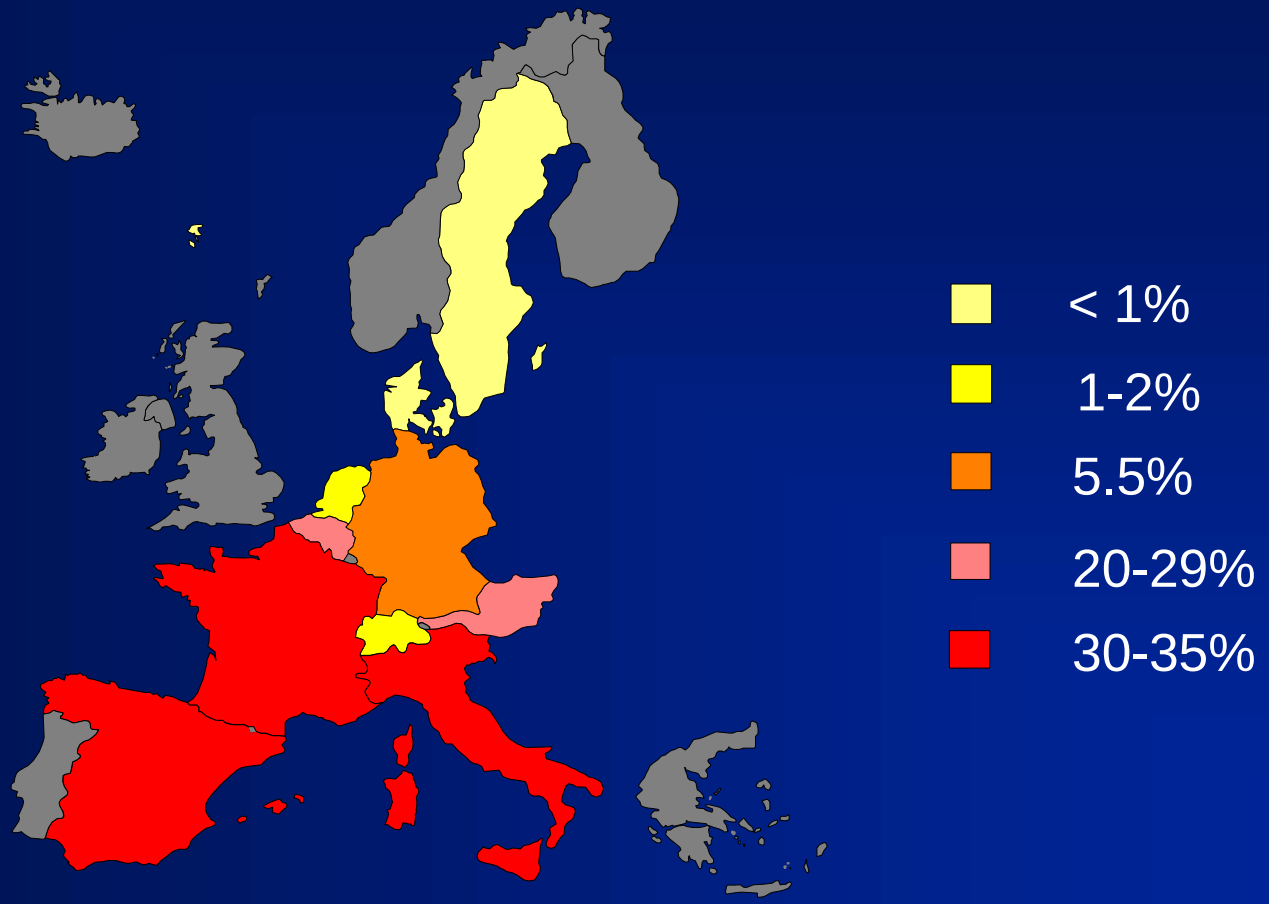
Surveillance of Antimicrobial Resistance: from Microbiology Laboratory Data to Epidemiological Networks

Dominique L. Monnet

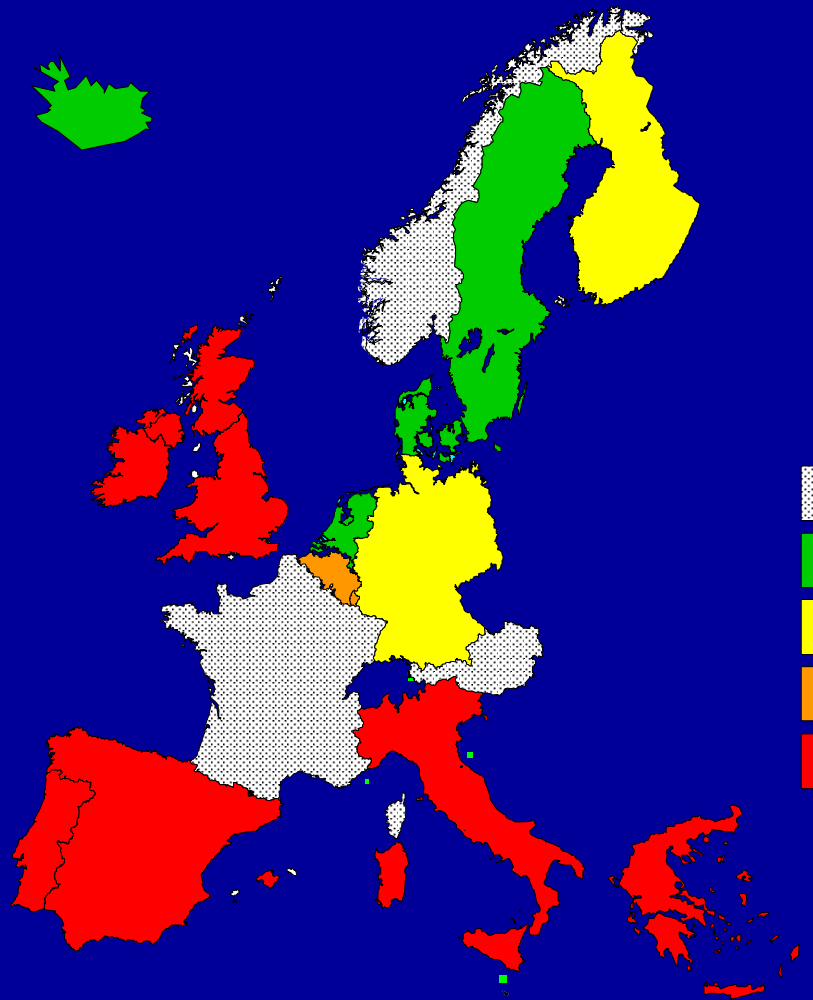
Antimicrobial Resistance Surveillance,
Dept. of Microbiological Research and Development,
Statens Serum Institut, Copenhagen, Danmark

MRSA in Europe, 1990-1991



Source: Voss A, et al. Eur J Clin Microbiol Infect Dis 1994;13:50-55.

Methicillin-Resistant *Staphylococcus aureus* (MRSA) in Blood Isolates, 2000



%MRSA	(# countries)
no data	(3)
<3	(4)
3-9	(2)
10-29	(2)
>30	(6)

Available from: URL: http://www.earss.rivm.nl/

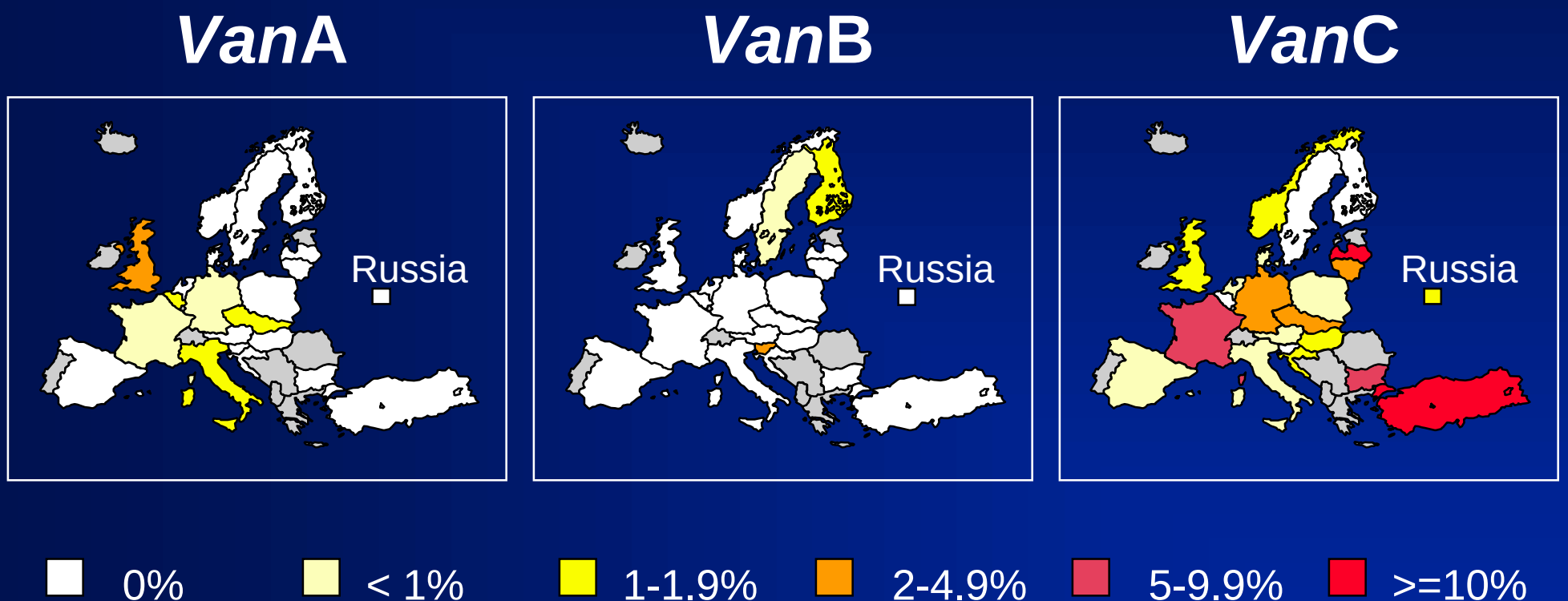
Source: European Antimicrobial Resistance Surveillance System (EARSS), RIVM, May 2000.

Vancomycin-Resistant Enterococci in Europe, 1995

- 1,706 enterococci in 9 European countries: B, F, D, I, NL, P, E, CH, UK
- 1.8% VRE (22 *van*A, 8 *van*B)
- 0.4% vancomycin-intermediate enterococci
- VR *E. faecium* in all countries except Spain
- Glycopeptide-resistant *E. faecalis* only in France, Germany, Portugal, Italy and Spain

Source: Grüneberg RN, Hryniewicz W. Int J Antimicrob Agents 1998;10:271-277.

Vancomycin-Resistant Enterococci in 27 European Countries, 1997



Source: Schouten R. 9th ECCMID, Berlin, 1999. Abstract P0136.

‘There are no reliable data in this area -- simply fragments of information and anecdotes that we use to draw an overall picture’.

T.F. O’Brien

Source: Neu HC, et al. Diagn. Microbiol. Infect. Dis. 1992;15:53S-60S.

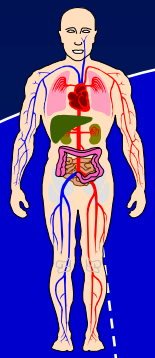
Comparison of Multicentric Resistance Data Sources

TYPE OF SOURCE	ADVANTAGES	LIMITATIONS
Resistance Studies	- isolates available	- limited time period
Resistance Surveys	- additional clinical data and data on unit practices	- limited time period - isolates not available
Reference Centers	- already exist - isolates available	- major sample bias
Nosocomial Infection Surveillance Systems	- already exist - clinical data on nosocomial infections	- only isolates associated with nosocomial infections
Resistance Surveillance Systems	- databases already exist in microbiology laboratories - adapted to objective	- no clinical data

Surveillance Studies vs. Systems

	Advantages	Limitations
Surveillance **Studies**	- isolates available - possibility of centralized testing	- additional workload - usually time-limited
Surveillance **Systems**	- no additional workload (once implemented) - on-going - possible rapid feed-back	- isolates not available

Surveillance of Antimicrobial Resistance in Europe, 1998



Private

SENTRY
Paul Ehrlich Soc.
Alexander Project
CEM/NET
Artemis
MYSTIC

s
TSN

SARISA

Public

WHO/Antimicrobial Resistance Monitoring

WHO/GASP

WHO-IUATLD/Global Project on Anti-TB Drug Res. Surv.

s
EU/EARSS
EU/ESAR
CDC/INSPEAR
EU/ENTER-Net
EU/EuroTB

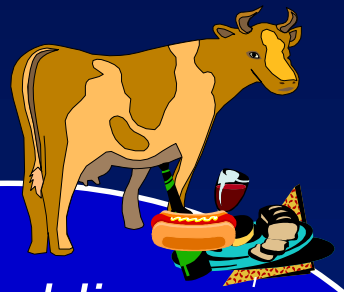
EU/ENARE
EU/ESAP

Public

s
EU/Enterococci in the food chain

EU/Risk assessment of potential transfer...

s
CDC/INSPEAR
EU/HARMONY
ESGARS



Public

s
EU/Antibiotic resistance in bacteria from animals

Private

s
FEFANA / *E. faecium* from animals

Legend

Surveillance

Research

s starting or planned

Source: Monnet DL. 1998.

What Is the Objective of Surveillance?

- Follow resistance trends?
- Alert for new resistance mechanisms?
- Detect colonized patients?
- Evaluate the effect of interventions to control antimicrobial resistance?
- Identify risk factors for antimicrobial resistance?

Definition of Public Health Surveillance

‘Ongoing and systematic collection, analysis and interpretation of outcome-specific data essential to the planning, implementation, and evaluation of public health practice, closely integrated with the timely dissemination of these data to those who need to know. The final link of the surveillance chain is the application of these data to the control and prevention of human disease and injury.’

Source: Thacker SB. Surveillance. *In* Gregg, ed. Field epidemiology, 1996:16-32.

Criteria for Evaluating Surveillance Systems

- Usefulness
- Simplicity
- Flexibility
- Acceptability
- Resources (direct costs)
- Sensitivity
- Predictive value positive
- Represenativeness
- Timeliness

Source: CDC/EPO. Klaucke DN et al. MMWR 1988;37(S-5):1-18.

Why Do We Need Antimicrobial Resistance Networks?

- To harmonize susceptibility testing methods
- To compare and improve resistance rates
- To improve alert for emerging resistance
- To test interventions and share experiences in the control of antimicrobial resistance

Problems

- Standardization of susceptibility testing
- Standardization of surveillance methodology
- Coordination of initiatives

Standardization and Quality of Susceptibility Testing

- Internal quality control
- External quality control
- Accreditation of microbiology laboratories?

Consensus on Minimal Data Set

- Patient ID (coded)?
- Hospital/unit ID?
- Blood only vs. all isolates?
- Quantitative data (diameter or MIC)

Standardization and Quality of Databases

- Level of stratification: hospital/type of unit/unit
- Similar coding system (WHONET?)
- Duplicate isolates

Duplicate Isolates (1): Urinary Tract Isolates, Finland, 1984

	%Trimethoprim-R *Escherichia coli*
Raw data	9.8
Repeat samples excluded	9.2

***P* > 0.10**

Source: Huovinen P. J. Antimicrob. Chemother. 1985;16:443-447.

Duplicate Isolates (2): ICU Isolates, France, 1991

	%Ceftazidime-R	
	E. cloacae	*P.aeruginosa*
Raw data	46	43
First isolate per patient only	33	26

Source: Jarlier V, et al. Intensive Care Med. 1996;22:1057-1065.

Duplicate Isolates (3): Neonatal ICU Isolates, Germany, 1996

	%MRSA	%Azlocillin-R *P.aeruginosa*
Raw data	1.7	26.1
Identical susceptibility patterns excluded	5.6	27.8
Identical PFGE types excluded	4.4	27.8

Source: Döring G et al. Clin. Microbiol. Infect. 1997;3(Suppl. 2):70.

Duplicate Isolates (4): All Hospital Isolates, United States, 1995

- 10 frequently (>250) and 10 infrequently (<100) encountered microorganisms
- Antimicrobial susceptibilities decreased an average 1.07% +/- 9.48% (NS)
- Large variations from one microorganism to another

Source: Tidwell BH, et al. Infect. Control Hosp. Epidemiol. 1995;16(4-Part2):P36.

A Solution for Duplicate Isolates: WHONET Software

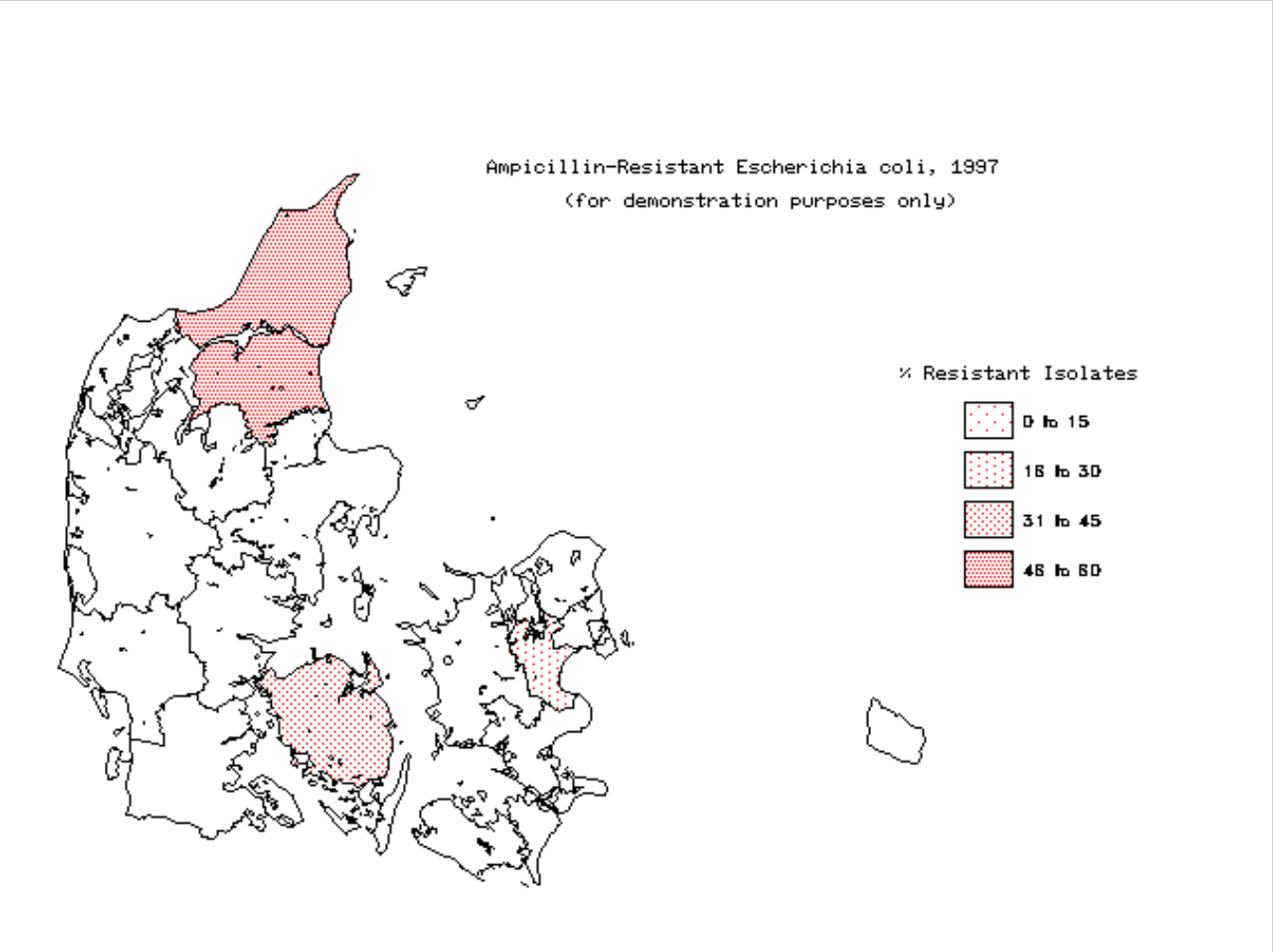
- Patient's first isolate
- Patient's most susceptible result (for each antibiotic)
- Patient's most resistant result (for each antibiotic)
- By interpretation (for each antibiotic, by this method %R+%I+%S may exceed 100%)

Source: Stelling JM, O'Brien TF. Clin. Infect. Dis. 1997; 24 Suppl 1:S157-68.

Feed-Back of Results

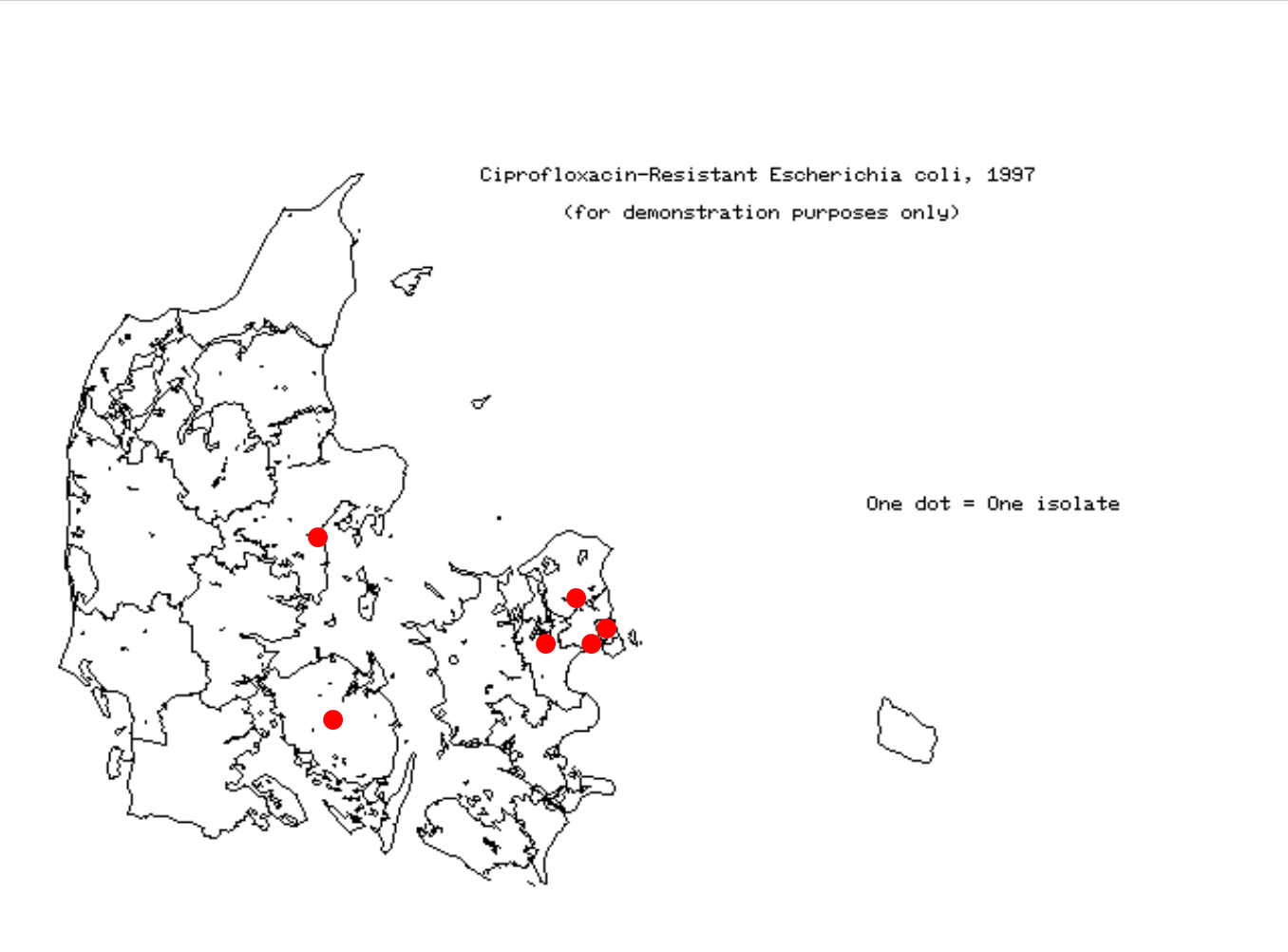
- Must be adapted to objective
- Choice of measurement unit: cases, frequency, incidence, incidence density
- Use graphic outputs

Feed-Back of Results



Fictive data (for demonstration purposes only).

Feed-Back of Results



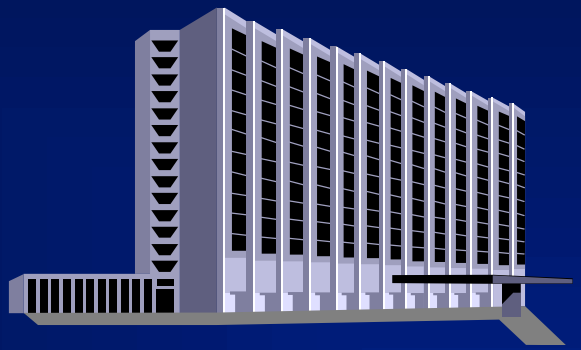
Fictive data (for demonstration purposes only).

What Is “Epidemiology” of Antimicrobial Resistance?

- Trends with geographic distribution?
- Epidemiologic typing?
- Studies on risk factors?

- Overuse
- Misuse
- Co-use

Antimicrobial Use



Antimicrobial Resistance in Hospitals

- IC practices
- Workload
- Outbreaks
- Reservoirs
- Patient transfer

Infection Control

Patients

- Intensive care
- Type of ICU
- Device utilization

Community

- Prevalence of resistance
- Antimicrobial use in humans and animals

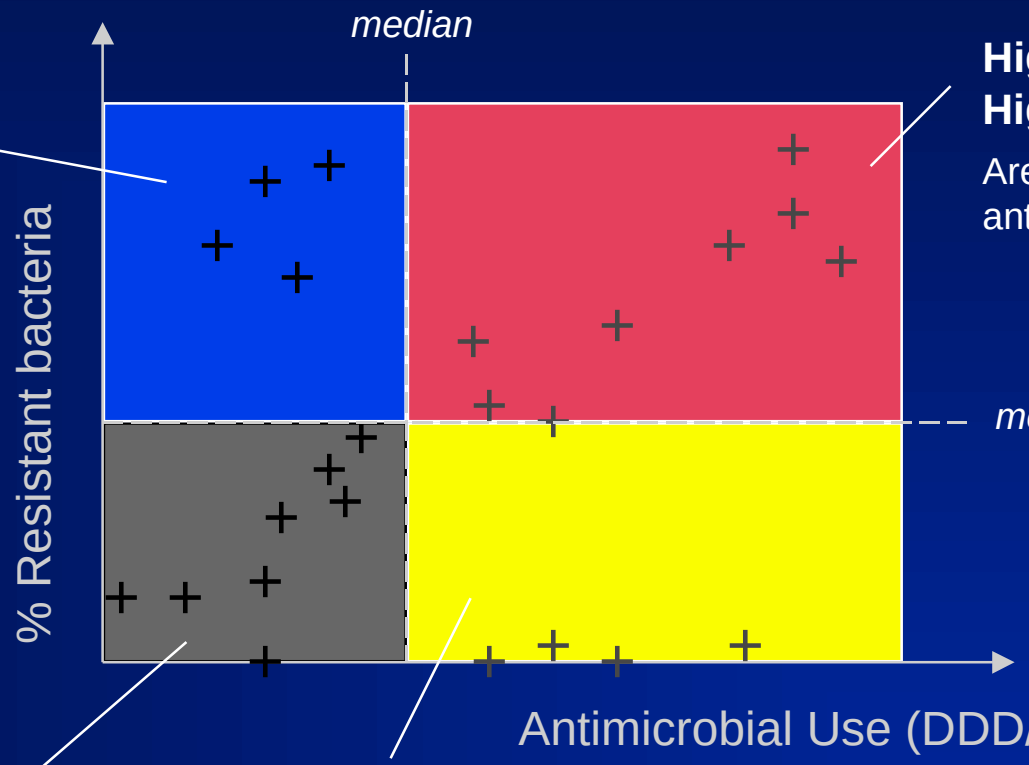
D.Monnet. Statens Serum Institut, Copenhagen, Denmark.

Are data available?
At which level?

- Antimicrobial resistance?
- Antimicrobial use?
- Infection control practices?

- Patient level?
- Unit level?
- Hospital level?

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

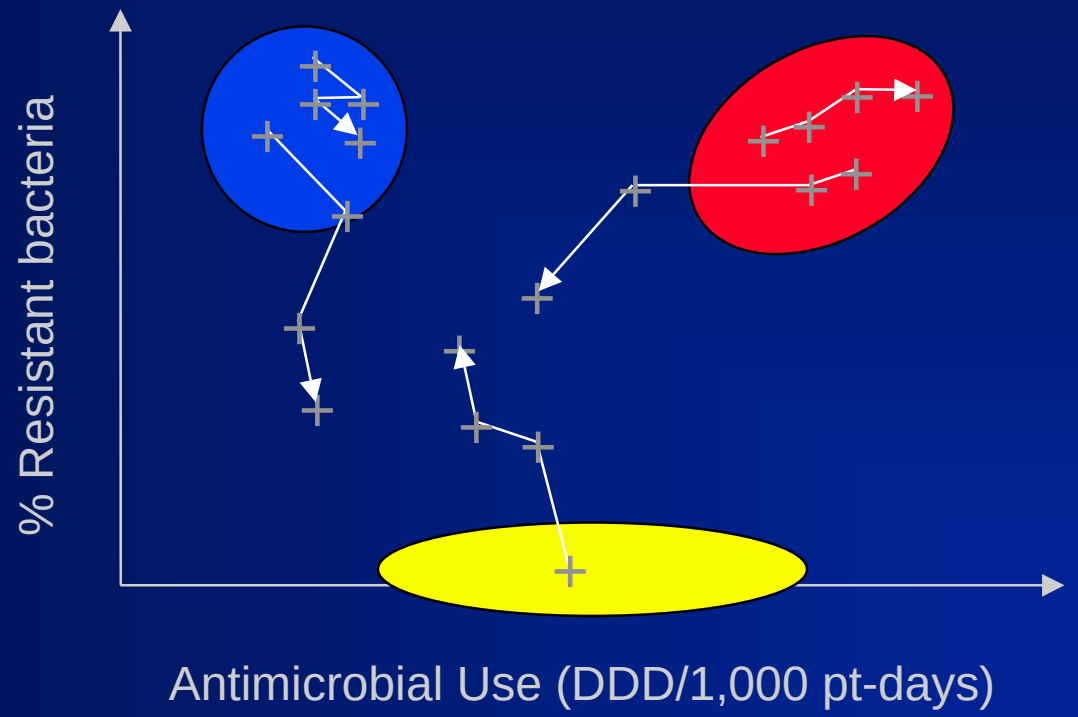
Low level of resistance
Low antimicrobial use

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

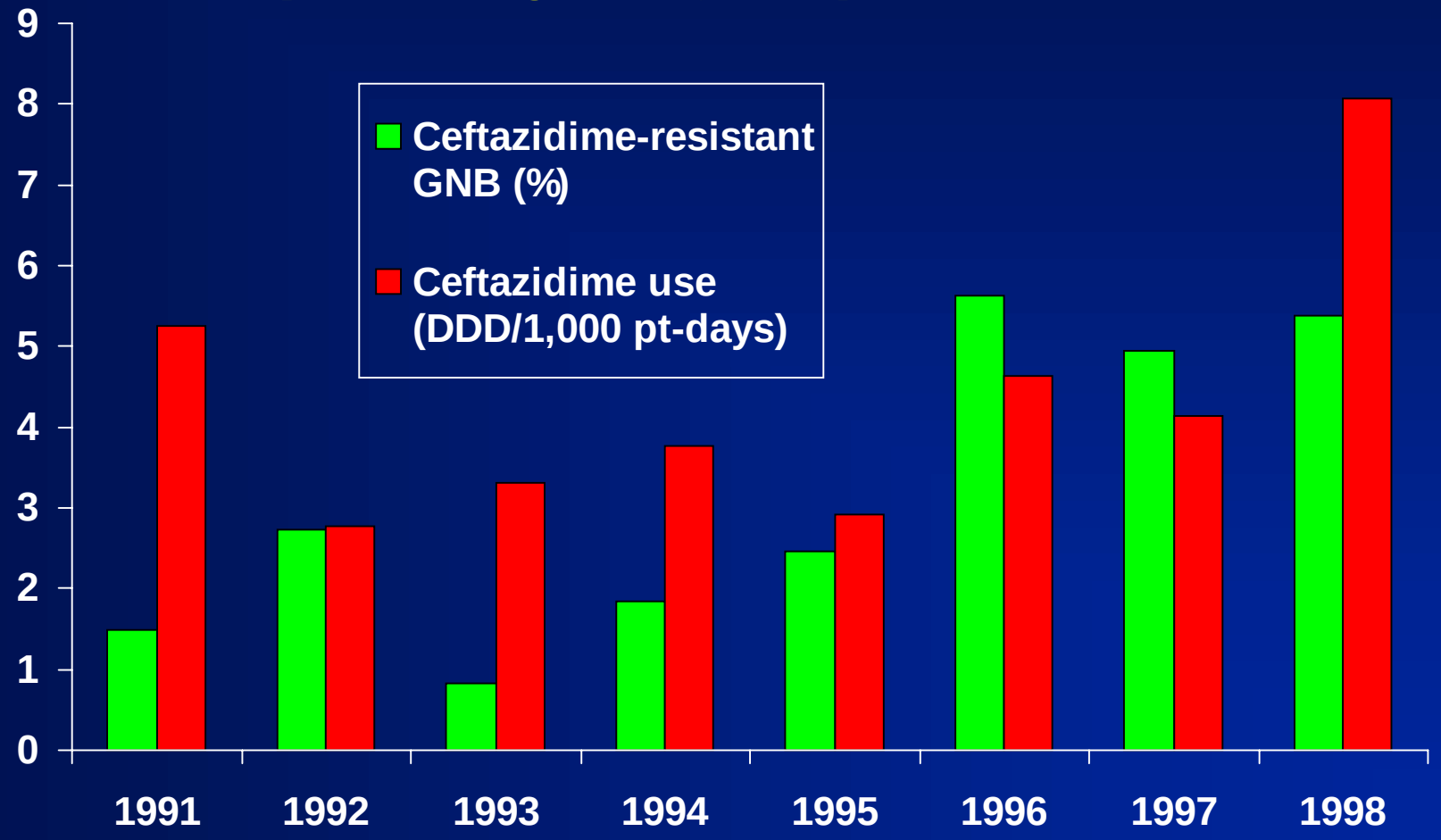
Adapted from: Infect Control Hosp Epidemiol 1998;19:388-394.

Taking Time into Account: Evaluating Interventions



D. Monnet. Statens Serum Institut, Copenhagen, Denmark.

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



Source: López-Lozano JM, Hospital Vega Baja, Orihuela (Alicante), Spain.

What Is Time Series Analysis?

- The analysis of time series, i.e. series of data collected over time at short intervals, as compared to the study period
- Ability to take into account the possible dependence of consecutive measurements
- In 1976, Box &Jenkins provided a practical method to build time series models

Why Use Time Series Analysis to Model Resistance Data?

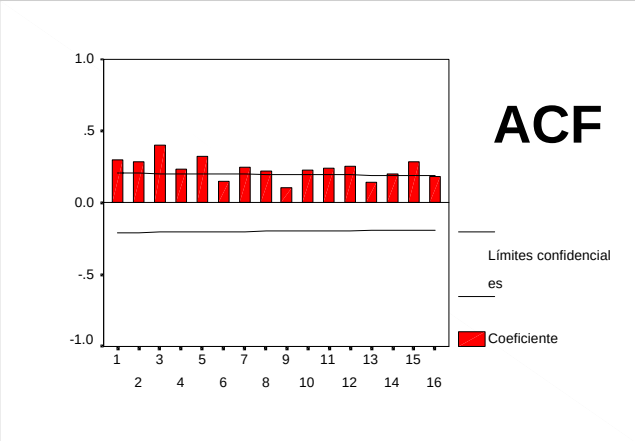
- Short-term variations of % resistant isolates
- Observations are necessarily correlated
- We should not disregard correlation between consecutive measurements of resistance

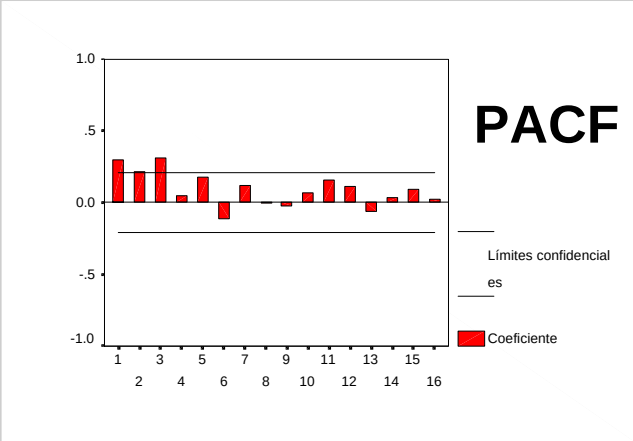
Box-Jenkins (ARIMA) Models

- AR (Autoregressive): previous values
- I (Integrated): trends
- MA (Moving Average): abrupt changes in the near past
- e.g., for ceftazidime-resistant gram-negative bacilli:
  %R(t) = 3.314 + 0.346 AR3 + 0.266 AR5

Building an ARIMA Model

- Model identification

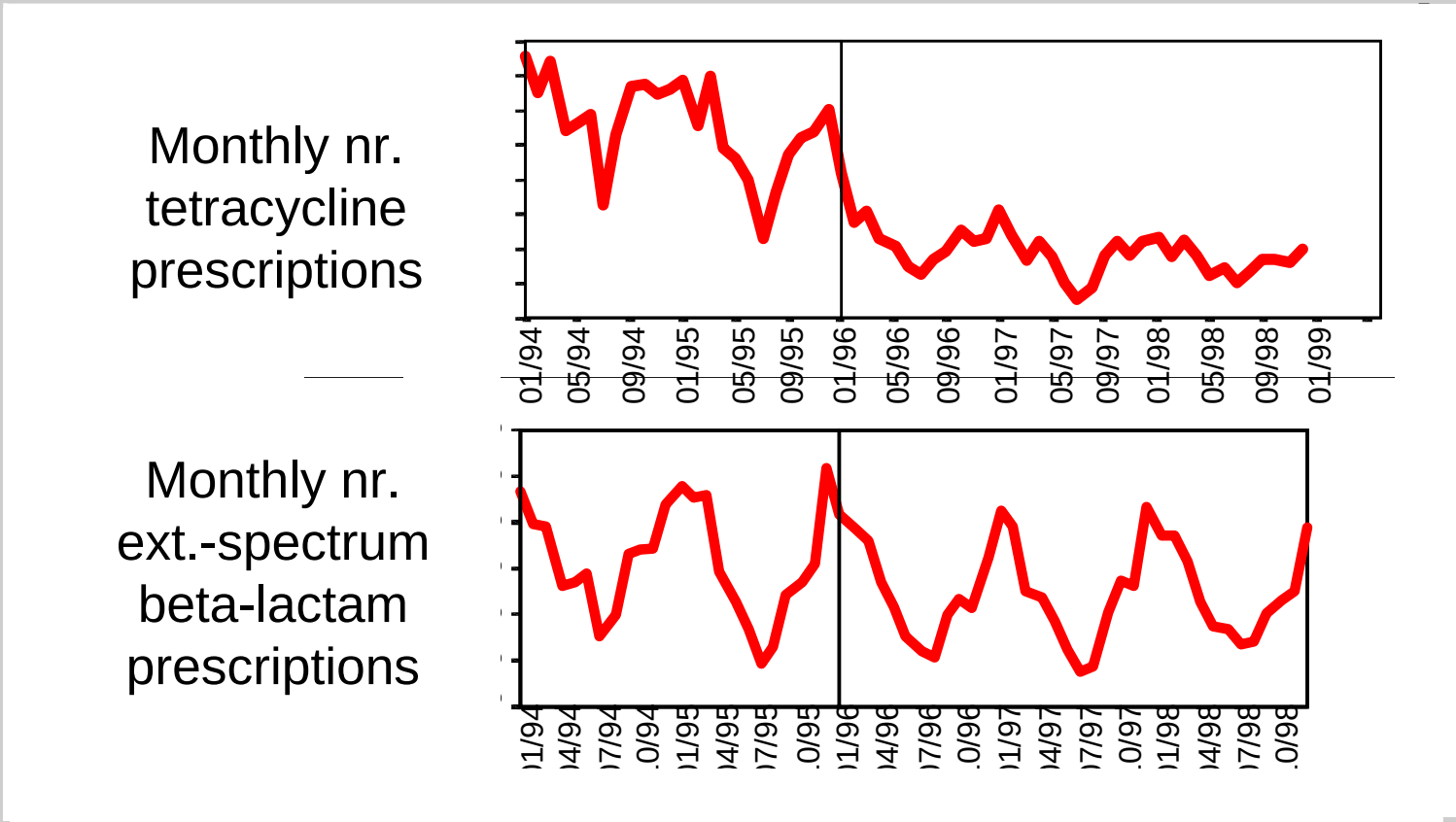




- Model estimation
- Diagnostics check on model adequacy

Source: Box GEP & Jenkins GM, 1976.

Change in the Subsidization of Antimicrobials, Denmark, 1996



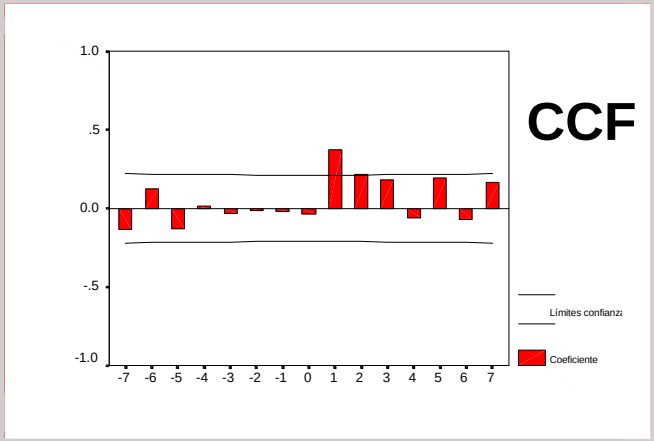
Source: Monnet DL, et al. 39th ICAAC, San Francisco (CA), 1999, abstr. 180.

Transfer Function (TF) Models

- Multivariate models
- To assess relationships between a target (output) series and one or several explanatory (input) series
- Previous applications in medicine, e.g.:
  - individual: exercise and blood glucose
  - population: climatic variables and mortality, influenza and mortality

Building a TF Model

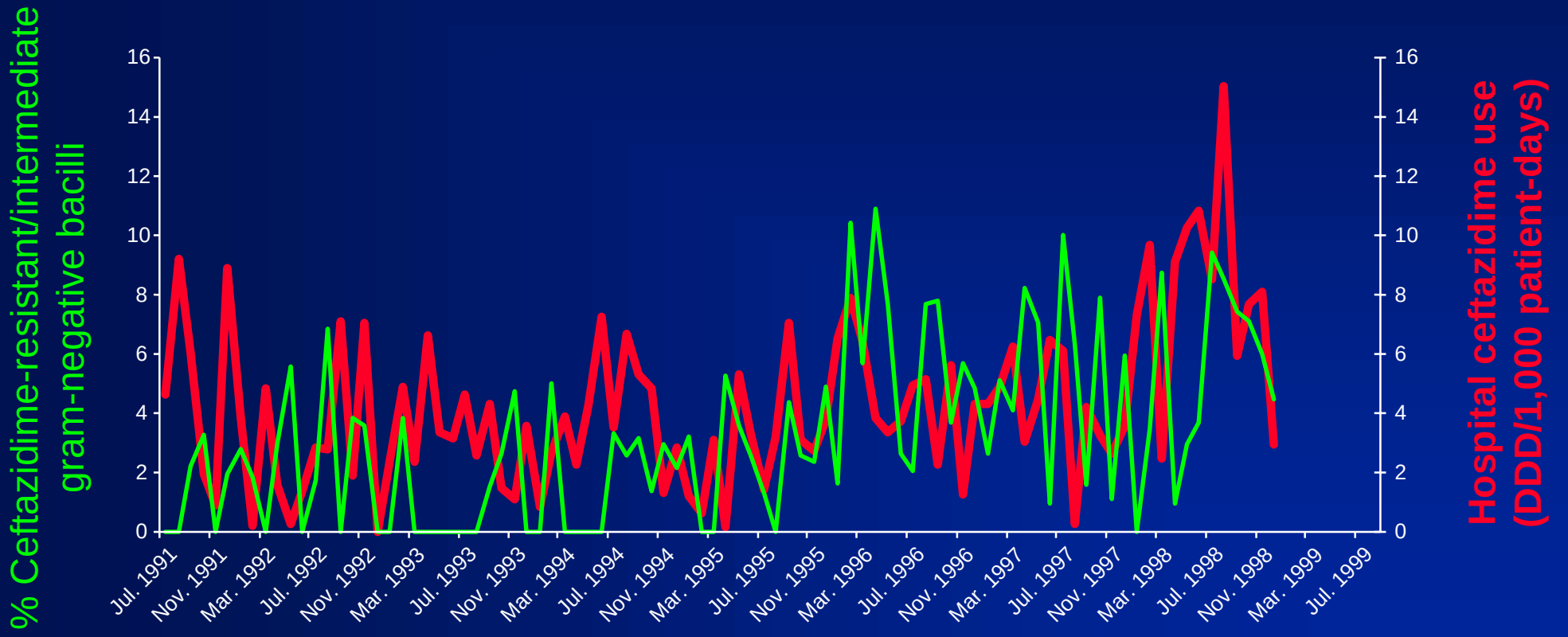
- Build an ARIMA model for both series
- Identify the lag between series



- Model estimation
- Diagnostics check on model adequacy

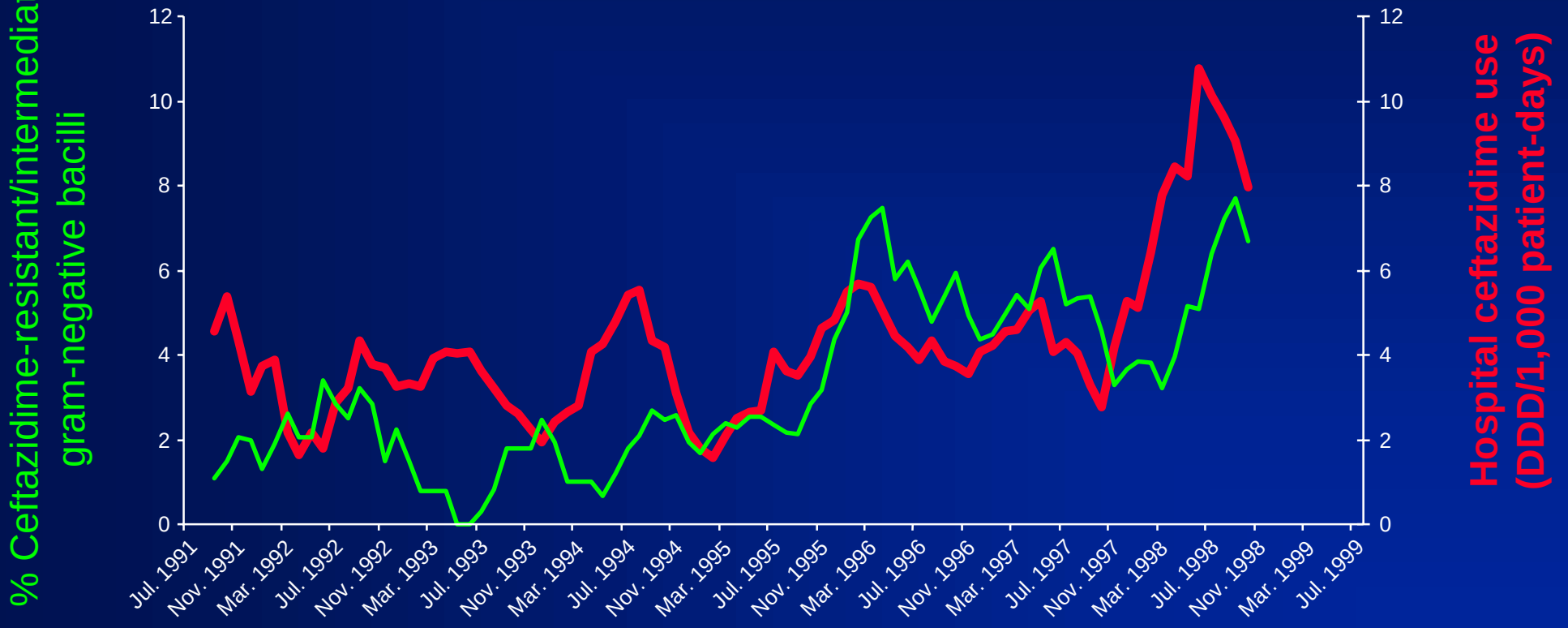
Source: Haugh LD. J Am Stat Assoc 1976;71:378-385.

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



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

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



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

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

Ceftazidime Use 1 month before

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

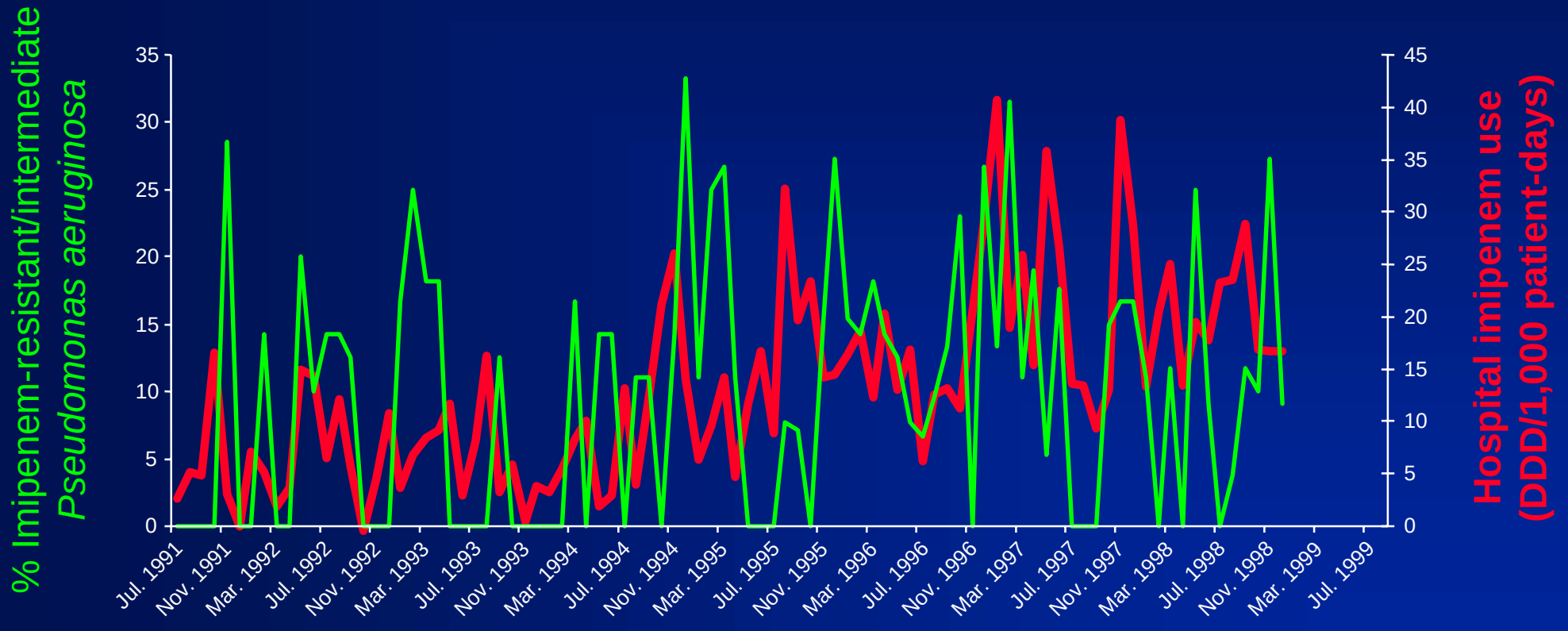
Percent Ceftazidime-Resistant/Intermediate Gram-Negative Bacilli and Ceftazidime Use Time Series: Goodness of Fit of Univariate and Multivariate Models

Model	AIC *	R^2 **	Residual Variance
AR(3,5)	432	0.38	6.86
AR(3,5) ULAG1	416	0.44	5.67

* AIC: Akaike Information Criterion
** R^2: determination coefficient

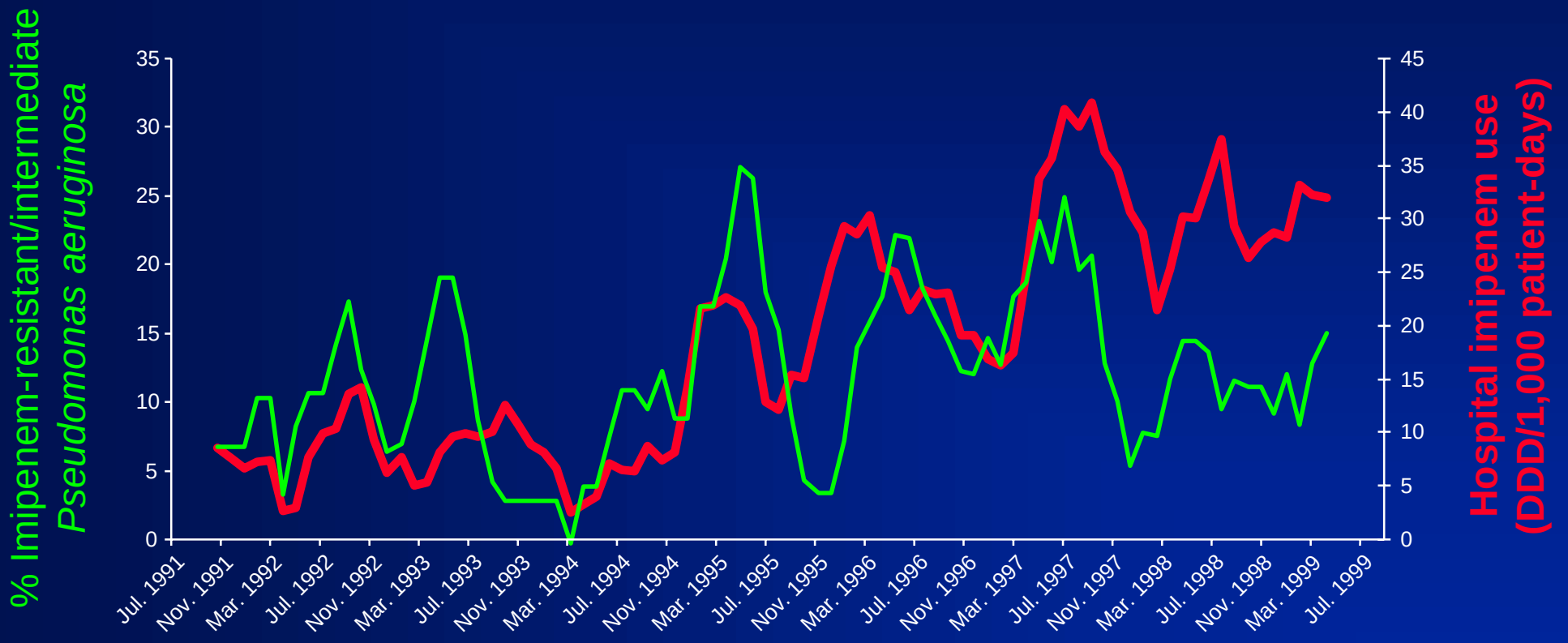
Source: López-Lozano JM, et al. Int J Antimicrob Agents 2000;14:21-30.

Monthly Percent Imipenem-Resistant/Intermediate *P. aeruginosa* and Hospital Imipenem Use, Hospital Vega Baja, Spain, 1991-1998



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

5-Month Moving Average Percent Imipenem-Resistant/Intermediate *P. aeruginosa* and Hospital Imipenem Use, Hospital Vega Baja, Spain, 1991-1998



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

Transfer Function Model for Percent Imipenem-Resistant/Intermediate *Pseudomonas aeruginosa* Series

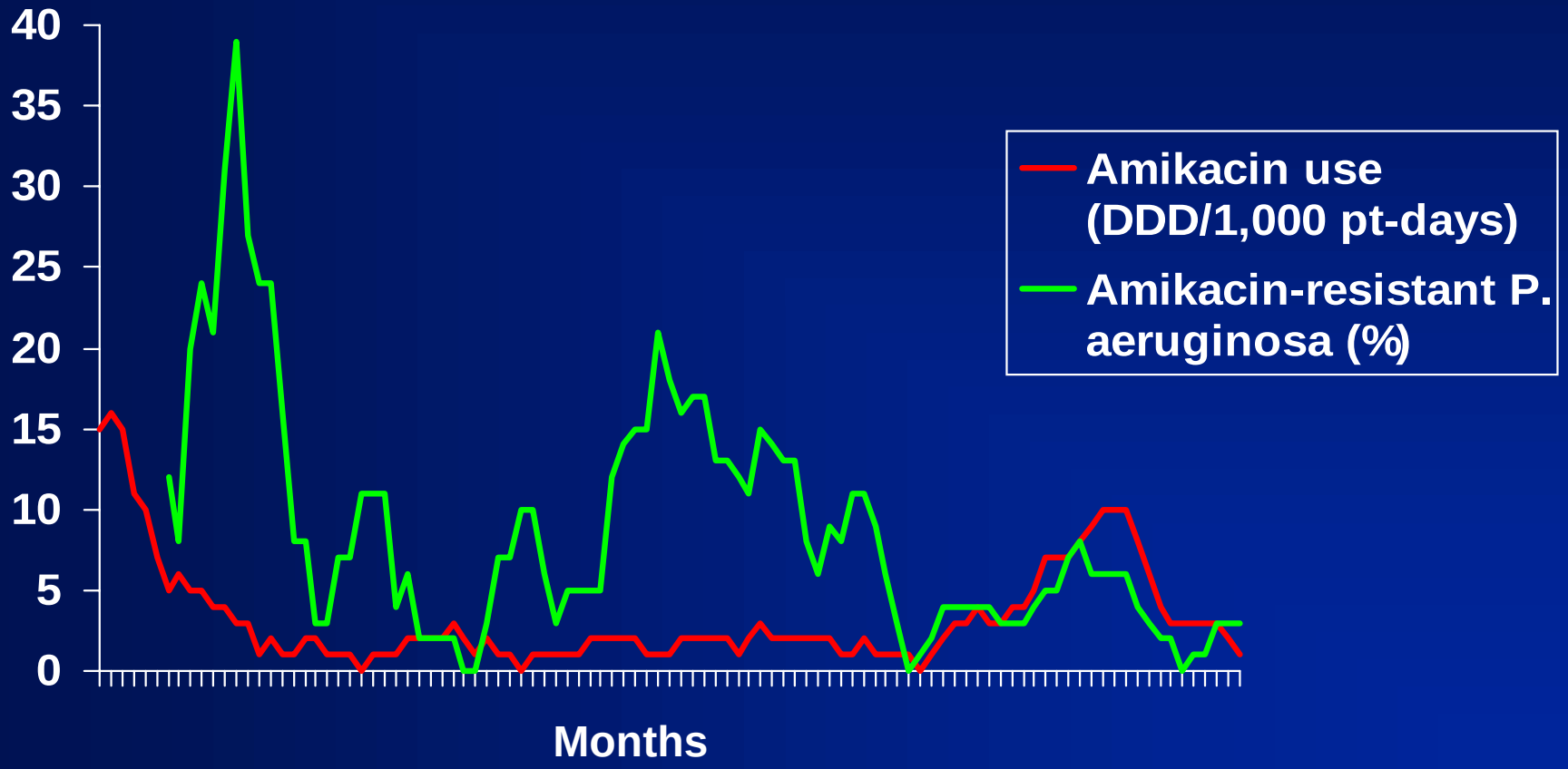
(taking into account hospital imipenem use)

Term	Parameter (SE)	T-ratio	P-value
Constant	4.388 (1.717)	2.56	< 0.05
AR5	-0.247 (0.108)	-2.28	< 0.05
MA1	-0.212 (0.106)	-2.00	< 0.05
MA6	-0.241 (0.105)	-2.29	< 0.02
ULAG1	0.400 (0.104)	3.83	< 0.001

Imipenem Use 1 month before

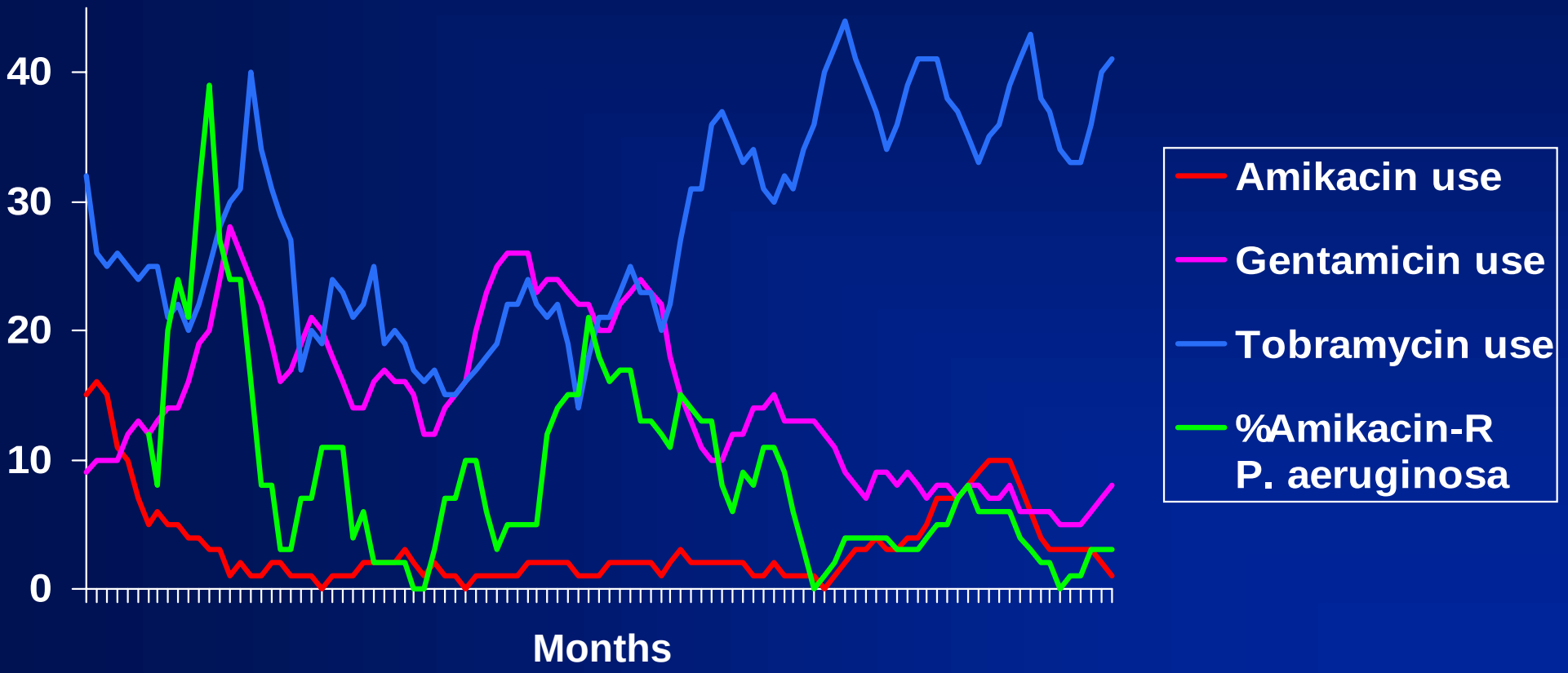
Source: López-Lozano JM, et al. Int J Antimicrob Agents 2000;14:21-30.

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



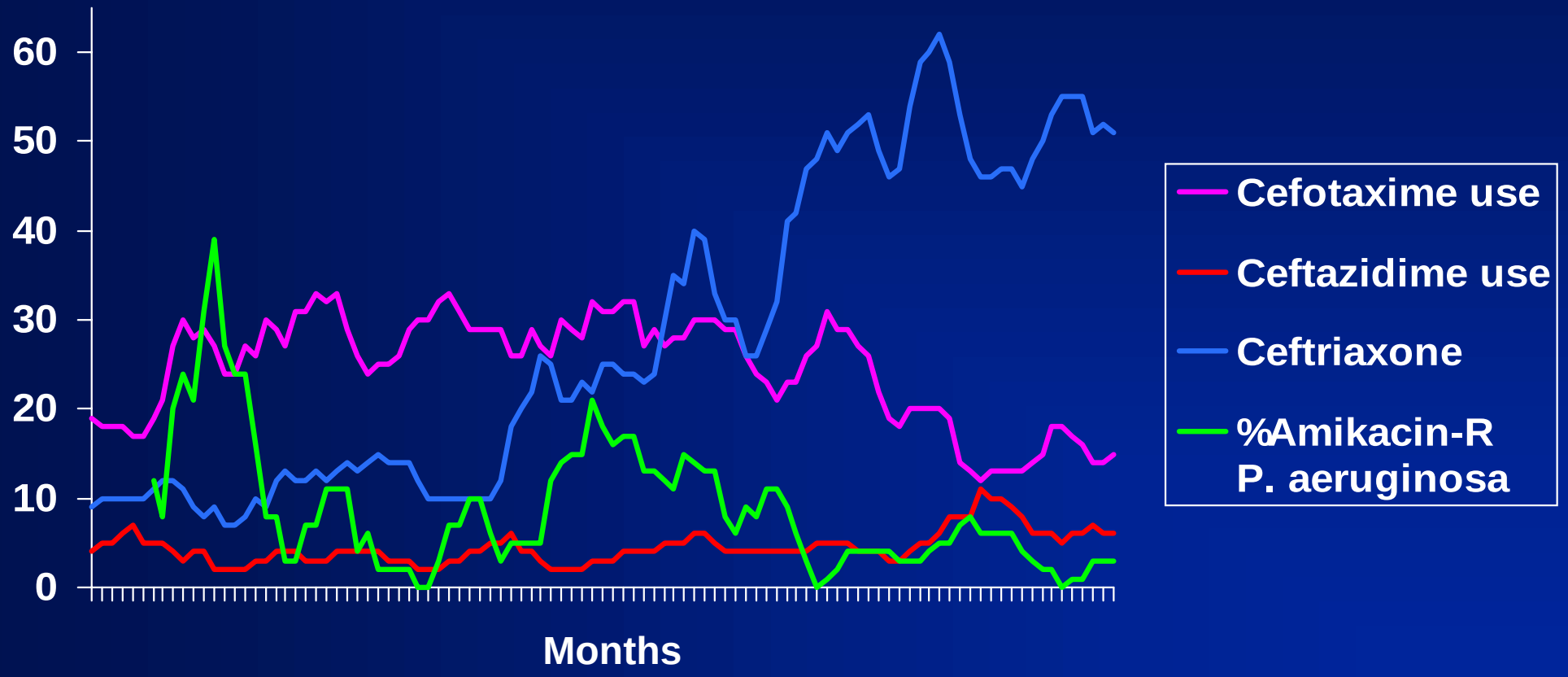
Source: López-Lozano JM, et al. 3rd Eur. Congr. Chemother., Madrid, 7-10 May 2000.

5-Month Moving Average Percent Amikacin-Resistant/Intermediate *P. aeruginosa* and Hospital Aminoglycoside Use, Hospital Vega Baja, Spain, 1991-99



Source: López-Lozano JM, et al. 3rd Eur. Congr. Chemother., Madrid, 7-10 May 2000.

5-Month Moving Average Percent Amikacin-Resistant/Intermediate *P. aeruginosa* and 3rd-Gen. Cephalosporin Use, Hospital Vega Baja, Spain, 1991-99



Source: López-Lozano JM, et al. 3rd Eur. Congr. Chemother., Madrid, 7-10 mai 2000.

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

(taking into account aminoglycoside and 3rd-gen. 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: López-Lozano JM, et al. 3rd Eur. Congr. Chemother., Madrid, 7-10 May 2000.

Conclusion (1)

- Make antimicrobial use and susceptibility data available from hospitals, at the patient or the hospital/unit level
- Modelling has proven difficult
- Multivariate time series analysis techniques, such as transfer function, can provide an answer

Conclusion (2)

- Many surveillance systems are available
- Need for standardization and coordination
- Use ”surveillance” studies for improving detection and evaluation of drugs
- Need for independent worldwide/regional public health surveillance networks
- **Monitor to prevent and control resistance!**