

USE AND RESISTANCE TO ANTIBIOTICS IN THE COMMUNITY

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Outline of Presentation

- ❖ Introduction
- ❖ Link between use and resistance
 - ❖ At population level
 - ❖ At individual level
- ❖ Conclusions

BACKGROUND

- ❖ Antibiotics are among the most common prescribed drugs
- ❖ Antibiotics have ecological impact in individuals and in the population
- ❖ Resistance to antibiotics is increasing world-wide in the community and in hospitals

USE OF ANTIBIOTICS

Where antibiotics are used	Types of use	Questionable use
Human use (50%)	20% hospital 80% community	20 – 50% unnecessary
Agricultural use (50%)	20% therapeutic 80% prophylactic/ growth promotion	40 – 80% highly questionable

Wise R et al. BMJ 1998; 317: 609

The panorama of antimicrobial resistance

❖ Community

- ❖ *S. pneumoniae* – pen/amox, 3rd Ceph
- ❖ *S. pyogenes* – ery/clinda
- ❖ Hi – ampi
- ❖ *E. coli* – ampi, FQs, TMP/SMX, AGs, 3rd Ceph
- ❖ *S. aureus* – CA – MRSA

❖ Hospital (nosocomial)

- ❖ ESKAPE – *E. faecium*, *S. aureus*, *K. pneumoniae*, *A. baumannii*, *P. aeruginosa*, *Enterobacter spec.*

MAJOR DETERMINANTS OF RESISTANCE DEVELOPMENT

- ❖ Selective antibiotic pressure
- ❖ Co - selection process
- ❖ Transferable resistance
 - ❖ clonal spread
 - ❖ horizontal gene transfer between bacteria

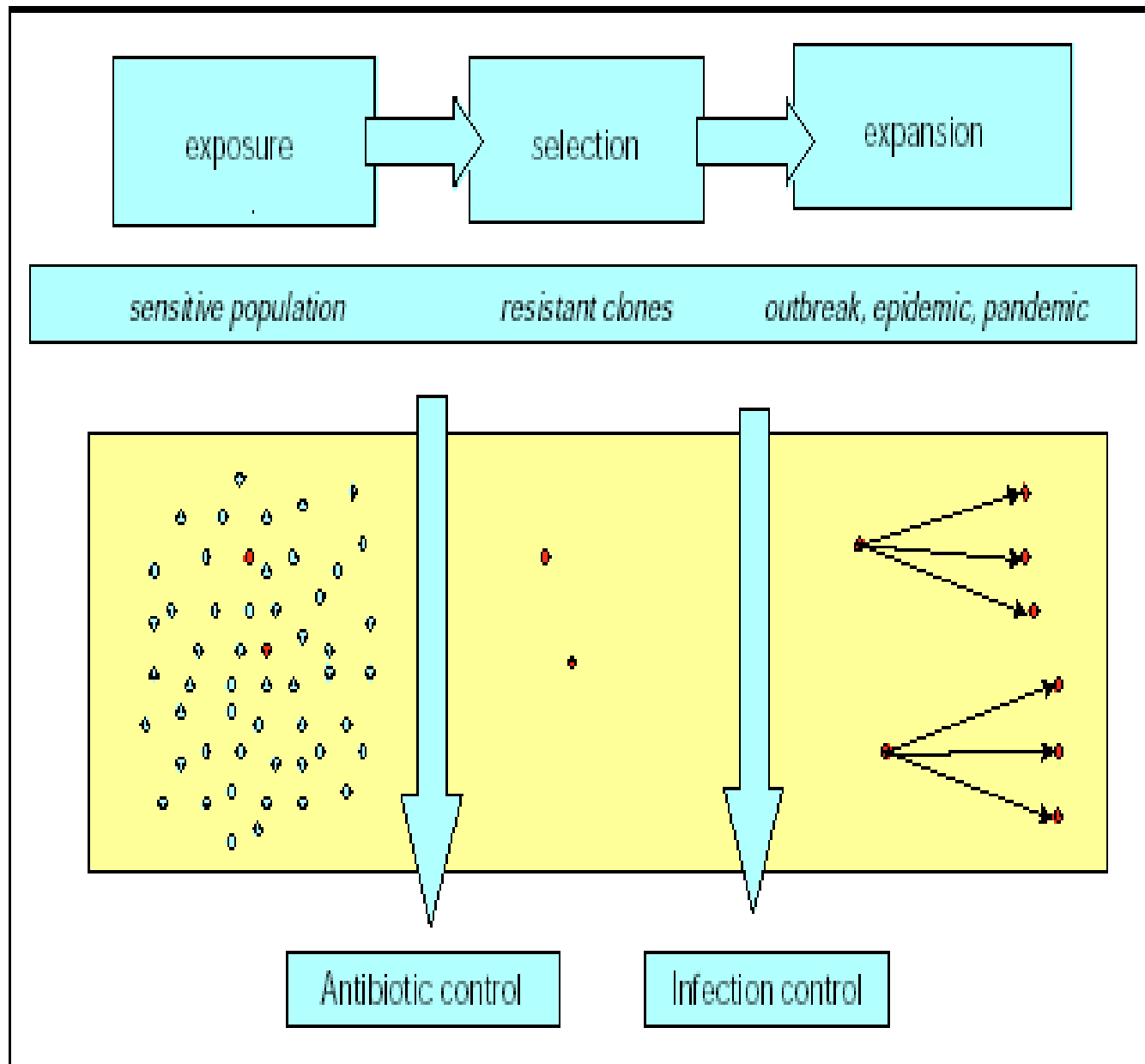


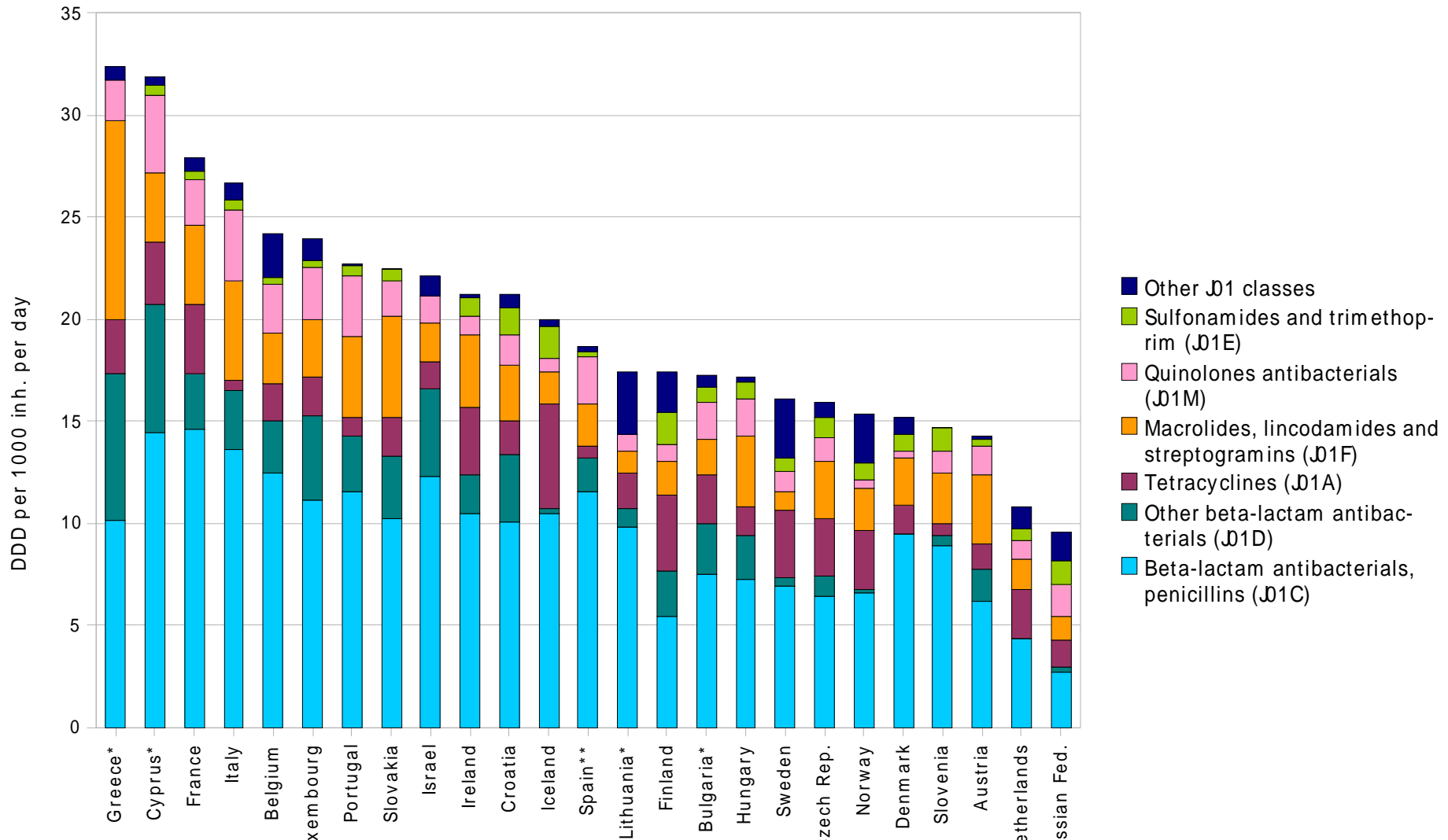
Figure 1. Model of resistance emergence and the crucial roles of antibiotic control and infection control in preventing outbreaks, epidemics and pandemics.

KEY FACTORS IN THE DEVELOPMENT OF ANTIMICROBIAL RESISTANCE

- ❖ total amount of antimicrobial usage
- ❖ drug used (class, group)
- ❖ dosage regimens
(dosage, duration, parenteral vs. oral, pharmacodynamics)
- ❖ frequency of cross-infections with resistant organisms
(poor hygiene, hospital, nursing homes)
- ❖ public behaviour and social conditions
(public expectation of receiving antibiotics for any infection, travel, overcrowding in long - term and day - care facilities, compliance)

Standing Medical Advisory Committee, 1998

Total Outpatient Antibiotic Use in 25 European Countries in 2006



* Greece, Cyprus, Lithuania, Bulgaria: total care, i.e. hospital and primary care combined.

** Spain: reimbursement data, which do not include over-the-counter sales without a prescription.

Country	Total outpatient antibiotic sales in 1997 DDD/1000 inhab/day	<i>S. pneumoniae</i> Penicillin intermediate and resistant (%)
France	36.51	53.3 – 66.5
Spain	32.44	50.1 – 65.6
Portugal	28.83	17.1 – 24.7
Slovak Republic	28.75*	51.4
Belgium	26.72	8 – 14.2
Luxembourg	25.58	30.4
Italy	23.99	9 – 16.8
Greece	22.69	31.6
Hungary	21.1*	40
Czech Republic	19.96*	7.1
Finland	19.34	4.8
Ireland	18.34	32.8
UK	18.04	10.8 – 19.5
Slovenia	17.56	15
Norway	14.5*	3
Austria	13.80	12.4
Germany	13.58	7.2
Sweden	13.51	3
Denmark	11.35	2.4
The Netherlands	8.96	3.2
Russia	11.2*	NA

**TOTAL OUTPATIENT
ANTIBIOTIC SALES
(1997 – 1998)
AND RESISTANCE
OF *S. PNEUMONIAE*
(1997 – 1999)**

*Cizman M. Int J Antimicrob Agents.
2003 Apr;21(4):297-307.*

* 1998 total use including hospital use, NA not available
Cars O et al. Lancet 2001; 357: 1851, Stratchounski L, et al.
Int J Antimicrob Agents 2001; 18: 283.
Schito GC et al. JAC 2000; 46: (T1) 3, Sahm DF, et al.
JAC 2000; 45: 457

STUDIES CORRELATING THE USE OF AMINOPENICILLINS AND CEPHALOSPORINS AND PREVALENCE OF RESISTANCE I.

- ❖ **The occurrence of PRSP linked to increased use of aminopenicillins**
Baquero F et al. JAC 1991; 28; Suppl C: 31
- ❖ **Prevalence of invasive PRSP correlated with the use of β - lactams**
Bronzwaer et al. Emerg Infect Dis 2002; 8: 278
- ❖ **Cephalosporins were slightly more important penicillin-resistance drivers than aminopenicillins in *S. pneumoniae***
Garcia –Rey C et al. J Clin Microbiol 2002; 40:159
- ❖ **The occurrence of β - lactamase producing strains of *M. catarrhalis* linked to increased use of cephalosporins**
Nissinen A et al. CID 1995; 21: 1193

STUDIES CORRELATING THE USE OF MACROLIDES AND PREVALENCE OF RESISTANCE II.

- ❖ The occurrence of erythromycin resistance in *S. pyogenes* correlates with increased use of erythromycin (macrolides)

Seppälä H et al. N Engl J Med 1997; 337: 441

Perez – Trallero E et al. Eur J Clin Microbiol Infect Dis 1998;16:25

Čížman M et al. Eur J Clin Microbiol Infect Dis 1999; 18:522

- ❖ The occurrence of erythromycin resistance in *S. pneumoniae* correlates with increased use of erythromycin (macrolides)

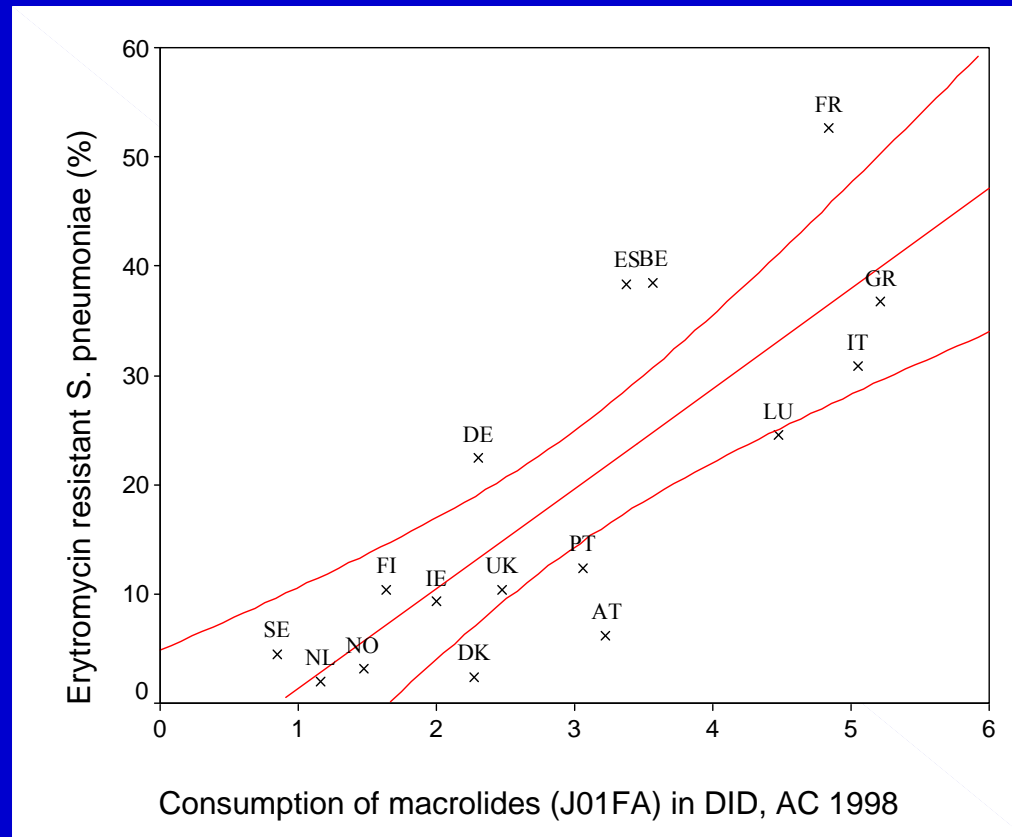
De Neeling J et al. JAC 2001; 48: 441

Nielsen HUK et al. 41th ICAAC 2001

Pihlajamäki M et al. Clin Infect 2001; 33: 483

Čížman M et al. JAC 2001; 47: 475

Correlation Between Macrolide Use and Macrolide-Resistant *Strept. pneumoniae*



Organism year of isolation [source of information]	Antibiotic resistance	Antibiotic use - ATC group (year of data)	No. of countries	Spearman correlation (r) (confidence interval)	P-value
<i>S. pneumoniae</i> 1999/2000 [8]	Erythromycin	Macrolides - J01FA (1998)	16	0.83 (0.67-0.94)	< 0.001

STUDIES CORRELATING USAGE OF A GROUP OF ANTIBIOTICS AND PREVALENCE OF RESISTANCE

- ❖ The occurrence of erythromycin resistance in *S. pneumoniae* indicates a correlation with increased use of newer long – acting macrolides

Baquero F. J Chemother 1999; 11: Suppl 1: 35
Granizo IJ et al. JAC 2000; 46:959
Nielsen HUK et al. 41th ICAAC 2001
Reinert RR et al. JAC 2002; 49: 61

STUDIES CORRELATING THE USE OF FLUOROQUINOLONES AND PREVALENCE OF RESISTANCE

- ❖ The occurrence of reduced susceptibility to fluoroquinolones of *S. pneumoniae* associated with increased use of fluoroquinolones

Chen DK et al. N Engl J Med 1999; 341: 233

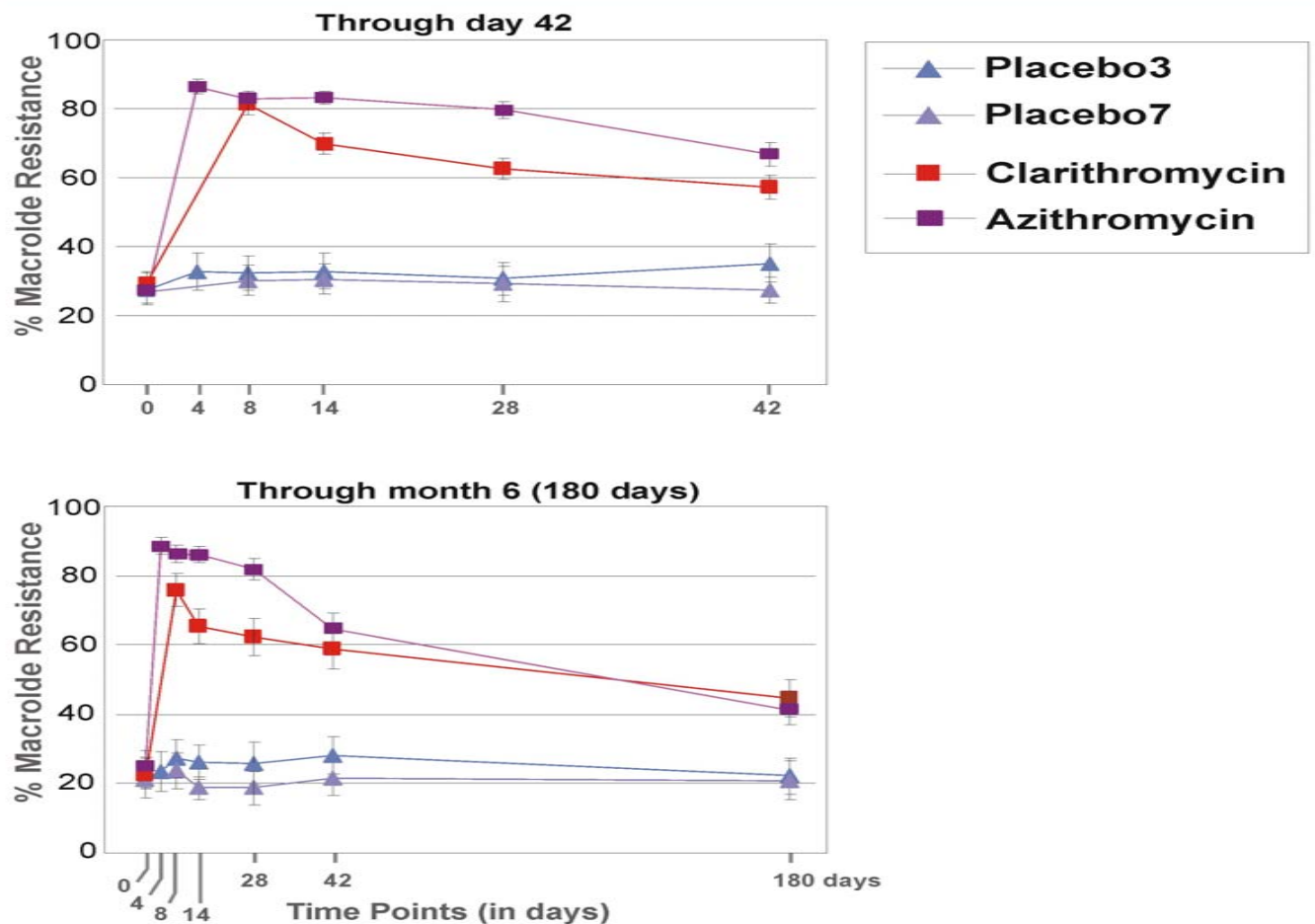
Linares J et al. N Engl J Med 1999; 341: 1546

- ❖ The occurrence of reduced susceptibility to fluoroquinolones of *E. coli* associated with increased use of fluoroquinolones

Goetsch W, et al. JAC 2000; 46: 223

Čížman M, et al. JAC 2001; 47: 502

Effect of Macrolide versus Placebo Use on Temporal Changes of Proportion of Macrolide-Resistant Oral Streptococci



Mean preantibiotic carriage of Mac-R streptococci was 28%

Use of both Clar and Azi resulted in a huge increase in resistant streptococci which persisted for at least 6 months ($P \leq 0.01$)

Macrolide use is the single most important driver for the emergence of macrolide resistance

STUDIES INDICATING REVERSAL OF RESISTANCE

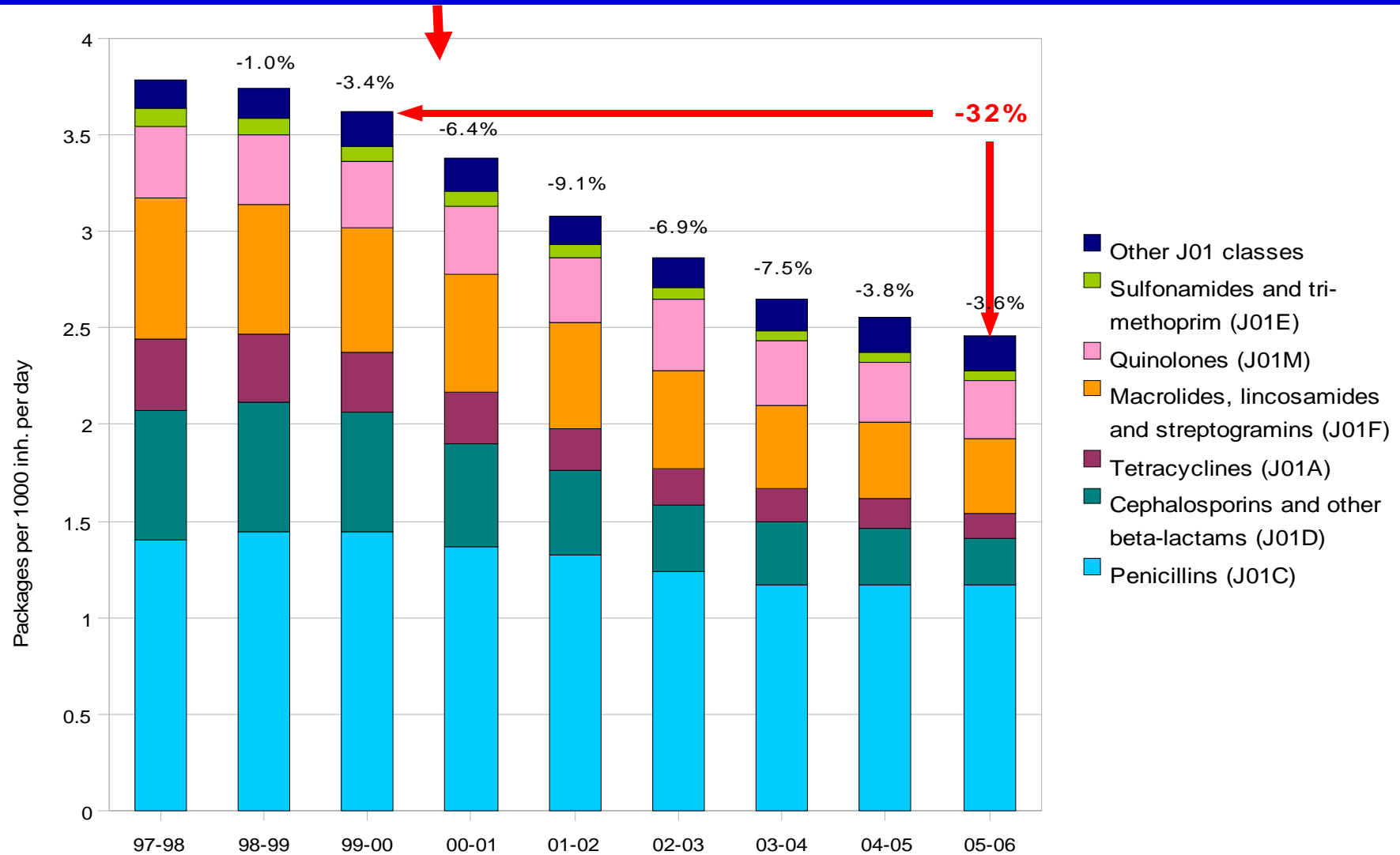
Country	Pathogen	Time period	Prevalence of resistance	Decreased consumption
Japan	<i>S. pyogenes</i>	1974	62% EryR	22% of all antibiotic
		1988	2% EryR	8% of all antibiotic
Finland	<i>S. pyogenes</i>	1992	19% EryR	2,44 DDD/1000 inh./day
		1996	9% EryR	1,38 DDD/1000 inh./day
Iceland	<i>S. pneumoniae</i>	1993	20% PRSP	10% of total antibiotic
		1997	13% PRSP	30% of TMP/SMX and macrolides

Fujito K et al. PIDJ 1994; 13: 1075

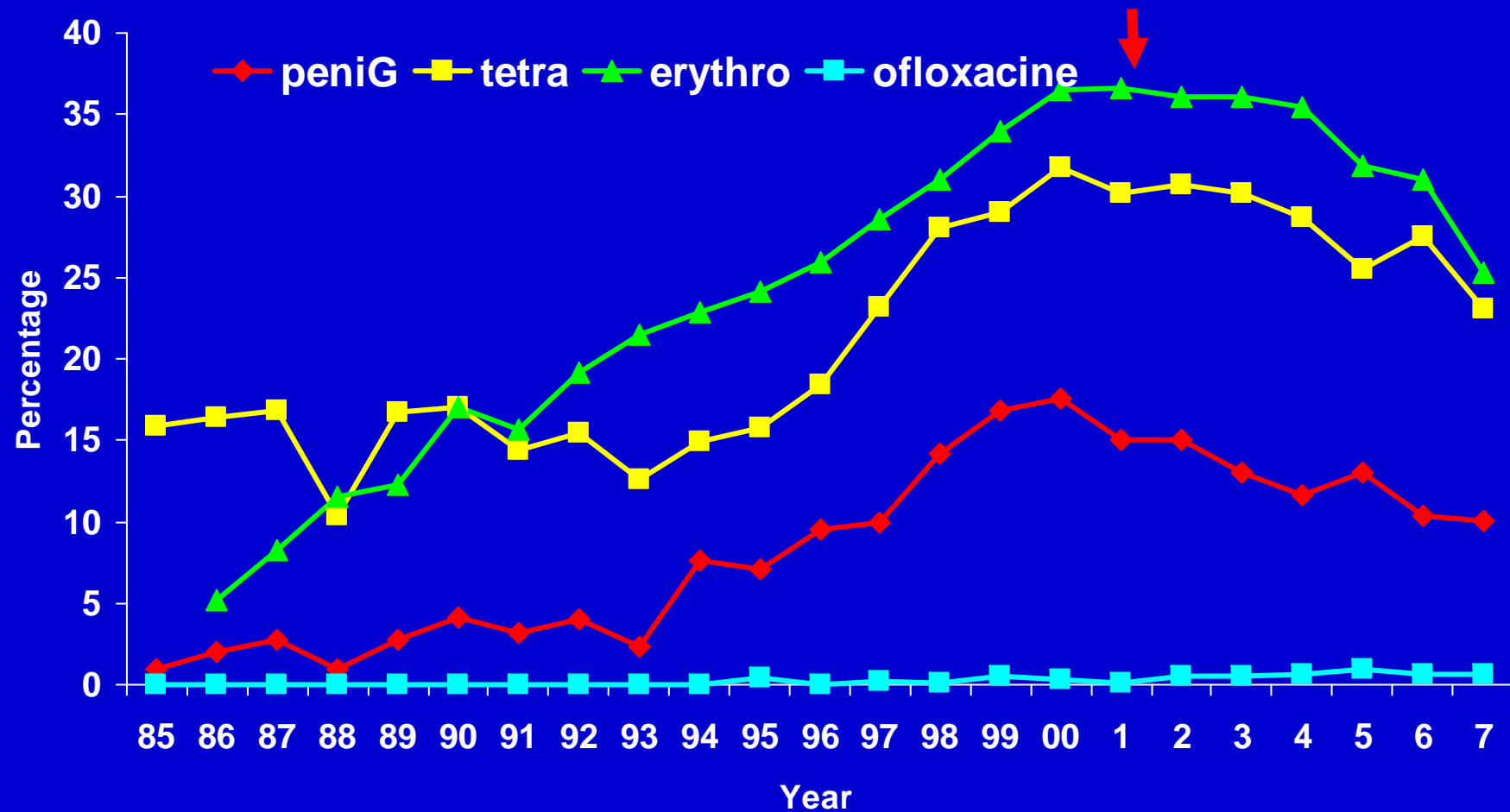
Seppälä H et al. N Engl J Med 1997; 337: 441

Kristinsson KG et al. 38th ICAAC 1998

Outpatient Antibiotic Use in Belgium Packages per 1,000 inhabitants per day 1997 – 2006, July to June

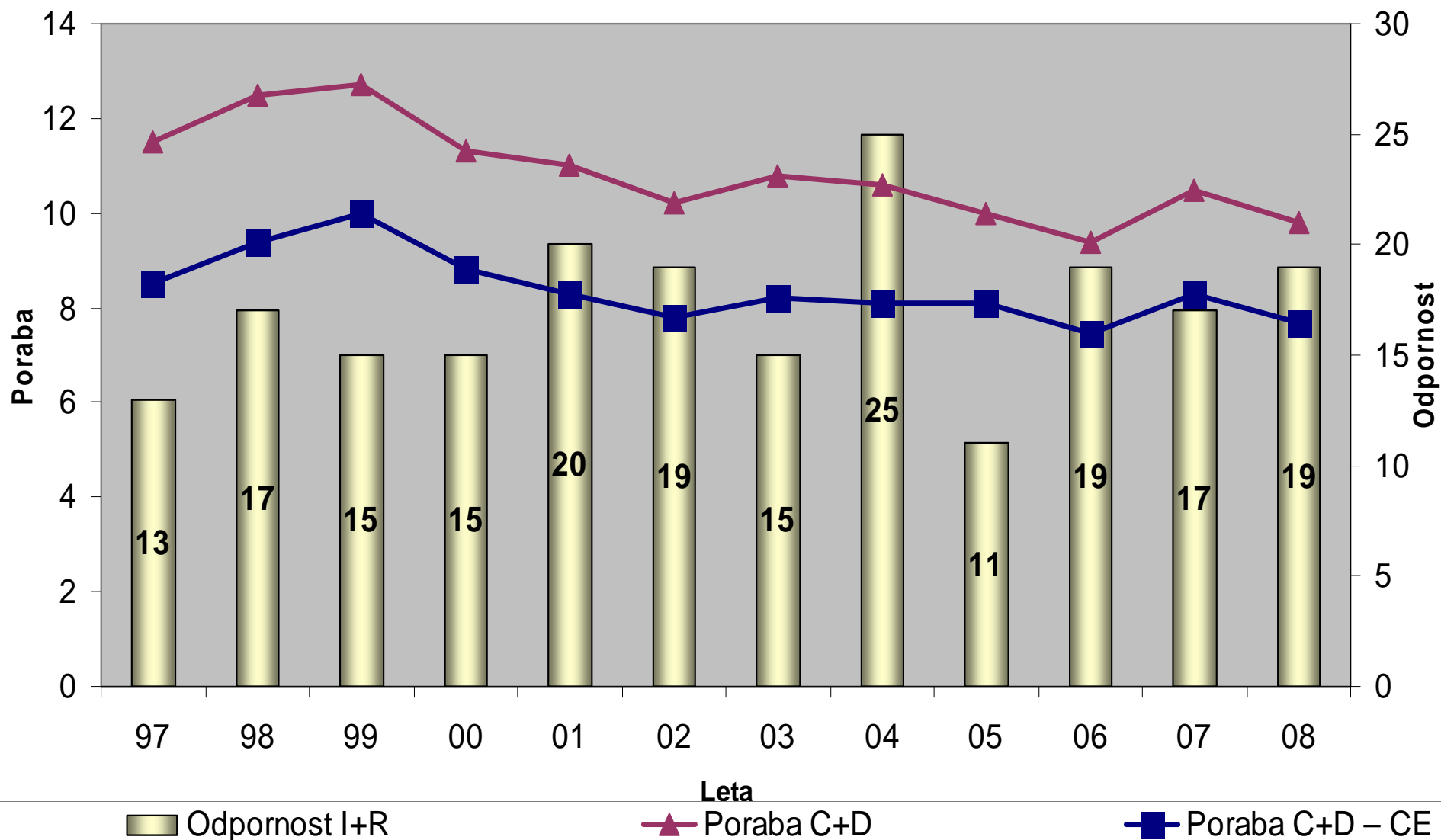


Antibiotic Resistance of *S. pneumoniae* in Belgium. 1985 - 2007

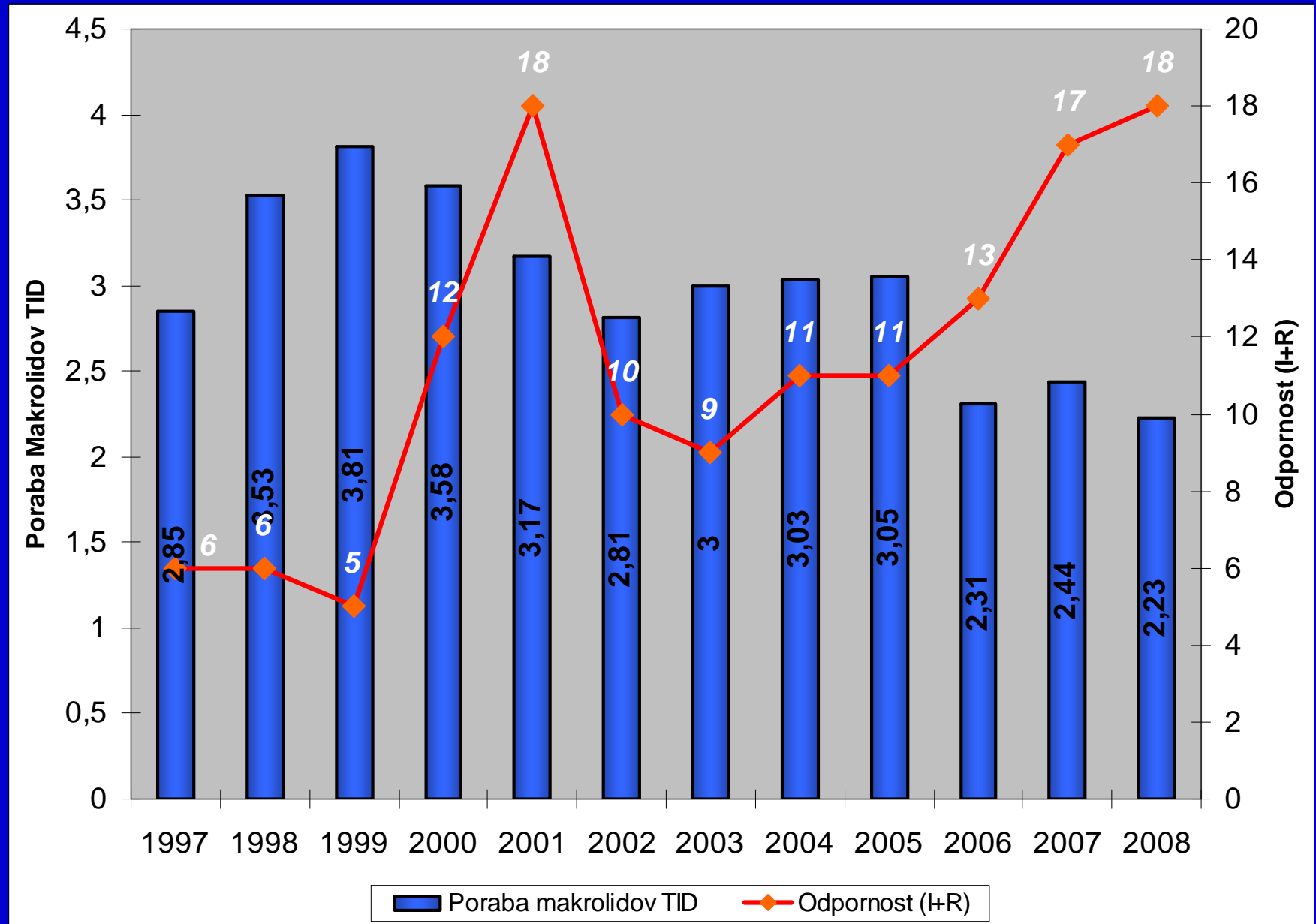


National Reference Centre *S. pneumoniae* (University of Leuven)

Correlation between use of penicillins, cephalosporins and resistance of *S. pneumoniae* to penicillin Slovenia 1997-2008



Use of macrolides and resistance of *S. pneumoniae* to macrolides in Slovenia 1997-2008



Macrolide resistance rates in respiratory pathogens in Slovenia following reduced macrolide use

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Received 26 July 2006; accepted 14 September 2006

Abstract

The aim of this study was to investigate the association between decreased use of macrolides and resistance of common respiratory pathogens in Slovenia from 1999 to 2004. Over a 6-year period the consumption of macrolides in Slovenia decreased by 21.3%, from 3.81 defined daily doses/1000 inhabitants per day (DID) to 3.0 DID. The use of short-acting, intermediate-acting and long-acting subclasses of macrolides decreased by 50%, 18% and 13%, respectively. In the same period, resistance of invasive strains of *Streptococcus pneumoniae* increased from 4.6% to 11.1% and resistance of non-invasive strains of *S. pneumoniae* and *Streptococcus pyogenes* increased from 12.8% to 20.2% and from 7.4% to 12.5%, respectively. Resistance increased significantly more in children than in adults ($P=0.05$) and was significantly correlated with increased use of intermediate-acting macrolides ($r=0.94$ for non-invasive *S. pneumoniae* and $r=0.96$ for *S. pyogenes*) in children. Resistance of *Haemophilus influenzae* and *Moraxella catarrhalis* was low and did not change. In children and adults, the emergence and spread of multidrug-resistant strains of invasive *S. pneumoniae* was observed. The decline in total macrolide use was not paralleled by reduced macrolide resistance rates of *S. pyogenes* and *S. pneumoniae* during the 6-year period. There was a strong correlation between the use of intermediate-acting macrolides and macrolide resistance of *S. pyogenes* and *S. pneumoniae* in children. Further reduction in the use of intermediate- and long-acting macrolides should be encouraged.

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Keywords: Macrolides; Antibiotic resistance; Antibiotic consumption

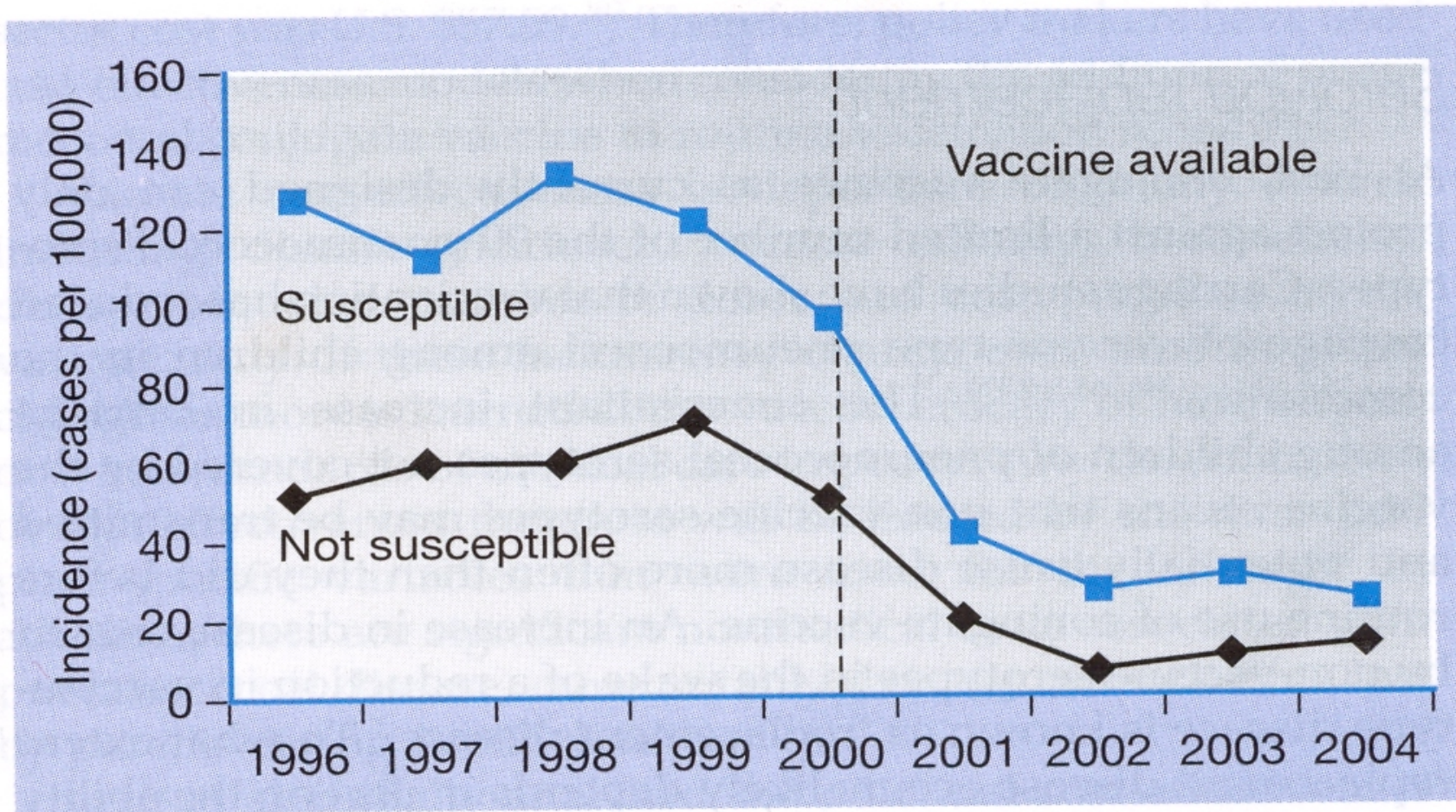


Figure 23–5 Effect of pneumococcal conjugate vaccine introduction in 2000 on rates of penicillin-susceptible and nonsusceptible invasive pneumococcal infections in the United States in children <2 years.³⁷⁵

CONCLUSION 1

- ❖ Antibiotic consumption in the community has a great impact on the development of antibiotic resistance in most common human pathogens
- ❖ There is an established but complex relationship between antibiotic consumption and the prevalence of antibiotic resistance

CONCLUSIONS 2

- ❖ High total antibiotic consumption and high broad spectrum antibiotic consumption should be avoided
- ❖ Narrow-spectrum antibiotics should be used whenever possible