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Relationship Between Antibiotic Consumption and Resistance in European Hospitals

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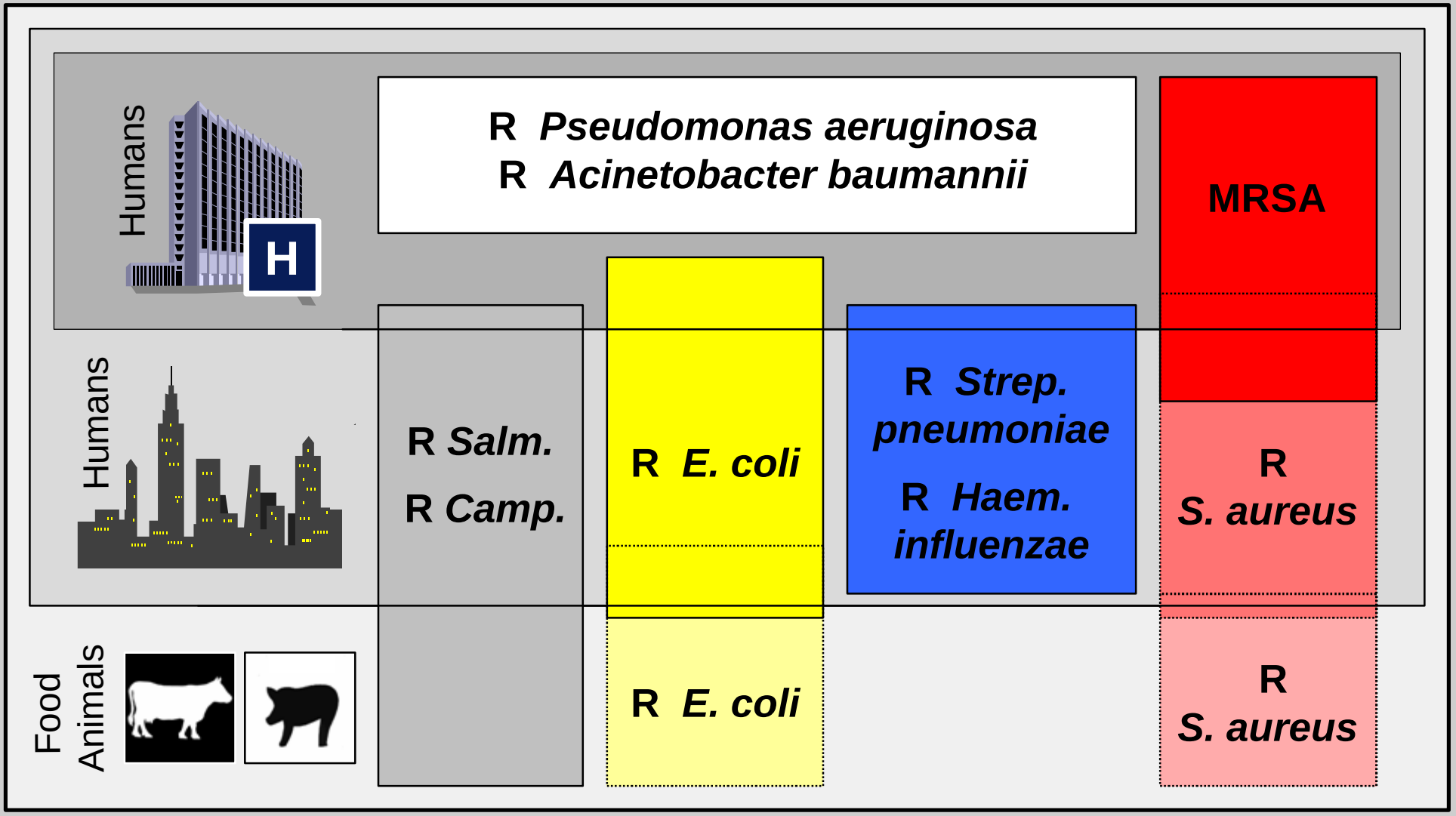
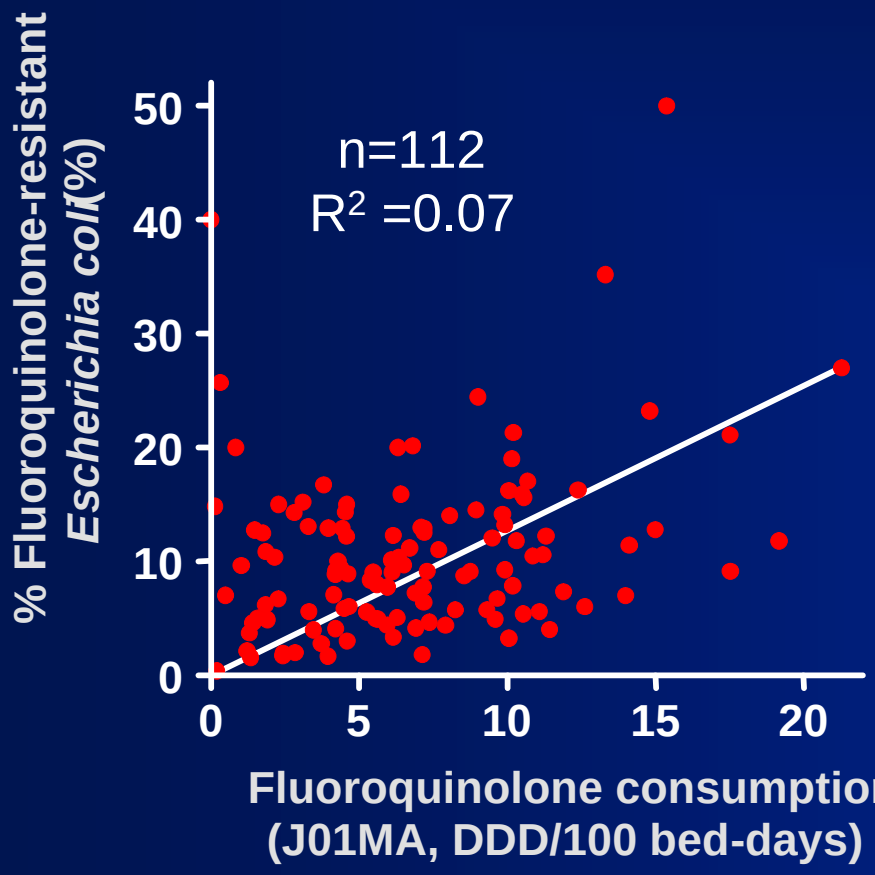
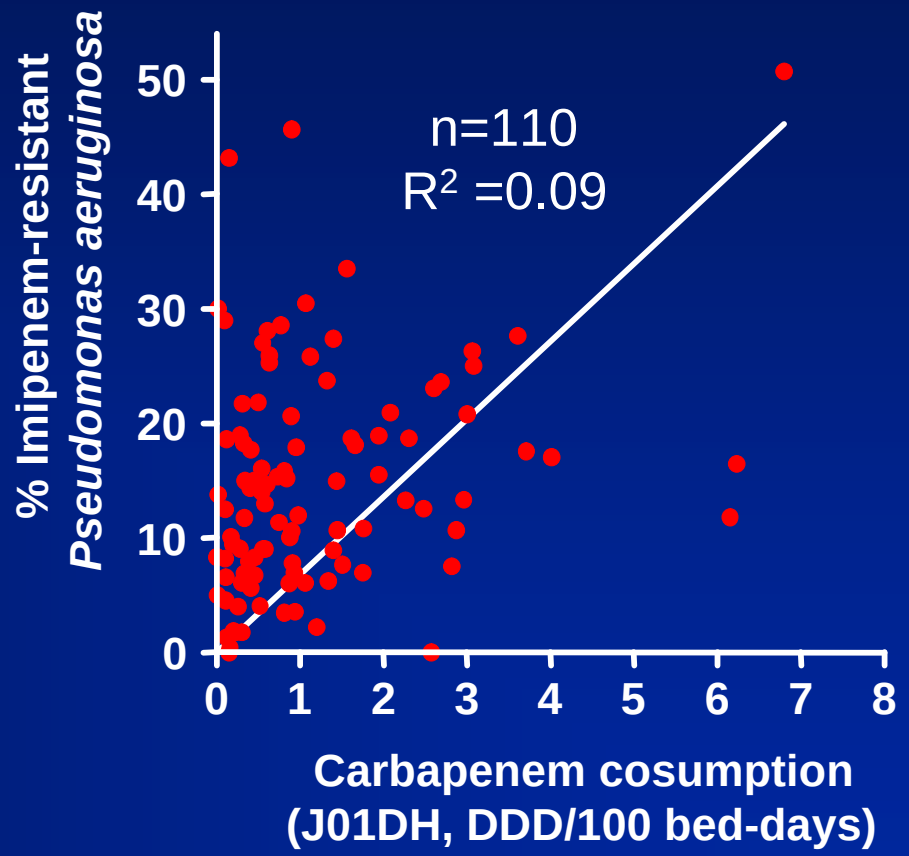
The World (of Antimicrobial Resistance) According to… Human Bacterial Pathogens and Their Habitat



le **MOND**e de la **R**ésistance **I**ntrinsèque et **A**cquise aux **AN**tibiotiques ;-).

Antimicrobial Consumption and Resistance: Examples from ARPAC European Hospitals, 2001



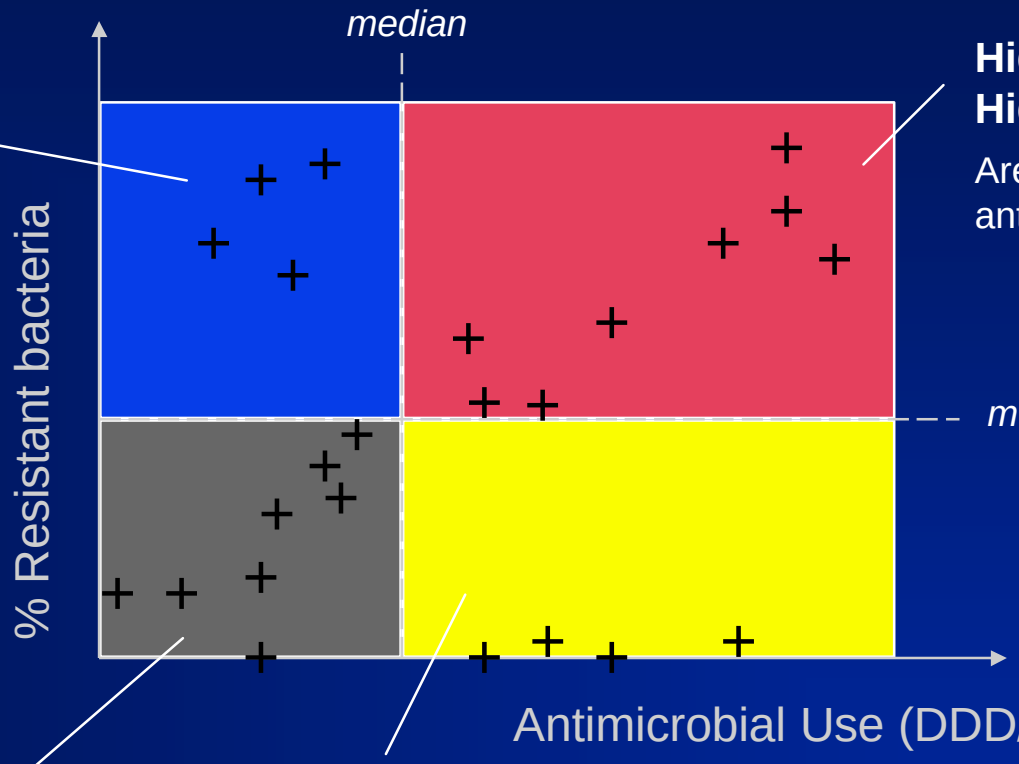


Source: ARPAC, 2004 (http://www.abdn.ac.uk/arpac/)

Usefulness of Antimicrobial Resistance and Antimicrobial Use Data Comparison

High level of resistance
Low antimicrobial use

Possible areas of improvement:
. infection control
. identif. of colonized patients upon admission
. appropriate dosage (low dose)
. use of other antimicrobials



High level of resistance
High antimicrobial use

Area of improvement: antimicrobial use

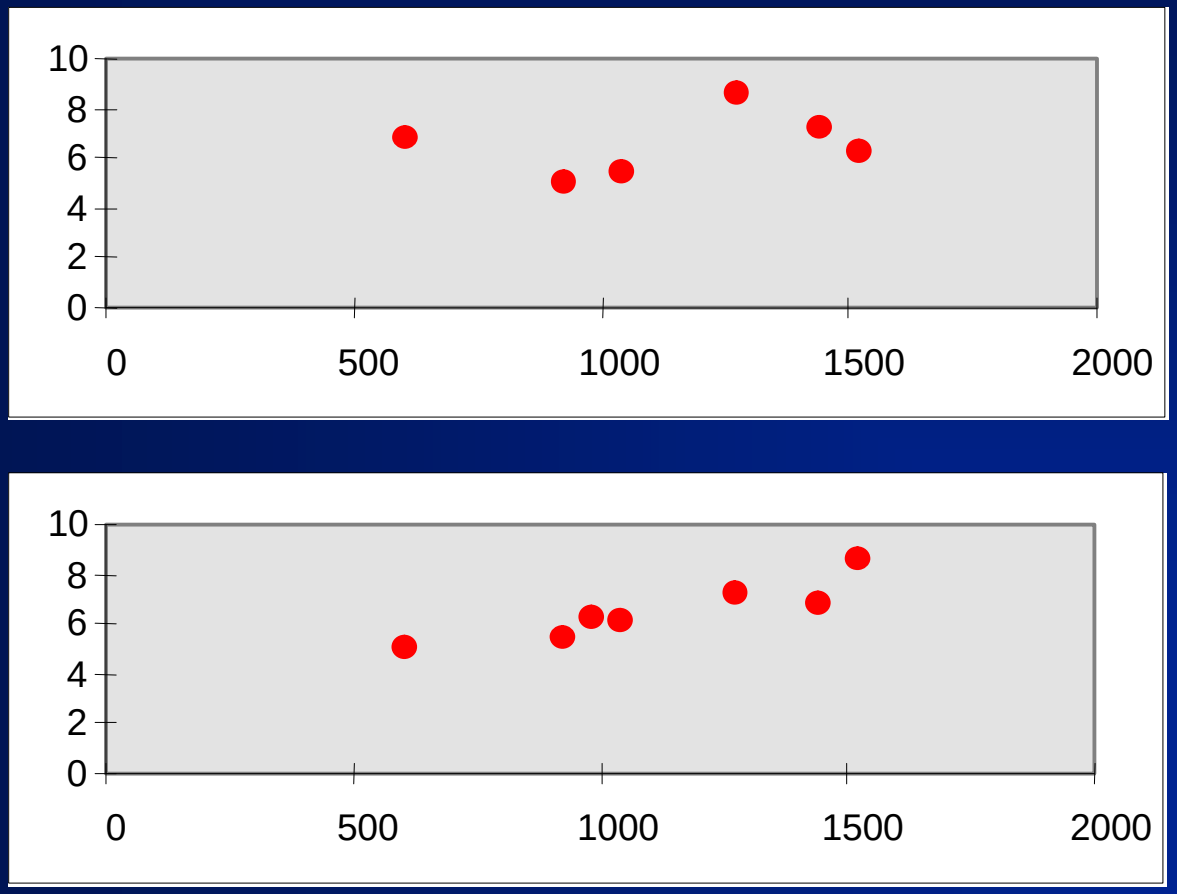
Low level of resistance
Low antimicrobial use

Low level of resistance
Relatively high antimicrobial use

Possible area of improvement: detection of resistance in the laboratory
Possible explanation: resistant bacteria has not been introduced in setting

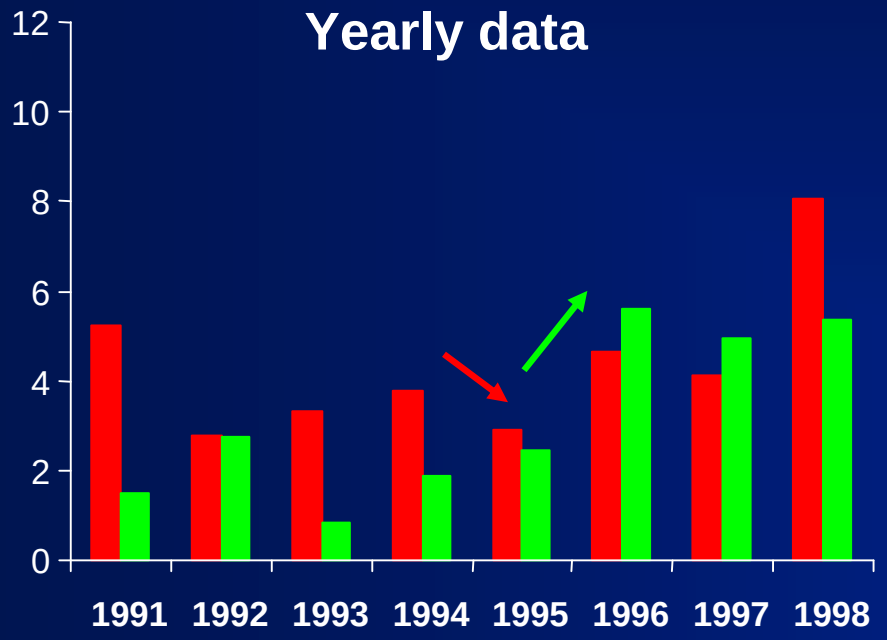
Source : Int J Antimicrob Agents 2000;15:91-101 (adapted from CDC/NNIS/ICARE Phase 1).

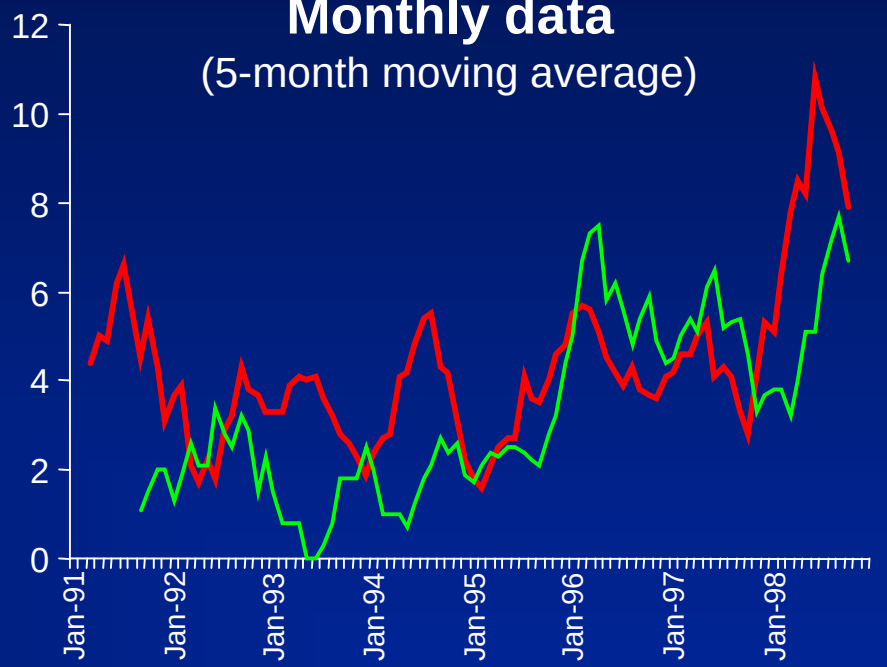
Gentamicin Use and %Gentamicin-Resistant Gram-Neg. Bacilli Isolates, Brussels, 1979-1986



Source: Goossens H, et al. Lancet 1986;2:804.

Percent Ceftazidime-Resistant/Intermediate Gram-Negative Bacilli and Hospital Ceftazidime Use, Hospital Vega Baja, Spain, 1991-1998





Ceftazidime use (DDD/1,000 pt-days)

Ceftazidime-resistant GNB (%)

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

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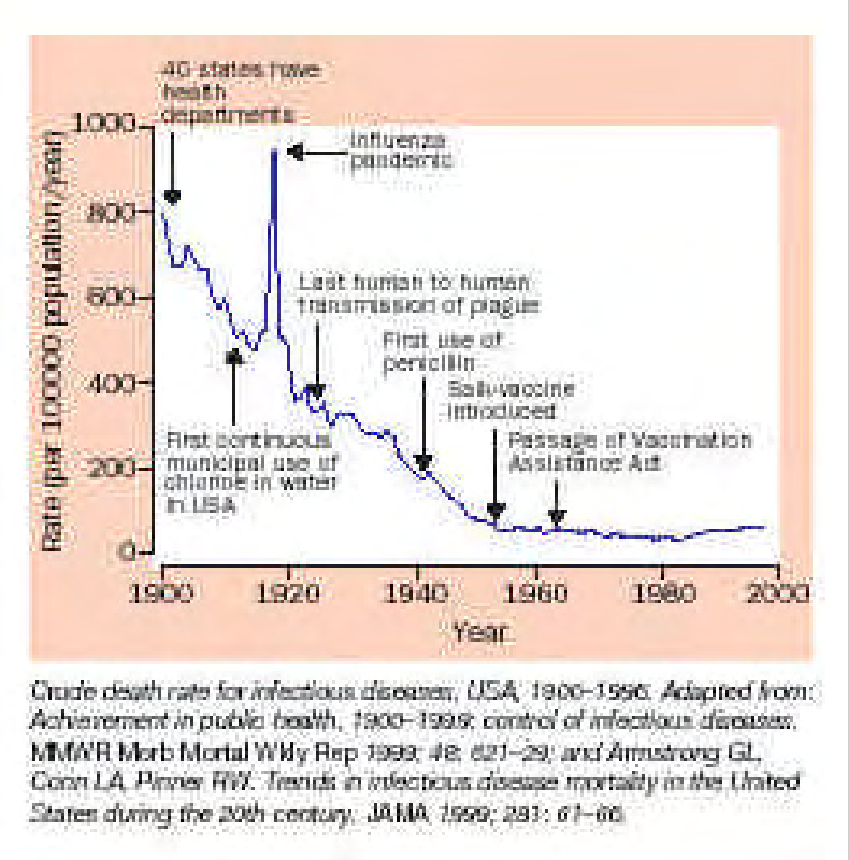
Examples of Time Series

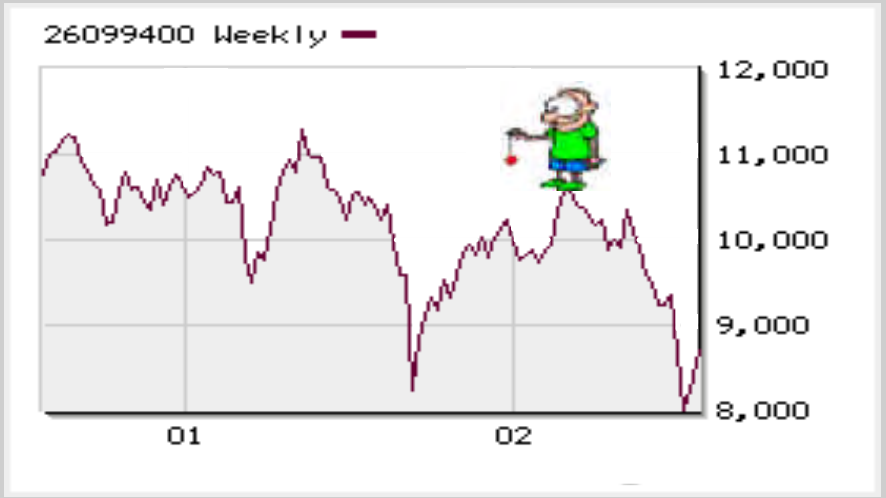
Crude Death Rates for Infectious Diseases, USA, 1900-1996



Crude death rate for infectious diseases, USA, 1900-1996. Adapted from: Achievement in public health, 1900-1999: control of infectious diseases. MMWR Morb Mortal Wkly Rep 1999; 48: 621-29; and Armstrong GL, Conn LA, Pinner RW. Trends in infectious disease mortality in the United States during the 20th century. JAMA 1999; 281: 61-66.

Source: Aiello AE & Larson EL. Lancet Infect Dis 2002;2:103-10.

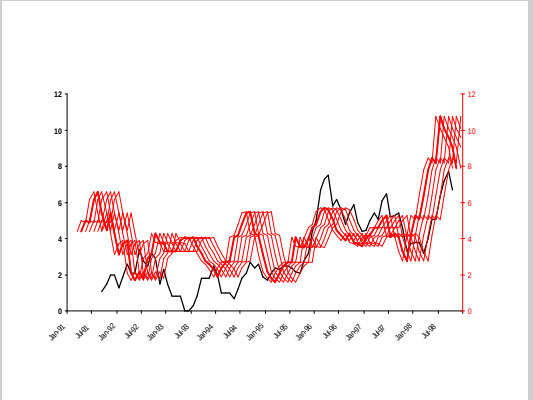
Dow Jones Industrial Average

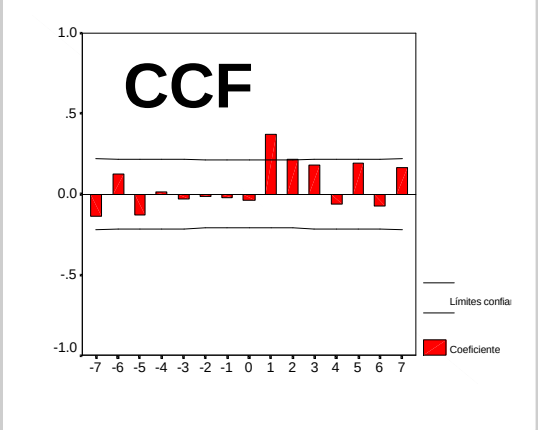


Source: FT Investor Financial Times, 7/29/2002.

Multivariate Time Series Analysis

- To assess relationships between a target (output) series and one or several explanatory (input) series
- Various types of models: transfer function (TF), polynomial distributed lag (PDL), etc.
- TF models: cross-correlation function (CCF) to identify time lags between series





Sources:
Helfenstein U. Stat Meth Med Res 1996;5:3-22.
Haugh LD. J Am Stat Assoc 1976;71:378-385.
Pankratz A. *Forecasting with dynamic regression models.* New York, NY: Wiley, 1991.

Transfer Function Model for Percent Ceftazidime-Resistant/Intermediate Gram-Negative Bacilli Series

(taking into account hospital ceftazidime use)

Term	Parameter (SE)	T-ratio	P-value
Constant	1.354 (0.760)	1.78	0.078
AR3	0.352 (0.096)	3.68	< 0.001
AR5	0.265 (0.098)	2.72	< 0.01
ULAG1	0.420 (0.096)	4.34	< 0.0001

R^2=0.44

Ceftazidime Use 1 month before

Average delay = 1 month
+1 DDD/1,000 patient-days = 6.5 days of treatment → +0.42 %R
e.g. from R = 5% → R = 5.42 %

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

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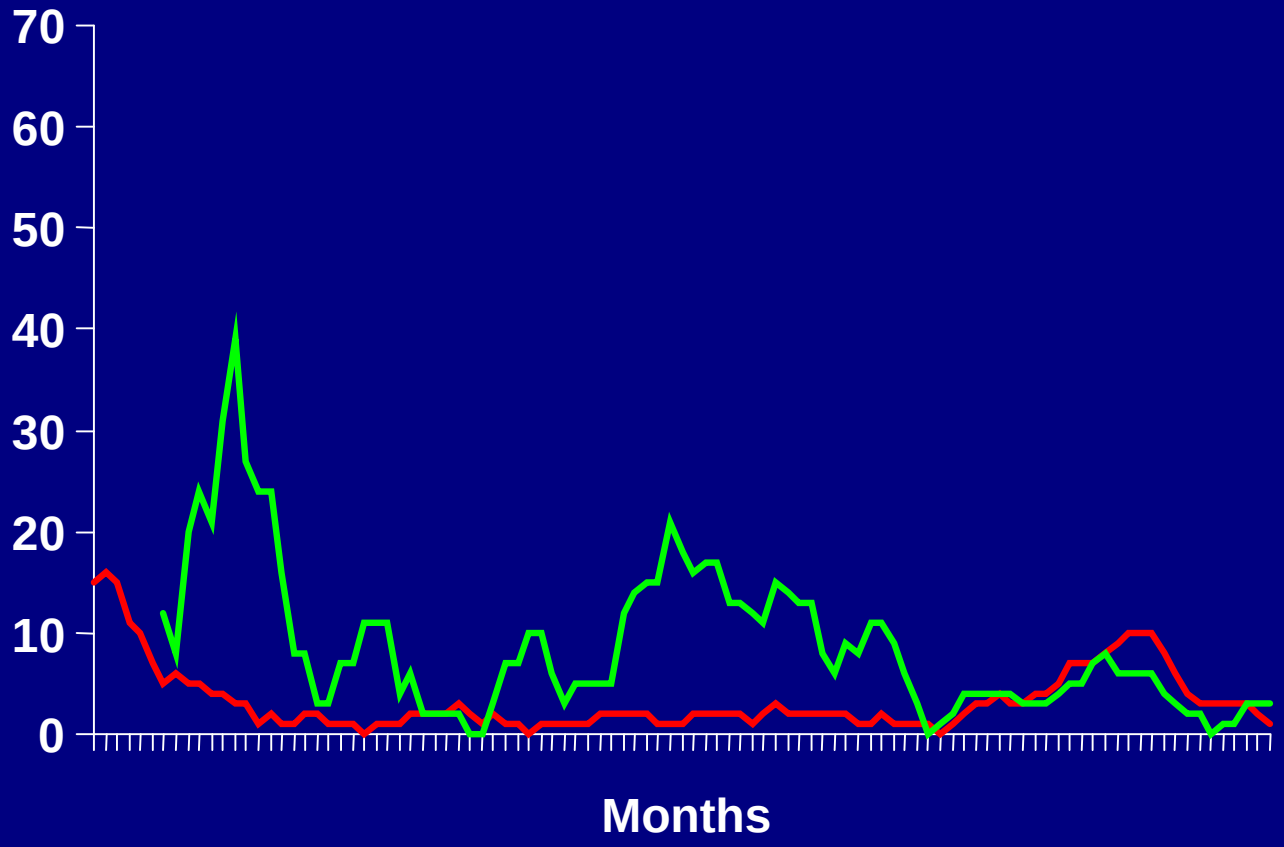
5-Month Moving Average Percent Amikacin-Resistant/Intermediate *P. aeruginosa* and Hospital Antimicrobial Use, Hospital Vega Baja, Spain, 1991-1999



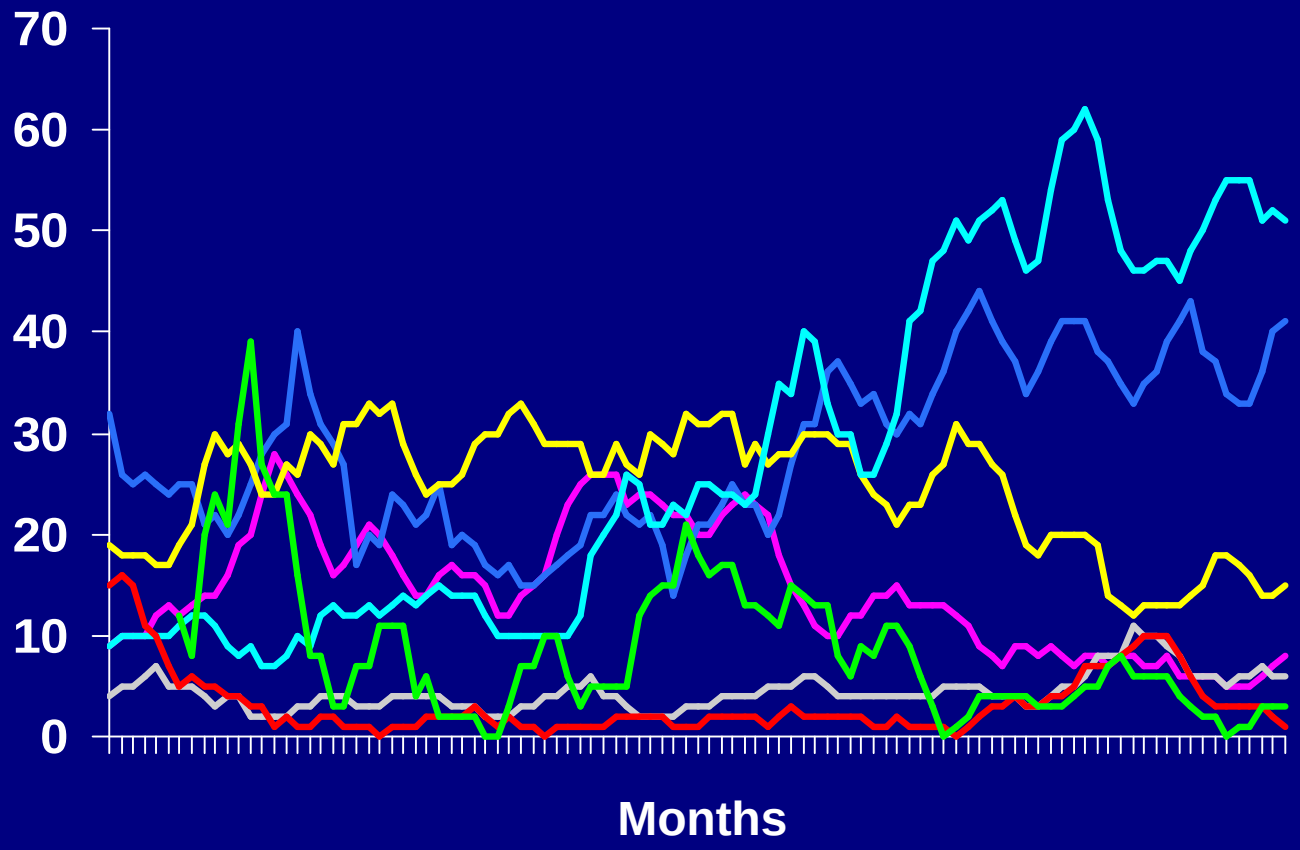
Amikacin use (DDD/1,000 pt-dys)

Amikacin-R P. aeruginosa (%)

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



- Gentamicin use (DDD/1,000 pt-dys)
- Tobramycin use (DDD/1,000 pt-days)
- Cefotaxime use (DDD/1,000 pt-dys)
- Ceftazidime use (DDD/1,000 pt-dys)
- Ceftriaxone (DDD/1,000 pt-dys)
- Amikacin use (DDD/1,000 pt-dys)
- Amikacin-R P. aeruginosa (%)

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

ViResiST

Transfer Function Model for Percent Amikacin-Resistant *Pseudomonas aeruginosa* Series

(taking into account aminoglycoside and 3rd-generation cephalosporin use)

Term	Order	Parameter (SE)	T-ratio	P-value
Constant	0	-20.741 (4.516)	-4.59	< 0.001
Amikacin	7	0.973 (0.391)	2.49	< 0.02
Gentamicin	7	0.420 (0.153)	2.75	< 0.01
Cefotaxime	3	0.297 (0.112)	2.66	< 0.01
Cefotaxime	6	0.437 (0.110)	3.98	< 0.001
AR	2	0.295 (0.091)	3.24	< 0.01

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

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Co-Resistances in Amikacin-Resistant/Intermediate and Susceptible *Pseudomonas aeruginosa* Isolates, Hospital Vega Baja, Spain, 1991-1999

Co-resistance	Amikacin-R/I no. (%)	Amikacin-S no. (%)	RR	P-value
Gentamicin-R/I	**78 (97.5)**	177 (17.5)	128.0	<0.0000001
Cefotaxime-R/I	**73 (91.3)**	840 (83.0)	-	*NS*
Ceftriaxone-R/I*	40 (81.6)	361 (74.7)	-	*NS*
Tobramycin-R/I	34 (42.5)	18 (1.8)	14.8	<0.0000001
Ceftazidime-R/I	15 (18.8)	37 (3.7)	4.6	<0.0000001

* only 55.3% of isolates were tested for susceptibility to ceftriaxone

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

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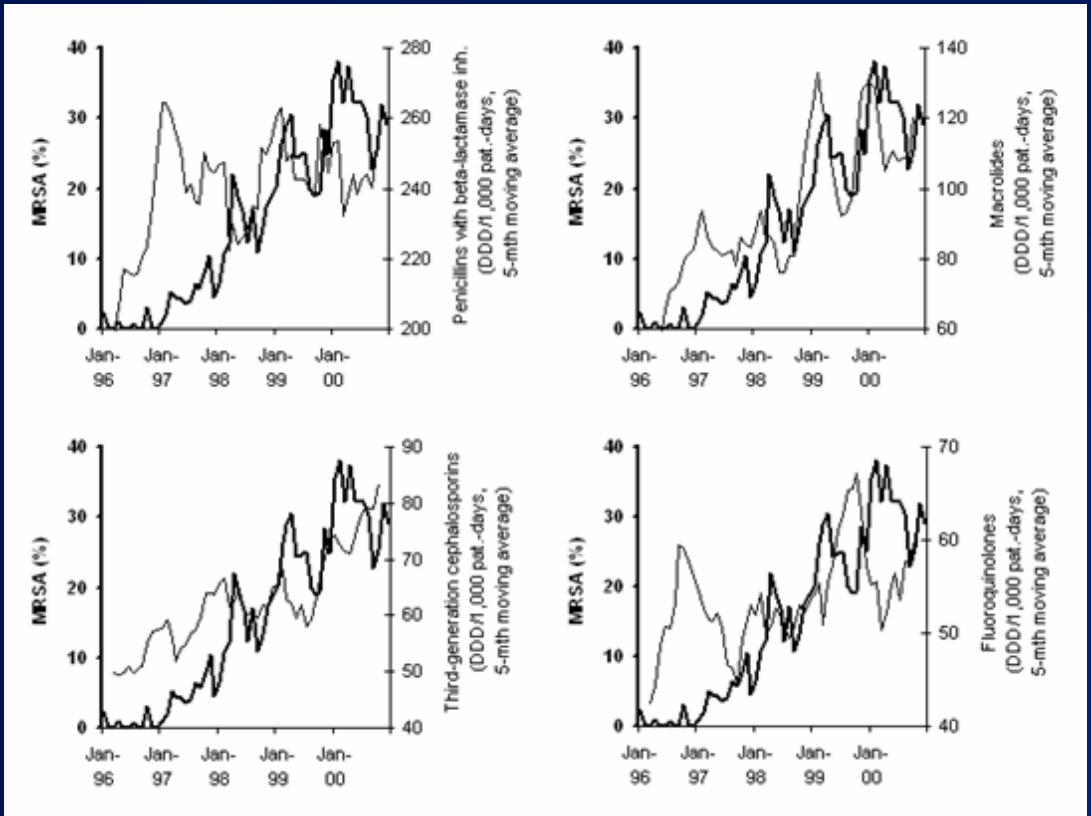
%MRSA and Monthly Use of Macrolides, Third-Generation Cephalosporins and Fluoroquinolones, Aberdeen Royal Infirmary, 01/1996-12/2001



Explaining variable for monthly %MRSA	Lag (months)	Estimated coefficient
%MRSA	1	0.420
Macrolide use	1,2,3	0.165
Third-generation cephalosporin use	4,5,6,7	0.290
Fluoroquinolone use	4,5	0.255
Constant	-	- 36.7

R^2=0.902

Source: Monnet DL, et al. Emerg Infect Dis 2004;10:1432-1441.

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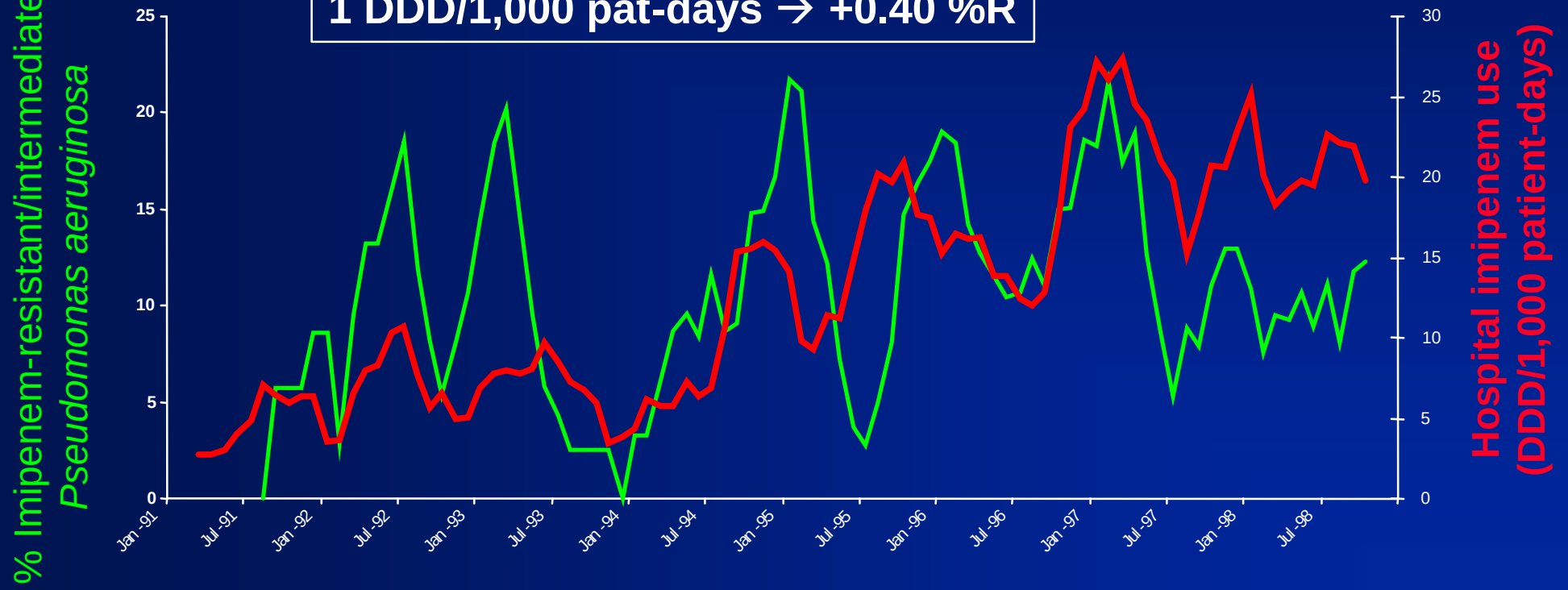
5-Month Moving Average Percent Imipenem-Resistant/Intermediate *P. aeruginosa* and Hospital Imipenem Use, Hospital Vega Baja, Spain, 1991-1999

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.

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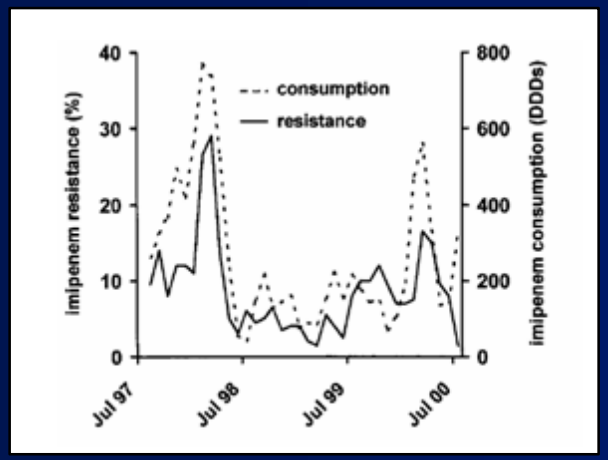
%Carbapenem-Resistant *Pseudomonas aeruginosa* and Carbapenem Use in 4 Hospitals, 1996-2003

Univ. Hospital, Ulm (D)

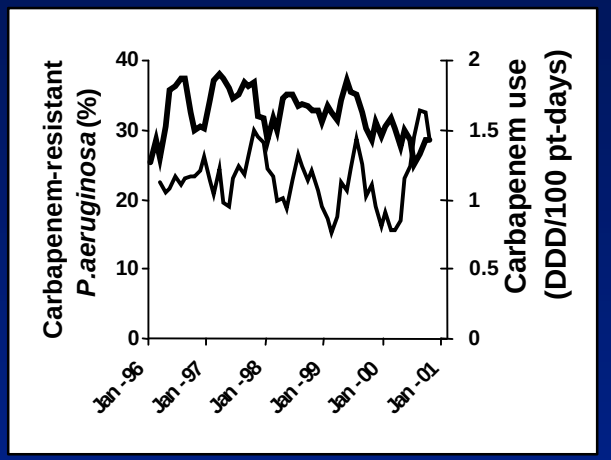
Lepper et al. AAC 2002;46:2920-5.



Average delay = 0-1 month

Univ. Hospital, Utah (USA)

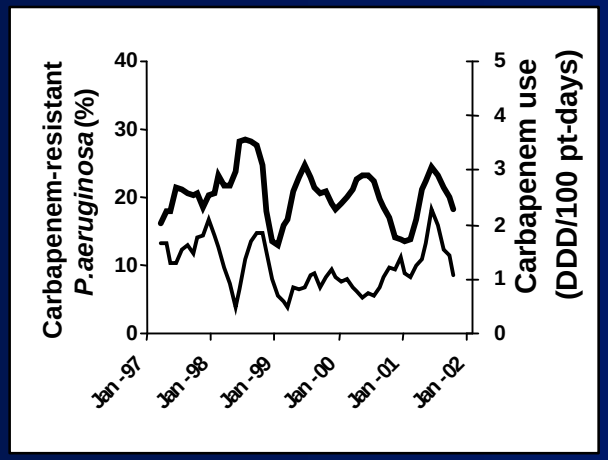
Samore MH, et al. Unpublished data.



Average delay = 0-1 month

Univ. Hospital, Antwerp (B)

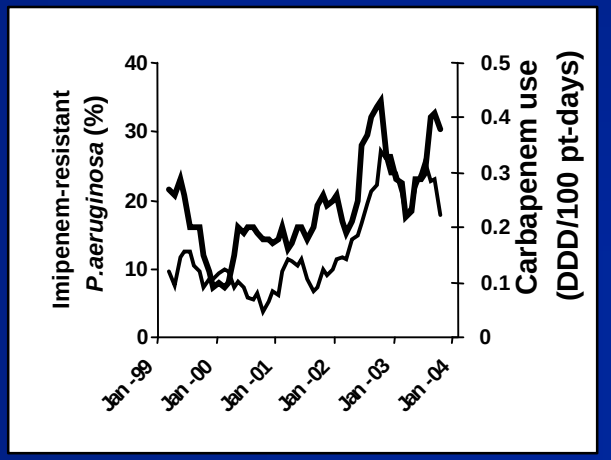
Goossens H, et al. Unpublished data.



Average delay = 0-2 months

Centre Hosp. Mulhouse (F)

Aujoulat O, Delarbre JM. ViResiST.



Average delay = n.a.

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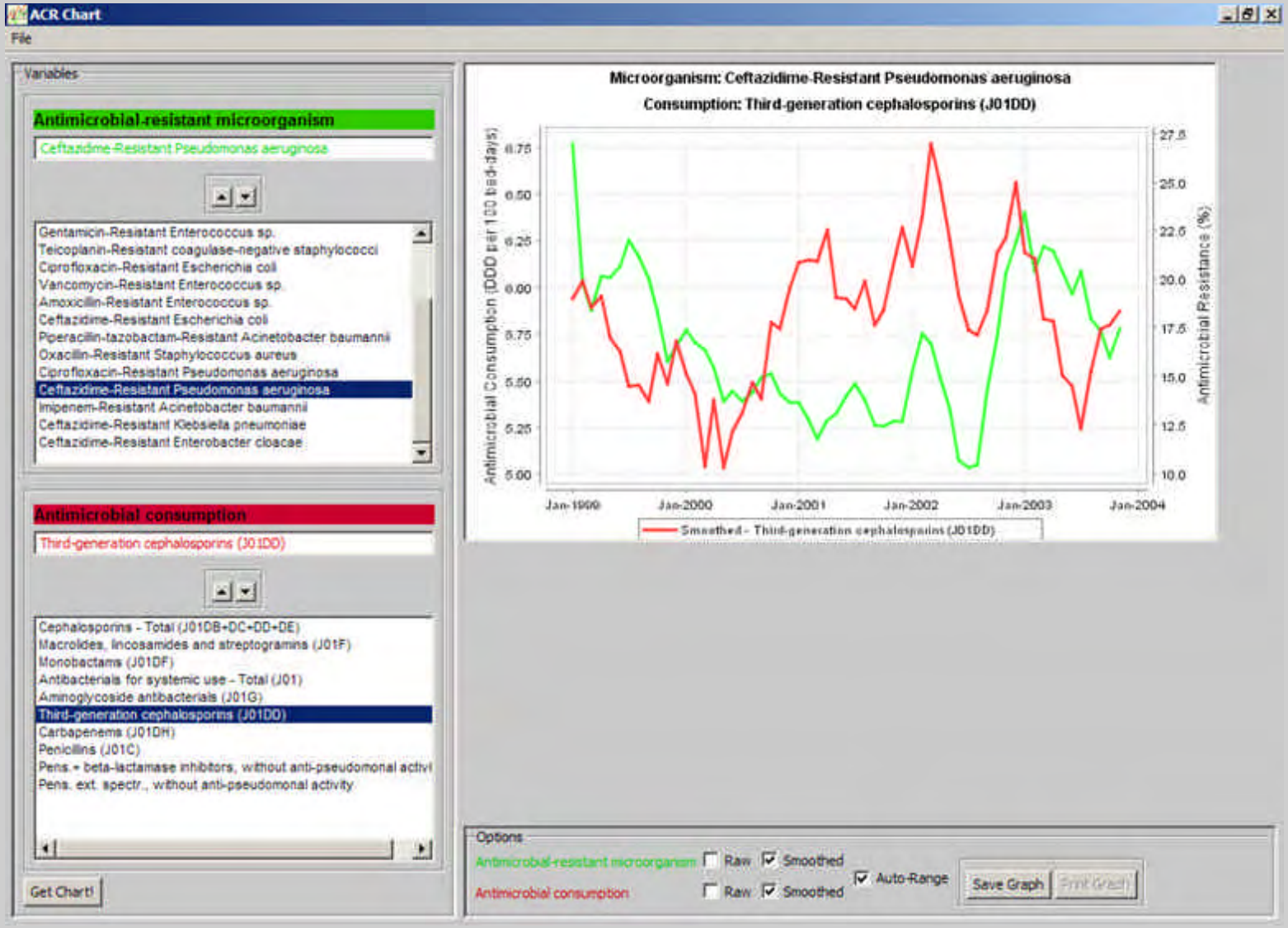
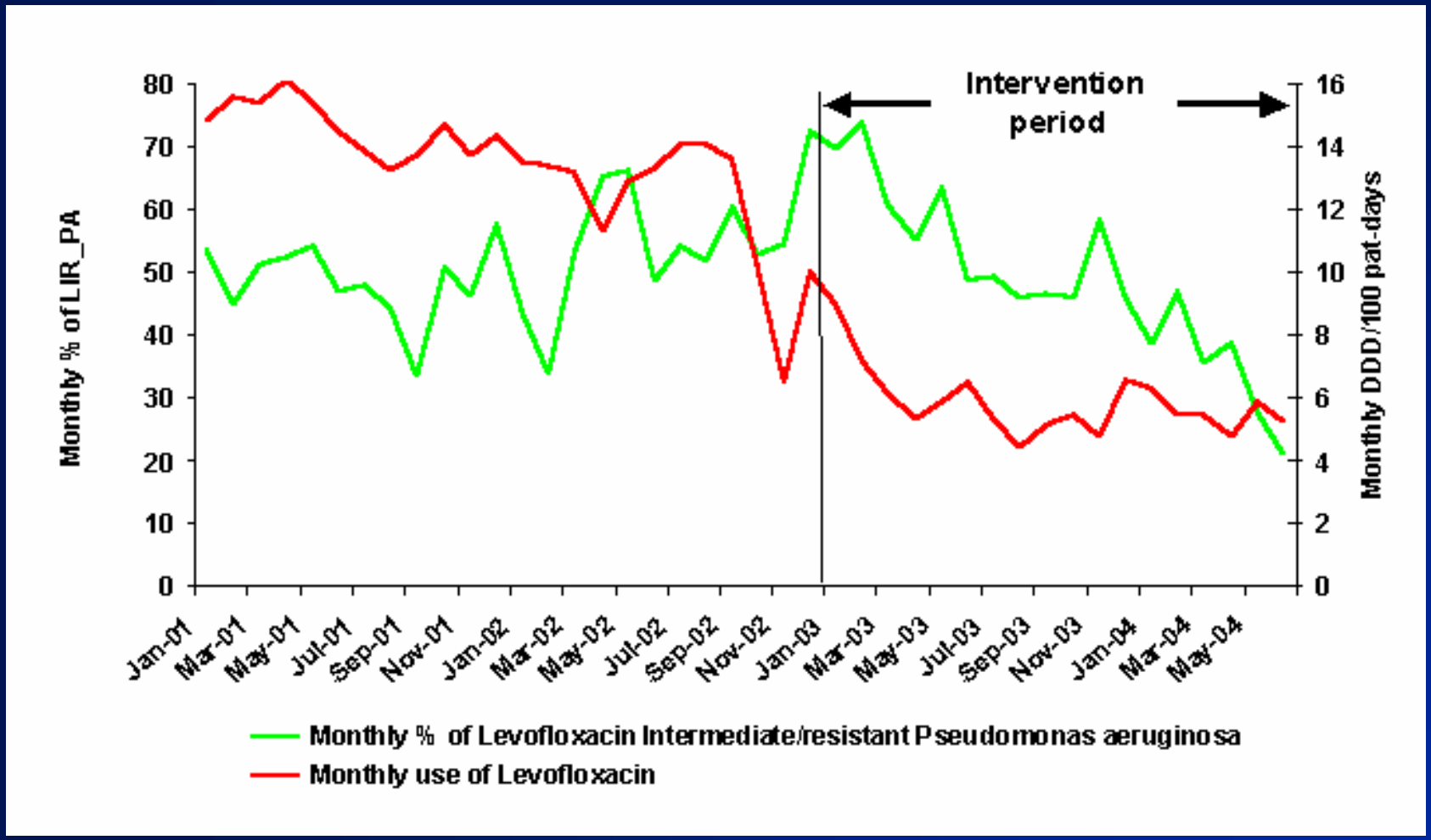
ACR Chart



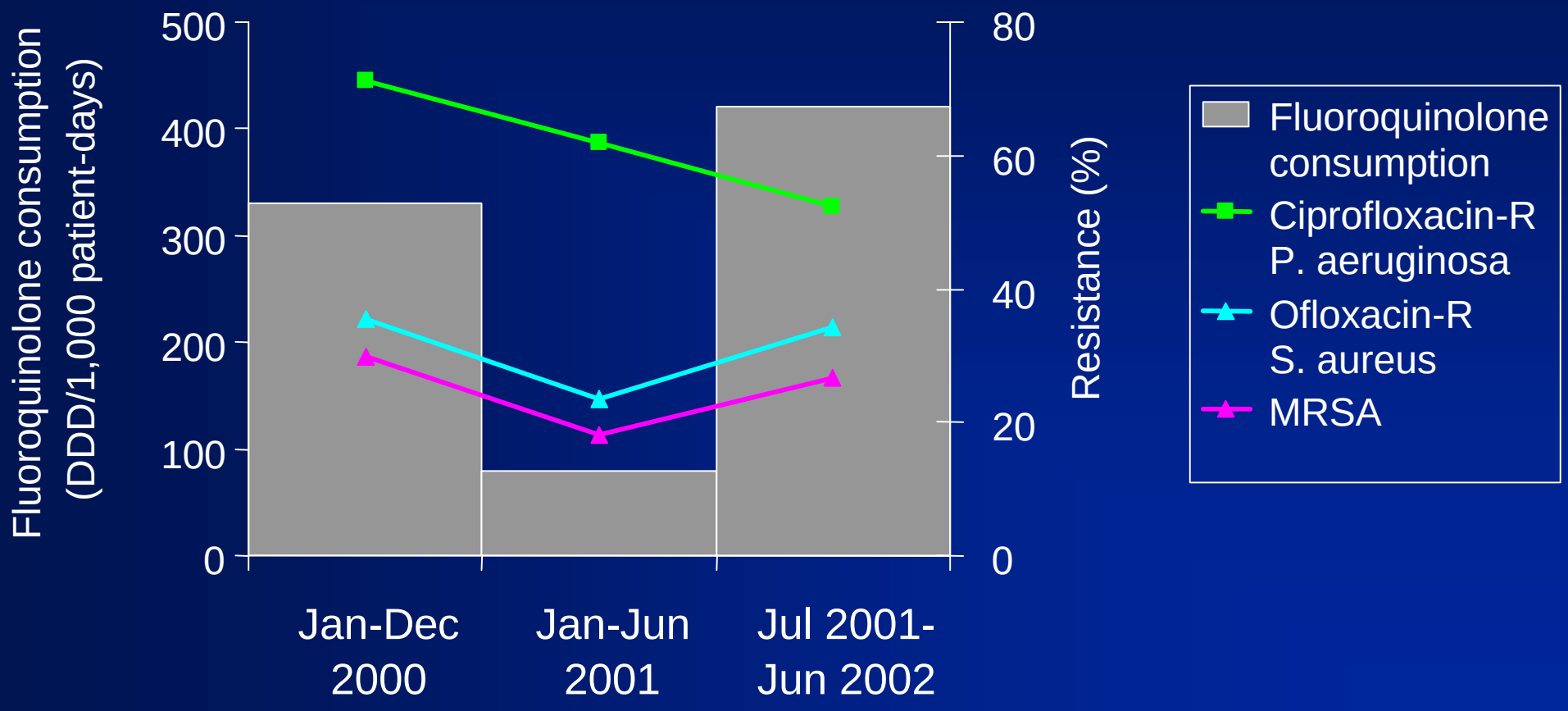
Source: Muller A, et al. (available free-of-charge, September 2005)

Effects of reduction of quinolone use on antibiotic susceptibility in *P. aeruginosa*, Pittsburgh (PA), 2001-2004



Source: Paterson DL, et al. 44th ICAAC, Washington (DC), 30-10/2-11-2004, abstr. K-347.

Effect of Restricting Fluoroquinolones, ICU, Saint-Etienne (F), 2000-2002

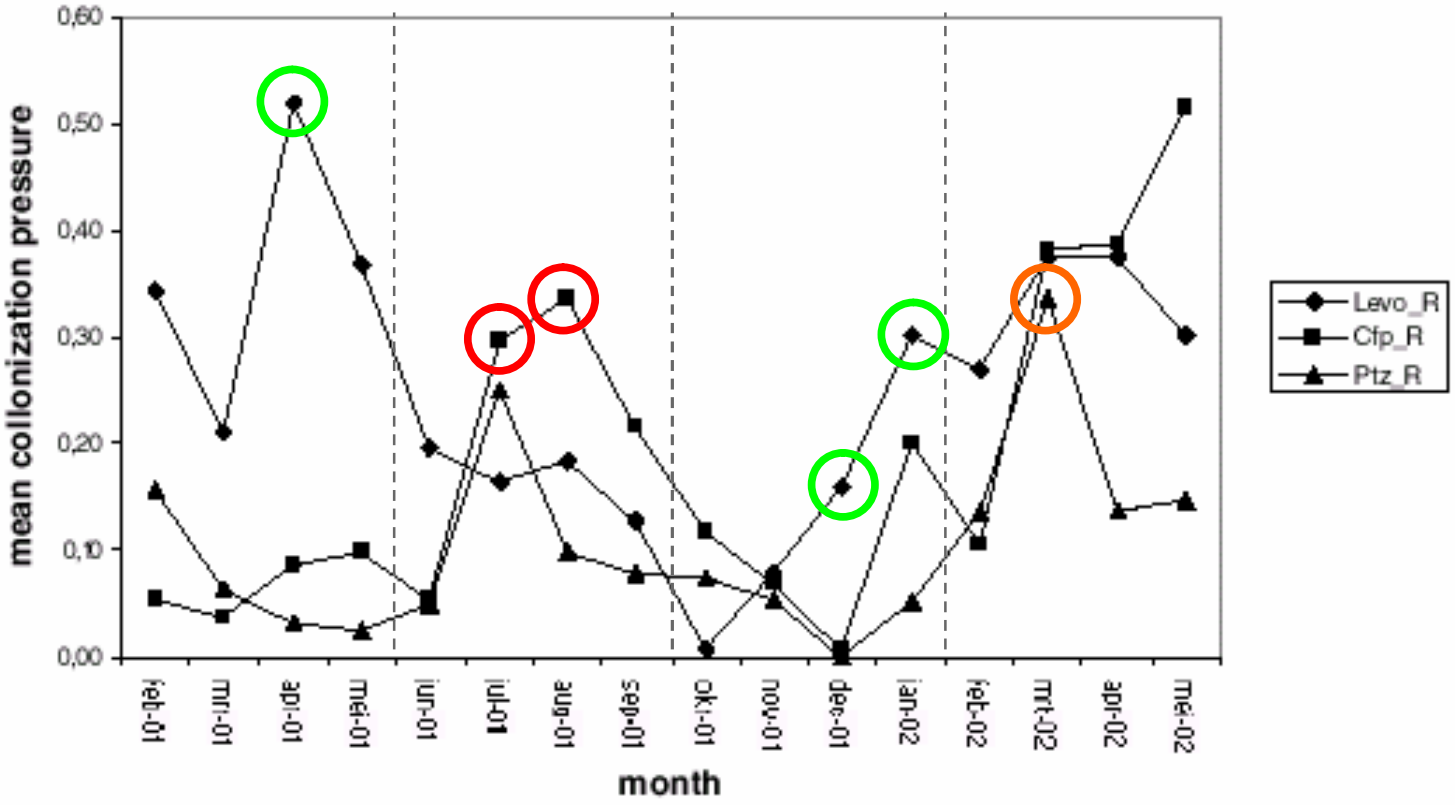


Source: Aubert G, et al. J Hosp Infect 2005;59:83-89.

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

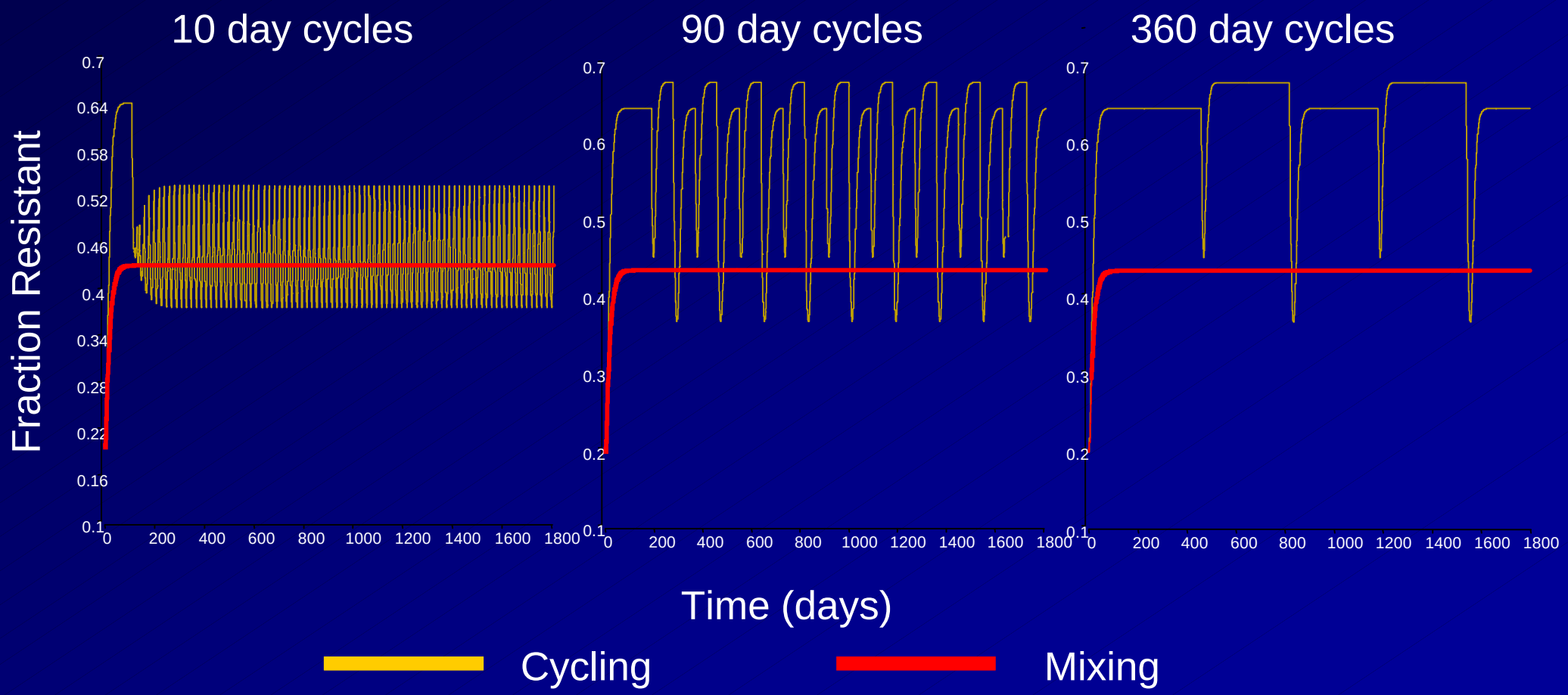
Proportion of patients treated (%)

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



Source: van Loon HJ, et al. AJRCCM, in press (published online, October 29, 2004).

Effect of Cycle Length



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

Areas for Future Research

- Adequation between studies at patient level and time series analyses?
- Are these relationships found in every hospital?
- More on the effect of interventions aiming at rationalizing antimicrobial prescriptions
- Short cycling vs. optimal mixing of prescriptions
- MRSA vs. antimicrobial consumption
- Outbreaks vs. endemic situations
- Interaction between infection control and antimicrobial consumption

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

↓

Carbapenems

↓

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

↓

Colistin

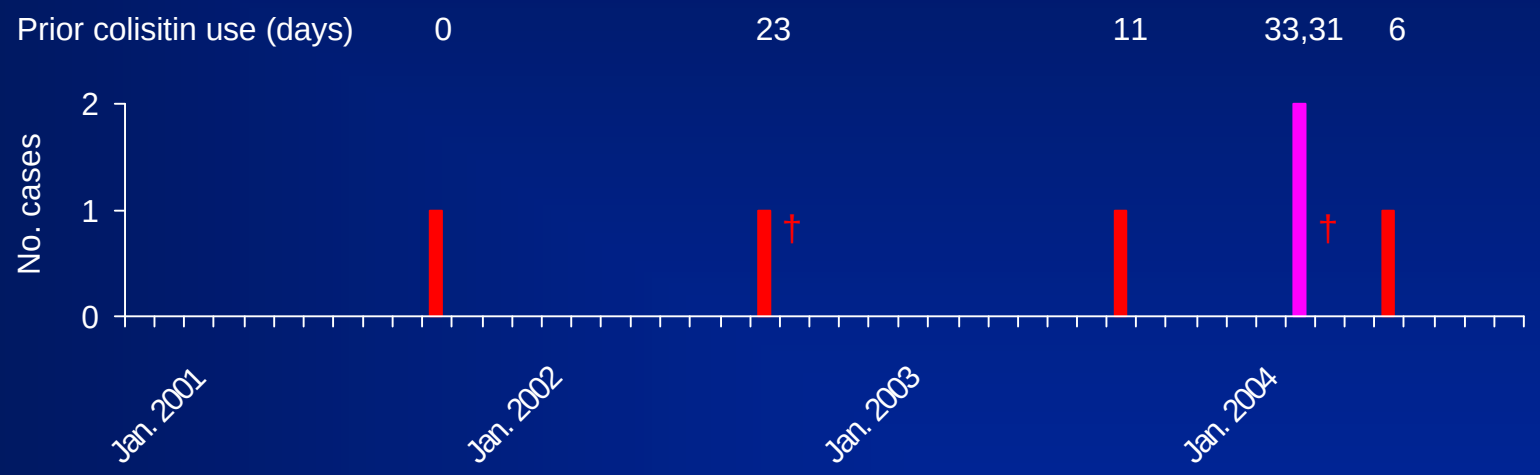
↓

Pan-resistant Gram-neg. bact.

Pan-Resistant Gram-Negative Bacilli

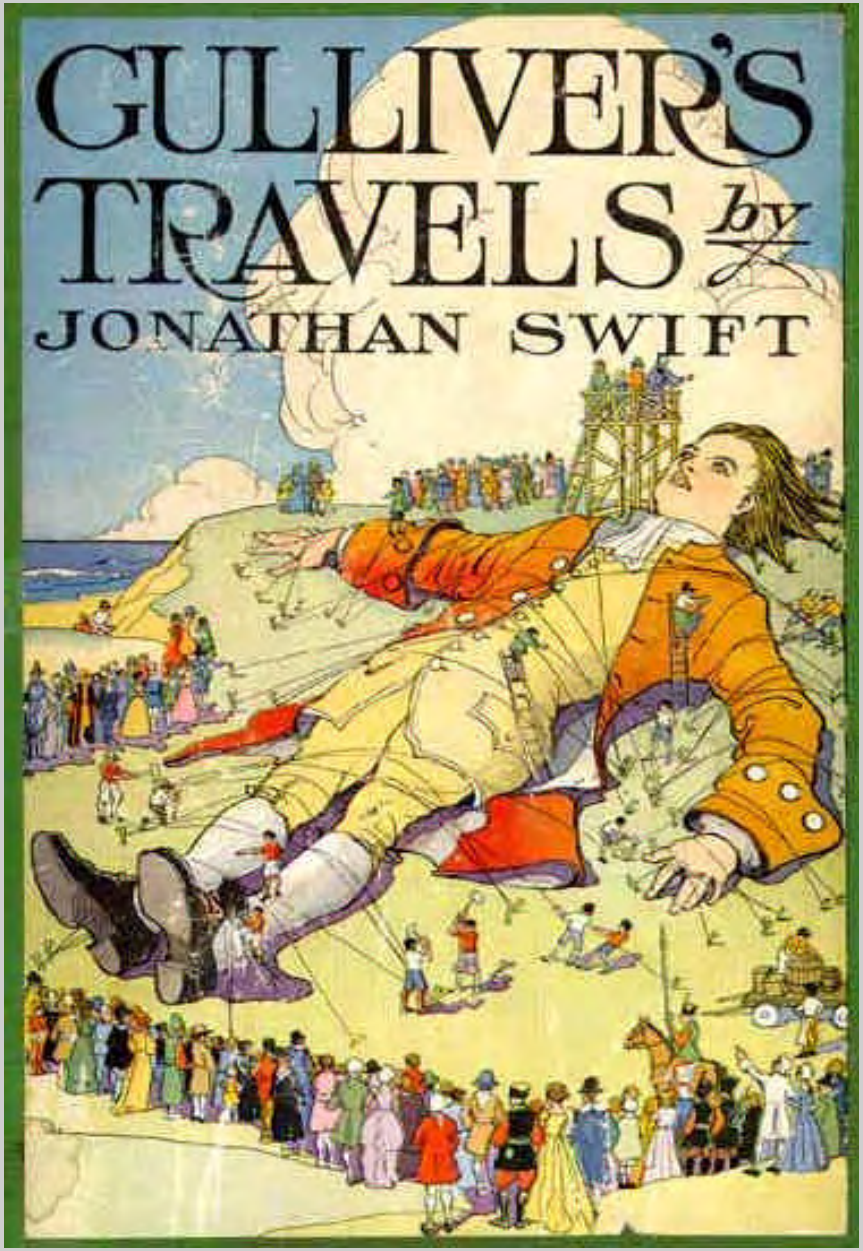
ICU, Henry Dunant Hosp., Athens, Greece, 2001-2004

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.



It's a numbers game!

Illustration: Prittie EJ.
Philadeplphia, PA: JC Winston, 1930.