



Does Resistance Disappear After Ceasing Inappropriate Use?

Dominique L. Monnet

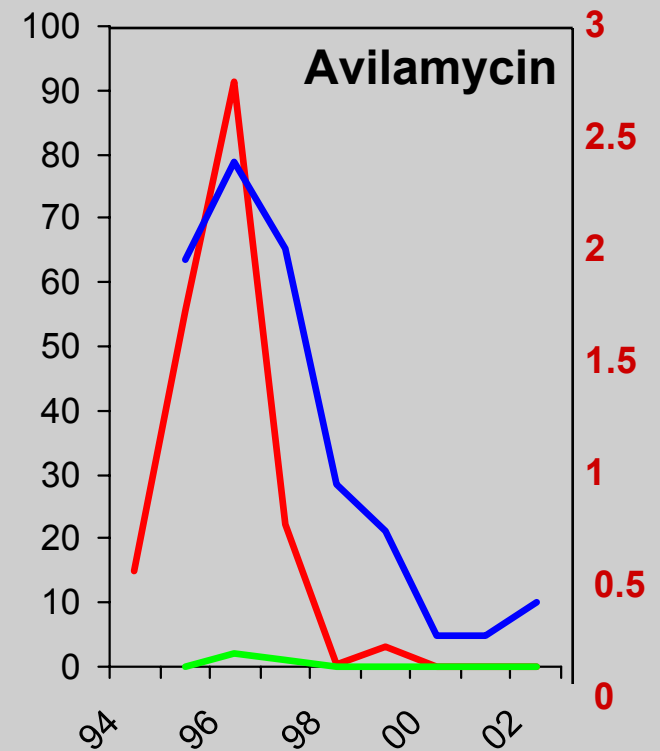
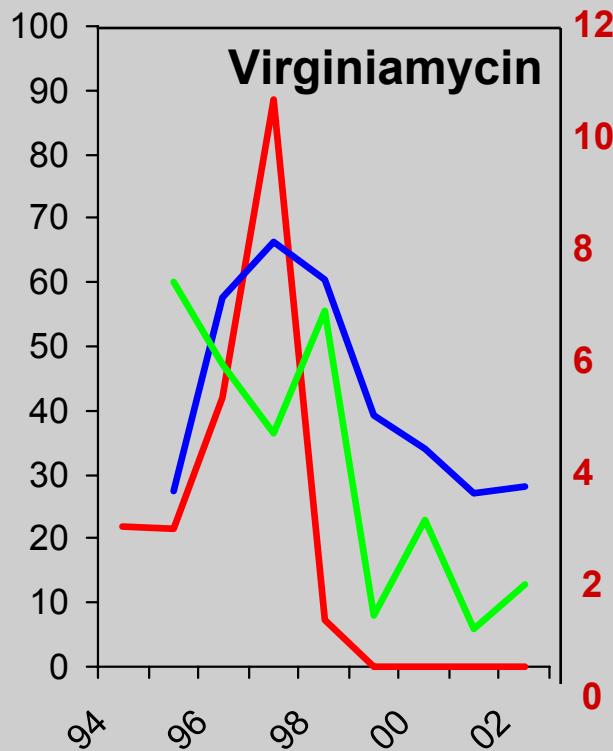
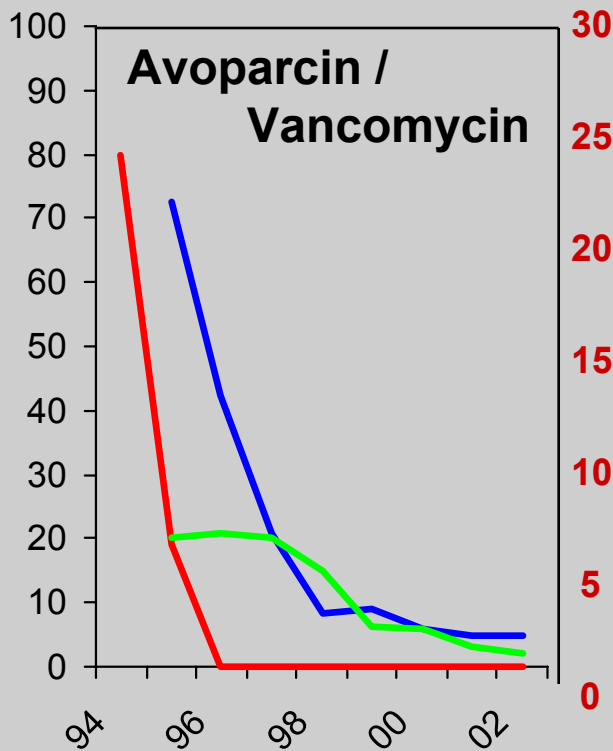
National Center for Antimicrobials and Infection Control,
Statens Serum Institut, Copenhagen, Denmark



Which Inappropriate Use Is Responsible for Resistance?

- Antibiotic not indicated (modifies ecological pressure)
- Another antibiotic could have been chosen (modifies ecological pressure)
- Dose is too low
- Duration is too long (modifies ecological pressure)

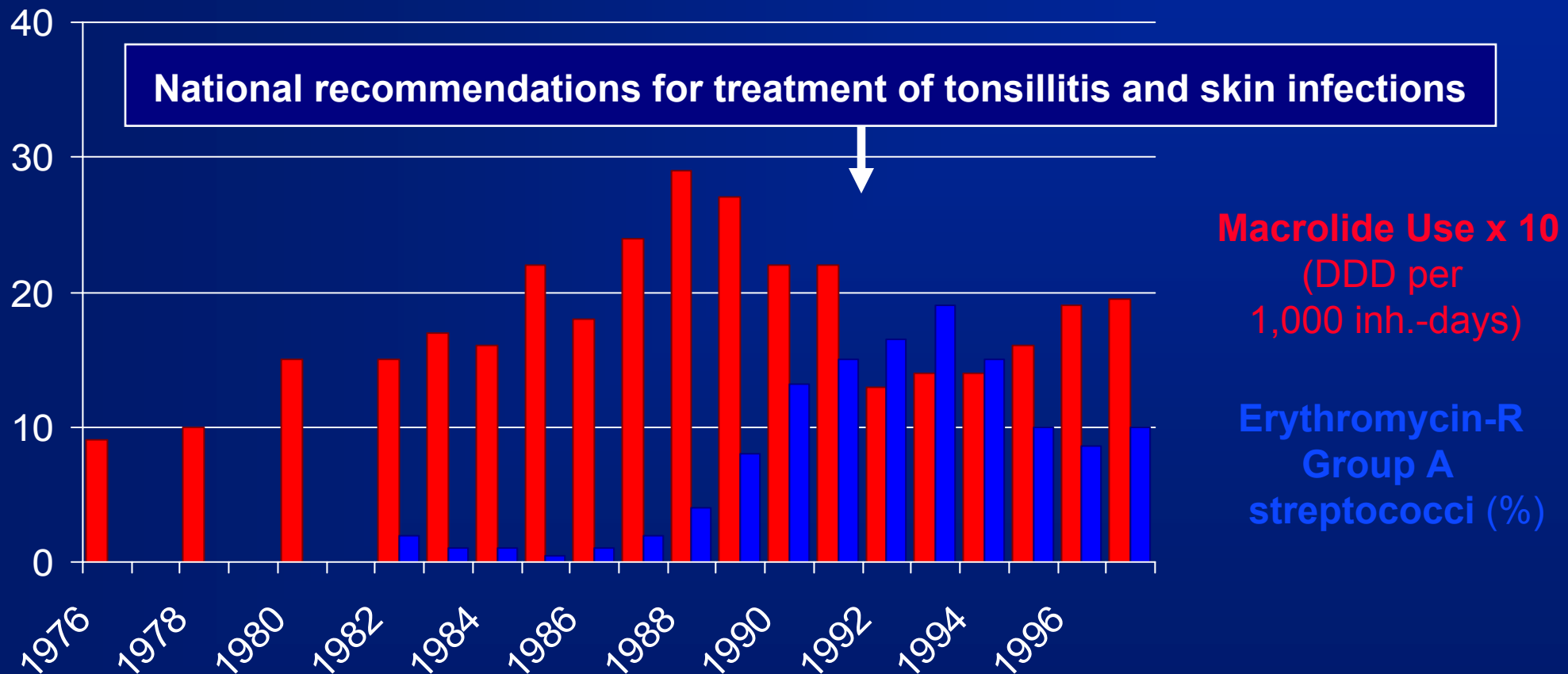
Changes in Use of Growth Promoters and Effects on Resistance in *E. faecium* Isolates from Animals, Denmark, 1994-2002



- Resistance in *Enterococcus faecium* isolates from broilers (%)
- Resistance in *Enterococcus faecium* isolates from pigs (%)
- Use of growth promoter (tonnes active compound)

Source:
 DANMAP report.
<http://www.danmap.org>

Macrolide Use and Erythromycin Resistance in Group A streptococci, Finland, 1976-1997

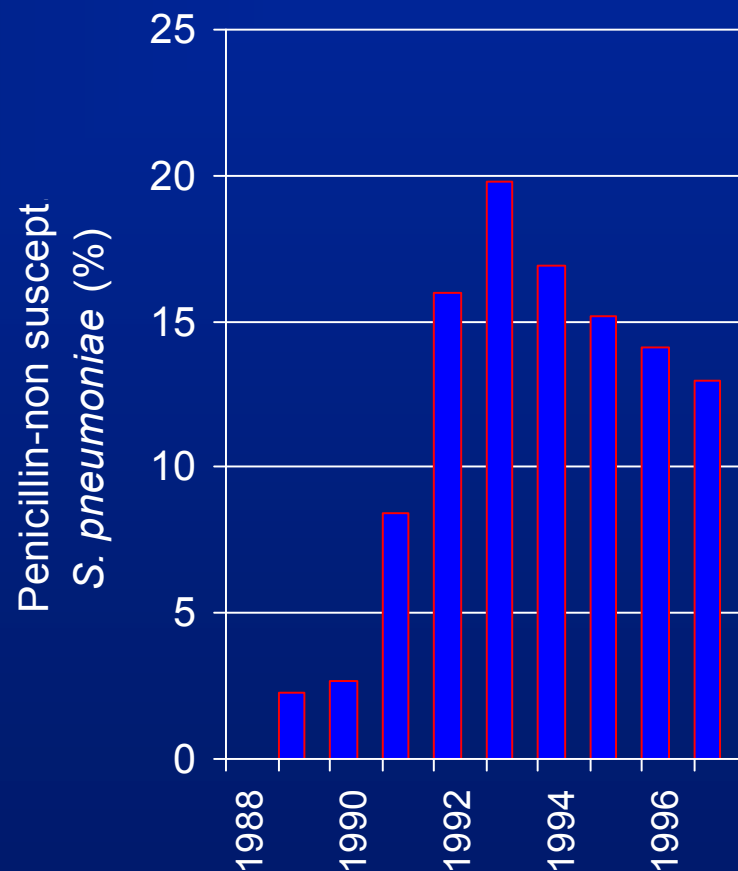


Sources : Seppälä H, et al. New Engl J Med 1997;337;441-6;
Huovinen P. Clin Microbiol Infect 1999;5(Suppl 4):12-16.

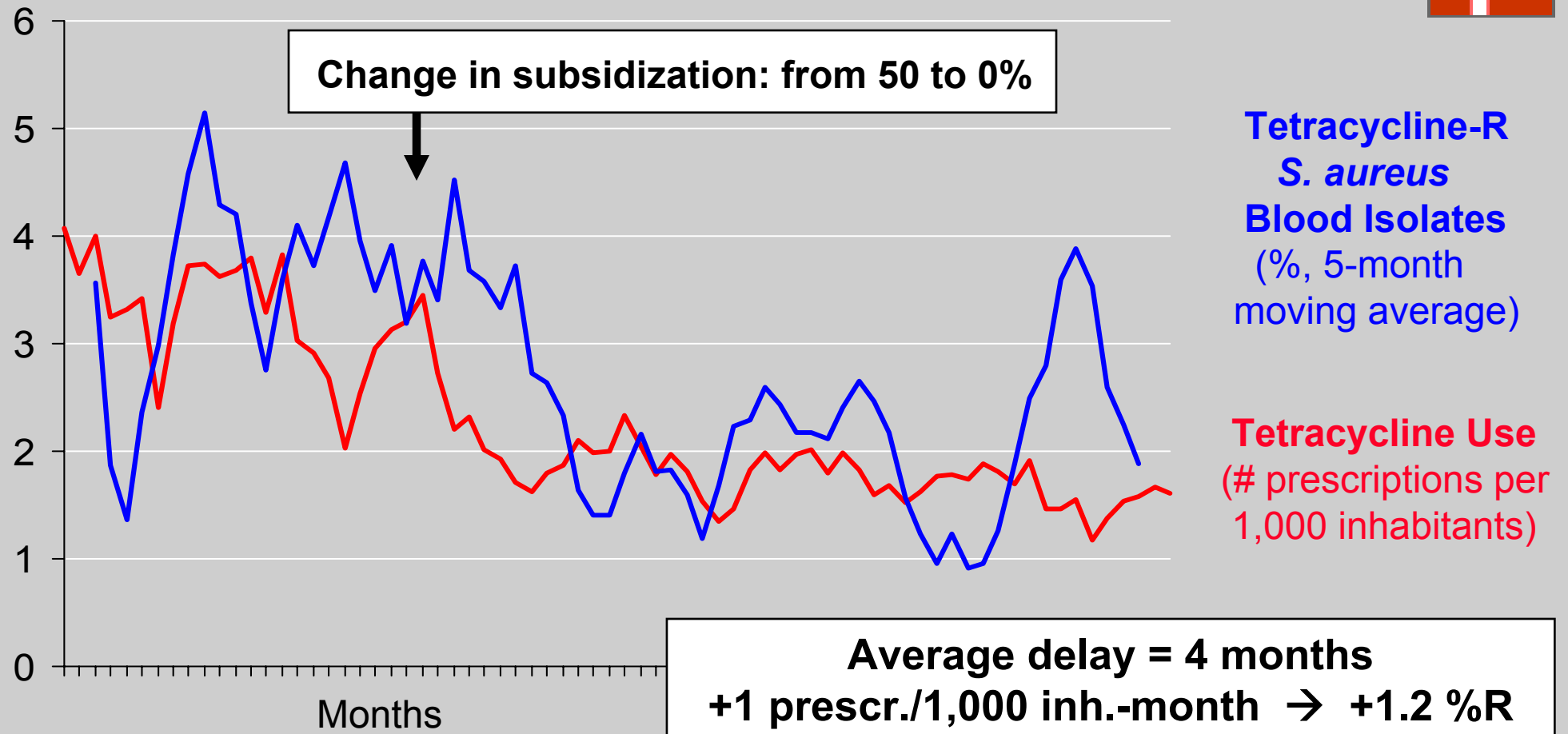
Control of *Streptococcus pneumoniae* with Reduced Susceptibility to Penicillin (PRSP) in Iceland by Prudent Use of Antibiotics



- Risk factors were: young age, antibiotic use and day-care center
- Focus on overuse in children
- Meetings with physicians, articles in the Icelandic Medical Journal and new guidelines
- Extensive coverage by public media resulted in changing parents' attitude towards antibiotics
- **10% decrease of total antibiotic sales (30% for macrolides and TMP-SX)**
- Exclusion from day-care not possible



Monthly Tetracycline Prescription Rate and Tetracycline Resistance in *S. aureus* Blood Isolates, Denmark, 01/1994-12/1999



5.2 Is a drastic decrease in trimethoprim consumption followed by a related decrease in trimethoprim resistance?

The observation that resistance is associated with a biological cost has led to the widespread idea that by reducing the volume of antibiotic use the frequency of resistant bacteria in a population can also be reduced. However, the existing studies do not allow us to make any firm conclusions regarding any potential reversibility in community settings.

This project aims to determine in a controlled clinical intervention study if, how rapidly and to what extent the frequency of trimethoprim resistance in *E. coli* can be decreased by a sudden and drastic reduction in trimethoprim use. From October 2004 until the end of September 2006 all physicians in Kronoberg county will substitute trimethoprim and cotrimoxazole with other antibiotics (pivmecillinam, fluoroquinolones, cephalosporins, nitrofurantoin). The frequency of resistance in this particular population has been continuously monitored since 1990 and consecutive quantitative data are stored in a database which allows serial analysis of resistance rates for all antibiotics used for UTI treatment, including trimethoprim. To evaluate the potential change in the distribution of *E. coli* phenotypes and genotypes, caused by the intervention, all isolated gram negative strains from June 2004 to December 2006 will in addition to the routine analyse of resistance, be stored for further analysis.

This type of strategy has been extensively discussed but to the best of our knowledge there has yet not been a full scale prospective study performed in a community setting. Thus, the obtained results will have general important implications with regard to the feasibility of this type of approach. If successful, this type of intervention could be used on a larger scale to reduce the frequency of resistant bacteria. Up to this date (March 2005) the reduction of trimethoprim/cotrimoxazole use is >80%.

Gunnar Kahlmeter, Martin Sundqvist

Table 5.1. Resistance in *E. coli* from “the project” compared to all *E. coli* 2004.

<i>E. coli</i> resistance to	Project patients	All <i>E. coli</i> 2004
Ampicillin	19%	19%
Mecillinam	<1% R; 8% I	<1% R; 6% I
Trimethoprim	12%	11%
Nalidixic acid	4%	4%
Nitrofurantoin	1%	0%



SWEDRES2004

A Report on Swedish Antibiotic Utilisation and Resistance in Human Medicine

STRAMA
The Swedish Strategic
Programme for Antibiotic
Use and Resistance

SMITTSKYDDSIINSTITUTET
Swedish Institute for Infectious Disease Control

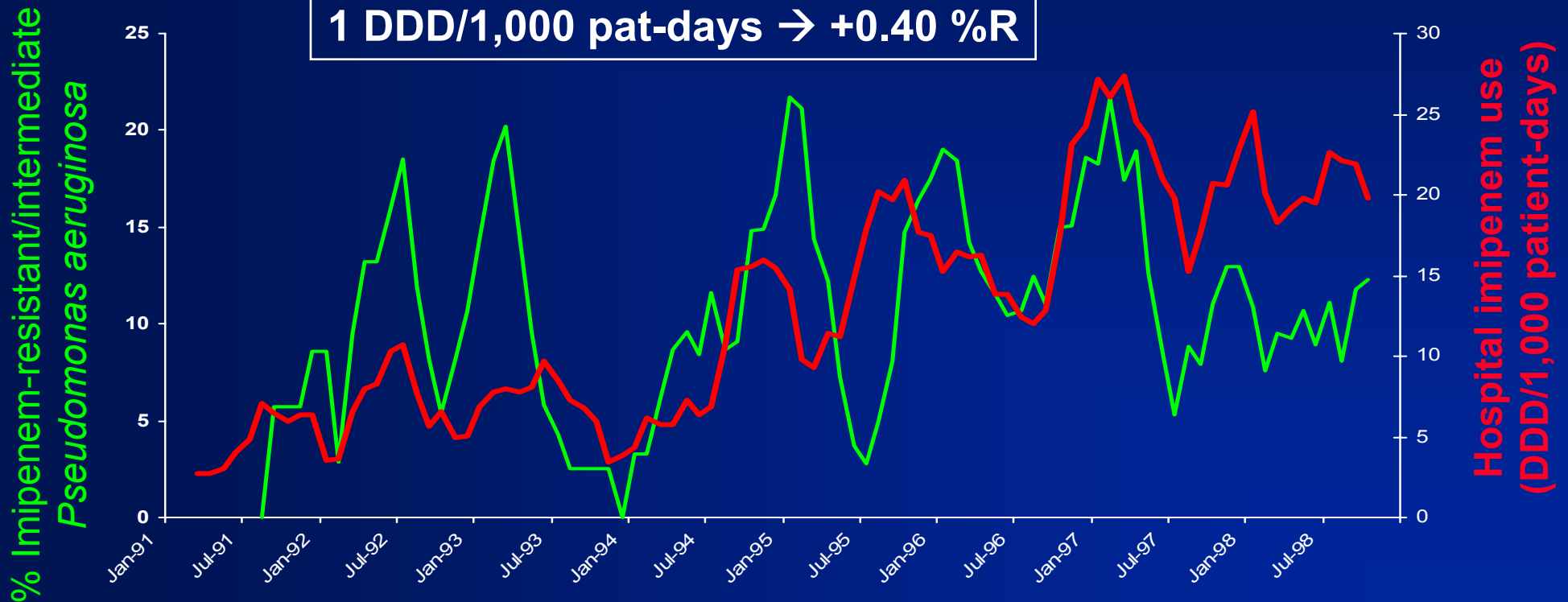


<http://www.strama.se>

5-Month Moving Average Percent Imipenem-Resistant/Intermediate *P. aeruginosa* and Hospital Imipenem Use, Hospital Vega Baja, Spain, 1991-1999



Average delay = 1 month
1 DDD/1,000 pat-days → +0.40 %R

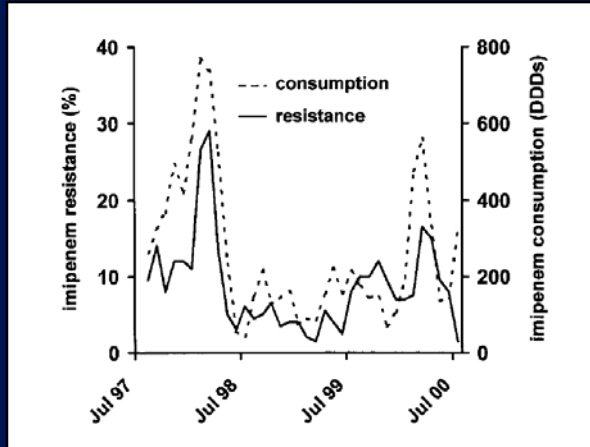


Updated from: López-Lozano JM, et al. Int J Antimicrob Agents 2000;14:21-30.

%Carbapenem-Resistant *Pseudomonas aeruginosa* and Carbapenem Use in 4 Hospitals, 1996-2003

Univ. Hospital, Ulm (D)

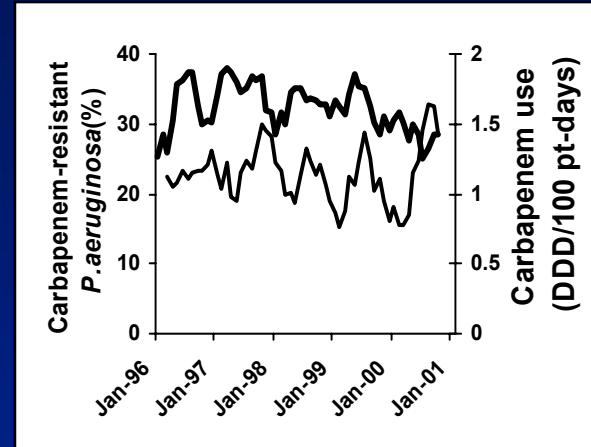
Lepper et al. AAC 2002;46:2920-5.



Average
delay
=
0-1 month

Univ. Hospital, Utah (USA)

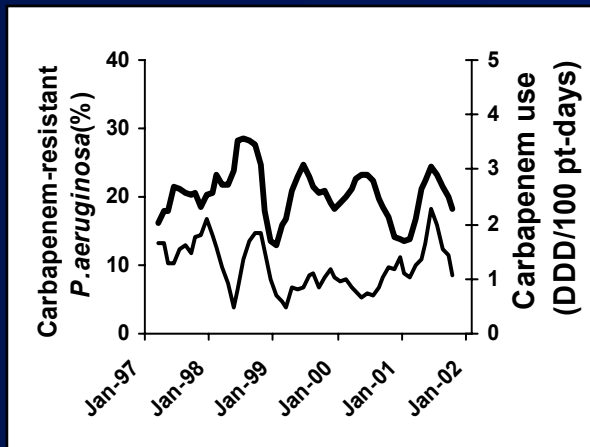
Samore MH, et al. Unpublished data.



Average
delay
=
0-1 month

Univ. Hospital, Antwerp (B)

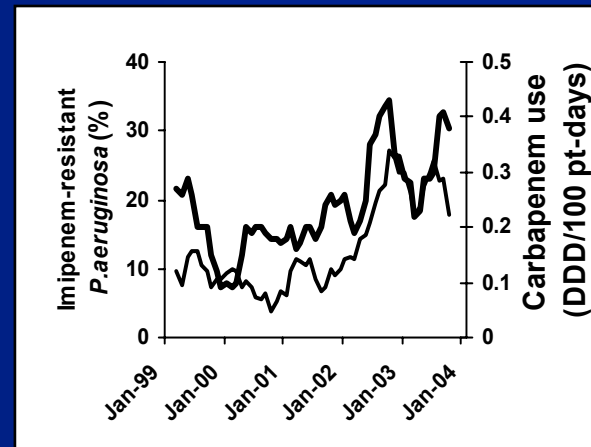
Goossens H, et al. Unpublished data.



Average
delay
=
0-2 months

Centre Hosp. Mulhouse (F)

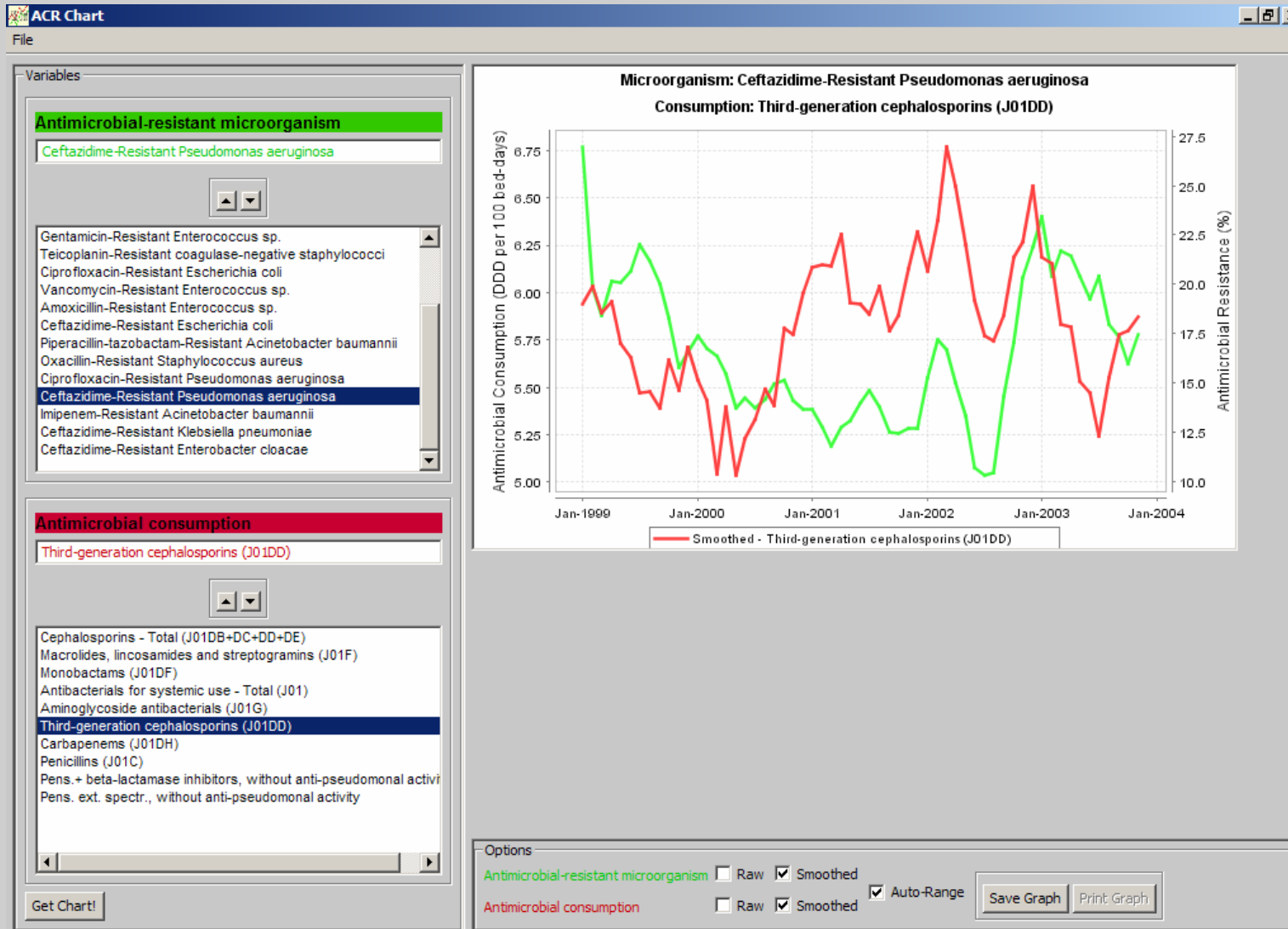
Aujoulat O, Delarbre JM. ViResiST.



Average
delay
=
n.a.

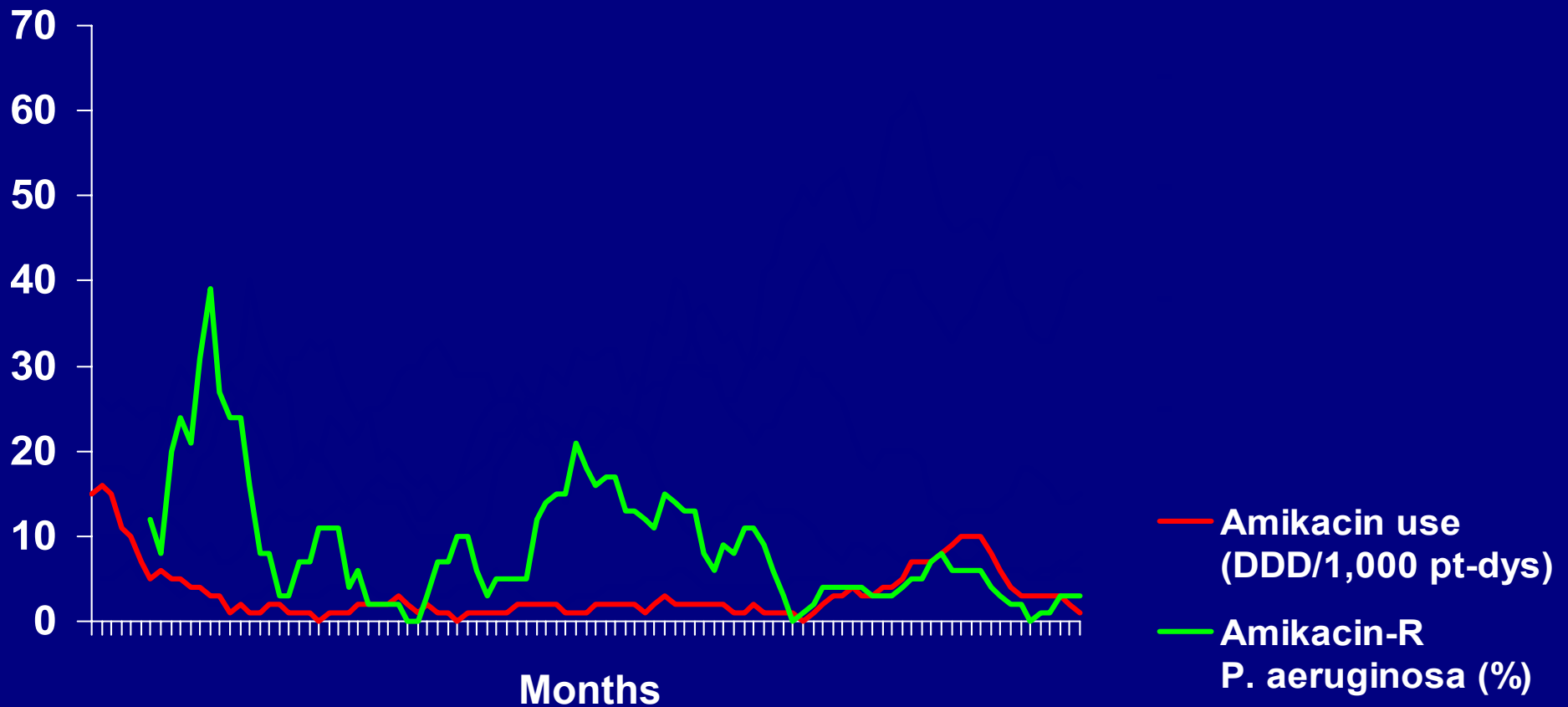
ViResiST

ACR Chart



Source: Muller A, et al. (available free-of-charge, September 2005)

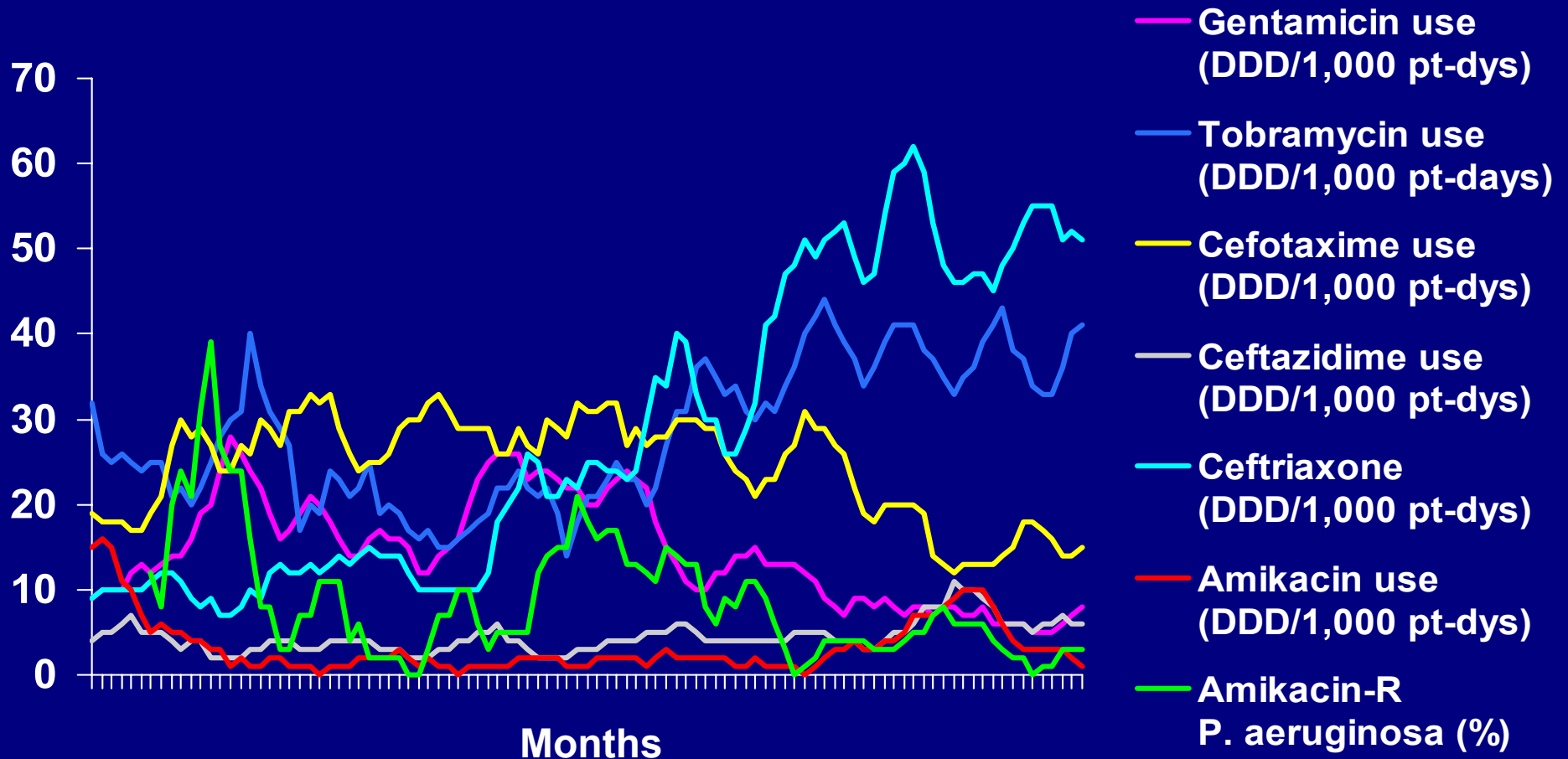
5-Month Moving Average Percent Amikacin-Resistant/Intermediate *P. aeruginosa* and Hospital Antimicrobial Use, Hospital Vega Baja, Spain, 1991-1999



Source : Monnet DL, et al. Clin Microbiol Infect 2001; 7(Suppl 5):29-36.

ViResiST

5-Month Moving Average Percent Amikacin-Resistant/Intermediate *P. aeruginosa* and Hospital Antimicrobial Use, Hospital Vega Baja, Spain, 1991-1999



Source : Monnet DL, et al. Clin Microbiol Infect 2001; 7(Suppl 5):29-36.

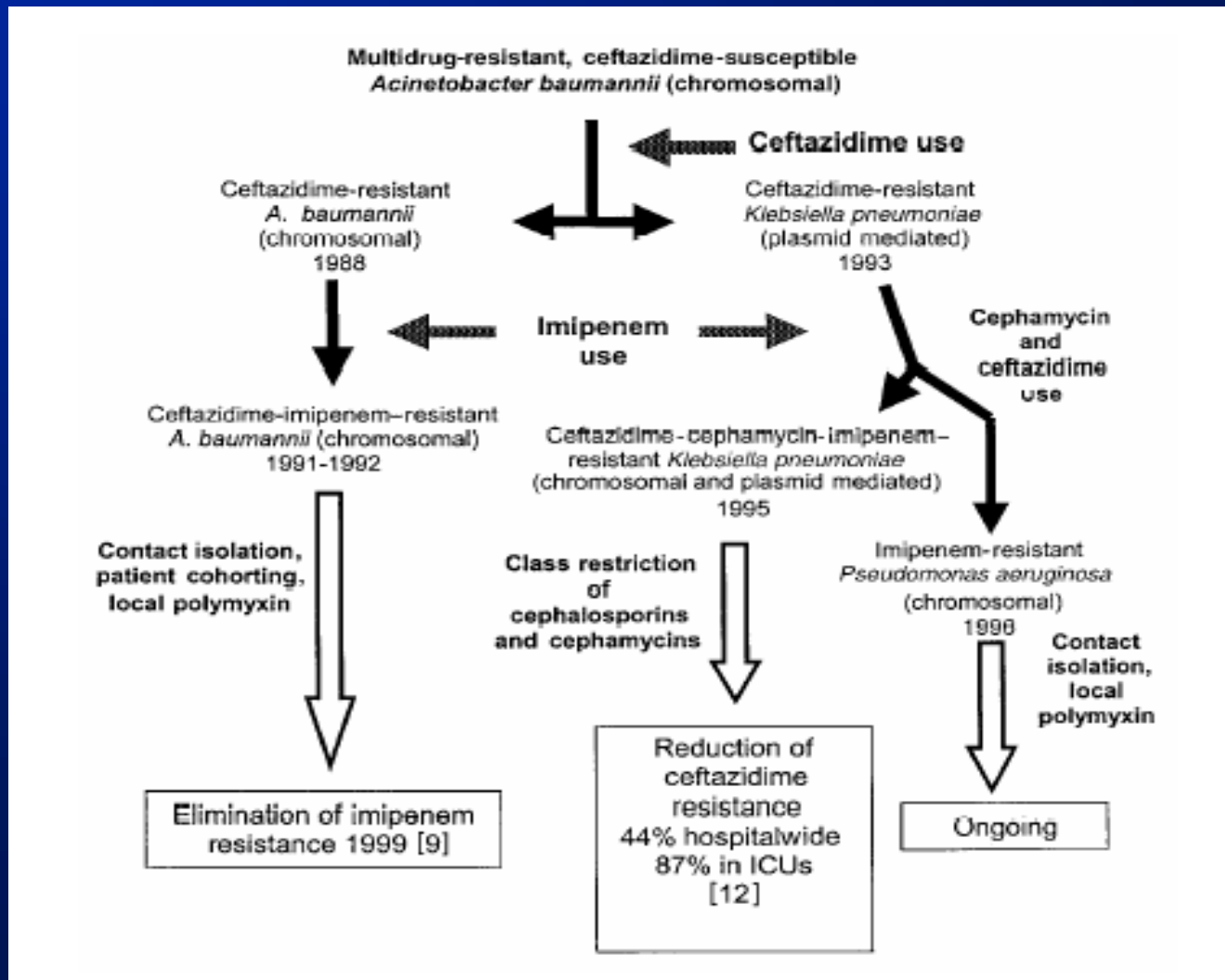


Dynamic Positive or Negative Relationship between Use of Various Antimicrobials and % Amikacin-R/ *Pseudomonas aeruginosa* (univariate analysis), Hospital Vega Baja, Spain, 07/1991-12/1999

Antimicrobials	Order	Parameter	T-ratio
Gentamicin	7	+ 0.45	+ 4.44
Cefotaxime	3	+ 0.36	+ 6.55
Tetracyclines	3	+ 0.35	+ 2.14
Cefoxitin	7	+ 0.32	+ 2.62
Ciprofloxacin (oral)	6	+ 0.28	+ 6.57
Penicillins G and V	6	+ 0.28	+ 4.65
Ampi- and amoxicillin	3	+ 0.15	+ 3.84
Co-trimoxazole	5	- 0.40	- 2.41
Imipenem	2	- 0.38	- 2.79
Cefuroxime	2	- 0.18	- 4.09
Vancomycin	1, 4, 5	+ 0.69, - 0.64, - 0.53	+ 2.77, - 2.45, - 2.05
Clindamycin	1, 2, 6	+ 0.30, - 0.32, + 0.48	+ 2.26, - 2.30, + 4.52

Source: López-Lozano JM, et al. 20th RICAI, Paris, 7-8 December 2000, abstr. 194/C15.

Antibiotic Cycling: “Squeezing the Resistance Balloon” at Multiple Sites, New York Hospital Queens (NY)



Source: Rahal JJ, et al. Clin Infect Dis 2002;34:499-503.

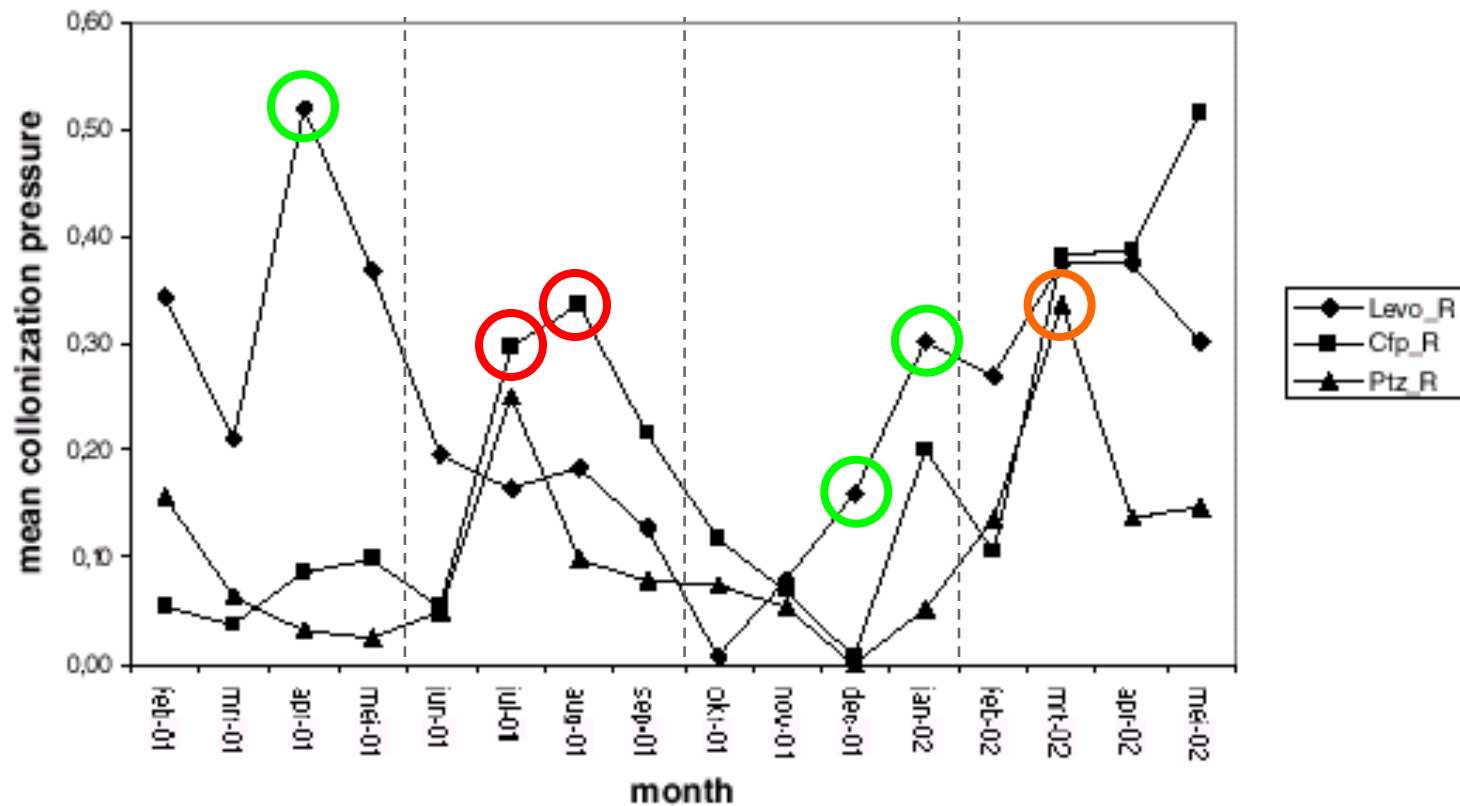
Antibiotic Rotation and Development of Gram-Negative Antibiotic Resistance, Surgical ICU, Utrecht (NL), 2001-2002



Proportion of patients treated (%)

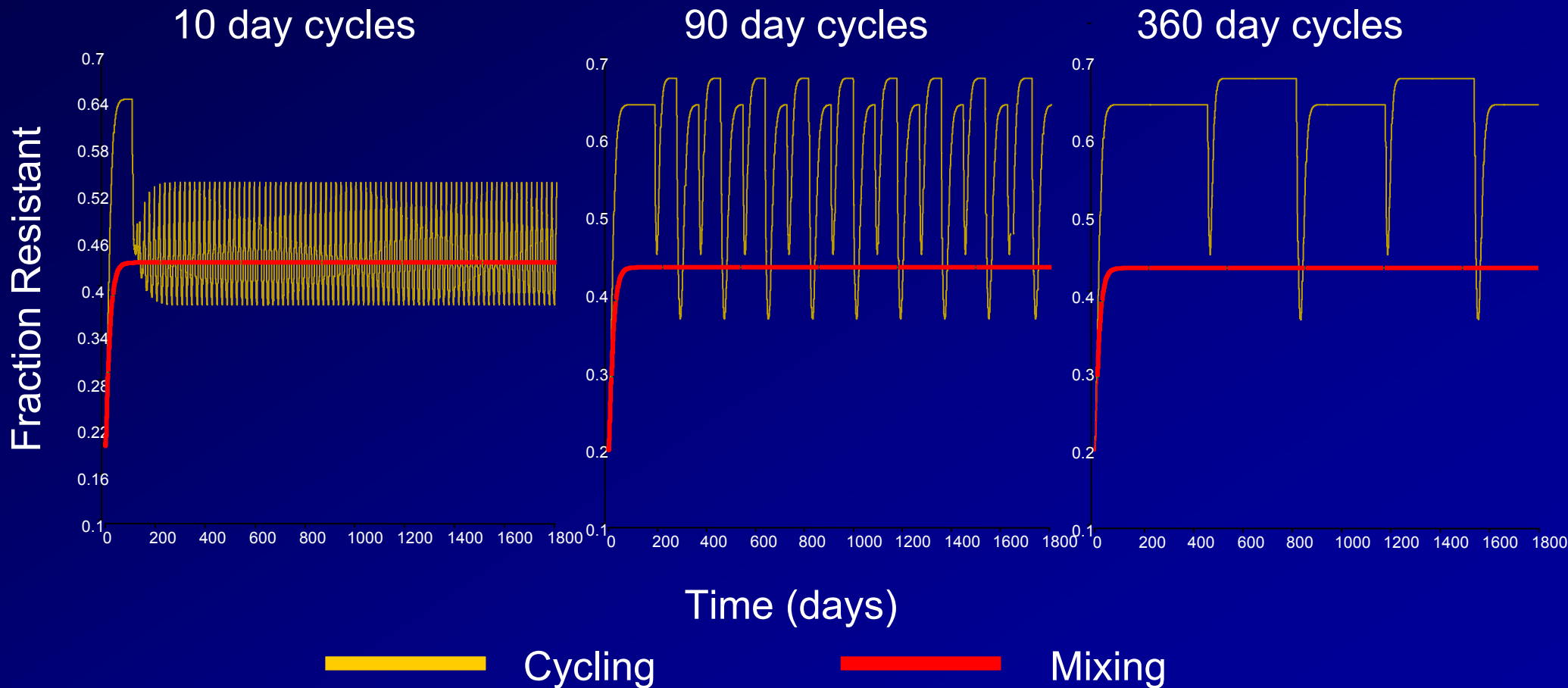
Levofloxacin
Cefpirome
Pip/Tazo

Levofloxacin	40	0	52	5
Cefpirome	0	44	0	0
Pip/Tazo	6	1	1	55



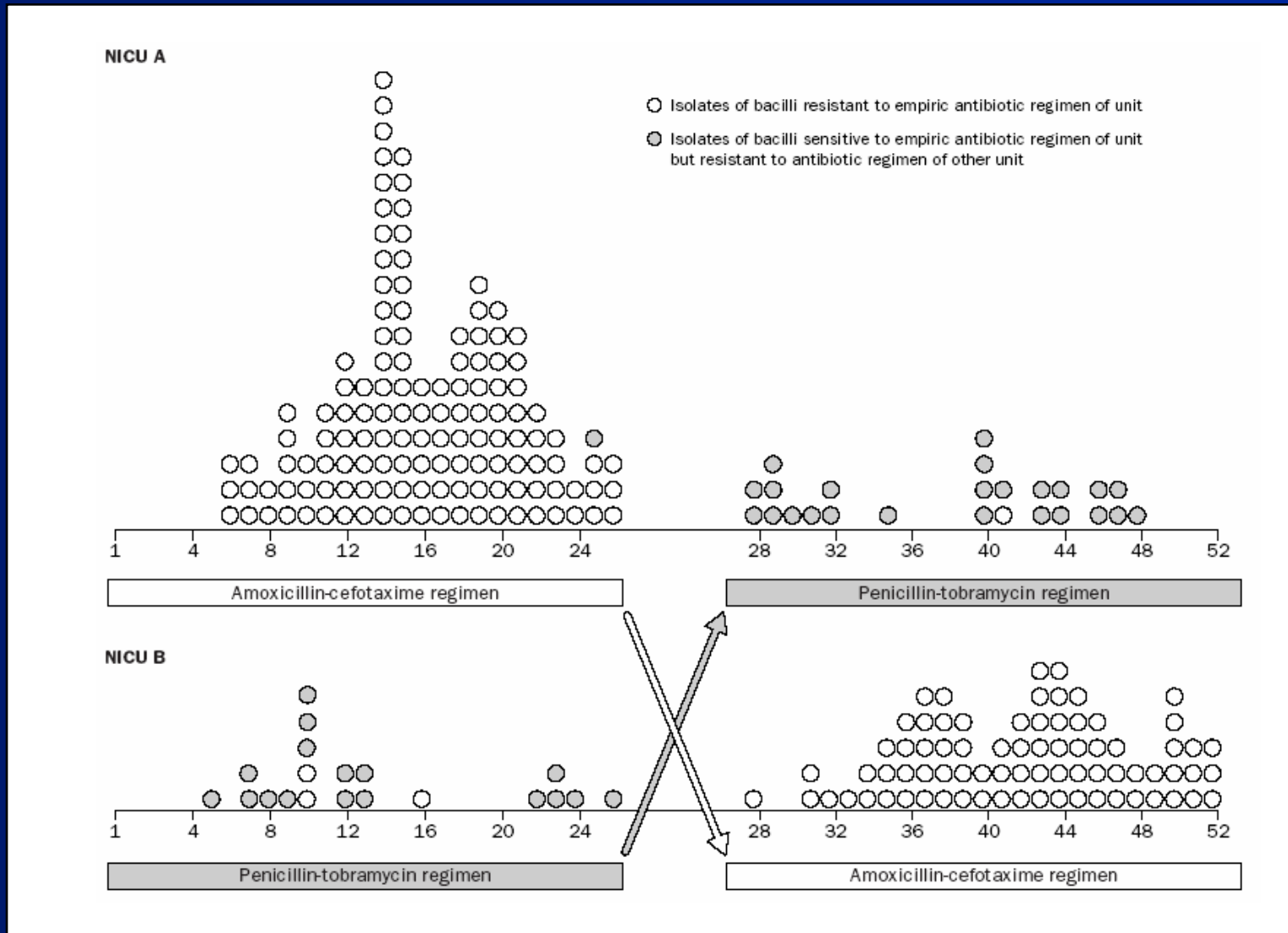
Source: van Loon HJ, et al. Am J Respir Crit Care Med 2005;171:480-7.

Effect of Antibiotic Cycle Length on Bacterial Resistance



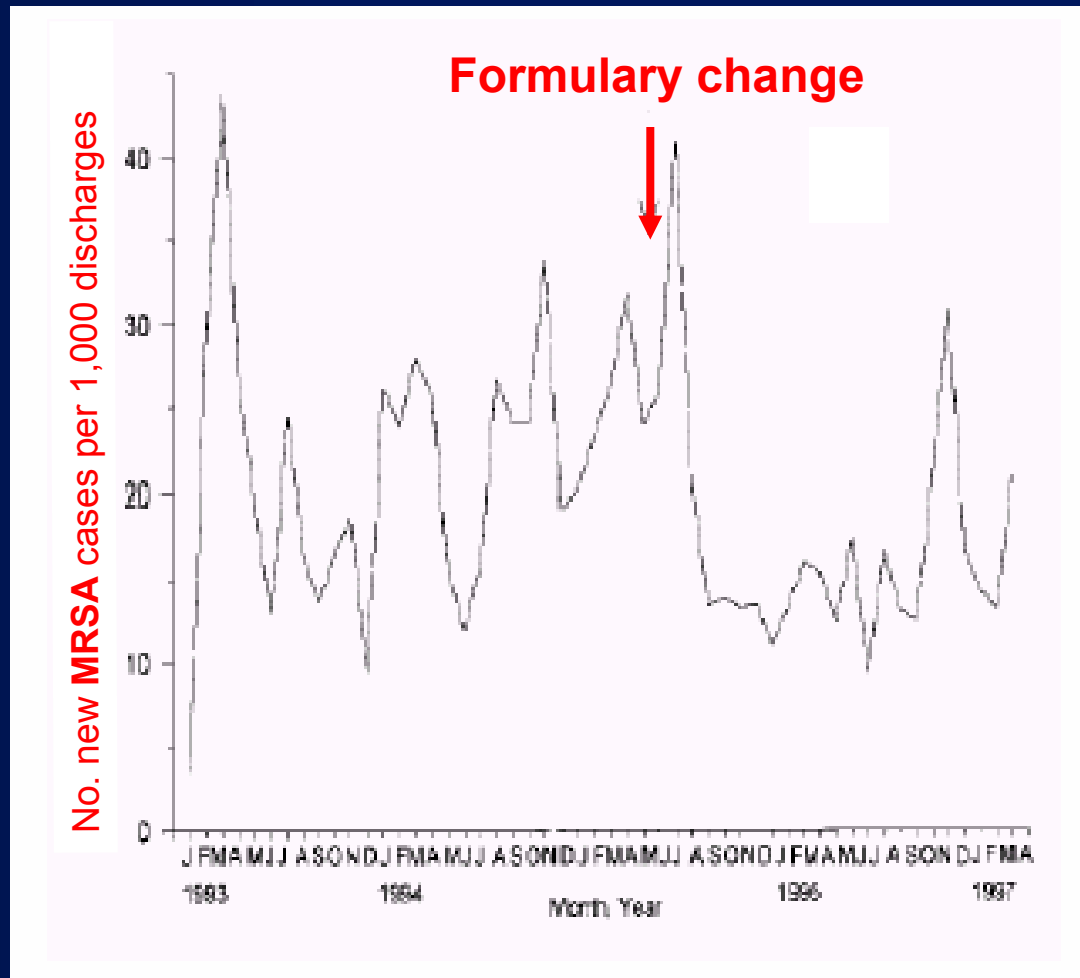
Source: Bergstrom CT, et al. Proc Natl Acad Sci USA 2004;101:13285-90.

Cross-Over of Empiric Antibiotic Regimens and Emergence of Resistance in Two ICUs, Rotterdam (NL)



Source: de Man P, et al. Lancet 2000;355:973-978.

Reduction of MRSA Incidence Following Changes in a Hospital Formulary, Brooklyn (NY), 1995-1997



- **Decreased use:**
cefotaxime,
cefazolin,
ceftazidime,
clindamycin,
vancomycin,
imipenem,
gentamicin
- **Increased use:**
ampicillin-
sulbactam,
piperacillin-
tazobactam

Source: Landman D, et al. Clin Infect Dis 1999;28:1062-1066.



Does Resistance Disappear After Ceasing Inappropriate Use?

- Resistance will not totally disappear, but...
- It will quickly decrease down to a level in relation to the size of the decrease in inappropriate use
- If the decrease in use is not compensated by an increase in use of another agent to which the bacteria is also resistant
- Until inappropriate use increases again
- How to reduce inappropriate use without "squeezing the balloon" or compromising patient care?

3rd-gen. cephs-R
Gram-neg. bact.



Carbapenems



Carbapenem-R,
colistin-S only
Gram-neg. bact.



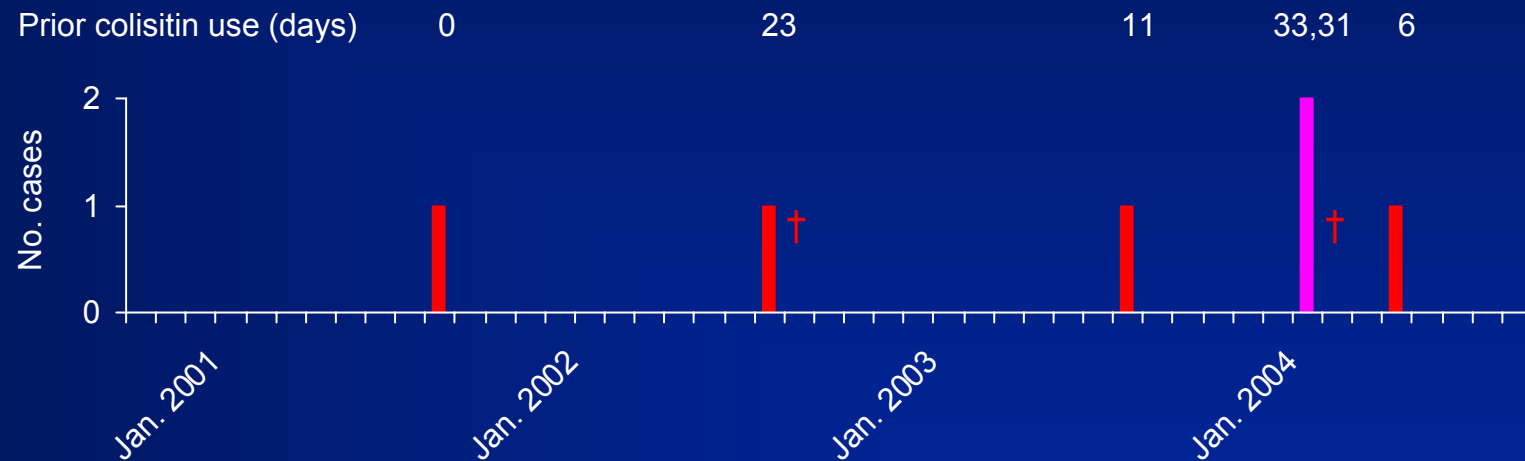
Colistin



Pan-resistant
Gram-neg. bact.

Pan-Resistant Gram-Negative Bacilli

 ICU, Henry Dunant Hosp., Athens, Greece, 2001-2004
Falagas ME, et al. BMC Infect Dis 2005;5:24.



 Hosp. Clinico San Carlos, Madrid, 08/2003-08/2004:
>20 pts with carbapenem-R, colistin-R *P. aeruginosa*
Sánchez A, et al. Rev Esp Quimioterap 2004;17:336-40.

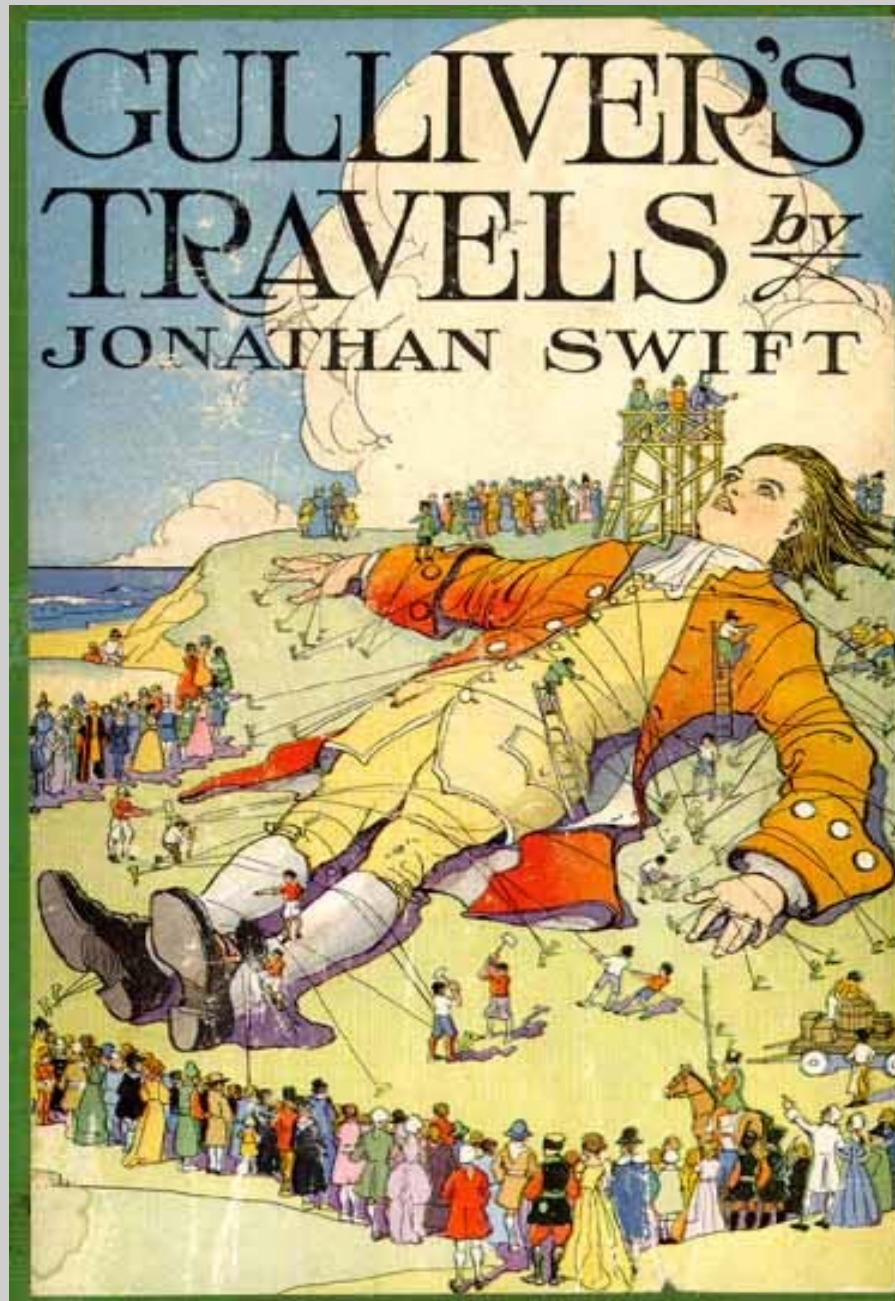


Illustration: Prittie E.J.
Philadelphia, PA: JC Winston,
1930.