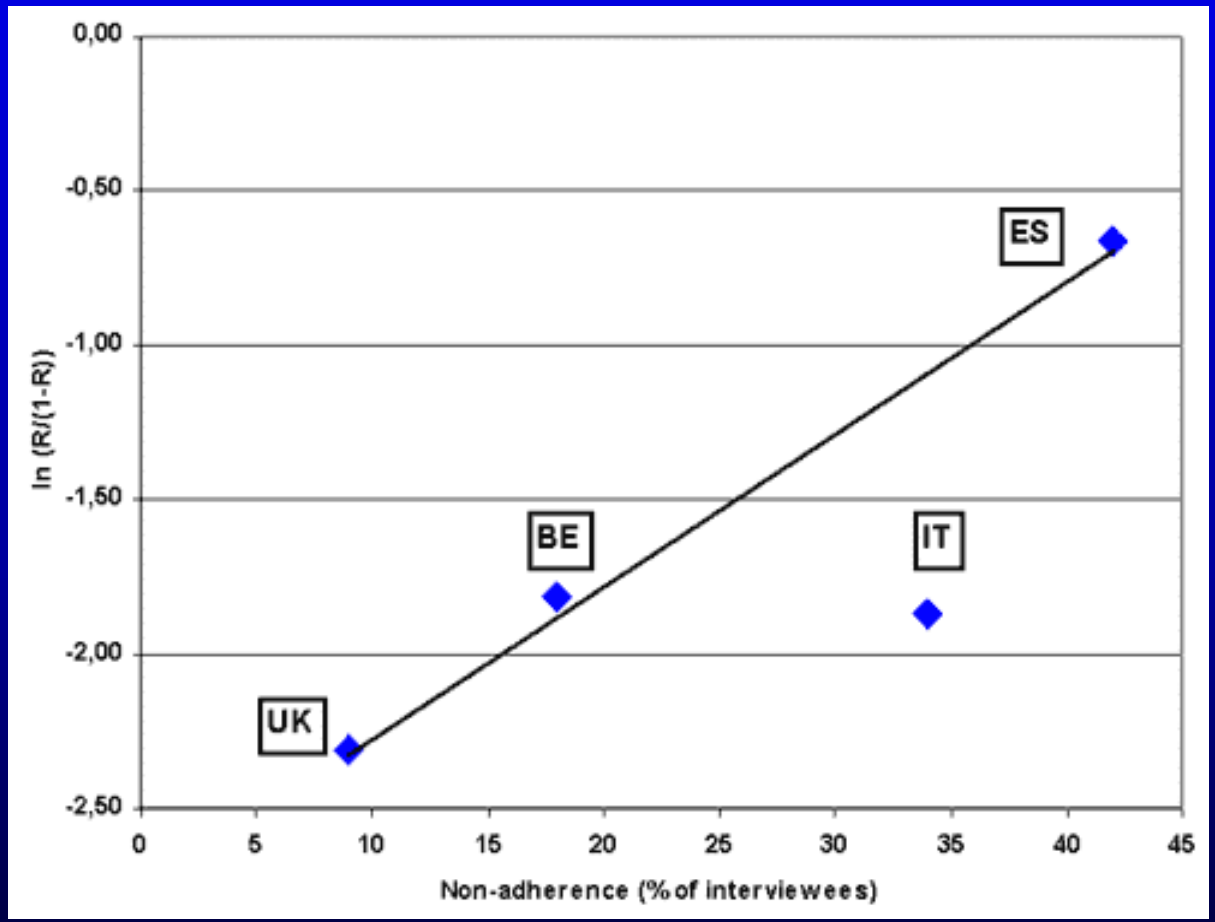
Association of Non – Adherent Antibiotic Use with Resistance in the Pneumococcus



The logodds of resistance of invasive isolates of *Streptococcus pneumoniae* to penicillin (PNSP; ln(R/(1-R))) is regressed against nonadherence rates to antibiotic therapy in four European countries

Bronzwaer et al, EID, March, 2002.

Low dose and long duration of β-lactam therapy as risk factors for penicillin-resistant pneumococcal carriage

	odds ratio	confidence interval
Oral β-lactams in past 30 days	3.0	1.1–8.3
Dose lower than clinically recommended	5.9	2.1–16.7
Treatment > 5 days	3.5	1.3–9.8

NB Data are based on 16 children carrying PRSP (of 864). Ten of these children had low dose, long duration treatment

Guillemot et al. *JAMA*. 1998.

Selection of Resistant Pneumococci by High Dose, Short Duration Amoxicillin Rx

RELATIVE RISK OF PRSP IN CARRIERS

HIGH DOSE vs LOW DOSE	0.78 (0.65 – 0.95)	P = 0.01
DAY 28 vs DAY 0 HIGH DOSE	1.22 (1.02 – 1.48)	P = 0.03
DAY 28 vs DAY 0 LOW DOSE	1.60 (1.36 – 1.89)	P < 0.001

Schrag et al, JAMA, 2001, 286: 49 - 56

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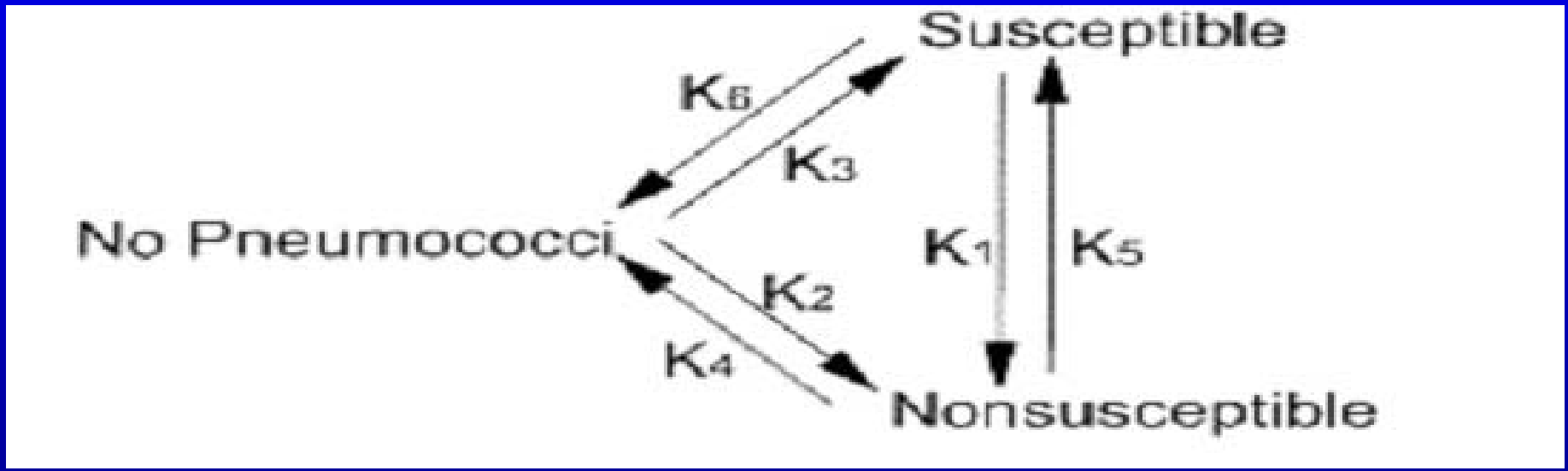
Therapy for malaria with pyrimethamine-sulfadoxine (fansidar) increases pneumococcal resistance to trimethoprim - sulphamethoxazole

Feikin et al, JID, 2000, 181, 1501 – 5.

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%)
SP	29/96	(30%)

TRANSITION RATE BETWEEN INITIAL VISIT AND 4-WEEK VISIT	K1	
No Treatment	2/24	(8%)
Cotrimoxazole	9/40	(23%)
SP	28/73	(38%)

Feikin et al, JID, 2000, 181, 1501 – 5.

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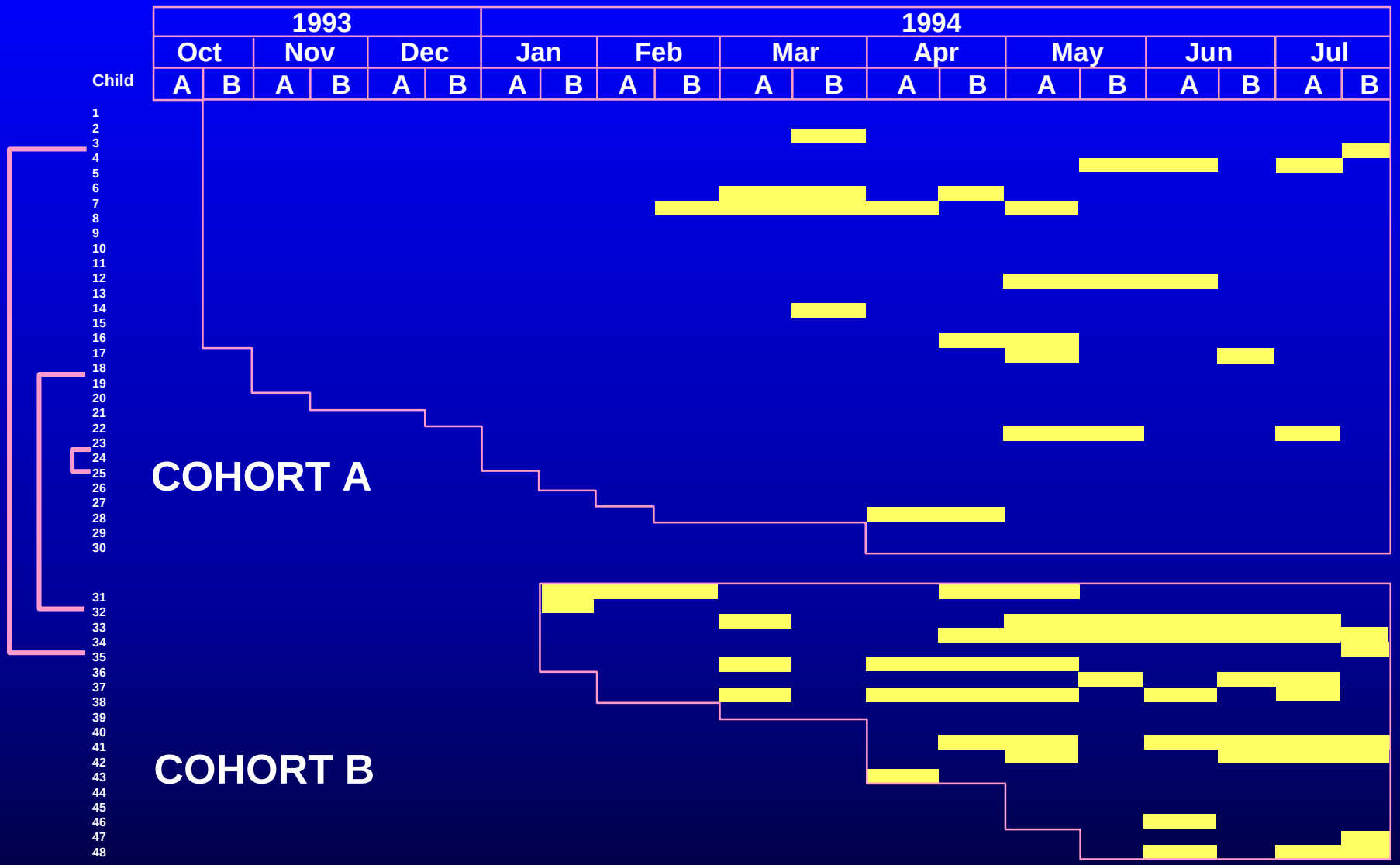

Isolation of *S. pneumoniae* 23 F, intermediately susceptible to penicillin and resistant to trimethoprim-sulfamethoxazole

Siblings

Yagupsky et al, JID, 1998, 177,1003-12.

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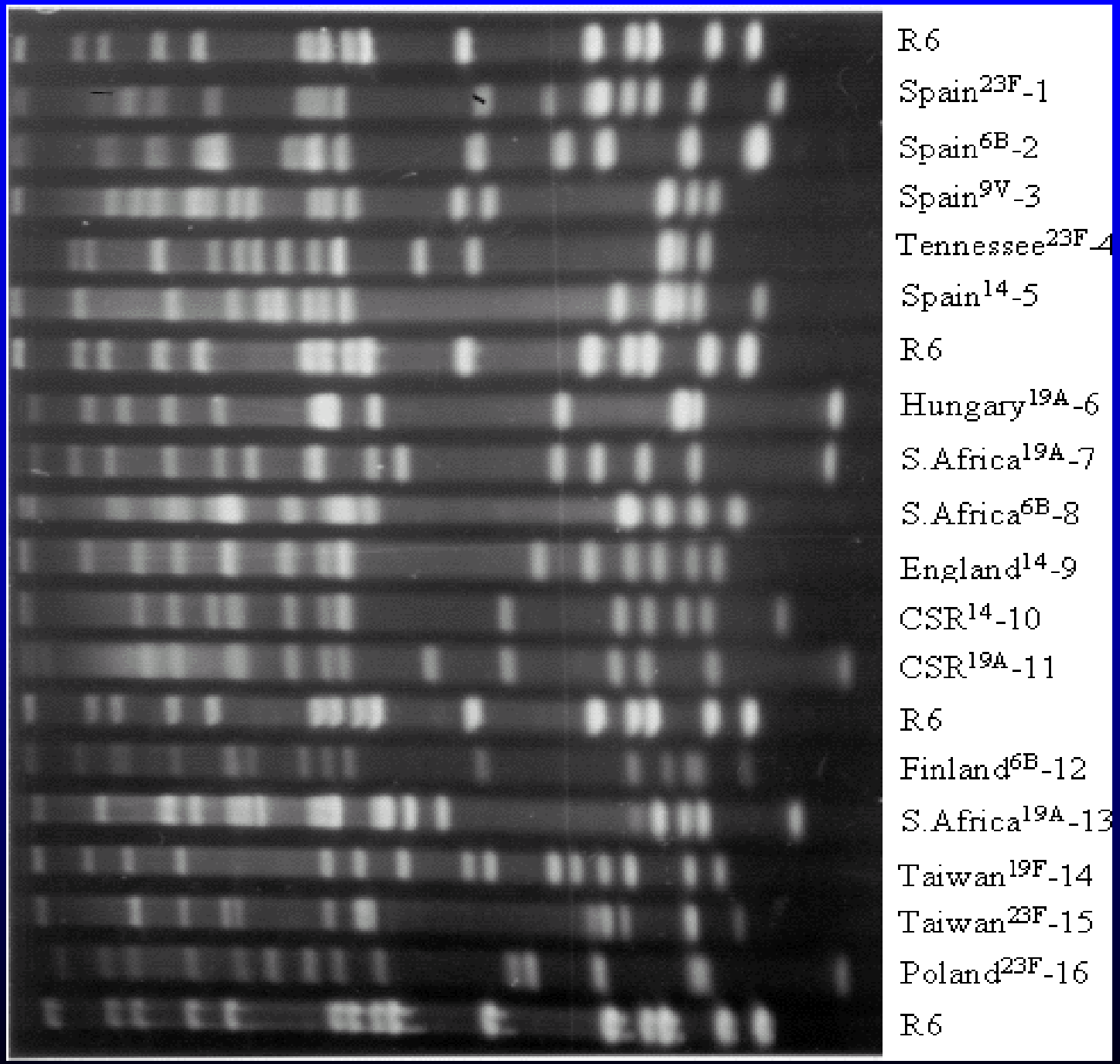
Clonal spread of *S. pneumoniae* 23F

Pneumococcal Molecular Epidemiology Network of the IUMS

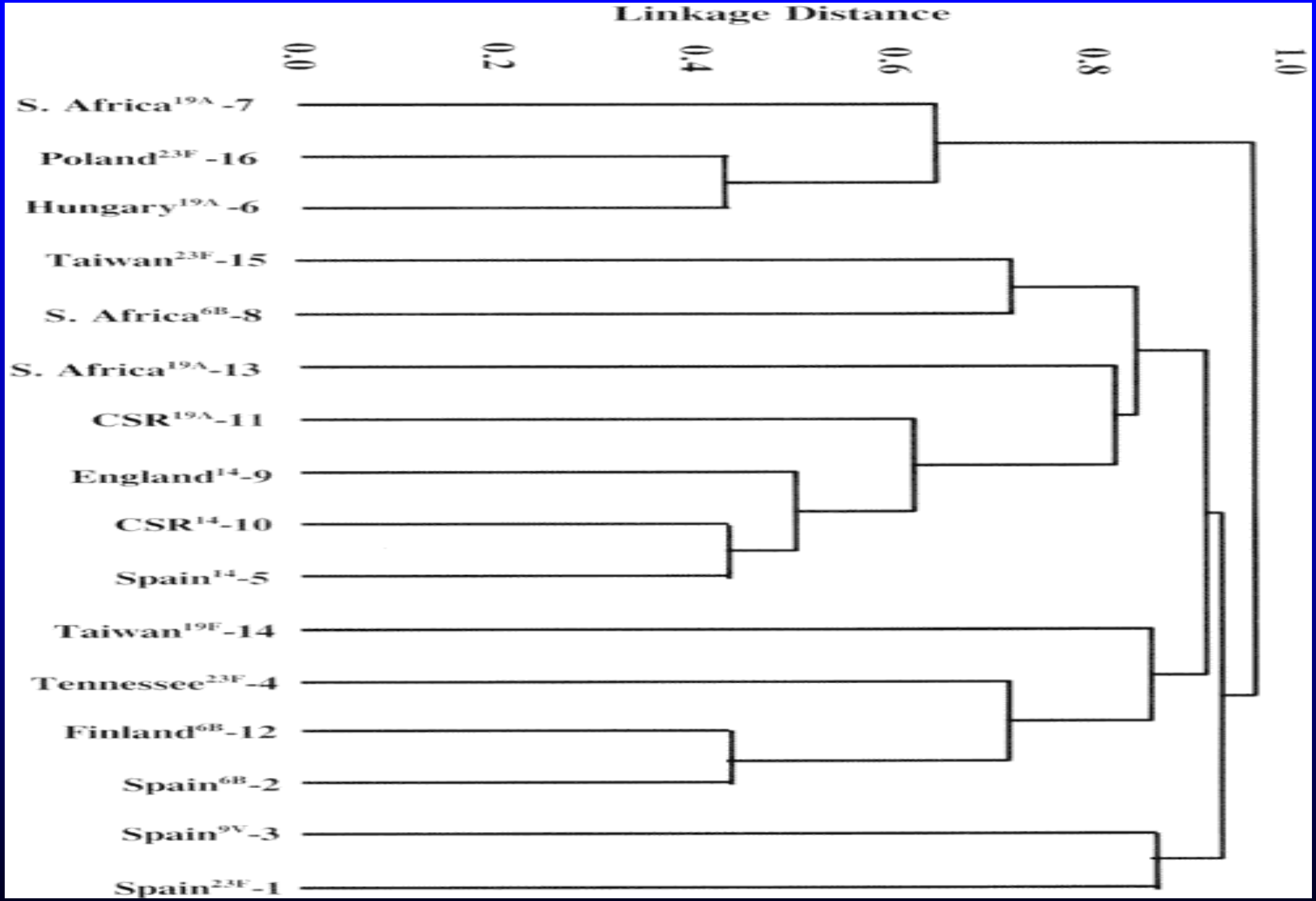
Nomenclature

COUNTRY	SEROTYPE ISOLATED	—	INTERNATIONAL CLONE NUMBER	—	SUBSEQUENT SEROTYPE
Eg. SPAIN	23F		- 1		- 19F

McGee *et al*, J Clin Microbiol, July, 2001



McGee *et al*, J Clin Microbiol, July, 2001



McGee *et al*, J Clin Microbiol, July, 2001

Clones of Penicillin – Resistant Pneumococci in the USA

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

Corso et al, MDR, 1998; 4: 325 – 337.

Clonality of Highly Penicillin – Resistant Pneumococci - USA

Spain ^{23F} - 1	123/672	18.3%
Spain ^{9V} – 3	96/672	14.3%
PFGE type 3	65/672	9.7%
Spain ^{6B} - 2	44/672	6.5%
PFGE type 5	42/672	6.3%
Tennessee ^{23F} – 4	33/672	4.9%
PFGE type 7	28/672	4.2%
PFGE type 8	25/672	3.7%
PFGE type 9	22/672	3.3%
PFGE type 10	20/672	3.0%
Taiwan ^{19F} - 14	11/672	1.6%
PFGE 12	8/672	1.2%
PFGE 13	7/672	1.0%
12 Clones	524/672	78.0%

Richter et al, 2002, CID; 34: 330-9

Emergence of FQ Resistance in Global Clones of Pneumococci

- 29 FQ resistant pneumococci with ofloxacin MIC's $\geq$ 4 µg /ml were identified from the Alexander project and from Northern Ireland.
- Clonality was determined by BOX – PCR and by pulse field electrophoresis
- 16 types were identified amongst the 29 strains INCLUDING
- 4 strains identical or closely related to SPAIN^{23F}-1
- These strains came from France and Spain
- 7 strains from France and N. Ireland identical to FRANCE^{9V}-3.

McGee et al, JAC, 2002, 49: 173 – 176

Increase in FQ Resistance in the Pneumococcus in Hong Kong

- Two studies of sequential clinical isolates from 6 Hospitals in Hong Kong - 1998 & 2000
- Levo MIC $\geq$ 4 µg/ml - → from 5.5% to 13.3%
- In Pen Resistant strains - → 9.2% to 27.3%
- Risk factors were:

  Patients $\geq$ 65yrs – 17.1% vs 9.1%(18-64) (P<0.001)

  Adults with COPD – 24.6% vs 9.3% (P = 0.01)
- All FQ resistant strains are a clone of SPAIN^{23F} – 1 resistant to penicillin (MIC 2-4 µg/ml) and cefotaxime (MIC 1-4 µg/ml)

Ho et al, JAC, 2001, 48,659-65.

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Impact of HIV on Penicillin – Resistance in the Pneumococcus

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

Crewe-Browne et al, CID, 1997

Emerging Problem

Cotrimoxazole - resistant and multiply resistant pneumococcal infections in HIV – infected patients on prophylaxis with the drug

Madhi et al, 2000, **Clin Infect Dis; 31: 170 -176.**

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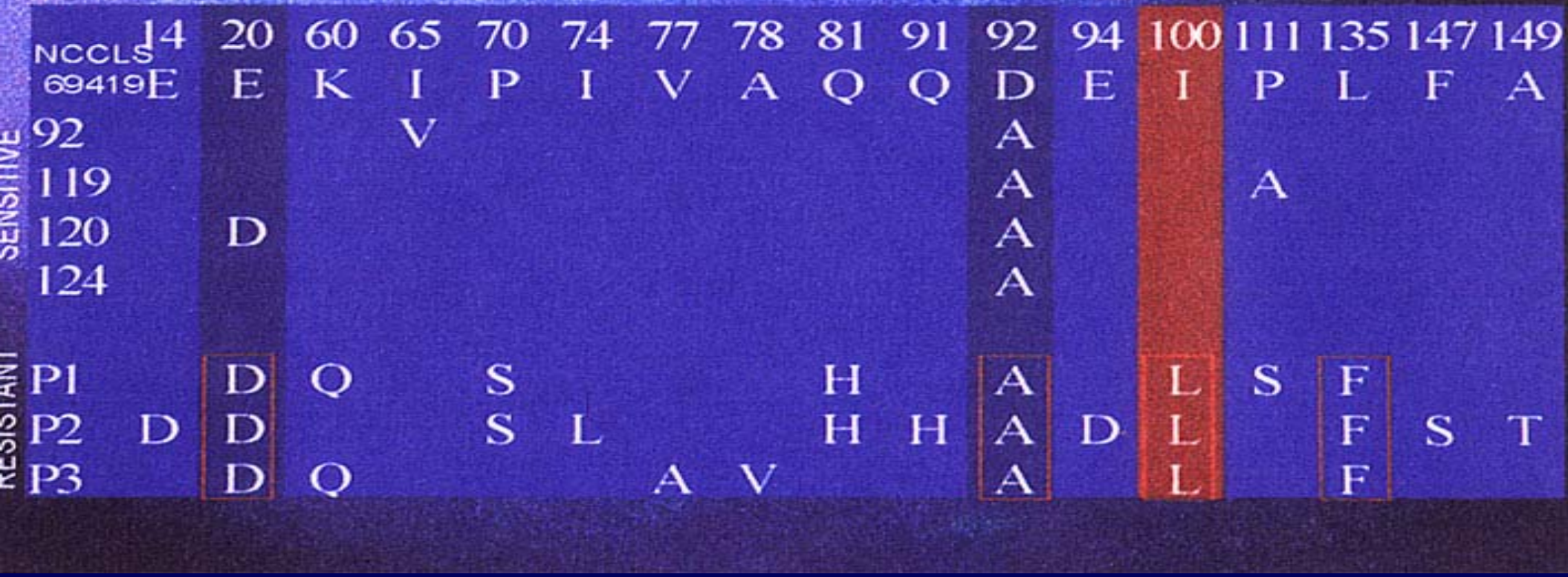
AMINO ACID SUBSTITUTIONS IN SENSITIVE AND RESISTANT DHFRS



	14	20	60	65	70	74	77	78	81	91	92	94	100	111	135	147	149
NCCLS 69419	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						
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

Adrian and Klugman, **AAC, 1997, 41: 2406 - 2413.**

New Mechanism of Tetracycline Resistance in Pneumococci

tet (O) discovered in 5 strains from Cape Town, South Africa - a single clone in children.

– remains rare, one subsequent report – from Seattle, Washington, USA

– none in 277 tetracycline – resistant strains screened in Europe.

This mechanism will probably will remain rare unless strains acquire genes conferring resistance to commonly prescribed antibiotics in children

Widdowson, Klugman, Hanslo, AAC, 1996, 40: 2891 –3.

Luna & Roberts, JAC, 1998, 42, 613-9.

Schmitz et al, Int J Antimicrob Agents, 2001,18, 433-6.

Molecular Insights Into Mechanisms of Resistance in the Pneumococcus

A staphylococcal plasmid has linearised, inserted into the pneumococcal genome, and confers chloramphenicol resistance in the pneumococcus

Could the enterococcal plasmid conferring vancomycin resistance do the same?

Widdowson, Adrian and Klugman, AAC, 2000, 44: 393 - 5.

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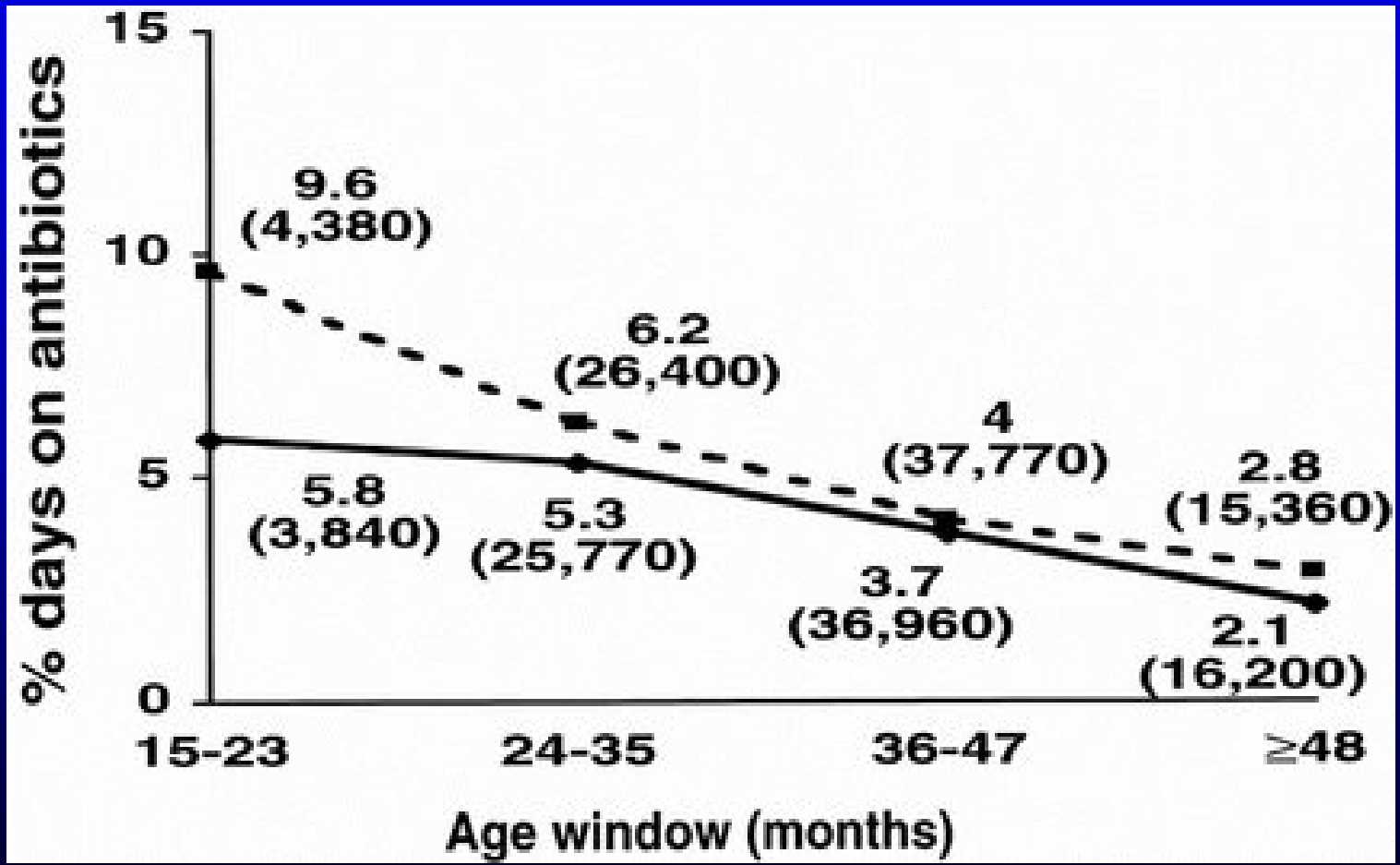
Impact of 9 – Valent Conjugate Vaccine on Carriage of Antibiotic – Resistant Pneumococci

Antibiotic resistance	Vaccinees n = 130		Controls n = 145	P
Penicillin	27	(21)	60 (41)	.0002
Chloramphenicol	2	(2)	5 (3)	--
Tertacycline	14	(11)	13 (9)	--
Erythromycin	8	(6)	6 (4)	--
Clindamycin	7	(5)	4 (3)	--
Rifampicin	2	(2)	1 (1)	--
Cotrimoxazole	30	(23)	51 (35)	.003
Any of the above	59	(45)	90 (62)	.005

Mbelle, et al, JID, 1999

Use of Pneumococcal Conjugate Vaccine Reduces Antibiotic Use

Risk of antibiotic use 0.83 (95% CI 0.79 to 0.87; $P < 0.001$).



Dagan et al, PIDJ, 2001;20:951-958

Interventions

- Education of patients, prescribers and guidelines to reduce inappropriate antibiotic use for viral upper RTI.
- Better diagnostic test to decrease empiric treatment
- Development of new drugs
- Strategies to reduce specific classes of antimicrobial use in order to decrease resistance are complicated by multiple resistance.
- Give antibiotics in short courses at high doses
- Pneumococcal conjugate vaccines interrupt the transmission of multiply resistant strains that belong to vaccine serotypes, and vaccinated children receive less antibiotics.

3rd International Symposium on Pneumococci and Pneumococcal Diseases

May 5 – 9, 2002
Anchorage, Alaska
The Hotel Captain Cook

http://www. asmusa.org/mtgsrc/isppd02.htm

Hosted by the Centers for Disease Control and Prevention's Arctic Investigations Program, John Hopkins University Center for American Indian and Alaska Native Health, and managed by the American Society for Microbiology.