The good and the bad uses of fluoroquinolones in Urology

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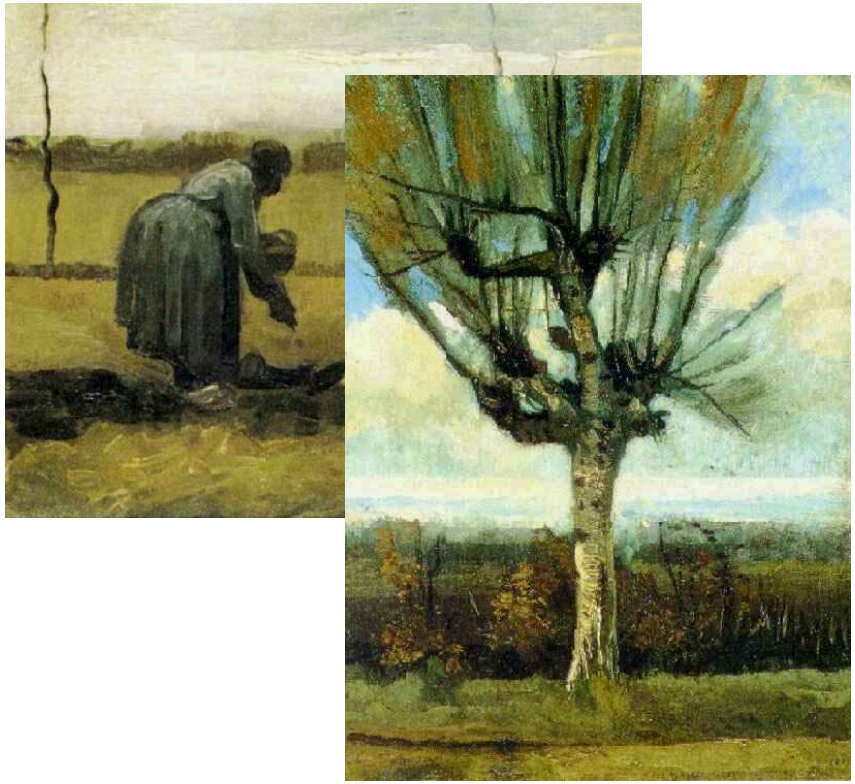
www.isap.org

Are antibiotics following a path to madness ?

discovery in soil bacteria and fungi

Are antibiotics following a path to madness ?



and then we all saw the blooming tree of semi-synthetic and totally synthetic antibiotics

Are antibiotics following a path to madness ?

and the General Surgeon told us
that the fighth was over

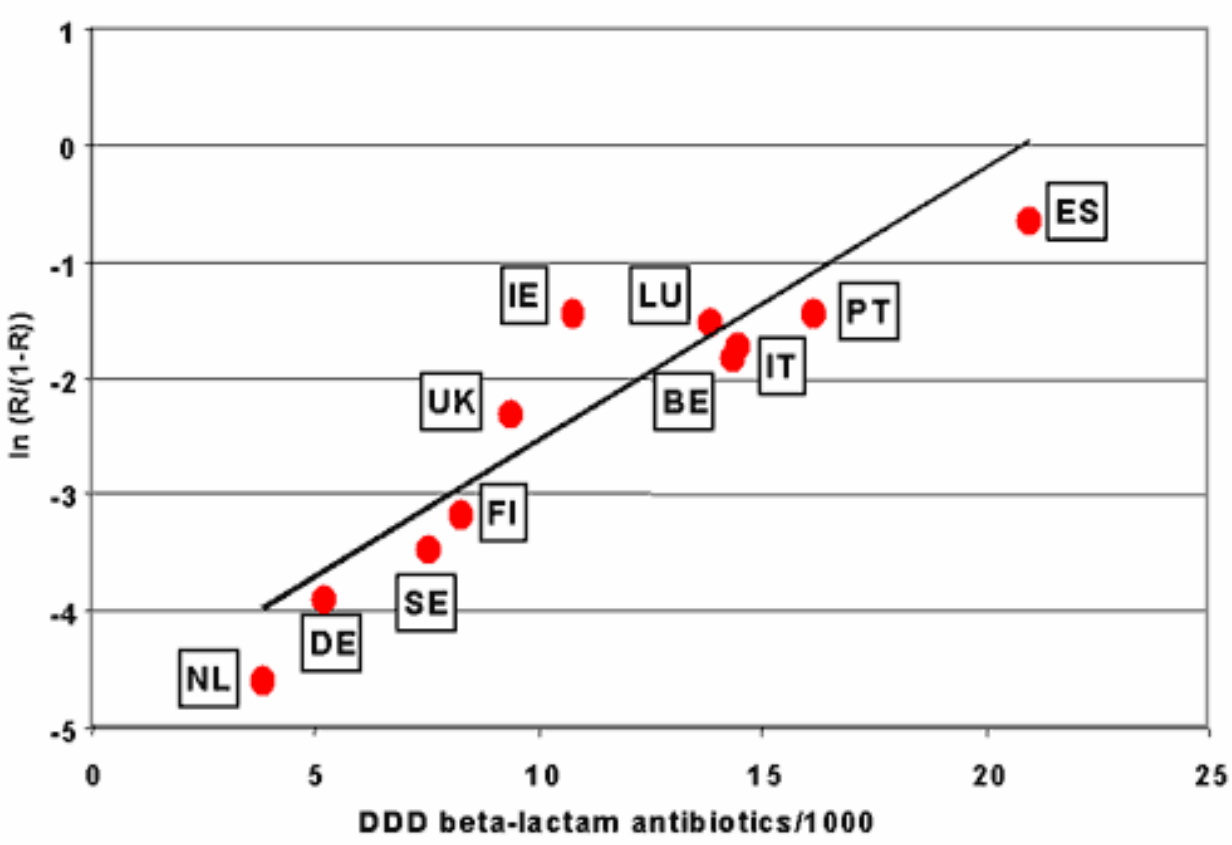
Are antibiotics following a path to madness ?

But…

Antibiotics and resistance...

- Is there a problem ?
  - ➔ Rising resistance and correlation with antibiotic use …
- Resistance in urinary nosocomial isolates …
  - ➔ what about quinolones uses in the community and the hospital ?
- What are quinolones (adavantages – downsides) ?
  - ➔ what are appropriate uses … and misuses ?
- Can this also reduce health care costs ? …

Overuse is one of the problems …
the classical situation in the community …



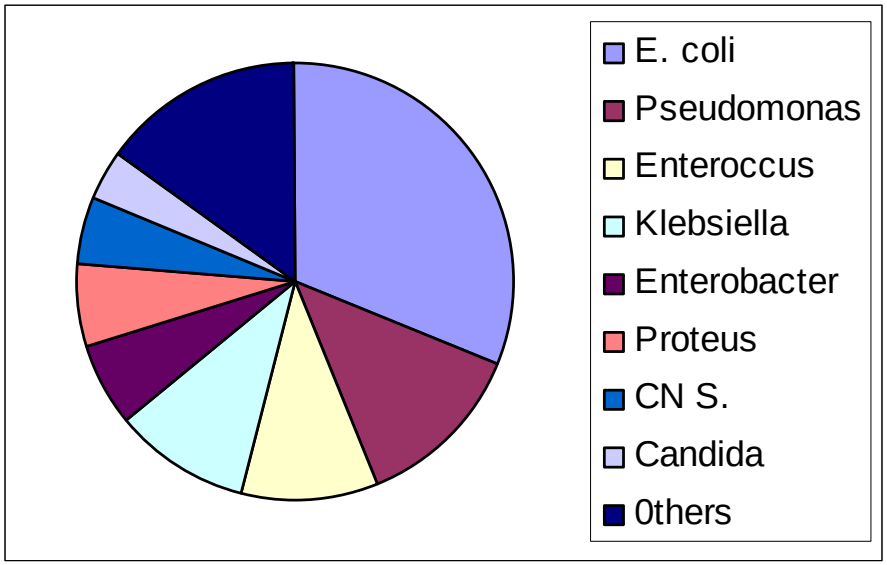
Risk of resistance to β-lactams among invasive isolates of *Streptoccus pneumoniae* regressed against outpatient sales of beta-lactam antibiotics in 11 European countries

- **resistance data are from 1998 to 1999; antibiotic sales data 1997.**
- **DDD = defined daily doses**

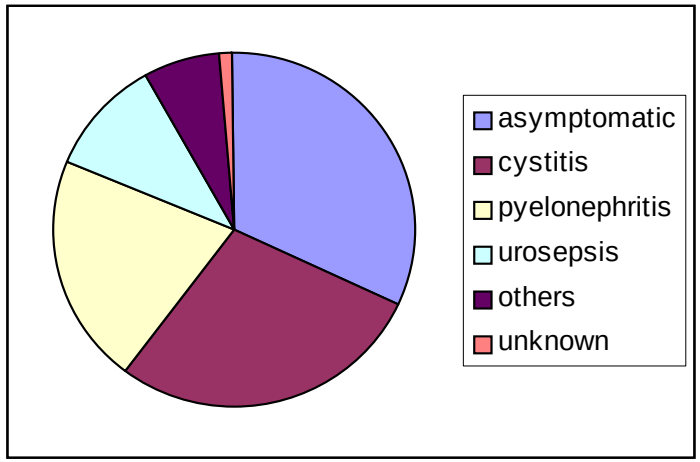
Bronzwaer SL, Cars O, et al. Emerg Infect Dis 2002 Mar;8(3):278-82

Organisms and resistance in nosocomial urological specimens …

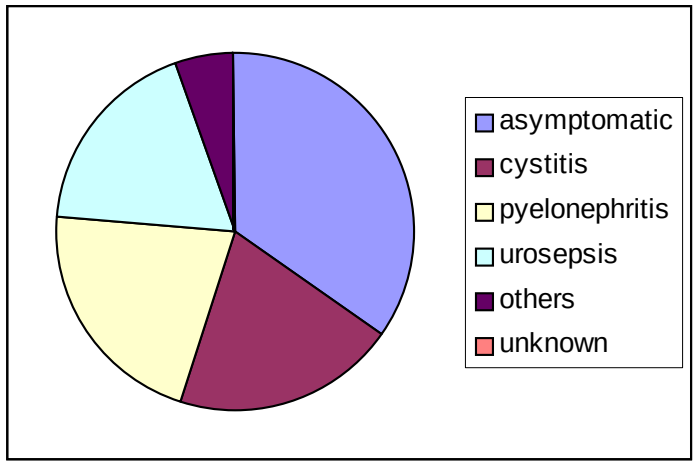
Distribution of microbial species in 486 patients with nosocomially acquired urinary tract infection



E. coli



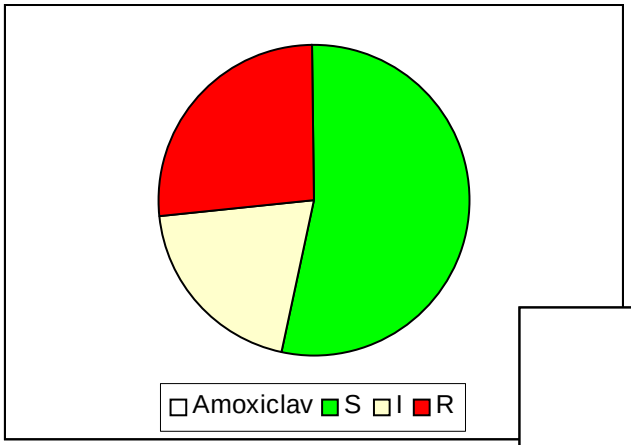
P. aeruginosa



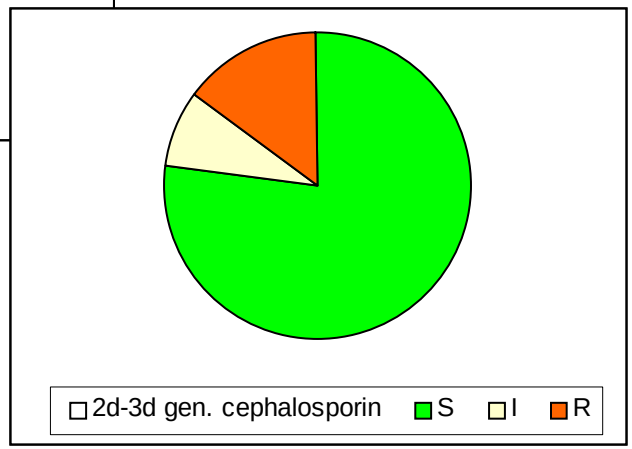
Johansen et al. Intern. J. Antimicrob. 2006; 28,Suppl.1:91-107
A study from the European Society of Infections in Urology (ESIU)

Organisms and resistance in nosocomial urological specimens …

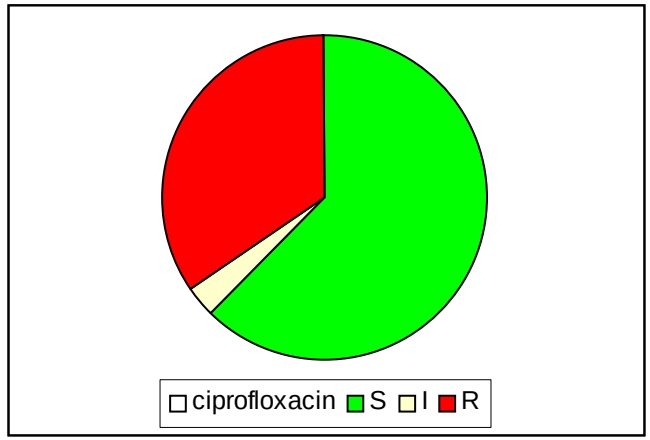
Resistance of *E. coli*



to amoxiclav



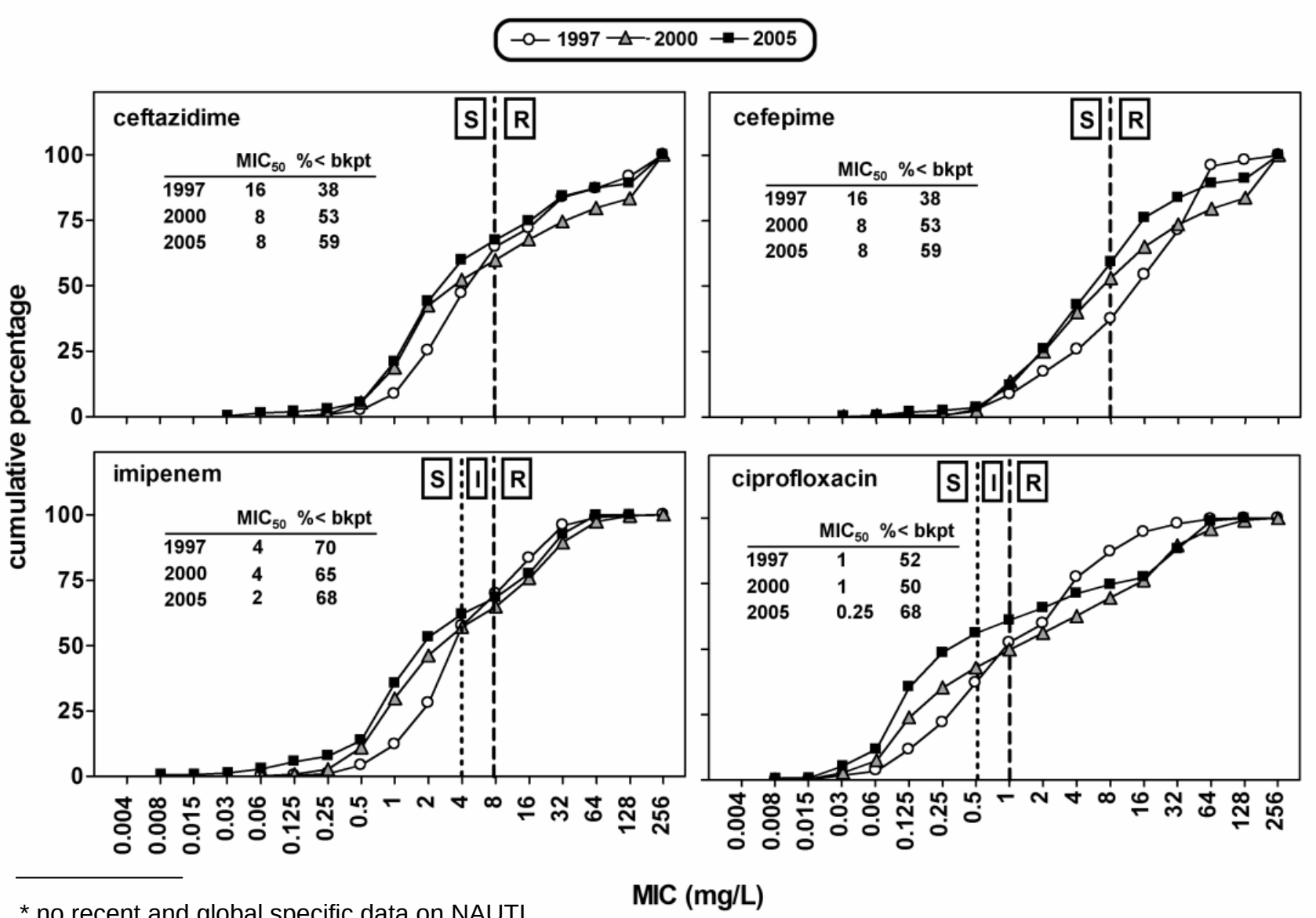
to 2d/3d gen. cephalosp.



to ciprofloxacin

Johansen et al. Intern. J. Antimicrob. 2006; 28,Suppl.1:91-107
A study from the European Society of Infections in Urology (ESIU)

Resistance of *P. aeruginosa* (all origins *)

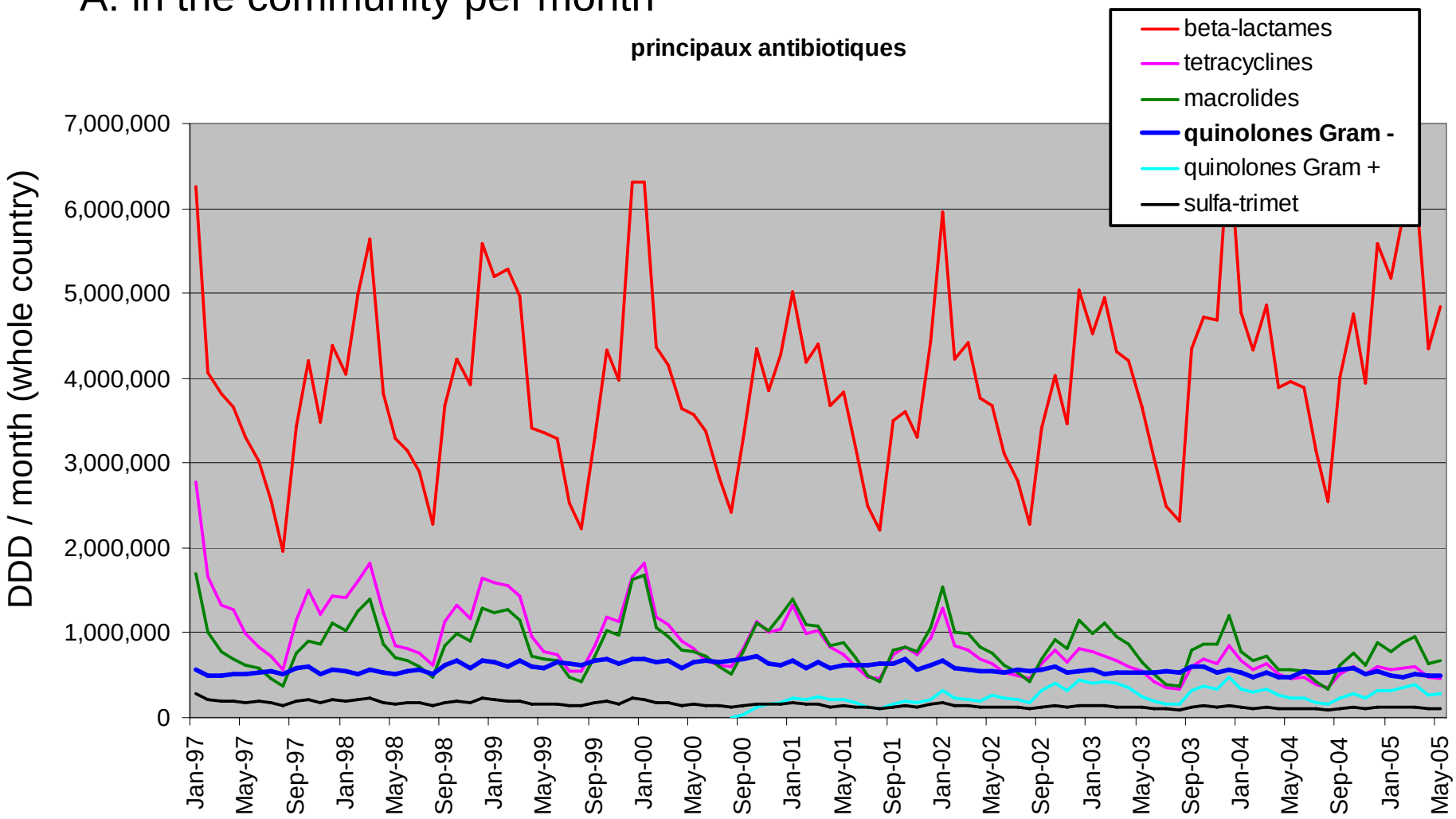


* no recent and global specific data on NAUTI…

Mesaros et al. CMI, in press; http://www.facm.ucl.ac.be

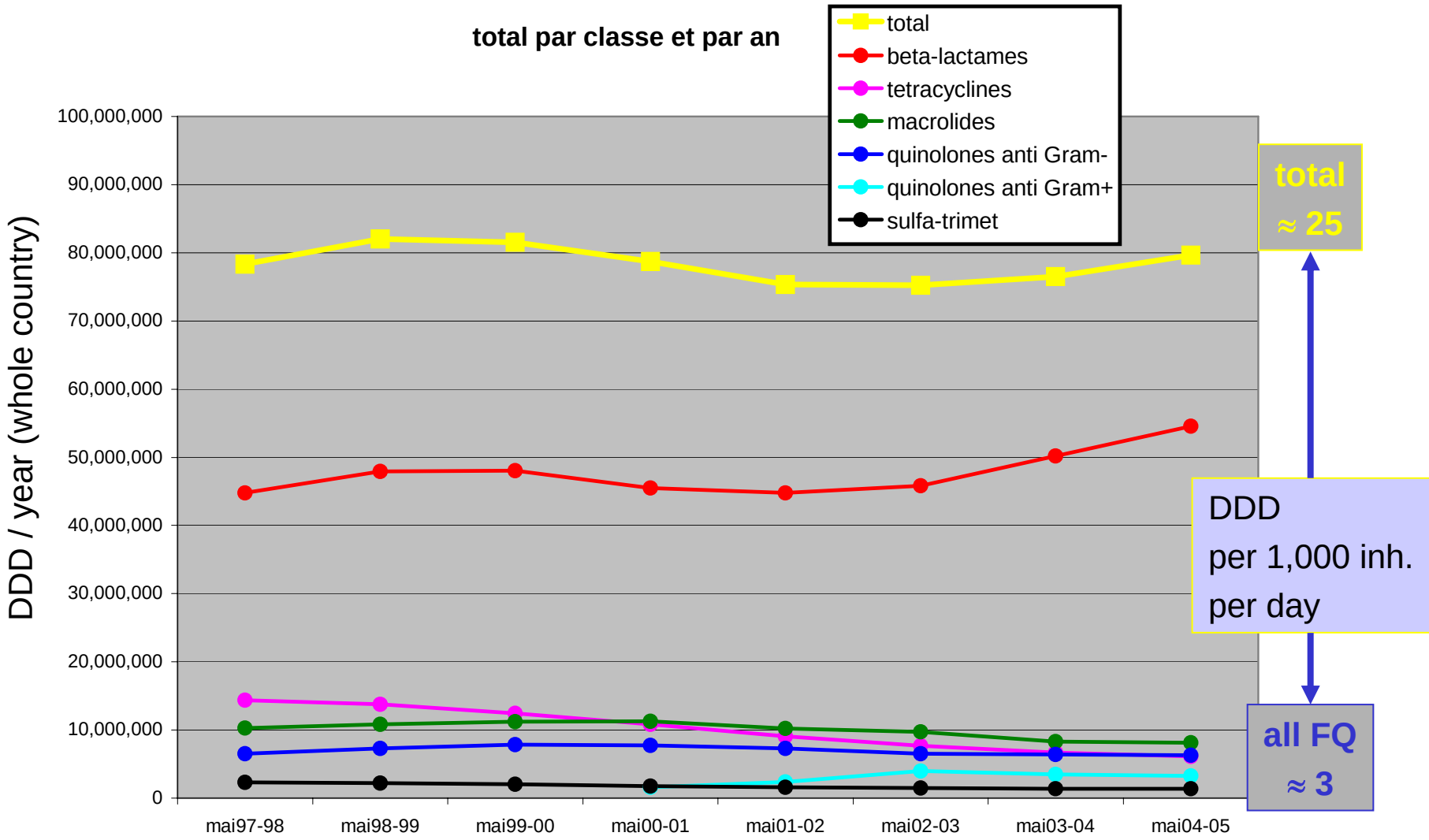
Do we use too much Gram (-) fluoroquinolones in Belgium ?

A: in the community per month



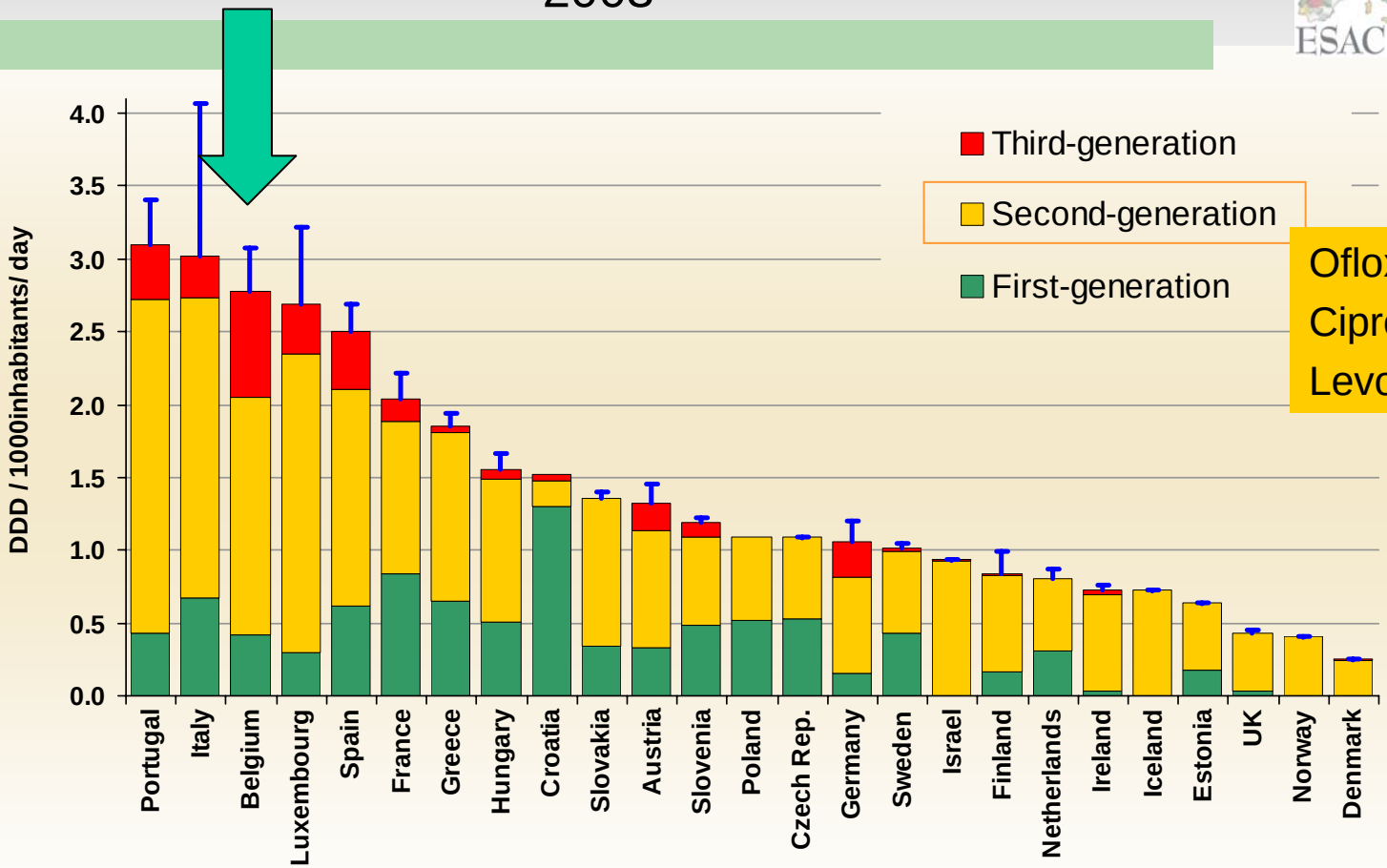
Do we use too much Gram (-) fluoroquinolones in Belgium ?

A: in the community : trends over years



Use of quinolones in the Community in Europe …

Outpatient use of quinolones in 25 European countries in 2003*

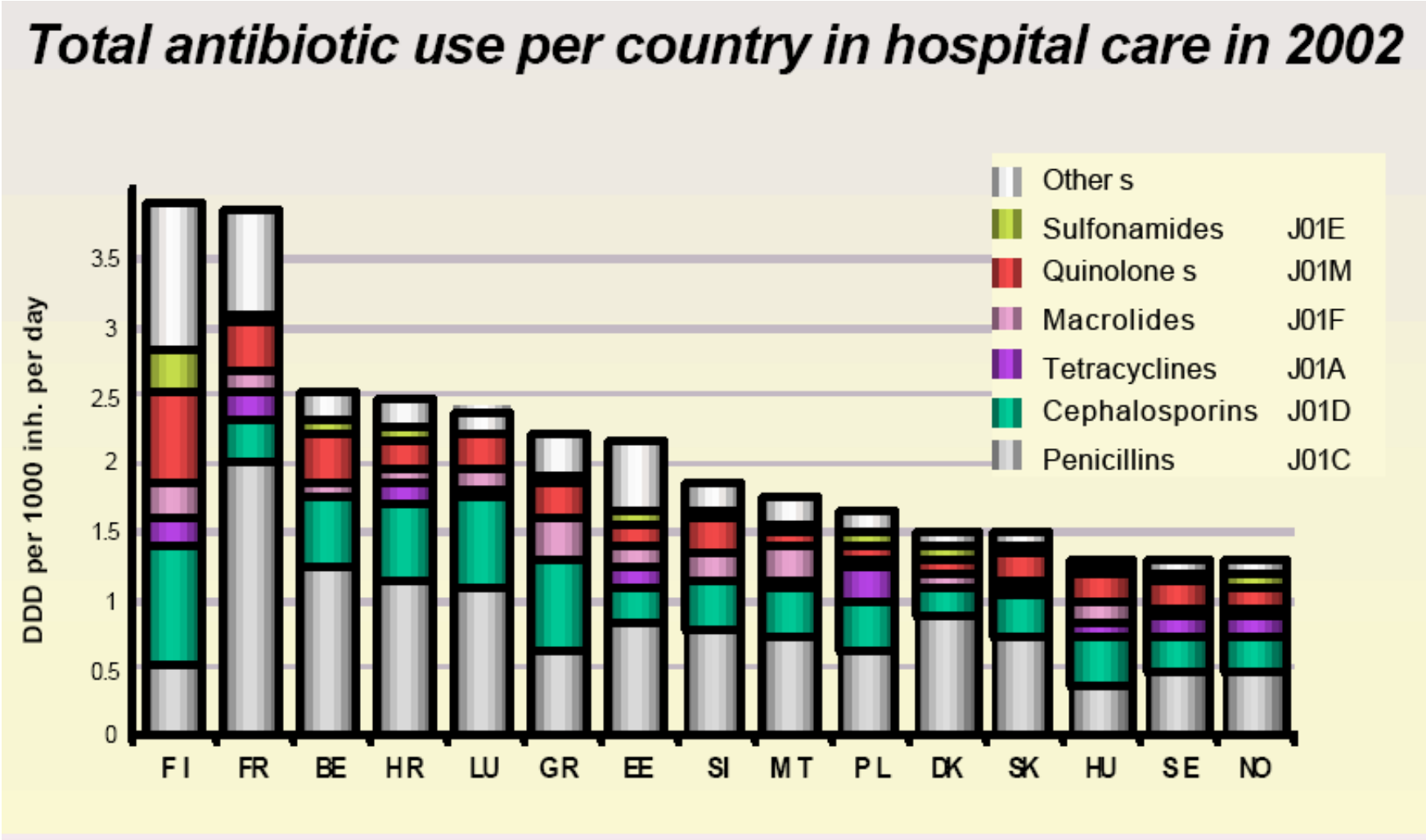


Ofloxacin
Ciprofloxacin
Levofloxacin

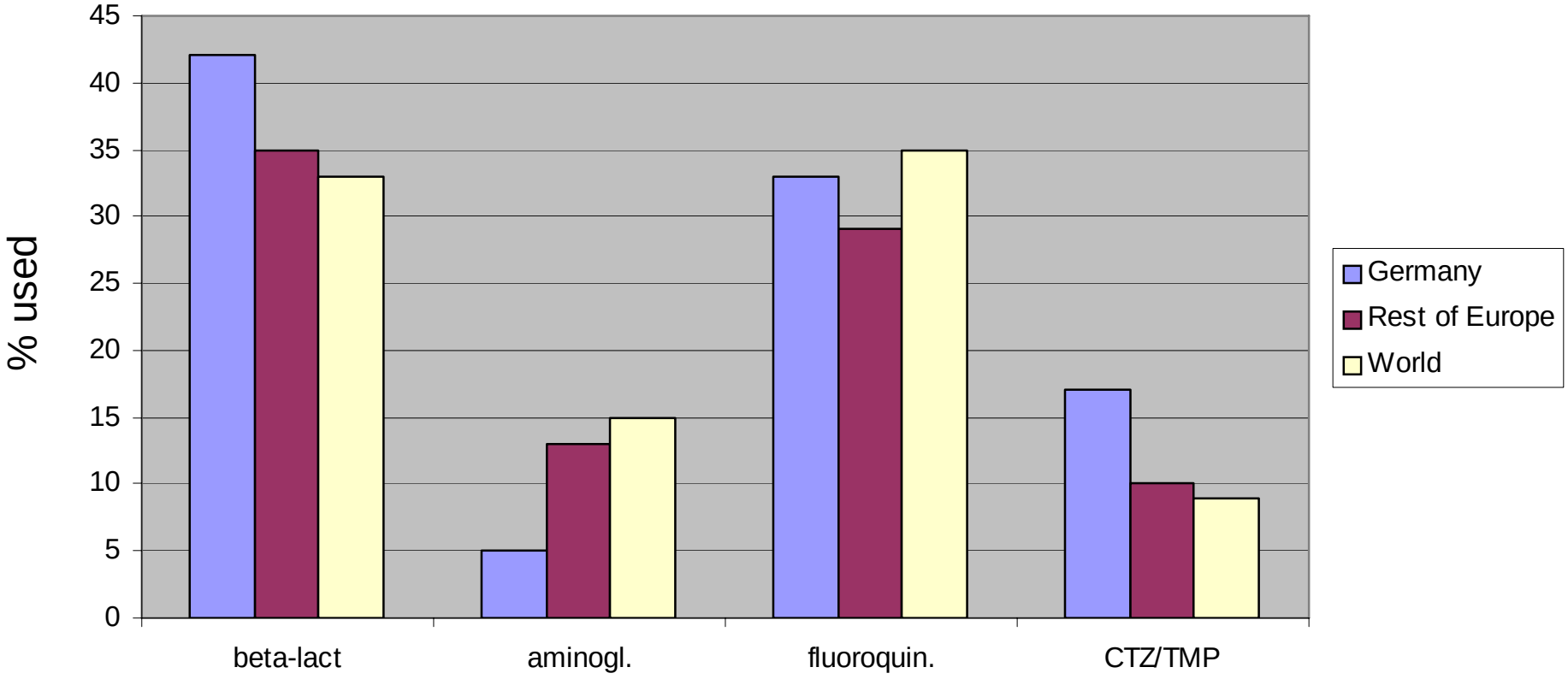
Blue error bar represents the difference in national quinolone use in 2003 expressed in DID between ATC/DDD versions 2004 and 2003 due to the change of DDD for levofloxacine from 250 to 500 mg.

* For Iceland total data are use; for Poland 2002 data are used.

Use of quinolones in Hospitals in Europe …



Antibiotics given in nosocomial urinary tract infections (hospitalized patients)



Johansen et al. Intern. J. Antimicrob. 2006; 28,Suppl.1:91-107
A study from the European Society of Infections in Urology (ESIU)

Thus, we are facing a problem… and looking for a solution …

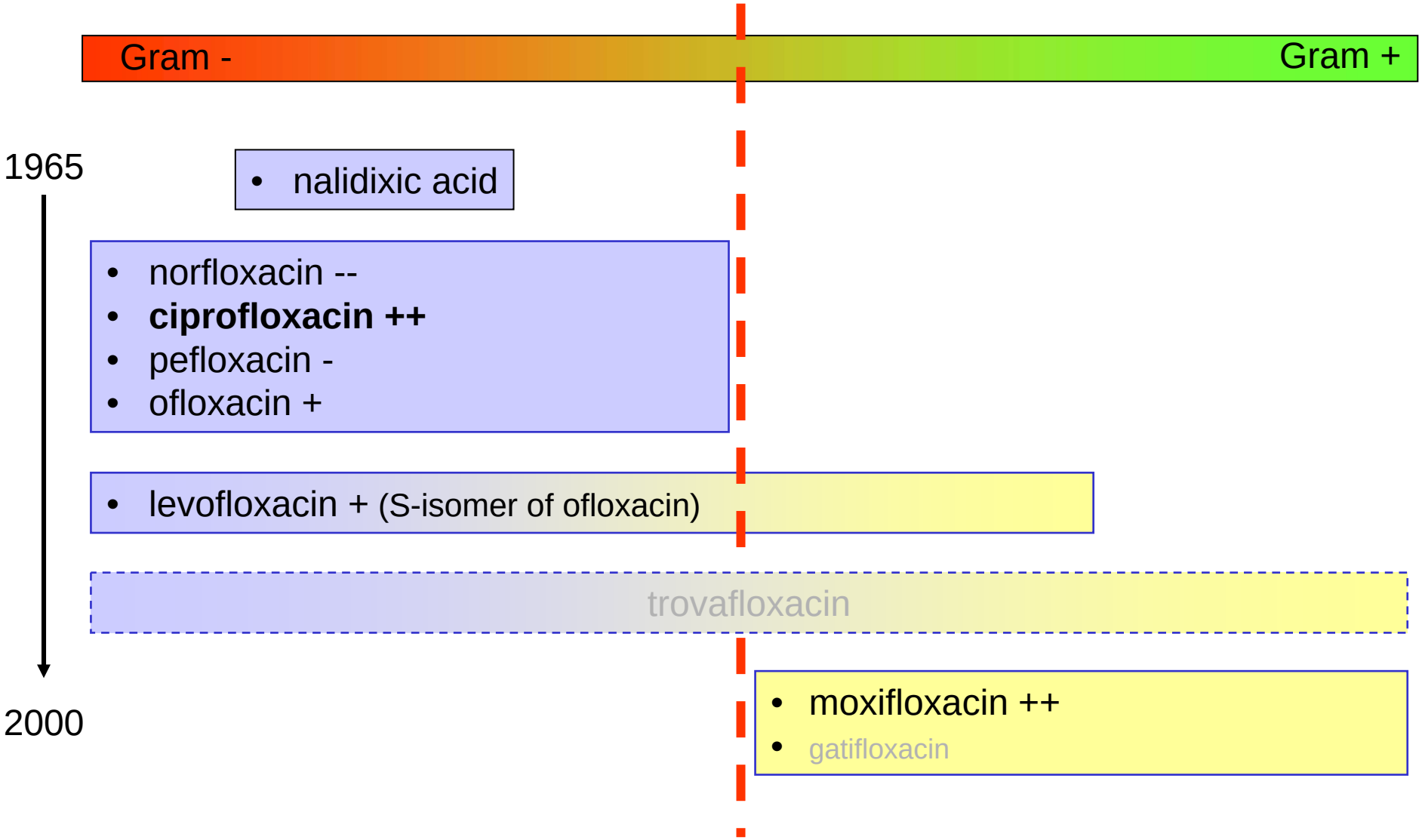
- Resistance rates are strong arguments for a critical antimicrobial policy
- Empiric therapy has to be initiated rapidly but culture must be taken before.
- Adjustment is important …
- Prophylaxis and treatment must be based on a continuous surveillance in Urology departments.
- Collaboration between urologists and microbiologists is decisive for good infection control.
- Facilities for preliminary culture of pathogens inside the urological ward may be useful

Johansen et al. Intern. J. Antimicrob. 2006; 28,Suppl.1:91-107
A study from the European Society of Infections in Urology (ESIU)

Where do we go from now ?

- Understand what quinolones are ?
- Are they causing more resistance ?
- What could be their limits
- What do guidelines say ?
- Do we use too much ?

Which (fluoro)quinolones ?



Main useful pharmacological properties and drawbacks ?

On the positive side

- bactericidal
- concentration (C_{max}) and dose (24h-AUC)-dependent, allowing for rational fine tuning of the therapy including against resistant strains, based on simple rules for posology…
  - ➔ C_{max}/MIC > 10; 24h-AUC/MIC > 125
- good tolerance in general
- excellent bioavailability (rapid oral switch possible…)

On the negative side

- a few side effects that require attention (tendinitis, CNS, ...) and incompatibility with divalent traivalent cations (Ca_{++}, Al^{+++})
- emergence of resistance
  - target mutation (relatively easy ...)
  - unanticipated cross-resistances due to efflux…
  - breakpoints (limits of susceptibility) have been set historically to high (NCCLS), are better with EUCAST, but still need attention

Quinolones side effects...

Table 3. Main side-effects of quinolones that contribute to the limitation of their use, the frequency observed, and the populations at risk

Side-effect	Quinolone	Frequency	Population at risk
Genotoxicity			Pregnant women
Gastrointestinal effects (nausea, vomiting > diarrhea)	Fleroxacin, sparfloxacin, grepafloxacin[a]	> 10%	
	Others	2–8% [243]	
Skin reaction: phototoxicity	Sparfloxacin[a], fleroxacin[a], lomefloxacin[a], Bay 3118[a]	> 10% [244]	
	Others	< 2.5%	Cystic fibrosis [245]
Skin reactions: rash	Clinafloxacin[a]	4% [243]	
	Gemifloxacin	2.8% [246]	Young women
Chondrotoxicity	Pefloxacin[a]	14% [247]	Children, pregnant women
	Others	1.5% in children (ciprofloxacin [248])	
Tendinitis	Pefloxacin[a]	2.7% [249]	Elderly, especially if on corticosteroid therapy [250]
	> Levofloxacin/ofloxacin ≥ ciprofloxacin > Others [252,253]	0.4%	Athletes in training [251]
Minor CNS effects	Trovafloxacin	2–11% dizziness	Elderly [254]
Major CNS effects	Levofloxacin	0.026% confusion, alteration in mentation and affect [243]	Co-administration of NSAID or of inhibitors of CYP 450 [255]
	Fleroxacin[a] [256]	8% insomnia [257]	
Cardiovascular effects	Sparfloxacin[a] (9–28 ms)	2.9%	Female gender
	Grepafloxacin[a] (10 ms)		Co-administration of other drugs (prolonging QTc interval or inhibiting CYP 450 metabolism)
	Moxifloxacin (6 ms)		
	Levofloxacin (3 ms)[b]		
	Gatifloxacin (2.9 ms)		
	Gemifloxacin (2.6 ms) [246,258–260]		Heart disease [254]
Minor hepatic effects (transaminase elevation)	Grepafloxacin	12–16% transaminase elevation [243]	
	Others	< 3% [261]	
Major hepatic effects	Trovafloxacin[a]	0.006% [243]	Treatment duration > 14 days [262]
Hypoglycaemia	Clinafloxacin[a]		Co-administration of oral hypoglycemic agents [264]
	Gatifloxacin		
	Levofloxacin (one fatal case [263]		
Haematological toxicity	Temofloxacin[a]	0.02% haemolysis, thrombocytopenia, renal failure [256]	
CYP 450 inhibition	Enoxacin[a], clinafloxacin[a] [256] > ciprofloxacin > lomefloxacin, ofloxacin > levofloxacin, sparfloxacin, gatifloxacin, moxifloxacin [262]		

[a]Side-effects have contributed to the withdrawal or limitation in use.
[b]Further studies have been requested from the manufacturer, as recent pharmacovigilance reports document a significant increase of the QTc interval, mainly in patients with concurrent medical conditions or other medications [243,265]; see also [266] for a recent study in the province of Varese, Italy, using prescription data on all incident users of several antibacterial and anti-arrhythmic drugs during the period July 1997 to December 1999.
NSAID, non-steroidal anti-inflammatory drug; CNS, central nervous system.

Van Bambeke F, Michot JM, Van Eldere J, Tulkens PM.
Quinolones in 2005: an update. Clin Microbiol Infect. 2005 Apr;11(4):256-80. PMID: 15760423

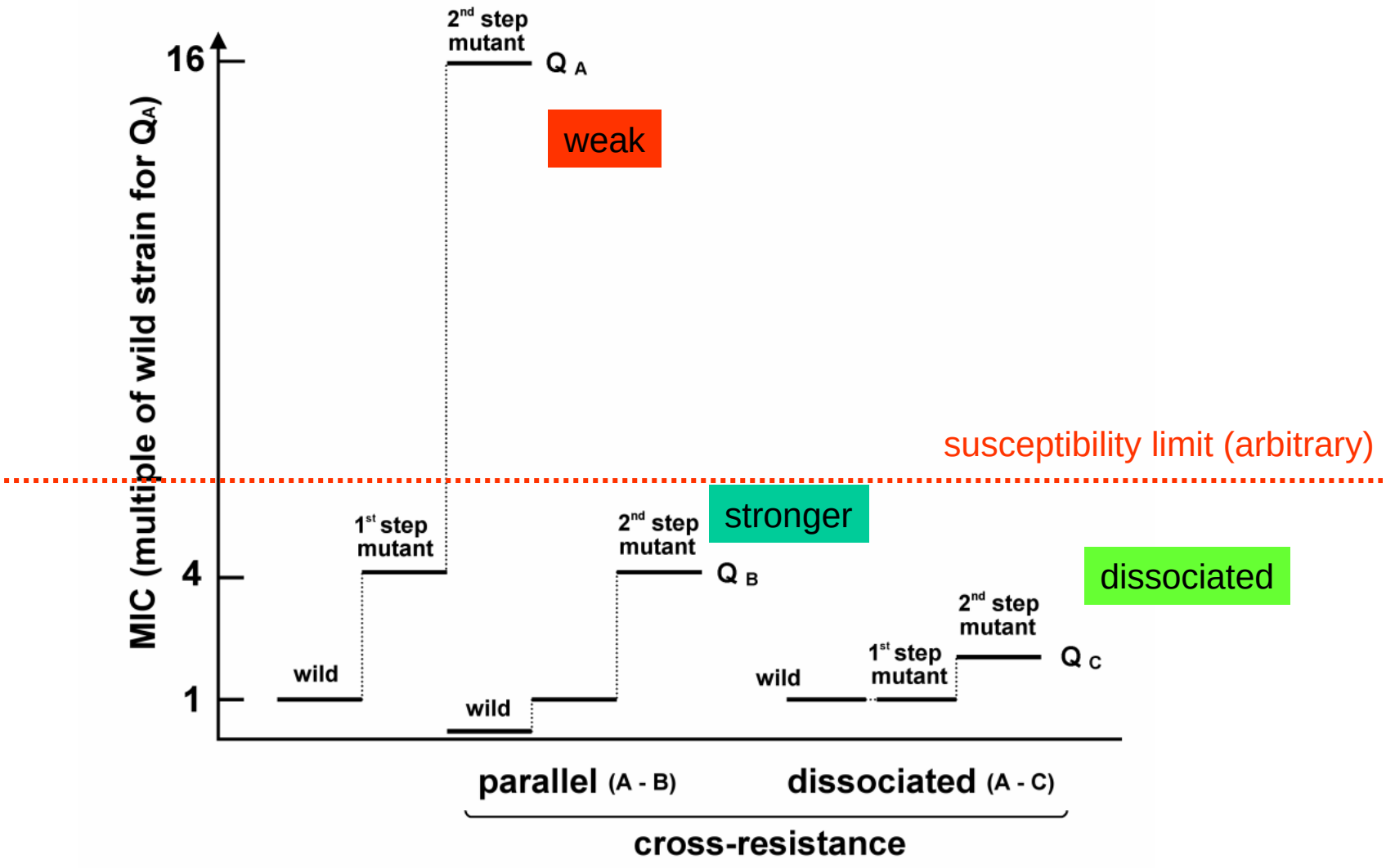
Quinolones side effects...: which are the populations (really) at risk ?

- pregnant women and children
- elderly, especially with corticoid therapy
- athletes in training (beware of the runners...)
- co-administration of NDSAIDs or drugs known for potential of $CytP_{450}$ interactions
- heart disease
- patients receiving neutralization anti-acids (Ca++/ Mg++ / Al+++) or Fe++

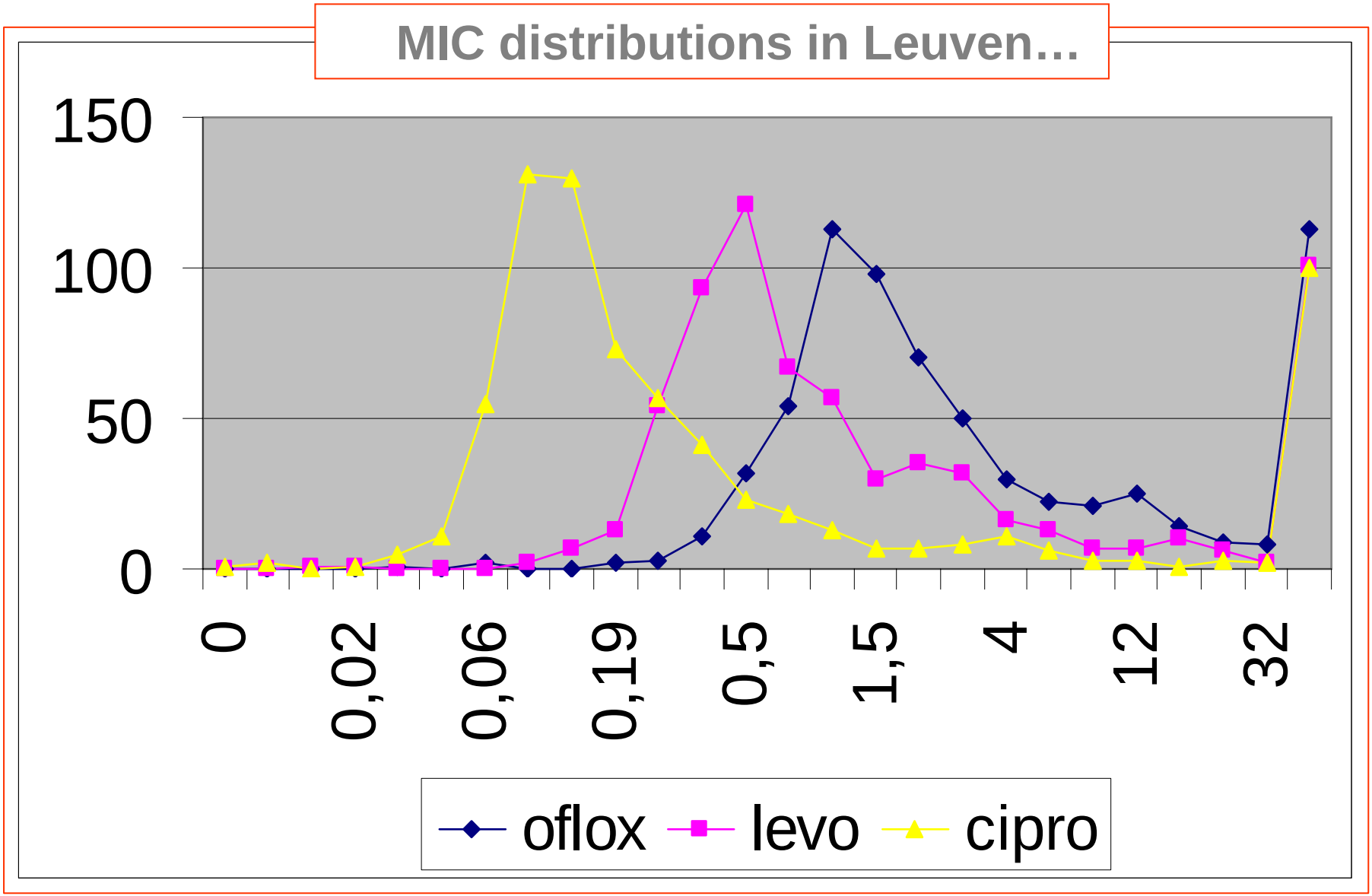
Resistance…

- long thought to be restricted to chromosomic mutations of the targets (DNA gyrase / topoisomerase)
  - high frequency of spontaneous mutations (10^{-7})
  - but limited horizontal and interbacterial spread …
- but, later on, observed in relation to decreased accumulation
  - loss of porins in Gram (-) bacteria
  - (over)expression of efflux
- now, seen through plasmidic-associated mechanisms (QnR)
  - risk of rapid horizontal spread …
- and very recently though fluoroquinolone-modifying enzymes !!
  (clinical significance still uncertain…)

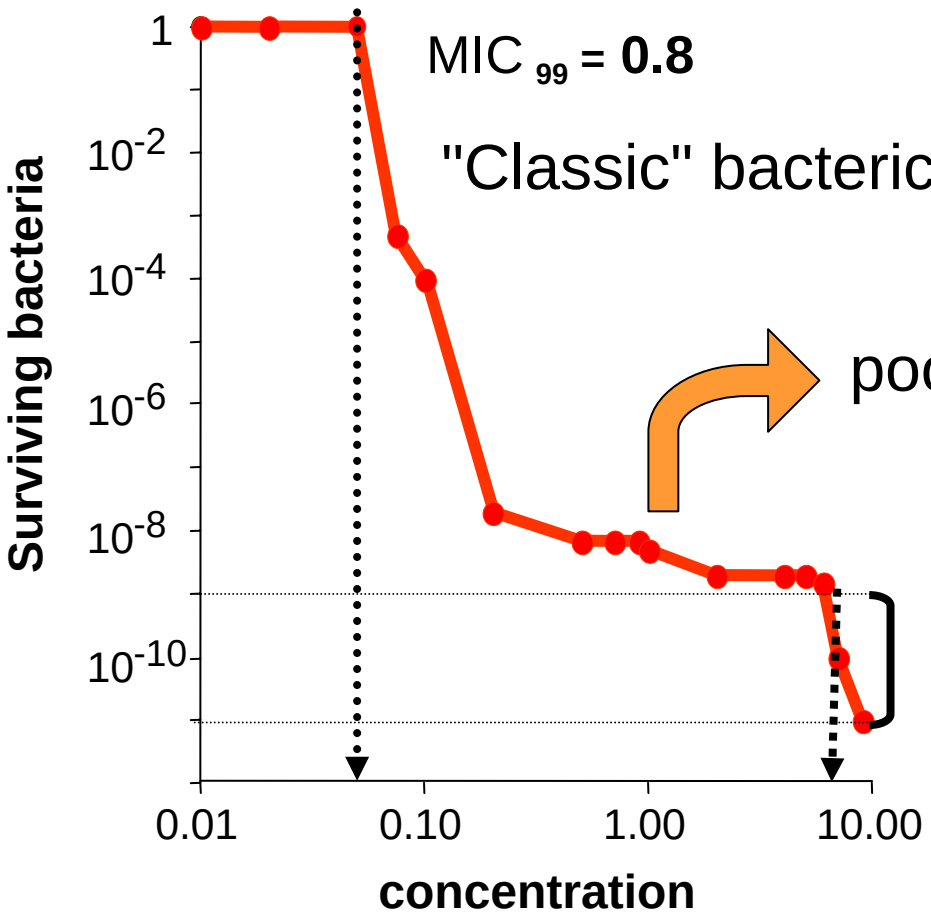
Resistance by target mutation: parallel and dissociated resistance and strong-versus weak fluoroquinolones



Application: look at MIC distributions where YOU are … to find "weak" quinolones



Mutant Prevention Concentration …



MIC $_{99}$ = **0.8**

"Classic" bactericidal effect

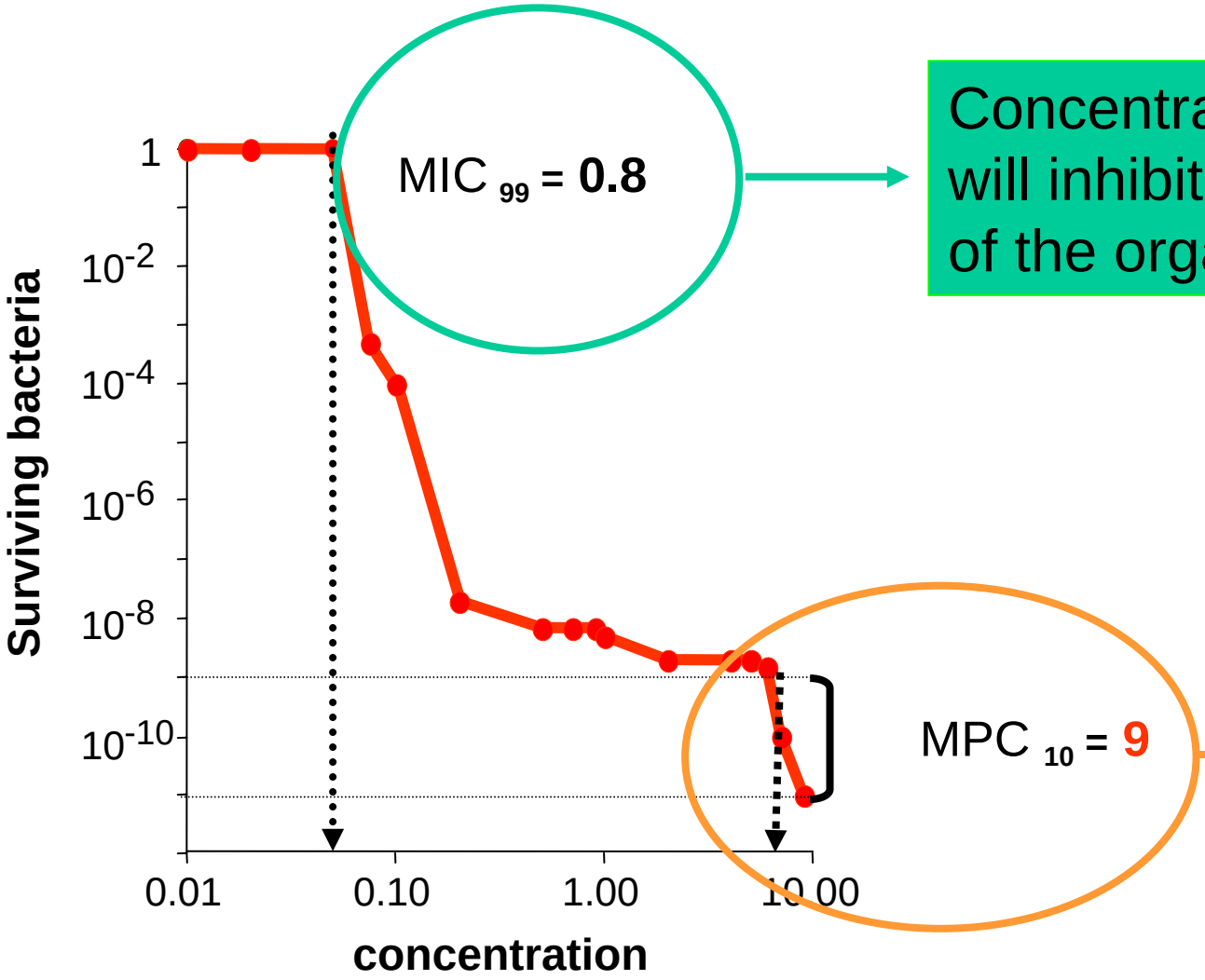
poorly sensitive organisms…

Elimination of resistant organisms

MPC $_{10}$ = **9**

Dong *et al:* AAC 1999; 43:1756-1758

Mutant Prevention Concentration …

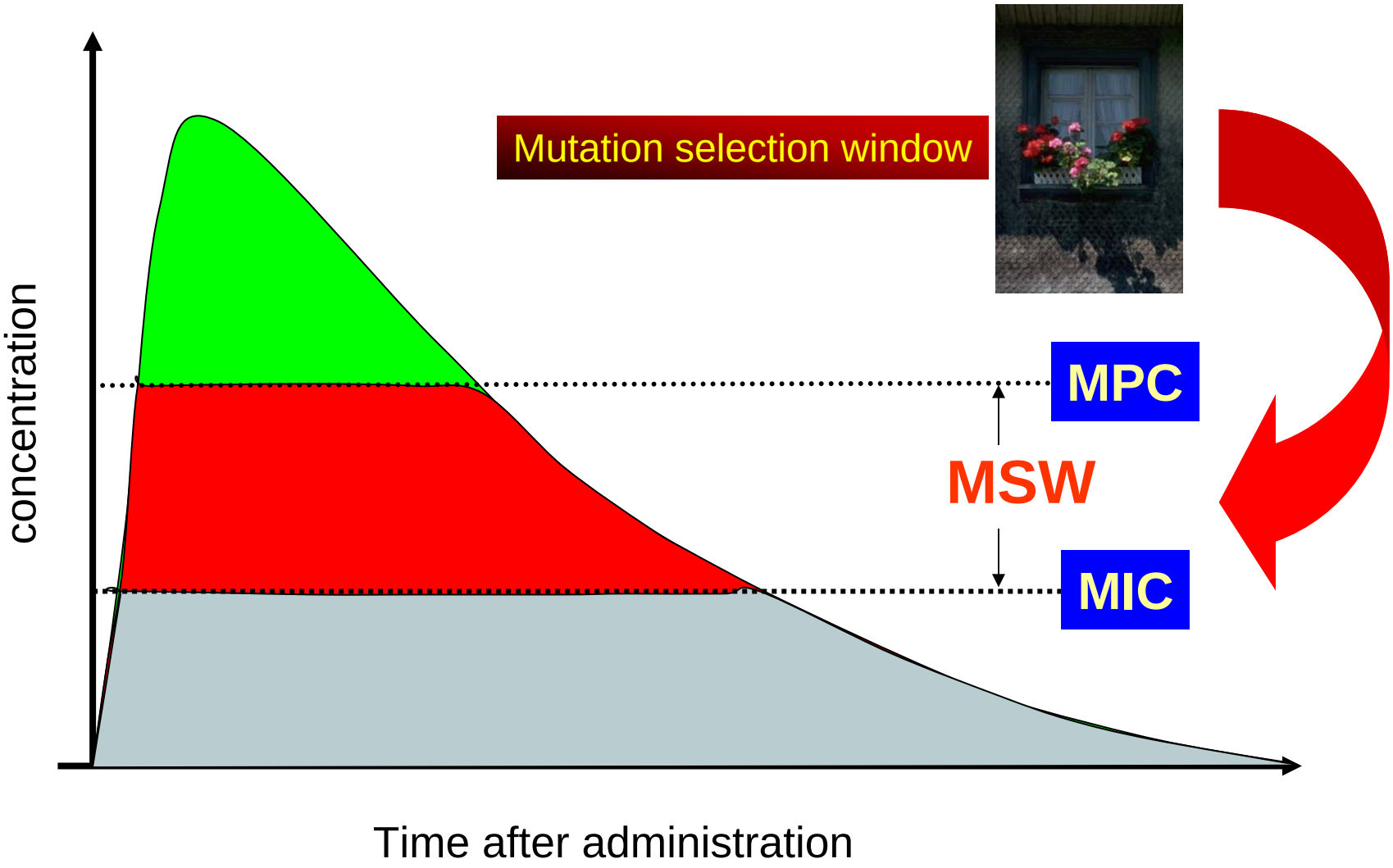


Concentration which will inhibit the majority of the organisms

Concentration needed to prevent the selection of resistant organisms

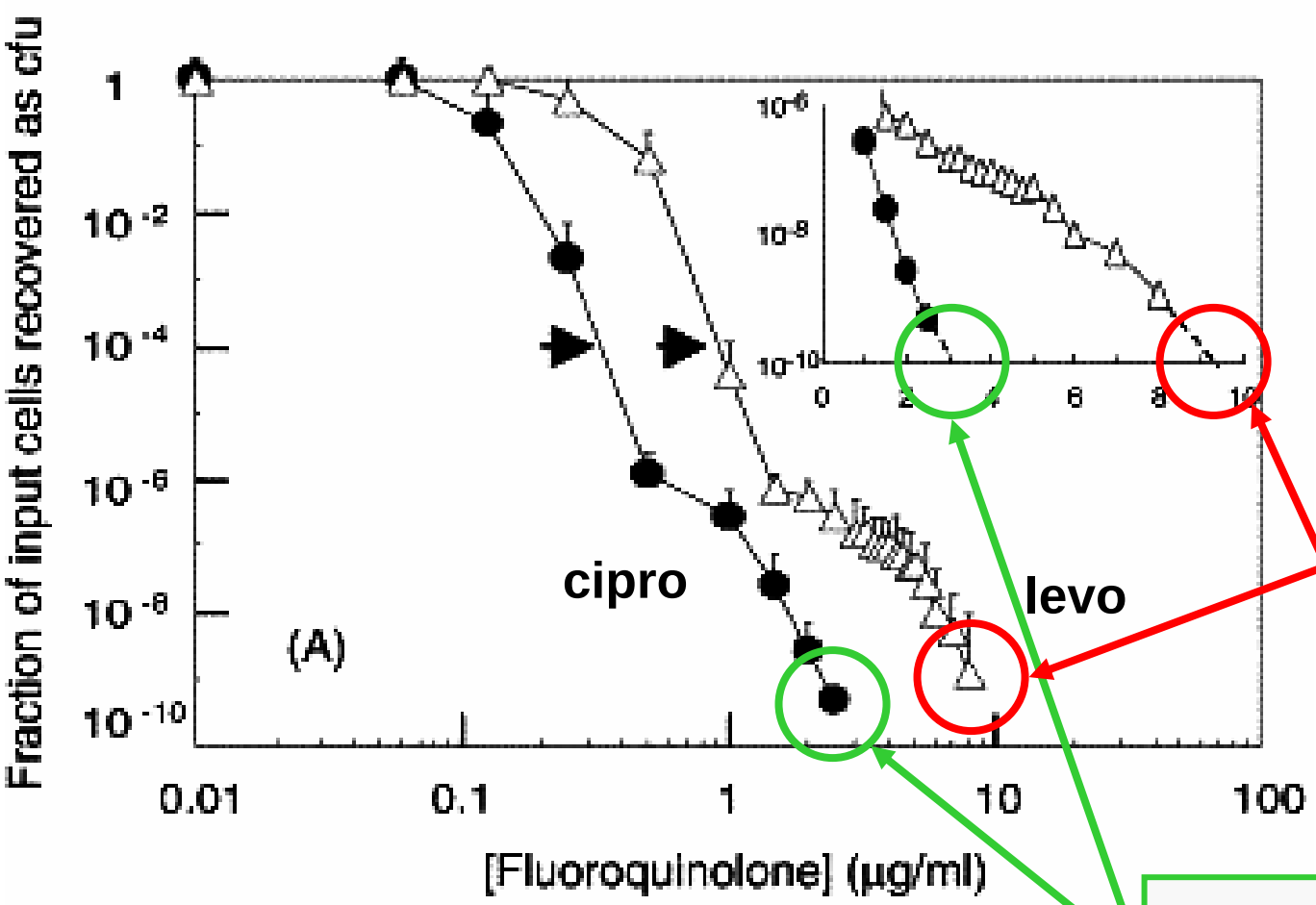
Dong *et al*; AAC 43:1756-1758

"Window" where selection of mutants/resistants may take place …



concept from Drlica & Zhao, Rev. Med. Microbiol. 2004, 15:73-80

Mutant Prevention Concentration of ciprofloxacin and levofloxacin in *P. aeruginosa* (clinical isolates) with "normal" susceptibility (MIC = 0.33 and 0.9 mg/L) …



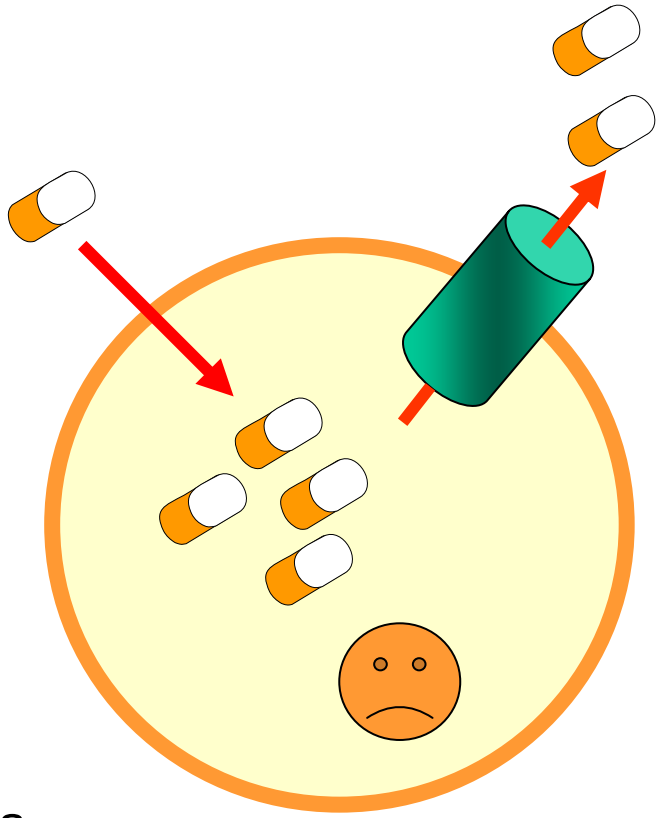
MPC levo = 9.5
(Cmax ~ 5 µg/ml

MPC cipro = 3
Cmax ~ 2.5 µg/ml

Hansen et al. I.J.Antimicrob. Agents 2006;27:120-124

Efflux and MIC ?

- efflux is a universal mechanism for cell protection against membrane-diffusing agents
- many drugs diffuse though membranes and become opportunistic substrates of efflux pumps
- for AB, efflux decreases the amount of drug in bacteria and impairs activity, increasing the MIC …
- insufficient drug exposure favors the selection of less sensitive organisms

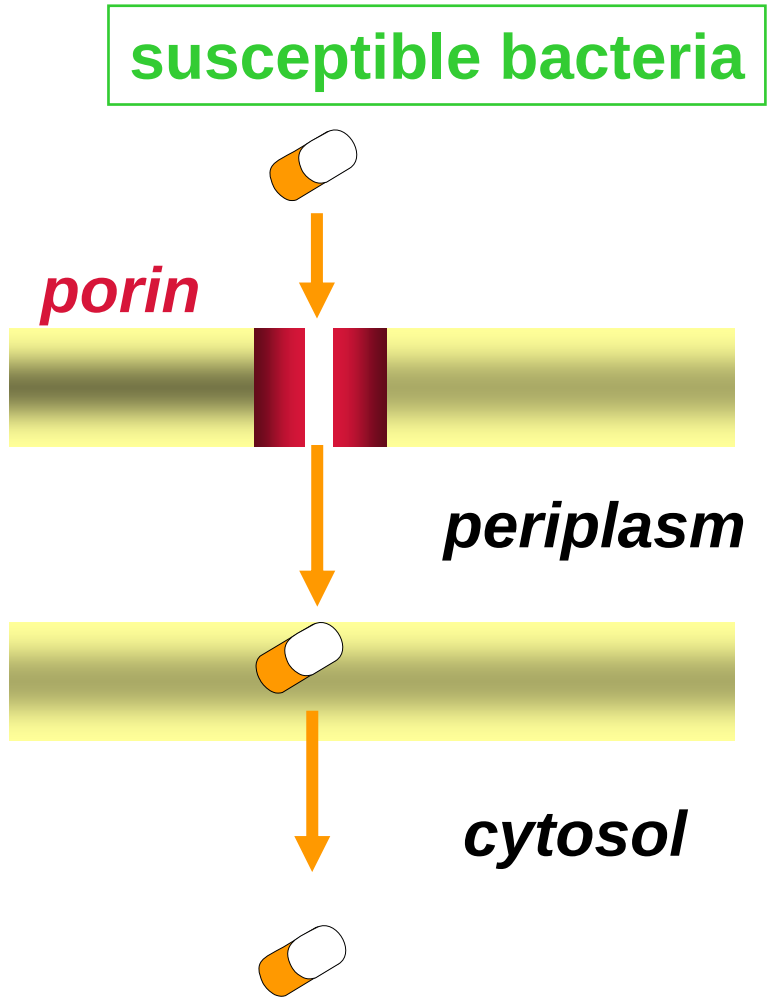


➔ the increase in MIC is modest and often leaves the strain categorized (falsely …) as "sensitive"…

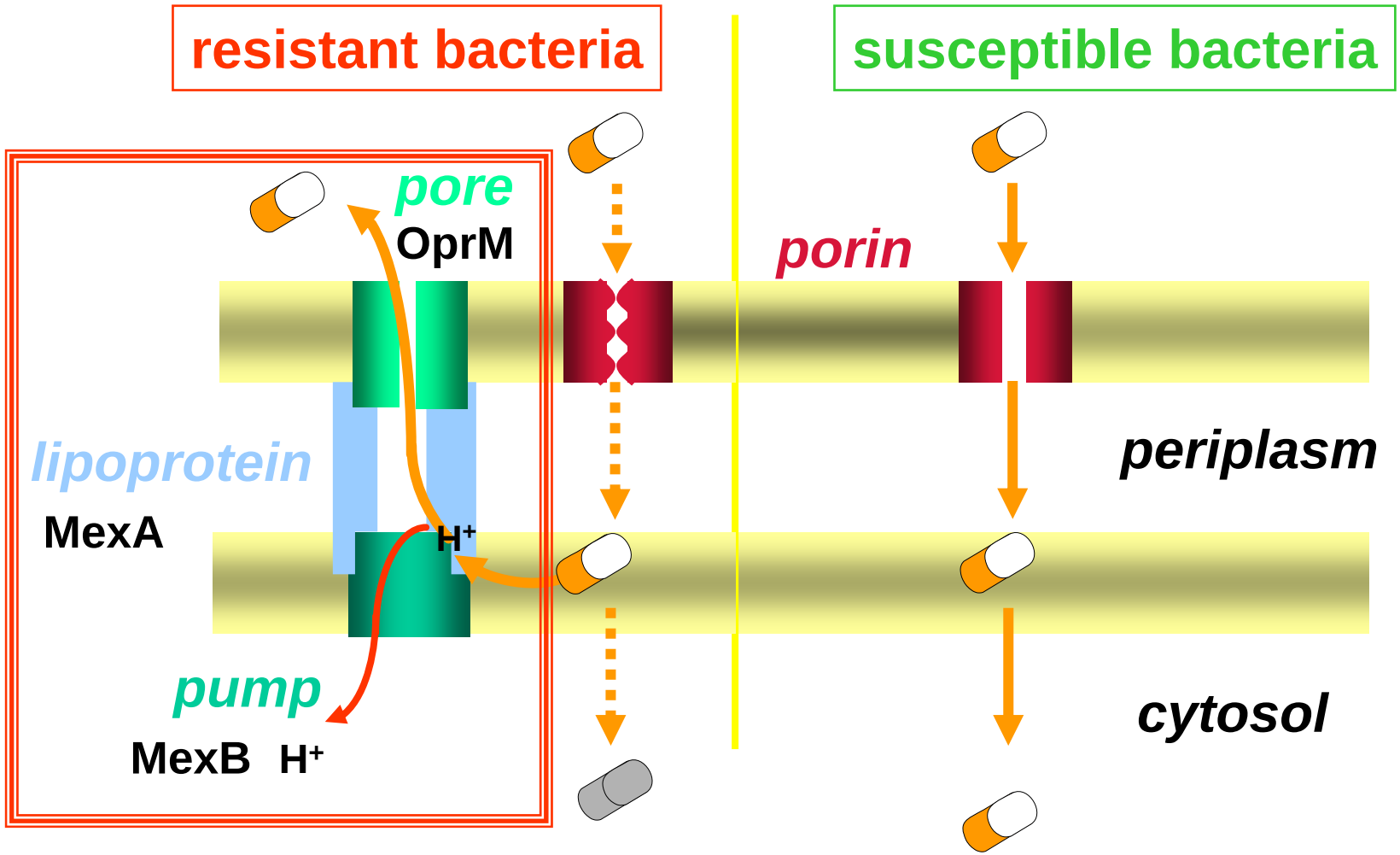
➔ true MIC determination may, therefore, become more and more critical …

Van Bambeke et al.
J Antimicrob Chemother. 2003;51:1055-65.

How does efflux work (Gram - bacteria) ?

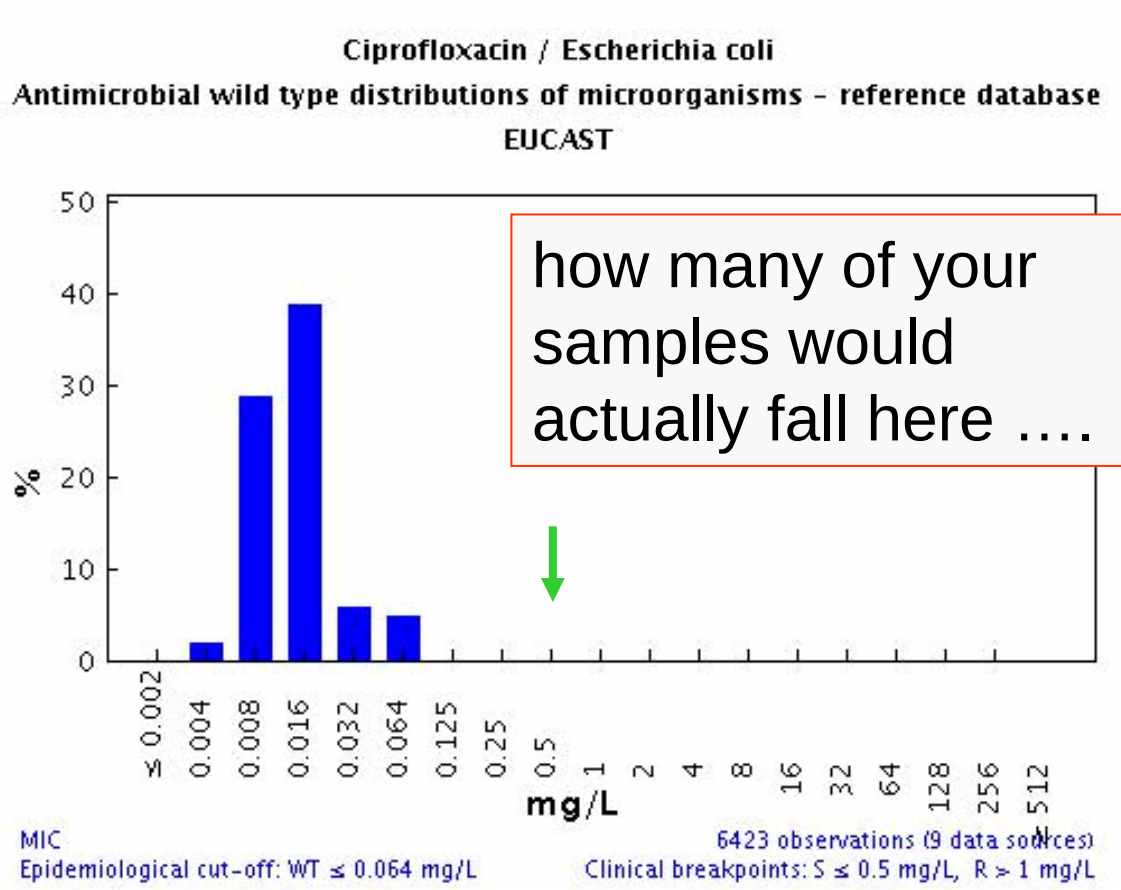


How does efflux work (Gram - bacteria) ?



expressed in wild-type strains!

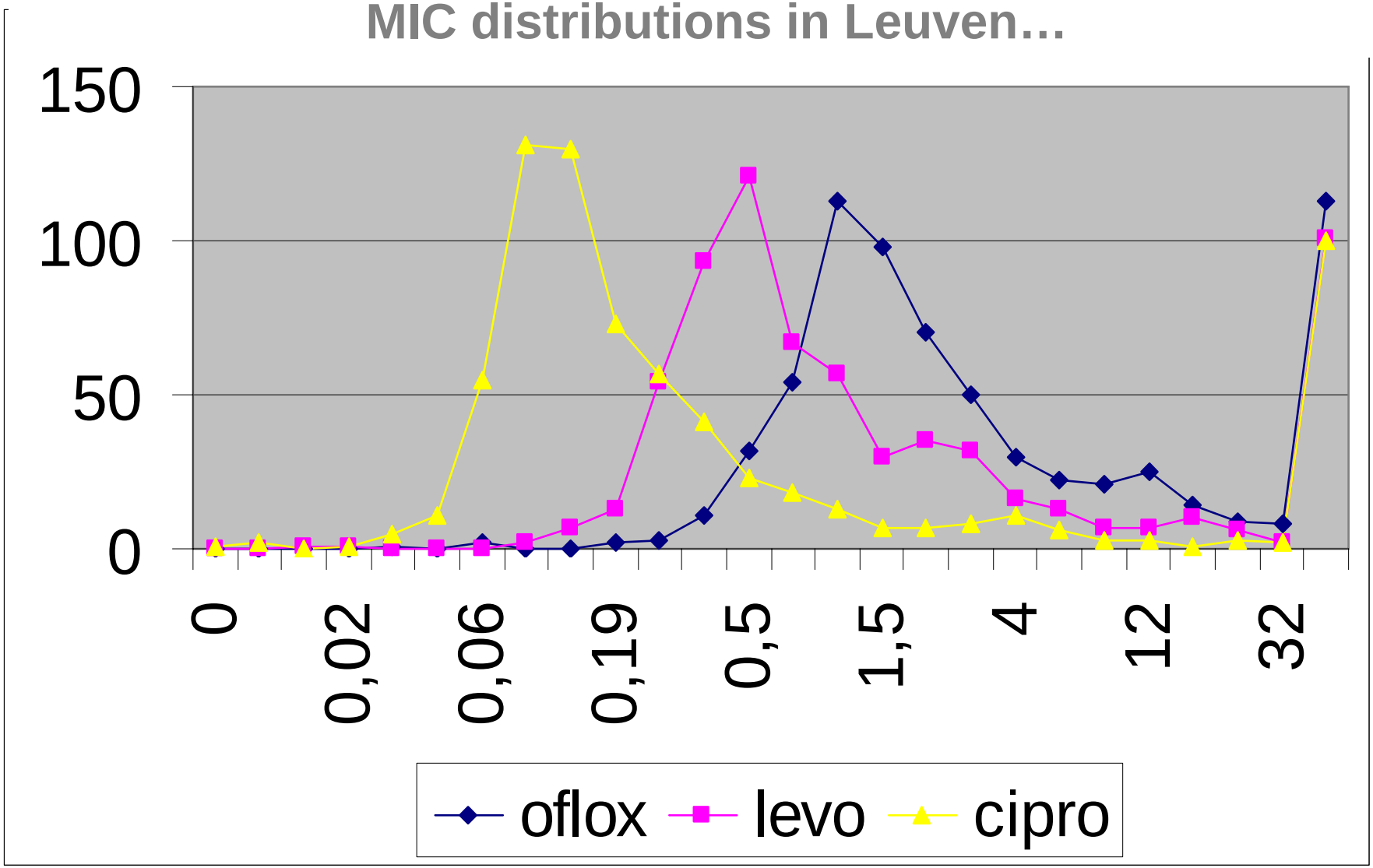
Why do you need to detect efflux ?



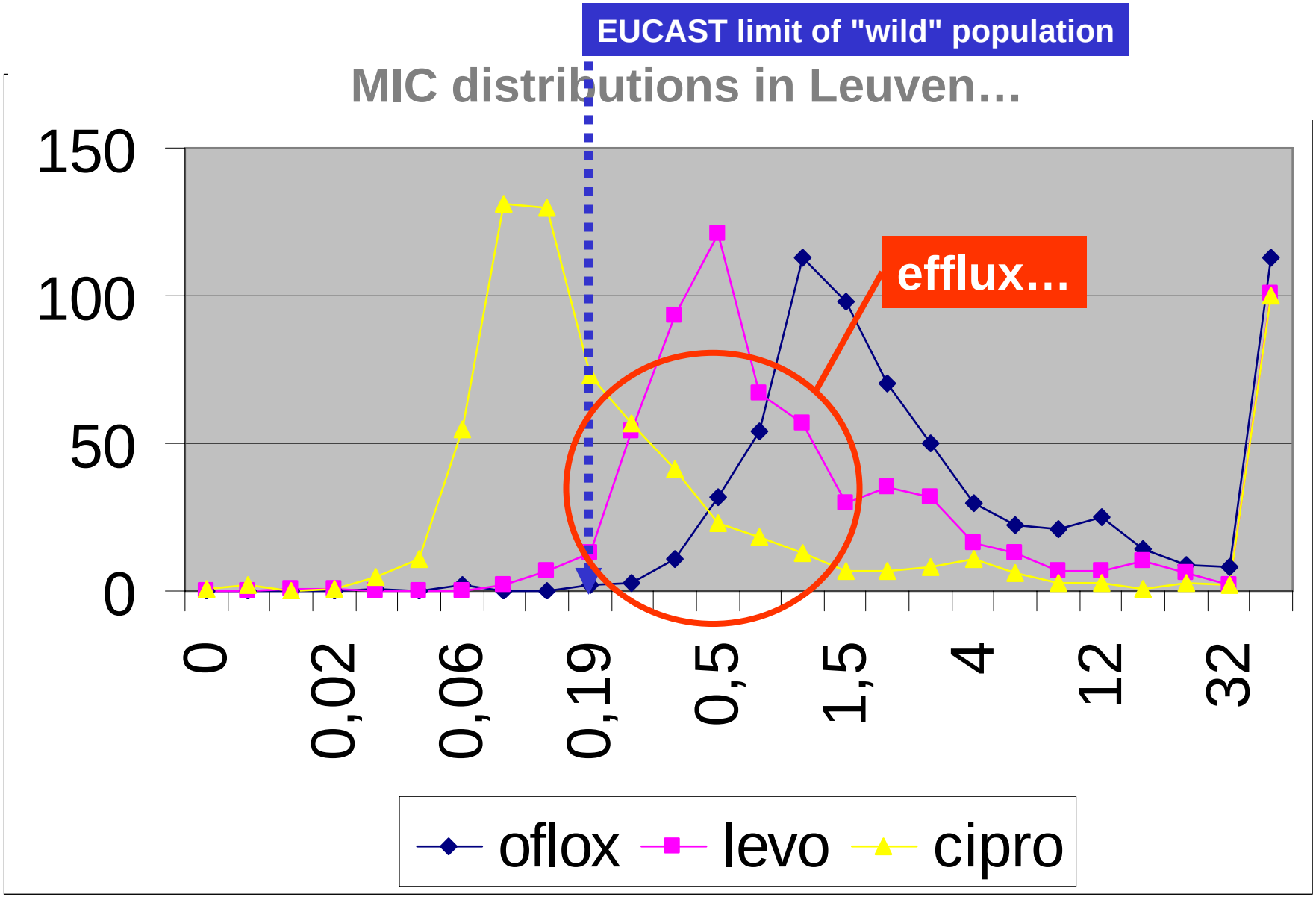
how many of your samples would actually fall here ….

But will be brought back to wild type distribution in the presence of efflux inhibitor ...

Application: look at MIC distributions where YOU are …

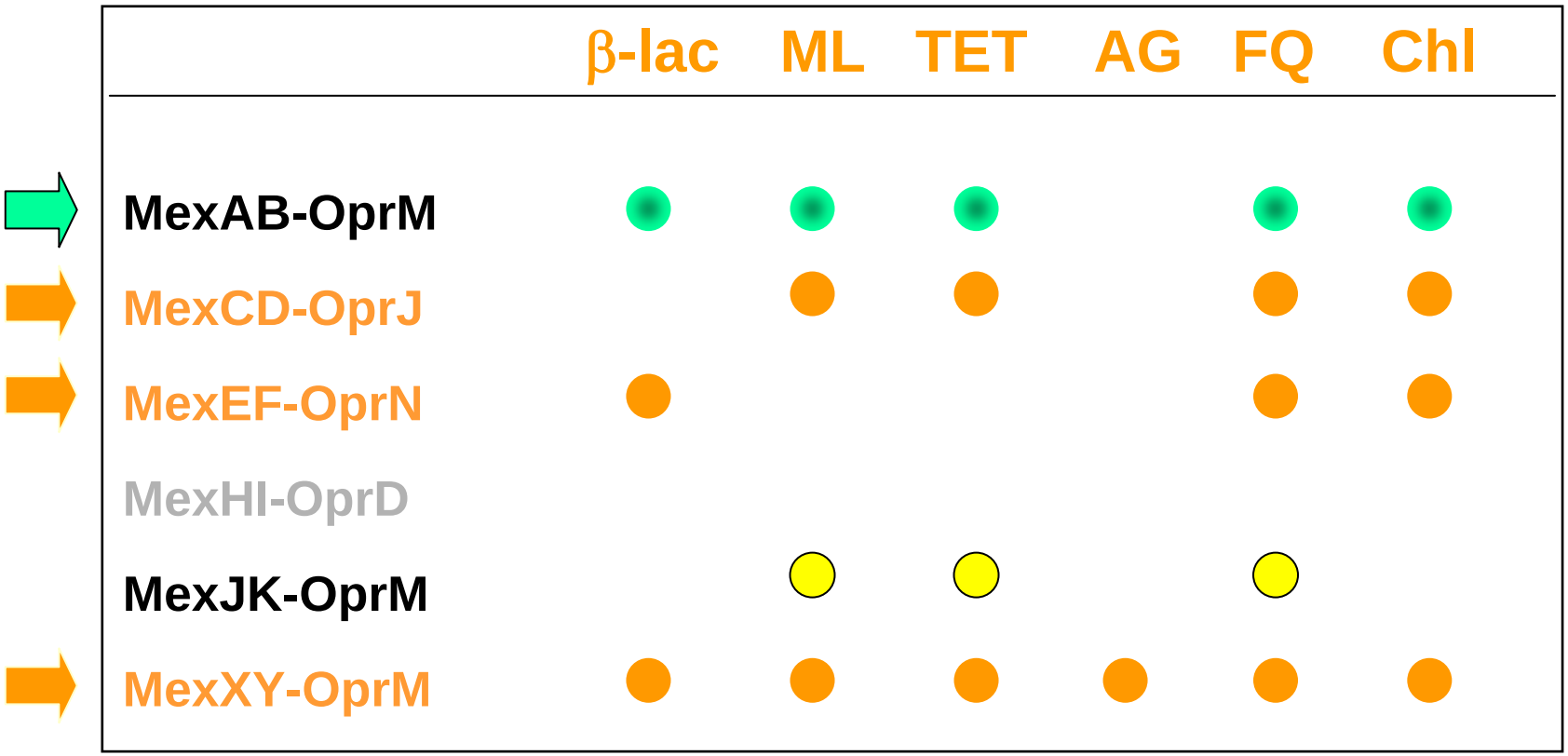


Application: look at MIC distributions where YOU are …



Why does efflux cause cross-resistance ?

(example with *P. aeruginosa*)



constitutive expression

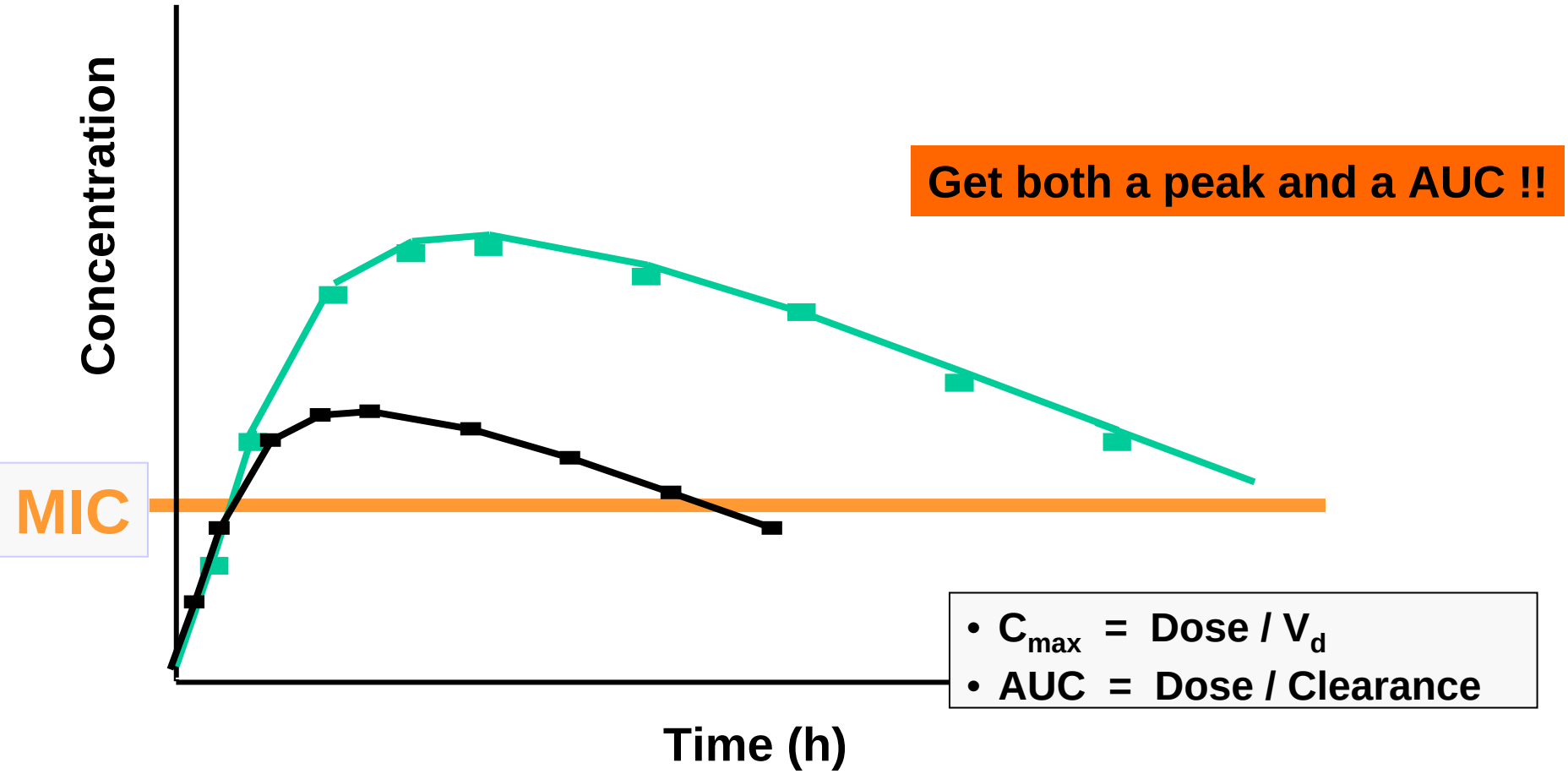
inducible expression

Van Bambeke et *al*. JAC (2003) 51:1055-65; Aeschlimann, Pharmacotherapy (2003) 23:916-24

Fluoroquinolones: get a peak and an AUC !

in order to optimize: AUC_{24h}/MIC ➡ should be > 125 *

C_{max}/MIC ➡ should be > 10



Application: choose a strong quinolone and use low enough break-points … or better … ask for an MIC and use PK/PD …

Drug	Typical daily dosage[a]	Typical PK values		Proposed PK/PD upper limit of sensitivity (μg/ml) for	
		C_{max} in mg/L total/free (dose)	$AUC_{24\ h}$ (mg × h/L) total/free	Efficacy[b]	Prevention of resistance[c]
Norfloxacin	800 mg	1.4/1.1 (400 mg PO)	14/11	0.1–0.4	0.1
Ciprofloxacin	1000 mg	2.5/1.75 (500 mg PO)	24/18	0.2–0.8	0.2
Ofloxacin	400 mg	4/3 (400 mg PO)	40/30	0.3–0.9	0.4
Levofloxacin	500 mg	4/2.8 (500 mg PO)	40/28	0.3–0.9	0.3
Moxifloxacin	400 mg	3.1/1.8 (400 mg PO)	35/21	0.2–0.7	0.2

Van Bambeke F, Michot JM, Van Eldere J, Tulkens PM.
Quinolones in 2005: an update. Clin Microbiol Infect. 2005 Apr;11(4):256-80. PMID: 15760423

Fluoroquinolones downsides in a (scientific) nutshell and how to cope with them

- true risk of emergence of resistance
  - ➔ have local epidemiological surveys
  - ➔ have cultures and susceptibility data (MIC) for all isolates in difficult situations
  - ➔ dose appropriately ...
  - ➔ use potent (not weak) quinolones...
  - ➔ do not use if not needed...
- a few side effects
  - ➔ avoid populations at risk

How do we go from here to clinical practice ?

European Urology

Eur Urol 2001;40:576–588

EAU Guidelines for the Management of Urinary and Male Genital Tract Infections [1]

Urinary Tract Infection (UTI) Working Group of the Health Care Office (HCO) of the European Association of Urology (EAU)

Members of the UTI Working Group: Kurt G. Naber (Chairman), Bo Bergman, Michael C. Bishop, Truls E. Bjerklund-Johansen, Henry Botto, Bernard Lobel, F. Jimenez Cruz, Francesco P. Selvaggi

How do we go from here to clinical practice ?

Table 2. Recommendations for antimicrobial therapy in urology [modified according to Naber et al., Chemother J 2000;9:165–170]

Diagnosis	Most frequent pathogen	Initial, empiric antimicrobial therapy	Therapy duration
Cystitis, acute, uncomplicated	*E. coli* *Klebsiella* *Proteus* *Staphylococcus*	Trimethoprim/sulfamethoxazole Fluoroquinolone[a] Alternatives: Fosfomycin trometamol Pivmecillinam Nitrofurantoin	3 days 3 days 1 day 7 days 7 days
Pyelonephritis, acute, uncomplicated	*E. coli* *Proteus* *Klebsiella* Other Enterobacteria *Staphylococcus*	Fluoroquinolone[a] Cephalosporin Gr. 2/3a Alternatives: Aminopenicillin/BLI Aminoglycoside	7–10 days

[a] Fluroquinolone with mainly renal excretion; BLI = β-lactamase inhibitor.

How do we go from here to clinical practice ?

Table 2. Recommendations for antimicrobial therapy in urology [modified according to Naber et al., Chemother J 2000;9:165–170]

Diagnosis	Most frequent pathogen	Initial, empiric antimicrobial therapy	Therapy duration
UTI with complicating factors	*E. coli* *Enterococcus* *Staphylococcus*	Fluoroquinolone[a] Aminopenicillin/BLI Cephalosporin Gr. 2 Cephalosporin Gr. 3a Aminoglycoside	3–5 days after defervescence or control/elimination of complicating factor
Nosocomial UTI	*Klebsiella* *Proteus*	In case of failure of initial therapy within 1–3 days or in clinically severe cases:	
Pyelonephritis, acute, complicated	*Enterobacter* Other Enterobacteria *Pseudomonas* *(Candida)*	Anti-*Pseudomonas* active: Fluoroquinolone, if not used initially Acylaminopenicillin/BLI Cephalosporin Gr. 3b Carbapenem ± Aminoglycoside In cases of *Candida* Fluconazole	

[a] Fluroquinolone with mainly renal excretion; BLI = β-lactamase inhibitor.

How do we go from here to clinical practice ?

Table 2. Recommendations for antimicrobial therapy in urology [modified according to Naber et al., Chemother J 2000;9:165–170]

Diagnosis	Most frequent pathogen	Initial, empiric antimicrobial therapy	Therapy duration
Prostatitis, acute, chronic	*E. coli* Other *Enterobacteria* *Pseudomonas*	Fluoroquinolone[a] Alternative in acute bacterial prostatitis: Cephalosporin Gr. 2	Acute: 2 weeks Chronic: 4–6 weeks or longer
Epididymitis, acute	*Enterococcus* *Staphylococcus* *Chlamydia* *Ureaplasma*	Cephalosporin Gr. 3a/b In case of *Chlamydia* or *Ureaplasma:* Doxycyline Macrolide	
Urosepsis	*E. coli* Other *Enterobacteria* After urological interventions– multiresistant pathogens: *Proteus* *Serratia* *Enterobacter* *Pseudomonas*	Cephalosporin Gr. 3a/b Fluorquinolone[a] Anti-*Pseudomonas* active Acylaminopenicllin/BLI Carbapenem ±Aminoglycoside	3–5 days after defervescence or control/elimination of complicating factor

[a] Fluroquinolone with mainly renal excretion; BLI = β-lactamase inhibitor.

What about Belgium ?

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Learning appropriate use of antibiotics (PK/PD and guidelines): a CD-rom course for healthcare professionals and students

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Laboratoire de microbiologie, cliniques universitaires UCL, Mont-Godinne

ABSTRACT

Objectives: In a context of growing resistance and limited supply of new molecules, a rational use of antibiotics should be a high priority. Our objective is to train healthcare professionals and students in PK/PD and in a correct implementation of guidelines, since this could help to improve antibiotic use in both short and mid-terms.

Methods: We developed a PK/PD – guidelines course on CD-rom, targeted to both physicians and pharmacists but also usable by students. The course was prepared by a team of 2 pharmacists, 1 clinical microbiologist, and 1 pharmacologist. Sources of information were (i) textbooks, review papers and primary papers by internationally recognized experts (ii) materials presented at training workshops of the International Society for Antiinfective Pharmacology (ISAP, www.isap.org) during the last 3 years, (iii) national and, if not available, international guidelines for the management of respiratory tract or urinary tract infections.

Results: The course is organized as a series of Power Point presentations covering in a progressive fashion the followings topics : (1) bases in microbiology (in vitro properties of antibiotics); (2) pharmacokinetics (definition of the main parameters), (3) pharmacodynamics, with (A) the concepts, (B) the methods and pertinent models, and (C) the data, including the parameters to take into account to optimize the dosage of the main antibiotic classes; (4) resistance, including (A) the main mechanisms and (B) the use of pharmacodynamics to avoid the selection of resistance; (5) the appropriate use (including appropriate dosages) of antibiotics in (A) respiratory tract and (B) urinary tract infections.

Conclusions: This course promotes continuous education in the pharmacology and pharmacotherapy of antibiotics, in a format easily usable for courses and seminars to both students and professionals.

INTRODUCTION

Optimizing the use of current antibiotics based on pharmacokinetics and pharmacodynamics and rational application of guidelines can contribute to the limitation of resistance development.

In this respect, education of students and healthcare professionals appears as a priority and can be facilitated by making available to them easy-to-consult informative supports.

OBJECTIVES

- to develop an educational programme in which pharmacists and infectious disease specialists train healthcare professionals and students in PK/PD and in a correct implementation of guidelines.
- to distribute to people following this course a CD-rom as a support that can be consulted at any time.

ACKNOWLEDGMENTS:
We thank W. Peetermans (KUL- UZ Gasthuisberg) for useful comments and Bayer Belgium for financial support

CONTENT OF THE CD-rom

Programme, please ...

1. Basic introduction to key microbiological parameters
2. Pharmacokinetics (PK) : the basics
3. Pharmacodynamics (PD)
   - A. the concepts
   - B. the methods
   - C. actual data on the main classes of antibiotics
4. Resistance
   - A. mechanisms and epidemiology
   - B. PK/PD to fight resistance
5. Clinical guidelines or how to implement PK/PD ...

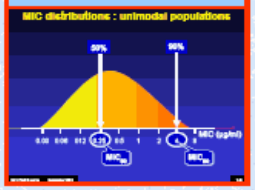
References

What you always wished to know but never dared to ask because it seemed so basic ... and did not know how to begin with all that stuff ...

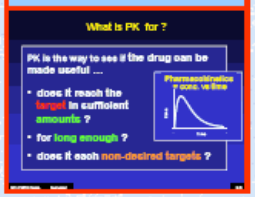
25 MB of information ...

Name	Size
0-Introduction-EN.ppt	2.632 KB
1-Microbiology-Basics-EN.ppt	1.552 KB
2-Pharmacokinetics-EN.ppt	468 KB
3A-Pharmacodynamics-concepts-EN.ppt	444 KB
3B-Pharmacodynamics-methods-EN.ppt	3.919 KB
3C-Pharmacodynamics-actual-data-EN.ppt	3.196 KB
4A-Resistance-mechanisms-EN.ppt	2.164 KB
4B-Resistance-and-PK-PD-EN.ppt	1.959 KB
5A-Guidelines-principles-EN.ppt	1.586 KB
5B-Guidelines-respiratory-tract-EN.ppt	2.180 KB
5C-Guidelines-urinary-tract-EN.ppt	2.353 KB

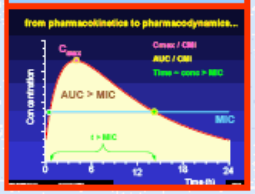
SECTION 1. DEFINITION OF MICROBIOLOGICAL PARAMETERS



SECTION 2. DEFINITION OF PK PARAMETERS

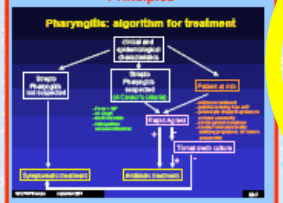


SECTION 3. DEFINITION OF PD PARAMETERS

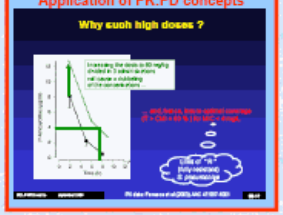


SECTION 4. GUIDELINES

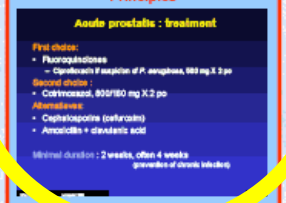
GUIDELINES RESPIRATORY TRACT INFECTIONS Principles



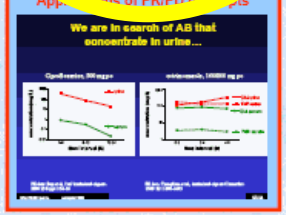
Application of PK:PD concepts



GUIDELINES URINARY TRACT INFECTIONS Principles



Application of PK/PD concepts



WHAT WE HOPE AND WHAT WE WILL DO:

- the CD-rom should be a continuous information source that
  - could be used for teaching pharmacology and pharmacotherapy of antibiotics to students and healthcare professionals.
  - may be easily consulted by healthcare professionals at any moment.
- We will regularly update it and plan to evaluate its impact on education of students and on the quality of antibiotic prescribing of junior physicians

Ampe et al., 15th ECCMID, 2005

Complicated cystitis:

Empiric therapy

Large spectrum antibiotic

- First choice: fluoroquinolone
  - Large spectrum
  - High concentratie in urine and urinary tract

Directed therapy

- According to the results of the antibiogram
- Choose antibiotic with the smallest spectrum

Duration of treatment:
7 to 14 days

Mild pyelonephritis

- Empiric therapy

  First choice:

  - **Oral fluoroquinolon in monotherapy**
  - **Ambulant therapy if possible**:
    - Patient can take oral medication
    - No severe sepsis
    - No renal insufficiency

  - No association of aminoglycoside except in severe sepsis
  - No first generation fluoroquinolone because of low serum concentrations
  - No ampicillin or first generation cephalosporins (or co-trimoxazole) because of resistance pattern in Belgium

  - If contra-indication to fluoroquinolones:
    - amoxicillin-clavulanic acid
    - Second generation cephalosporins
    - temocillin

Severe pyelonephritis (hospital)

- Empiric therapy
  - first choice:
    - Fluoroquinolone
    - Initially parenteral therapy
    - Switch IV-oral and ambulant therapy when possible
  - Alternatives:
    - Temocillin
    - Second generation cephalosporin
    - Amoxicilline-clavulanic acid
    - if septic shock: Association of aminoglycoside to cephalo-2 or amoxiclav

Directed therapy

Based on urine culture with antibiogram

- first choice :
  - Fluoroquinolone
  - Cotrimoxazol
  - Only if enterococ:
    - amoxicillin
    - ampicillin
    - If necessary combination with aminoglycoside
- Ambulant therapy: see next slide

Switch IV-per os and ambulant treatment

- Based on:
  - Clinical recovery (symptoms and fever disappeared)
  - Antibiogram of the urine culture
  - If possible after 24-48 h
  - Ambulant therapy if possible:
    - Patient can take oral medication
    - No severe sepsis
    - No renal insufficiency
  - Patients who fail to improve after 48-72 h of ambulant therapy based on urine culture and the initial antibiotic:
    - parenteral fluoroquinolone or
    - alternative

Regimens

Antibiotic	duration	dose
Ciprofloxacin	7 – 14 days*	250-500 mg X 2, po
		200-400 mg X 2, IV
Levofloxacin		250-500 mg X1, po or IV
Ofloxacin		200-400 mg X1, po or IV
Amoxi-clav	14 days	500 mg X 3, po
		1 g X 4, IV
Cefuroxim		500 mg X 2, po
		750 mg – 1.5 g X 3, IV
Temocillin		1 g X 2, IV
Cotrimoxazol		160/800 mg X2, po of IV
Ampicillin		1 g X 4, IV
Amoxicillin		400 mg X 3 of X 4, po

* 7 days: mild infection; 14 days: severe infection

BAPCOC guidelines, 2002

Severe pyelonephritis in the pregnant woman

- allowed
  - Nitrofurantoin
  - Cephalosporins
  - Amoxicillin
  - Cotrimoxazol (folic acid antagonism minimal if short treatment using recommanded dose)

- Not allowed
  - Fluoroquinolones
  - Cotrimoxazol during last weeks of pregnancy (risic op hyperbilirubinemia and icterus in the neonatus)
  - Fosfomycin (avoid during first 3 months)

Acute prostatis : treatment

First choice:

- Fluoroquinolones
  - Ciprofloxacin if suspicion of *P. aeruginosa,* 500 mg X 2 po

Second choice :

- Cotrimoxazol, 800/160 mg X 2 po

Alternatieves:

- Cephalosporins (cefuroxim)
- Amoxicillin + clavulanic acid

Minimal duration : 2 weeks, often 4 weeks

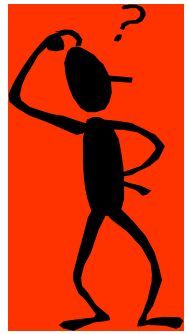
(prevention of chronic infection)

Chronic prostatis: treatment

Problems:

- Little antibiotics penetrate well in the non-inflammated prostate
- Infection focus can consist of little calculi or abcesses that are difficult to treat.
- High probability of relapsing infections

➔DIFFICULT TO TREAT



Chronic prostatis: antibiotic treatment

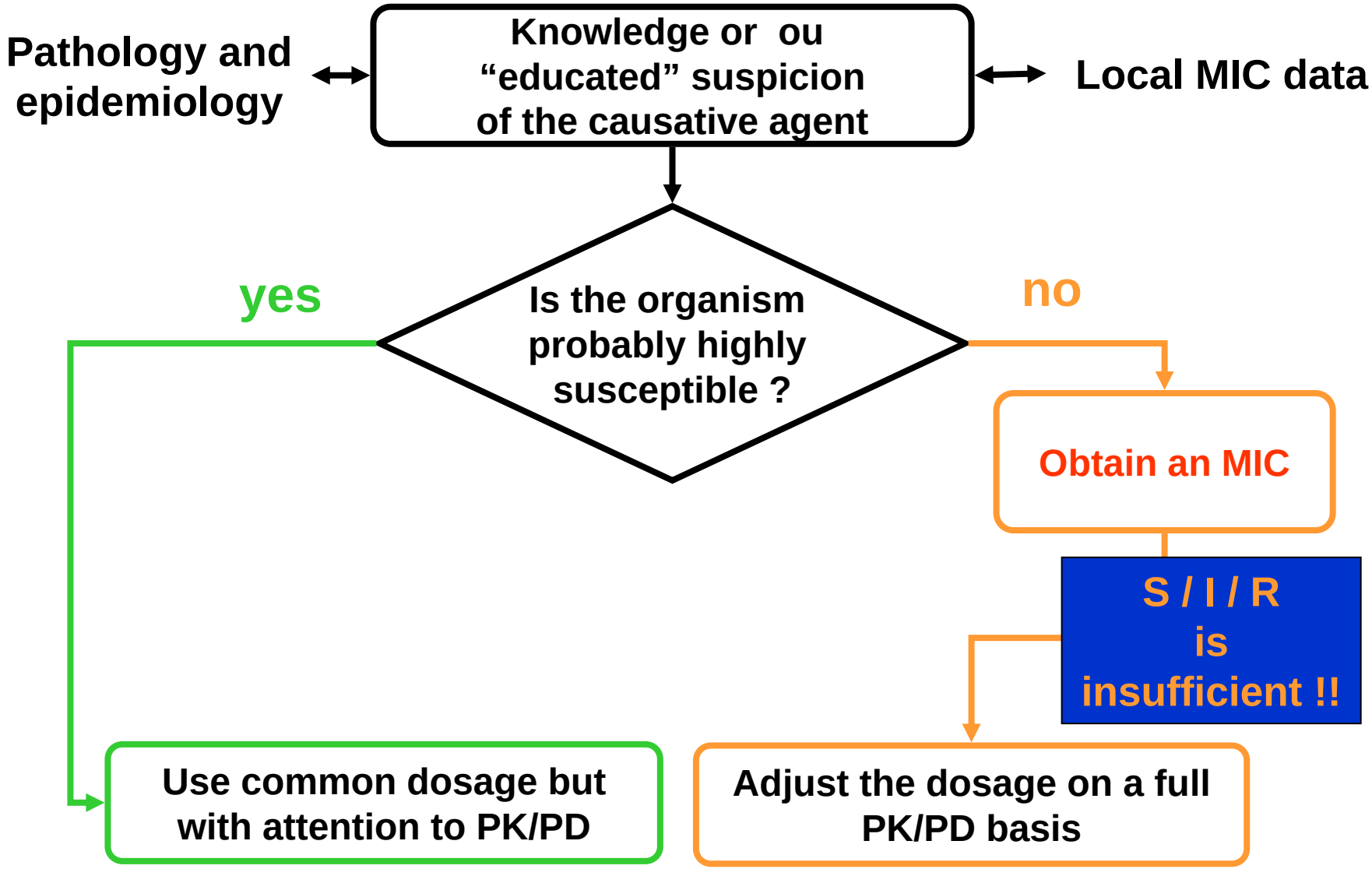
Primary antibiotics

- Only lipophilic and basic molecule penetrate the acidic environnement of the prostate:

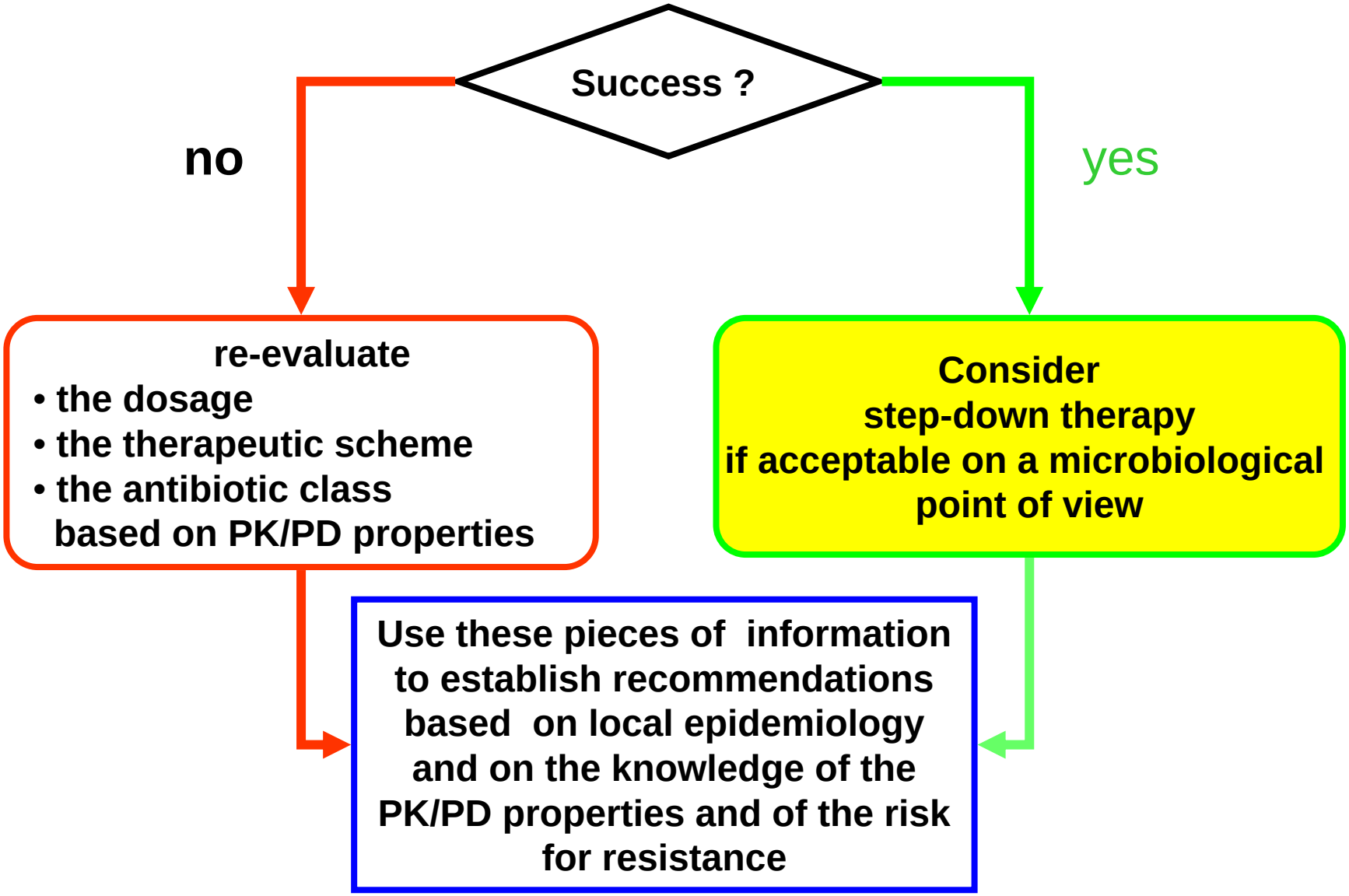
  - **Good for:**
    - ciprofloxacin: (500 mg 2X/day): 30 days
    - Trimethoprim (800/160 mg 2x/day): 3 months
    - Macrolides (not for empiric therapy because of spectrum)

  - **Bad for:**
    - penicillins
    - cephalosporins
    - Tetracyclins
    - Nitrofurantoin
    - vancomycin

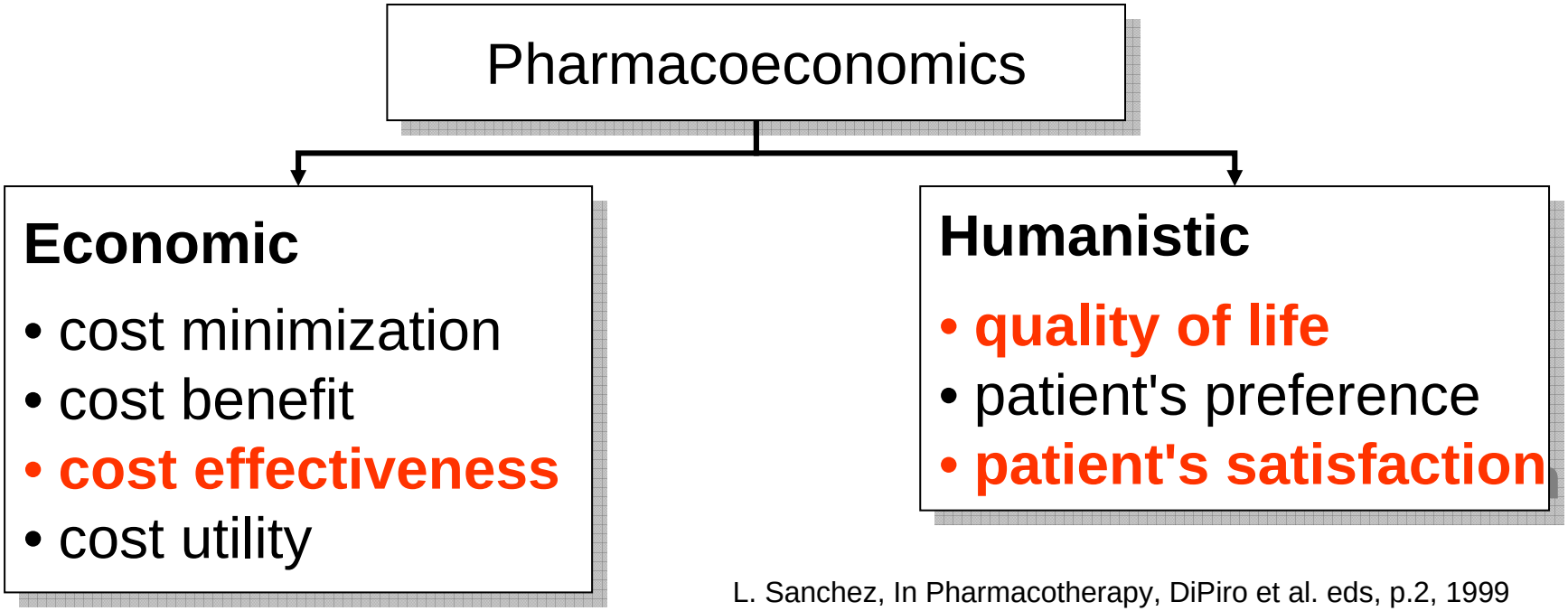
A clinical algorithm ...



A clinical algorithm (follow.) ...



And what about health care costs ?

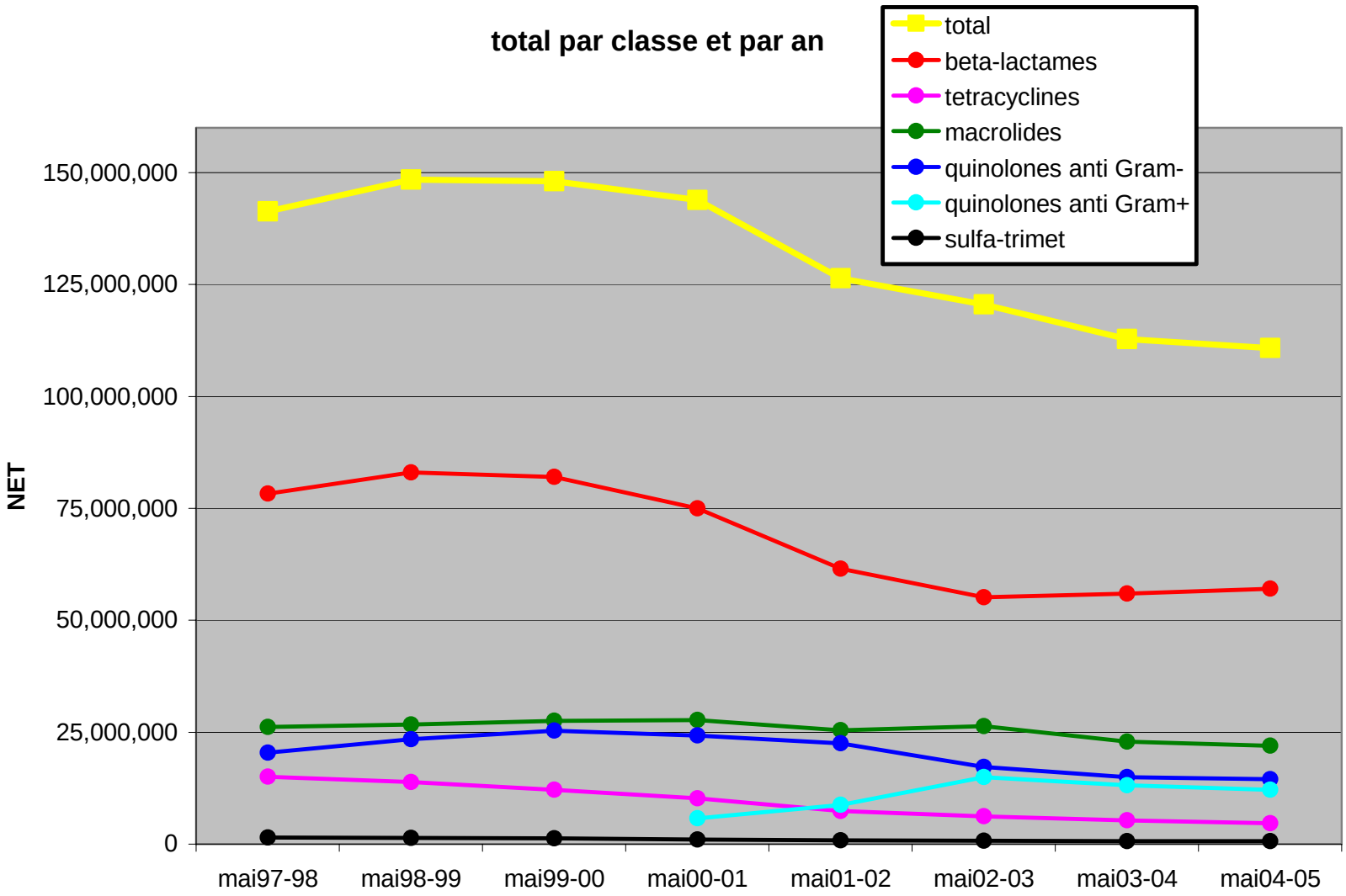


L. Sanchez, In Pharmacotherapy, DiPiro et al. eds, p.2, 1999

- Pharmacoeconomics of antibiotics is still largely underdeveloped outside the USA (but US-based models cannot easily be applied);
- However, comparisons identifying differences in
  - amount of money needed to reach a given (better ?) clinical outcome;
  - expenses related to the same (or better) quality of life and patient's satisfaction;

  may already suggest interesting avenues for further fine-tuning therapeutic guidelines

Prices in Belgium…



Rational bases for the choice of an antibiotic

- Know your LOCAL epidemiology
  - ➢ obtain MIC distributions from your microbiologists…
- know the PK profile of the drugs you consider to purchase
  - ➢ aim at obtaining > 90 % efficacy against the organisms of interest (AUC, peak, time above MIC) with a standard dosage, ...
- include a safety margin (MPC …)
- Compare products on that basis first …
- Remember that
  - no antibiotic (if possible) is the best…
  - but that treatment failures (when treatment is needed) cost a lot … (so that cheap but 2d class antibiotics may not be a bargain...)

Please, act rationally…

www.facm.ucl.ac.be

APUA
ALLIANCE FOR THE PRUDENT USE OF ANTIBIOTICS
Consumer Information | Practitioner Information

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