Merging systems pharmacology with PK/PD analysis to enhance drug discovery: the case of novel antibiotics

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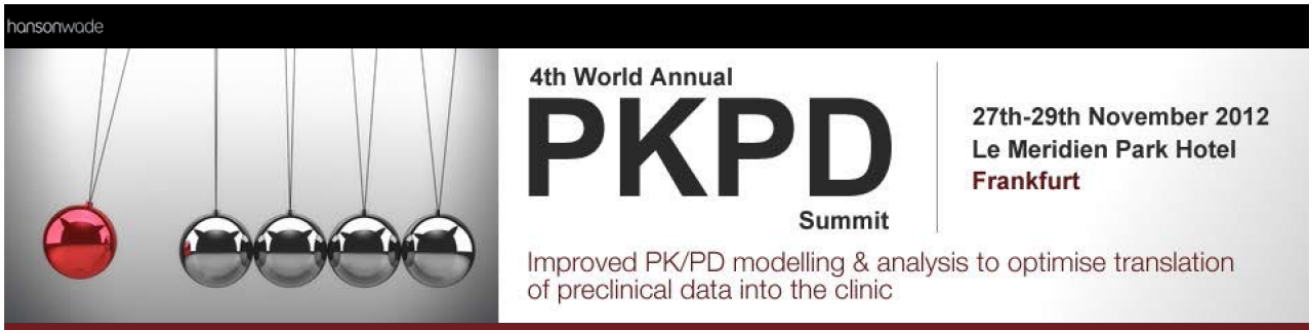
with ideas and data borrowed from colleagues at the

- **International Society of Antiinfective Pharmacology** (***ISAP***),
- **European Committee for Antibiotic Susceptibility Testing** (***EUCAST***)
- **European Study Group of Pharmacodynamics/Pharmacokinetics** (***ESPAG***)



What is it all about ?

- Is there a crisis with antibiotics ?
  - Resistance is growing, but …
  - New compounds are less and less reaching the market
- How applying a systems pharmacology approach can lead to enhanced quantitative drug discovery and development
- How PK/PD can prevent the emergence and spreading of resistance
- Using novel antimicrobials as an example of how an integrated approach can lead to more informed decision making

The antibiotic crisis *

1. Resistance

* A pictorial view using 4 paintings of Van Gogh (who stayed briefly in Belgium when moving from Holland to France) and selected Belgian and International data

Are antibiotics following a path to madness ?

1928 - …

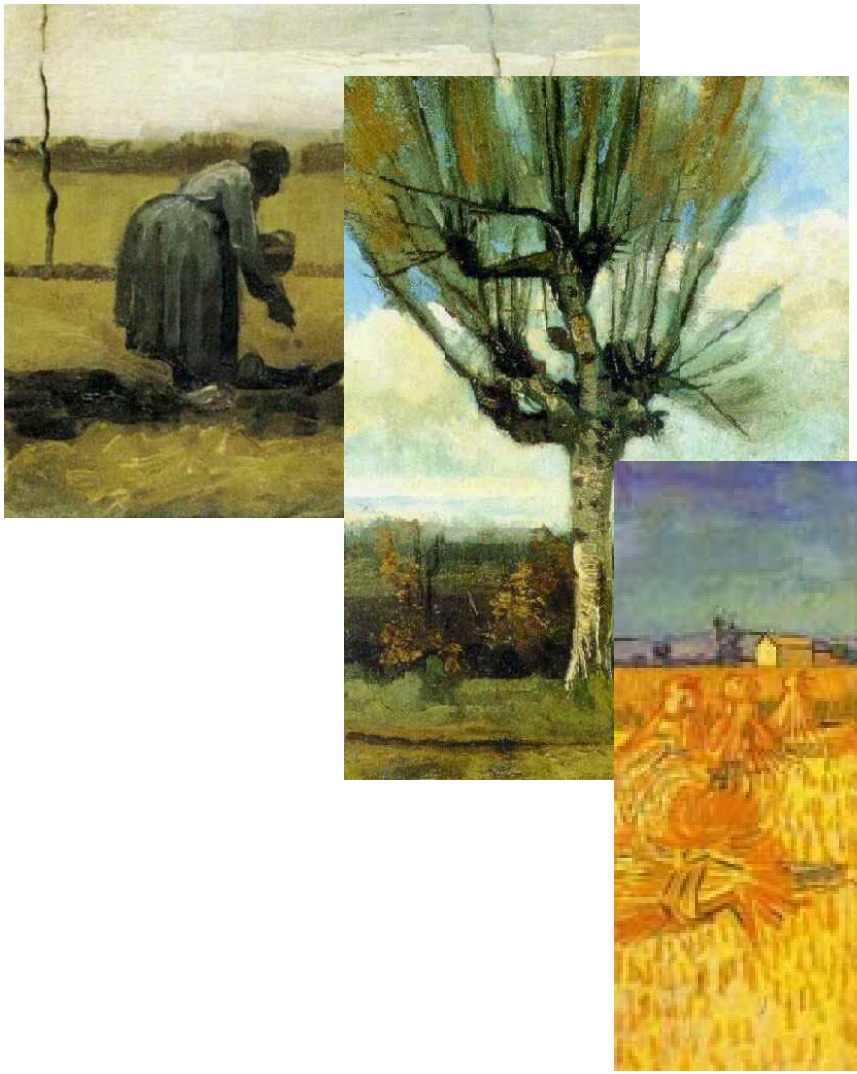
discovery in soil bacteria and fungi

Are antibiotics following a path to madness ?

1950 – 1980 …

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

Are antibiotics following a path to madness ?



and the US General Surgeon told us that the fight was over

1970 …

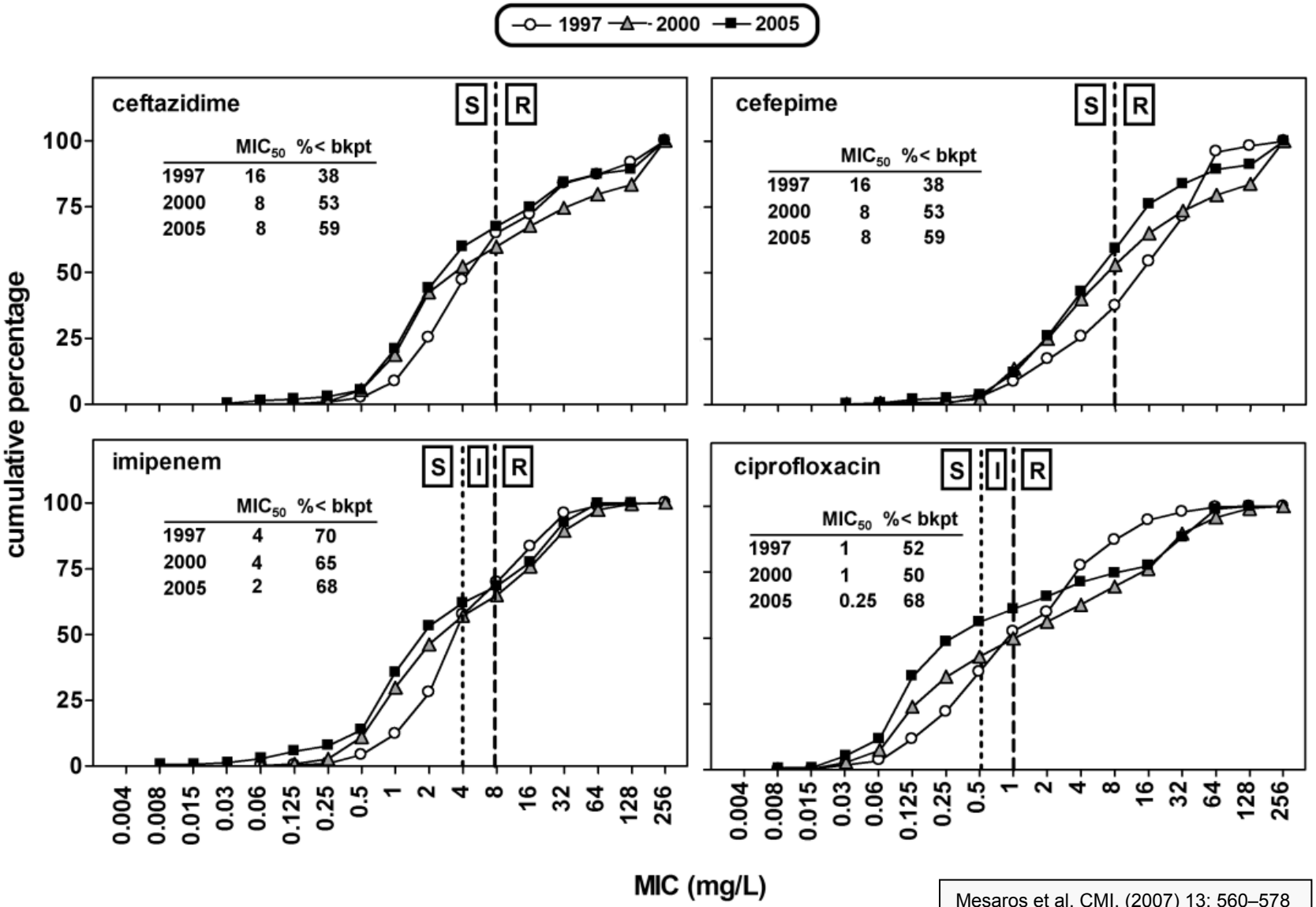
Are antibiotics following a path to madness ?

But…

2012 …

Extent of resistance of *P. aeruginosa*

(International data – EUCAST breakpoints)



Mesaros et al. CMI, (2007) 13: 560–578

The hidden risk of therapy (at the corner of your street …)

International Journal of Antimicrobial Agents 36 (2010) 513–522

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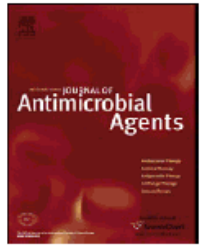
journal homepage: http://www.elsevier.com/locate/ijantimicag

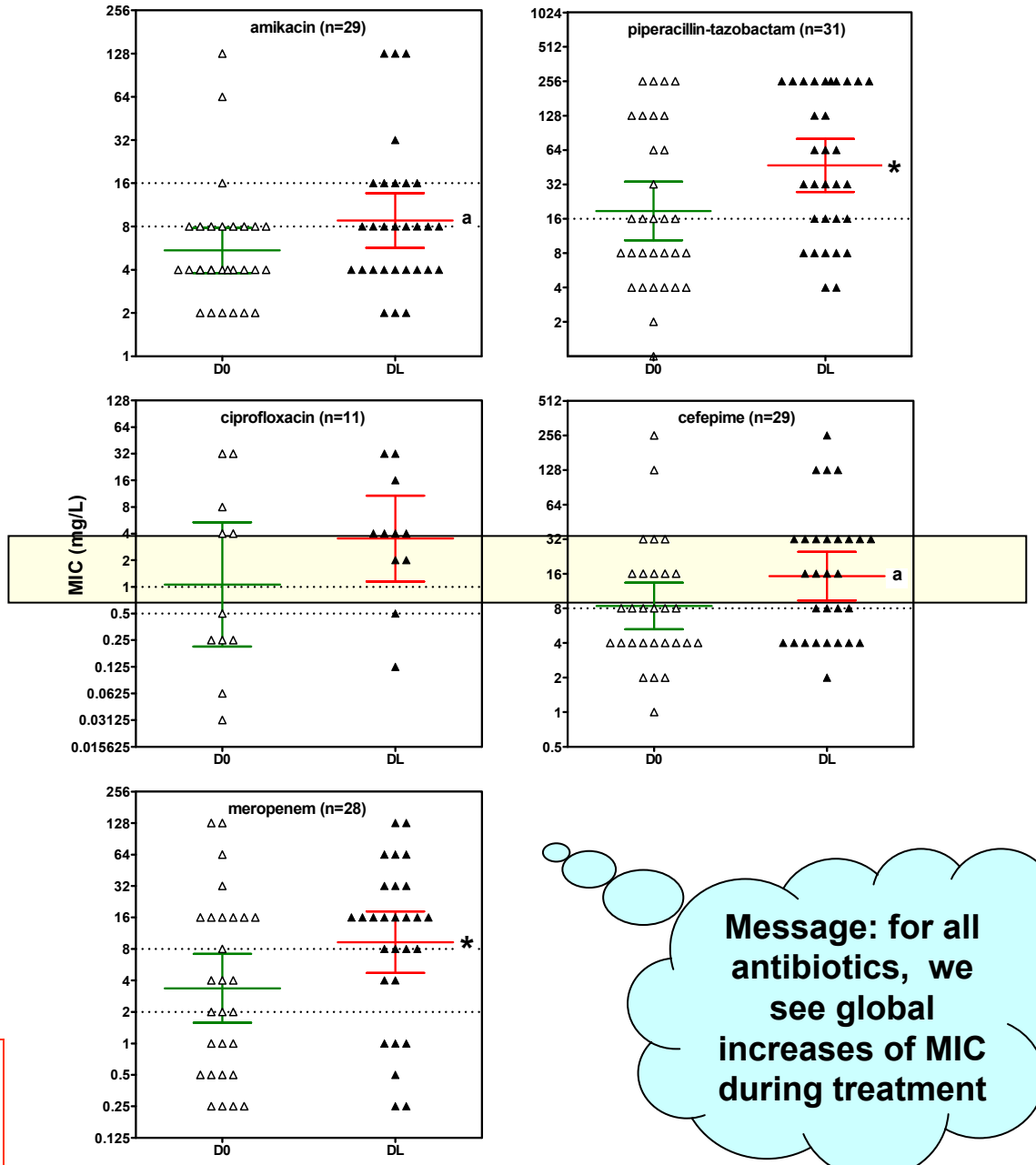


In vivo development of antimicrobial resistance in *Pseudomonas aeruginosa* strains isolated from the lower respiratory tract of Intensive Care Unit patients with nosocomial pneumonia and receiving antipseudomonal therapy

Mickaël Riou[a,1], Sylviane Carbonnelle[a,2], Laëtitia Avrain[a,b], Narcisa Mesaros[a,3], Jean-Paul Pirnay[c], Florence Bilocq[c], Daniel De Vos[c,d], Anne Simon[e], Denis Piérard[f], Frédérique Jacobs[g], Anne Dediste[h], Paul M. Tulkens[a,*], Françoise Van Bambeke[a], Youri Glupczynski[i]

[a] *Unité de Pharmacologie Cellulaire et Moléculaire & Louvain Drug Research Institute, Université catholique de Louvain, Brussels, Belgium*
[b] *Coris BioConcept, Gembloux, Belgium*
[c] *Laboratory for Molecular & Cellular Technology, Queen Astrid Military Hospital, Neder-over-Heembeek, Brussels, Belgium*
[d] *Department of Molecular and Cellular Interactions, Vrije Universiteit Brussel, Brussels, Belgium*
[e] *Laboratoire de Microbiologie, Cliniques Universitaires St-Luc, Brussels, Belgium*
[f] *Laboratorium voor Microbiologie, Universitair Ziekenhuis Brussel, Brussels, Belgium*
[g] *Clinique des Maladies Infectieuses, Hôpital Erasme, Brussels, Belgium*
[h] *Laboratoire de Microbiologie, Centre Hospitalier Universitaire Saint-Pierre, Brussels, Belgium*
[i] *Laboratoire de Microbiologie, Cliniques Universitaires UCL de Mont-Godinne, Yvoir, Belgium*

Do you remain effective while treating ?



- D0: initial isolate
  DL: last isolate obtained
- individual values with geometric mean (95 % CI)
- S (lowest line) and R (highest line) EUCAST breakpoints

* $p < 0.05$ by paired t-test (two-tailed) and Wilcoxon non-parametric test

[a] $p < 0.05$ by Wilcoxon non-parametric test only

Note: stratification by time between D0 and DL gave no clue (too low numbers)

Message: for all antibiotics, we see global increases of MIC during treatment

What is it all about ?

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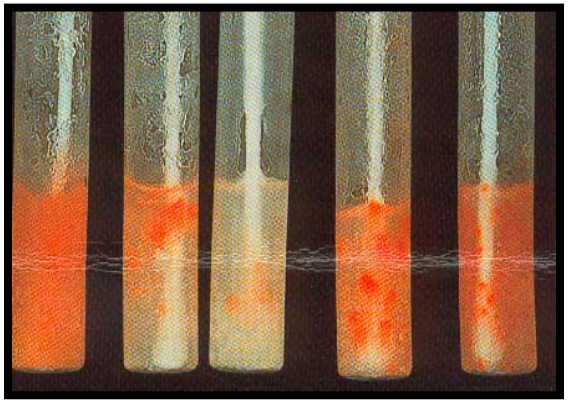
The original process of discovery and assessment

Waksman and Fleming …

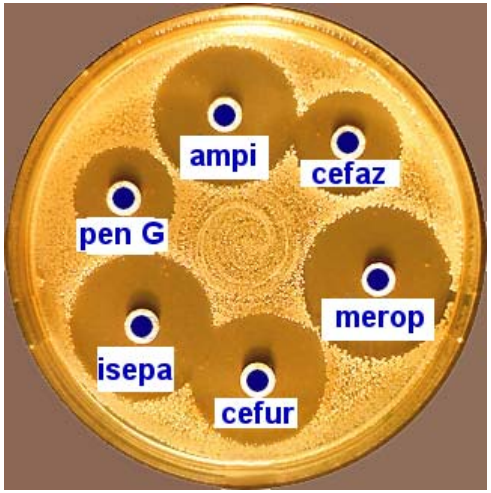
From the point of view of human benefit, never was a Nobel prize so justifiably awarded as was the award to Selman Waksman for the discovery of streptomycin and other antibiotics produced from *Streptomyces spp*. Waksman and his talented team (many of whom went on to make important antibiotic discoveries in their own right) developed the concept of **systematic screening** of microbial culture products for biological activity, a technology which has provided the foundation of the antibiotic industry, and for this alone his name should rank high in any pantheon of microbiology.

J. Davies: In Praise of Antibiotics, ASM News
http://www.asm.org/memonly/asmnews/may99/feature6.html

And it remains like that for long …



identification

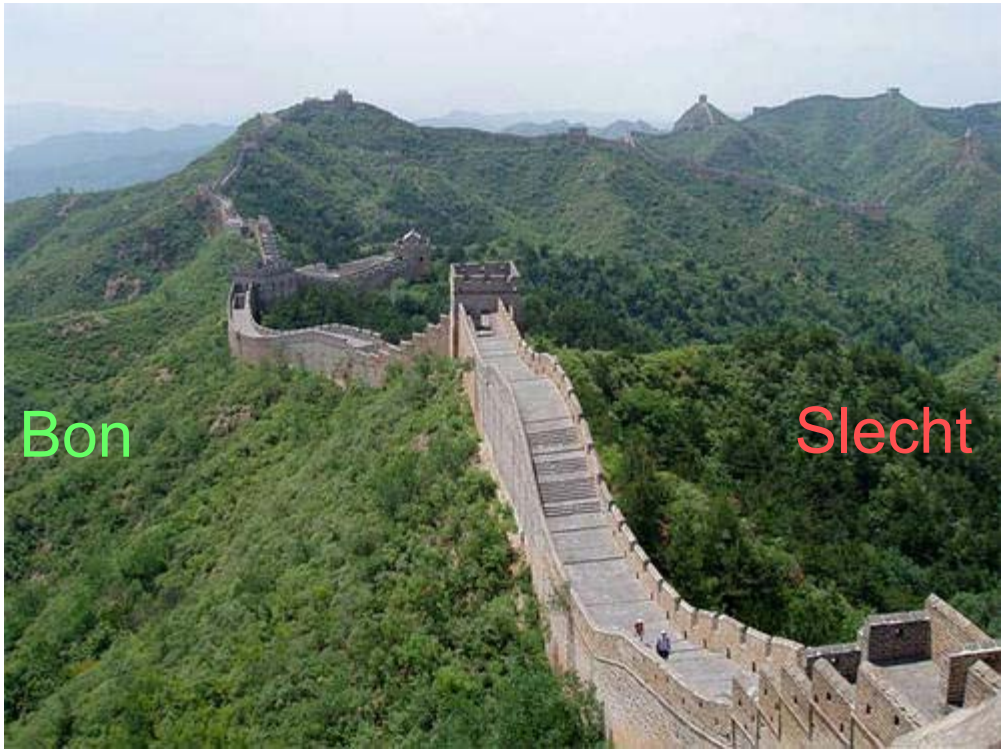


sensitivity → **S - I - R**

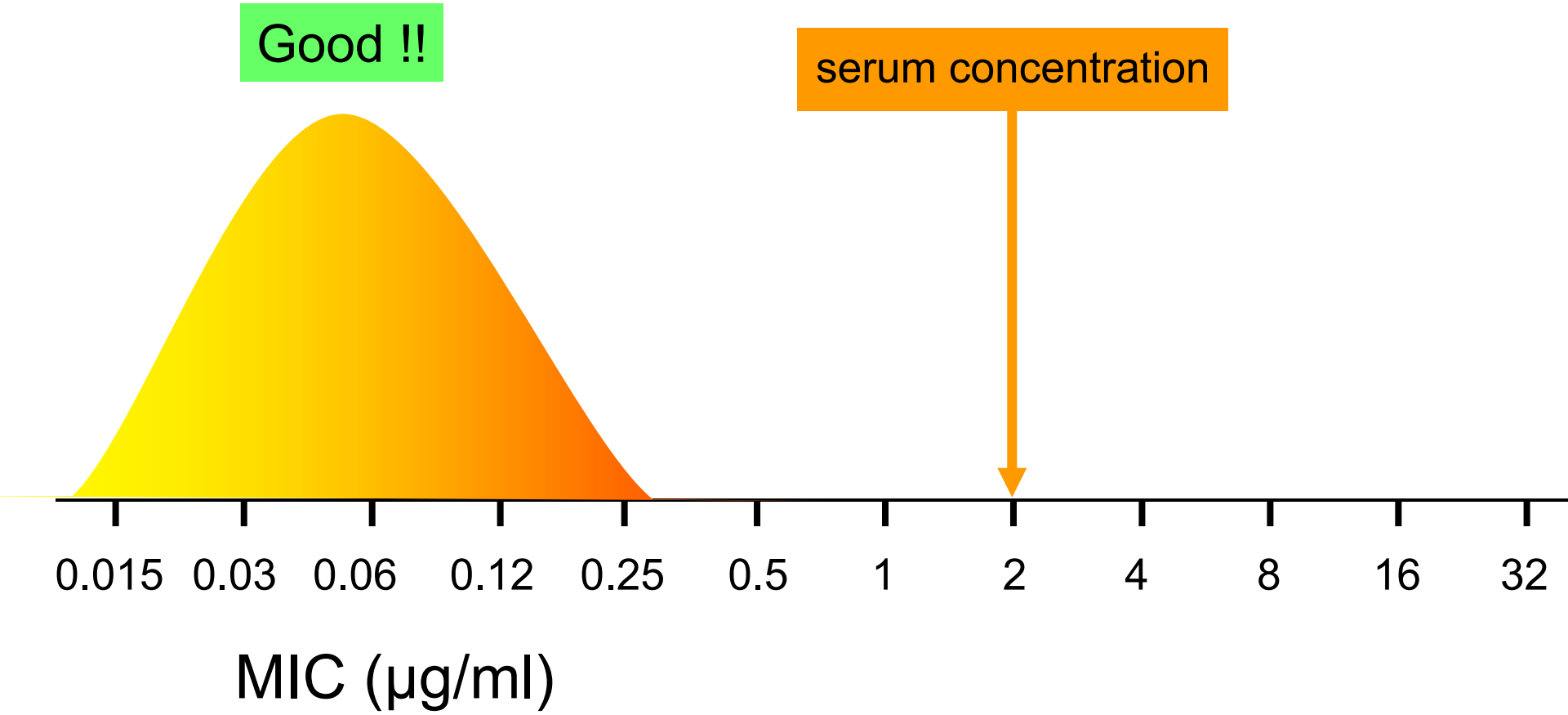
by static techniques

Why do we need S - I - R ?

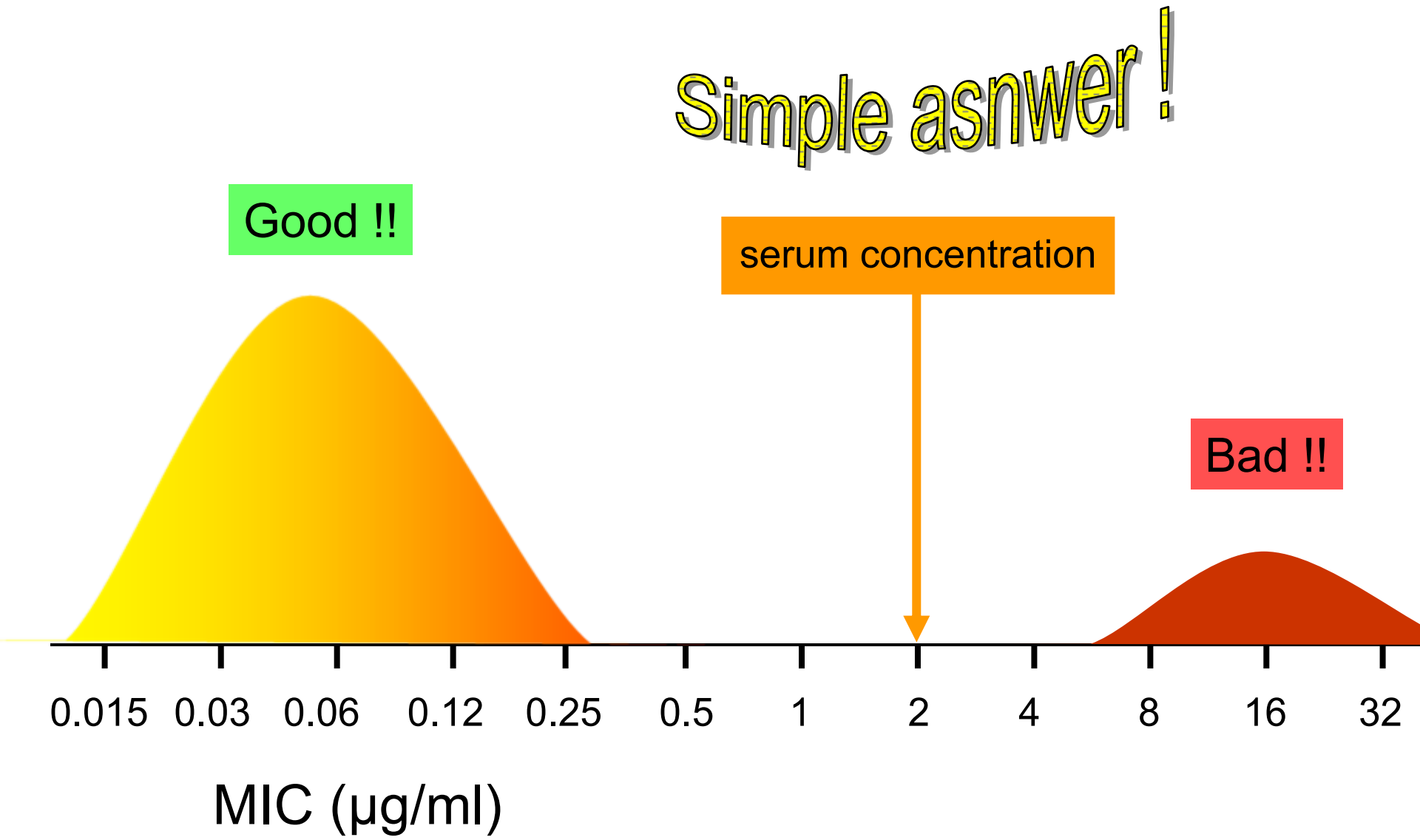
To be honest, I always wondered …



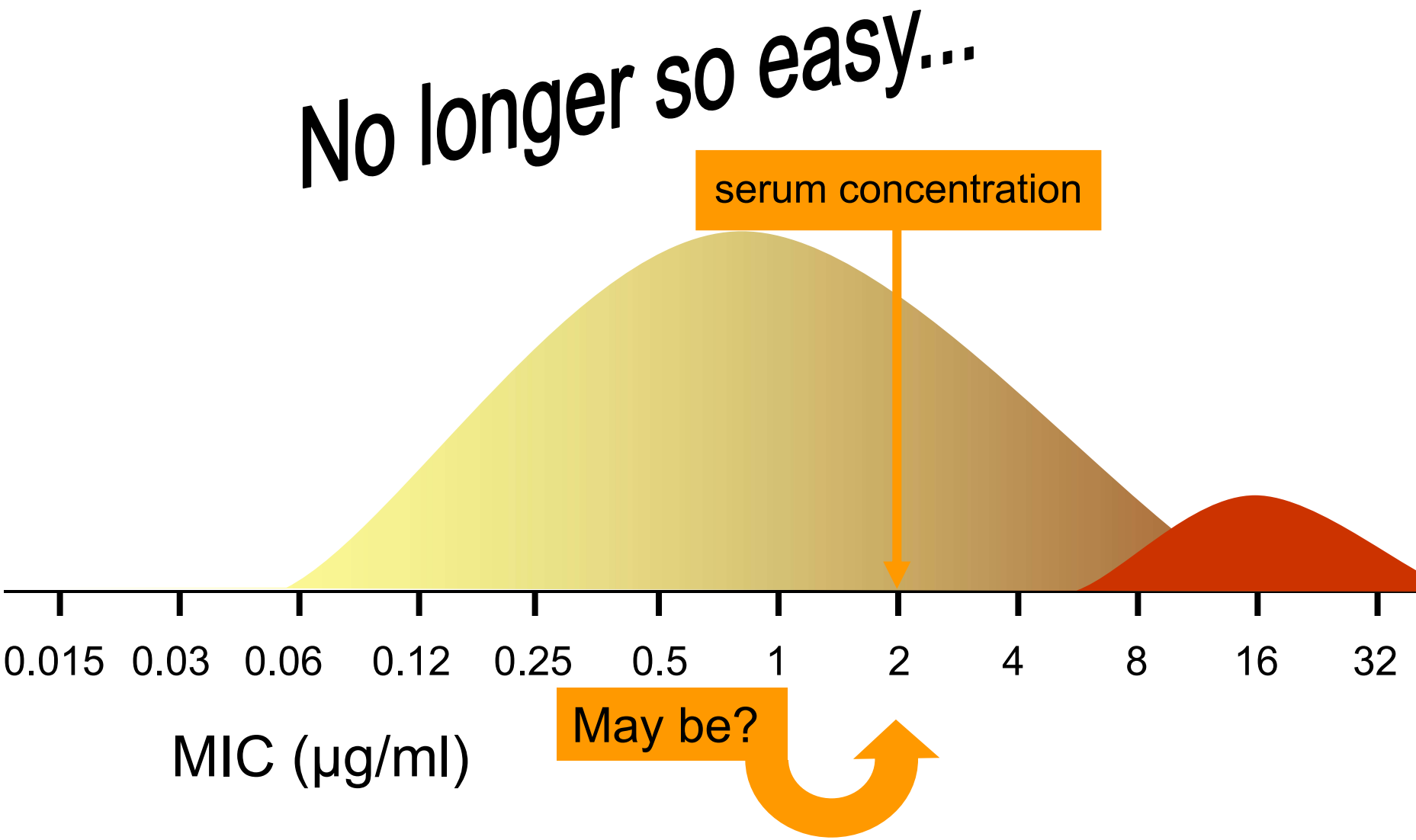
An easy time …


Good !!
serum concentration
0.015
0.03
0.06
0.12
0.25
0.5
1
2
4
8
16
32
MIC (µg/ml)

Becoming bad, but not for the microbiologist



But today …

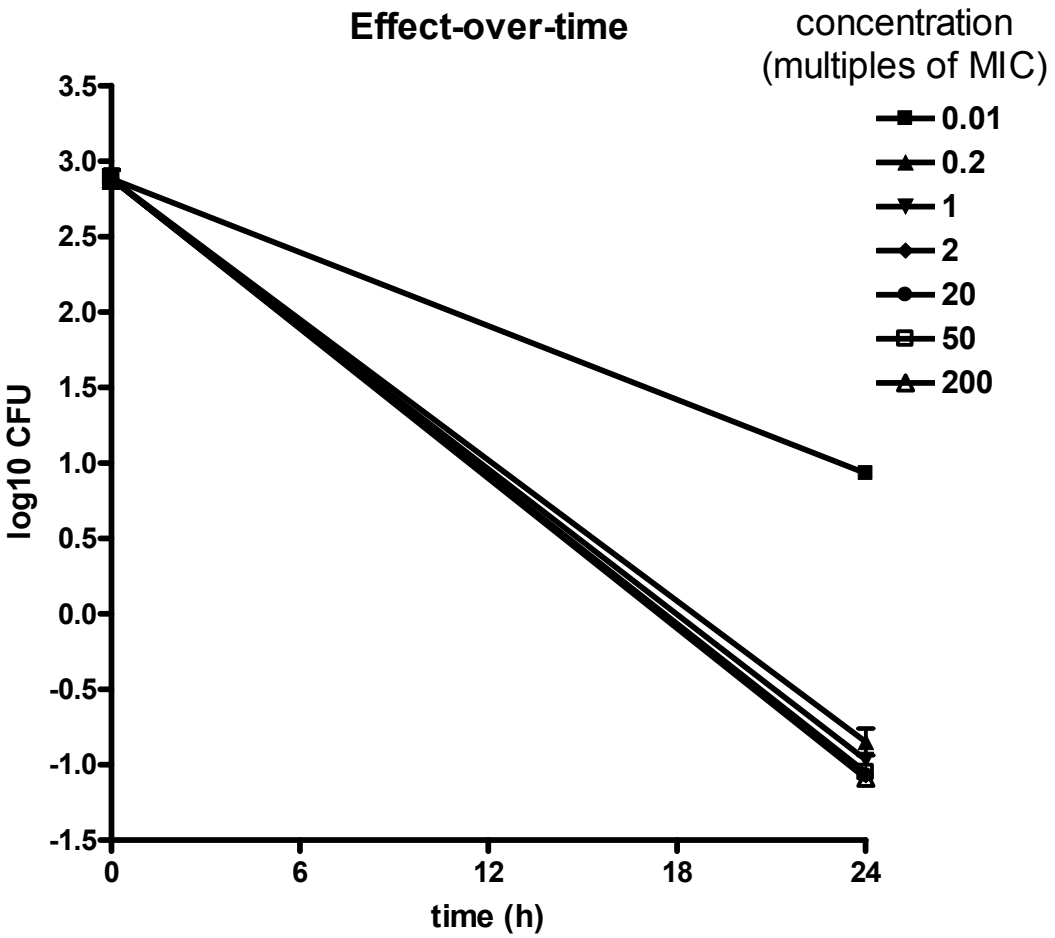

No longer so easy...
serum concentration
0.015
0.03
0.06
0.12
0.25
0.5
1
2
4
8
16
32
MIC (µg/ml)
May be?

PK/PD of antibiotics

- in vitro
- animal data
- clinical implementation
- resistance

Simple response to an antimicrobial

an example with ceftobiprole and *S. aureus* (one strain)



Lemaire et al. Antimicrob. Agents Chemother. 2009, 53:2289-97

Simple response to an antimicrobial

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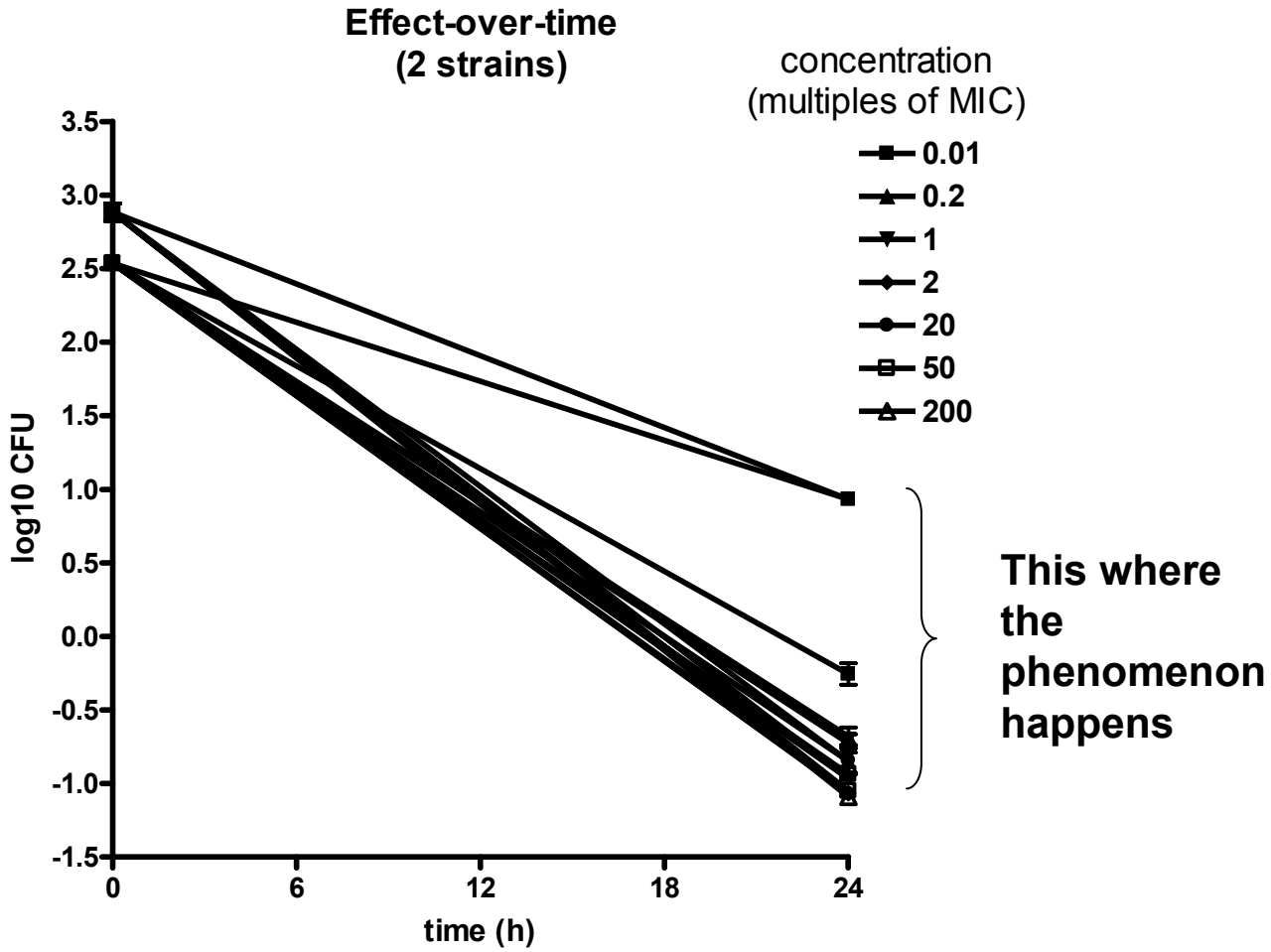
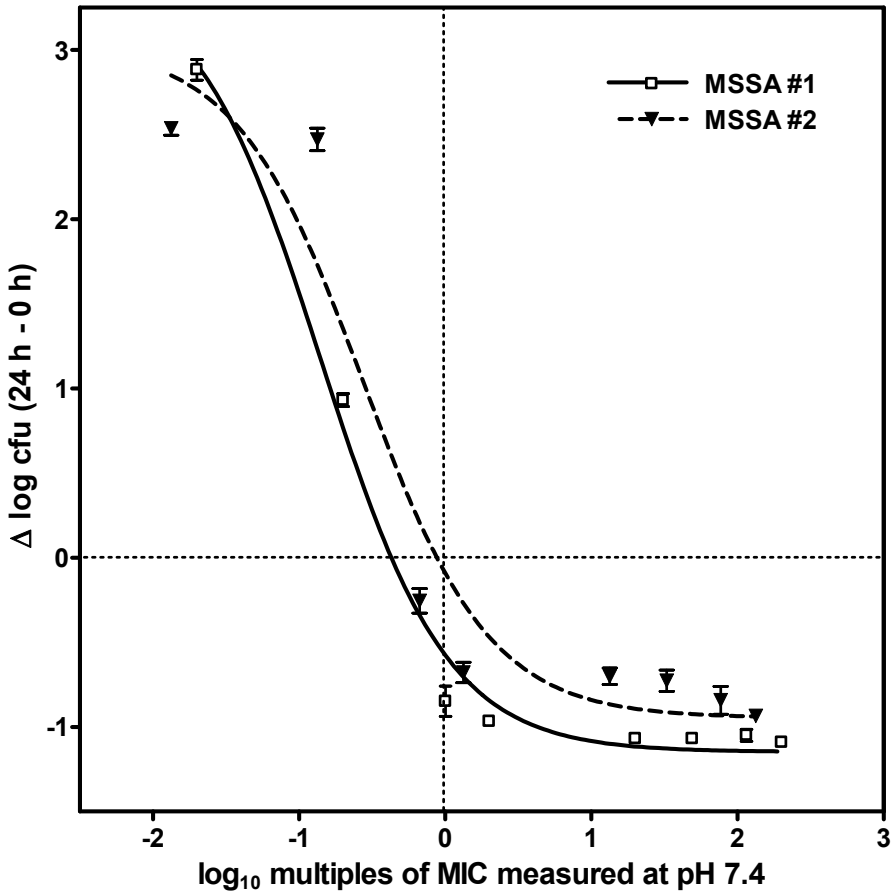


Lemaire et al. Antimicrob. Agents Chemother. 2009, 53:2289-97

Response to an antimicrobial: the model

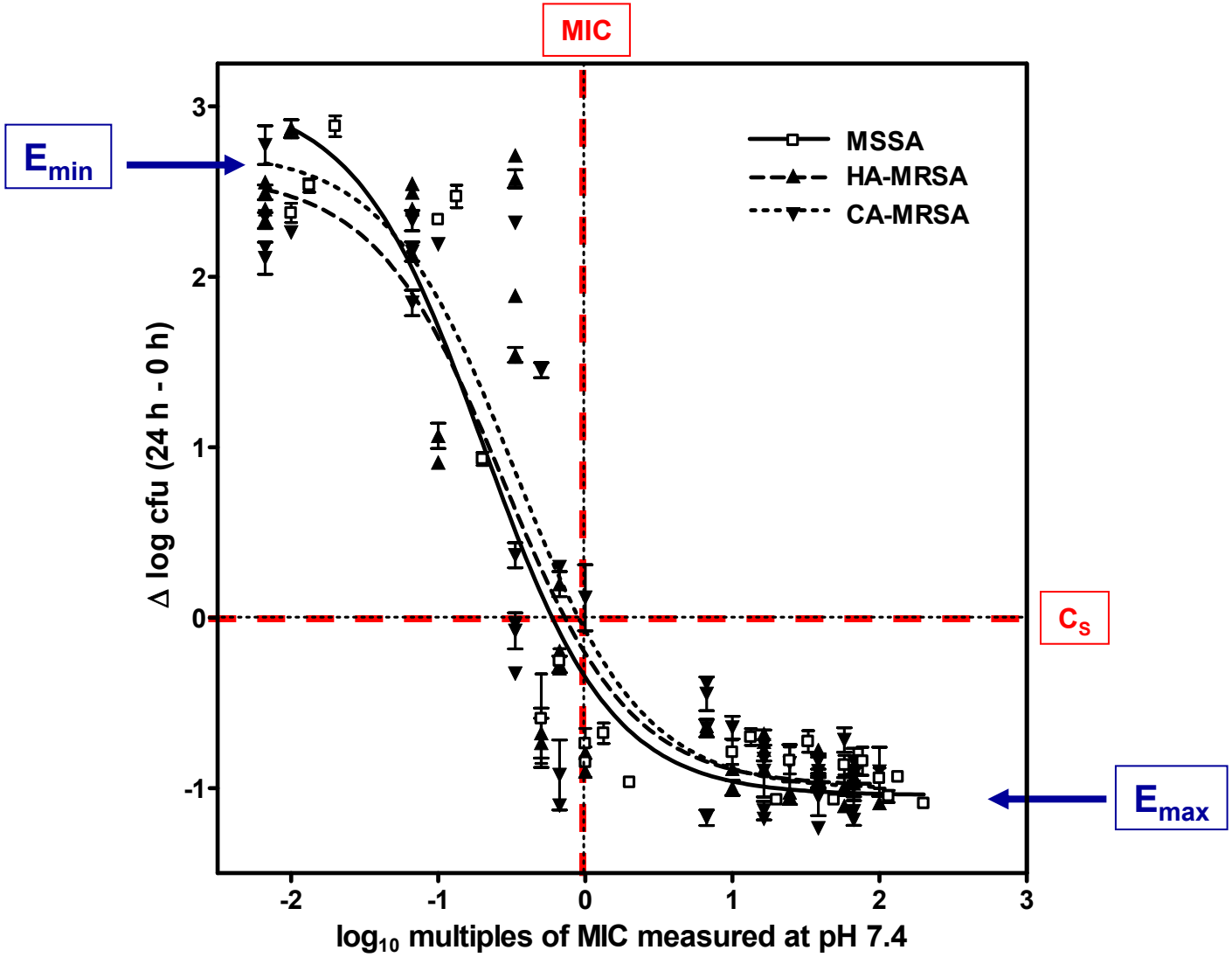
an example with ceftobiprole and *S. aureus* (2 strains)



Lemaire et al. Antimicrob. Agents Chemother. 2009, 53:2289-97

Response to an antimicrobial: a first model

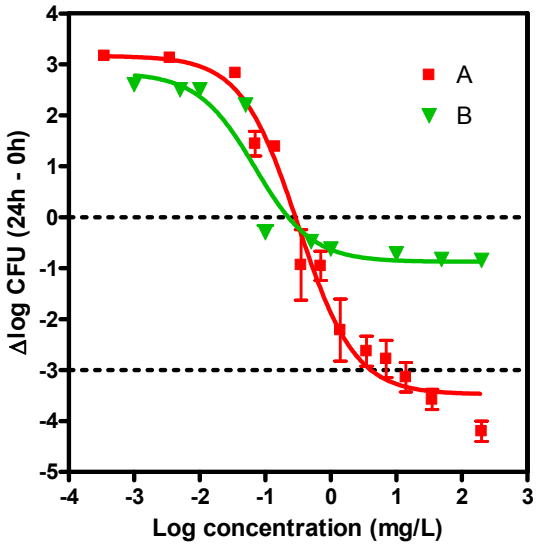
an example with ceftobiprole and *S. aureus* (multiple strains)



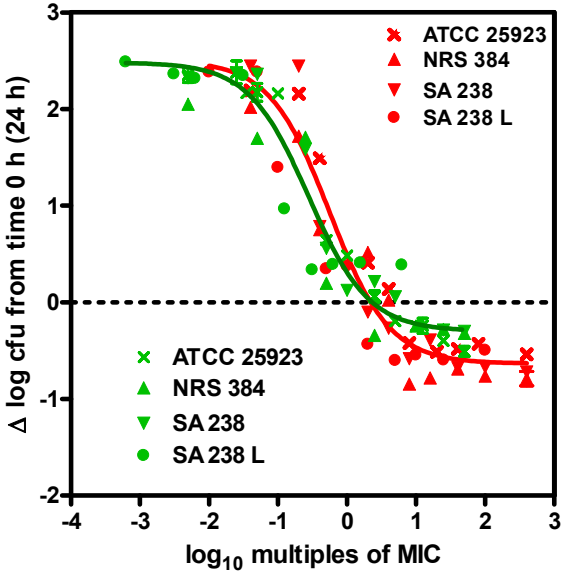
Lemaire et al. Antimicrob. Agents Chemother. 2009, 53:2289-97

How can this first model be exploited ?

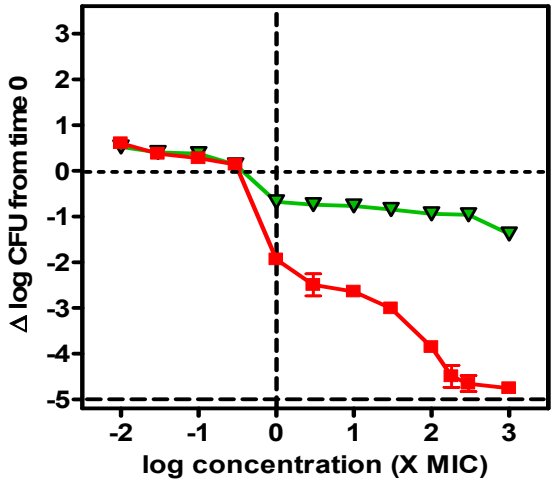
Bactericidal *vs.* Static



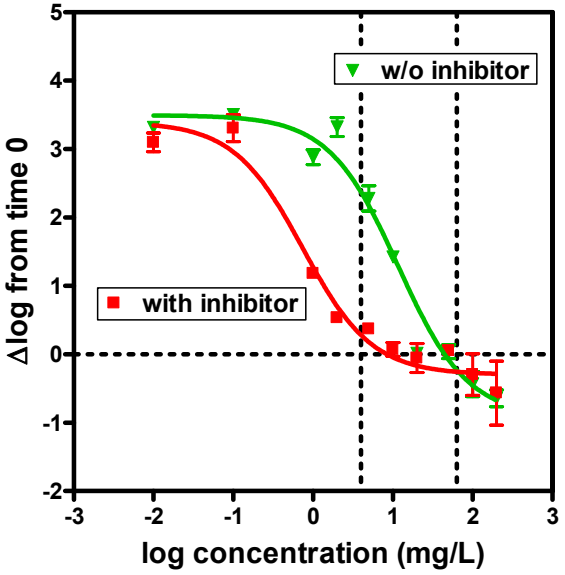
old vs. new



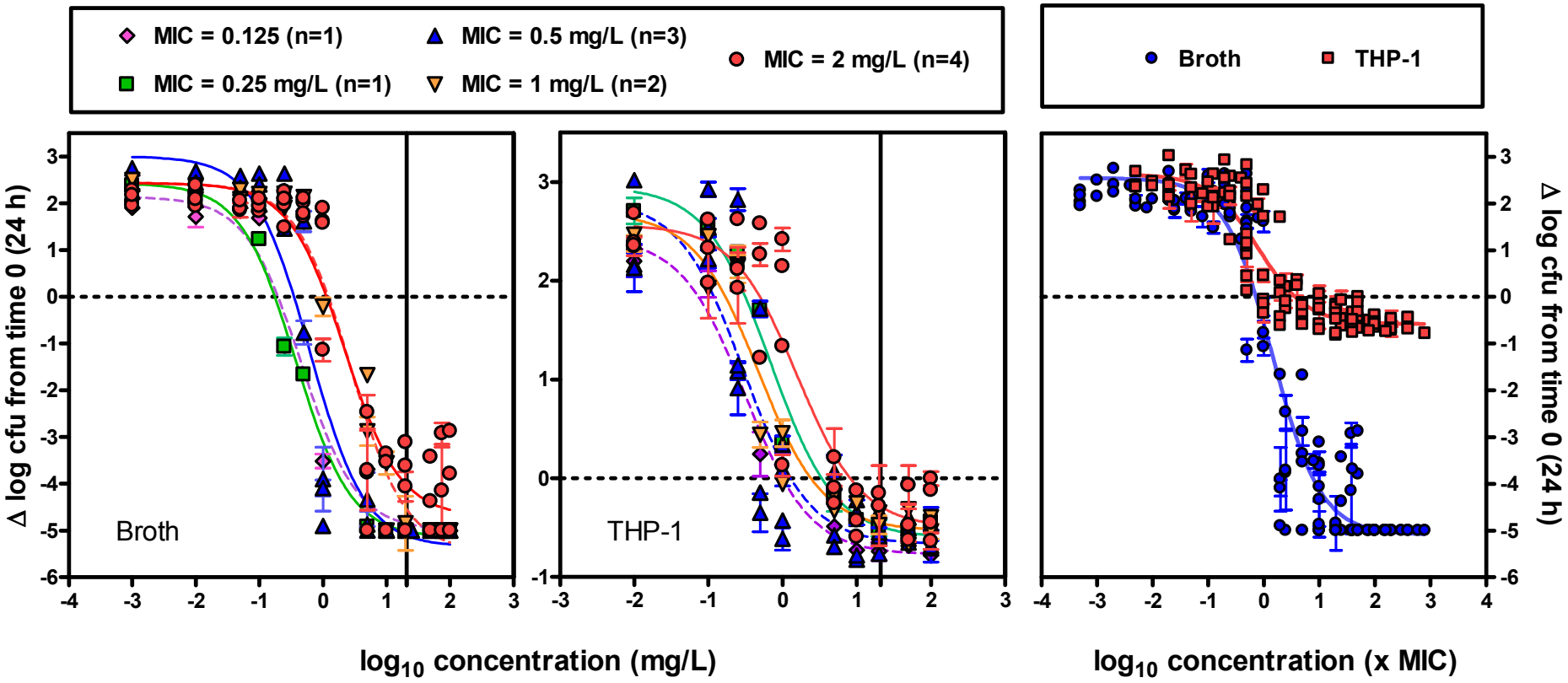
bimodal A vs B



inhibitor of degradation (intracellular)

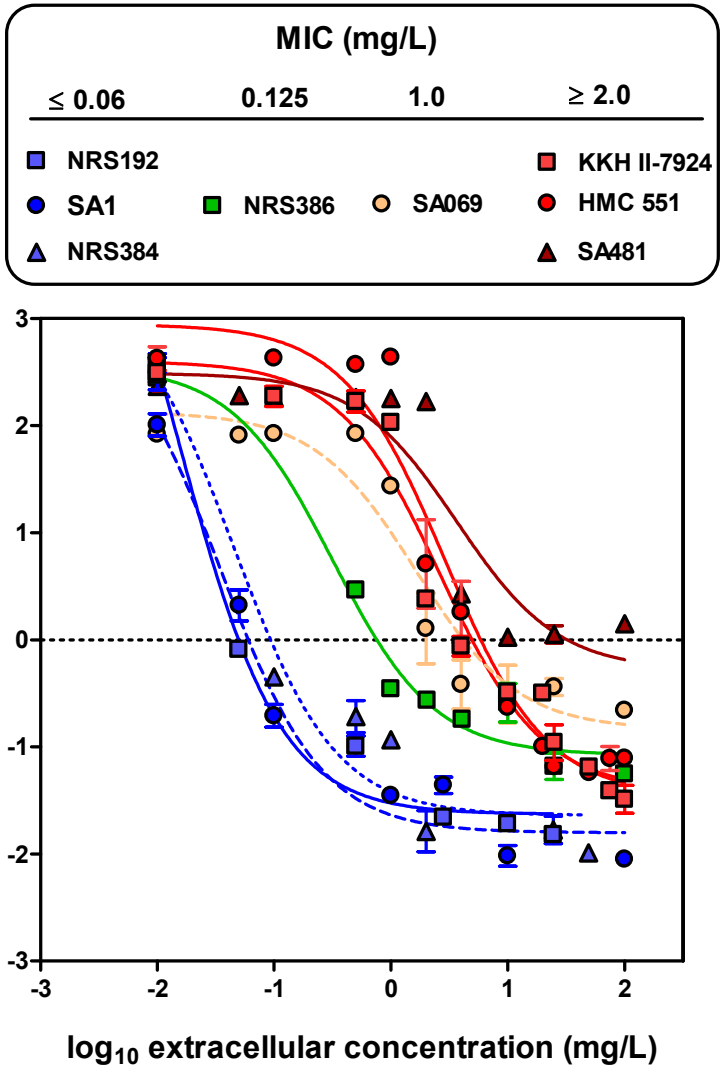


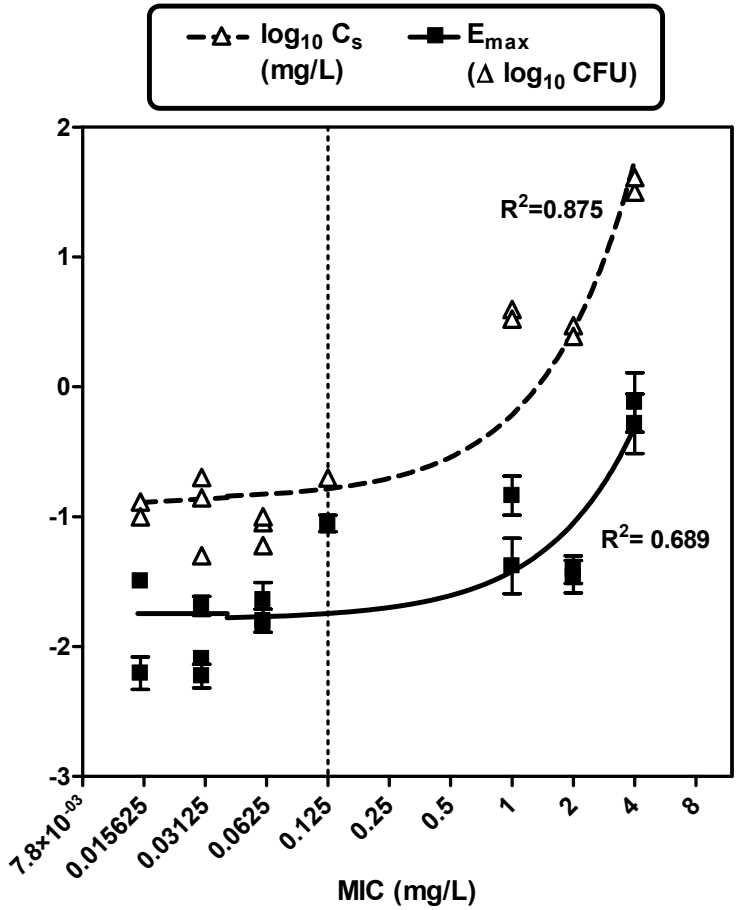
Special models: intracellular bacteria



Melard et al. J. Anticrob. Chemother. 2012: in press

Special models: intracellular breakpoint

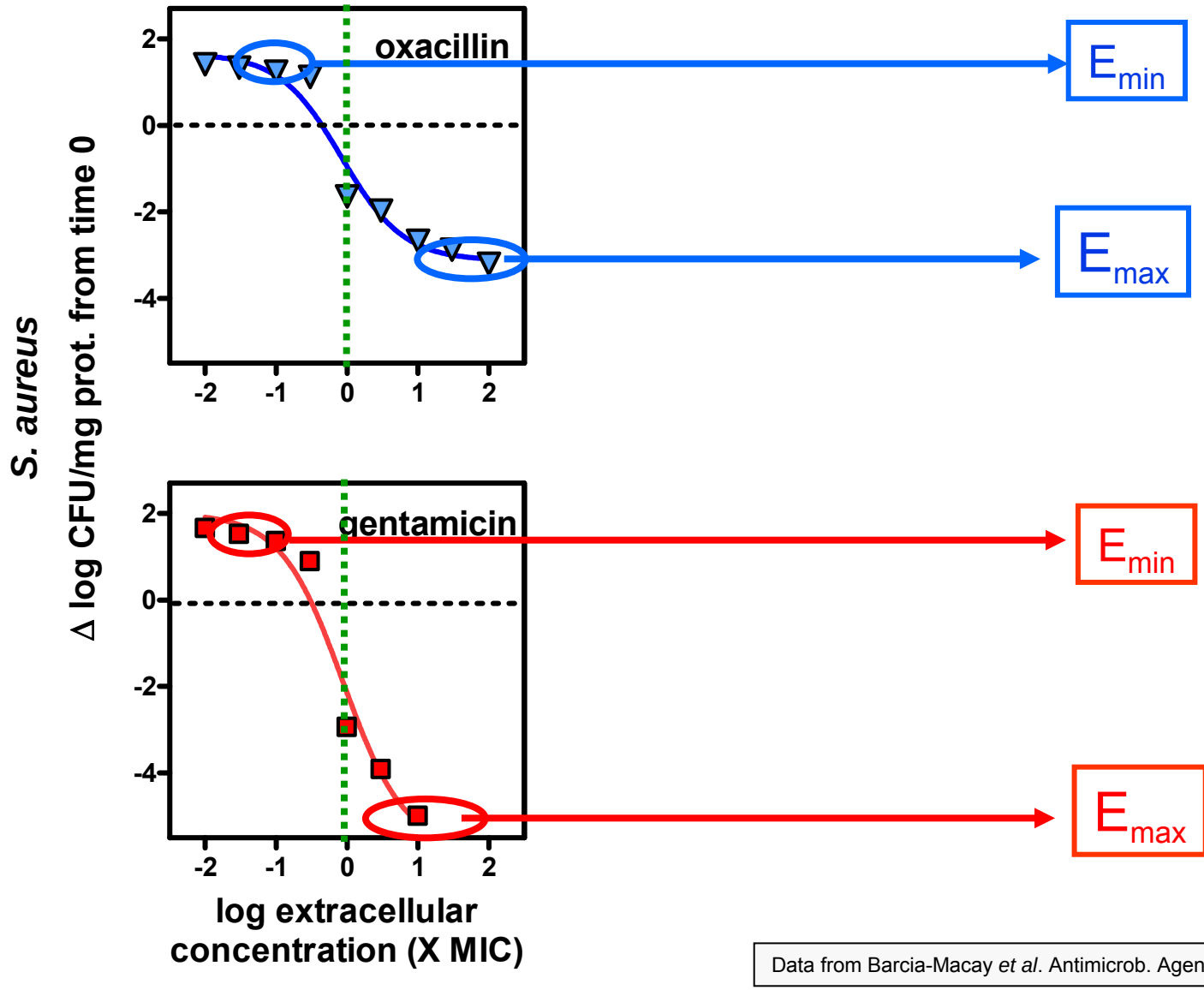




Lemaire et al. J. Anticrob. Chemother. 2011, 66:596-607

Moving to humans (via animals)

What is the relationship between MIC and effect?



E_{min}

E_{max}

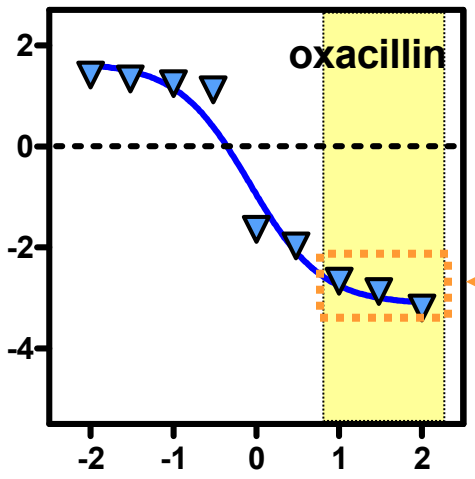
E_{min}

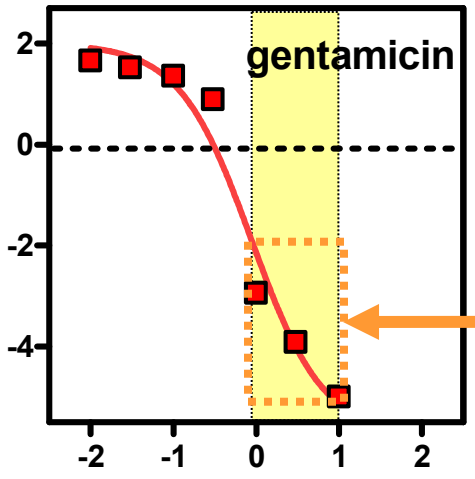
E_{max}

It looks as if they are all concentration-dependent…

Data from Barcia-Macay *et al*. Antimicrob. Agents Chemother. (2006) 50:841-851

But here comes pharmacokinetics …





S. aureus

Δ log CFU/mg prot. from time 0

log extracellular concentration (X MIC)

Weak concentration-dependence (max. effect) over the C_{min}–C_{max} range

➔ TIME will emerge as the main parameter in vivo

C_{min}–C_{max}

high concentration-dependence over the C_{min}-C_{max} range ➔ the time is less important than the actual concentration

- data from Barcia-Macay *et al*. Antimicrob. Agents Chemother. (2006) 50:841-851
- C_{min}-Cmax: Principles and Practice of Infectious Diseases, 7th Ed. Mandell *et al*. eds., Elsevier

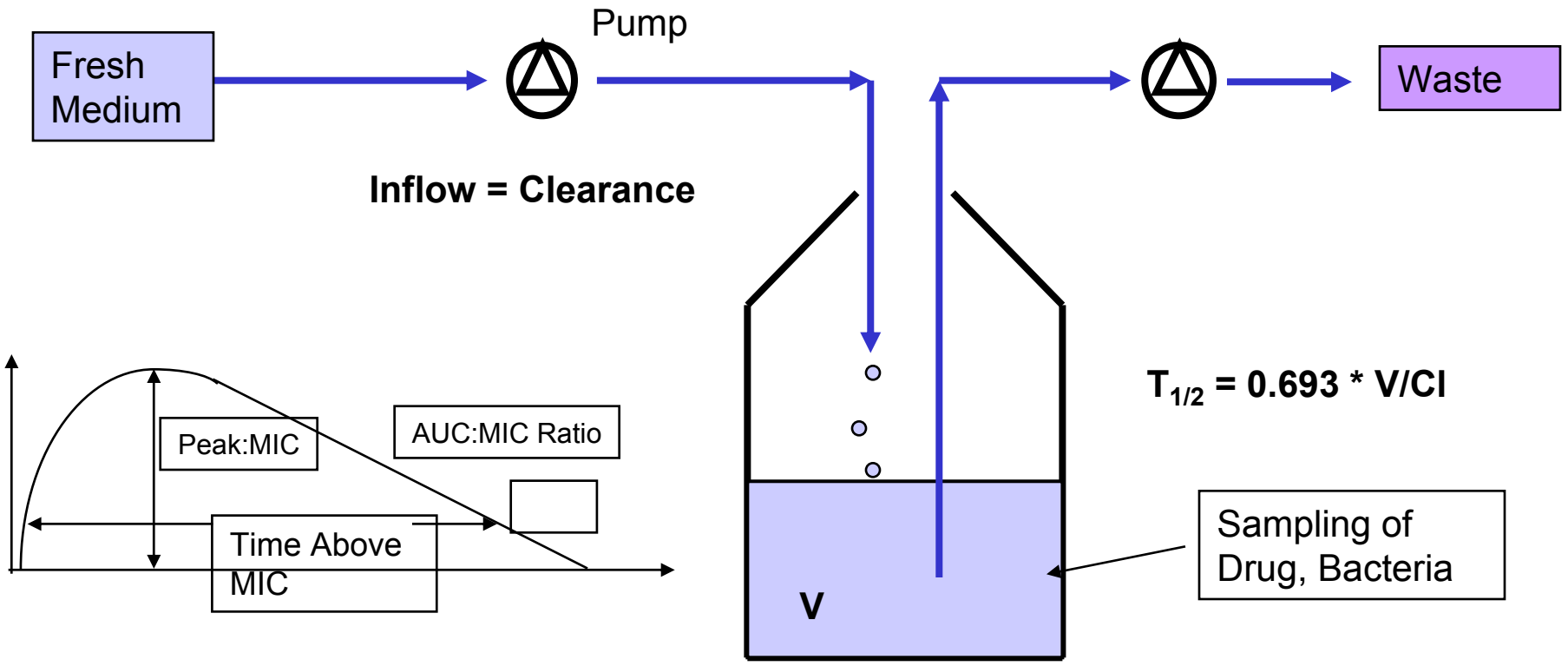
Conclusions so far ...

- Contrary to most beliefs, all antibiotics are concentration-dependent (like any other drug);
- **but** it is is all about at which serum concentration E_{max} will be obtained **and** how large it is (compared to untreated controls) ....

- If E_{max} is small and obtained at a **low concentration/MIC ratio** (relative to what you could reach in serum), all what you are left with is time ... and you get *in vivo* a **time-dependent antibiotic** (viz. β-lactams, vancomycin, ...)

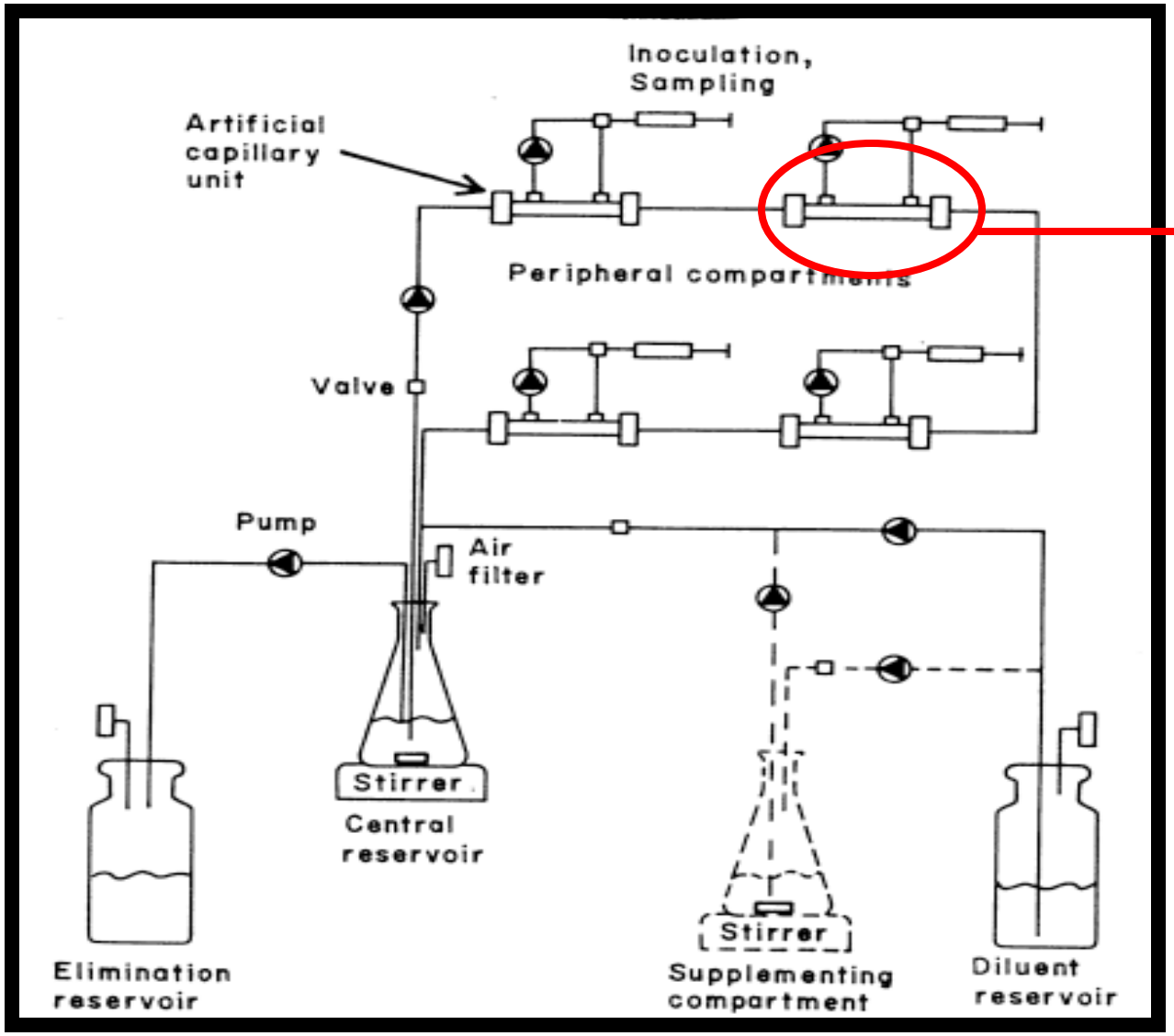
  ➔ BEWARE ! If the MIC rises, you will need to increase the concentration to reach your (weak) E_{max} or to use low breakpoints if wishing to avoid clinical failures (viz. cephalosporins ...) ...

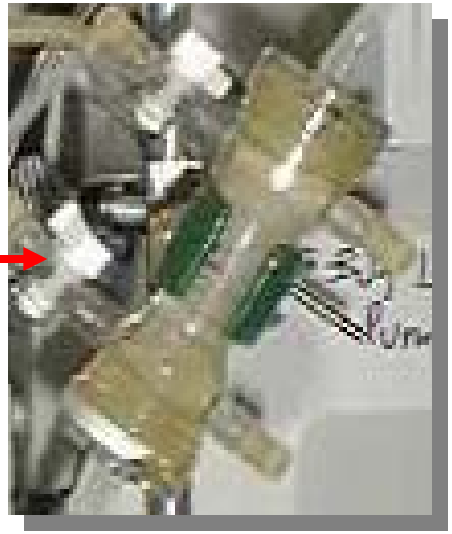
You can test this in vitro



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

Ad you can even mimic compartments





The clinical classification of antibiotics *

- **primarily time-dependent**
  (maximal effect at low concentration/MIC ratio and no post-antibiotic effect)
  - β-lactams / flucytosine

  favour time > MIC

- **primarily C_{max} dependent**
  (effect progressing over the clinically achievable concentrations AND marked post-antibiotic effect)
  - aminoglycosides
  - fluoroquinolones

  favour C_{max} / MIC

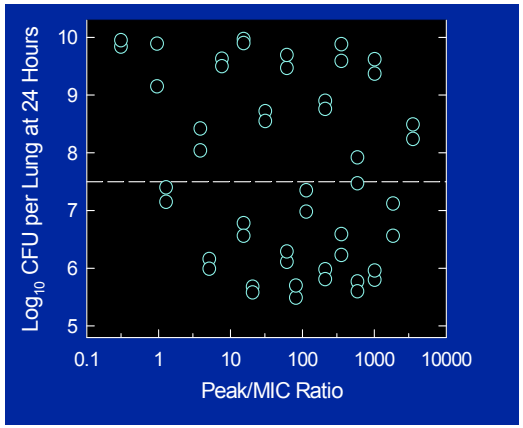
- **primarily AUC_{24h}-dependent**
  (effect progressing modestly over clinically achievable concentrations; significant post-antibiotic effect; half-lifes > 4h)
  - most other antibiotics and fluoroquinolones

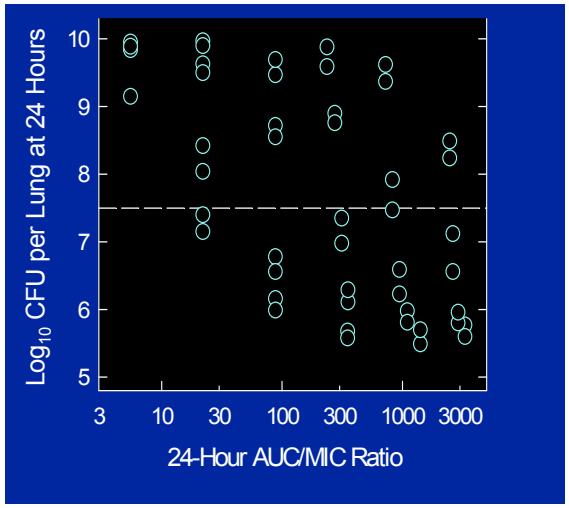
  favour total daily dosage

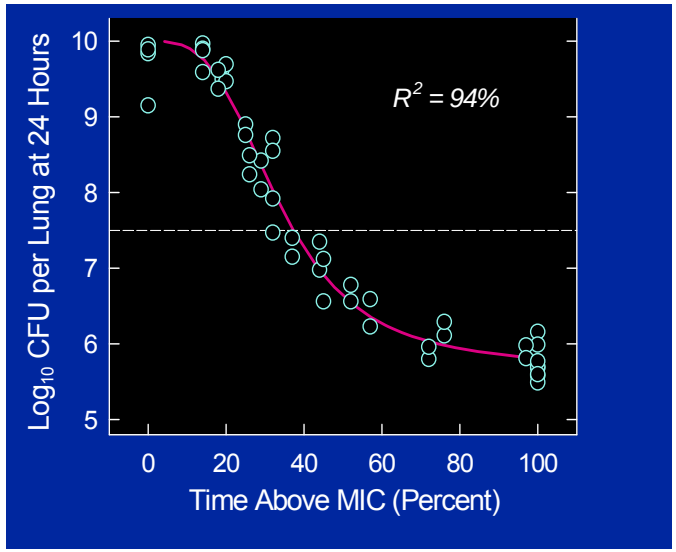
---

* assuming human pharmacokinetics and susceptible strains

The story of β-lactams in neutropenic mouse *

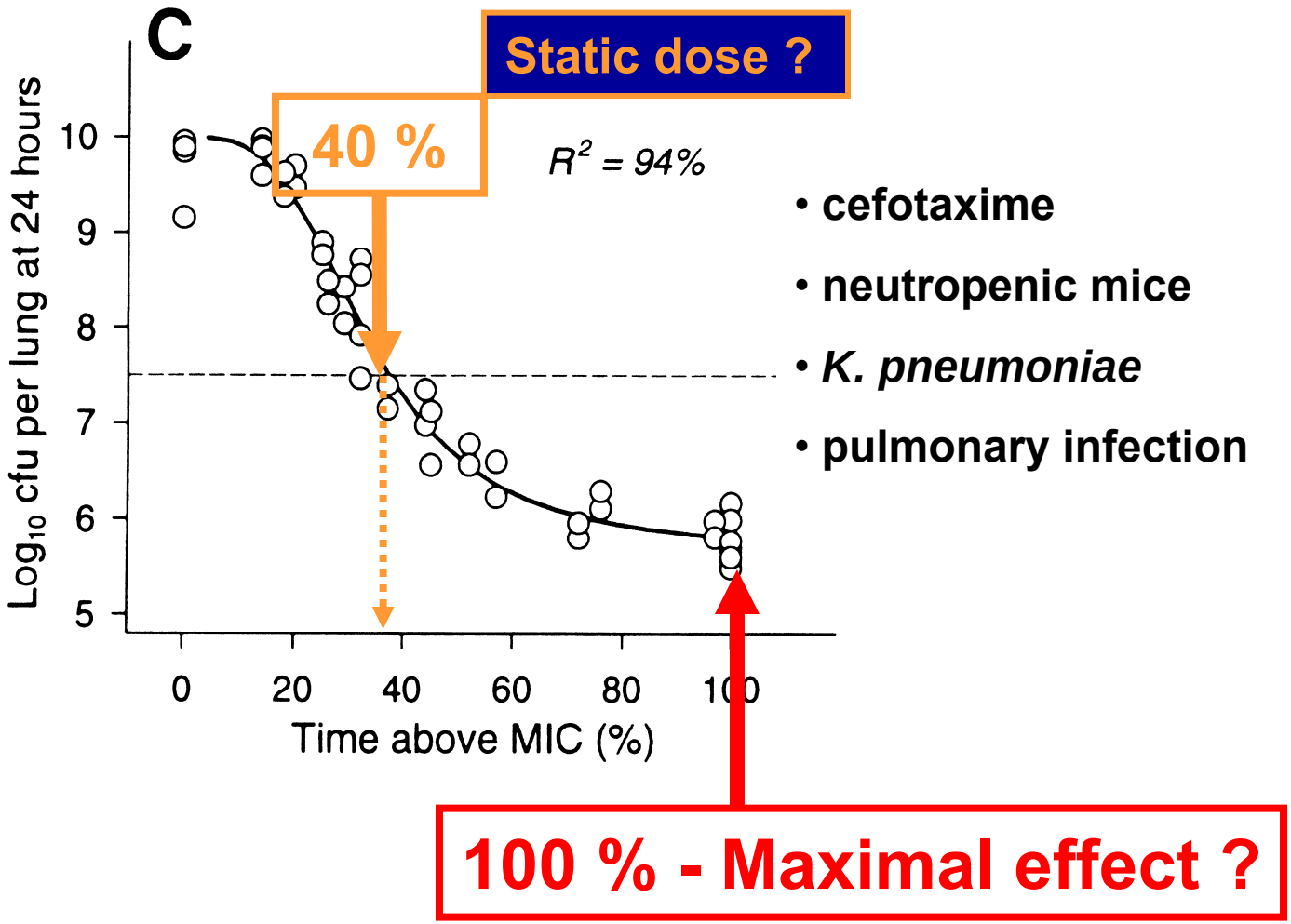




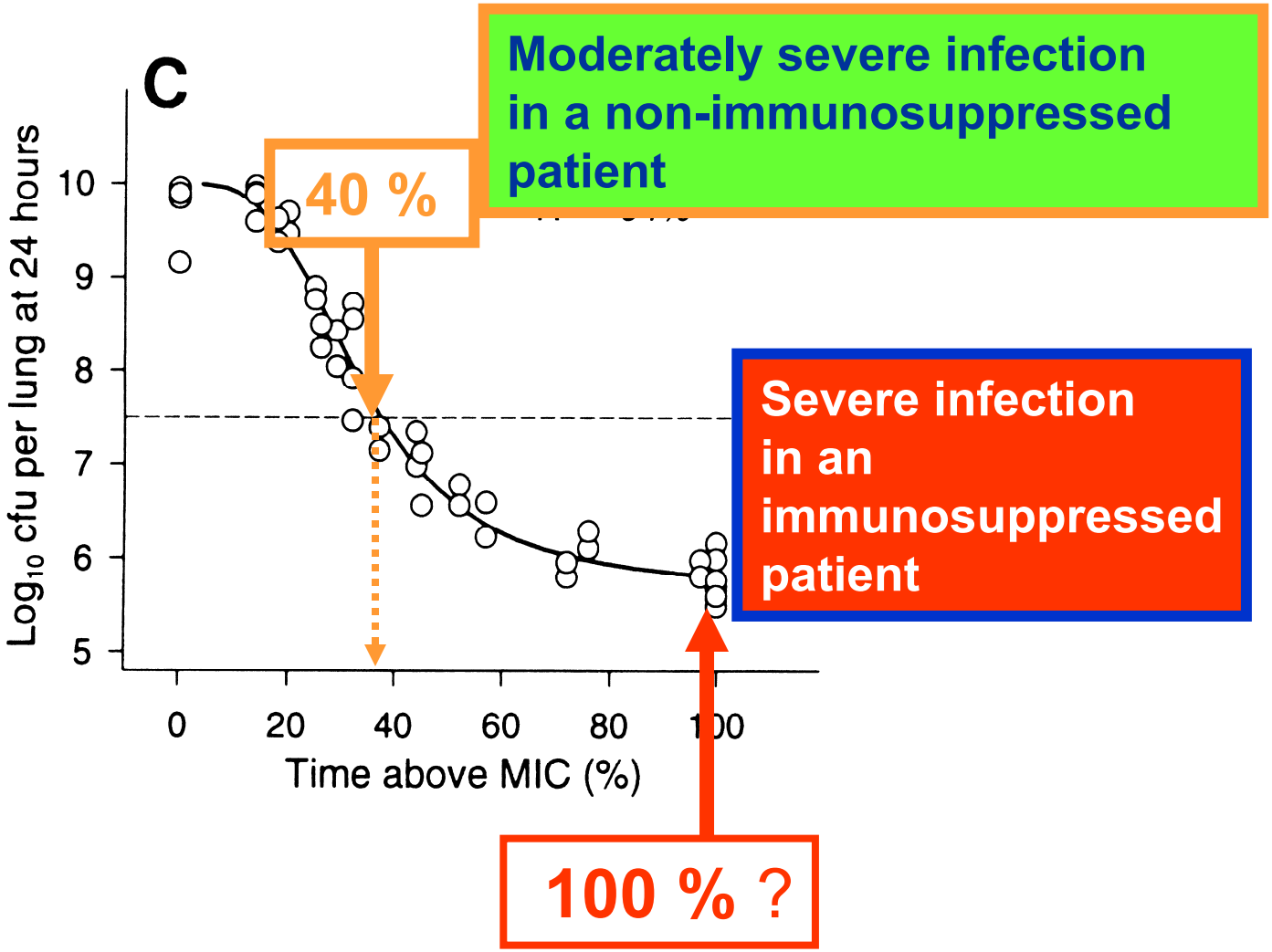


* creating distinct C_{max}, AUC and T> MIC profiles by manipulating the shedule of administration
W. Craig, Madison, WI (several publications)

But how much time above MIC is necessary ?

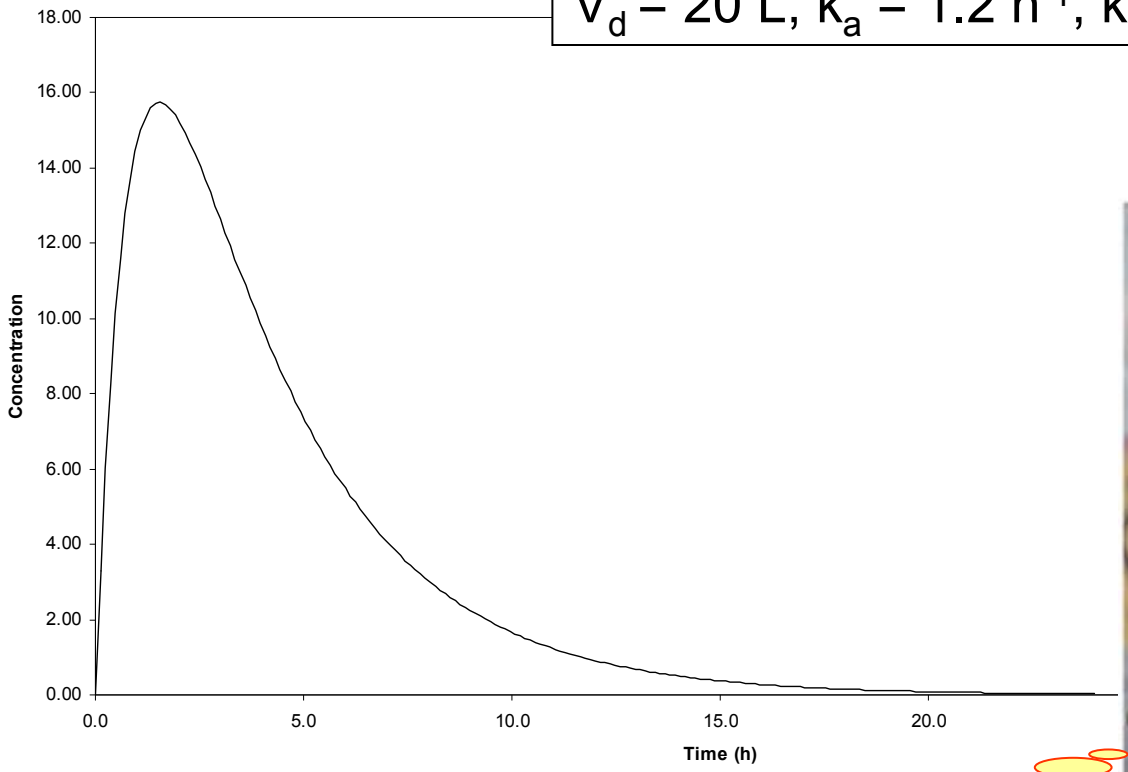


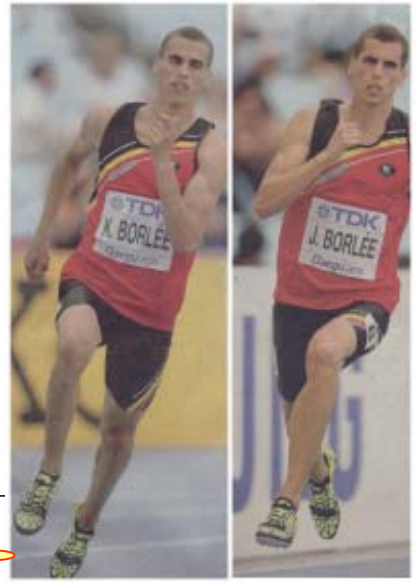
Here is a proposal ...



But there are variation of PK in individuals...

Concentration-time profile of a beta-lactam in volunteers
V_d = 20 L, k_a = 1.2 h^{-1}, k_e = 0.3 h^{-1}





Unlike the Belgian 400 m run team, we are not all (almost) equal

What is, indeed, a standard patient ?

weight

age

physical

Kim Clijsters pose avec sa fille Jada. AFP

condition

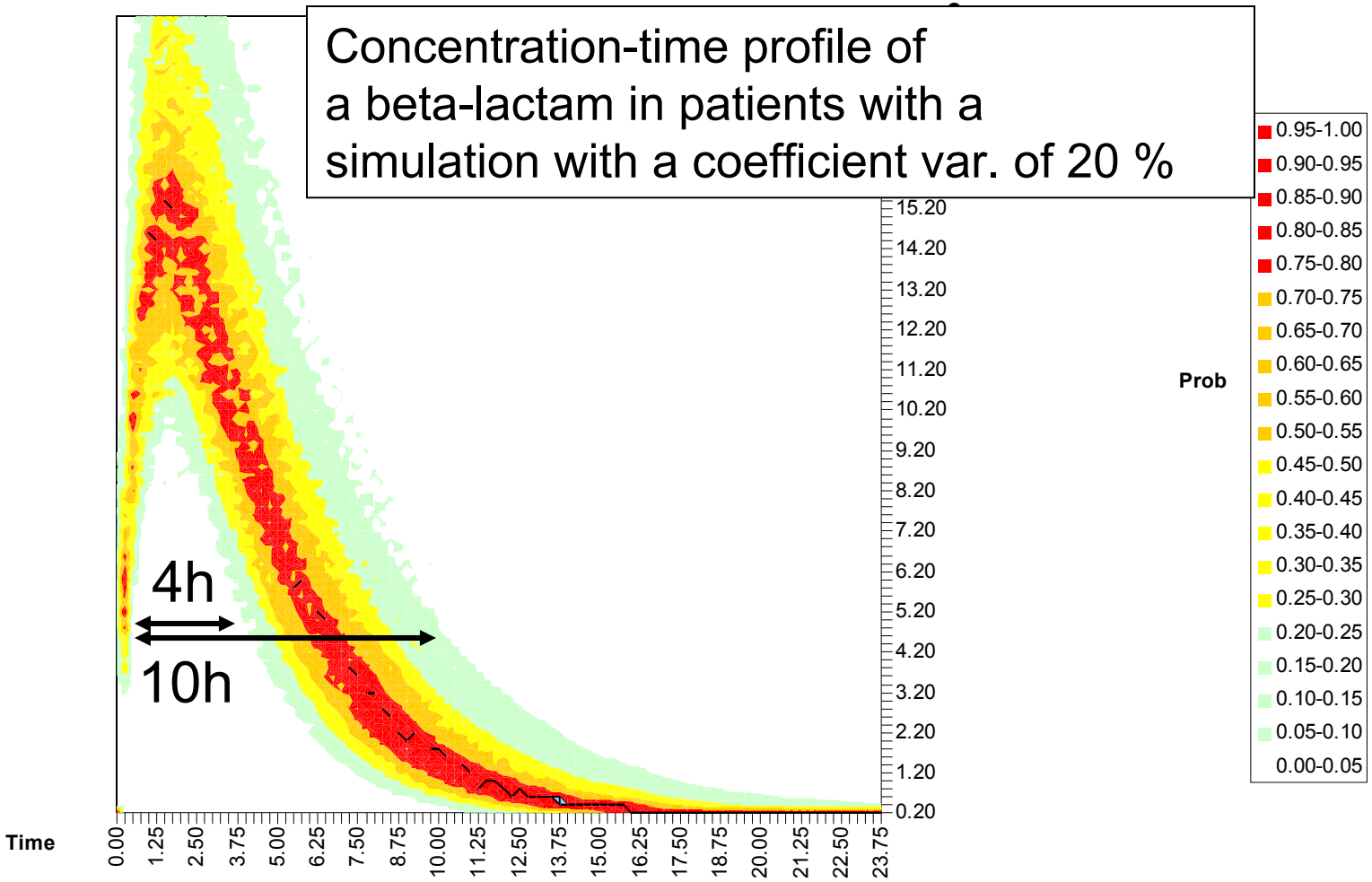
race

size

disease

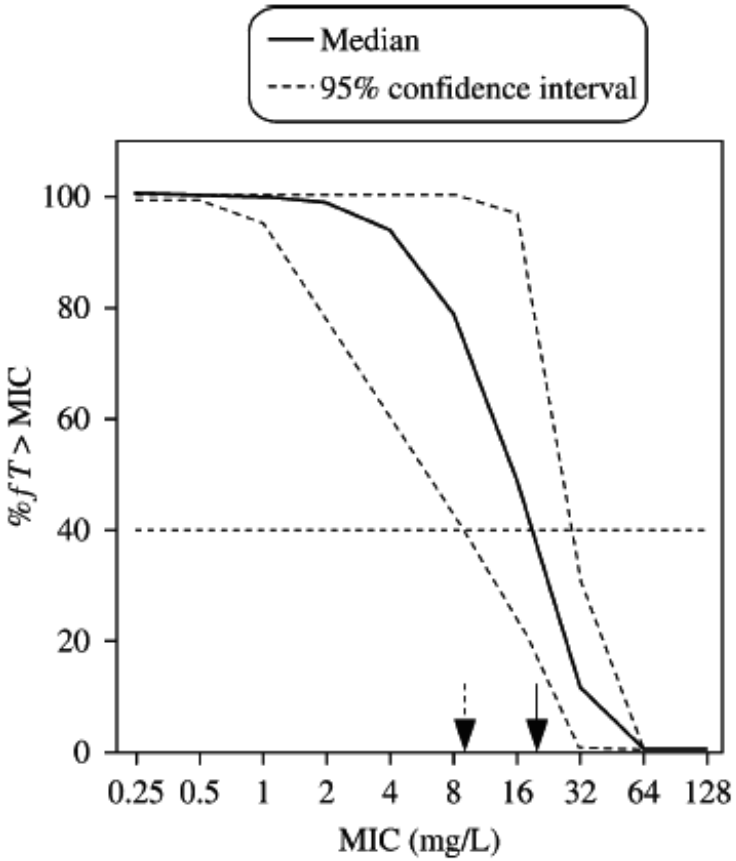
elimionation functions

Variation of PK in individuals...



Mouton, Int J Antimicrob Agents apr 2002

Monte Carlo Simulations and target attainment rate for "*f* T > MIC" (40 %)



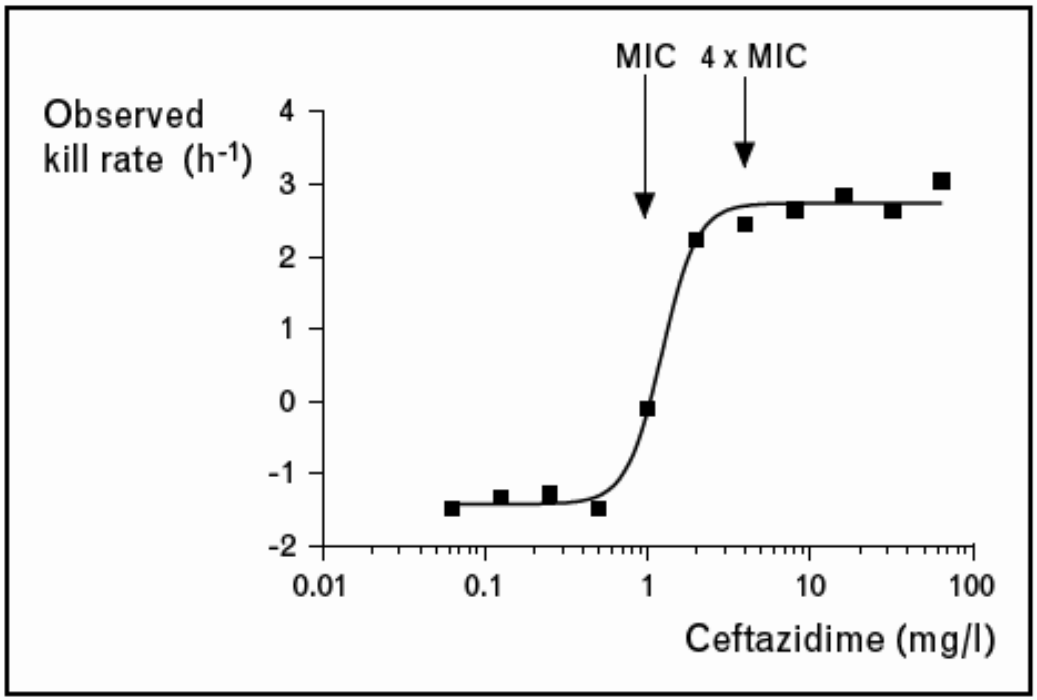
Temocillin (6-methoxy-ticarcillin) 2 g every 12h

Figure 2. Probabilities of target attainment of temocillin (as obtained with the Monte Carlo simulation: solid line, median value; dotted lines, 95% confidence interval) for the currently registered treatment (2 g every 12 h), using the pharmacokinetic data of the six patients treated according to this dosage and schedule in this study (twice daily group). The abscissa shows the MIC range used for the simulations and the ordinate the fraction of time (as a percentage) during which free serum levels remain above the corresponding MIC. The horizontal dotted line indicates the 40% $fT >$ MIC limit achieving a bacteriostatic effect and survival for penicillins in animal models with Gram-negative bacteria.[1] The highest MIC at which this target will be obtained is shown by the vertical arrows (arrow with solid line, median; arrow with dotted line, 95% probability).

De Jongh et al. J. Antimicrob. Chemother. (2008) 61, 382–388

But you may like to be 4 x above the MIC …

Figure 2 Relationship between concentration of ceftazidime and kill rate



The relationship follows a Hill-type model with a relatively steep curve; the difference between no effect (growth, here displayed as a negative kill rate) and maximum effect is within two to threefold dilutions. The maximum kill rate is attained at around four times the minimum inhibitory concentration (MIC). Modified with permission from [16].

Mouton JW, Vinks AA. Curr Opin Crit Care. 2007 Oct;13(5):598-606.

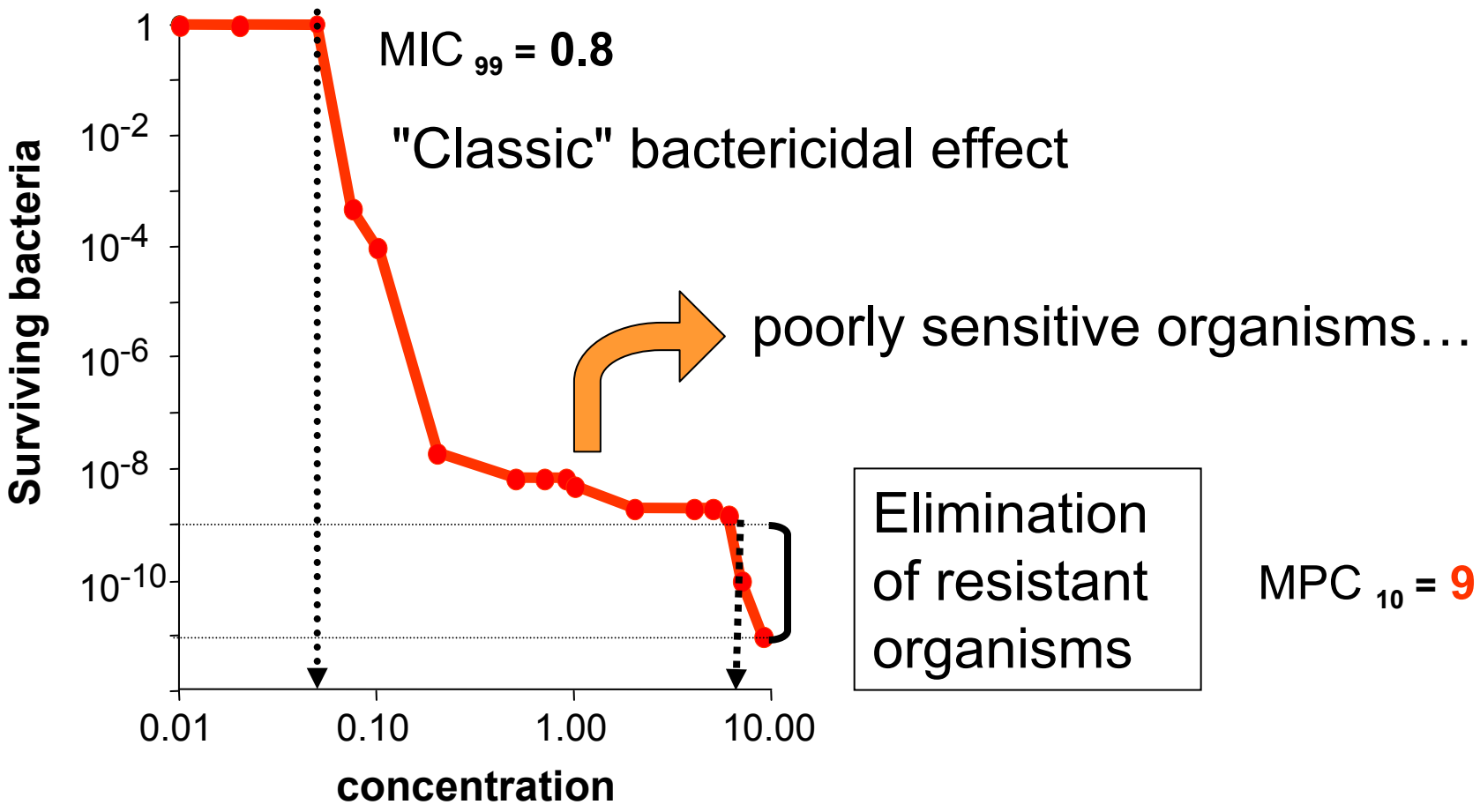
The problem with the fluroquinolones … and the link to resistance

Drug	Typical daily dosage[a]	Typical PK values: C_{max} in mg/L total/free (dose)	Typical PK values: $AUC_{24\,h}$ (mg × h/L) total/free	Proposed PK/PD upper limit: Efficacy[b]	Proposed PK/PD upper limit: Prevention of resistance[c]	Breakpoints (mg/L)[d]: NCCLS (S/I/R)
Norfloxacin	800 mg	1.4/1.1 (400 mg PO)	14/11	0.1–0.4	0.1	≤4/8/>16[j]
Ciprofloxacin	1000 mg	2.5/1.75 (500 mg PO)	24/18	0.2–0.8	0.2	≤1/2/>4[k]
Ofloxacin	400 mg	4/3 (400 mg PO)	40/30	0.3–0.9	0.4	≤2/4/8[l]
Levofloxacin	500 mg	4/2.8 (500 mg PO)	40/28	0.3–0.9	0.3	≤2/4/8[l]
Moxifloxacin	400 mg	3.1/1.8 (400 mg PO)	35/21	0.2–0.7	0.2	≤1/2/4[m]

NCCLS, National Committee for Clinical Laboratory Standards (Clinical and Laboratory Standards Institute) (http://www.ncc

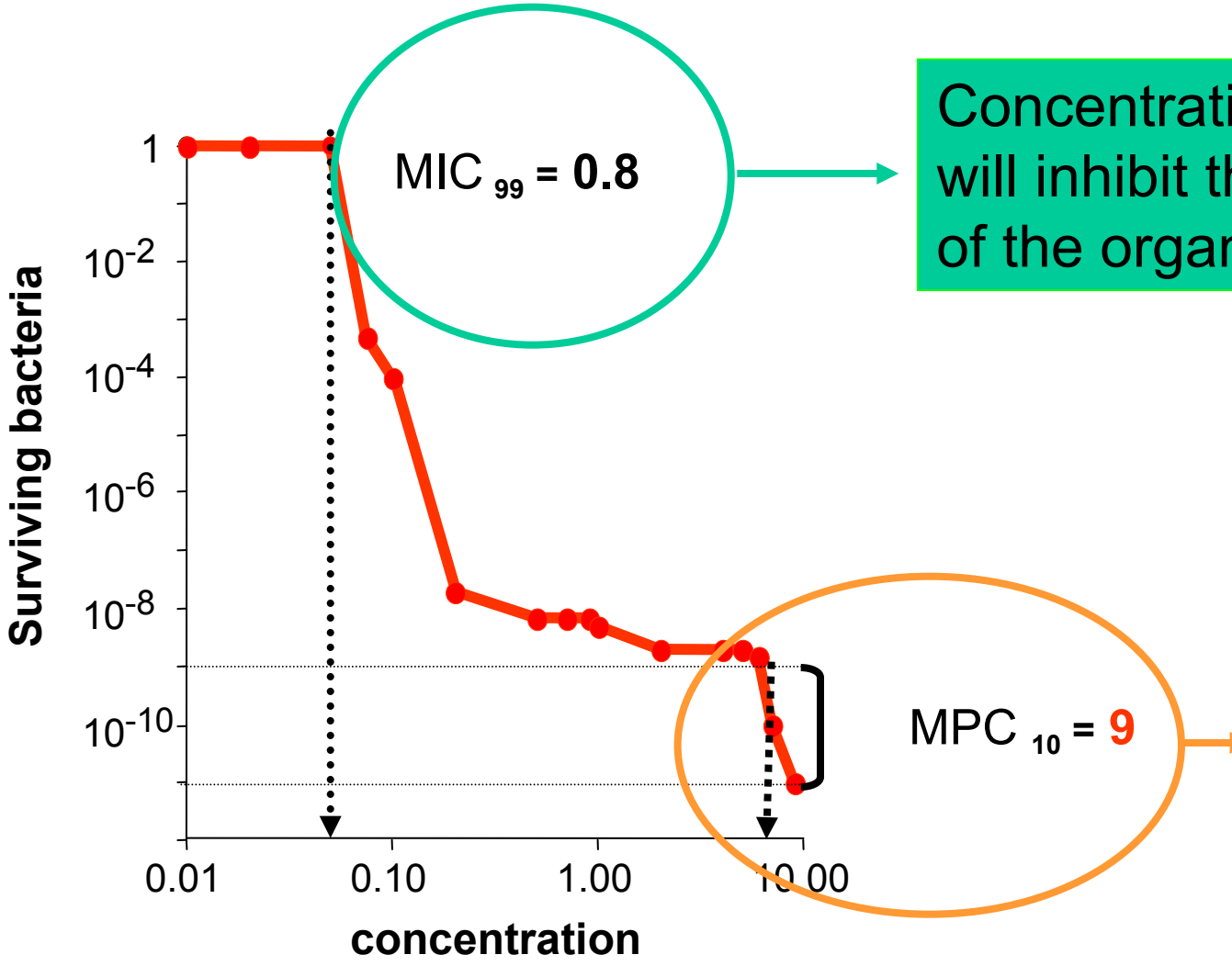
Van Bambeke F, Michot JM, Van Eldere J, Tulkens PM.
Quinolones in 2005: an update. Clin Microbiol Infect. 2005 Apr;11(4):256-80. PMID: 15760423

Mutant Prevention Concentration …



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

Mutant Prevention Concentration …

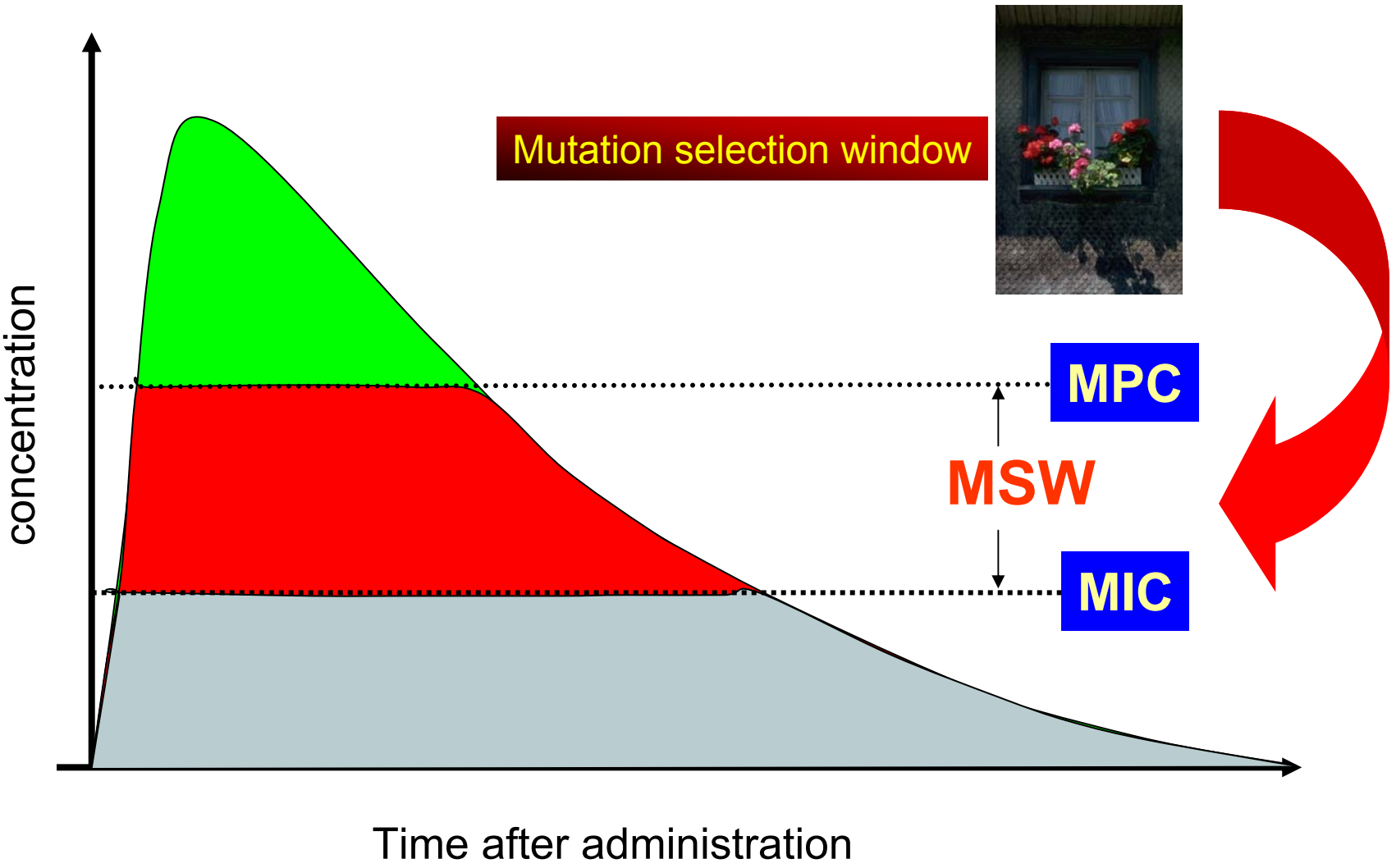


Concentration which will inhibit the majority of the organisms

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

PK/PD breakpoints for fluroquinolones

Drug	Typical daily dosage[a]	Typical PK values: C_{max} in mg/L total/free (dose)	Typical PK values: $AUC_{24\ h}$ (mg × h/L) total/free	Proposed PK/PD upper limit of sensitivity (µg/ml) for: Efficacy[l]	
Norfloxacin	800 mg	1.4/1.1 (400 mg PO)	14/11	0.1–0.4	0.5-1
Ciprofloxacin	1000 mg	2.5/1.75 (500 mg PO)	24/18	0.2–0.8	0.5-1
Ofloxacin	400 mg	4/3 (400 mg PO)	40/30	0.3–0.9	0.5-1
Levofloxacin	500 mg	4/2.8 (500 mg PO)	40/28	0.3–0.9	1-2
Moxifloxacin	400 mg	3.1/1.8 (400 mg PO)	35/21	0.2–0.7	0.5-1

EUCAST breakpoints

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EU in action …

European Medicines Agency
Standard Operating Procedure

Title: Harmonisation of European Breakpoints set by EMEA/CHMP and EUCAST		Document no.: SOP/H/3043
Applies to: Product Team Leaders in the Human Pre-Authorisation Unit, (Co)Rapporteurs, External Experts, EUCAST		Effective Date: 14 February 2005
PUBLIC		Review Date: 14 February 2007
		Supersedes: N/A
Prepared by	Approved by	Authorised for issue by
Name: Bo Aronsson	Name: Agnès Saint Raymond	Name: Patrick Le Courtois
Signature: On file	Signature: On file	Signature: On file
Date: 10 Feb 05	Date: 10 Feb 05	Date: 10 Feb 05

1. Purpose

To describe the interaction between EMEA/CHMP and EUCAST in the process of harmonisation of European breakpoints.

EMEA and EUCAST have set up an agreement that makes EUCAST responsible for defining breakpoints for new molecules proposed for registration in Europe.

EUCAST breakpoints will be accepted by EMEA and put into the "Summary of Product Characteristics", which is part of legal documents accompanying the marketing authorization in EU.

I was not alone…

not too long ago …

G. Drusano

W.A. Craig

FDA

1998

since 1999

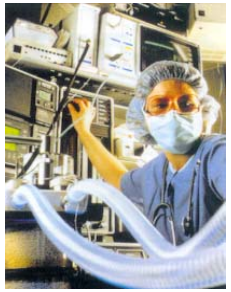
… and again this year

ICAAC 2012

52nd ICAAC – Sept. 9-12 - San Francisco

EMA

1999



and to clinical practice