Pharmacodynamics of antibiotics: Correlation between kinetics and activity

Paul M. Tulkens

Cellular and Molecular Pharmacology Unit
& Centre for Clinical Pharmacy
Catholic University of Louvain, Brussels, Belgium

www.facm.ucl.ac.be

International Society for Anti-infective Pharmacology (ISAP)

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Pharmacodynamics of antibiotics: Correlation between kinetics and activity

- Rising resistance and correlation with antibiotic use …
- Did we use antibiotics in a rational way ? …
- What is pharmacodynamics and how can it help you ? …
- Can we prevent (or slow down the emergence of) resistance ? …
- Can we also reduce health care costs ? …

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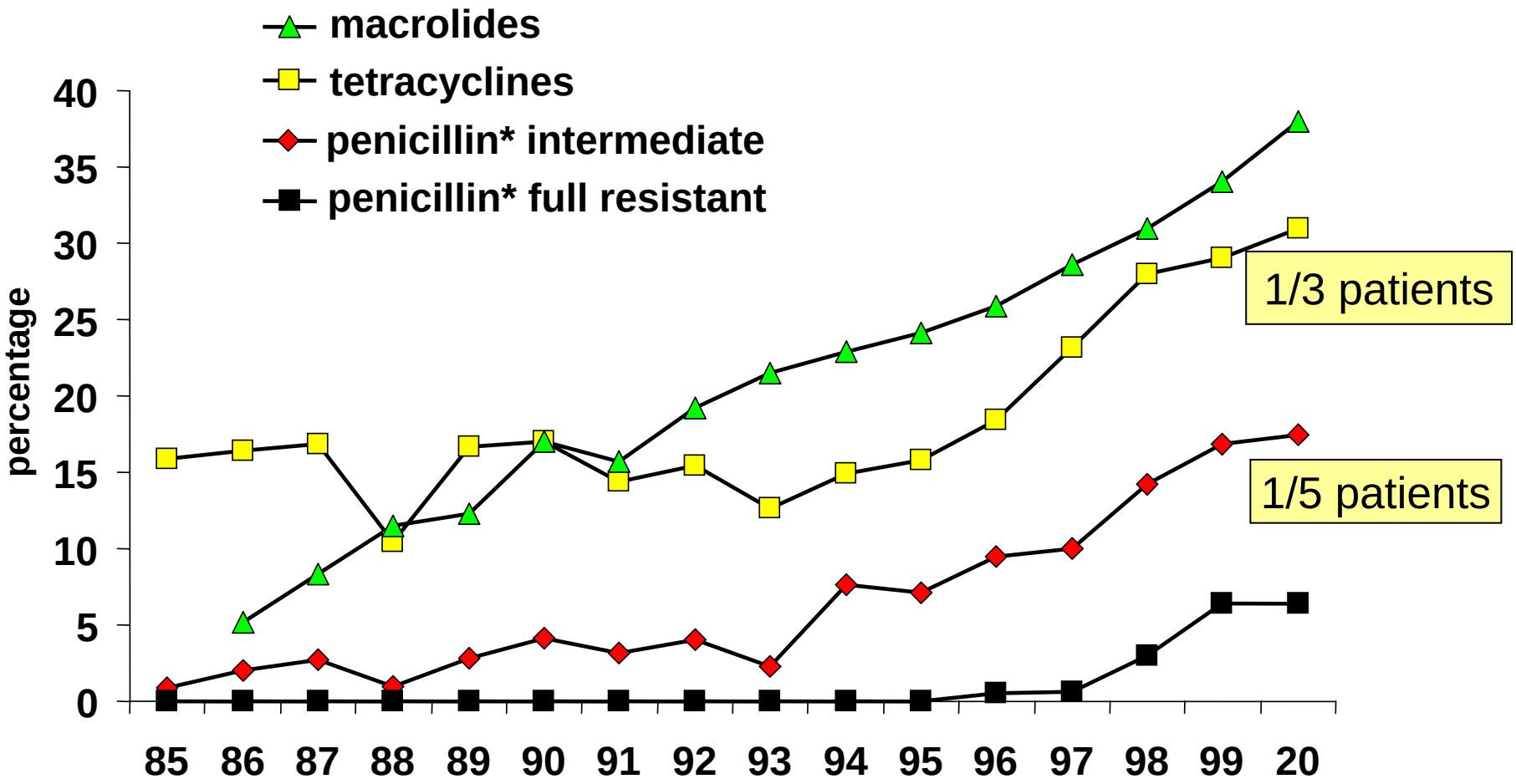
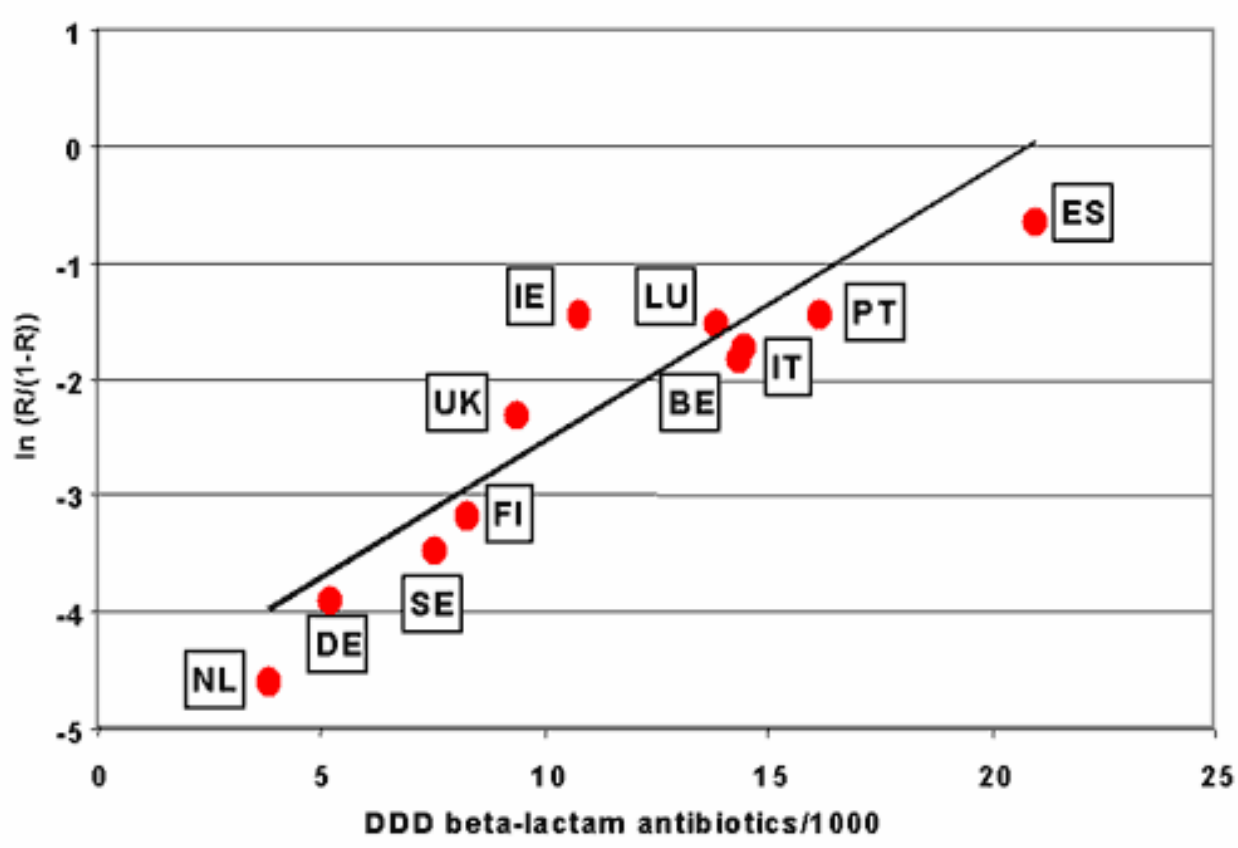
Resistance is the problem …



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

Belgian Reference Laboratory for pneumococci, Leuven, 2000

Overuse is also the problem …



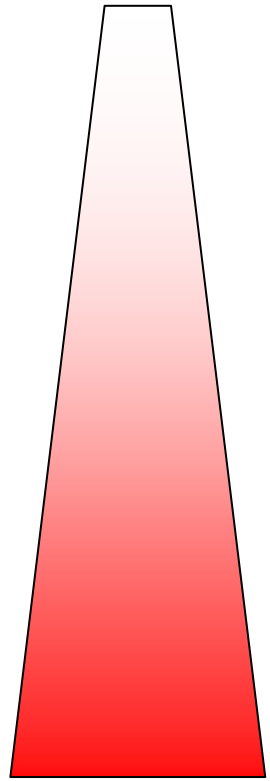
Risk of resistance to β-lactams among invasive isolates of *Streptoccus pneumoniae* regressed against outpatient sales of beta-lactam antibiotics in 11 European countries

- **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" ?

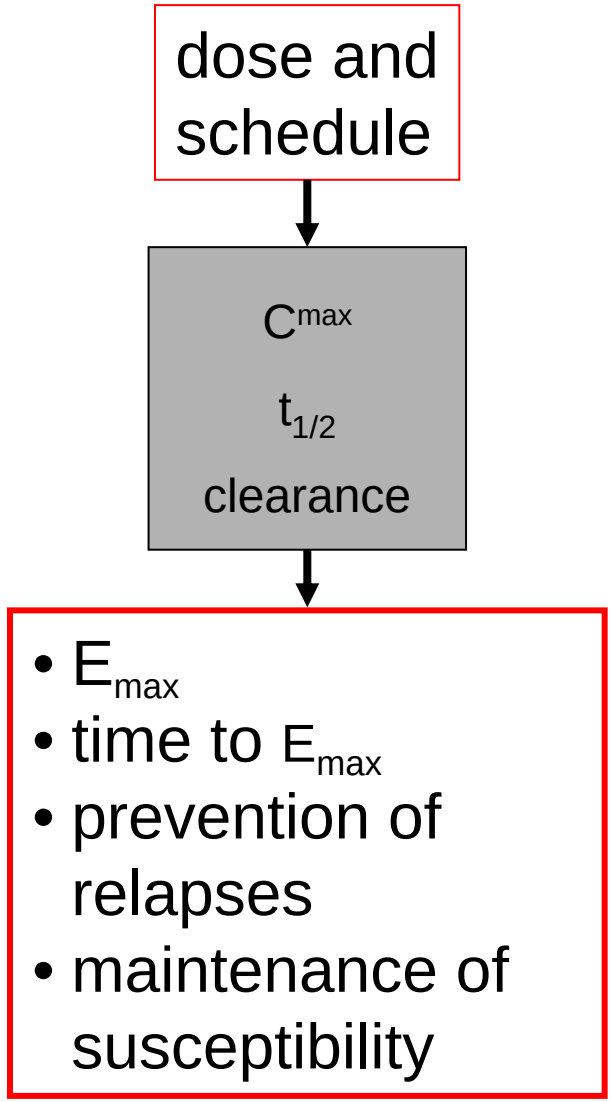
- be globally efficacious
  - ➔ **pharmacodynamics (PK/PD)**
- avoid selection of resistance
  - ➔ **"mutant prevention concentration"**



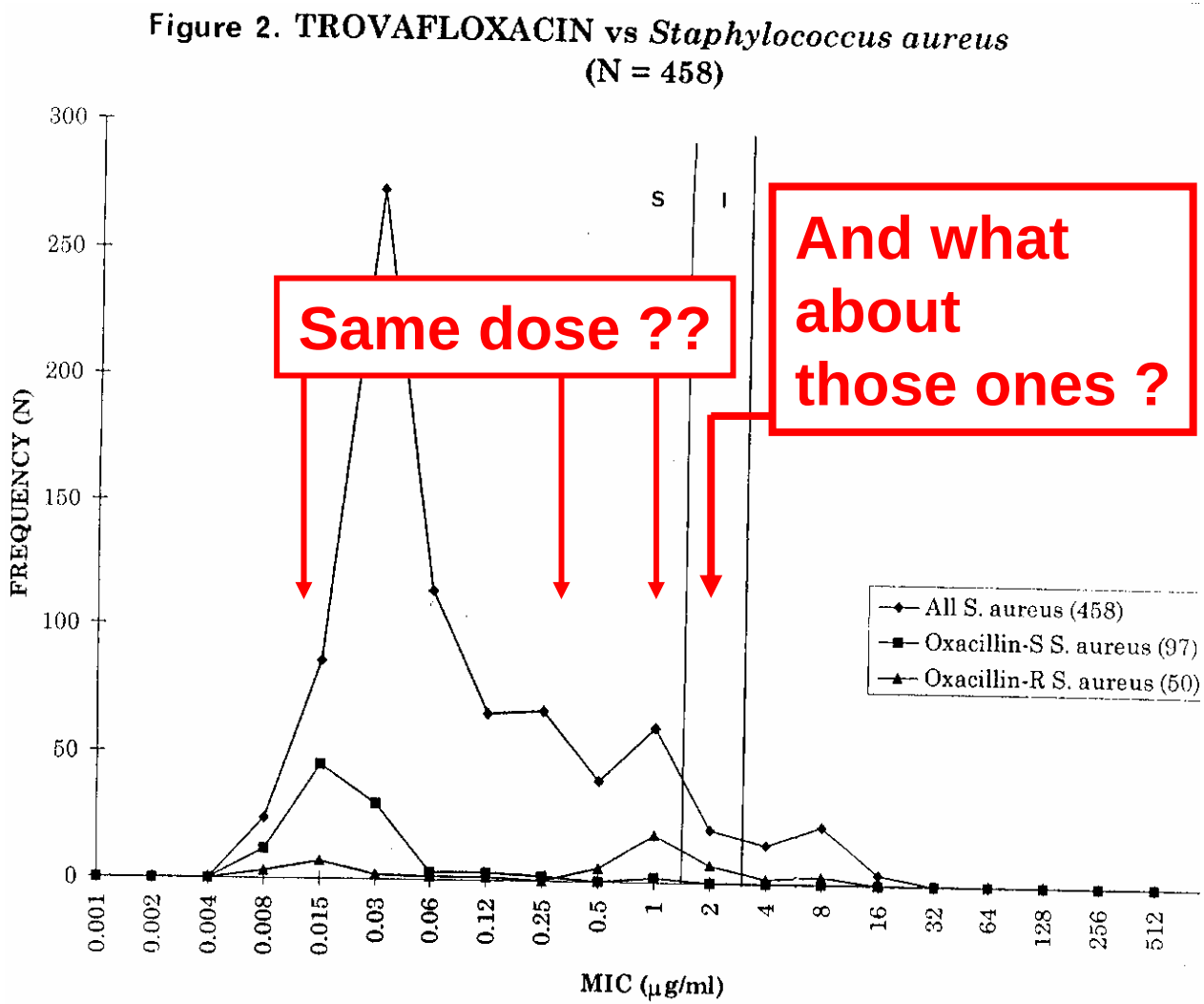
What is Pharmacokinetics / Pharmacodynamics (PK/PD) ?

- 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...



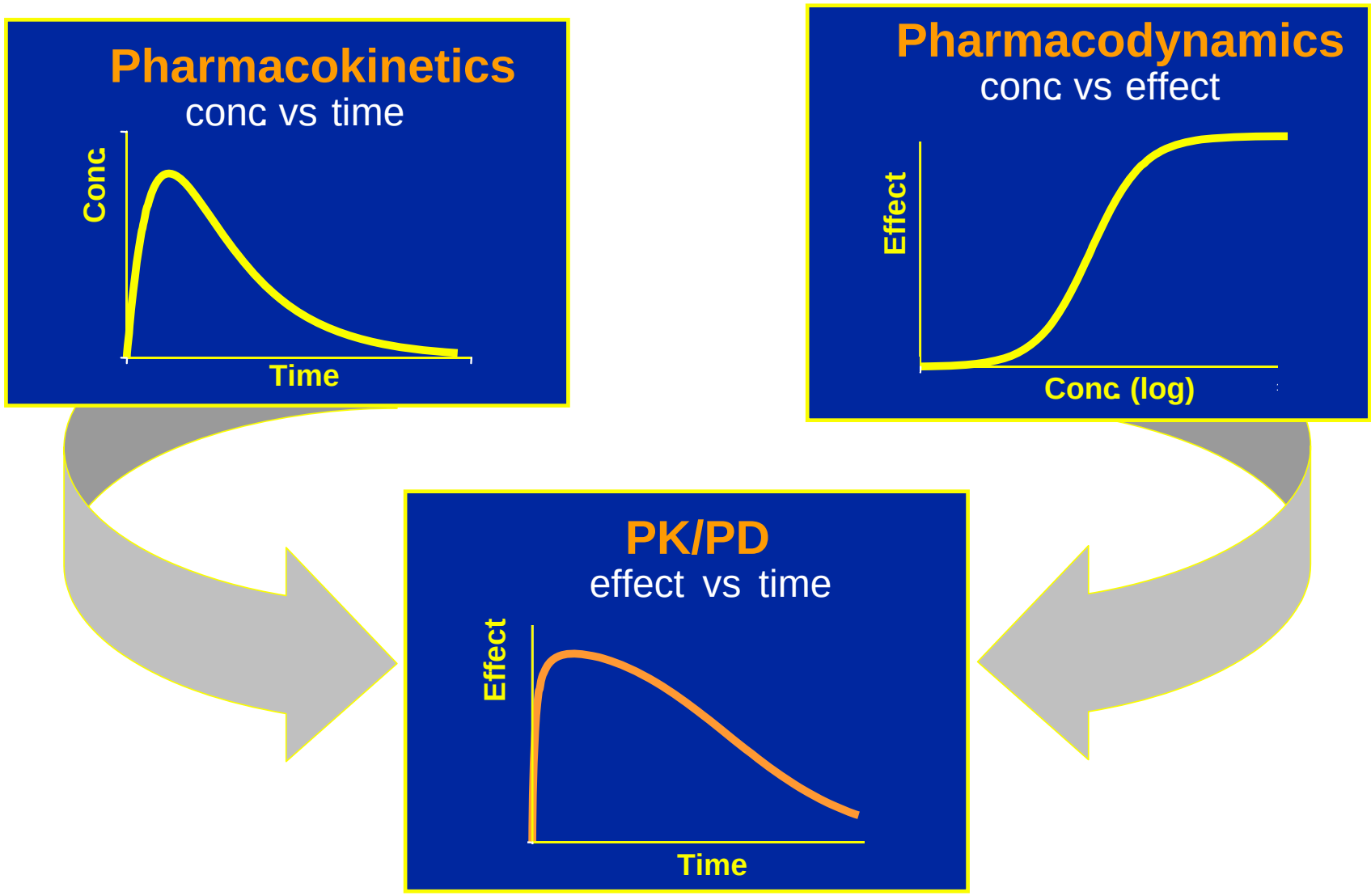
Breakpoints tend to set up quantic limits in what is fundamentally a **continuous** distribution ...

What are "Pharmacodynamic indices" ?

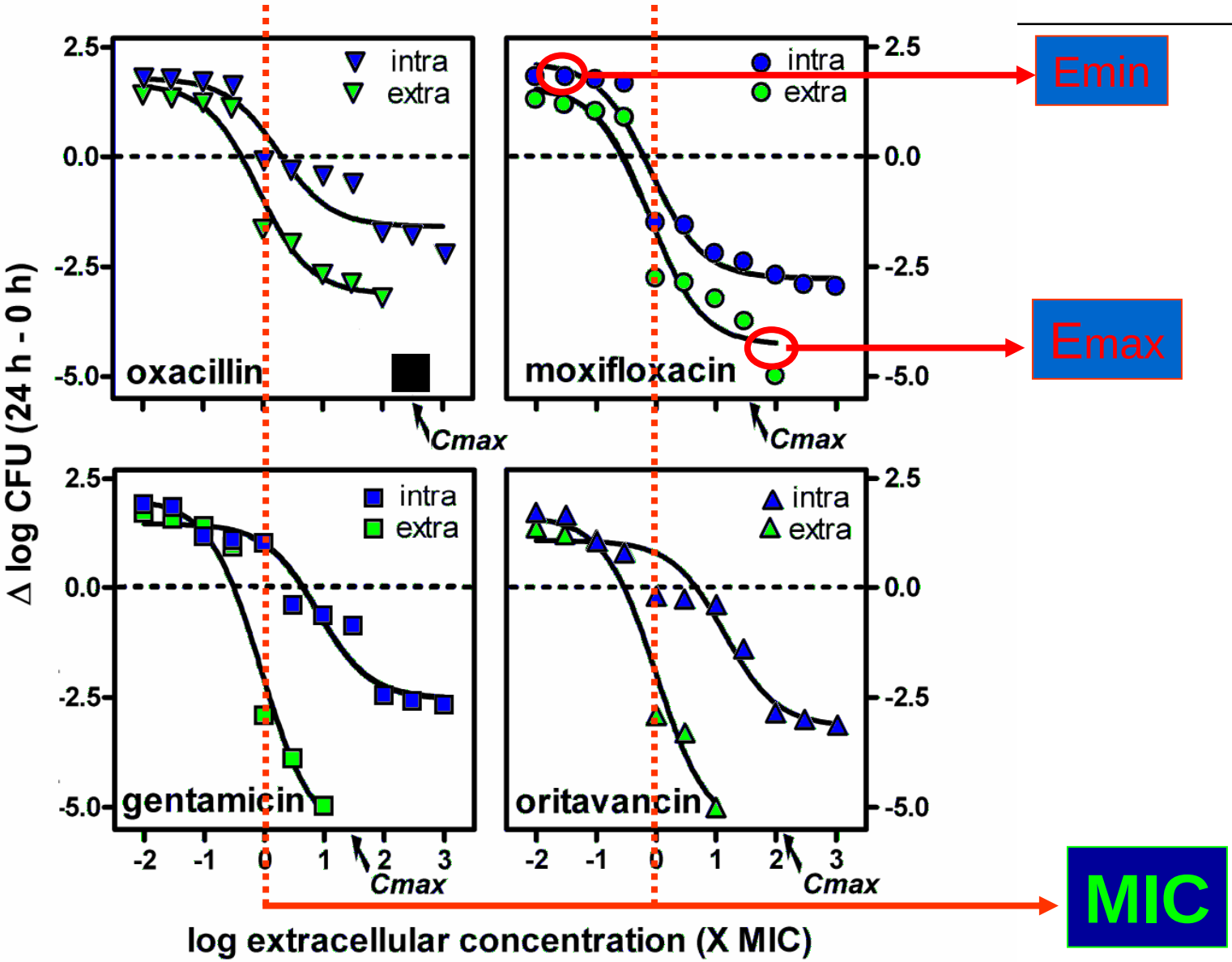
- all drugs have pharmacokinetic properties that describe the way the body handles them
  - antibiotics are no exception …
  - you need to consider the C_{max} and the clearance (that will result in a given half-life) to describe the **drug exposure**

- 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...

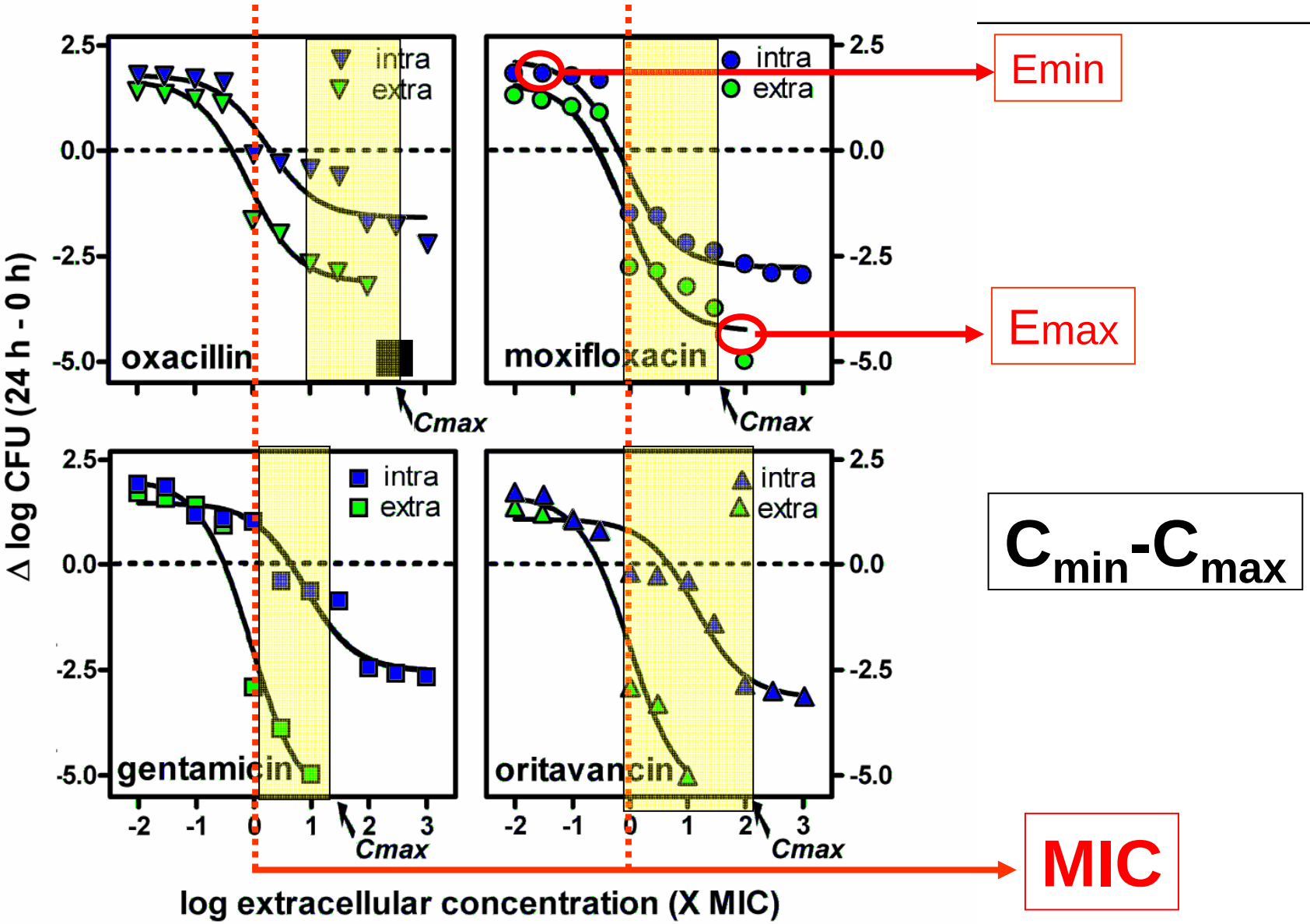


Example of a pharmacodynamic relationship



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

And what if we put pharmacokinetics ?



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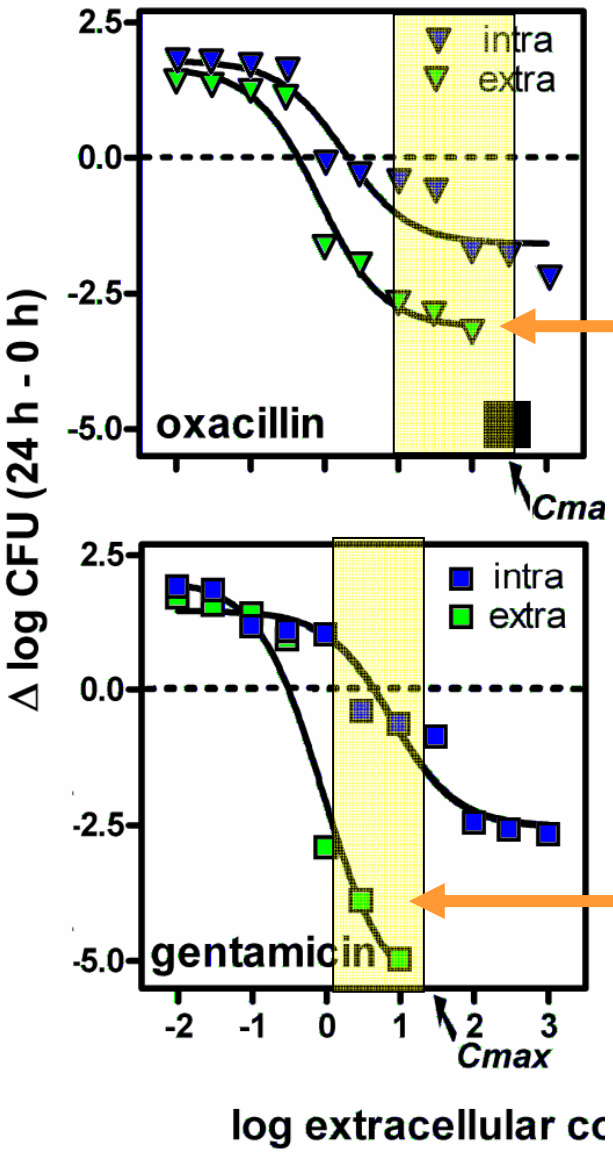


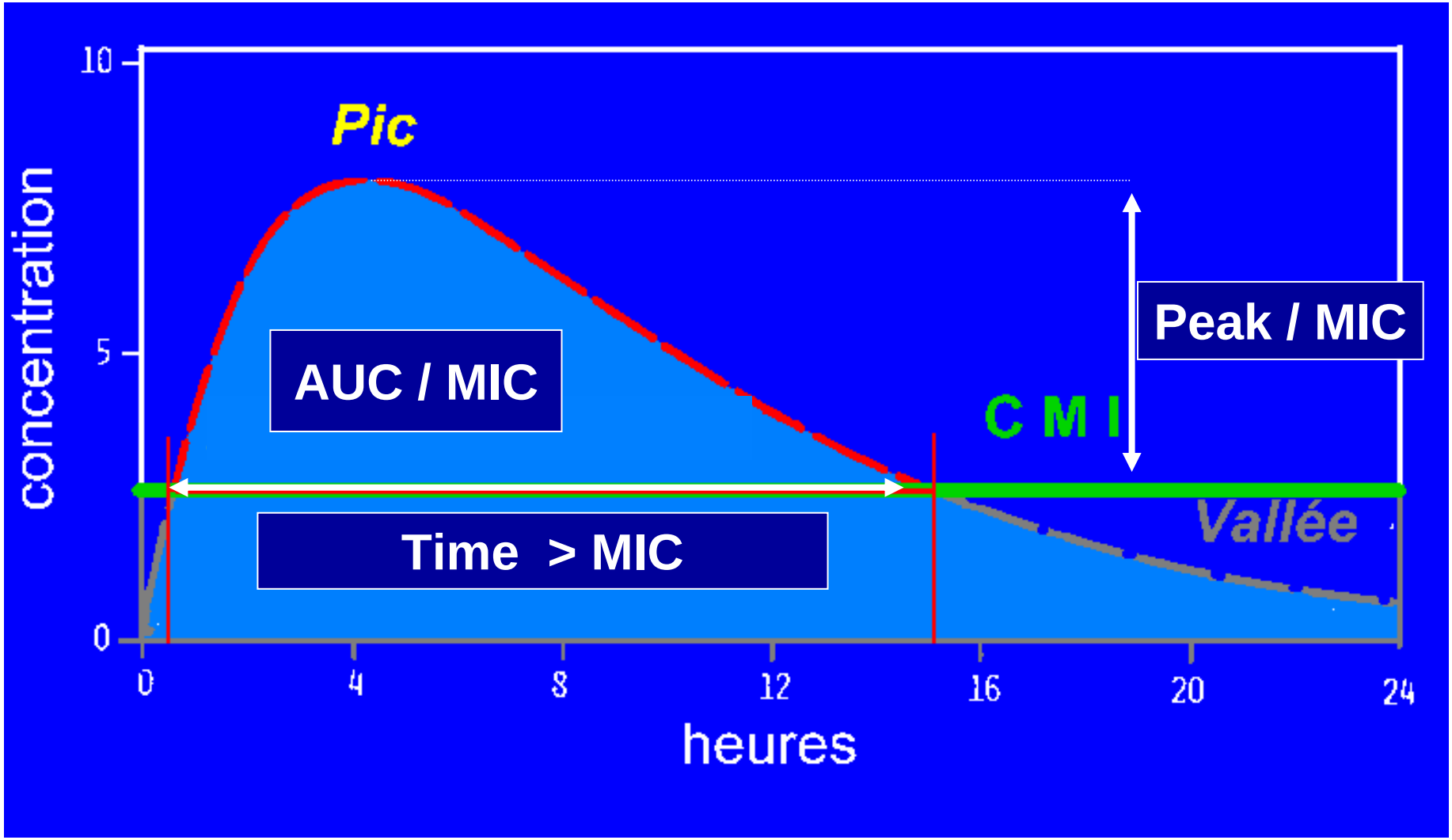
low concentration dependency

C_{min}-C_{max}

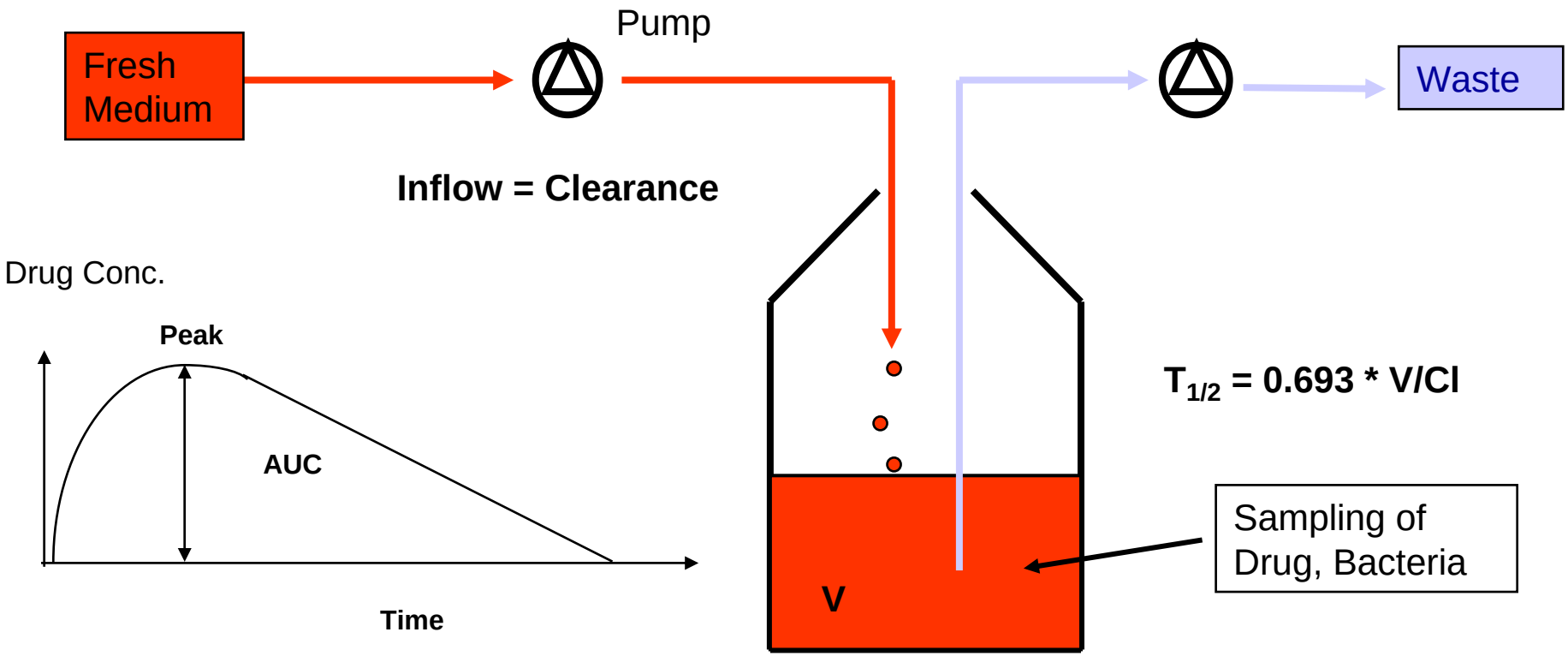
high concentration dependency

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 …

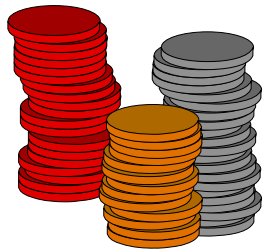
Which antibiotics are

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

dependent

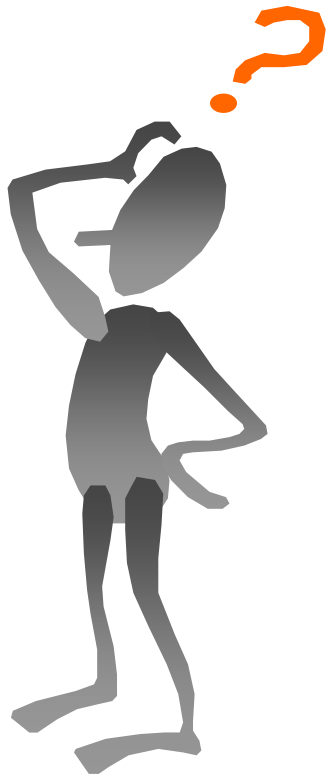
in

clinically meaningful conditions ?



Main PK/PD properties of antibiotics

Available antibiotics can be divided in 3 groups :



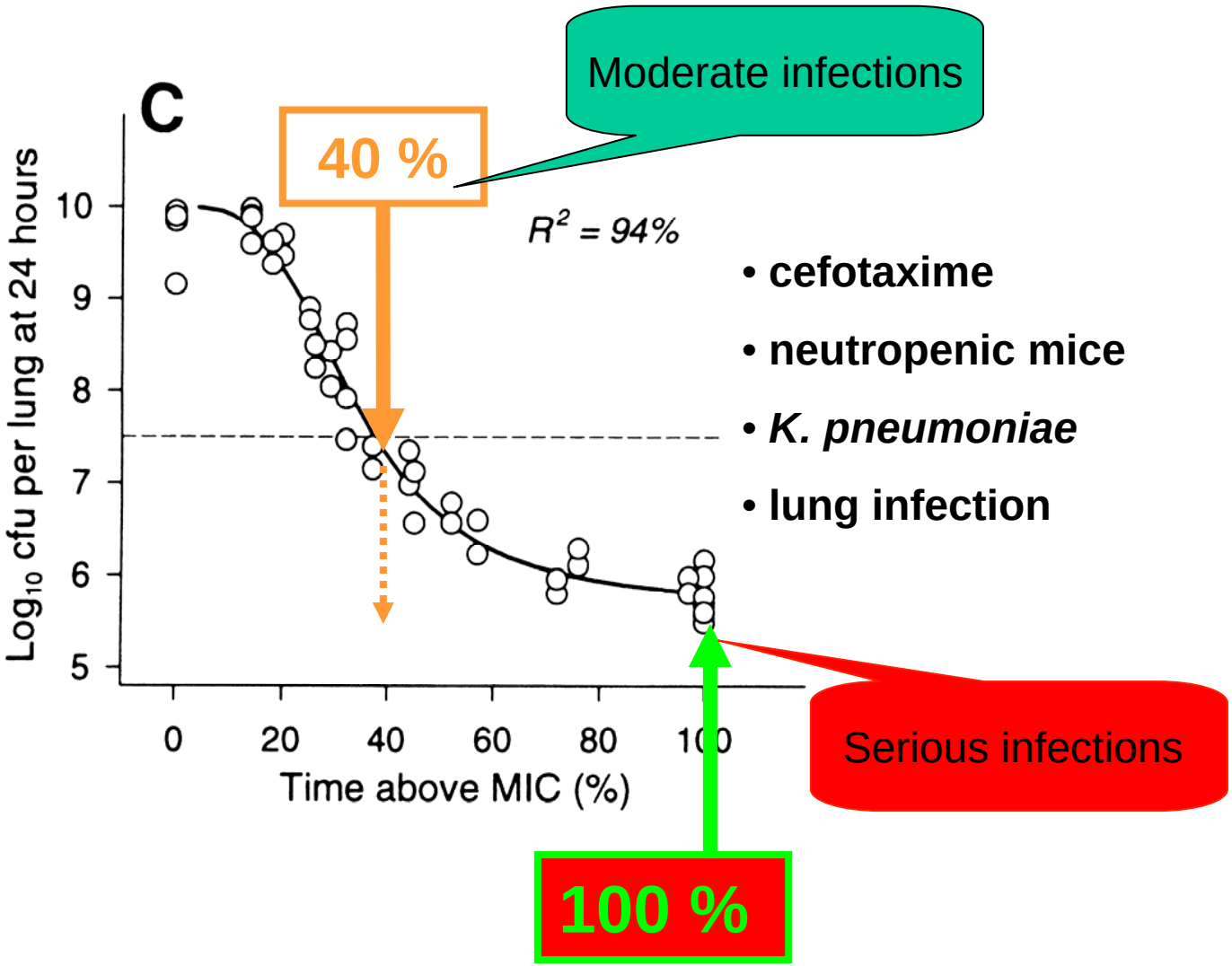
Antibiotics Group # 1

(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**	**Maximalize the exposure time**

How long should you stay above the MIC ?



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

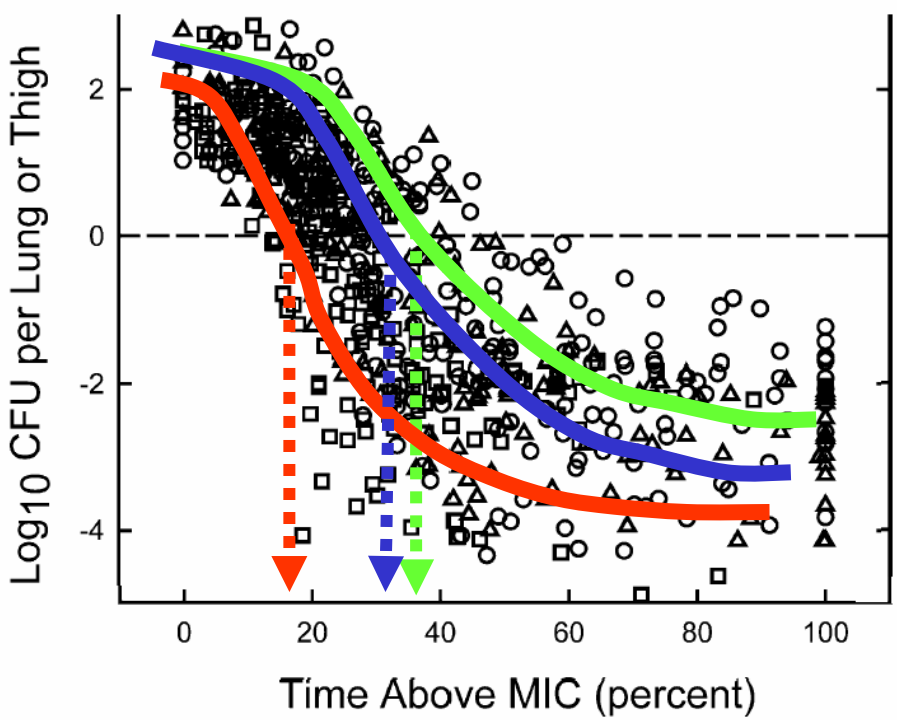


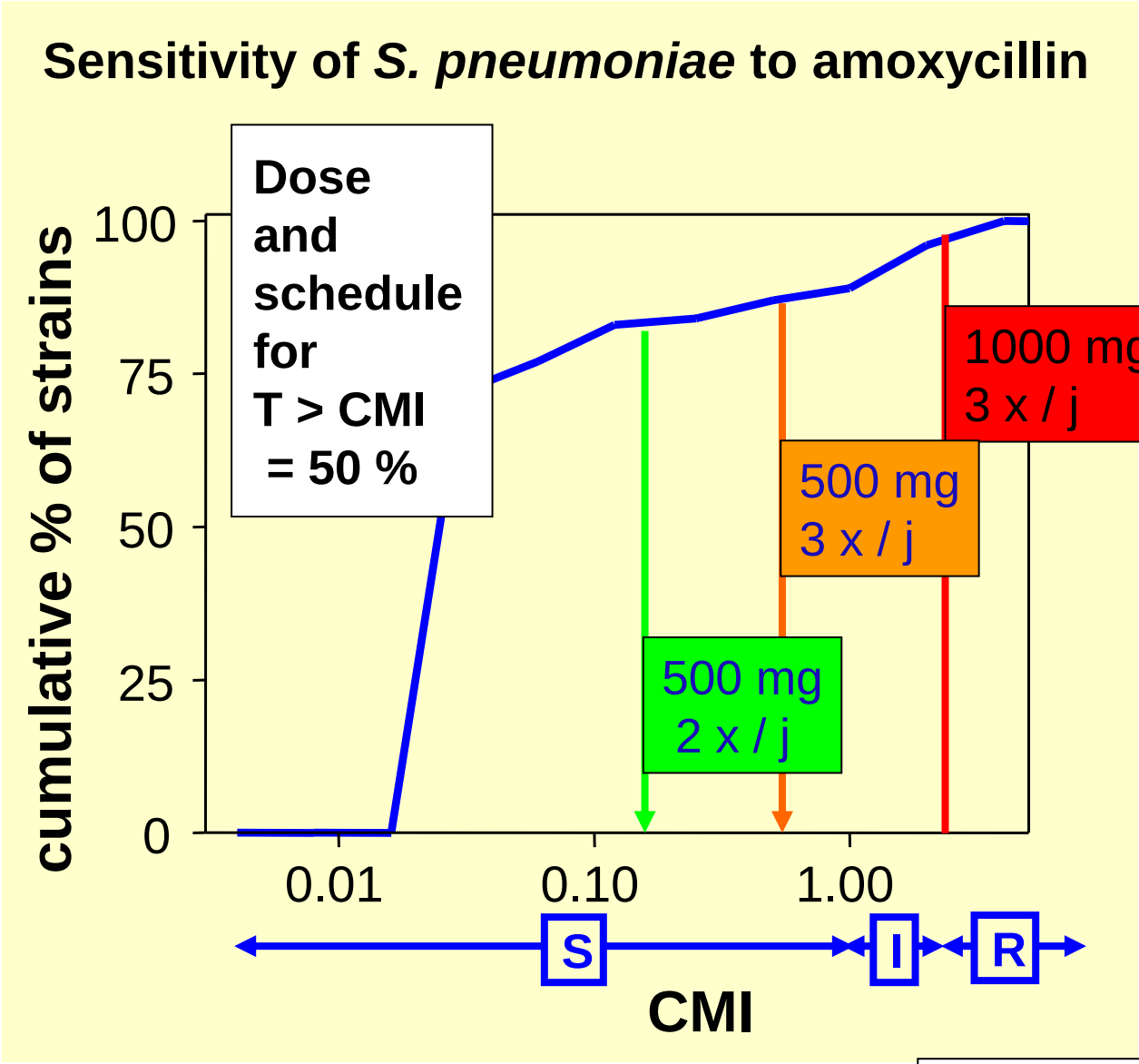
Fig. 7. Relationship between the change in $\log_{10}$ CFU per thigh or lung fo[r] [various pathogens following 24 h of therapy with different] doses o[f] penicillins (△), cephalosporins (○), and carbapenems (□).

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**

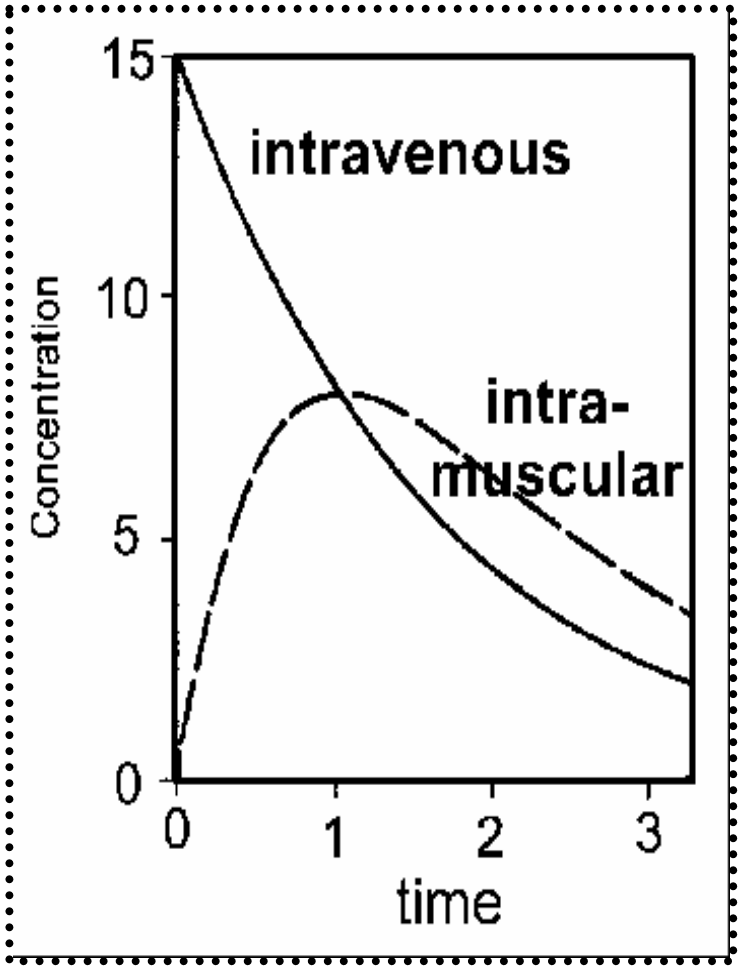
Antibiotics Group # 3

(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 / CMI**	**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

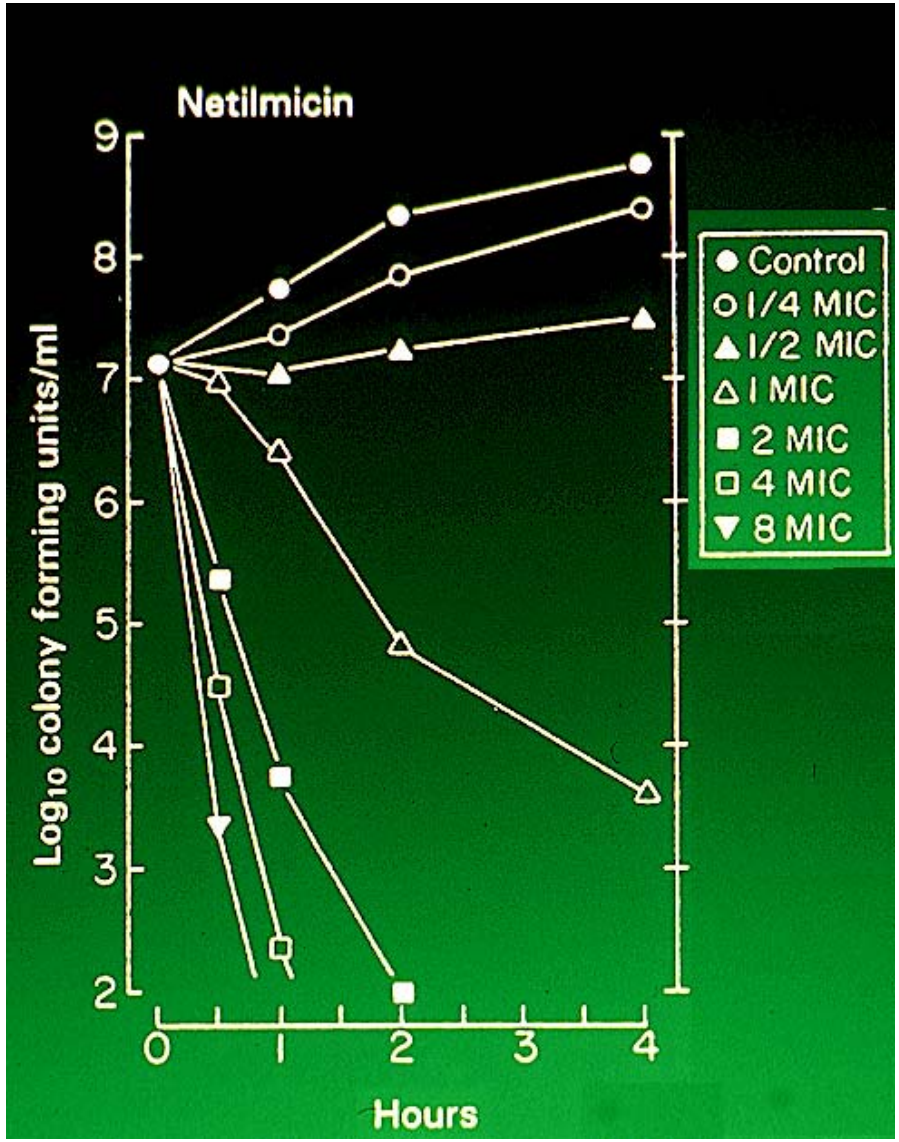
➡ peak = dosis / Vd

➡ dosis = peak x Vd

➡ dosis = MIC x 8 x Vd

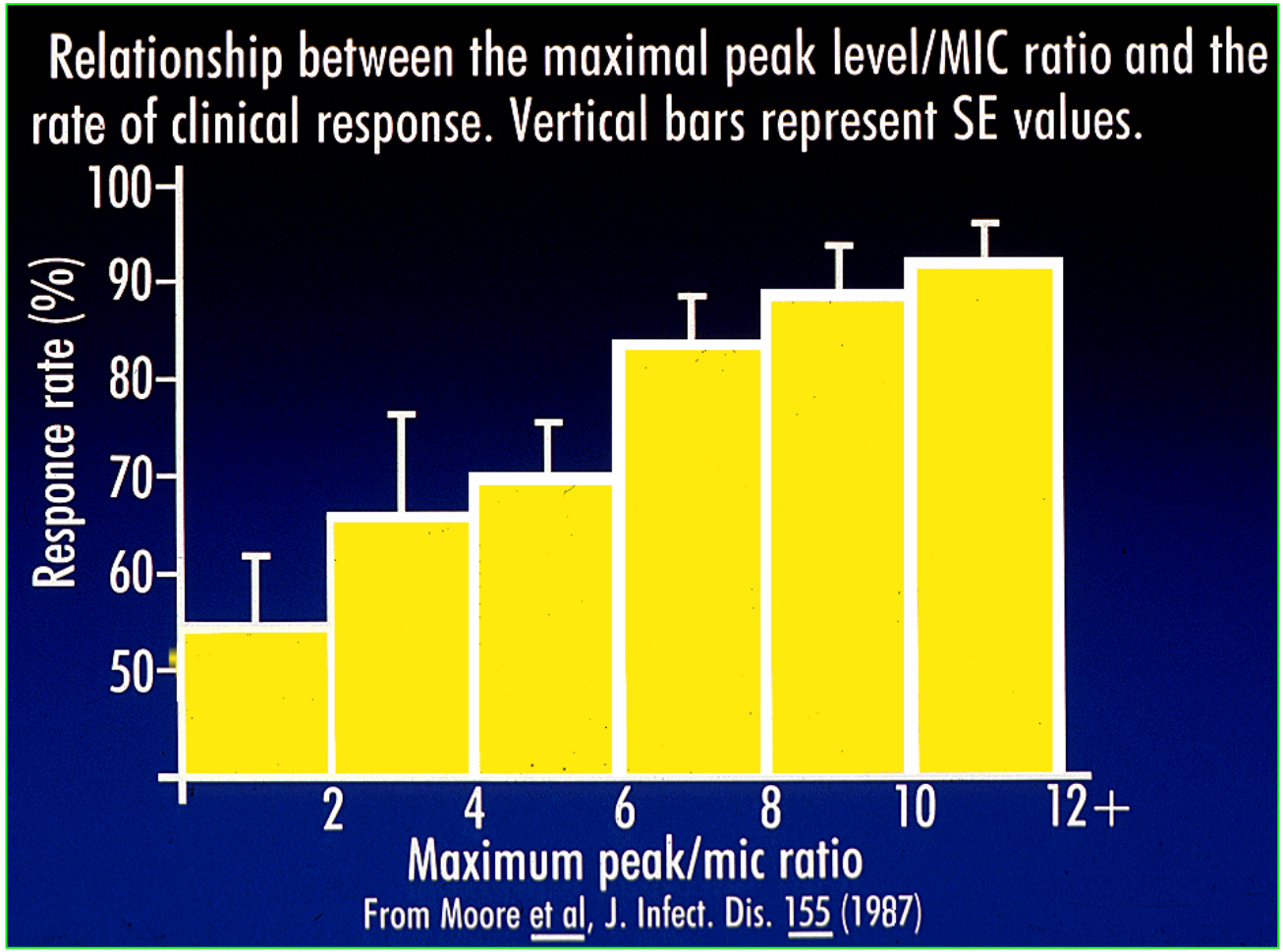
Aminoglycosides: why a peak ?

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



Aminoglycosides: why a peak ?

Clinical efficacy is linked to peak/MIC ratio

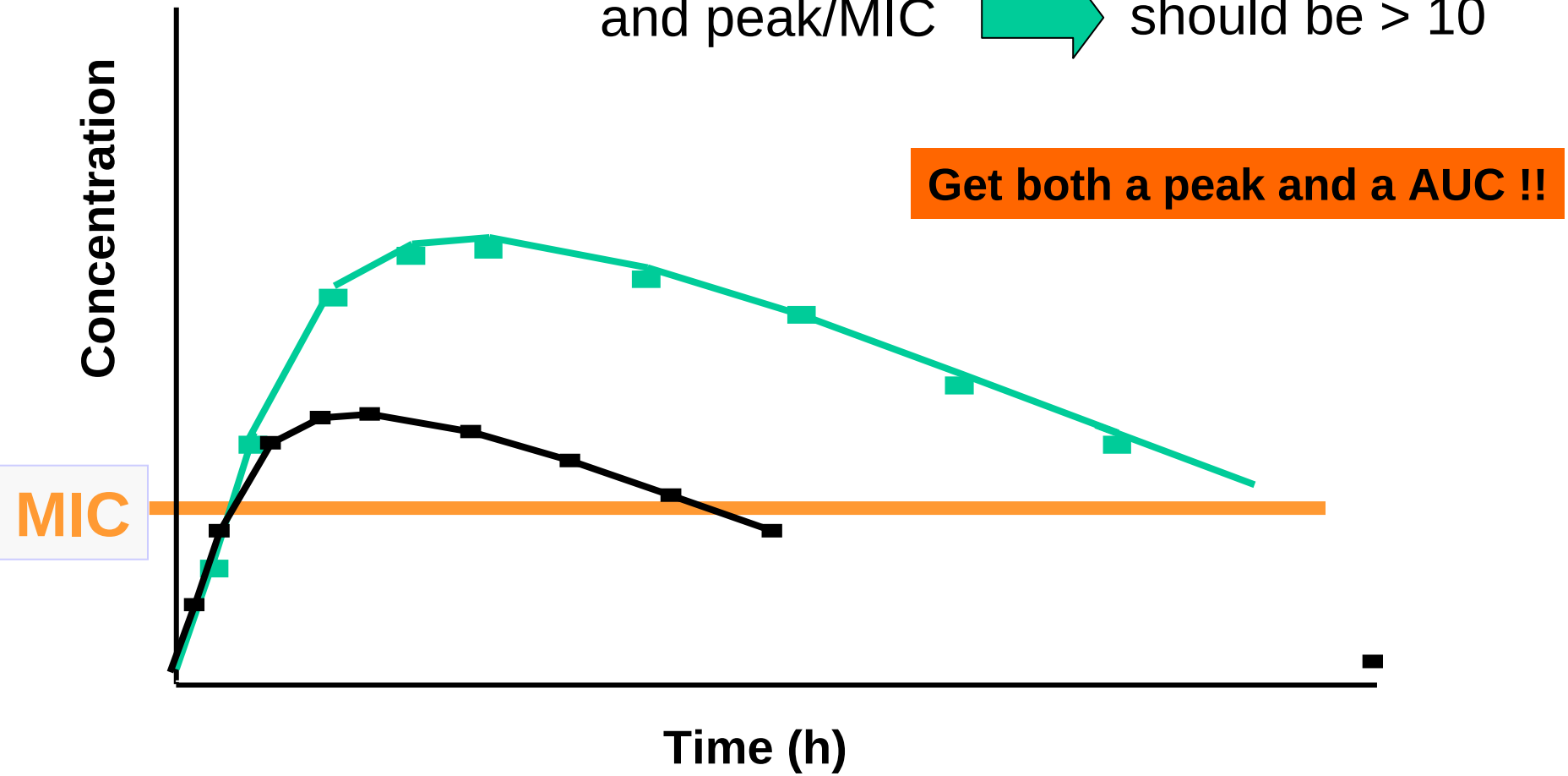


Fluoroquinolones: get a peak and an AUC !

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

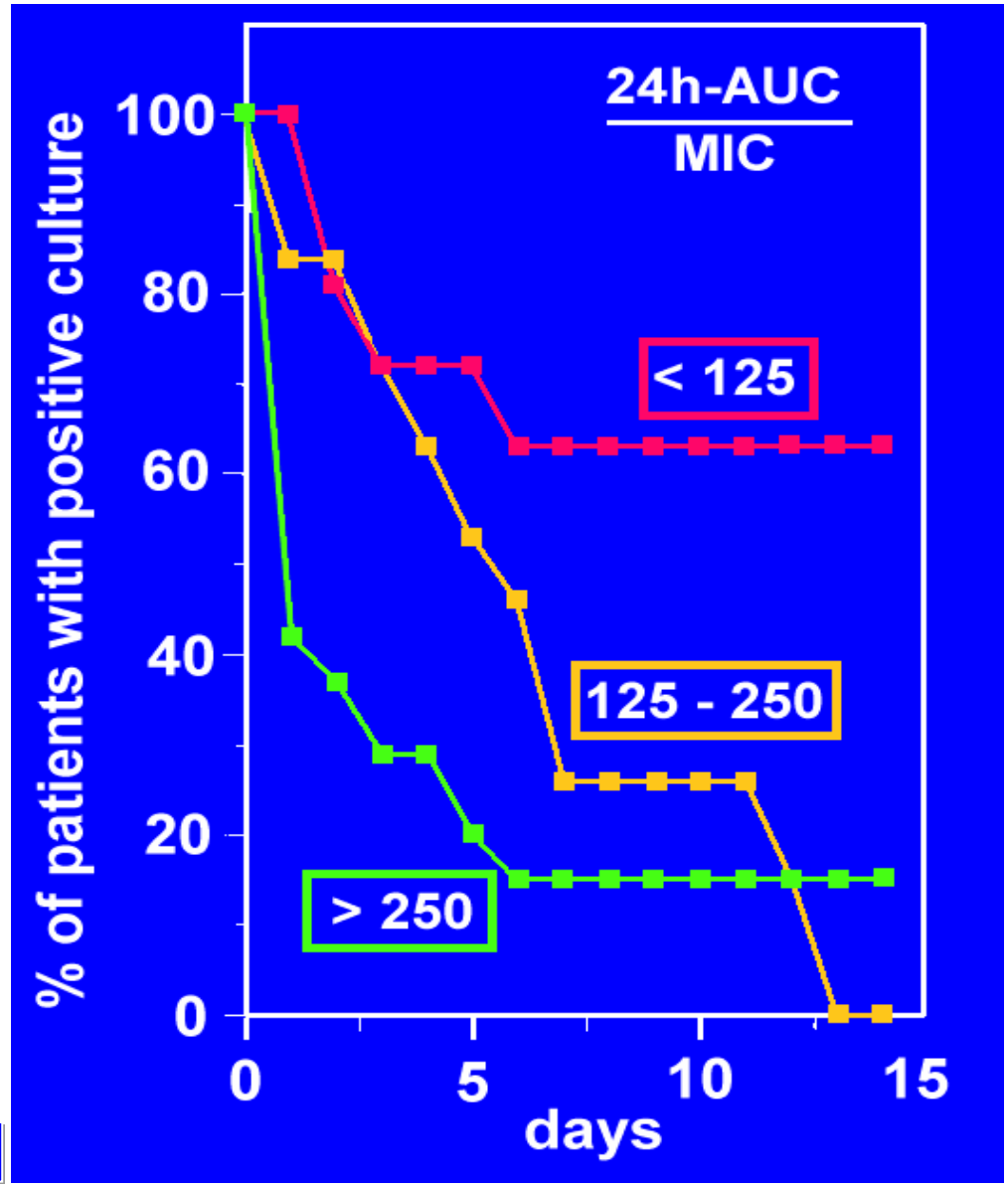
and peak/MIC → should be > 10

Get both a peak and a AUC !!



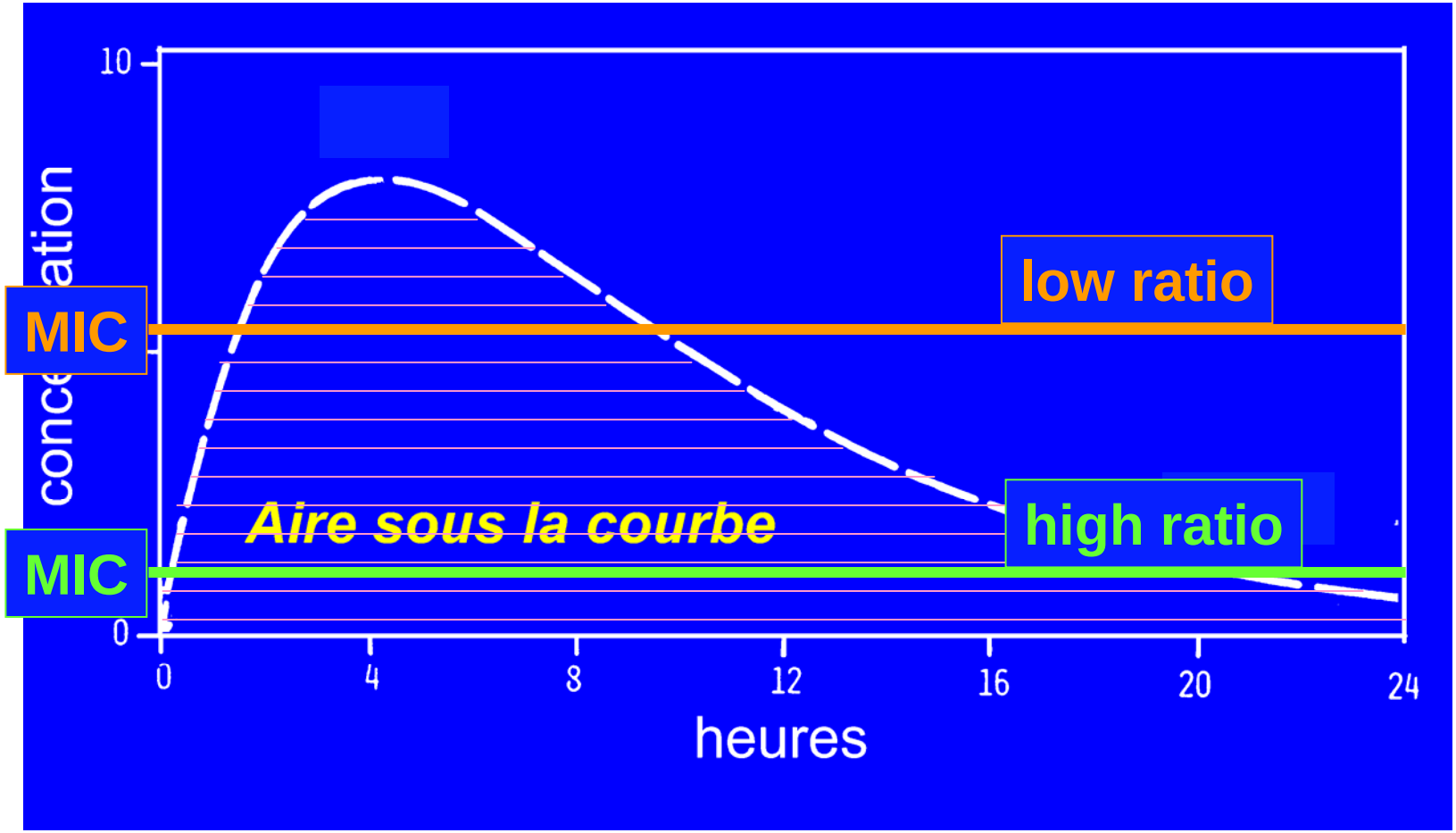
Why an AUC / MIC > 125 for fluoroquinolones ...

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

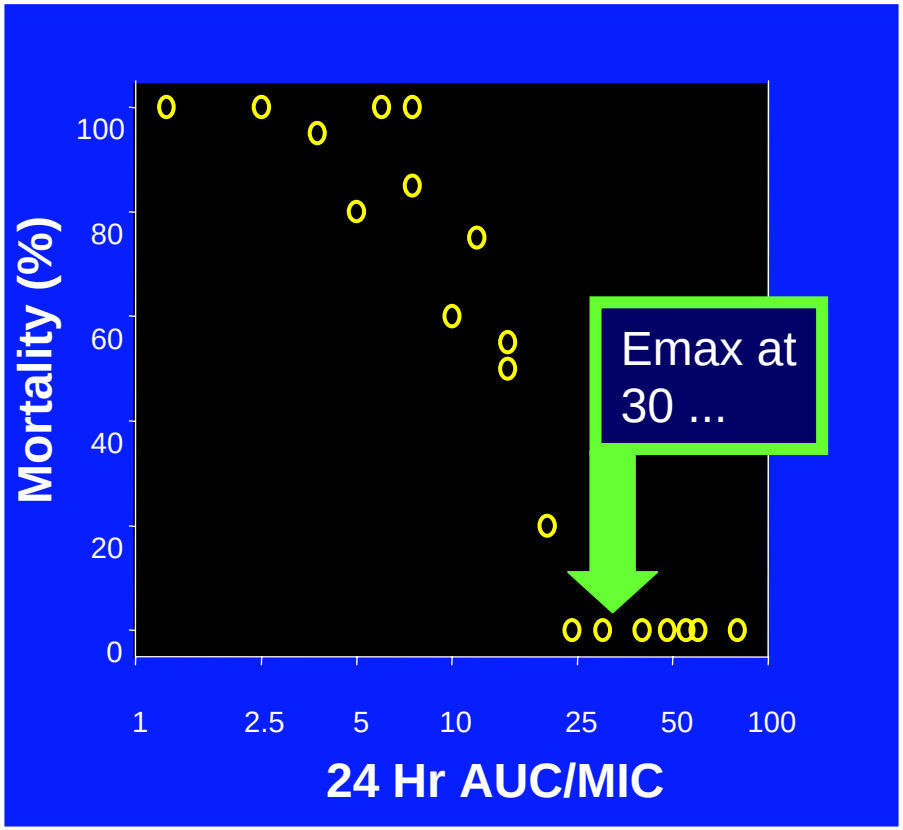
AUC/MIC_{24h} =125 : a magical number??

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

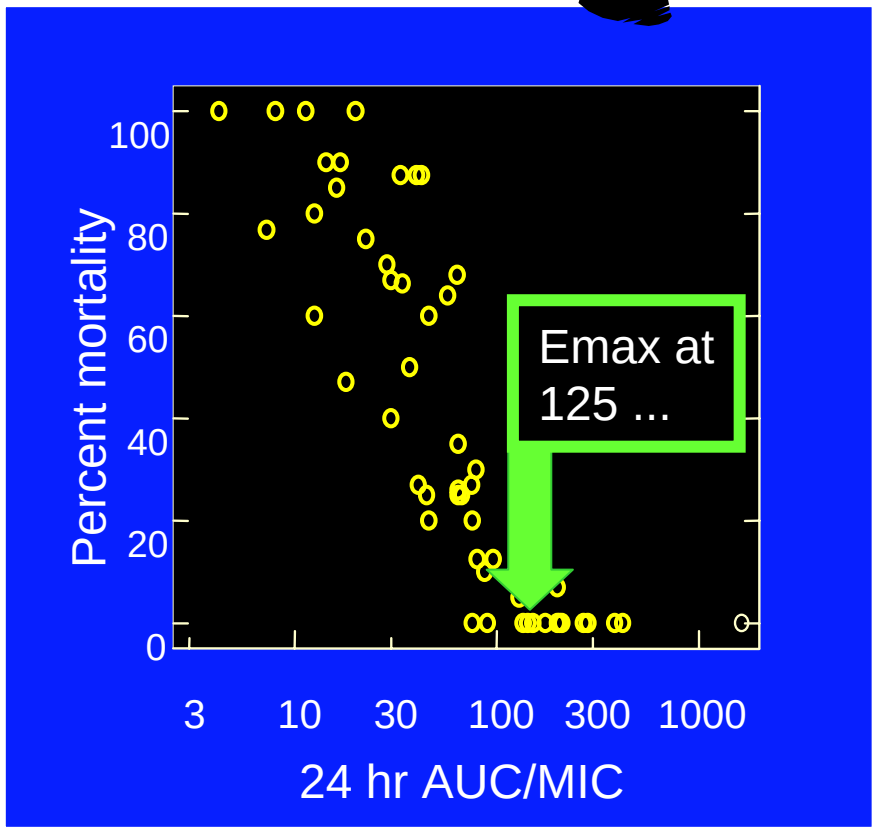
- a large MIC
- or a too low dosage
  (AUC is proportional to the dosage)

Is 125 good for all ??

The saga of *S. pneumoniae* ...



non-neutropenic



neutropenic

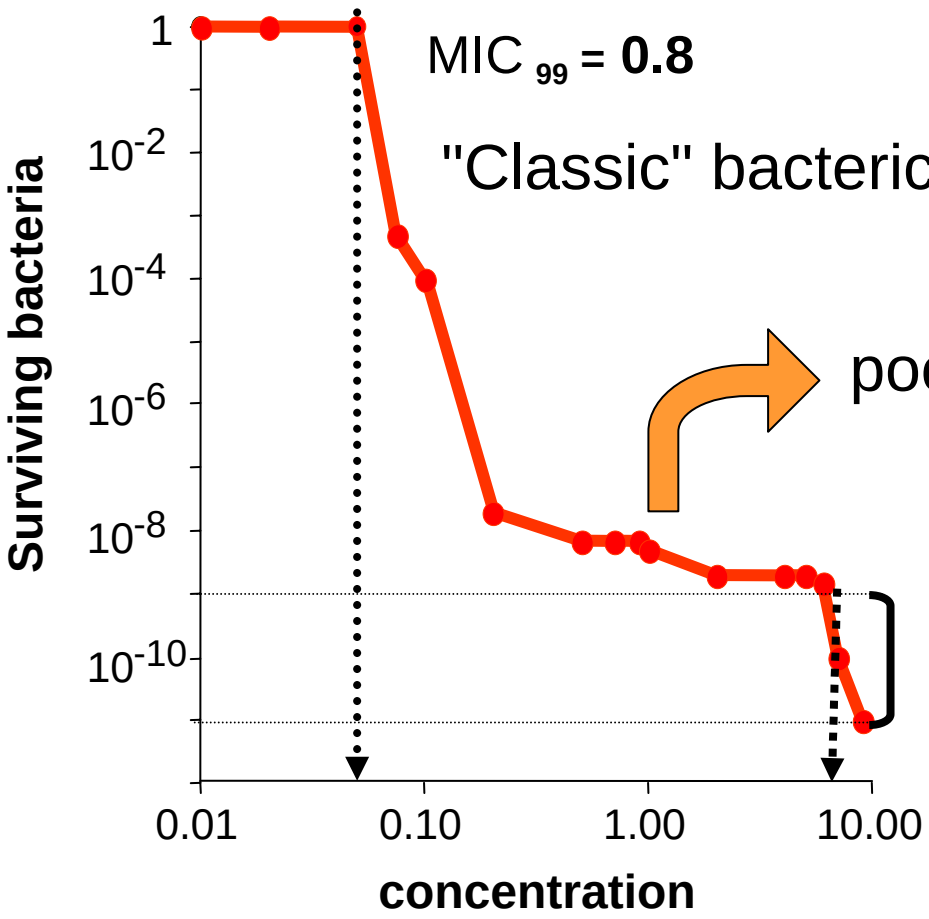
How to optimize the AUC / MIC ratio ?

AUC = dosis / Cl

→ Adjust the daily dosis
~ target AUC

→ Adapt the number of administrations
~ pharmacokinetics of the drug

Mutant Prevention Concentration …



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

"Classic" bactericidal effect

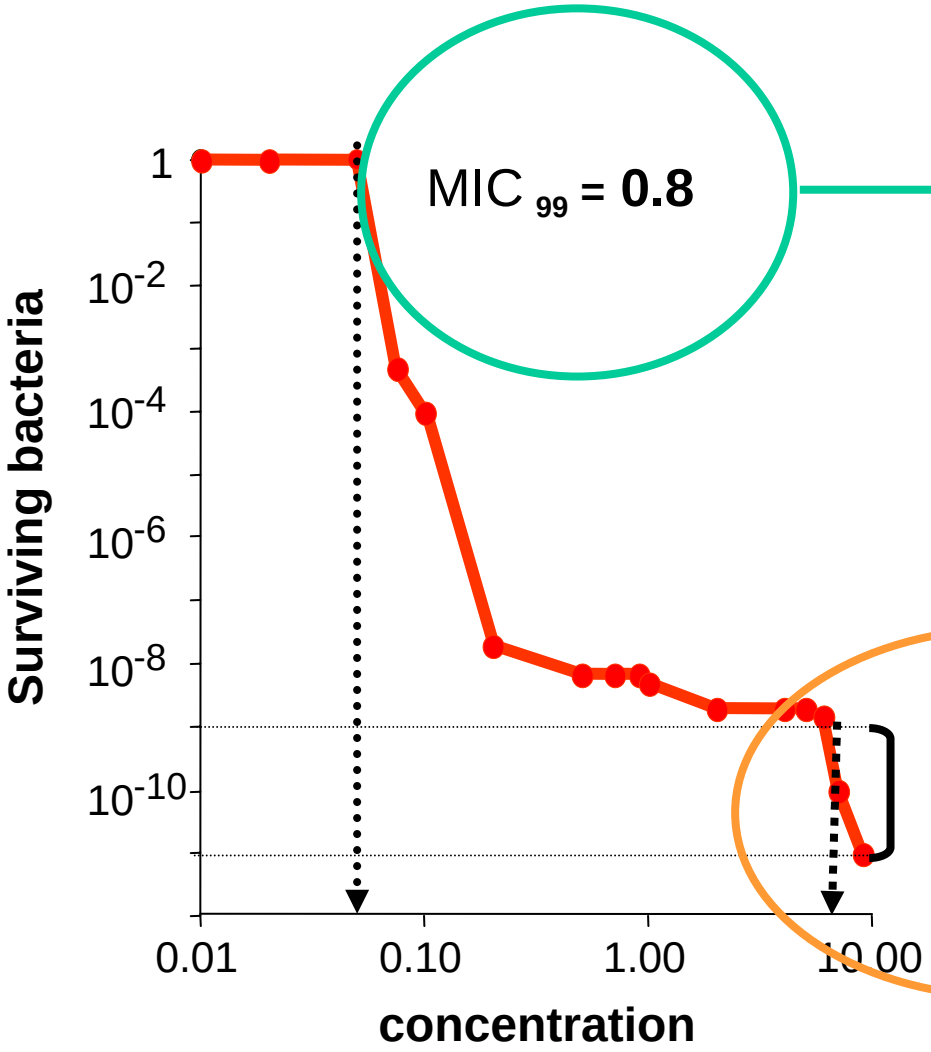
poorly sensitive organisms…

Elimination of resistant organisms

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

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

Mutant Prevention Concentration …

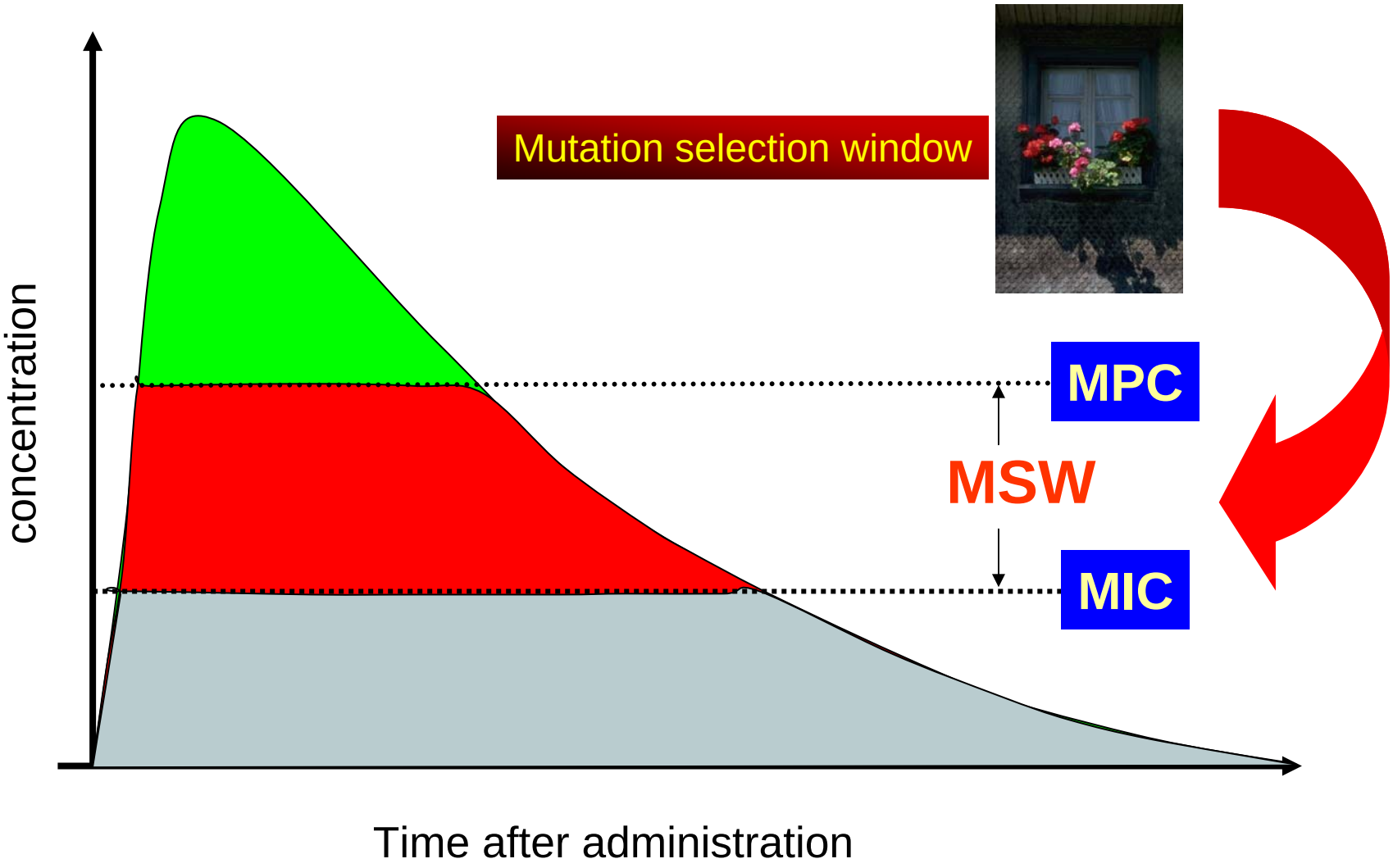


Concentration which will inhibit the majority of the organisms

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

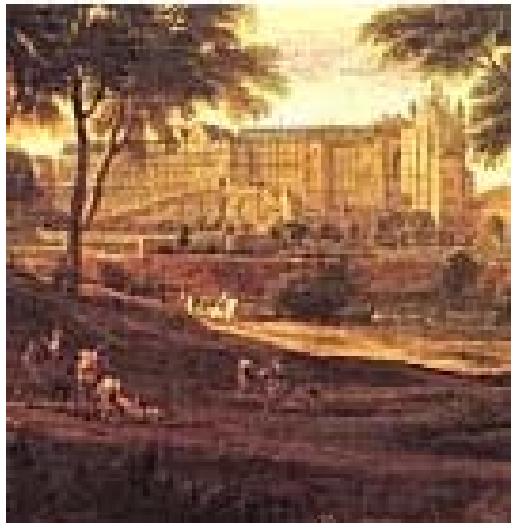
So, let us accept values with some degree of precaution

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

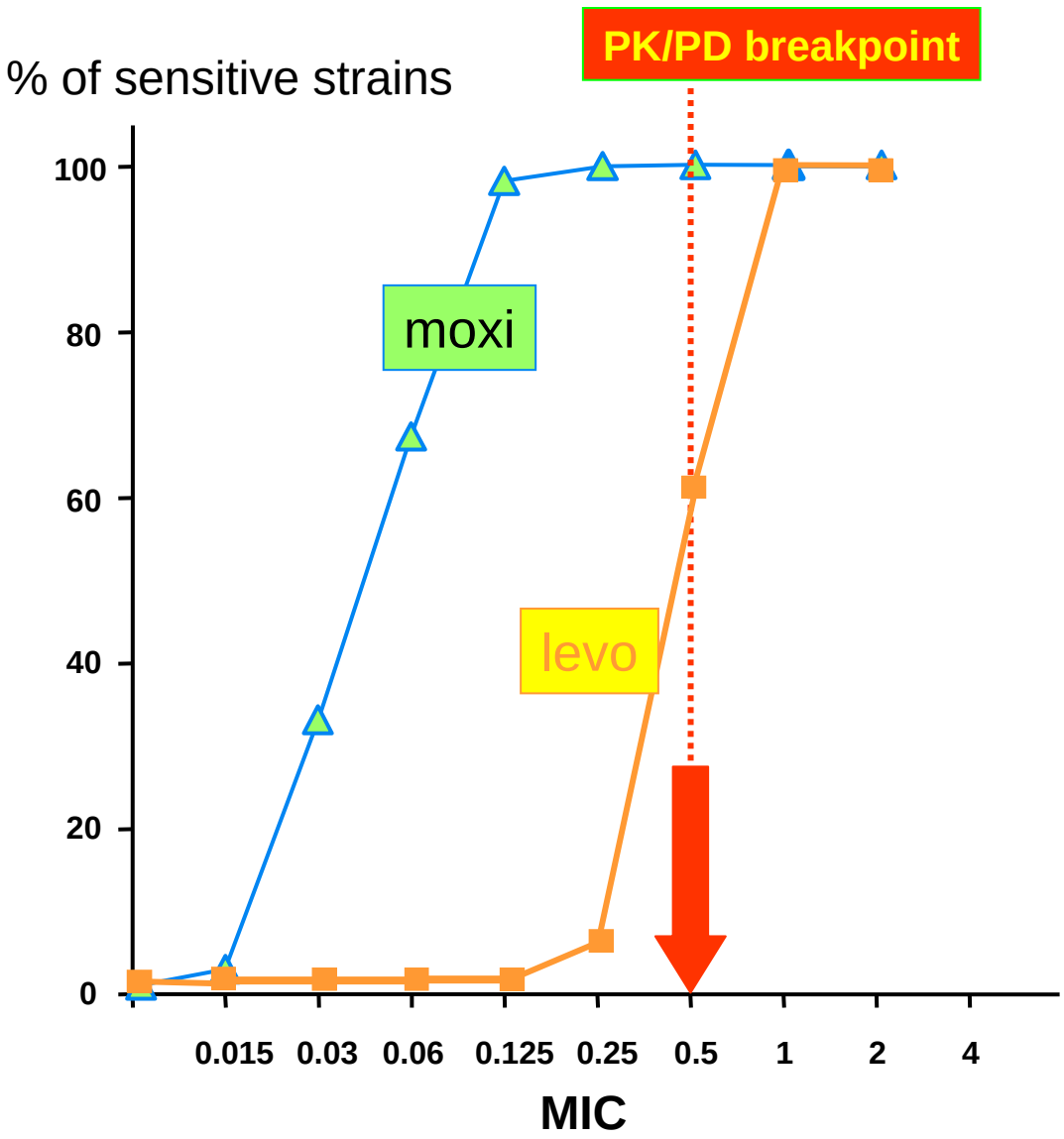


A proposal for PK/PD based-breakpoints for fluoroquinolones...

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

PK/PD in action …



Levofloxacin 500 mg 1X / jr

- AUC [(mg/l)xh] 47
- peak [mg/l] 5

➔ MIC_{max} < 0.5

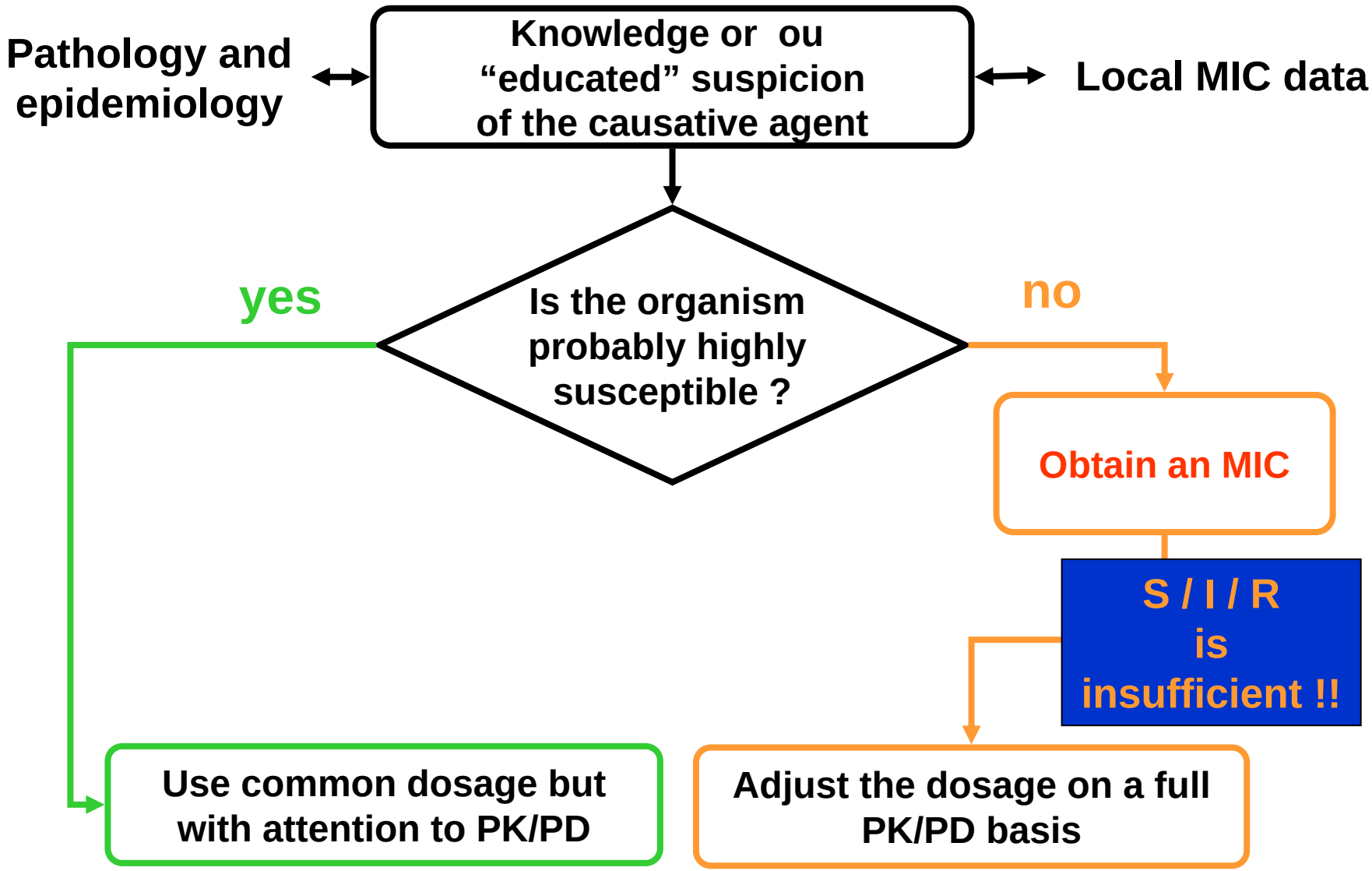
Moxifloxacin 400 mg 1X /jr

- AUC [(mg/l)xh] 48
- peak [mg/l] 4.5

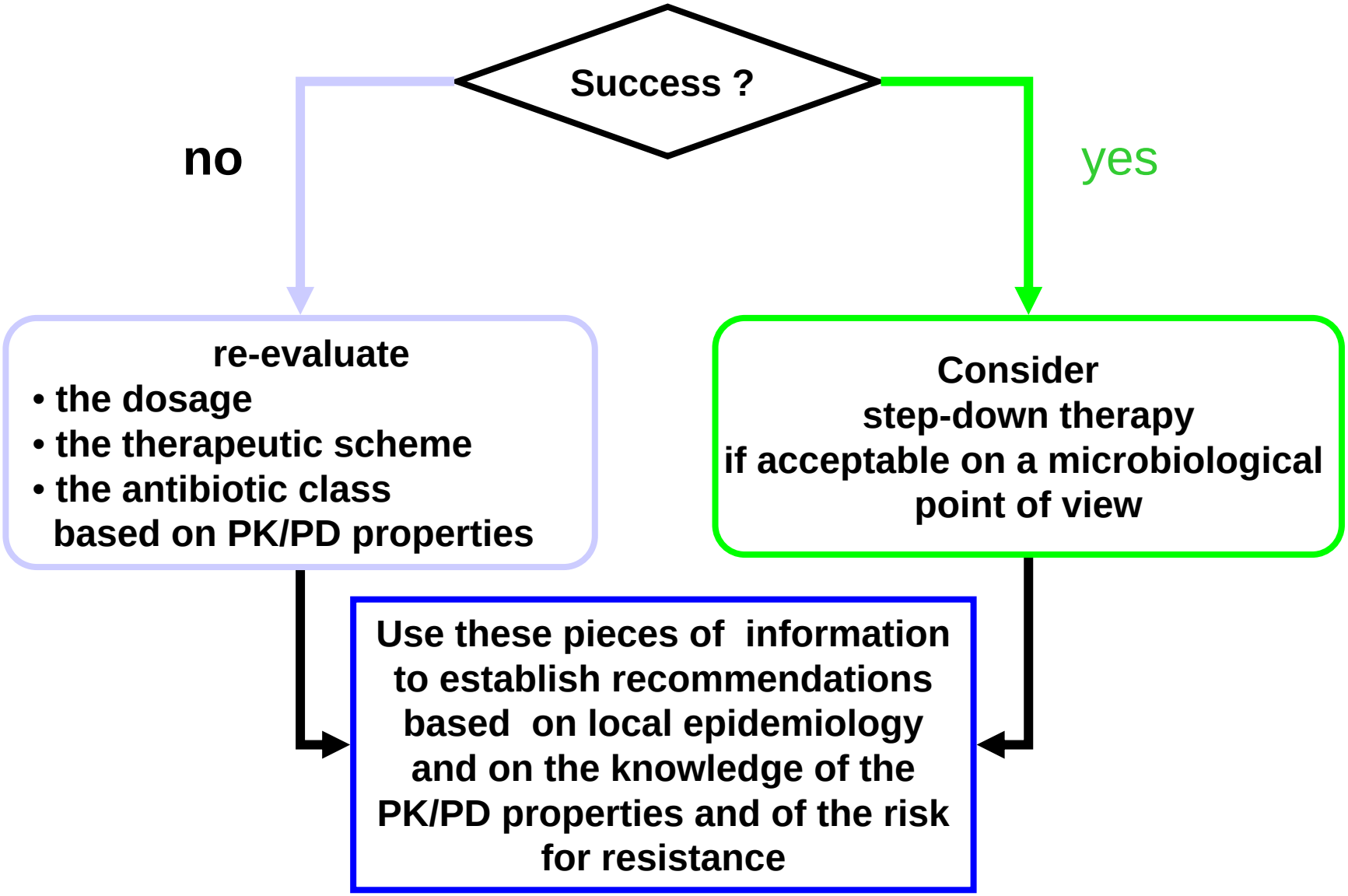
➔ MIC_{max} < 0.5

MIC data: J. Verhaegen et al., 2003

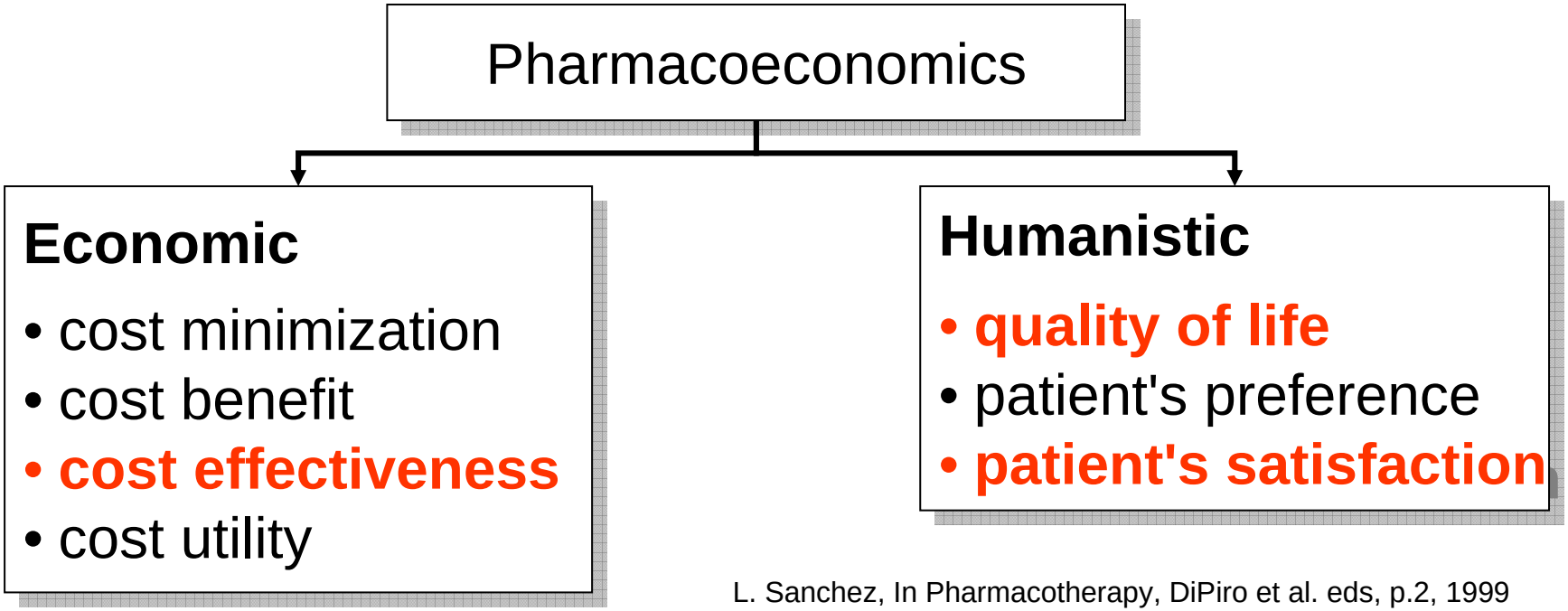
A clinical algorithm ...



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

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 …

Please, act …

www.antiinfectieux.org

W.A. Craig, MD
M.N. Dudley, Pharm.
G.L. Drusano, MD
J.J. Schentag, Pharm.
A. McGowan, MD
X. Zao, PhD
V. Firsov, MD
S. Zinner, MD
A. Dalhoff, PhD
…

F. Van Bambeke, Pharm.
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H. Chanteux, Pharm.
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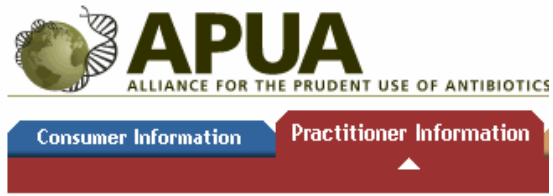

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