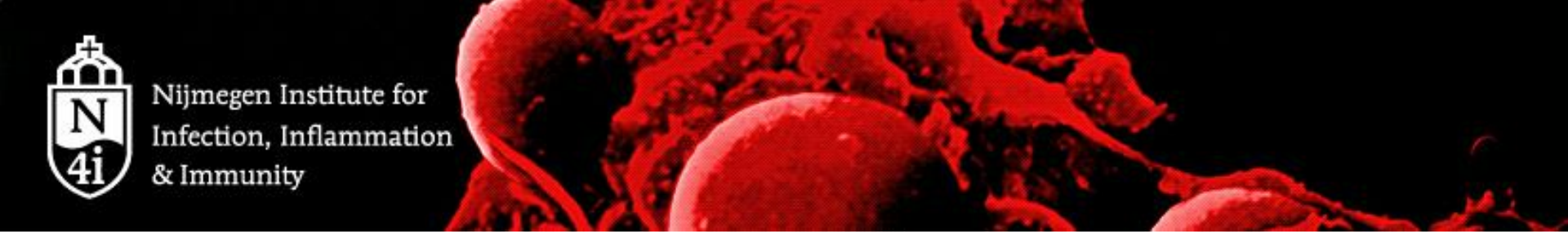



# Consumption of antibiotics in hospitals. Antimicrobial stewardship.

Inge C. Gyssens MD PhD
Radboud university medical center, Nijmegen, The Netherlands
Hasselt University, Belgium

# Outline

1. Antibiotic use in hospitals

- Global geographic variations
- Huge inter-hospital differences, <u>not always explained by case-mix</u>
- Huge intra-hospital variations, ICU vs psychiatric ward
- Antimicrobial consumption depends on
  - Cultural factors
  - Socio-economic factors
  - Health regulations

  Sources: ESAC, ESAC-Net, national publications

2. Antimicrobial stewardship

- why
- what
- how: strategies for old drugs, current drugs, new drugs
- levels: global, national

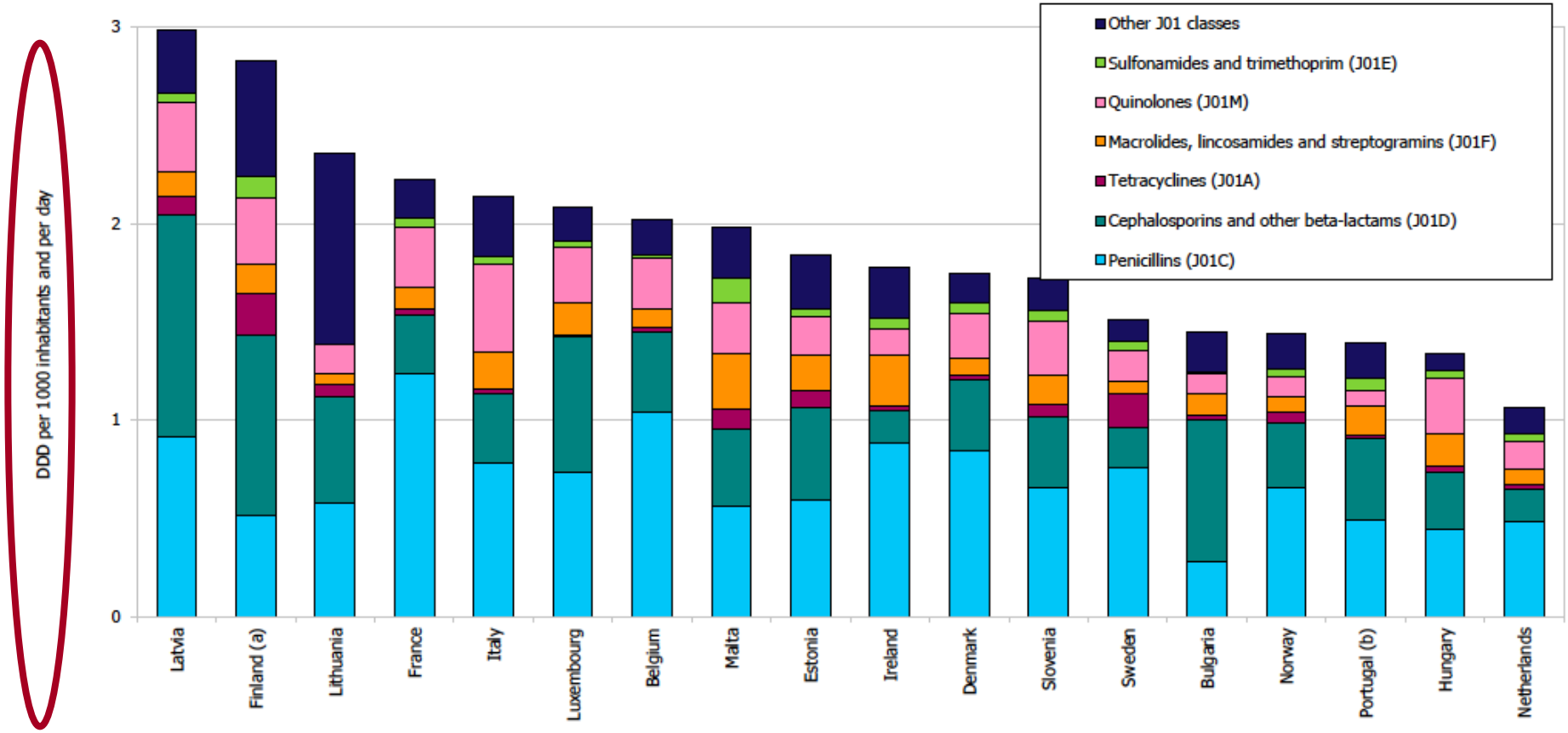
# ANTIBIOTIC USE IN HOSPITALS

**Table 4.2. Consumption of antibacterials for systemic use (ATC group J01) in the hospital care sector, EU/EEA countries, 1997-2010, expressed as DDD per 1 000 inhabitants and per day.**

| Country | 1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Belgium | 2.0 | 2.0 | 2.2 | 2.2 | 2.2 | 2.2 | 2.3 | 2.1 | 1.9 | | 1.9 | 1.7 | | 2.0 |
| Bulgaria | | | | | | | | | | 1.4 | 1.4 | 1.5 | 1.6 | 1.5 |
| Denmark | 1.3 | 1.3 | 1.3 | 1.4 | 1.4 | 1.5 | 1.5 | 1.6 | 1.6 | 1.7 | 1.8 | 1.8 | 1.8 | 1.8 |
| Estonia | | | | | | 8.6 | 2.4 | 2.3 | 2.5 | 2.1 | 1.9 | 2.0 | 1.6 | 1.8 |
| Finland [(a)] | 3.5 | 3.7 | 3.7 | 3.8 | 3.9 | 3.9 | 3.6 | 3.4 | 3.5 | 3.4 | 3.2 | 3.2 | 3.2 | 2.8 |
| France | 3.3 | 3.0 | 3.1 | 3.2 | 2.9 | | 2.8 | 2.5 | 2.6 | 2.3 | 2.2 | 2.2 | 2.2 | 2.2 |
| Greece | 2.1 | 2.1 | 2.2 | 2.3 | 2.2 | 2.2 | 2.3 | | | | | | 3.3 | |
| Hungary | | | | | 1.2 | 1.3 | 1.5 | 1.3 | 1.4 | 1.4 | 1.2 | 1.2 | 1.3 | 1.3 |
| Iceland | | | | | | | | | | 0.6 | | | | |
| Ireland | | | | | | | | 0.7 | 0.7 | 1.9 | 2.1 | 1.6 | 1.4 | 1.8 |
| Italy | | | | | | | | | 0.2 | | 1.5 | 2.3 | | 2.1 |
| Latvia | | | | | | 6.2 | | 4.7 | 3.9 | 3.2 | 3.5 | 2.8 | 2.2 | 3.0 |
| Lithuania | | | | | | | | | | | | | | 2.4 |
| Luxembourg | 2.0 | 1.9 | 2.2 | 2.2 | 2.1 | 2.4 | 2.4 | 2.0 | 2.1 | 2.1 | 2.2 | 2.2 | | 2.1 |
| Malta | 1.6 | 2.5 | 2.6 | 2.4 | 1.9 | 1.7 | 2.0 | 1.8 | 1.4 | 1.7 | 1.3 | 1.4 | 1.4 | 2.0 |
| Netherlands | 0.6 | 0.6 | 0.7 | 0.6 | 0.6 | 0.7 | | | | | | | | 1.1 |
| Norway | | 1.1 | | | 1.1 | 1.3 | 1.4 | 1.3 | 1.3 | 1.5 | 1.5 | 1.7 | 1.5 | 1.4 |
| Poland | | 3.0 | 3.4 | 2.4 | 2.4 | 1.7 | | | | | | | | |
| Portugal [(b)] | | | | | | | | | | | | | 1.4 | 1.4 |
| Romania | | | | | | | | | | | | | 2.6 | |
| Slovakia | | | 1.3 | 1.2 | 1.4 | 1.5 | 1.4 | 1.6 | 1.9 | 1.7 | 1.9 | 1.8 | 1.9 | |
| Slovenia | 0.5 | 1.6 | 1.7 | 1.8 | 1.7 | 1.8 | 1.8 | 1.6 | 1.7 | 1.7 | 1.7 | 1.7 | 1.8 | 1.7 |
| Sweden | 1.3 | 1.3 | 1.3 | 1.3 | 1.3 | 1.3 | 1.4 | 1.4 | 1.5 | 1.5 | 1.3 | 1.5 | 1.5 | 1.5 |

*[(a)] Finland: data include consumption in remote primary health care centres and nursing homes.*
*[(b)] Portugal: data correspond to public hospitals only.*

**Figure 4.1. Consumption of antibacterials for systemic use (ATC group J01) in the hospital sector in EU/EEA countries, 2010, at group level 3, expressed as DDD per 1 000 inhabitants and per day.**



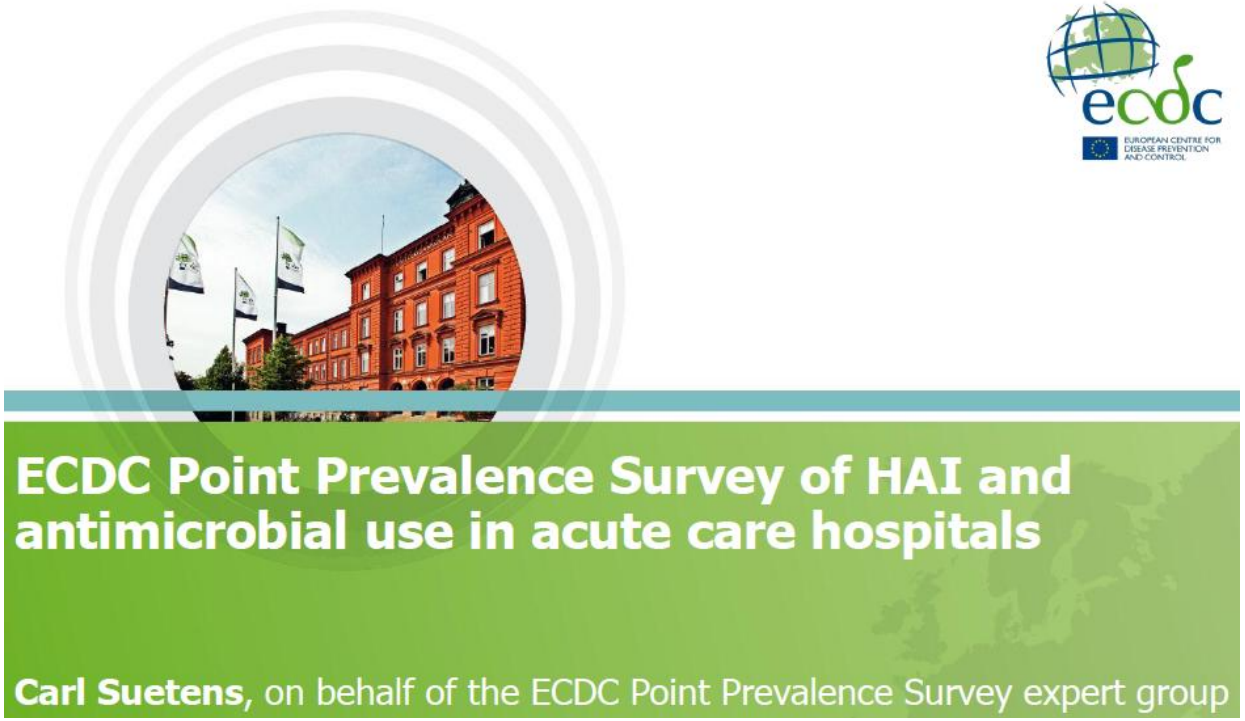

*[a] Finland: data include consumption in remote primary health care centres and nursing homes.*
*[b] Portugal: data correspond to public hospitals only.*

Council Recommendation of 15 November 2001 on the prudent use of antimicrobial agents in human medicine (2002/77/EC)

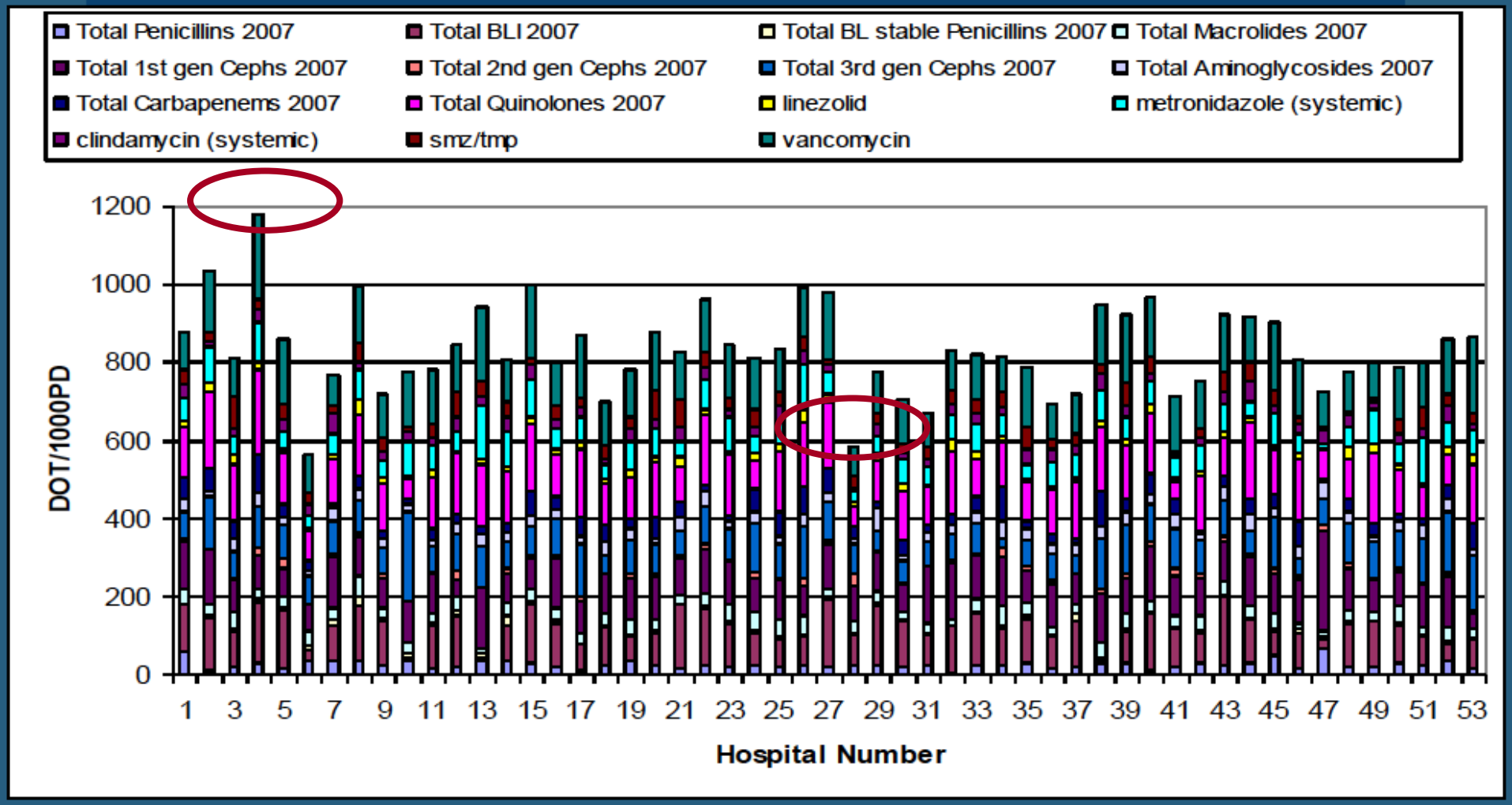
Specific or additional recommendations based on ECDC PPS results:

- Report hospital antimicrobial consumption to ESAC-Net in defined daily dose per number of patient-days rather than per number of inhabitants.

…



# Antibiotic Use in 53 UHC Hospitals 2007




Pakyz et al. *Arch Intern Med.* 2008;168(20):2254-2260, update

Courtesy Ron Polk

National annual surveillance reports at www.swab.nl since 2001

# NETHMAP 2012

Consumption of antimicrobial agents and antimicrobial resistance among medically important bacteria in the Netherlands

National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

SWAB

# MARAN 2012

Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands

CENTRAL VETERINARY INSTITUTE
WAGENINGEN UR

LEI
WAGENINGEN UR

Universiteit Utrecht

Food and Consumer Product Safety Authority
Ministry of Economic Affairs, Agriculture and Innovation

National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

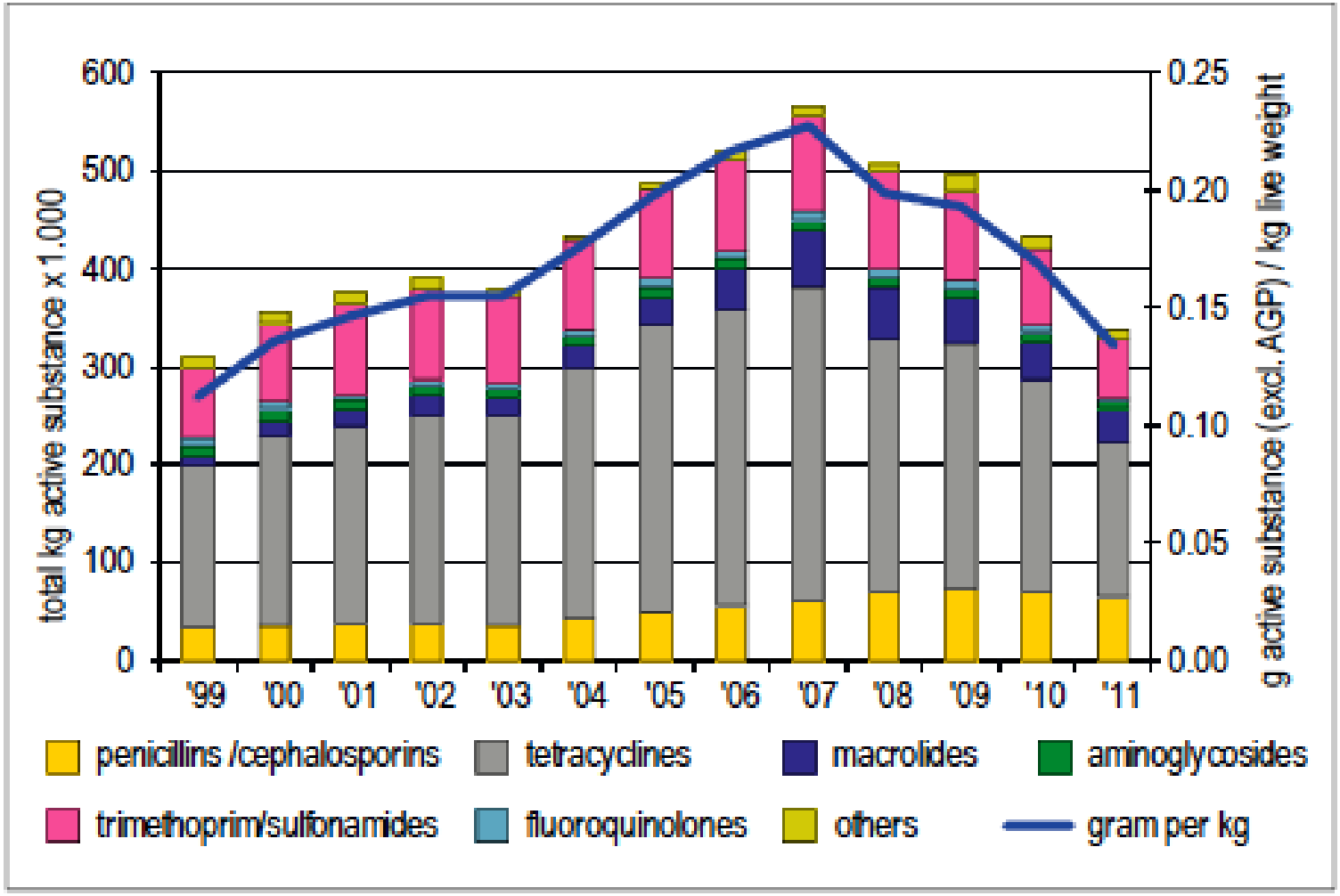



Figure ABuse01. Veterinary therapeutic sales from 1999-2011 (FIDIN, 2012; vertical bars). The line presents the the trends in grams of active ingredients used per kg live weight.

# Hospitals

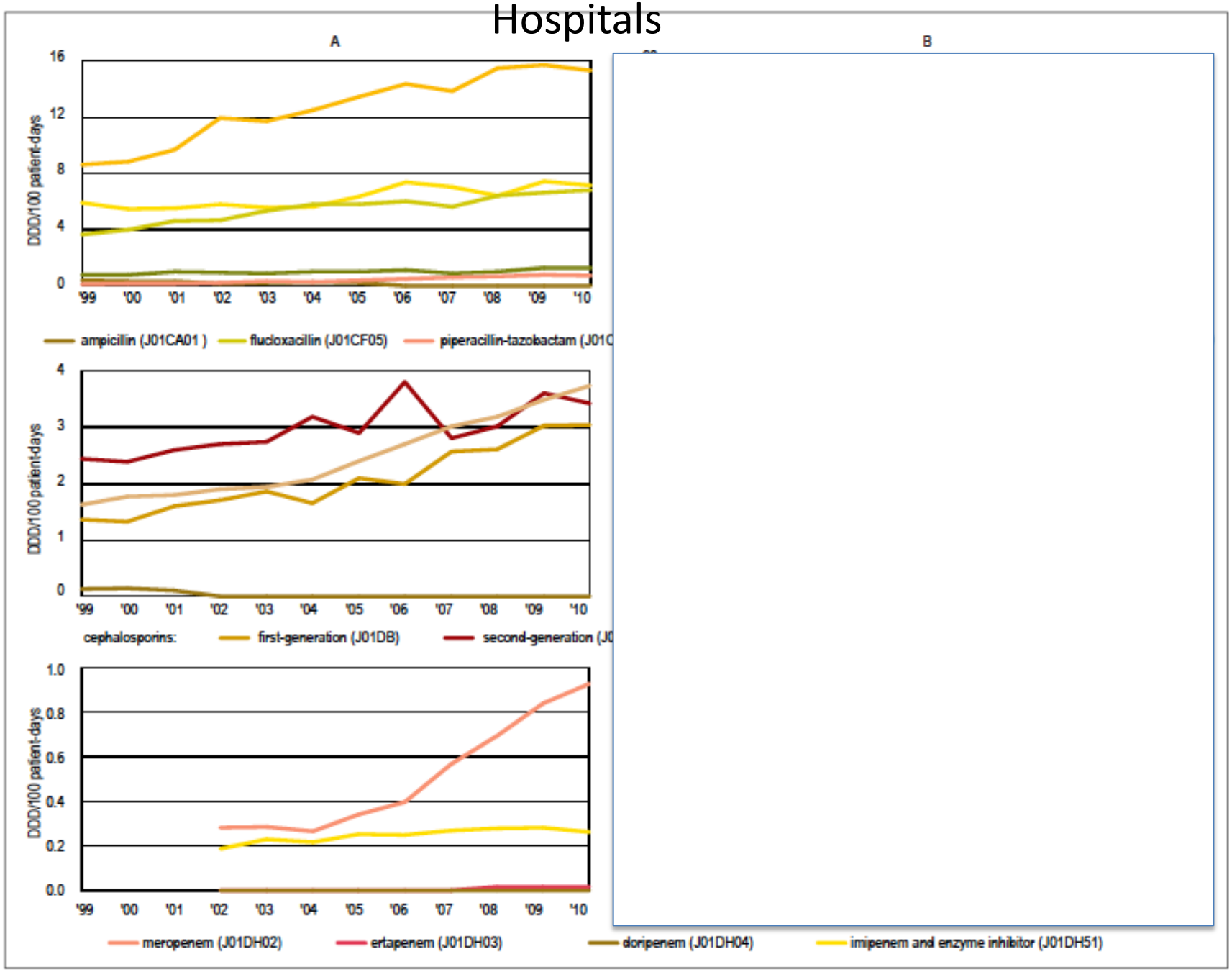



Figure 3.4. Use of beta-lactams in hospitals, expressed as DDD/100 patient-days (A) and DDD/100 admissions (B), 1999-2010 (SWAB).

# Hospitals

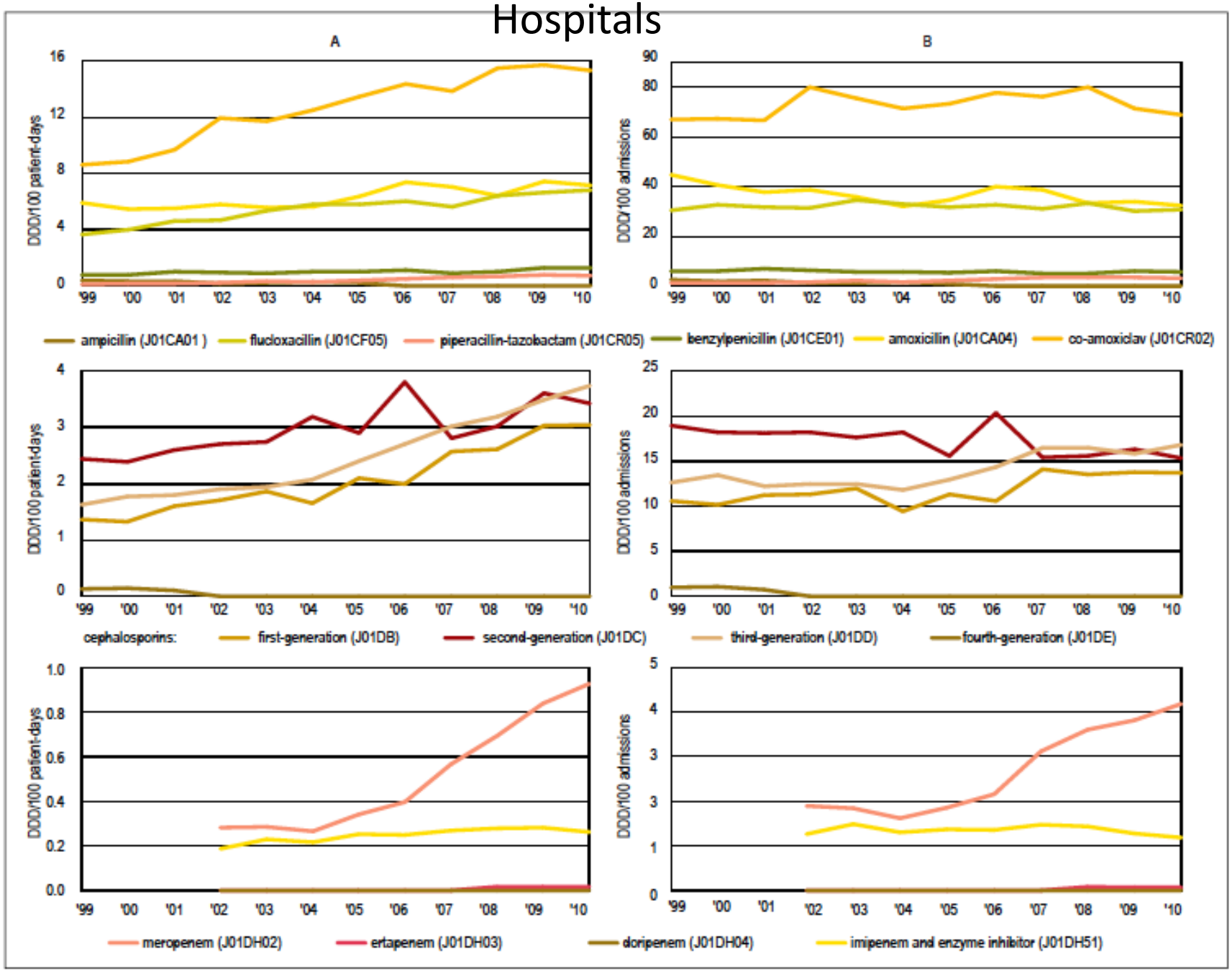



Figure 3.4. Use of beta-lactams in hospitals, expressed as DDD/100 patient-days (A) and DDD/100 admissions (B), 1999-2010 (SWAB).

*J Antimicrob Chemother* 2012; **67**: 2283–2288
doi:10.1093/jac/dks190 Advance Access publication 25 May 2012

Journal of Antimicrobial Chemotherapy

# Intensification of antibiotic use within acute care hospitals in the Netherlands

H. M. Kwint[1,2], P. D. van der Linden[3], M. M. B. Roukens[1] and S. Natsch[1]* on behalf of SWAB's Working Group on Surveillance of Antimicrobial Use†

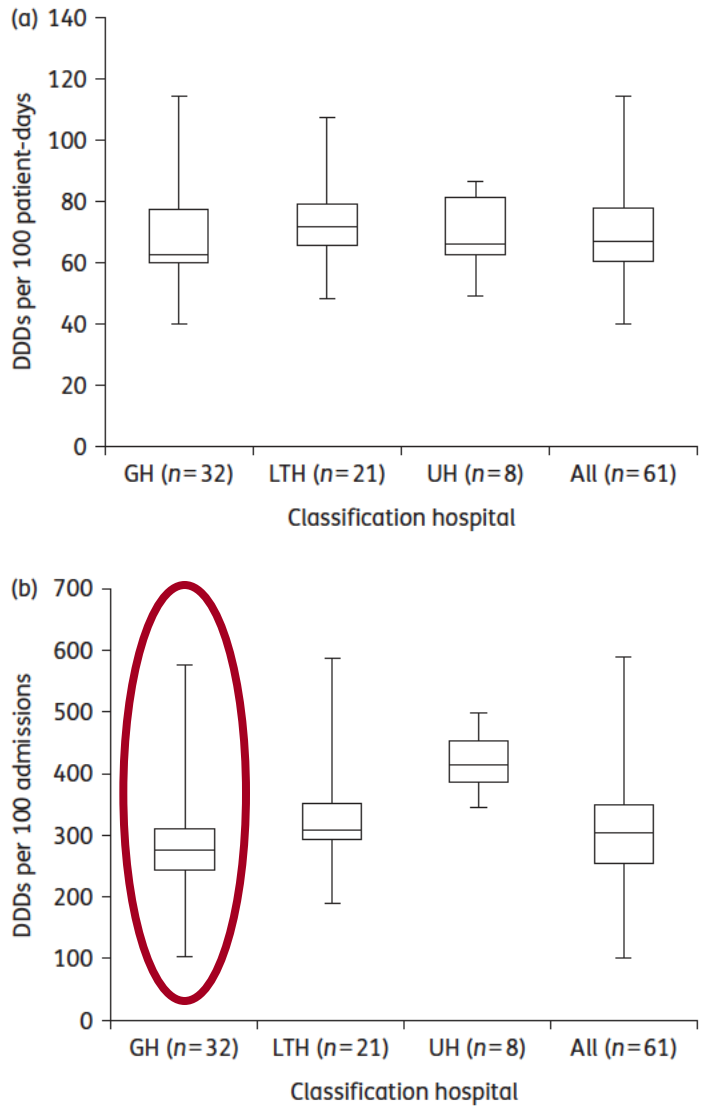



**Figure 2.** Variance in total use of antibiotics for systemic use (J01) in Dutch hospitals, 2009: university hospitals (UH) versus large teaching hospitals (LTH) versus general hospitals (GH). (a) Use in DDDs per 100 patient-days. (b) Use in DDDs per 100 admissions.

# Conclusion 1

1. Antibiotic use in hospitals

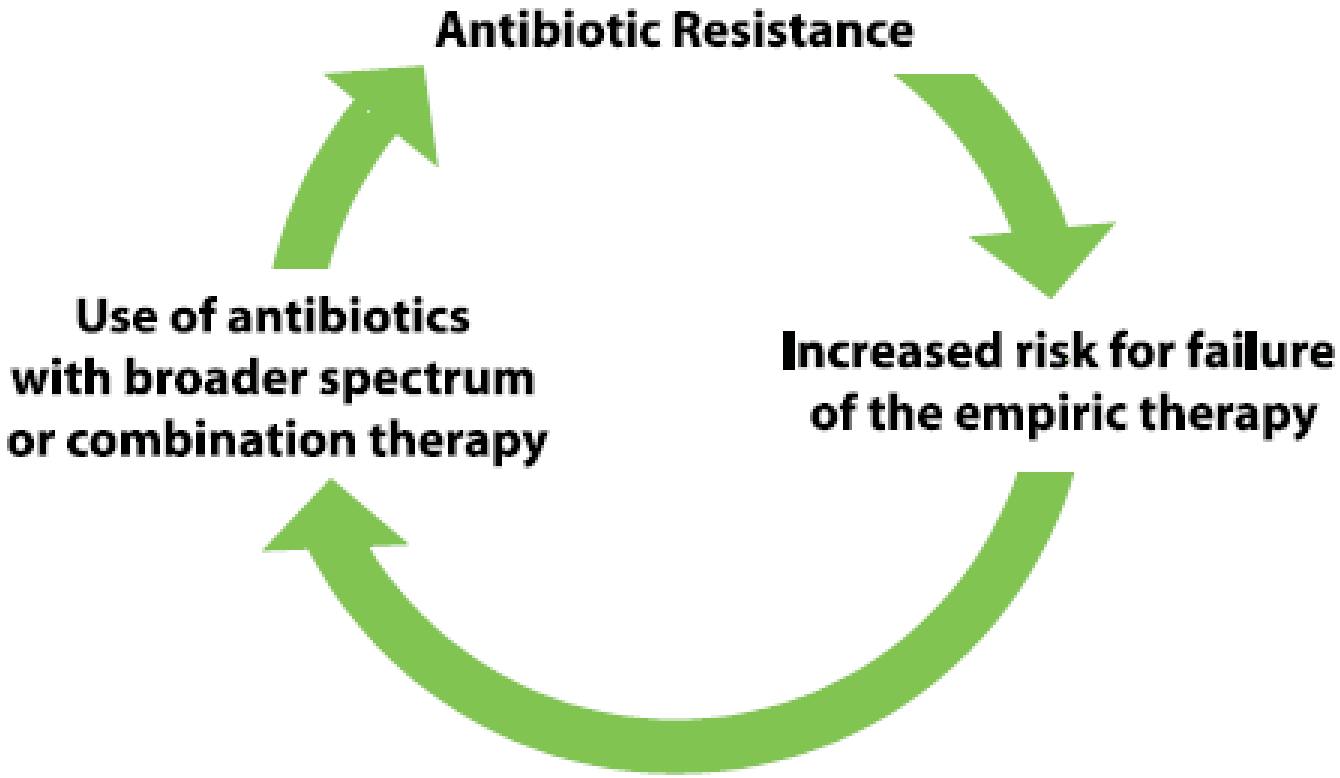
- Global geographic variations
- Huge inter-hospital differences <u>not always explained by case-mix</u>
- Huge intra-hospital variations, Antimicrobial consumption depends on
  - Cultural factors
  - Socio-economic factors
  - Health regulations

  Sources: ESAC, ESAC-Net, national publications

2. Antimicrobial stewardship

- why, what
- how: -old drugs, current drugs, new drugs
- Levels: global, national,

**Figure 17.** The clinician's dilemma of empiric therapy.




Nordberg P, Monnet DL, Cars O. Antibacterial drug resistance [Background document for the WHO project: Priority Medicines for Europe and the World. 'A Public Health Approach to Innovation']. 2004. Available from: http://soapimg.icecube.snowfall.se/stopresistance/Priority_Medicine_Antibacterial_background_docs_final.pdf

# ANTIMICROBIAL STEWARDSHIP

# Definition

- The primary goal of a stewardship program is to maximize clinical outcomes while minimizing the unintended consequences of antimicrobial use, such as toxicity, selection of pathogenic organisms, and emergence of resistance.

Dellit et al. SHEA  IDSA Guidelines

Clinical Therapeutics/Volume 35, Number 6, 2013 · Antimicrobial Stewardship

*Editorial*

# Antimicrobial Stewardship: Impact and Challenges

Susan Hadley, MD
Professor of Medicine, Tufts University School of Medicine
Department of Medicine, Division of Geographic Medicine and Infectious Disease
Tufts Medical Center, Boston, Massachusetts

"The recognition that misuse of antimicrobials affects the society of patients and not just an individual patient by influencing the healthcare setting microflora and risk of transmission of resistant organisms empowered Antimicrobial stewardship development"

GUIDELINES

# Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship

Timothy H. Dellit,[1] Robert C. Owens,[2] John E. McGowan, Jr.,[3] Dale N. Gerding,[4] Robert A. Weinstein,[5] John P. Burke,[6] W. Charles Huskins,[7] David L. Paterson,[8] Neil O. Fishman,[9] Christopher F. Carpenter,[10] P. J. Brennan,[9] Marianne Billeter,[11] and Thomas M. Hooton[12]

Clinical Infectious Diseases 2007;44:159–77

# EDUCATION VS RESTRICTION

Interventions to improve antibiotic prescribing practices for hospital inpatients (Review)

# Antimicrobial stewardship: Interventions

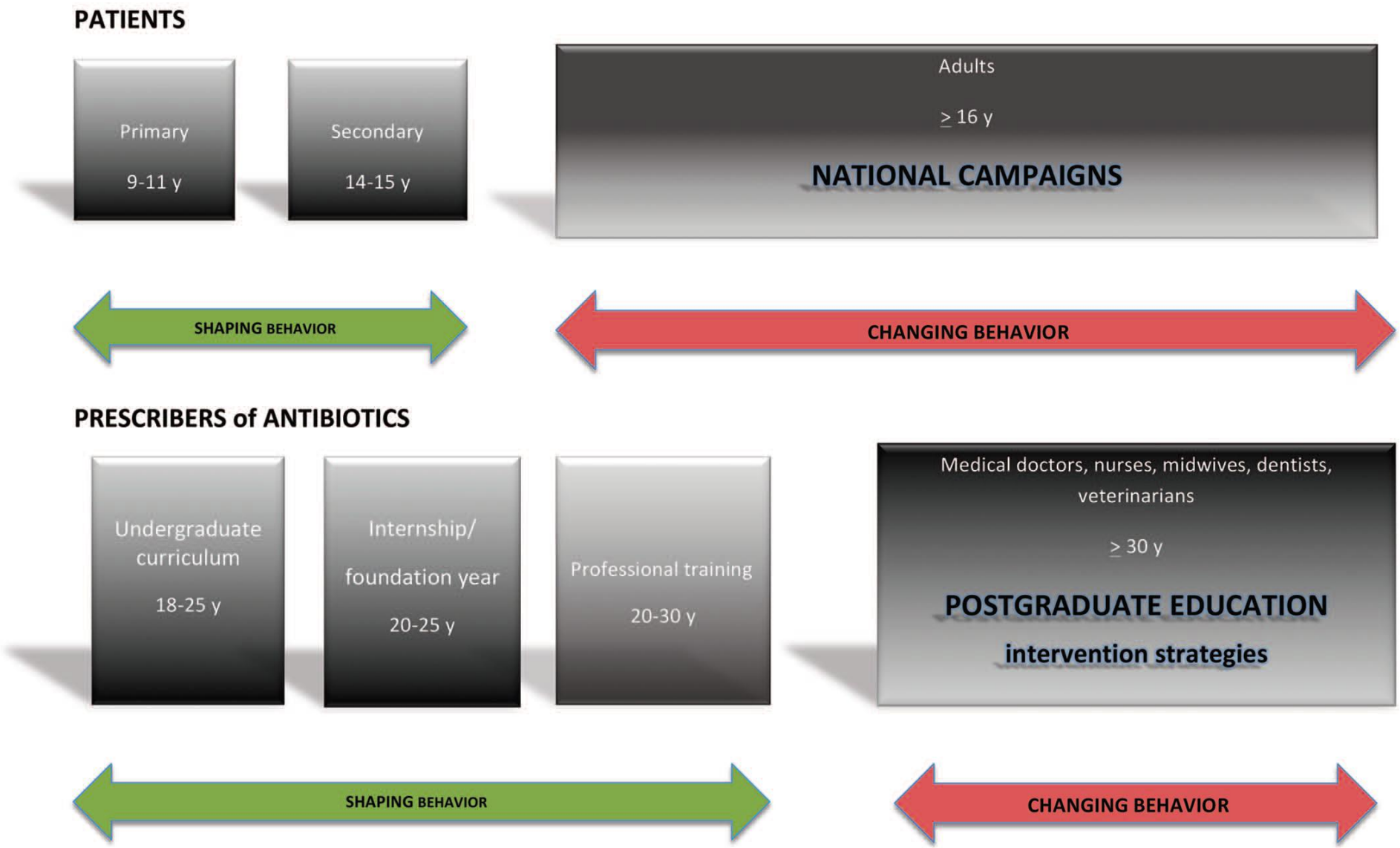
| Educational measures and active interventions | |
|---|---|
| Passive educational measures | • Developing/updating local antibiotic guidelines<br>• Educational sessions, workshops, local conferences |
| Active interventions | • Clinical rounds discussing cases<br>• Prospective audit with intervention and feedback<br>• Reassessment of antibiotic prescriptions, with streamlining and de-escalation of therapy<br>• Academic detailing, educational outreach visits |
| Restrictive measures | • Limiting number of antibiotics on the hospital formulary<br>• Antibiotic order form (compulsory)<br>• Automatic stop order<br>• Formulary restriction and preauthorization<br>• Limiting reporting of susceptibilities by the microbiology laboratory<br>• Regulating contacts with the pharmaceutical industry |
| Supportive/supplemental measures | • Multidisciplinary antimicrobial stewardship team<br>• Consultancy service (infectious diseases, pharmacy, microbiology)<br>• Computer-assisted management program<br>• Parenteral to oral conversion<br>• Therapeutic drug monitoring service |

Pulcini & Gyssens, How to educate prescribers Virulence 2013;4:1-11

# Why do educational interventions often fail?

- They come to  late! ....  in the curriculum
- Changing behaviour is much more difficult than shaping behaviour

# Education on prudent antimicrobial use




Pulcini&Gyssens, How to educate prescribers Virulence 2013

INVITED ARTICLE CLINICAL PRACTICE

Ellie J. C. Goldstein, Section Editor

CLINICAL PRACTICE • CID 2012:55 (15 August) • 587

# Is the "Low-Hanging Fruit" Worth Picking for Antimicrobial Stewardship Programs?

**Debra A. Goff,[1] Karri A. Bauer,[1] Erica E. Reed,[1] Kurt B. Stevenson,[2,3] Jeremy J. Taylor,[1] and Jessica E. West[2]**

[1]Department of Pharmacy, The Ohio State University Wexner Medical Center, [2]Division of Infectious Diseases, College of Medicine, and [3]Division of Epidemiology, College of Public Health, The Ohio State University, Columbus

*J Antimicrob Chemother* 2012; **67**: 2289–2296
doi:10.1093/jac/dks193 Advance Access publication 23 May 2012

Journal of Antimicrobial Chemotherapy

# Antibiotic stewardship and early discharge from hospital: impact of a structured approach to antimicrobial management

**M. Dryden[1]*, K. Saeed[1], R. Townsend[2], C. Winnard[2], S. Bourne[1], N. Parker[1], J. Coia[3], B. Jones[3], W. Lawson[4], P. Wade[5], P. Howard[6] and S. Marshall[7]**

# Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship

Timothy H. Dellit,[1] Robert C. Owens,[2] John E. McGowan, Jr.,[3] Dale N. Gerding,[4] Robert A. Weinstein,[5] John P. Burke,[6] W. Charles Huskins,[7] David L. Paterson,[8] Neil O. Fishman,[9] Christopher F. Carpenter,[10] P. J. Brennan,[9] Marianne Billeter,[11] and Thomas M. Hooton[12]

***Formulary restriction and preauthorization requirements for specific agents.*** Most hospitals have a pharmacy and therapeutics committee or an equivalent group that evaluates drugs for inclusion on the hospital formulary on the basis of considerations of therapeutic efficacy, toxicity, and cost while limiting redundant new agents with no significant additional benefit. Antimicrobial restriction—either through formulary limitation by this method or by the requirement of preauthorization and justification—is the most effective method of achieving the process goal of controlling antimicrobial use.

Example

# AUDIT AND FEEDBACK AND FORMULARY RESTRICTION

*Journal of Antimicrobial Chemotherapy* (2005) **56**, 1094–1102
doi:10.1093/jac/dki374
Advance Access publication 18 October 2005

JAC

# Quality improvement of surgical prophylaxis in Dutch hospitals: evaluation of a multi-site intervention by time series analysis

Marjo E. E. van Kasteren[1,2]*, Judith Mannien[3], Bart-Jan Kullberg[1,2], Annette S. de Boer[3], Nico J. Nagelkerke[3], Marja Ridderhof[4,5], Jan C. Wille[6] and Inge C. Gyssens[4,5]

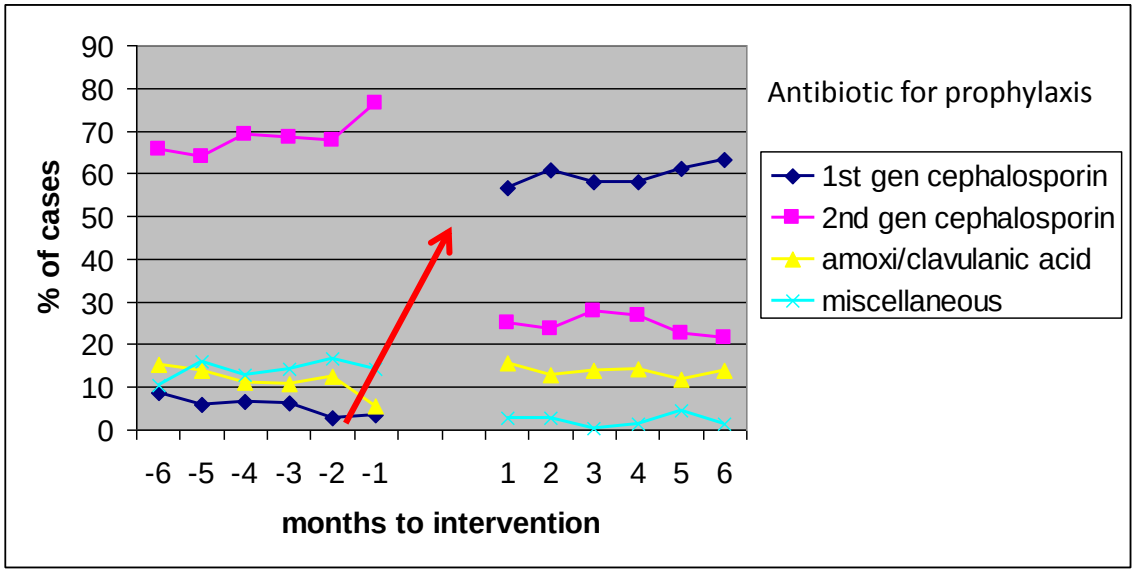
Multi faceted intervention

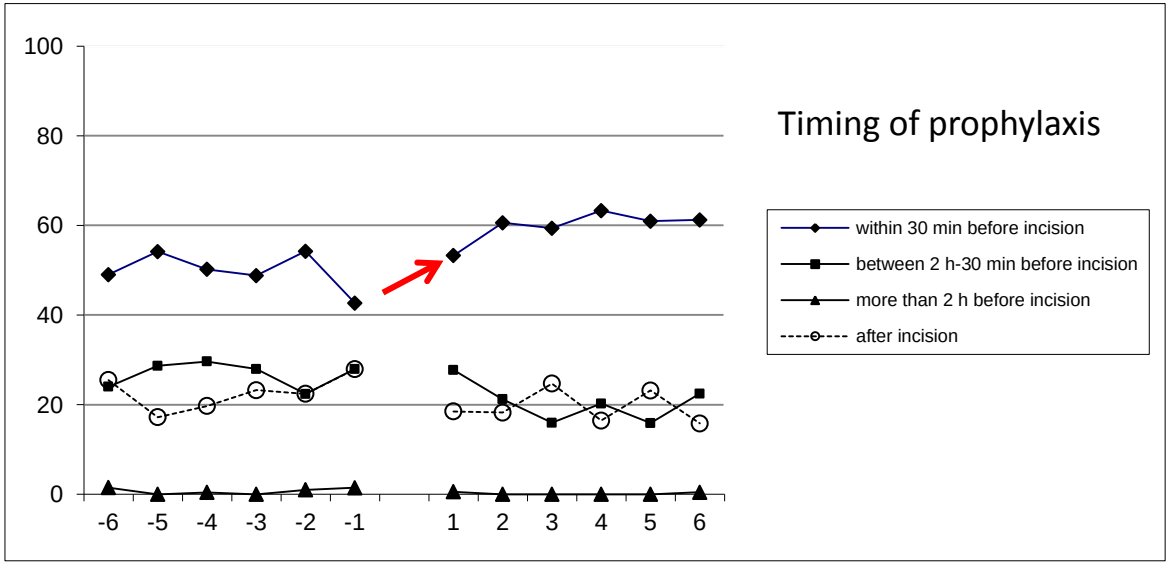
**Table 3.** Observed and expected outcomes of quality parameters before and after the intervention

| Parameter of antibiotic prophylaxis | Observed before intervention, no. inappropriate (total) | % | Observed after intervention, no. inappropriate (total) | % | Expected after intervention, no. inappropriate (total) | % | *P* value, observed–expected |
|---|---|---|---|---|---|---|---|
| Indicated but not administered | 51 (1763) | 2.9 | 26 (2050) | 1.3 | 55 (2050) | 2.7 | <0.01 |
| Antibiotic less effective | 88 (1712) | 5.1 | 36 (2024) | 1.8 | 64 (2024) | 3.2 | <0.01 |
| Antibiotic more toxic | 327 (1712) | 19.1 | 241 (2024) | 11.9 | 387 (2024) | 19.1 | <0.01 |
| Antibiotic more expensive | 1275 (1712) | 74.5 | 454 (2024) | 22.4 | 1550 (2024) | 76.6 | <0.01 |
| Antibiotic broader spectrum | 1458 (1712) | 85.2 | 688 (2024) | 34.0 | 1751 (2024) | 86.5 | <0.01 |
| Antibiotic in therapeutic use | 1295 (1712) | 75.6 | 686 (2024) | 33.9 | 1579 (2024) | 78.0 | <0.01 |
| Antibiotic choice not cefazolin | 1646 (1712) | 96.1 | 758 (2024) | 37.5 | 1893 (2024) | 93.5 | <0.01 |
| Duration exceeding single dose | 779 (1699) | 44.2 | 631 (2015) | 31.4 | 944 (2015) | 46.8 | <0.01 |
| Timing first dose inappropriate | 822 (1627) | 50.5 | 779 (1976) | 39.4 | 1024 (1976) | 51.8 | <0.01 |

Largest effect with the restrictive component of the intervention: the change of antibiotic

# Audit and feedback: a picture tells more than a 1000 words..



Now something completely different..

# THE DRUG SHORTAGES PROBLEM

# Survey on antibiotic shortages in the EU

- Shortages affect the care of critically ill patients

- Shortages lead to the use of more expensive and broad-spectrum or less efficacious substitute agents. These substitutes may further accelerate the emergence and selection of antibiotic resistance

- For instance, replacing piperacillin by piperacillin/tazobactam for susceptible *Pseudomonas spp,* minocycline by tigecycline for methicillin-resistant *Staphylococcus aureus or penicillin*

  by ceftriaxone for streptococcal infections broadens the spectrum of therapy unnecessarily and increase healthcare costs

# Shortage of antimicrobial agents in Europe: Results of an international survey

ECCMID 2007; #P1105

stephan.harbarth@hcuge.ch

S. Harbarth, P.M. Filius, S. Natsch, F. Mackenzie, I. Gyssens
on behalf of the ESCMID Study Group on Antibiotic Policies (ESGAP)

## Background

Shortages of antimicrobial agents have affected the U.S. since the late 1990s. In two IDSA surveys conducted in 1999 & 2000, members indicated that shortages had affected numerous therapeutic indications.

There is little information available regarding the shortage of antimicrobial agents in Europe.

## Objectives

This survey attempted to determine to what extent shortages have already influenced prescribing practices in European hospitals.

## Methods

The study was conducted as an international, 9-item survey sent out via email in October 2006 to 384 hospitals throughout Europe. The subjects were infectious disease physicians, clinical microbiologists or pharmacists. Data were entered in a spreadsheet, checked for accuracy, and transported to SPSS for descriptive analysis.

## Participating countries

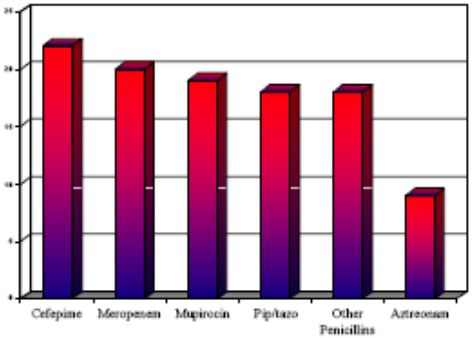

## Results

- Participants from 28 countries and 83 hospitals responded (response rate, 22%).

Shortage duration ranged from 1 week to 18 months

- There was great variability in the duration of the shortages (range: 1 week - 18 months).

## Most frequently affected agents




## Results (2)

- Other shortages: Shortages of other cephalosporins, colistin, doxycycline, rifampicin, vancomycin, nitrofurantoin, fosfomycin, amphotericin B, amikacin and tobramycin occurred infrequently.
- Substitutes were either more expensive (e.g. carbapenems instead of cefepime), more broad-spectrum (e.g. cefuroxim, ceftriaxone or co-amoxiclav instead of oxacillin and penicillin), or less efficacious (e.g. neomycin and chlorhexidine instead of mupirocin nasal ointment).

## Consequences

- 45 hospitals (54%) had to develop

33% of hospitals had trouble finding equivalent drugs or substitutes

- informed by the producer or distributor about the upcoming shortage.

## Conclusions

- A substantial number of hospital pharmacies in Europe have experienced antimicrobial drug shortages within the last 12 months.
- Shortage of meropenem, mupirocin and cefepime were considered to have the largest impact on patient care.
- Shortage-triggered policy changes may negatively affect antimicrobial prescribing patterns and expenses.
- This survey provides important information that will guide further ESGAP initiatives to document and ultimately prevent shortages.

Another problem affecting prudent use

# FORGOTTEN ANTIBIOTICS

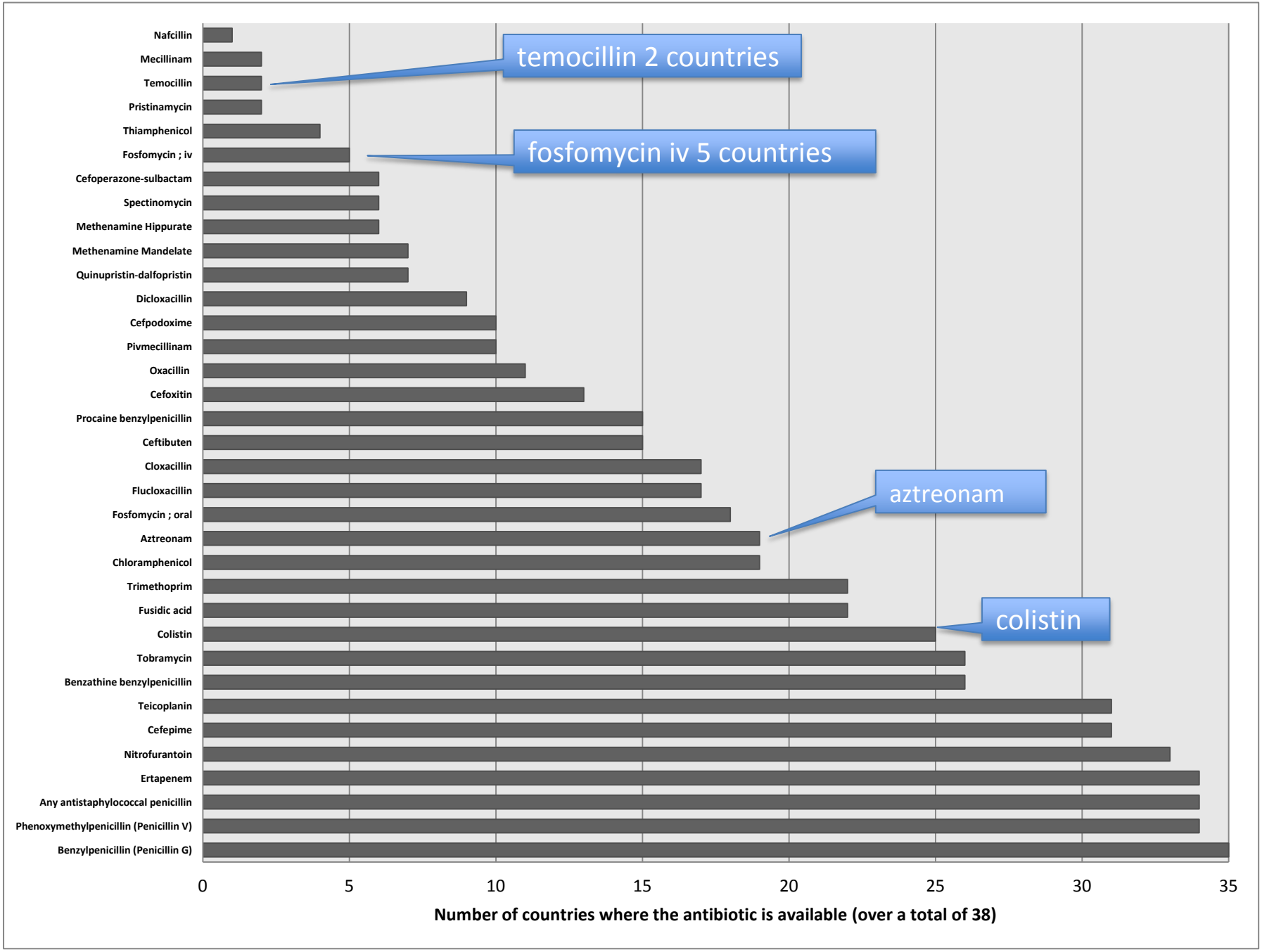
Louis D. Saravolatz, Section Editor

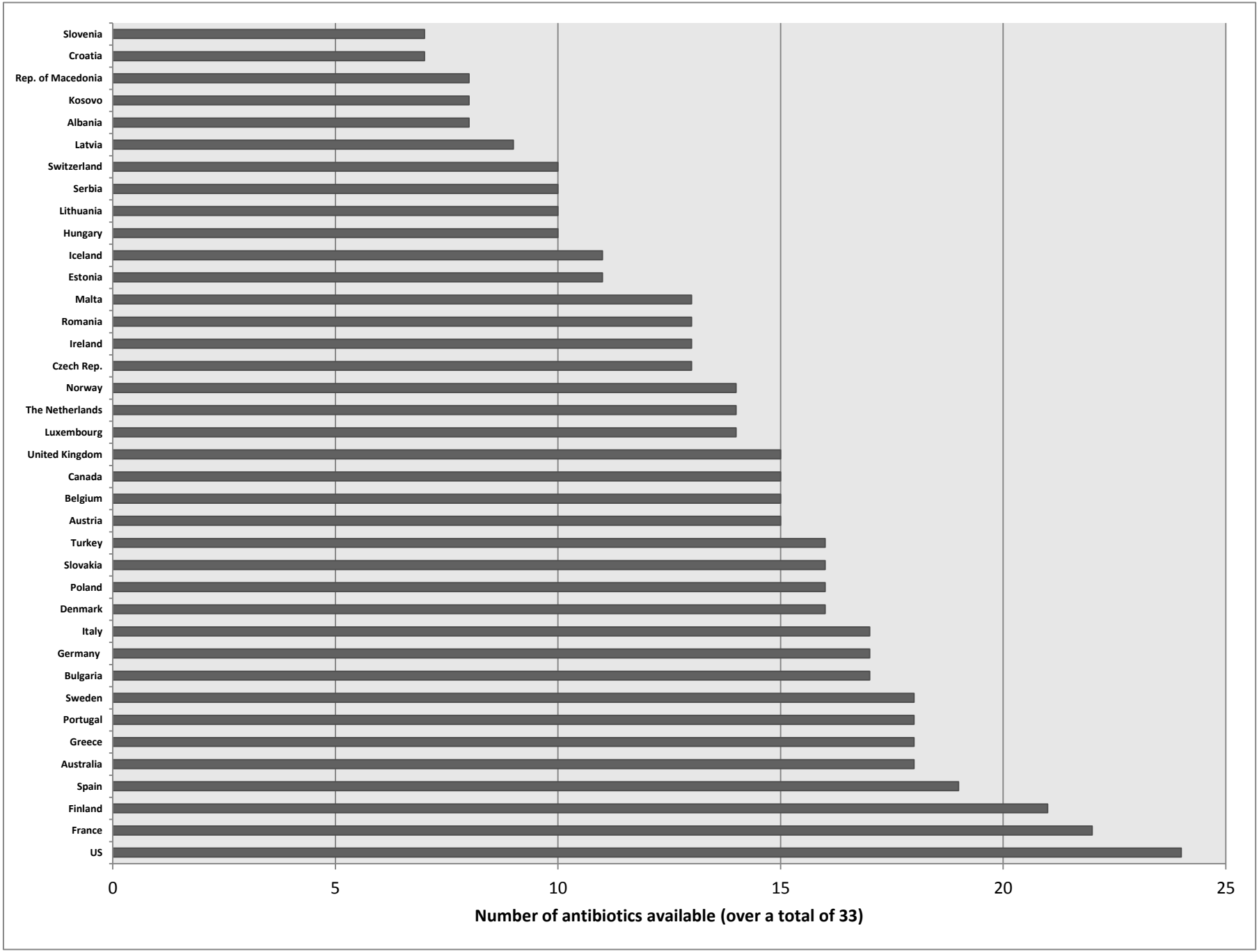
# Forgotten Antibiotics: An Inventory in Europe, the United States, Canada, and Australia

**Céline Pulcini,[1] Karen Bush,[2] William A. Craig,[3] Niels Frimodt-Møller,[4] M. Lindsay Grayson,[5] Johan W. Mouton,[6] John Turnidge,[7] Stephan Harbarth,[8] Inge C. Gyssens,[9,10] and the ESCMID Study Group for Antibiotic Policies**

[1]Centre Hospitalier Universitaire de Nice, Service d'Infectiologie and Université de Nice Sophia-Antipolis, Faculté de Médecine, France; [2]Biology Department, Indiana University, Bloomington; [3]University of Wisconsin, School of Medicine and Public Health, Madison; [4]Department of Clinical Microbiology, Hvidovre Hospital, Copenhagen, Denmark; [5]Infectious Diseases Department, Austin Health and Department of Medicine, University of Melbourne, Victoria, Australia; [6]Department of Medical Microbiology, Radboud University Nijmegen Medical Centre and Department of Medical Microbiology and Infectious Diseases, Canisius Wilhelmina Hospital, the Netherlands; [7]SA Pathology, The University of Adelaide, SA, Australia; [8]Geneva University Hospitals and Medical School, Switzerland; [9]Department of Medicine, Radboud University Nijmegen Medical Centre and Department of Medical Microbiology and Infectious Diseases, Canisius Wilhelmina Hospital, the Netherlands; and [10]Hasselt University, Diepenbeek, Belgium

- A survey was performed in 38 countries among experts including hospital pharmacists, microbiologists and infectious diseases specialists in Europe, the US, Canada and Australia.
- An international expert panel selected systemic antibacterial drugs for their potential to treat infections caused by resistant bacteria or their unique value for specific pathogens or indications.


Nafcillin
Mecillinam
Temocillin
Pristinamycin
Thiamphenicol
Fosfomycin ; iv
Cefoperazone-sulbactam
Spectinomycin
Methenamine Hippurate
Methenamine Mandelate
Quinupristin-dalfopristin
Dicloxacillin
Cefpodoxime
Pivmecillinam
Oxacillin
Cefoxitin
Procaine benzylpenicillin
Ceftibuten
Cloxacillin
Flucloxacillin
Fosfomycin ; oral
Aztreonam
Chloramphenicol
Trimethoprim
Fusidic acid
Colistin
Tobramycin
Benzathine benzylpenicillin
Teicoplanin
Cefepime
Nitrofurantoin
Ertapenem
Any antistaphylococcal penicillin
Phenoxymethylpenicillin (Penicillin V)
Benzylpenicillin (Penicillin G)
temocillin 2 countries
fosfomycin iv 5 countries
aztreonam
colistin
0
5
10
15
20
25
30
35
Number of countries where the antibiotic is available (over a total of 38)


Slovenia
Croatia
Rep. of Macedonia
Kosovo
Albania
Latvia
Switzerland
Serbia
Lithuania
Hungary
Iceland
Estonia
Malta
Romania
Ireland
Czech Rep.
Norway
The Netherlands
Luxembourg
United Kingdom
Canada
Belgium
Austria
Turkey
Slovakia
Poland
Denmark
Italy
Germany
Bulgaria
Sweden
Portugal
Greece
Australia
Spain
Finland
France
US
0
5
10
15
20
25
Number of antibiotics available (over a total of 33)

# Conclusion 2

1. Antibiotic use in hospitals

- Global geographic variations
- Huge inter-hospital differences
- Huge intra-hospital variations, not always explained by case-mix
- Antimicrobial consumption depends on
  - Cultural factors
  - Socio-economic factors
  - Health regulations

  Sources: ESAC, ESAC-Net, national publications

2. Antimicrobial stewardship

- why
- what
- how: strategies for old drugs, current drugs, new drugs
- levels: global, national

# Questions

- Should we involve the Ministries of Education in national intersectoral coordinating mechanisms on antimicrobial resistance?
- Should we involve Academia for education of students in antimicrobial stewardship principles (the undergraduate curriculum)?
- Should Regulators  act against antimicrobial drug shortages?
- Should the access of forgotten antibiotics be facilitated?

- How to preserve the value of newly developed antibiotics in the future?