Pharmacodynamics of antibiotics as a means to improve and curb the emergence of resistance

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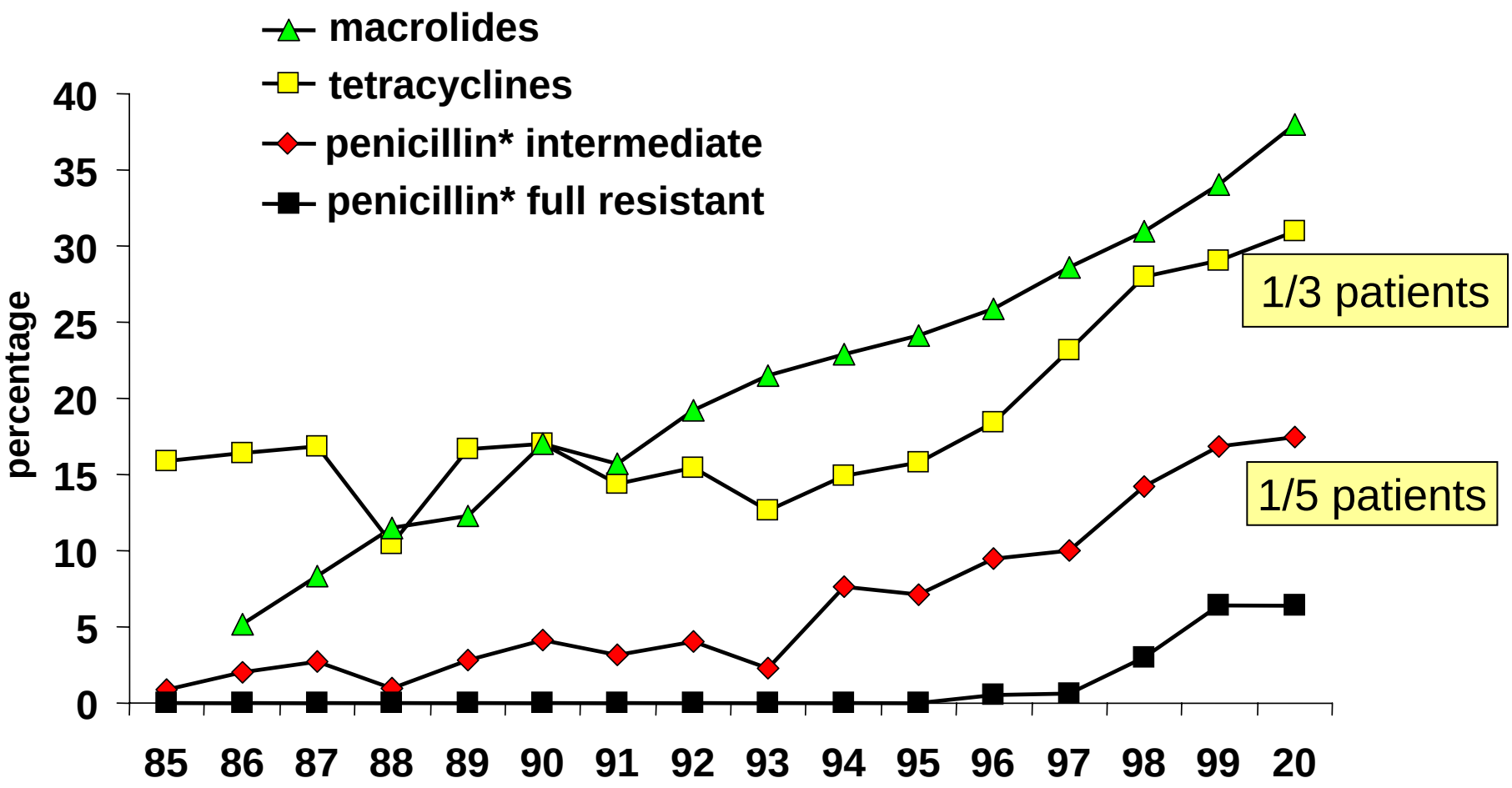
Why pharmacodynamics ?

- Rising resistance and correlation with antibiotic use …
- What is pharmacodynamics of antibiotics
- What can we do with that…
  - for the clinical laboratory and the clinician …
  - for the health authorities
- Can pharmacodynamics help in preventing (or slowing down the emergence of) resistance ? …
- Can we also reduce health care costs ? …

Resistance is the problem …

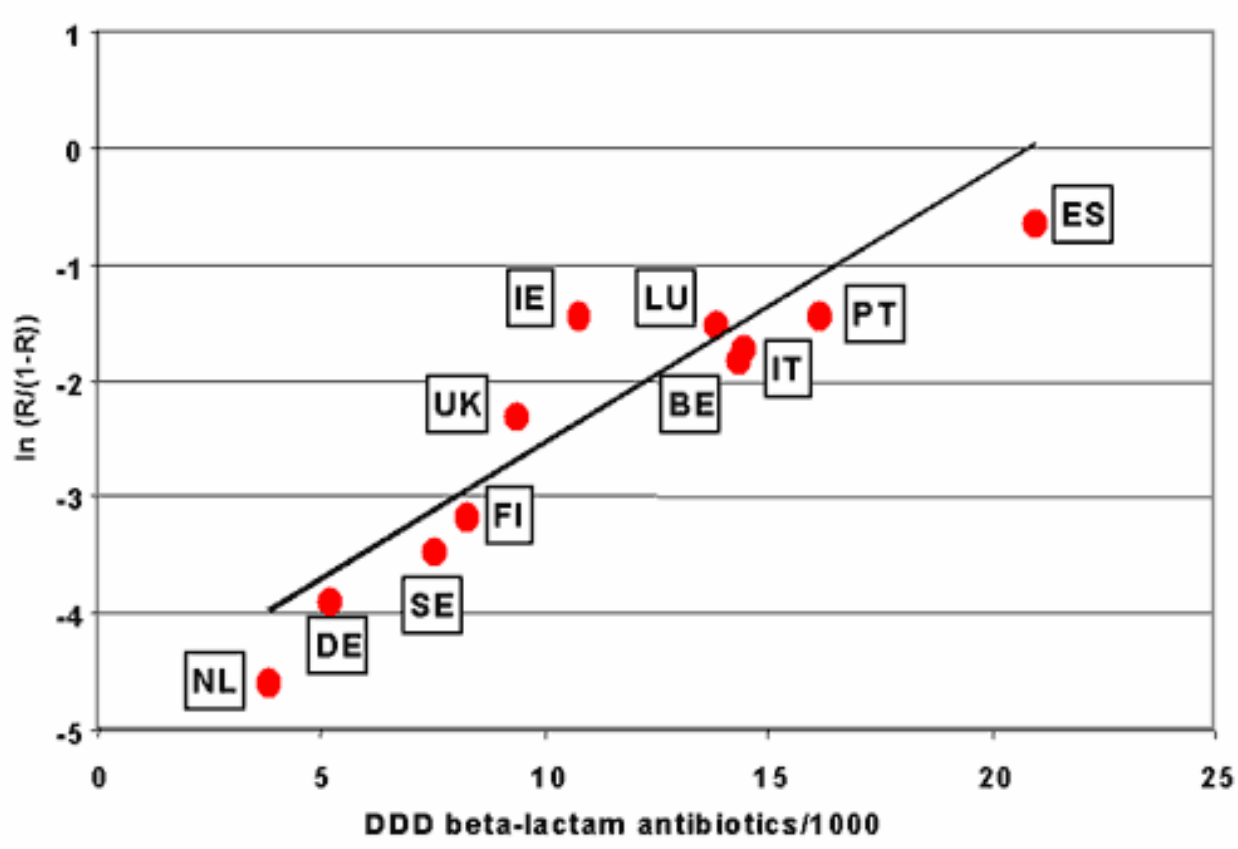
the example of the *S. pneumoniae* in Belgium



* all β-lactams (= penicillins, cephalosporins, …)

Belgian Reference Laboratory for pneumococci, Leuven, 2000

Overuse is also the problem …
the example of beta-lactams in Europe



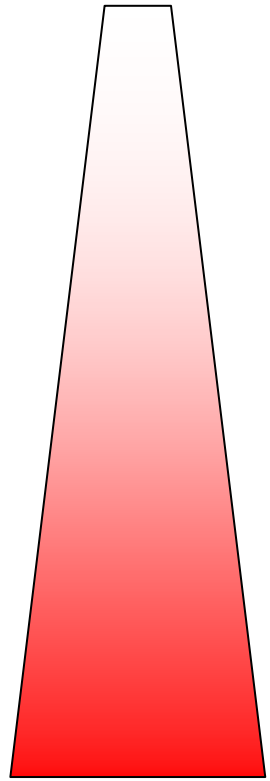
Risk of resistance to β-lactams among invasive isolates of *Streptoccus pneumoniae* regressed against outpatient sales of beta-lactam antibiotics in 11 European countries

- **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

How can you be "better" ?

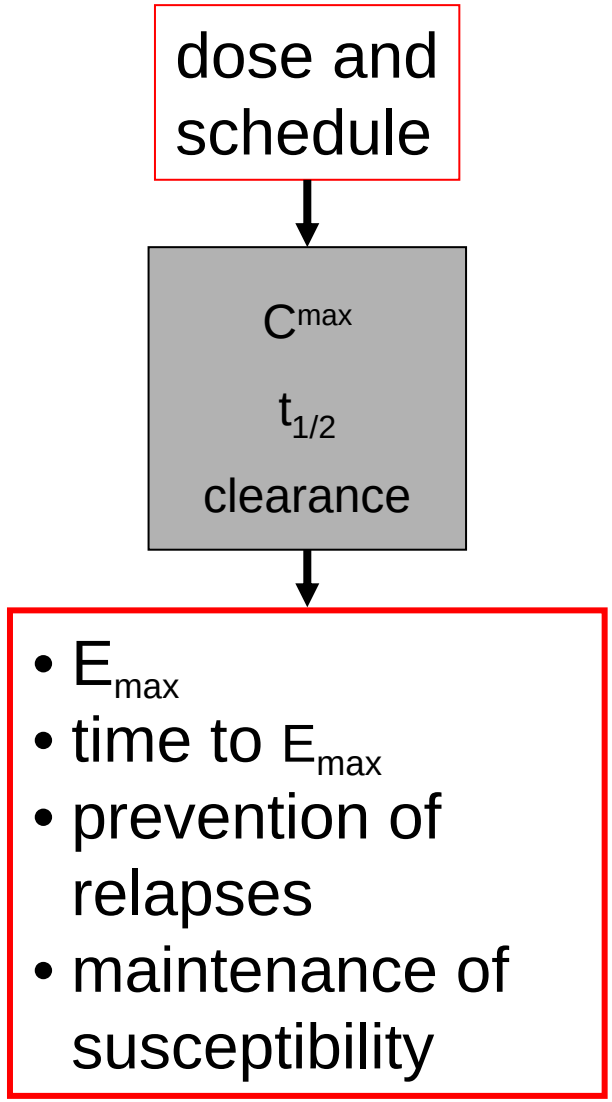
- be globally efficacious
  - ➔ **pharmacodynamics (PK/PD)**
- avoid selection of resistance
  - ➔ **"mutant prevention concentration"**



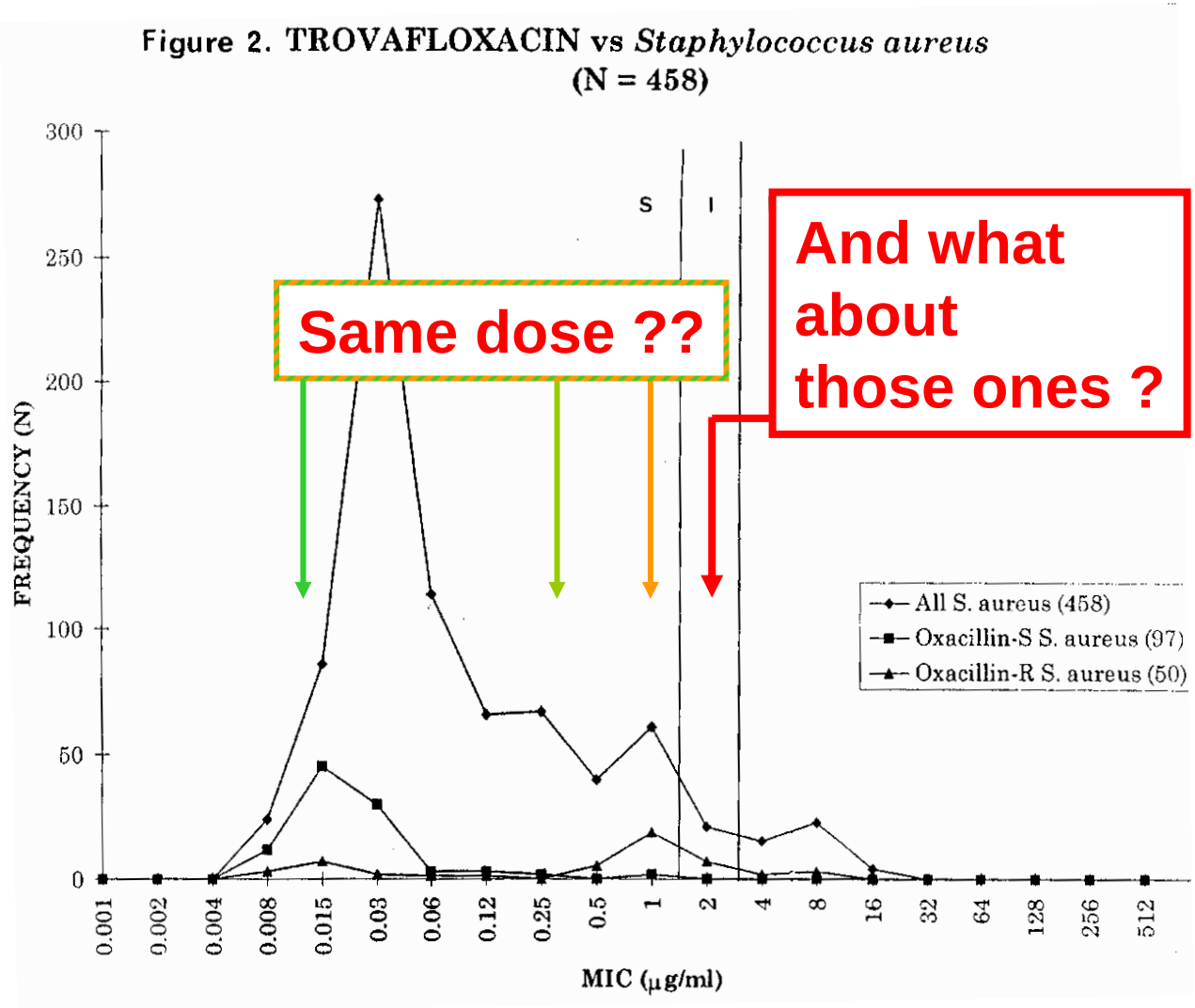
What is Pharmacokinetics / Pharmacodynamics (PK/PD) ?

- Pharmacokinetics:
  what the body does to the drug
  - ➔ absorption, distribution, serum and tissue levels elimination, …

- Pharmacodynamics (of AB):
  what the drug does to the bacteria
  - ➔ static vs. bactericidal effect, rate of kill, eradication, prevention of resistance….



The problem as seen from a question of the FDA...



Breakpoints tend to set up quantic limits in what is fundamentally a **continuous** distribution ...

And the answer by the European Agency for Evaluation of Medicinal Products (EMEA)

The European Agency for the Evaluation of Medicinal Products

25 March 1999

EMEA/9880/99 Rev. 1

EMEA Discussion Paper on Antimicrobial Resistance

London, 27 July 2000
CPMP/EWP/2655/99

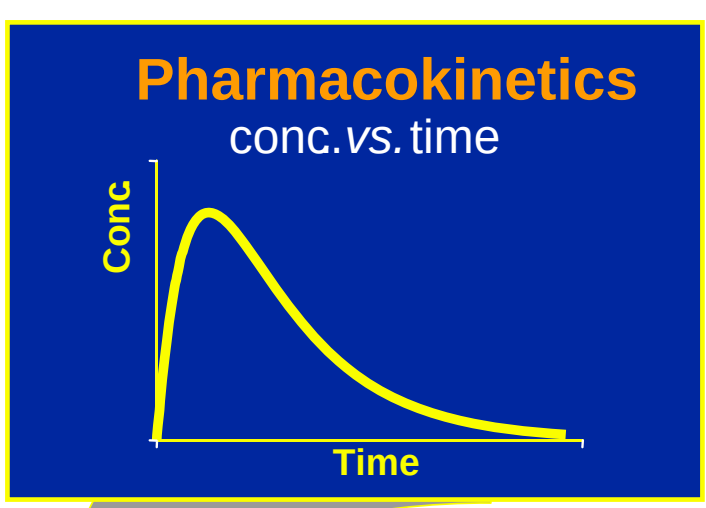
POINTS TO CONSIDER ON PHARMACOKINETICS AND PHARMACODYNAMICS IN THE DEVELOPMENT OF ANTIBACTERIAL MEDICINAL PRODUCTS

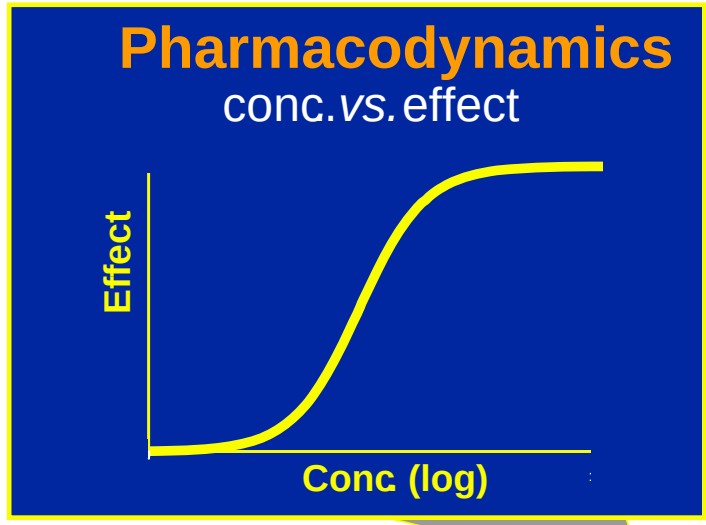
What are "Pharmacodynamic indices" ?

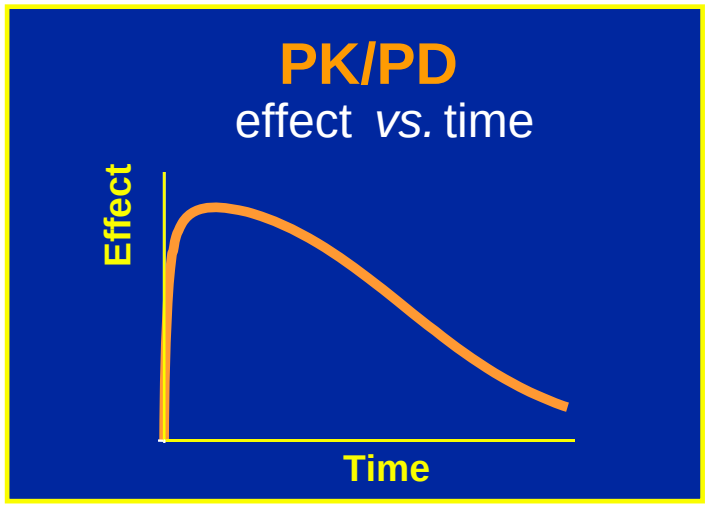
- all drugs have pharmacokinetic properties that describe the way the body handles them
  - antibiotics are no exception …
  - you need to consider the C_{max} and the clearance (that will result in a given half-life) to describe the **drug exposure**

- a drug needs to bind to its target to act …
  - antibiotics are again no exception, but the target is the bacteria …
  - the antibiotics can be studied in vitro to look at the extent of their action at increasing concentrations (like the binding of a ligand to its receptor in conventional pharmacology). This is **drug pharmacodynamics**…

Pharmacokinetics ➔ Pharmacodynamics...

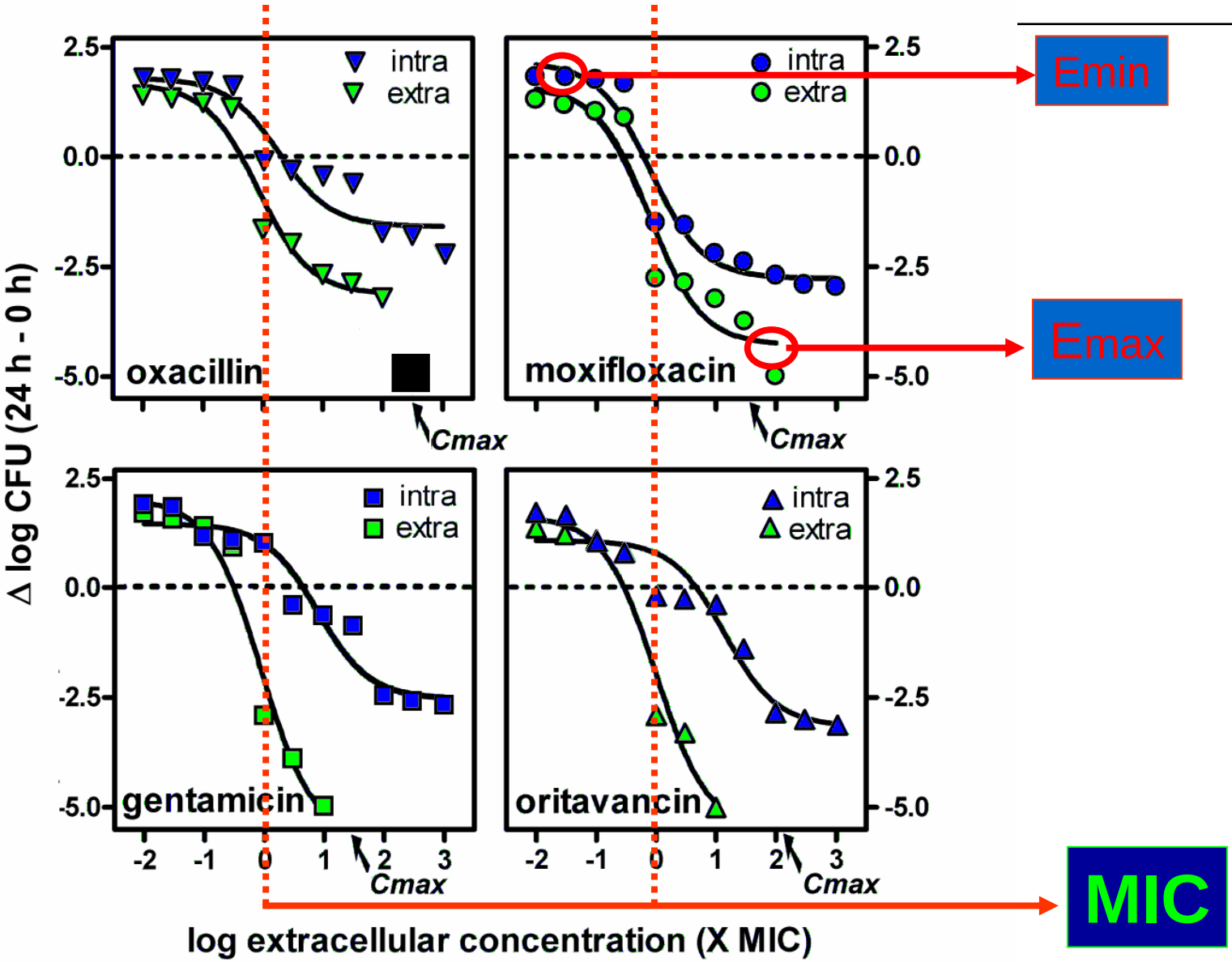






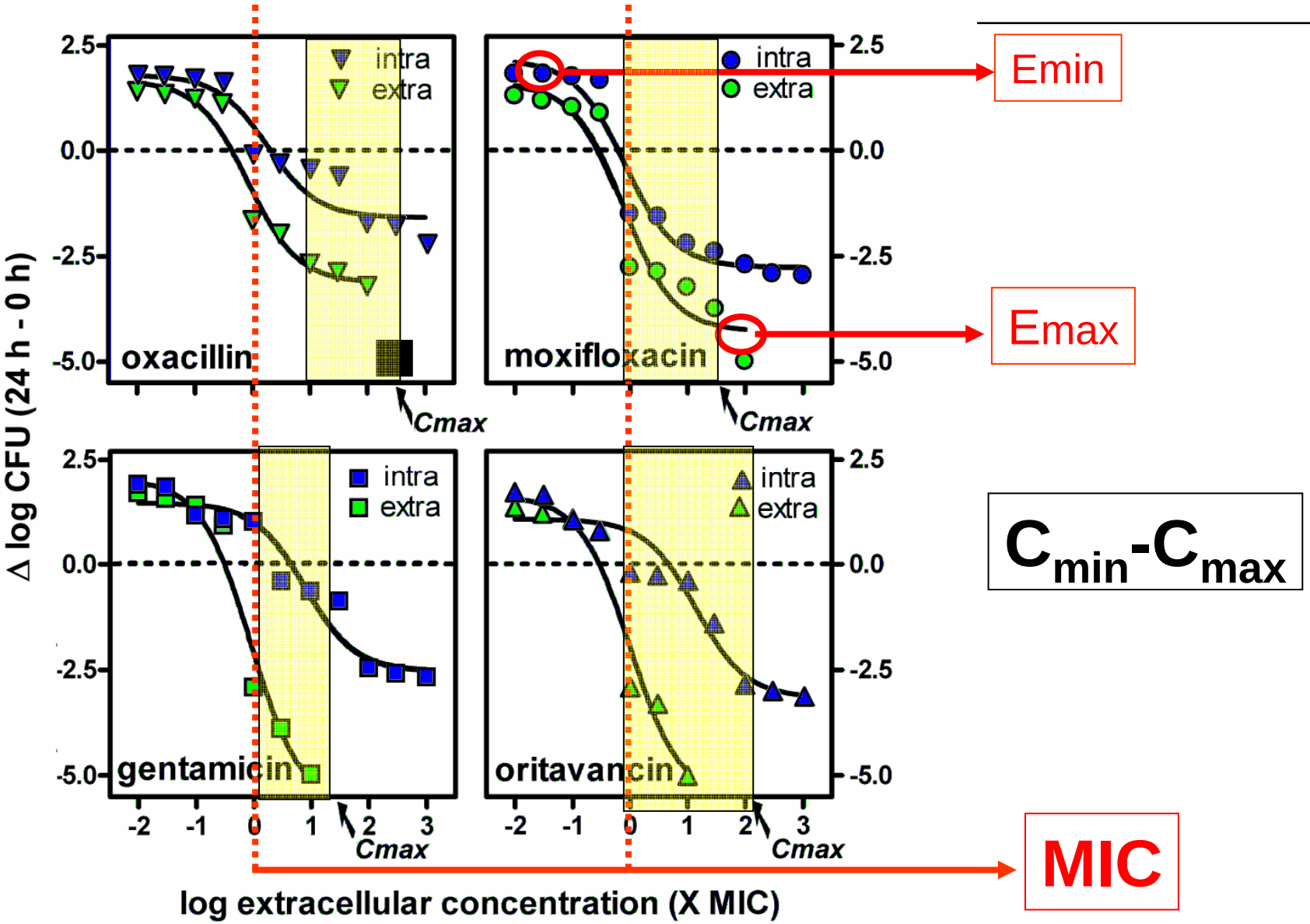
H. Derendorf,
ISAP PK/PD workshop 2002

Example of a pharmacodynamic relationship



Barcia-Macay et al. Antimicrob. Agents Chemother. 2006; 50(3):841-51

And what if we put pharmacokinetics ?



Barcia-Macay et al. Antimicrob. Agents Chemother. 2006; 50(3):841-51

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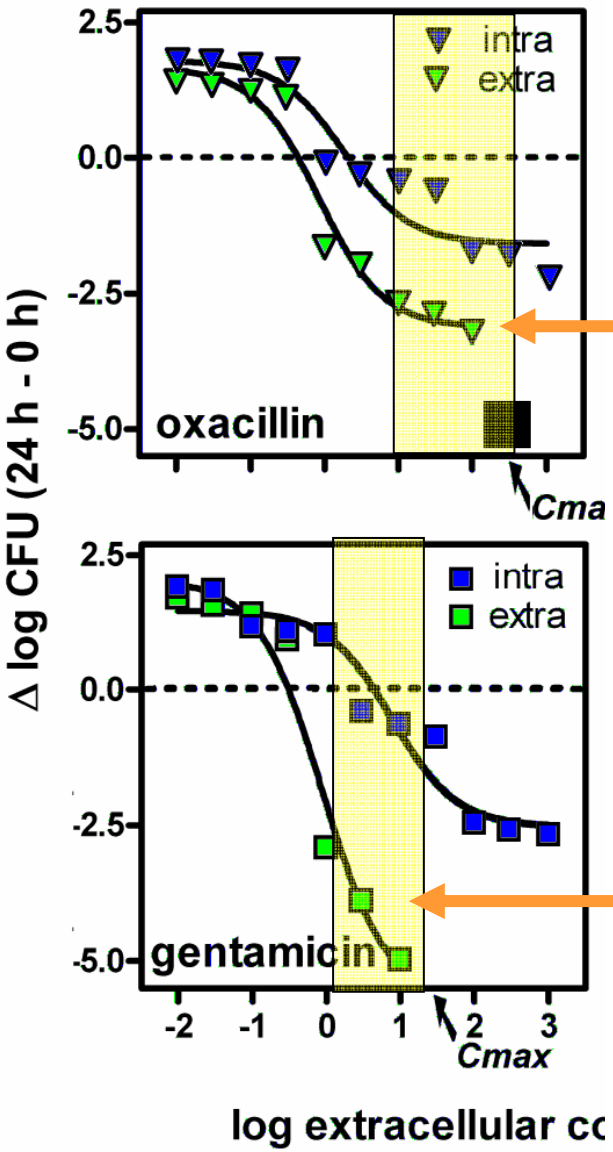


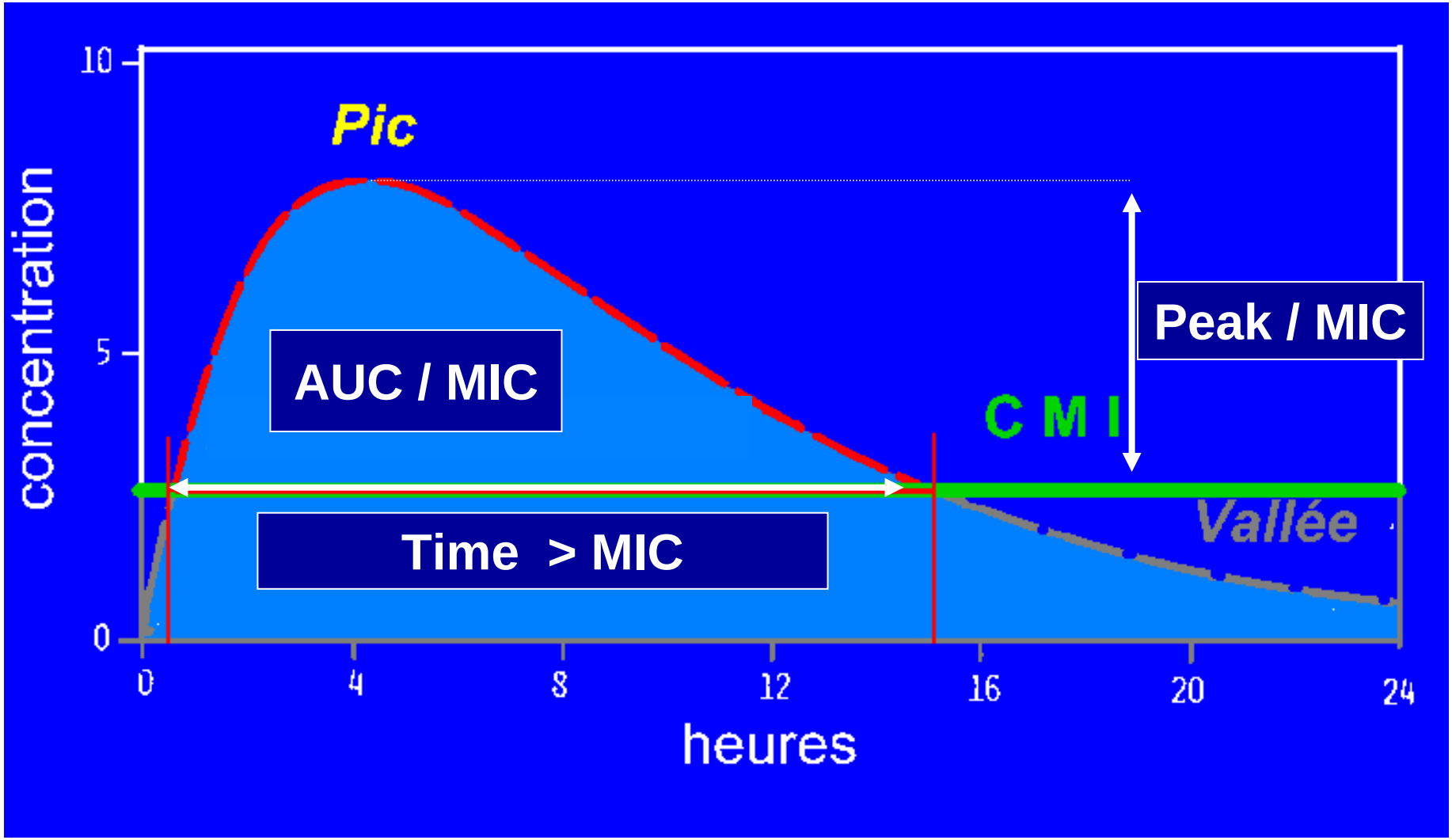
low concentration dependency

C_{min}-C_{max}

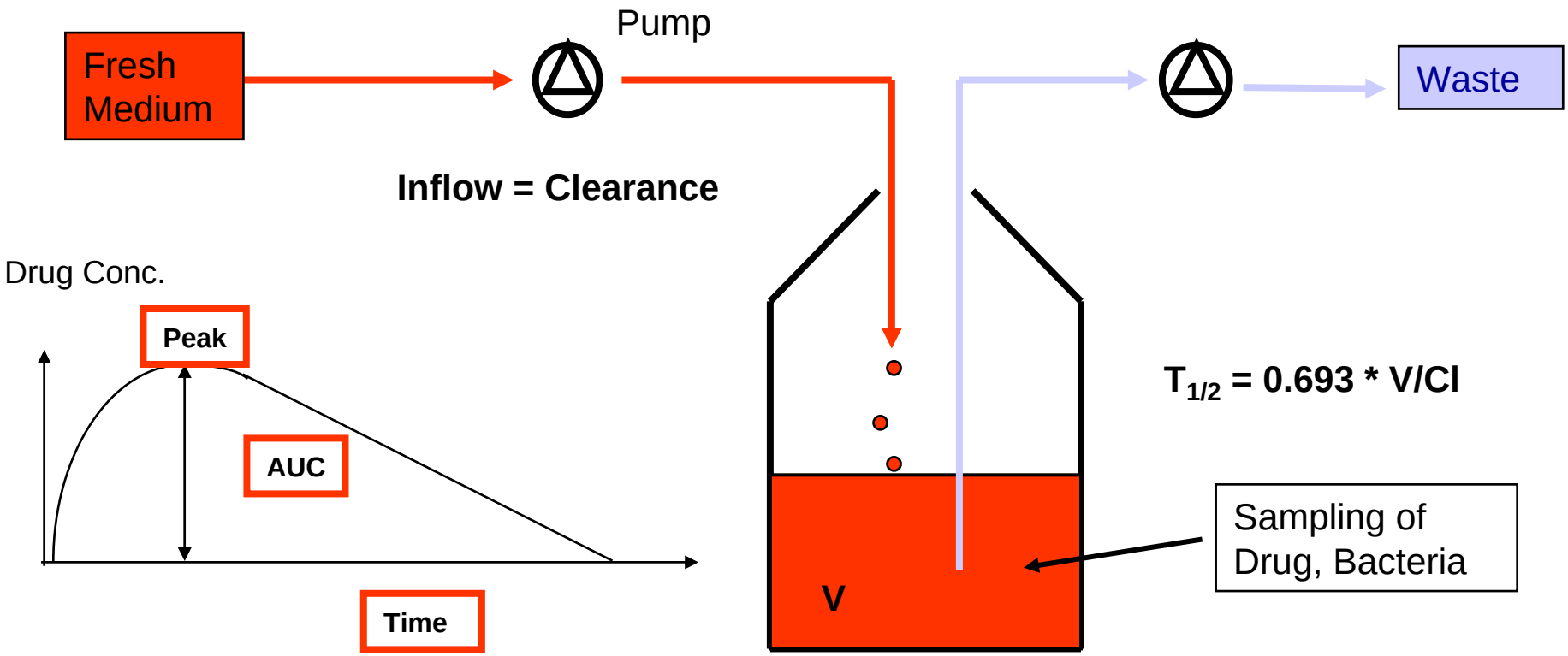
high concentration dependency

Barcia-Macay et al. Antimicrob. Agents Chemother. 2006; 50(3):841-51

From Pharmacokinetics to Pharmacodynamics of AB …



A simple dynamic model …



Adapted from M.N. Dudley, ISAP / FDA Workshop, March 1st, 1999

Pharmacodynamics: the basic question …

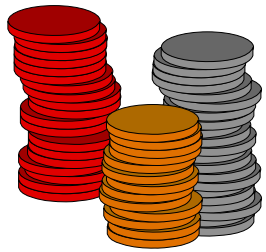
Which antibiotics are

- **time-**
- **AUC**
- **peak-**

dependent

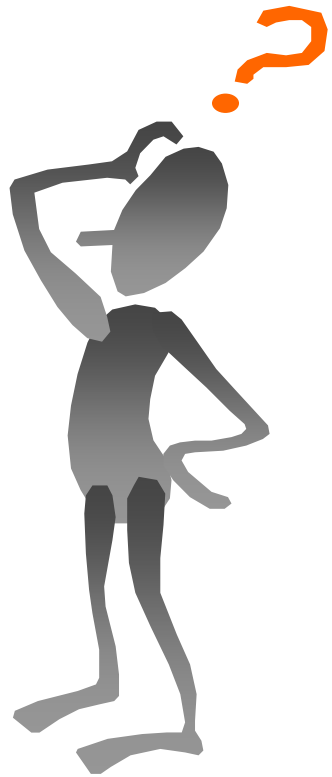
in

clinically meaningful conditions ?



Main PK/PD properties of antibiotics

Available antibiotics can be divided in 3 groups :



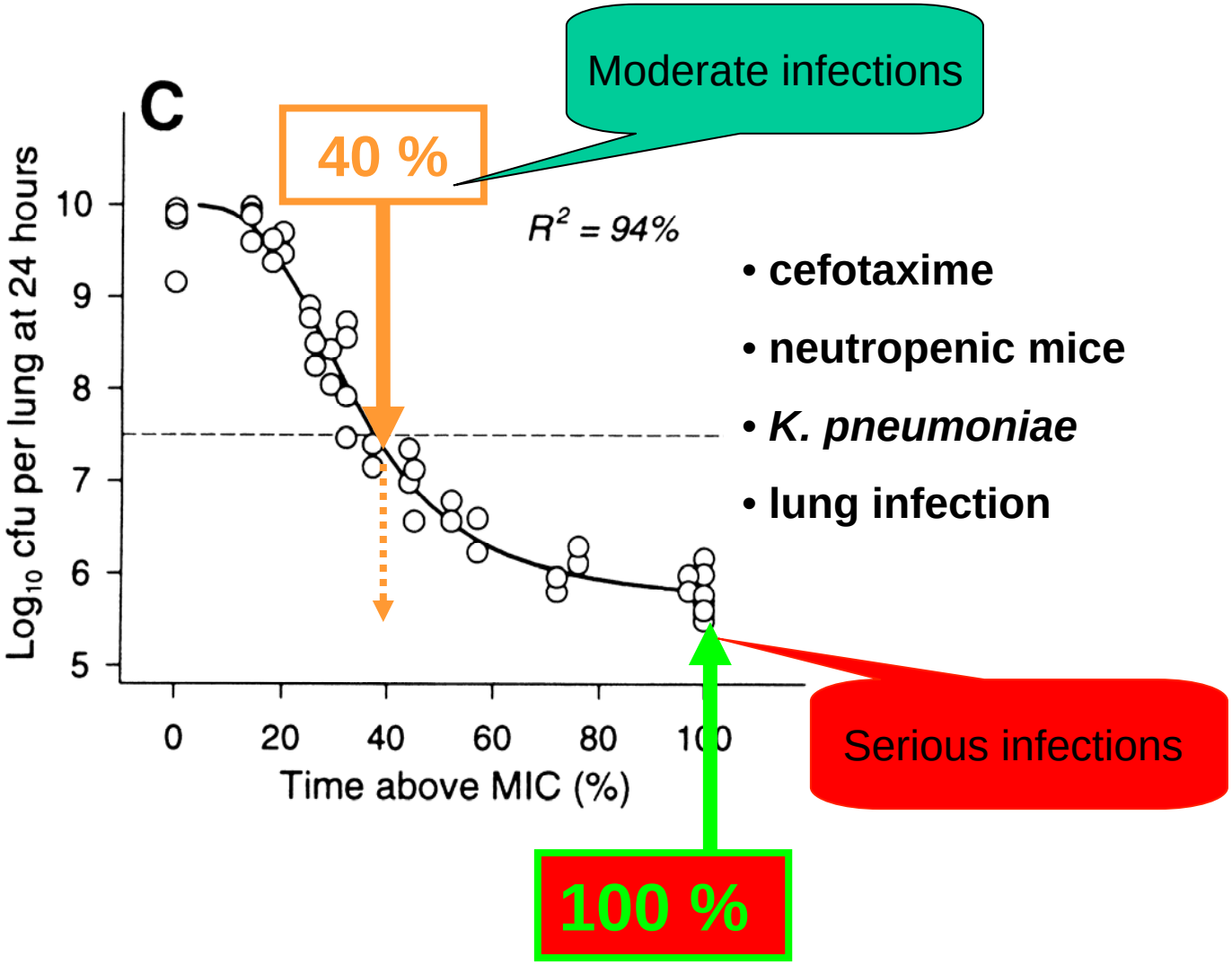
Antibiotics Group # 1

(after W.A. Craig, 2000; revised 2002 and 2003)

1. Antibiotics with time-dependent effects and no or little persistent effects

AB	PK/PD parameter	Goal
β-lactams	**time above the MIC**	**Maximize the exposure time**

How long should you stay above the MIC ?



Do all β-lactams have similar PK/PD properties ?...

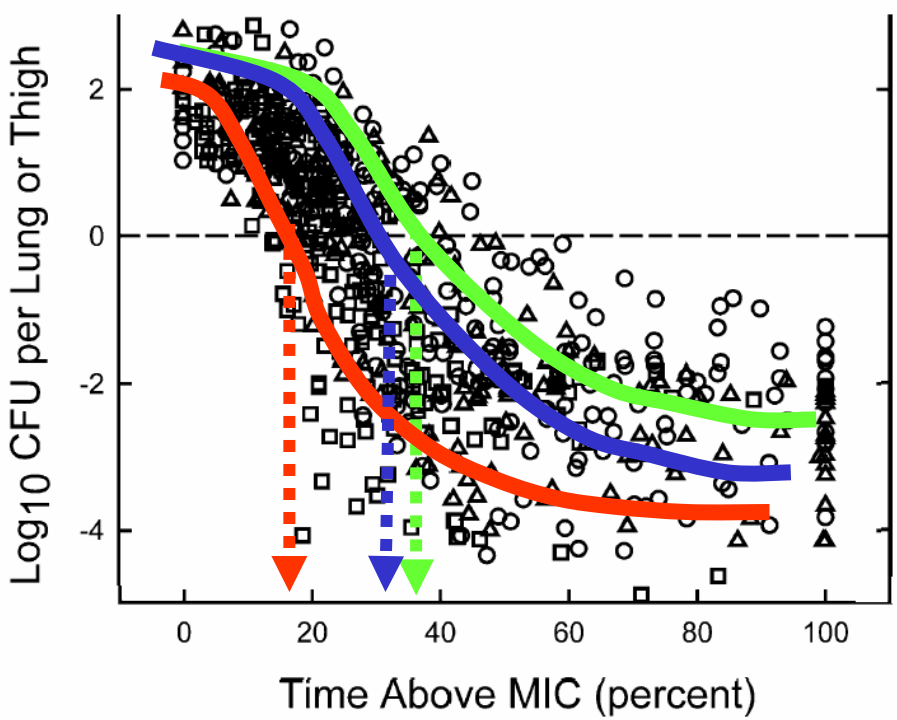


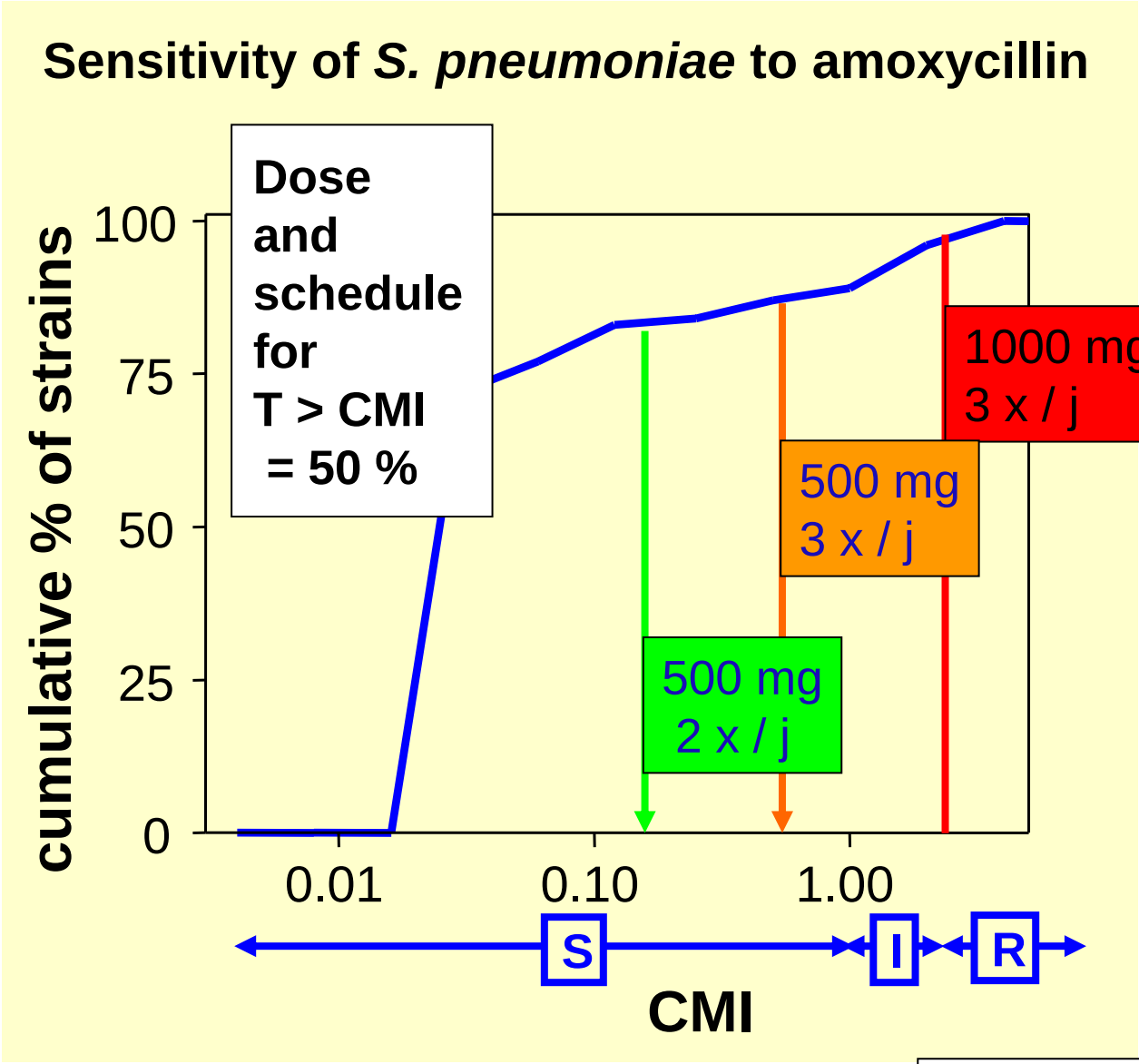
Fig. 7. Relationship between the change in $\log_{10}$ CFU per thigh or lung fo[illegible] [illegible] following 24 h of t[illegible] with different doses o[illegible] penicillins (△), cephalosporins (○), and carbapenems (□).

different pathogens

- same shape of dose response
- diff. In **T > MIC** for a static effect (penicill. > carbap.)
- diff **E_{max}** (penicill. < carbap.)

Andes & Craig Int. J. Antimicrob. Agents 2002, 19: 261-268

Dosing amoxycilline for respiratory tract infections in Belgium



MIC data: J. Verhaegen et al., 2001

Antibiotics Group # 2

(after W.A. Craig, 2000; revised 2002 and 2003)

2. Antibiotics with time-dependent effects, no or little influence of concentration, but marked, persistent effects

AB	PK/PD parameter	Goal
glycopeptides tetracyclines macrolides linezolid streptogramins	**AUC / MIC**	**optimize the amount of antibiotic**

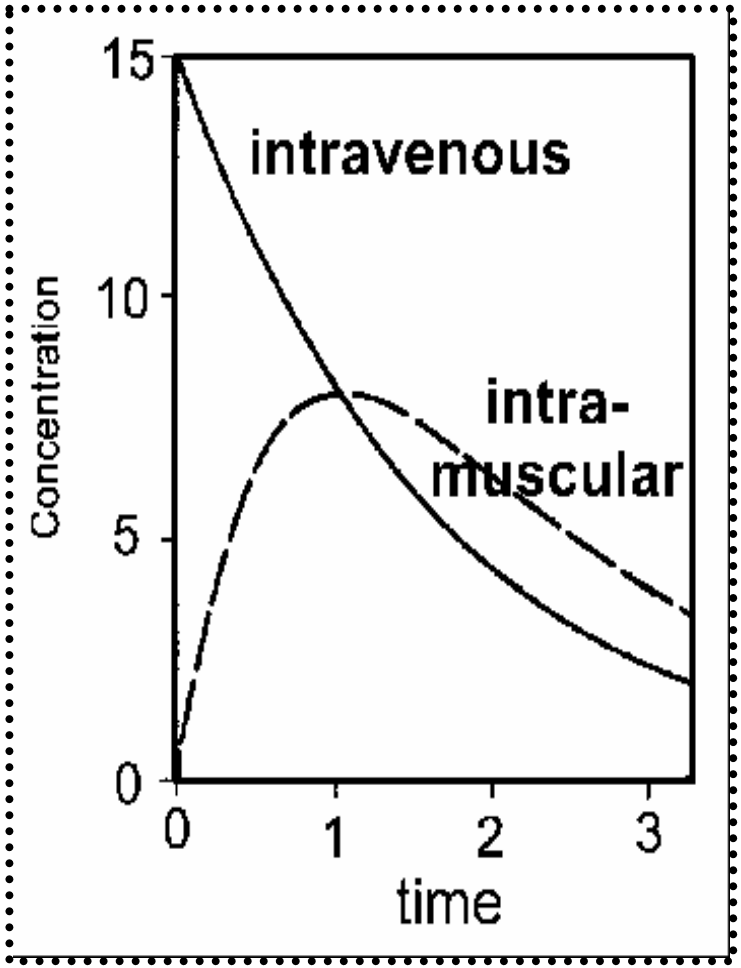
Antibiotics Group # 3

(after W.A. Craig, 2000; revised 2002 and 2003)

3. Antibiotics with concentration-dependent bactericidal activity and prolonged persistent effects (post-antibiotic effects)

AB	PK/PD parameter	Goal
aminoglycosides fluoroquinolones daptomycin ketolides	**Peak and AUC / MIC**	**optimize the peak and the amount of antibiotic**

Aminoglycosides: get a peak !



1. Appropriate mode of administration

➡ IV route

2. Calculation of the necessary peak value

➡ minimal peak: = MIC / 8

3. Calculation of the adequate dosis

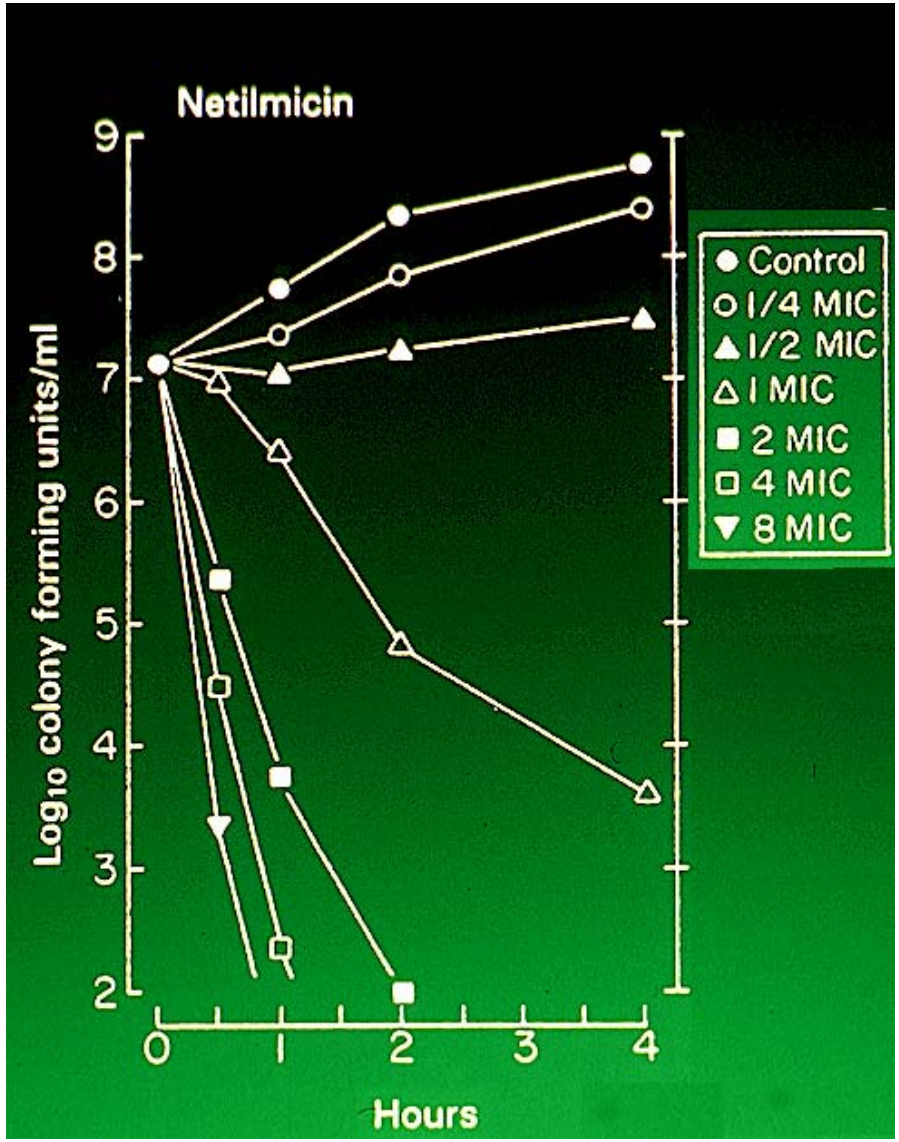
➡ peak = dosis / Vd

➡ dosis = peak x Vd

➡ dosis = MIC x 8 x Vd

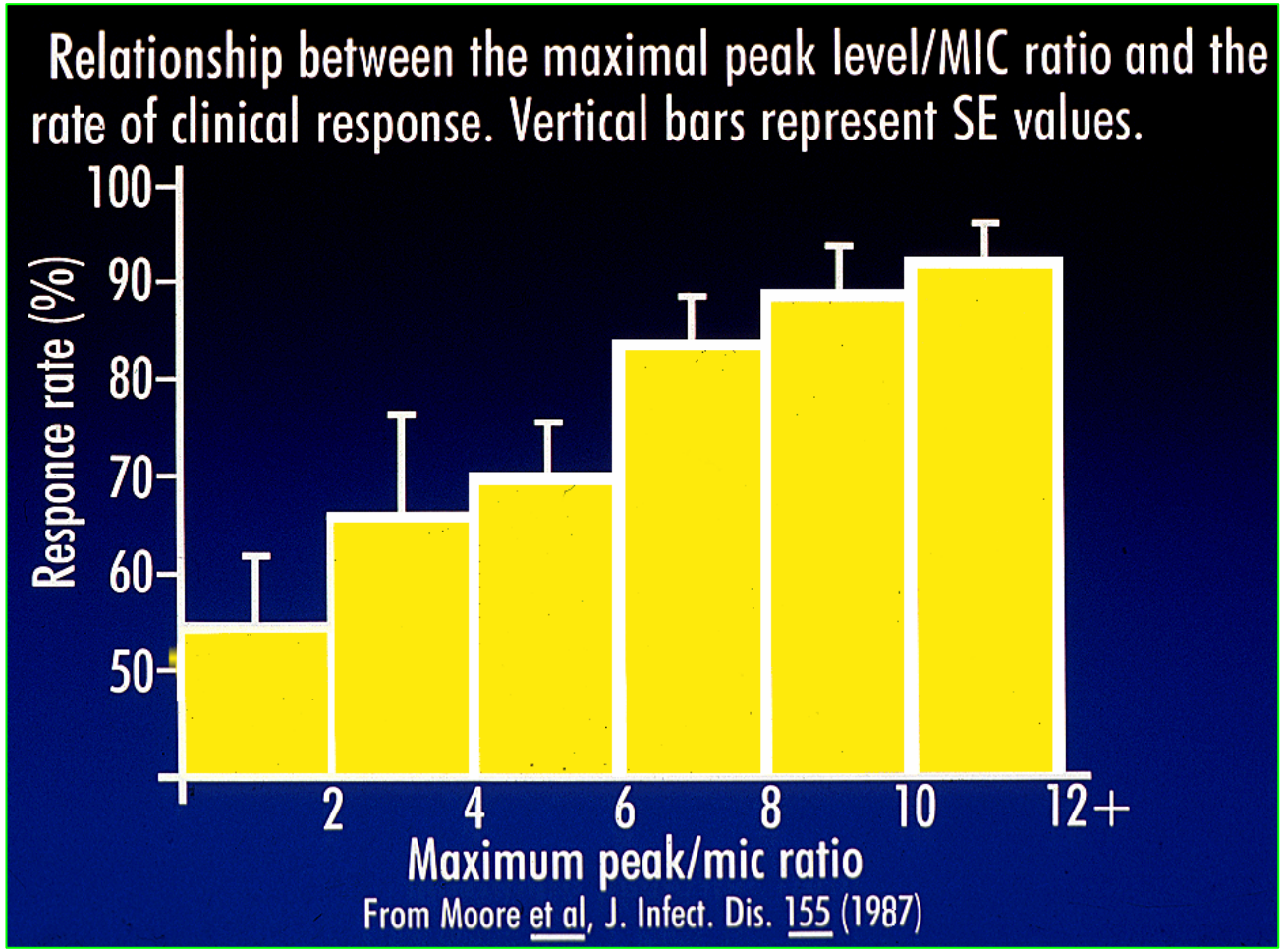
Aminoglycosides: why a peak ?

Aminoglycosides are concentration-dependent drugs in the clinically meaningful concentration range ...



Aminoglycosides: why a peak ?

Clinical efficacy is linked to peak/MIC ratio

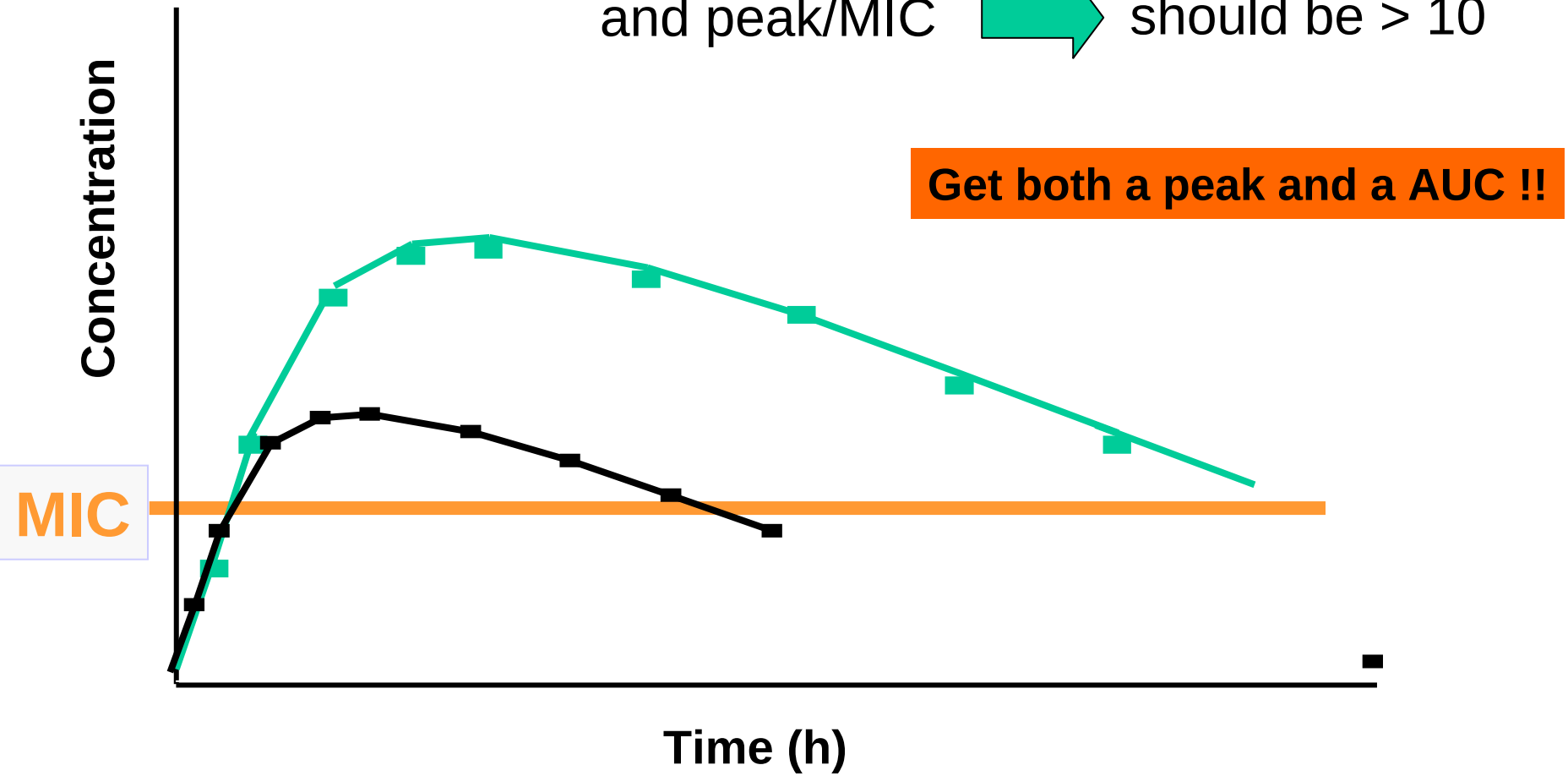


Fluoroquinolones: get a peak and an AUC !

increase the amount administered,
in order to optimize AUC/MIC → should be > 125 *

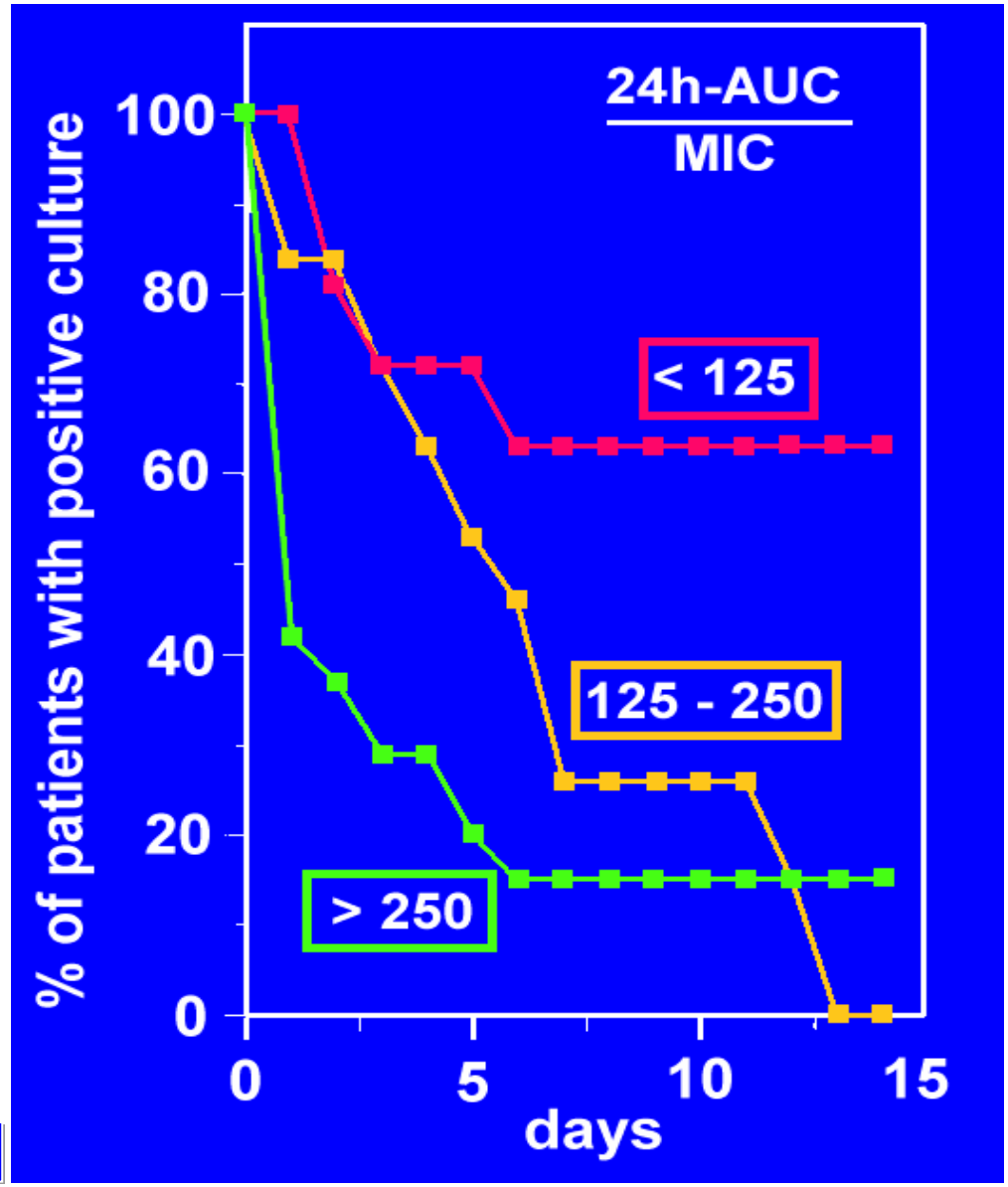
and peak/MIC → should be > 10

Get both a peak and a AUC !!



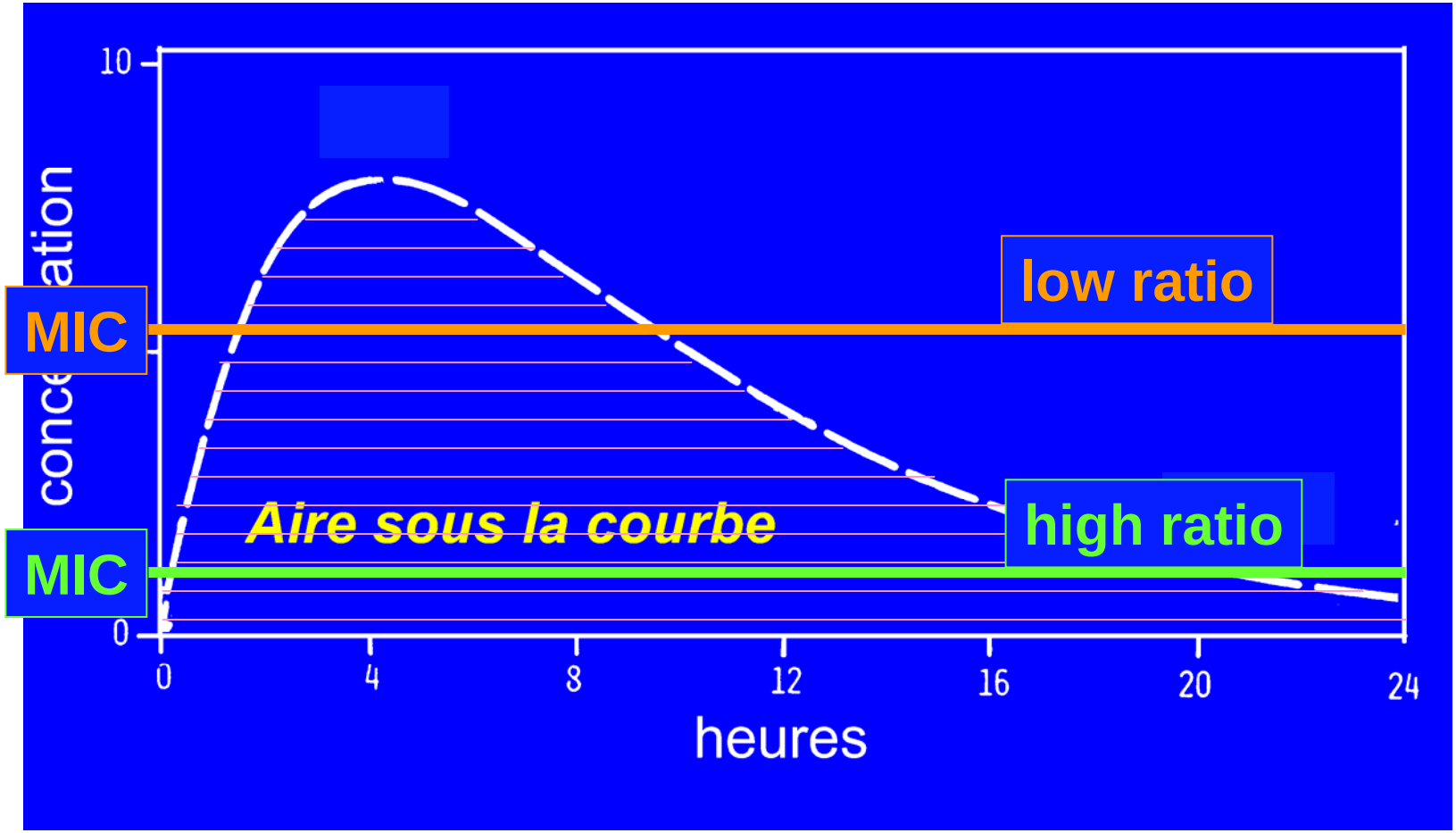
Why an AUC / MIC > 125 for fluoroquinolones ...

AUC / MIC
is
one parameter …



Forrest et al., AAC, 1993

What do you mean by PEAK /MIC > 10 and AUC / MIC > 100



AUC_{24h} = dose / clearance

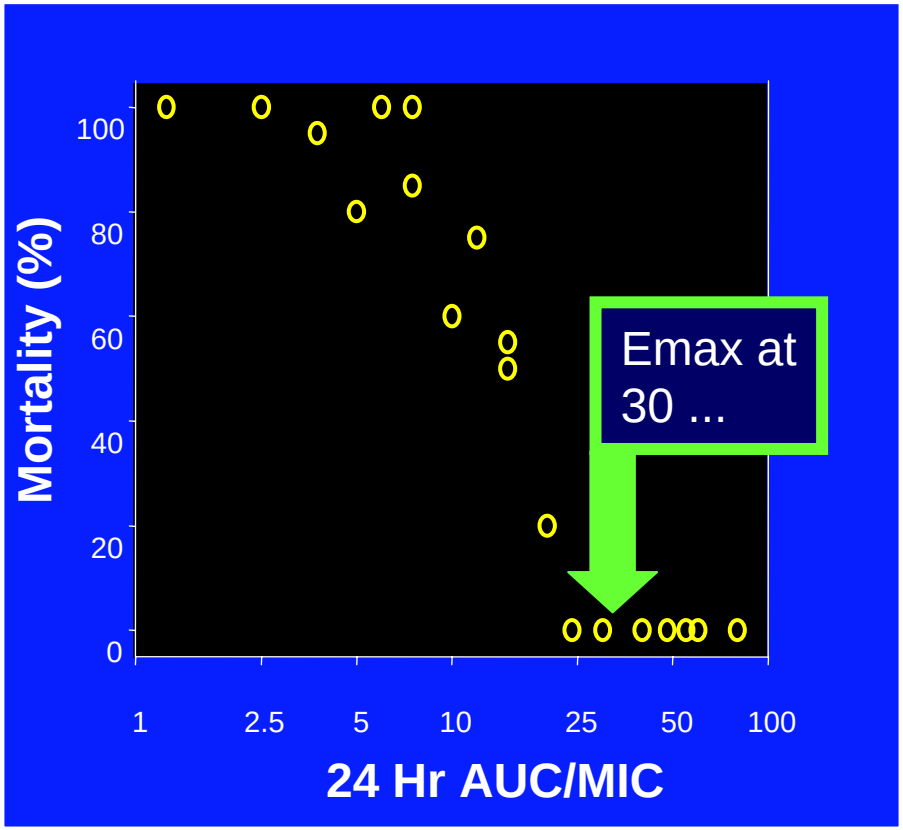
AUC/MIC_{24h} =125 : a magical number??

125 was the limit below which failure rates became unacceptable because of either

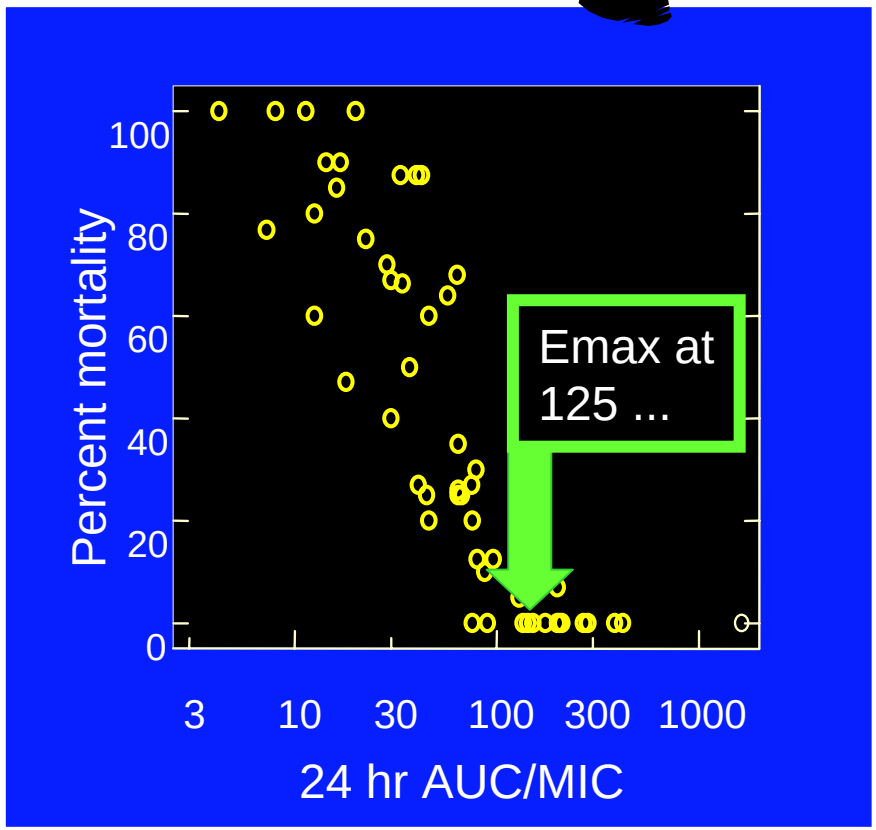
- a large MIC
- or a too low dosage
  (AUC is proportional to the dosage)

Is 125 good for all ??

The saga of *S. pneumoniae* ...



non-neutropenic



neutropenic

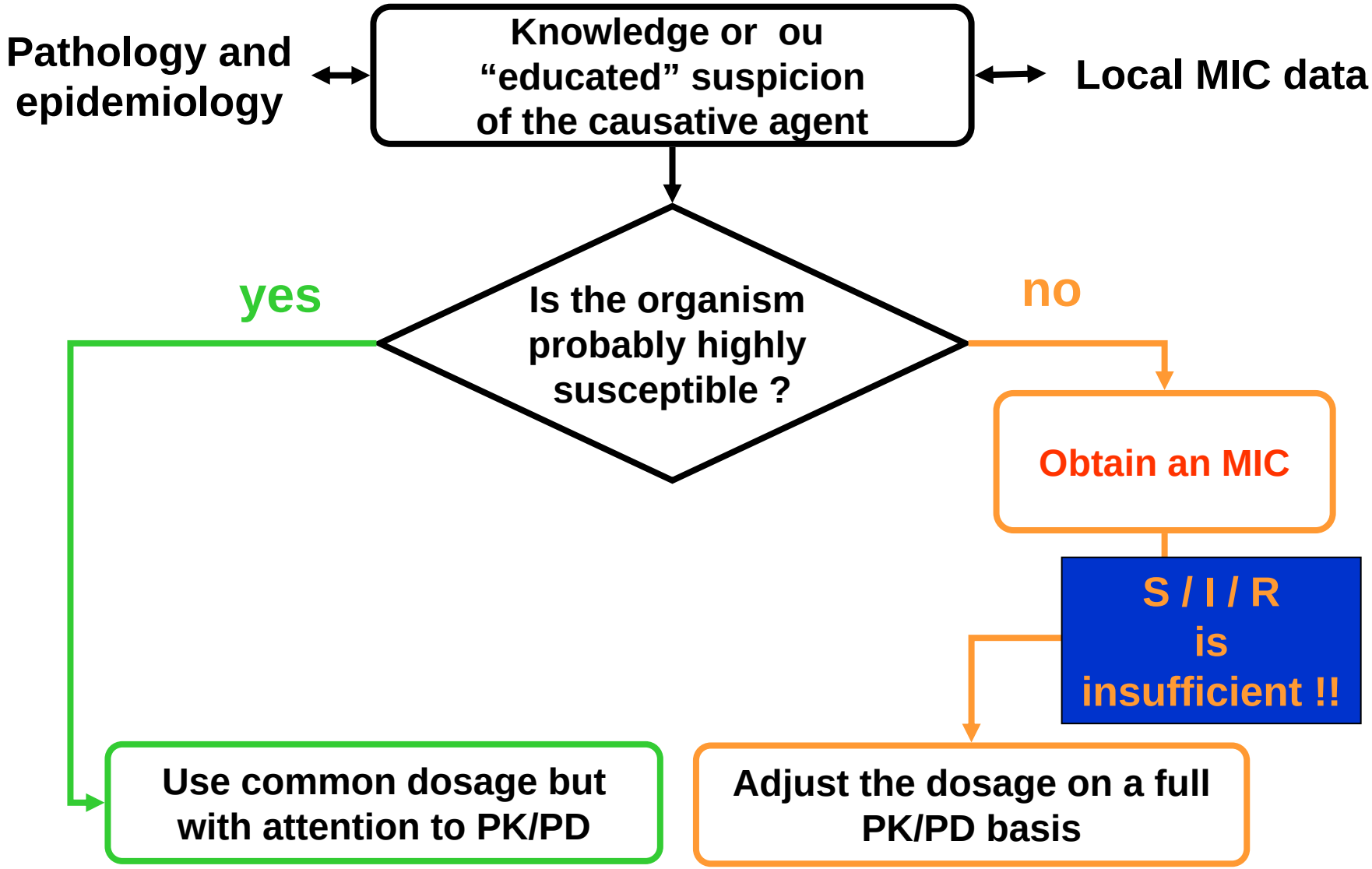
How to optimize the AUC / MIC ratio ?

AUC = dosis / Cl

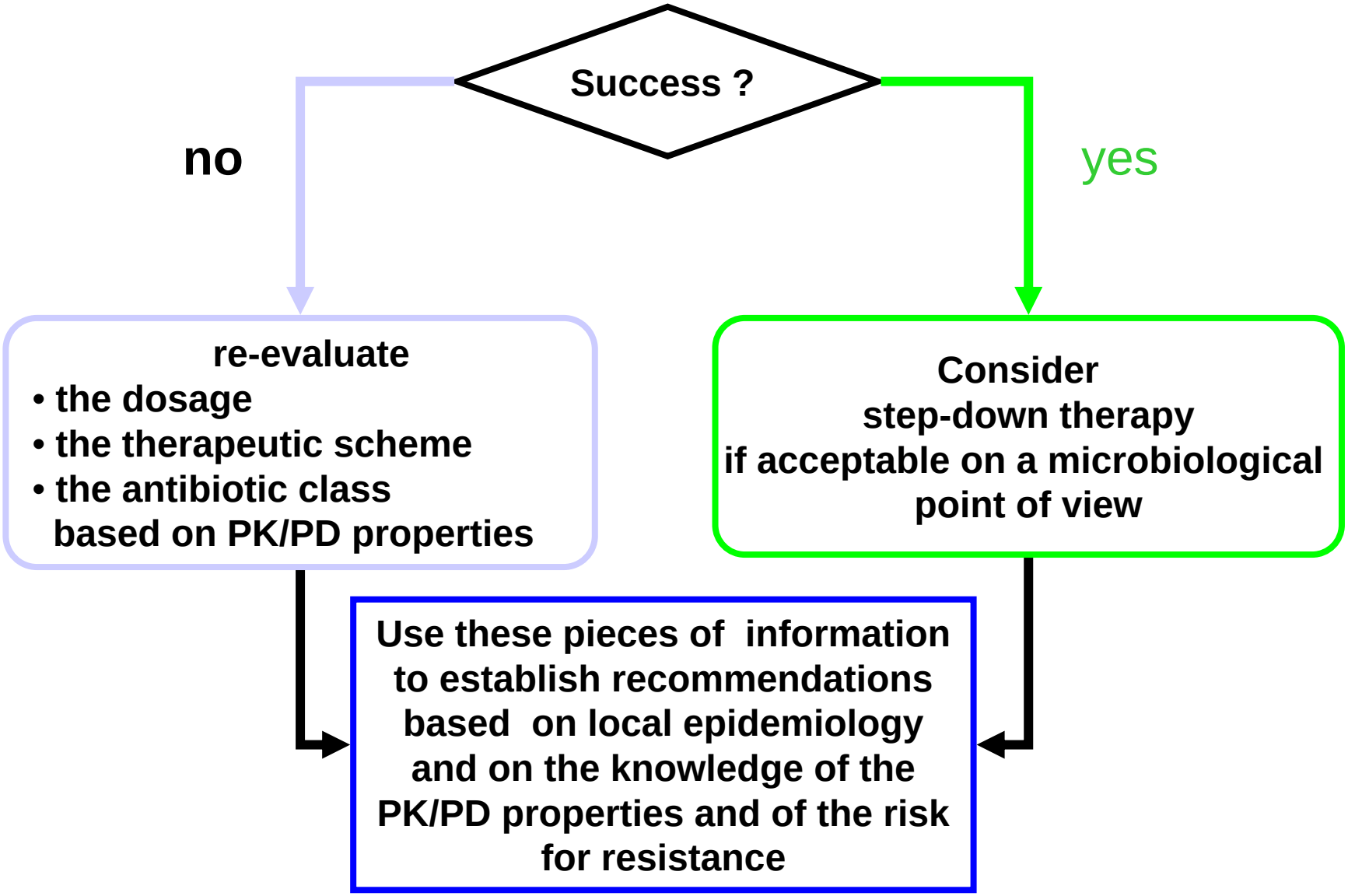
→ Adjust the daily dosis
~ target AUC

→ Adapt the number of administrations
~ pharmacokinetics of the drug

A clinical algorithm ...



A clinical algorithm (follow.) ...



Why pharmacodynamics ?

- Rising resistance and correlation with antibiotic use …
- What is pharmacodynamics of antibiotics
- What can we do with that…
  - for the clinical laboratory and the clinician …
  - **for the health authorities**
- Can pharmacodynamics help in preventing (or slowing down the emergence of) resistance ? …
- Can we also reduce health care costs ? …

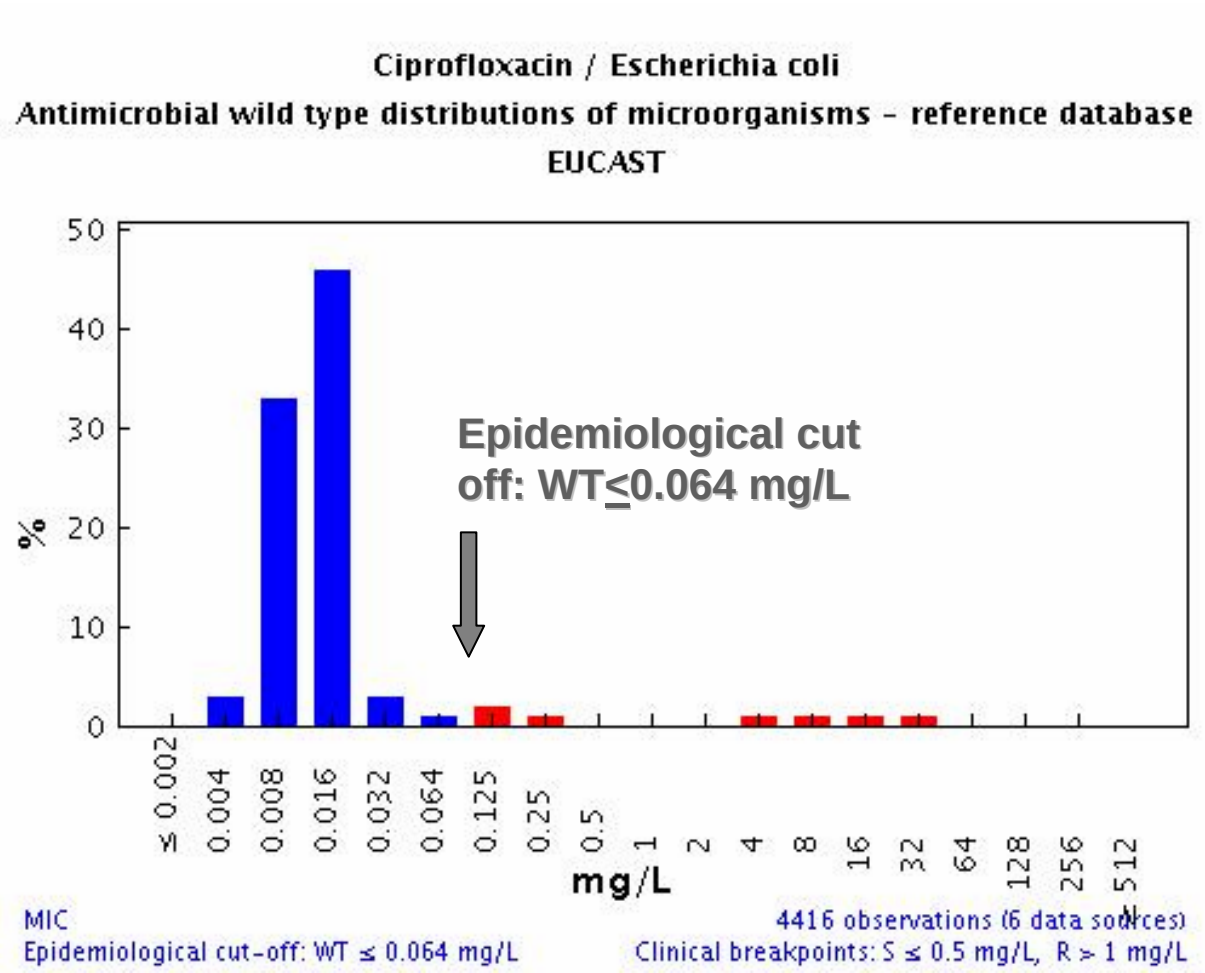
Can we use this to set better breakpoints ?

The next slides describe the EUCAST procedure for harmonizing European breakpoints and reach rational values.

European Committee for antibiotic susceptibility testing

1. Data on dosing, formulations, clinical indications and target organisms are reviewed and differences which might influence breakpoints are highlighted

2. Multiple MIC-distributions are collected, the wild type MIC distribution is defined and tentative epidemiological cut-off values determined (WT ≤X mg/L)



3. Existing national clinical breakpoints are compared

4. Pharmacokinetic data are collected and evaluated

Pharmacokinetic data are collected from various sources, particularly data from patients. If the data allow it and if necessary, population pharmacokinetic models are developed.

These are necessary for PK/PD analyses, including Monte Carlo simulations

5. Pharmacodynamic data are evaluated

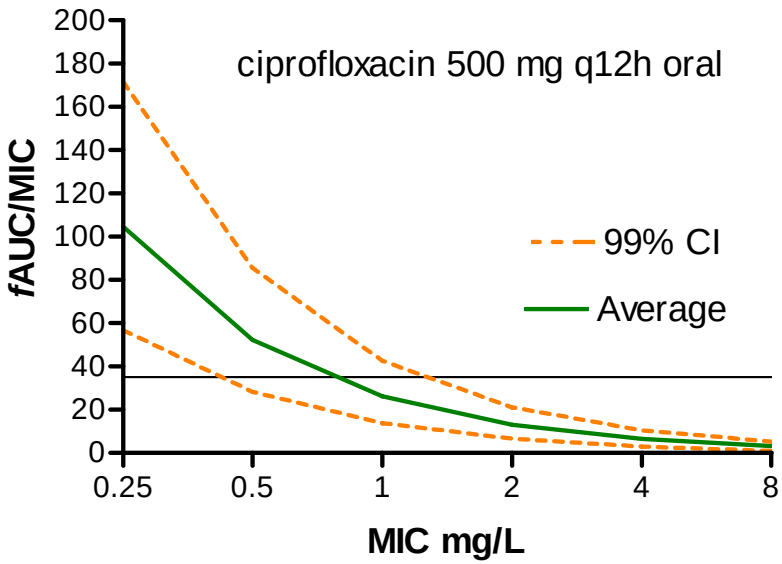
The PK/PD index value resulting in optimal outcome is determined from:

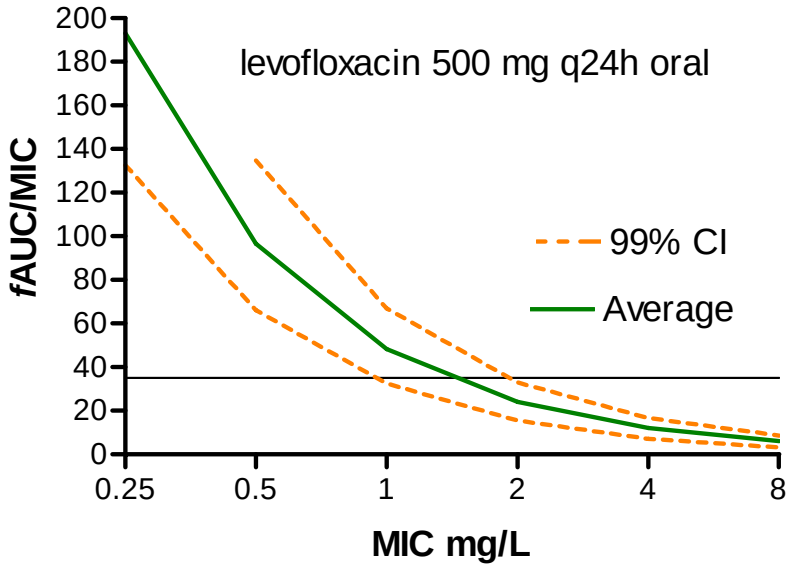
- in vitro data
- animal studies
- clinical trials

The efficacy of the drugs is assessed quantitatively.

Relationships between concentration time profiles and emergence of resistance are evaluated

Monte Carlo simulations are performed and a PK/PD breakpoint calculated based on conventional dosing regimens





S = 0.5 mg/L

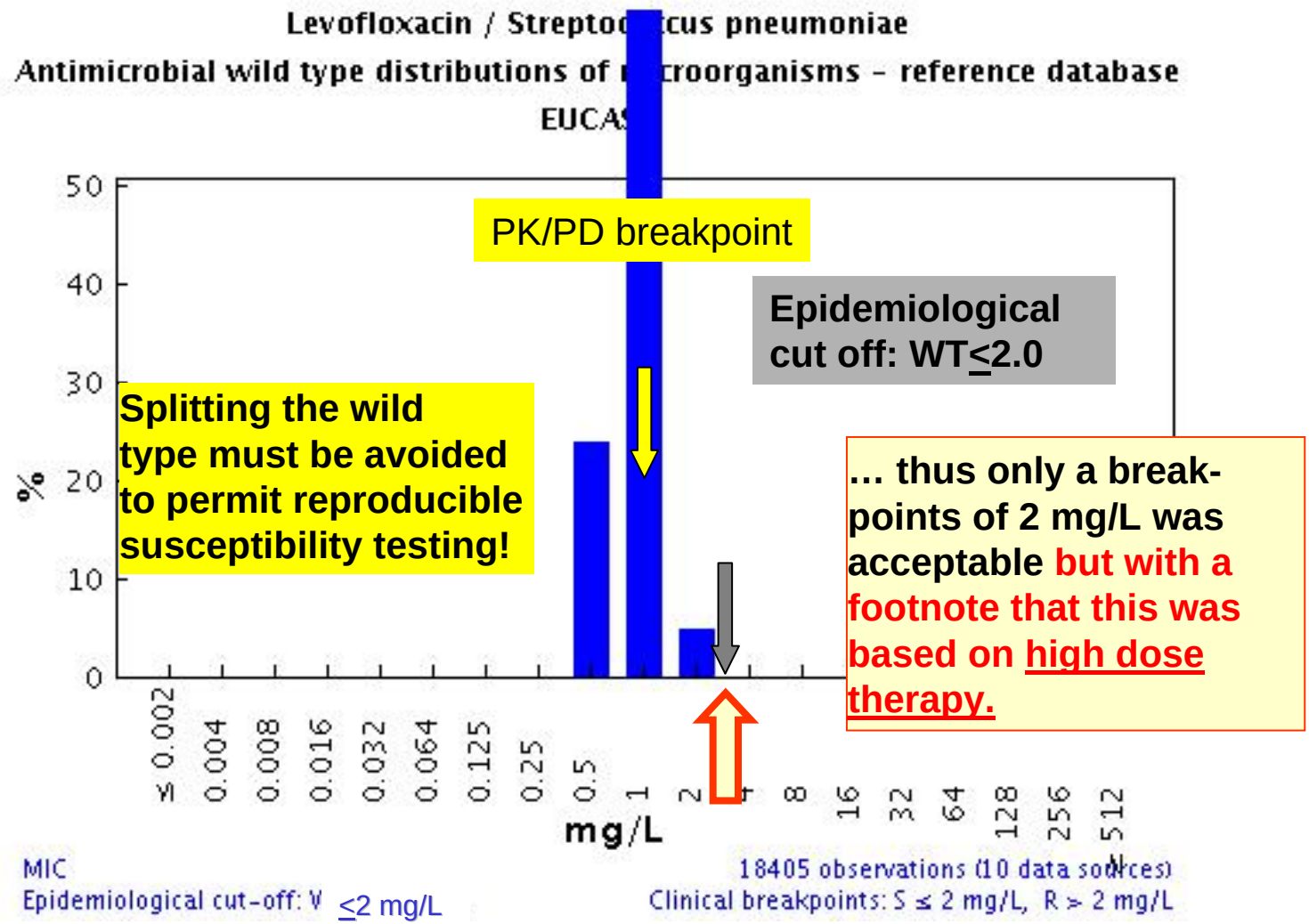
PK/PD

S = 1 mg/L

5. Clinical data relating outcome to MIC-values, wild type and resistance mechanisms are assessed in relation to the tentative breakpoint

”Minimum requirement for S-category” is that the highest MIC value of the wild type MIC-distribution is consistent with the MIC derived from the PK/PD index needed for optimal efficacy based on free drug”.

6. PK/PD breakpoints are checked against target species wild type MIC distributions to avoid splitting the wild type to obtain tentative breakpoints - example levofloxacin



7. Tentative breakpoints by the EUCAST Steering Committee are referred to the national breakpoint committees for comments.
When steering committee and national committees agree the tentative breakpoints are subjected to the EUCAST consultation process:

8. Consultation process on tentative breakpoints:

- EUCAST general committee

- Expert committees (Neisseria, Anaerobes, others)

- pharmaceutical industry, AST device manufacturers

- others via EUCAST website

9 . Rationale document prepared and published on website

How to implement EUCAST breakpoints

- The national breakpoint committees have committed themselves to implementing EUCAST breakpoints – which means that anyone using the one of the European national systems will gradually adhere to the European breakpoint system

- Breakpoints as presented in EUCAST tables can be directly applied to MIC distributions (local and national surveillance, EARSS, etc)

- Systems for automated susceptibility testing can be set up with EUCAST MIC breakpoints.

- Through an agreement between EMEA, EFPIA and EUCAST new antimicrobials will be given breakpoints through EUCAST as part of the registration process. The SPC for these drugs will contain only EUCAST breakpoints.

EUCAST websites are found at

www.eucast.org

The EUCAST websites are accessed via **www.eucast.org**

This is a section of the official ESCMID website giving details of all EUCAST activities including

- constitution
- organization
- committee member lists
- meetings
- EUCAST documents
- clinical MIC breakpoint tables
- MIC distributions for wild type bacteria and fungi
- epidemiological MIC cut-off values

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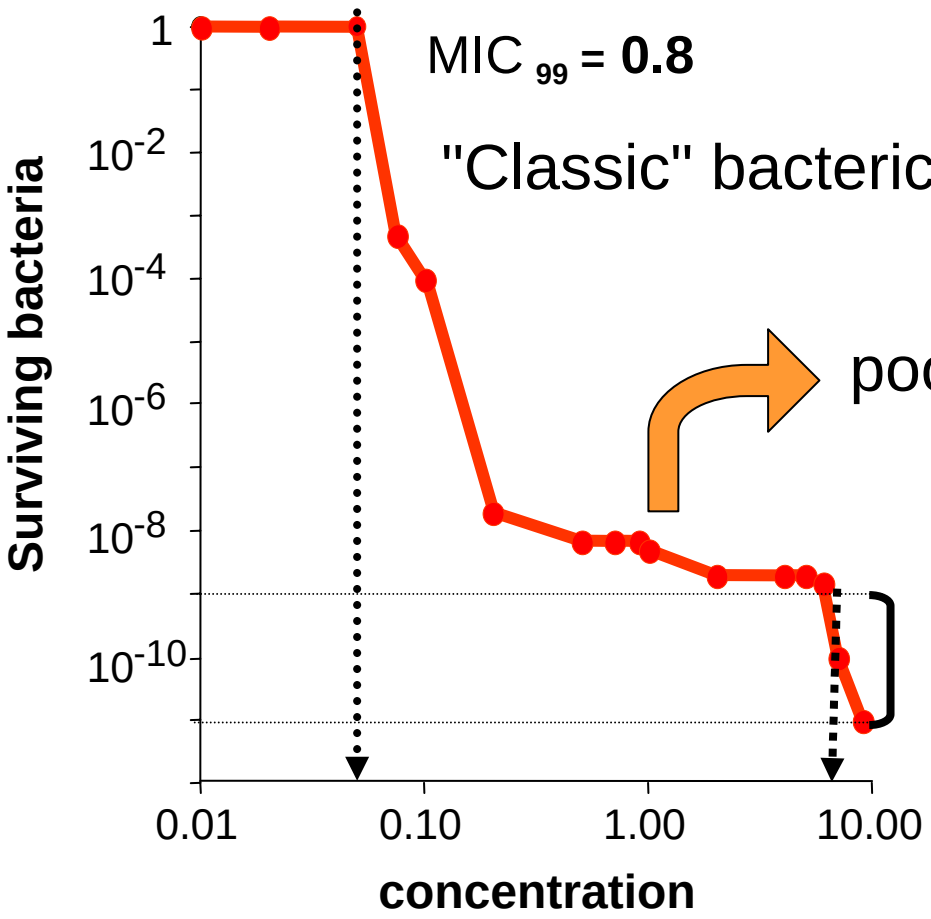
Mutant Prevention Concentration …



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

"Classic" bactericidal effect

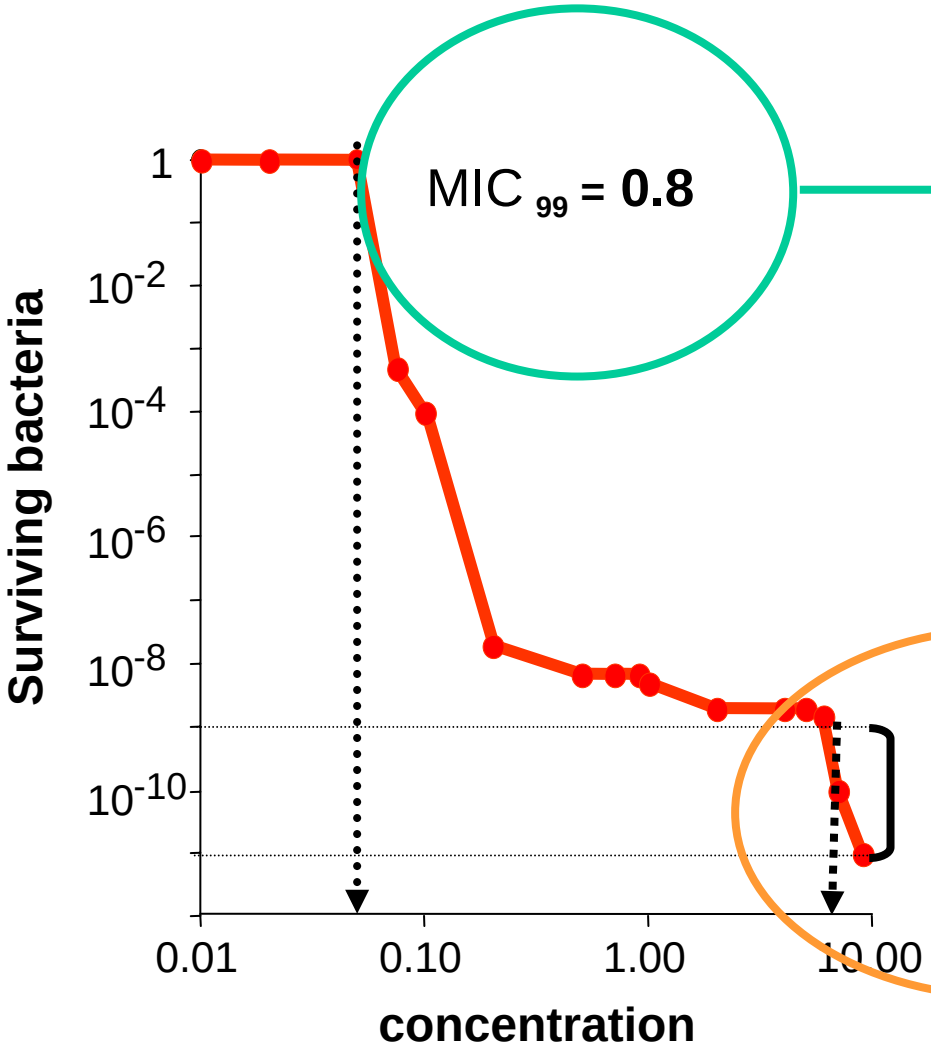
poorly sensitive organisms…

Elimination of resistant organisms

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

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

Mutant Prevention Concentration …

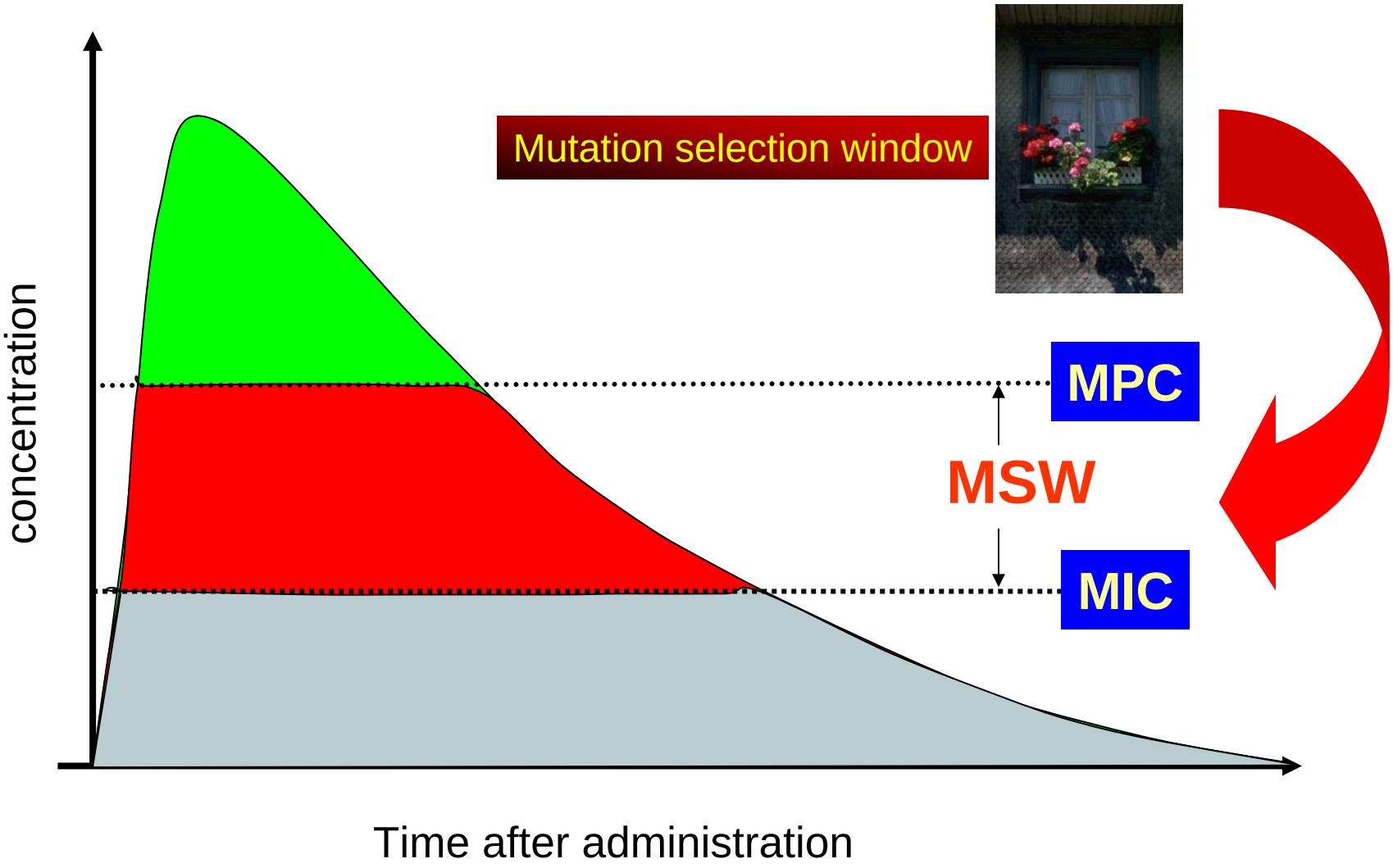


Concentration which will inhibit the majority of the organisms

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

Which are the MPC values compared to
- MIC for *S. pneumoniae*
- C_{max} for a standard dose ?

Molecule	MIC	MPC		C_{max}
levoflox. (500 mg)	1	8		≈ **6**
moxiflox. (400 mg)	0.25	1		≈ **4**

Adapted from D. Croisier, 2005, Bondeau et al., 2001, and Hansen et al, 2003

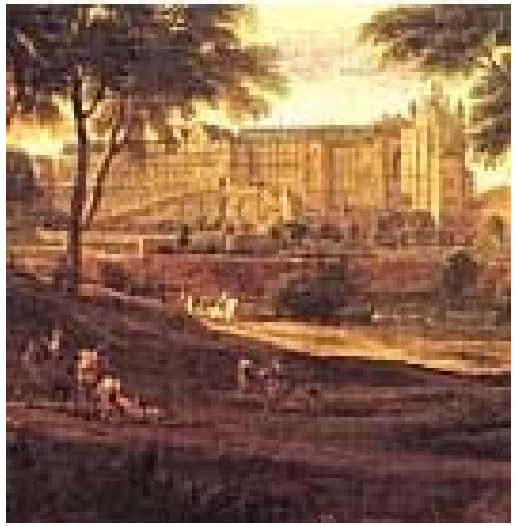
So, let us accept values with some degree of precaution

If you wish to prevent resistance

➔ peak / MIC > 10
(which covers the MPC)

If you believe your patient is not a healthy mouse …

➔ AUC_{24h} / MIC > 100



A proposal for PK/PD based-breakpoints for fluoroquinolones...

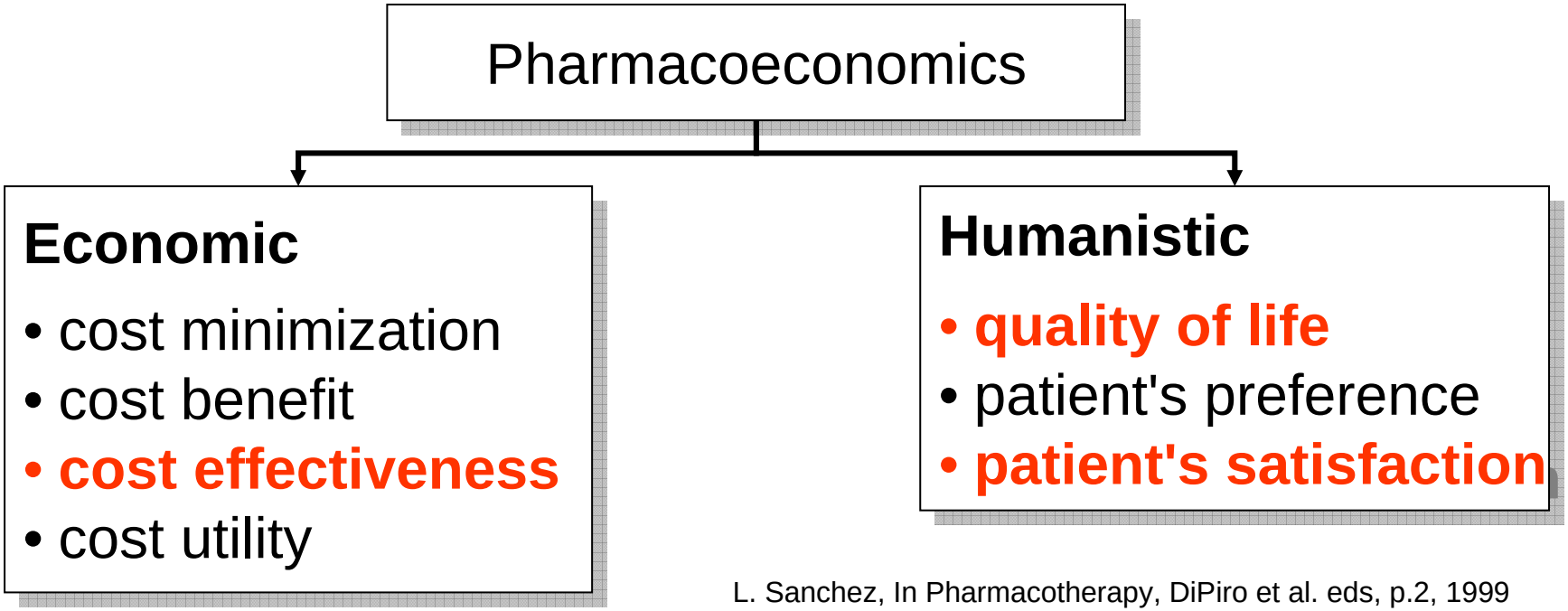
Drug	Typical daily dosage[a]	Typical PK values		Proposed PK/PD upper limit of sensitivity (μg/ml) for	
		C_{max} in mg/L total/free (dose)	$AUC_{24\ h}$ (mg × h/L) total/free	Efficacy[b]	Prevention of resistance[c]
Norfloxacin	800 mg	1.4/1.1 (400 mg PO)	14/11	0.1–0.4	0.1
Ciprofloxacin	1000 mg	2.5/1.75 (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

Why pharmacodynamics ?

- Rising resistance and correlation with antibiotic use …
- What is pharmacodynamics of antibiotics
- What can we do with that…
  - for the clinical laboratory and the clinician …
  - for the health authorities
- Can pharmacodynamics help in preventing (or slowing down the emergence of) resistance ? …
- **Can we also reduce health care costs ? …**

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

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 …

Here is where you will find more information …

www.facm.ucl.ac.be

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