Société belge d'infectiologie et de microbiologie clinique
Belgische vereniging voor infectiologie en klinische microbiologie

30th Symposium : What will change in your daily practice with the new EUCAST breakpoints for antibiotic susceptibility testing
Elewijt, 26-05-2008

Tournament in front of Castle Steen (1635-37)
Musée du Louvre, Paris

PK/PD as a basis for clinically-relevant breakpoints

Paul M. Tulkens

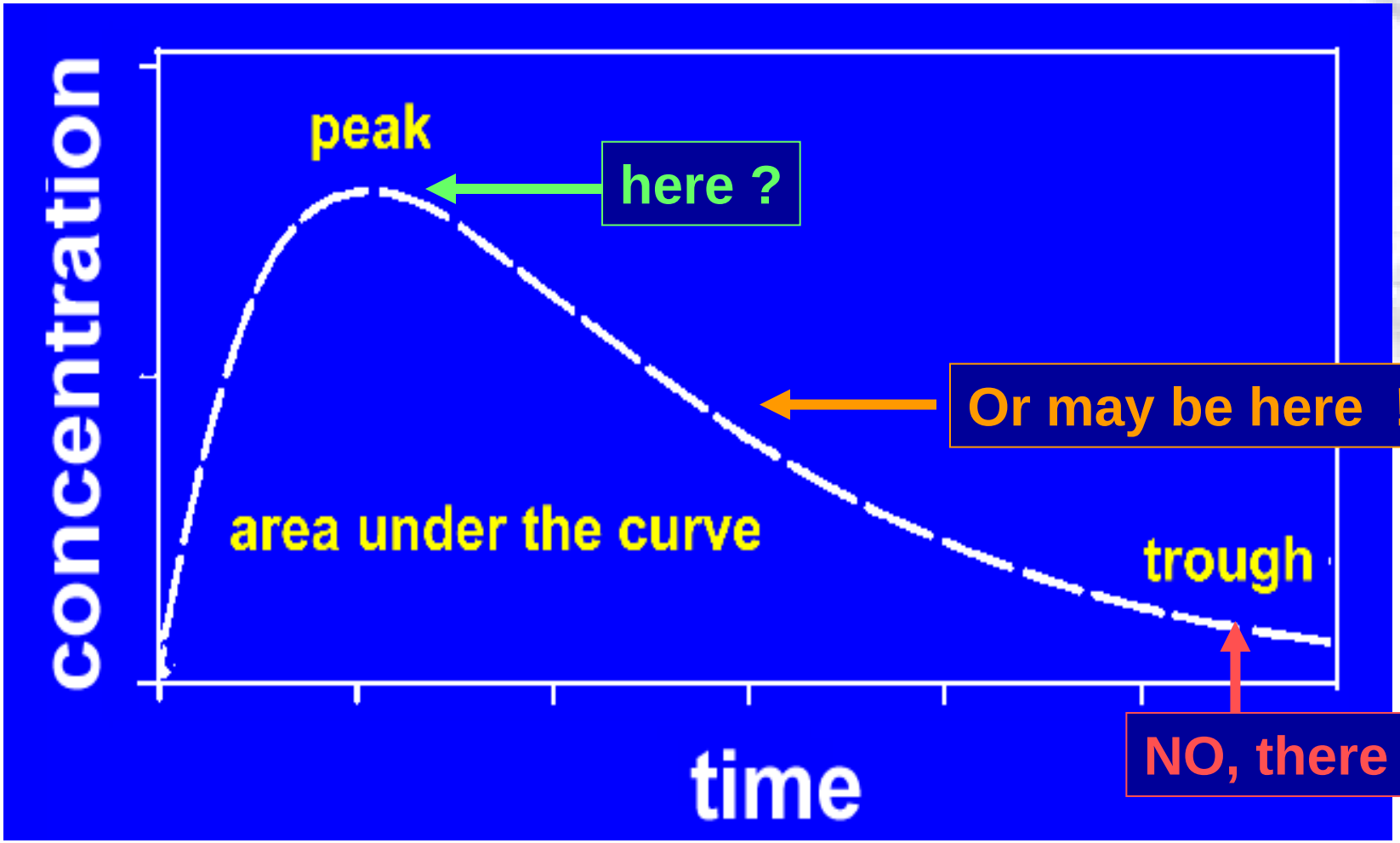
1 Unité de pharmacologie cellulaire et moléculaire & Centre de Pharmacie clinique, Université catholique de Louvain, Brussels

2 Member of the Steering Committee of EUCAST
(as representative of the International Society of Chemotherapy)

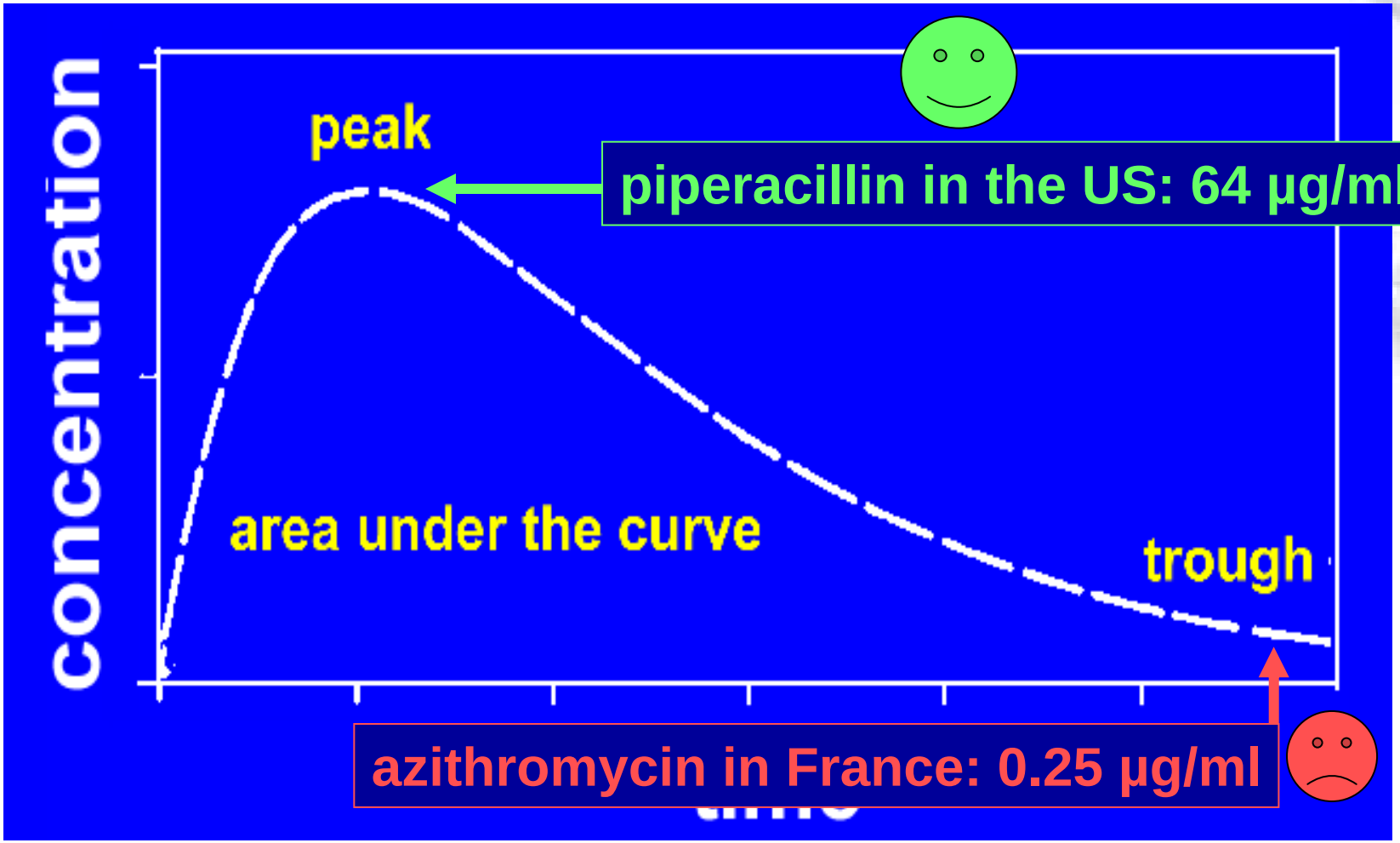
Optimal use of antibiotics ...

- Did we use the antibiotics on a **rational** fashion ?
- What can we do to curb the **emergence of resistance** ?
- Can we reduce the **overall costs** ?

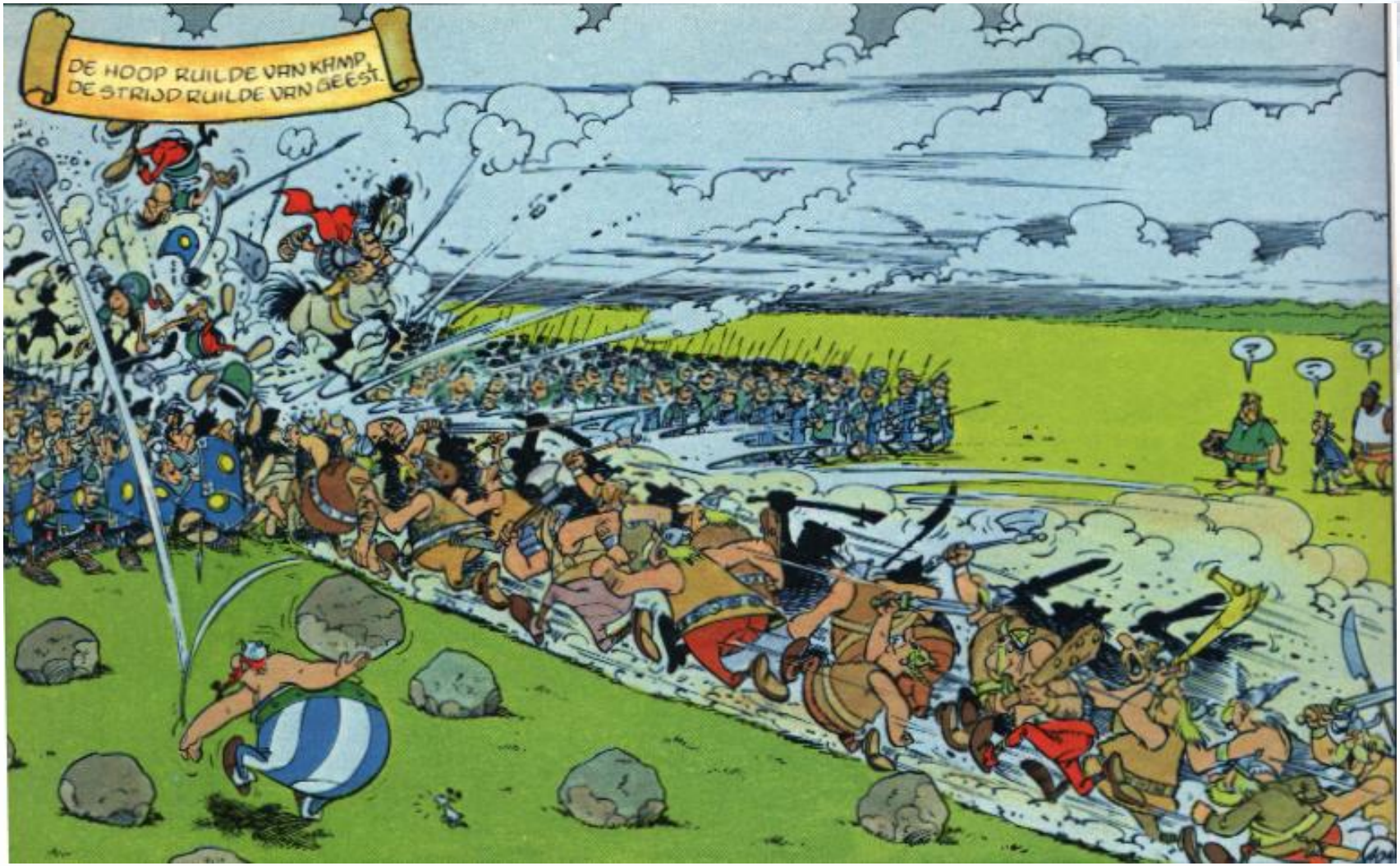
Where should the breakpoint be ?



Where should the breakpoint be ?



And there were fierce battles …



From Mouton, 8th ISAP symposium, Nijmegen, 2001

And everyone in Europe came with his/her own (mathematical) recipe…

Table 1
Breakpoint systems used in various countries in Europe until 2001

Country	Committee		Reference
France	CASFM	Formula based on pk: $(c_{max}/3 + ct1/2 + C4h)3 \cdot M\ (1-k)$[a]	[60]
Great Britain	BSAC	Formula based on pk: $C_{max} \cdot f \cdot s/(e \cdot t)$[b]	[61]
The Netherlands	CRG	70–80% T > MIC for non–protein-bound fraction	[62]
Sweden	SRGA	Pharmacokinetic profile and frequency distribution, species dependent	[63]
Norway	NWGA	67% T > MIC	[64]
Germany	DIN	Pharmacokinetic profile, frequency distributions, efficacy	[65]

[a] C_{max}, maximum serum concentration; Ct1/2, concentration in serum after one half-life; C4h, minimum quantity obtained over 4-h period that corresponds approximately to 10 bacterial generations; k, degree of protein binding.

[b] C_{max}, maximum serum concentration at steady state, usually 1 h postdose; e, factor by which C_{max} should exceed MIC (usually 4); t, factor to allow for serum half-life; f, factor to allow for protein binding; s, shift factor to allow for reproducibility and frequency distributions (usually 1).

As a result …

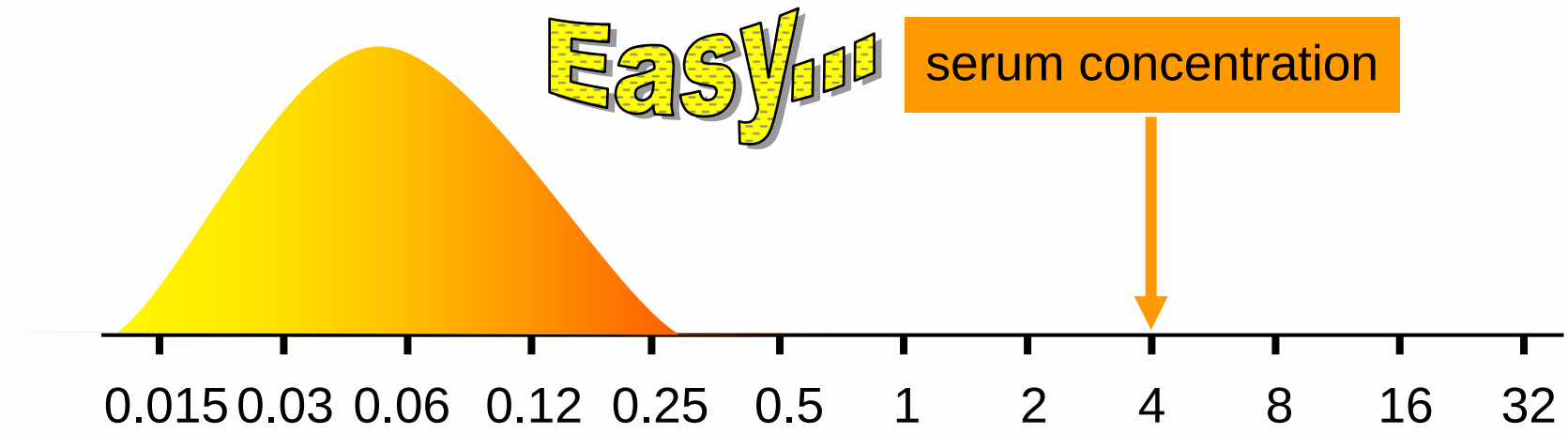
cefotaxime vs. *E.coli*		S≤ / R
BSAC	United Kingdom	2 / ≥4
CA-SFM	France	4 / >32
CRG	The Netherlands	4 / >16
DIN	Germany	2 / ≥16
NWGA	Norway	1 / ≥32
SRGA	Sweden	0.5 / ≥2

Yet, breakpoints were used everyday by clinical microbiology laboratories to advise clinicians about useful antibiotics against the bacteria they are after …

But some did not bother about recipes…

In the US, the NCCLS made breakpoints

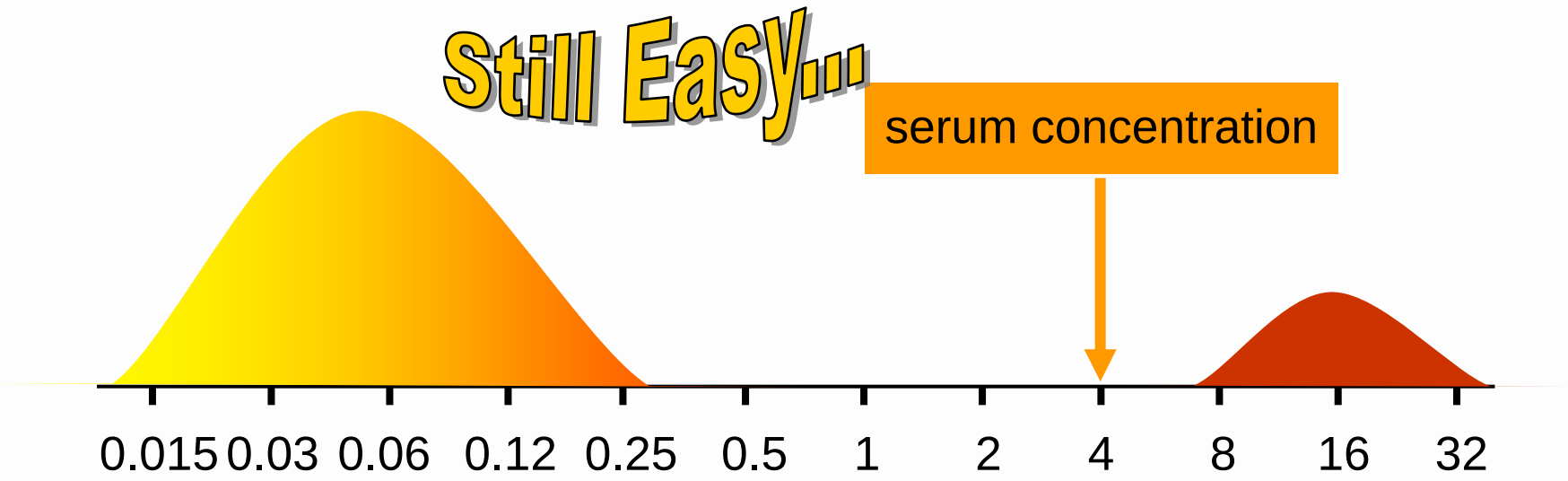
- based on MIC frequency distributions (to distinguish distinct populations)
- clinical data were taken into consideration from the 1980's only
- with little attention to the pharmacokinetic profiles in patients …



But some did not bother about recipes…

In the US, the NCCLS made breakpoints

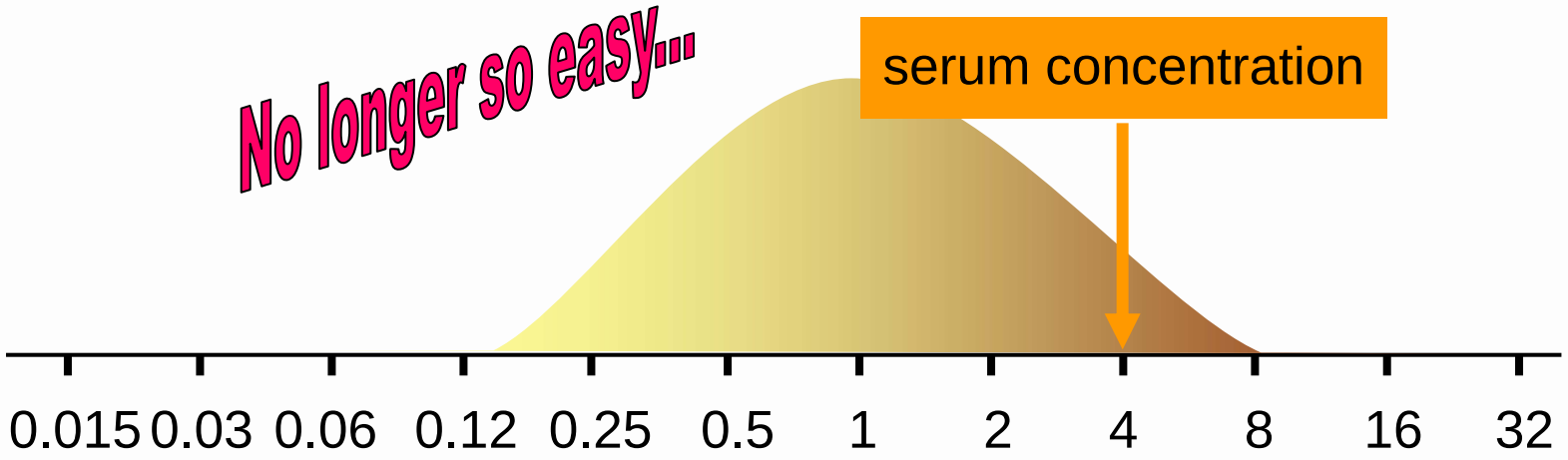
- based on MIC frequency distributions (to distinguish distinct populations)
- clinical data were taken into consideration from the 1980's only
- with little attention to the pharmacokinetic profiles in patients …



But some did not bother about recipes…

In the US, the NCCLS made breakpoints

- based on MIC frequency distributions (to distinguish distinct populations)
- clinical data were taken into consideration from the 1980's only
- with little attention to the pharmacokinetic profiles in patients …



So, what was THE problem ?

- Europe had a number of different breakpoint-setting authorities … and, therefore (?), **MANY** different breakpoints … *

- In the U.S.A., the NCCLS defined the breakpoints, but those were not (always) rational and realistic, and, in any case, were <u>always</u> linked to the US situation (posologies, modes of administration, type of resistance, etc…)

---

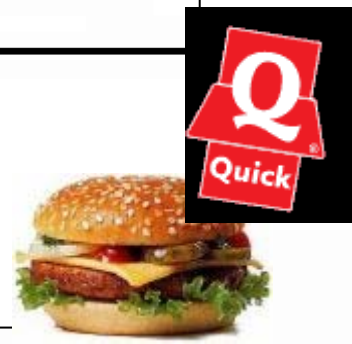
* having no national breakpoint-setting authority to tell them what to do, Belgian microbiologists most often used the NCCLS breakpoints …

Was that truly bad ?

Table 2. Pharmacokinetic parameters

Drug	Typical daily dosage[a]	Typical PK values: C_{max} in mg/L total/free (dose)	Breakpoints (mg/L)[d]: NCCLS (S/I/R)
Norfloxacin	800 mg	1.4/1.1 (400 mg PO)	≤4/8/>16[j]
Ciprofloxacin	1000 mg	2.5/1.75 (500 mg PO)	≤1/2/>4[k]
Ofloxacin	400 mg	4/3 (400 mg PO)	≤2/4/8[l]
Levofloxacin	500 mg	4/2.8 (500 mg PO)	≤2/4/8[l]
Moxifloxacin	400 mg	3.1/1.8 (400 mg PO)	≤1/2/4[m]

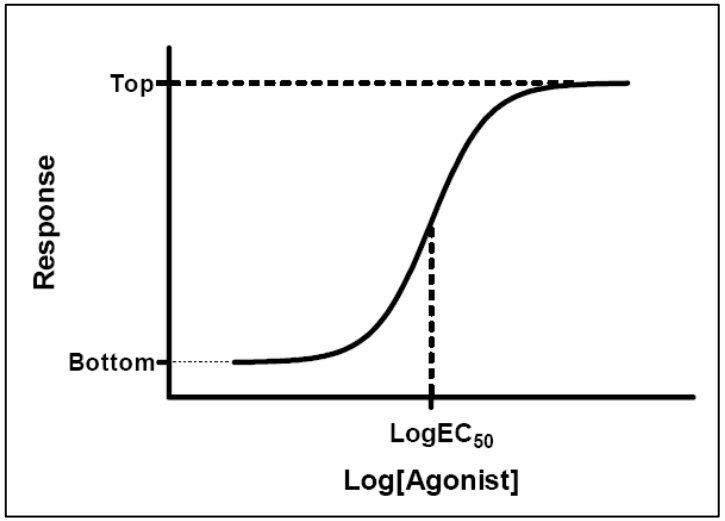
[i]For *Strep. pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis.*
[j]Enterobacteriaceae and *P. aeruginosa.*
[k]*Staphylococcus aureus*, Enterobacteriaceae and *P. aeruginosa.*
[l]*Strep. pneumoniae, Staph. aureus,* Enterobacteriaceae and *P. aeruginosa.*
[m]*Strep. pneumoniae.*



Van Bambeke et al., Clin Microbiol Infect. 2005 Jun;11(6):513

A short introduction to pharmacology …

- *Corpora non agunt nisi fixata …* [1]
- The law of mass action … [2]
- Antibiotics are no exception … [3]



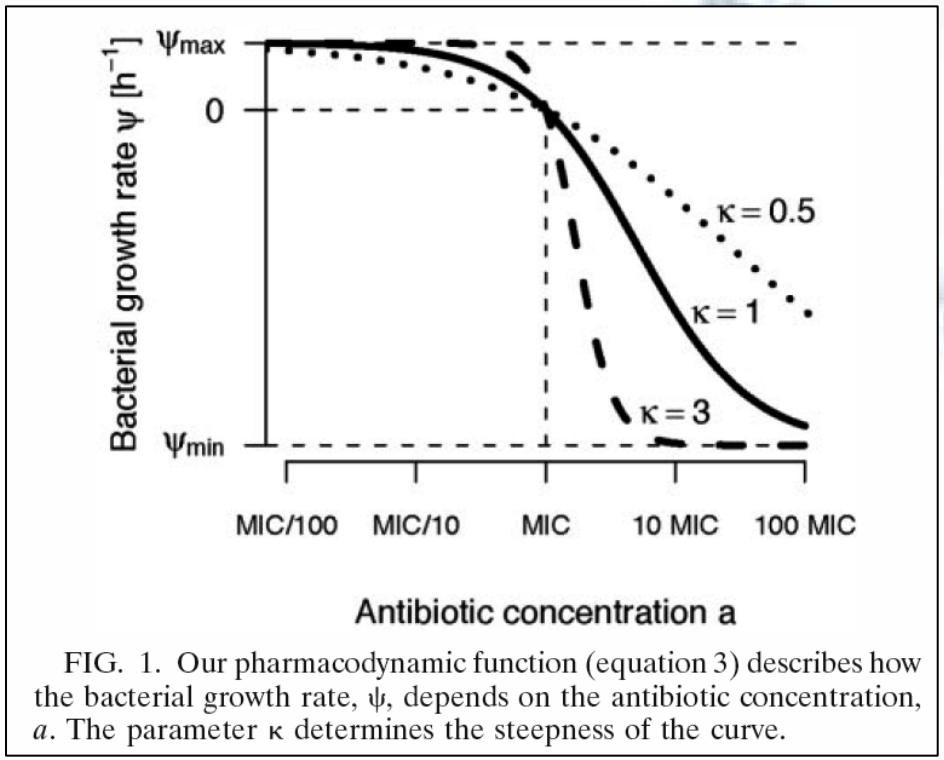
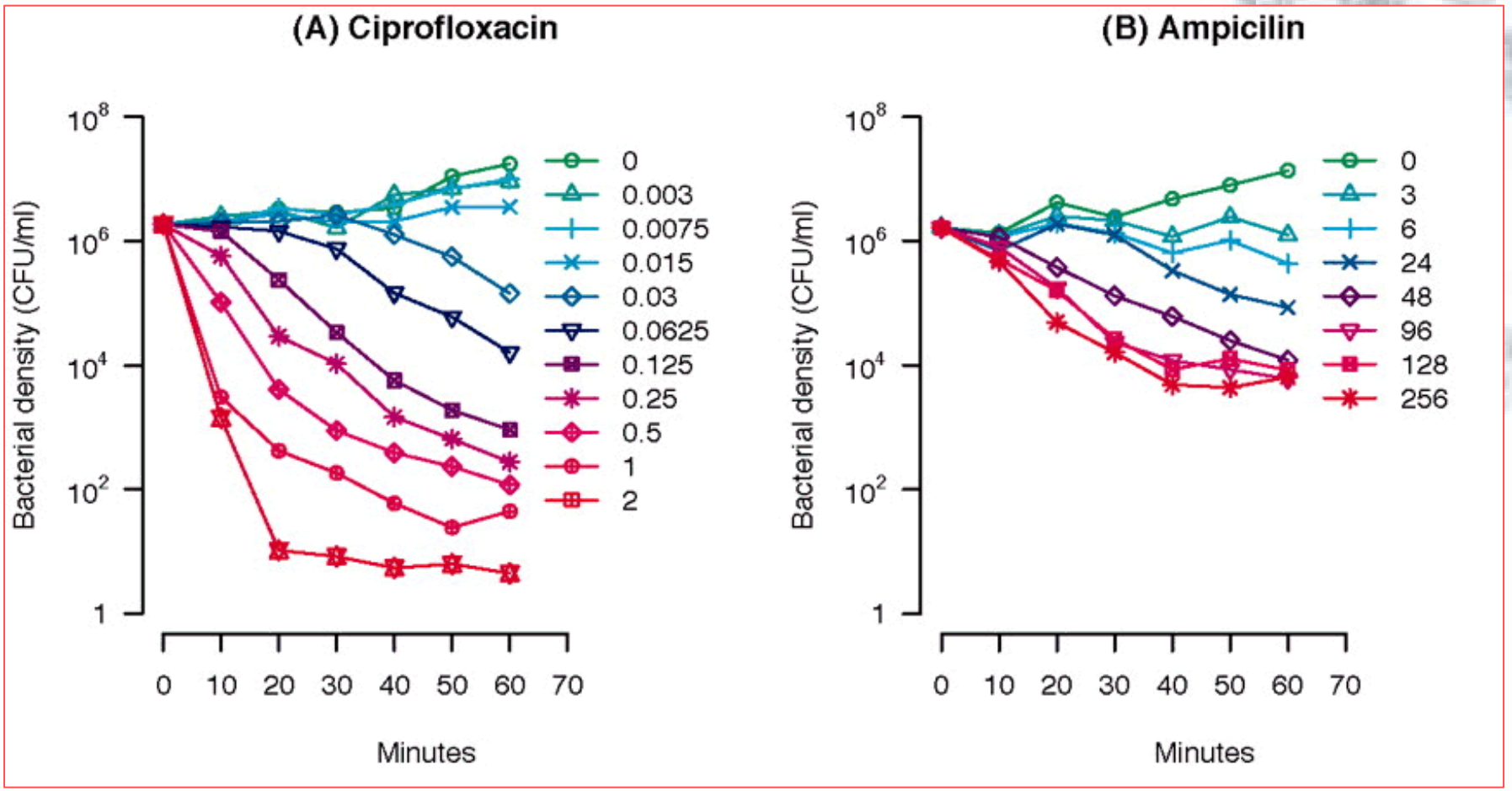


FIG. 1. Our pharmacodynamic function (equation 3) describes how the bacterial growth rate, ψ, depends on the antibiotic concentration, *a*. The parameter κ determines the steepness of the curve.

[1] Ehrlich, P. Lancet 1913, II, 445-451.
[2] Waage, P. & Guldberg, C. M. *Forhandlinger: Videnskabs-Selskabet i Christiana* 1864, 35.
[3] Reggoes et al., Antimicrob Agents Chemother. 2004;48:3670-6.

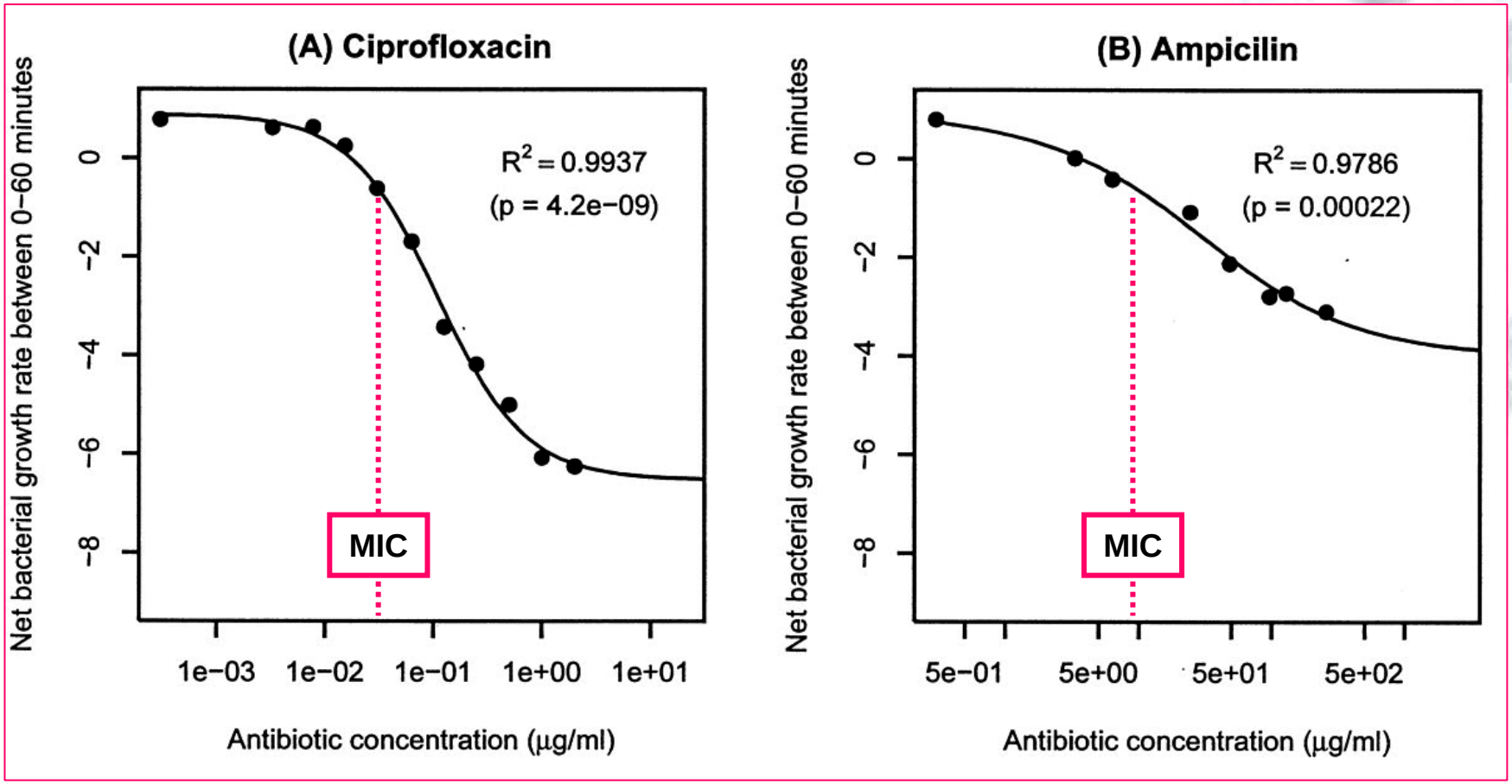
Concentration and time …



Time-kill curves of *E. coli* CAB1 exposed to ciprofloxacin (0 to 2 µg/ml) or to ampicillin (0 to 256 µg/ml)

Reggoes et al., Antimicrob Agents Chemother. 2004;48:3670-6.

Concentration at a given time …

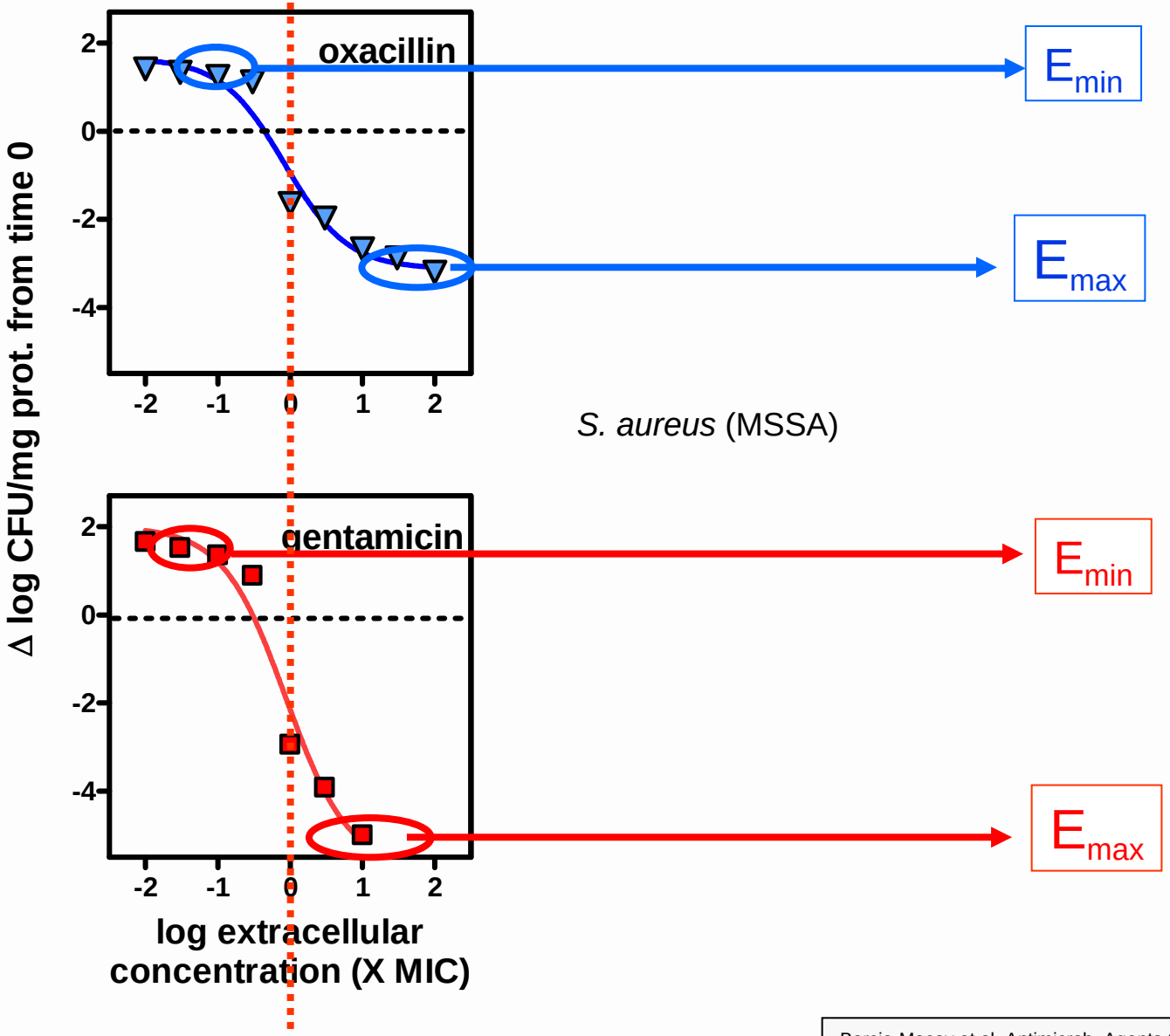


Fitting the pharmacodynamic function to the time-kill curves.

Reggoes et al., Antimicrob Agents Chemother. 2004;48:3670-6.

Can we reproduce this in Belgium?

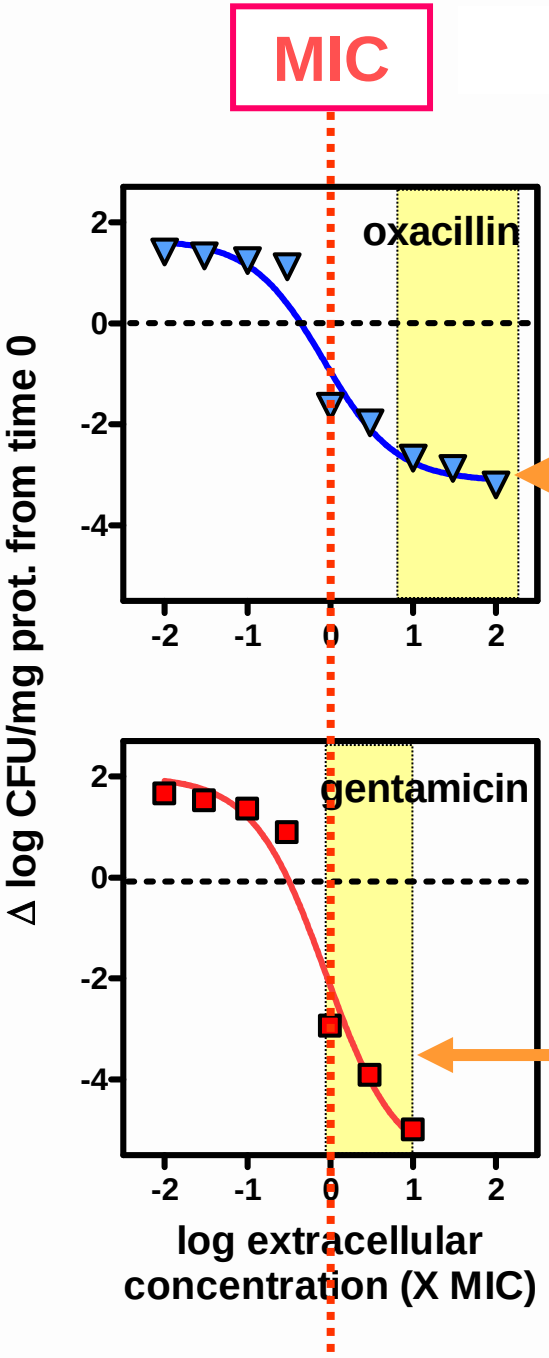
MIC



S. aureus (MSSA)

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

But where is pharmacokinetic ?



weak concentration-dependency

C_{min}-C_{max}

high concentration dependency

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

What PK/PD tells us…. (1/1)

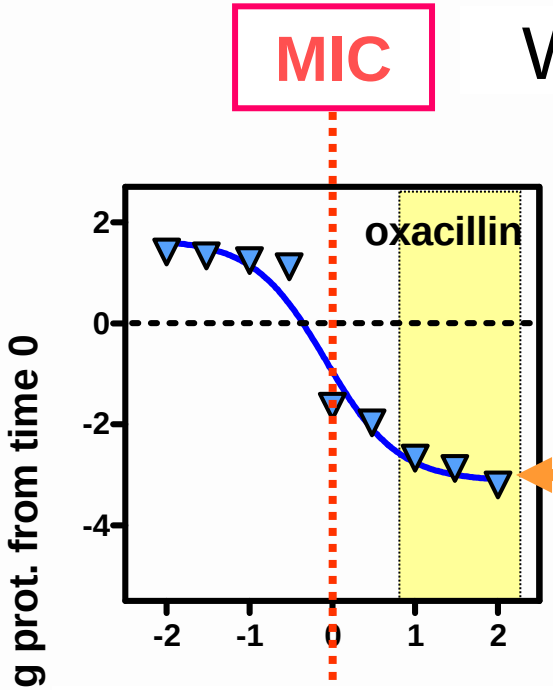
- As predicted by Ehrlich and Waage & Guldberg, all antibiotics are concentration-dependent (like all other drugs);
- **but** is is all about at which serum concentration E_{max} will be obtained **and** how large it is (compared to untreated controls) ....

  – If E_{max} is small and obtained at a **low concentration/MIC ratio** (relative to C_{max}-C_{min} in serum), activity will be optimal once you are above the MIC …

  – all you will be left with is **time** ... and you get, *in vivo,* a **time-dependent antibiotic** (viz. β-lactams …)

➔ BEWARE ! If the MIC rises to near the C_{min}-C_{max} range, time-dependent antibiotics may become concentration dependent …

Why are β-lactams time-dependent ?



You are here (above the MIC)!

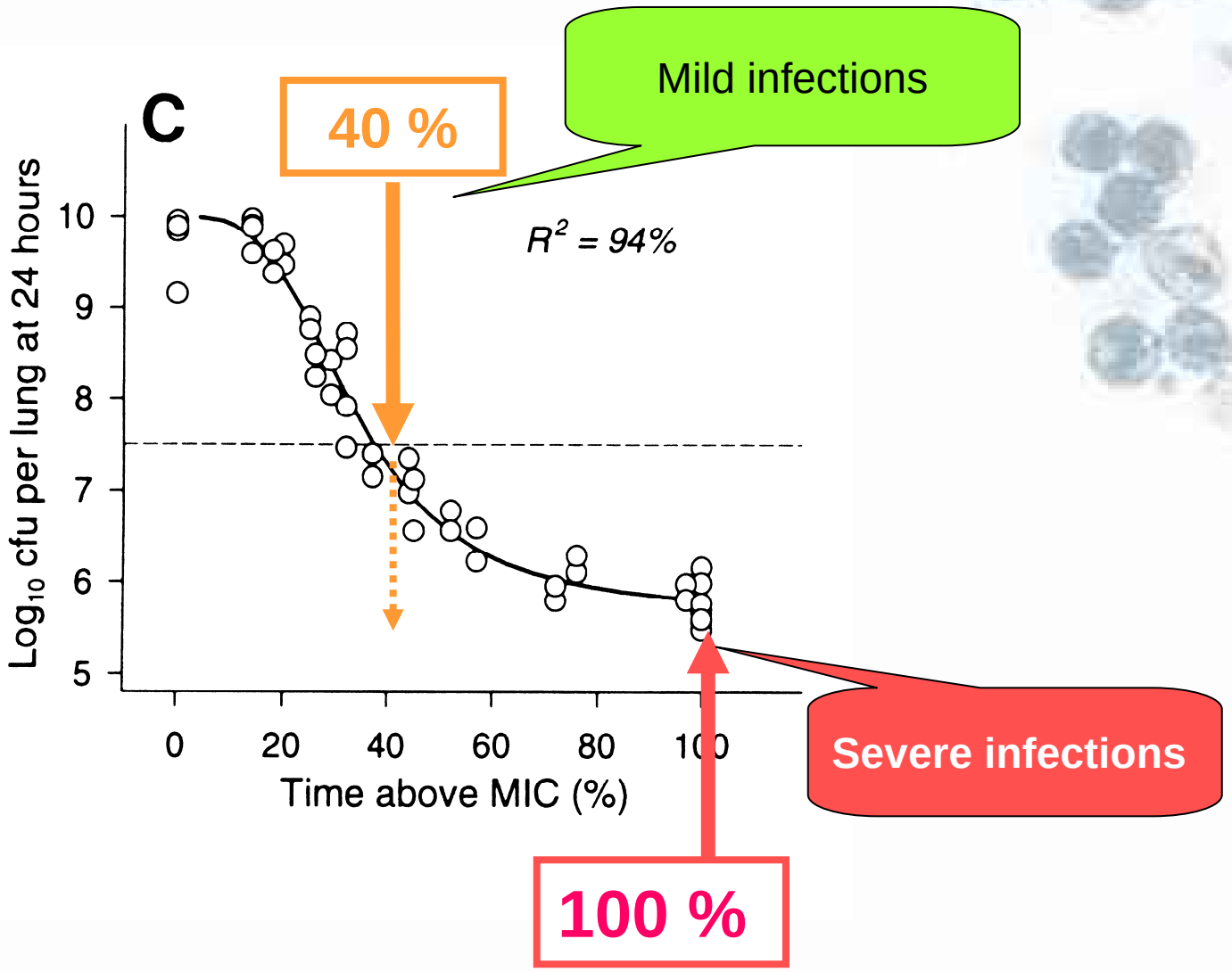
C_{min}-C_{max}

➔ **BEWARE !**

If the MIC rises to near the C_{min}-C_{max} range, time-dependent antibiotics may become concentration dependent within the clinically achievable C_{min}-C_{max} because the curve will be shifted to the right…

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

How long must a β-lactam stay above the MIC ?



Typical pharmacokinetics of a model β-lactam IV *

time (hours)	serum concentration (mg/L) for 0.5 g	1 g	2 g
0	25	50	100
4	12.5	25	50
8	6	12	25
10	3	6	12
12	1.5	3	6
24	0.75	1.5	3

How much do **you** get if given every 12h ?

* single administration; 2h half-life; V_d = 0.2 l/kg

Typical pharmacokinetics of a model β-lactam IV *

time (hours)	serum concentration (mg/L) for 0.5 g	1 g	2 g
0	25	50	100
4	12.5	25	50
6	6	12	25
8	3	6	12
10	1.5	3	6
12	0.75	1.5	3

How much do **you** get if given every **8 h** ?

* single administration; 2h half-life; V_d = 0.2 l/kg

Typical pharmacokinetics of a model β-lactam IV *

How much do **you** get if given every **6 h** ?

erum concentration (mg/L) for

	0.5 g	1 g	2 g
2	25	50	100
4	12.5	25	50
6	6	12	25
8	3	6	12
10	1.5	3	6
12	0.75	1.5	3

* single administration; 2h half-life; V_d = 0.2 l/kg

β- lactams : what can you really do ?

I guess 10 µg/ml is the limit if you use it optimally (2 to 3 x / day and up to a total of 4 to 6 g/day…

PK / PD breakpoints for β-lactams: 8 µg/ml

Pharmacokinetics / Pharmacodynamics in action ...

β- lactams : what can you really do ?

I guess 10

optimally (2

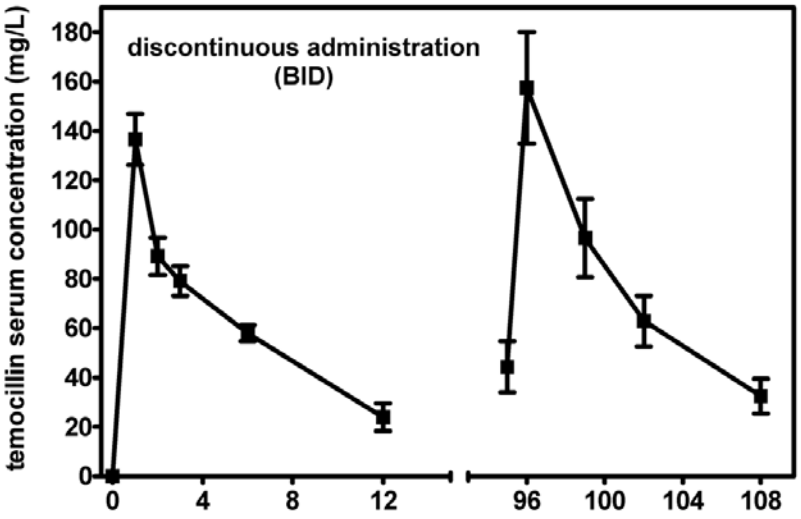
of 4 to 6 g/

PK / P

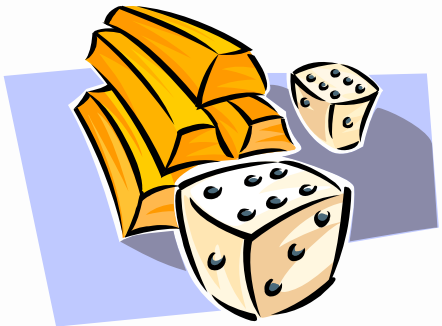
Cephalosporins - EUCAST clinical MIC breakpoints

Cephalosporins Click on antibiotic name to see wild type MIC distributions.		*Enterobac-teriaceae*[2]	*Pseudo-monas*[3]	Ac
Cefazolin	RD	--	--	
Cefepime	RD	1/8	8/8	
Cefotaxime	RD	1/2	--	
Ceftazidime	RD	1/8	8/8	
Ceftriaxone	RD	1/2	--	
Cefuroxime	RD	8/8[5]	--	

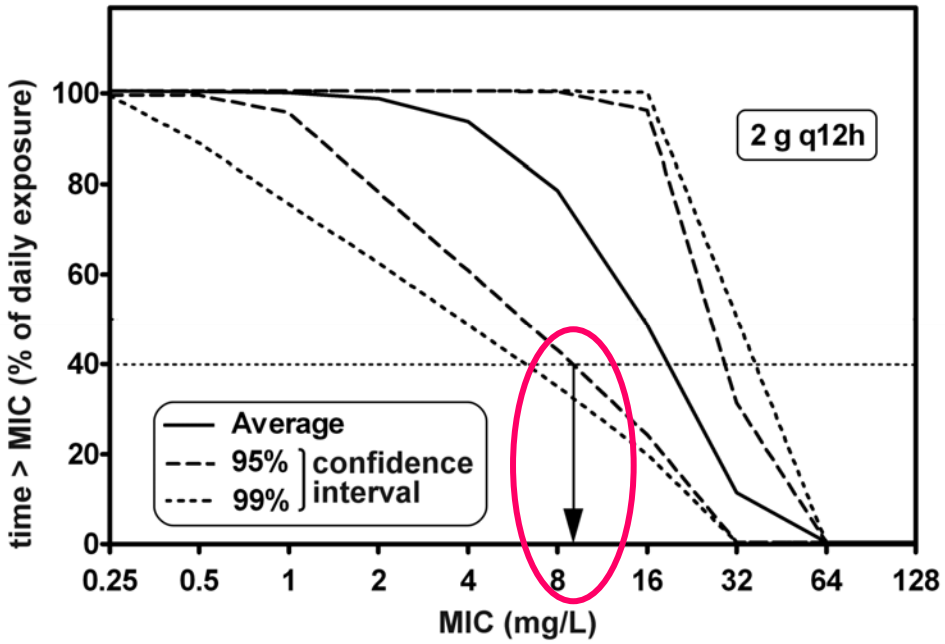
Setting up a breakpoint for a "Belgian" antibiotic (temocillin – 4 g /day)



actual data



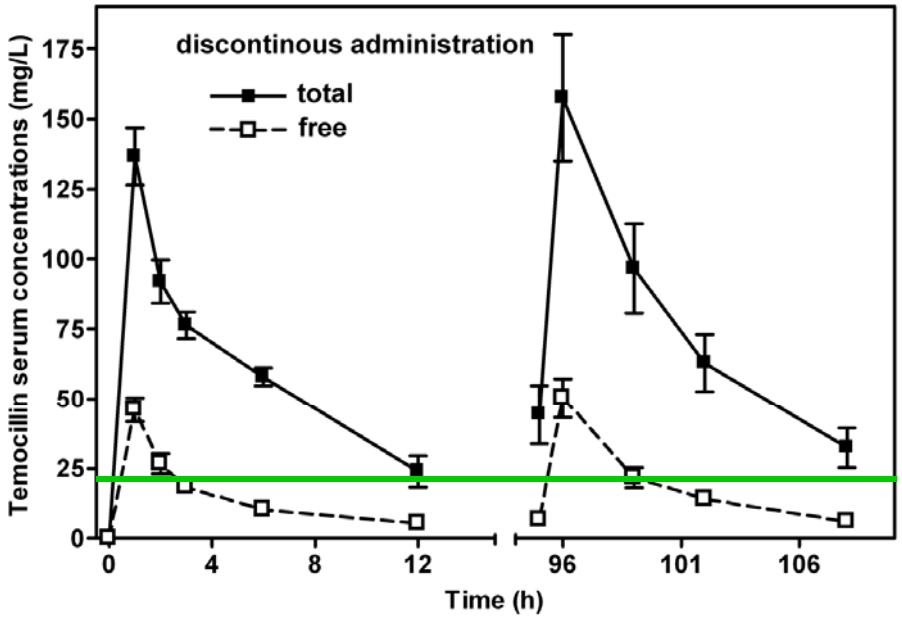
target attainment rate after Monte-Carlo simulation

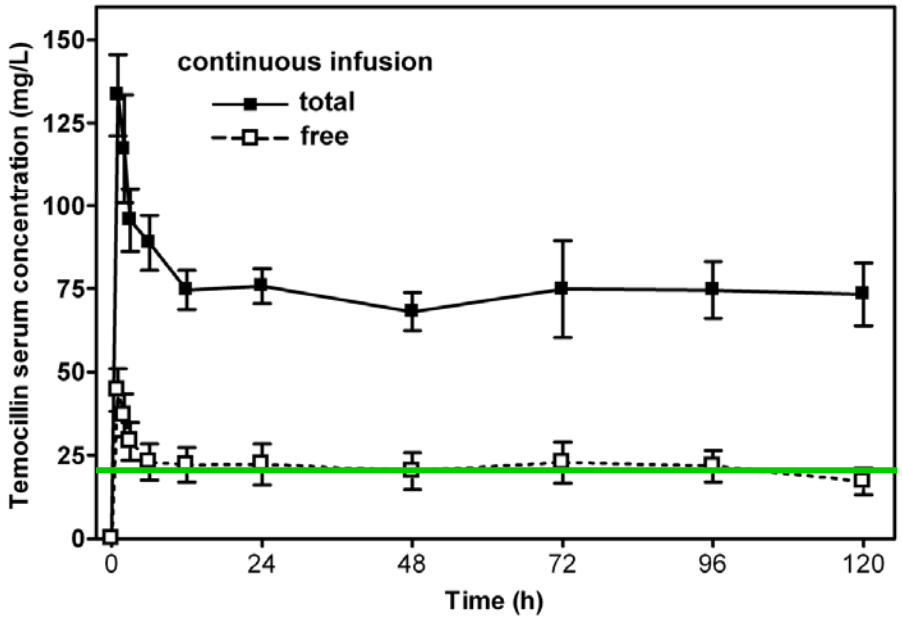


J. Antimicrob. Chemother. 2008 Feb;61(2):382-8

And what with continuous infusion …

(4 g/day)

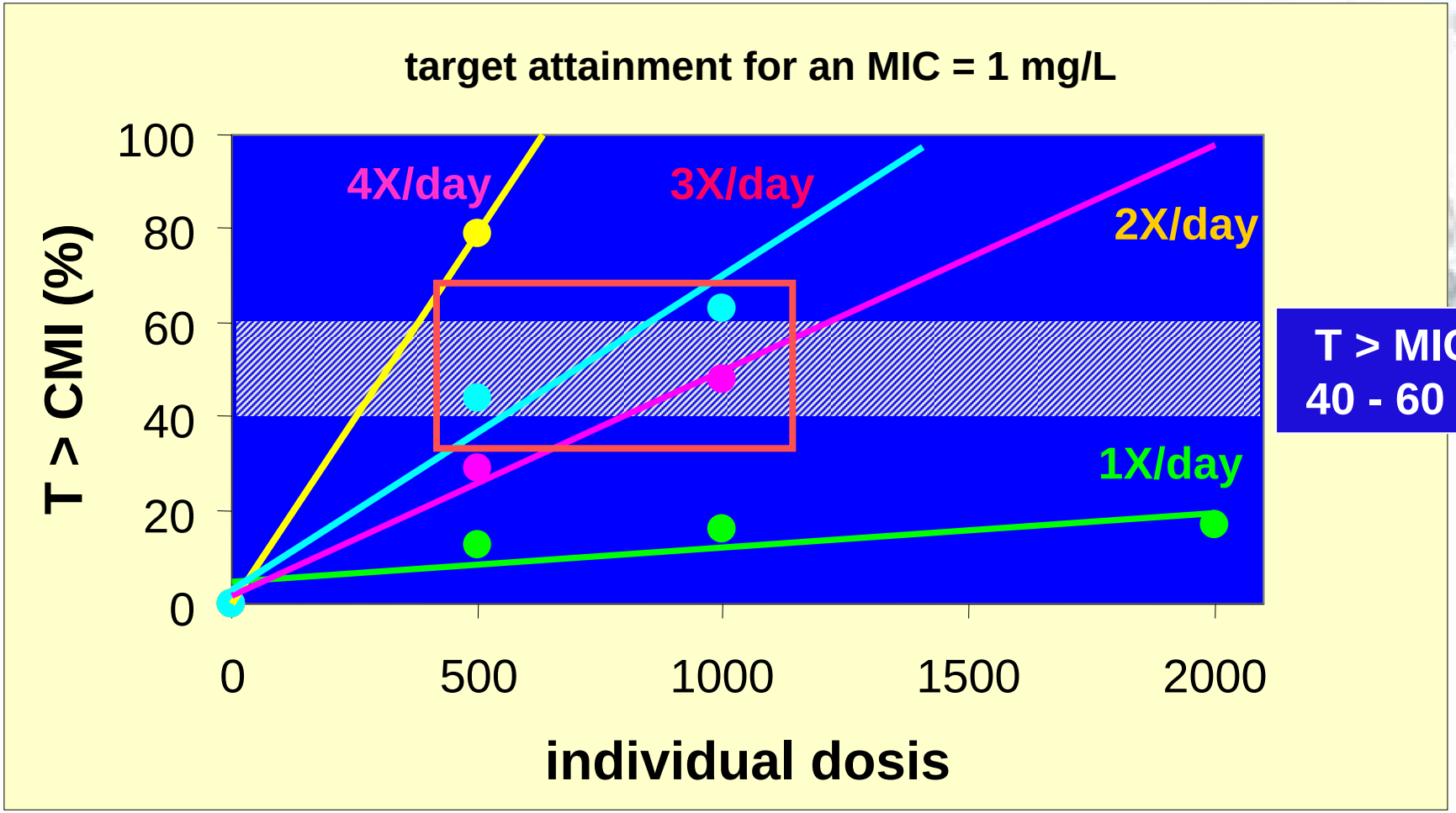




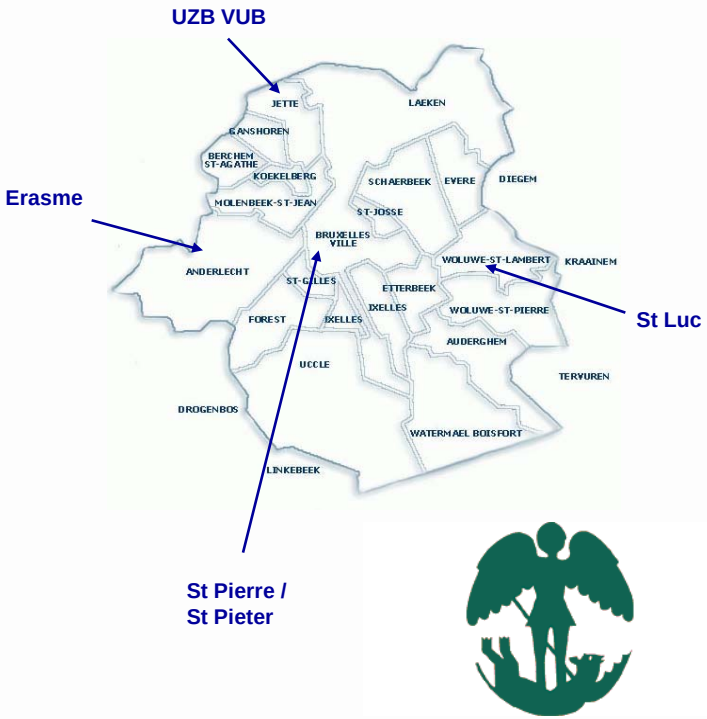
Concentration at equilibrium (free): 23 ± 2 (12 - 42)

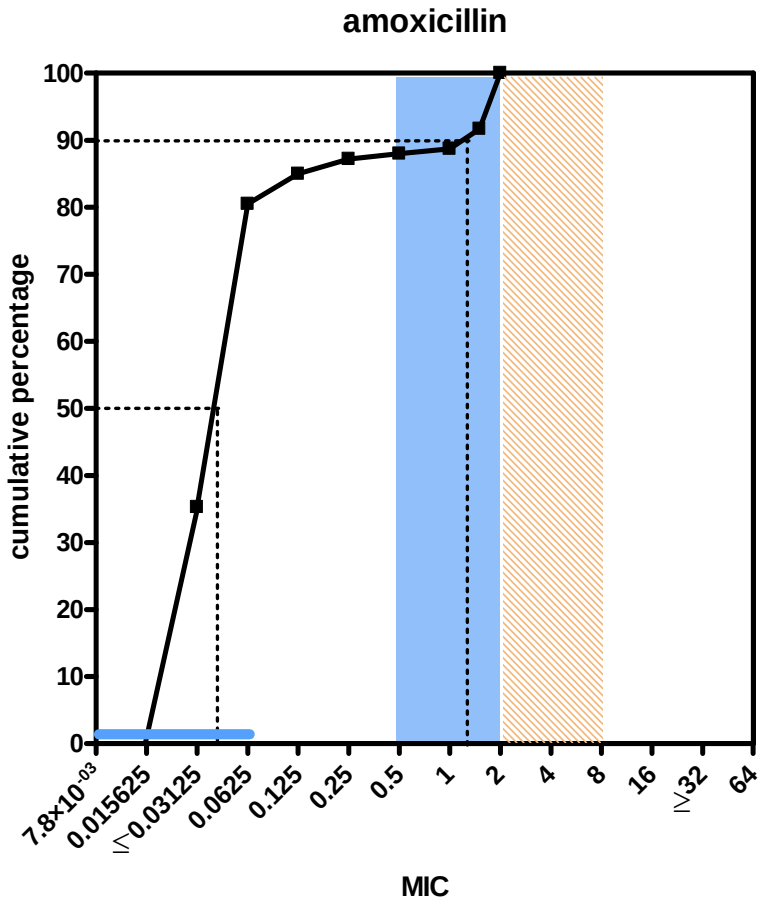
J. Antimicrob. Chemother. 2008 Feb;61(2):382-8

A few words about oral amoxicillin and S. pneumoniae



S. pneumoniae : why we may have problems (soon ?) …

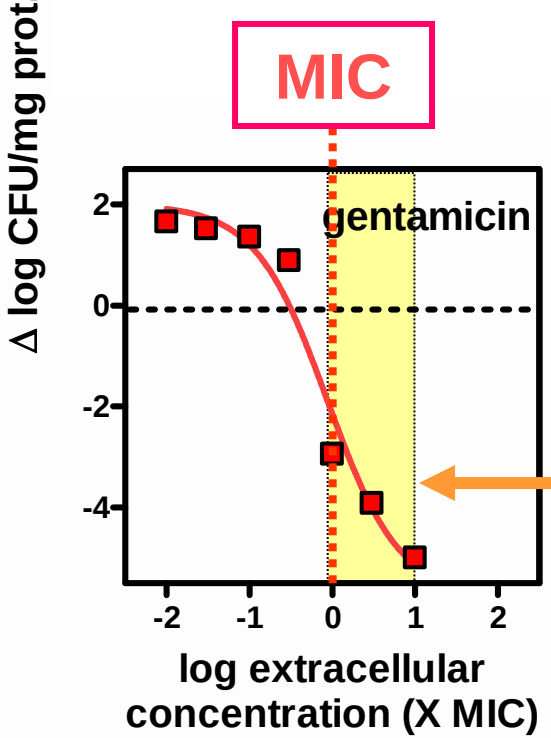




EUCAST breakpoint: 0.5/2

Epidemiological survey of antibiotic resistance in a Belgian collection of CAP isolates of *Streptococcus pneumoniae* (SP)
A. Lismond, F. Van Bambeke, S. Carbonnelle, F. Jacobs, M. Struelens, J. Gigi, A. Simon, . Van Laethem, A. Dediste, D. Pierard, A. De Bel, & P.M. Tulkens, RICAI, Paris, 2007 / ECCMID, Barcelona, 2008

But all antibiotic are not β-lactams …



C_{min}-C_{max}

high concentration dependency

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

What PK/PD tells us (2/2) ...

- If E_{max} is large and obtained at serum concentrations higher than the usual C_{max}/MIC ratio, you get *in vivo* a **concentration- and AUC-dependent antibiotic** (viz. fluoroquinolones...)

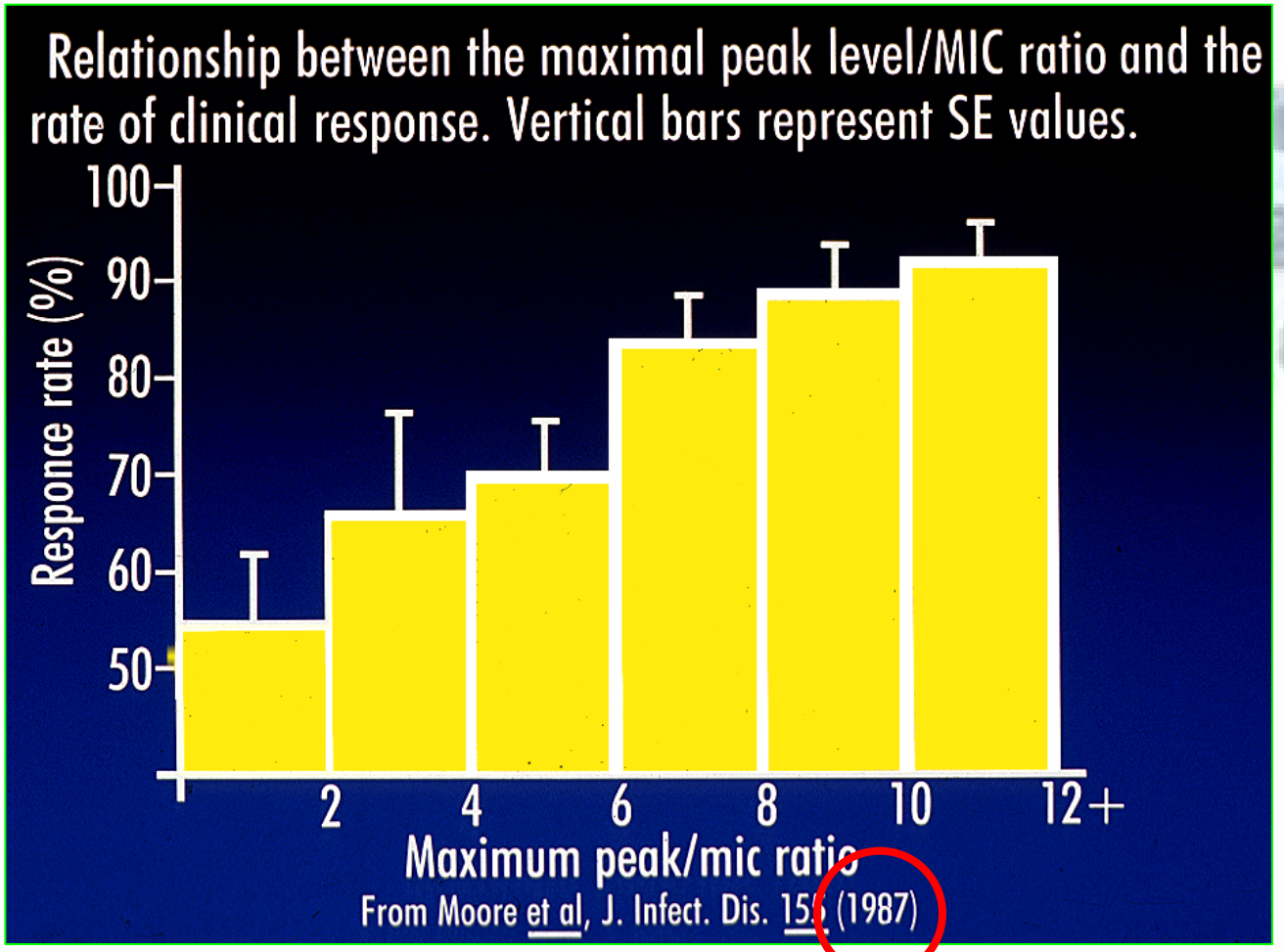
  ➔ **BEWARE:** the MIC of the offending organism is also critical ... since the rate of eradication is proportional to the C_{max}/MIC ratio

  ➔ **HINT:** if you increase the unit dose (say, give 200 mg instead of 100), you increase both the C_{max} and the AUC …

    ➔ if you want to change only the C_{max}, you must change the <u>schedule</u> of administration (i.e. move from 3 x 1 g to 1 x 3 g)

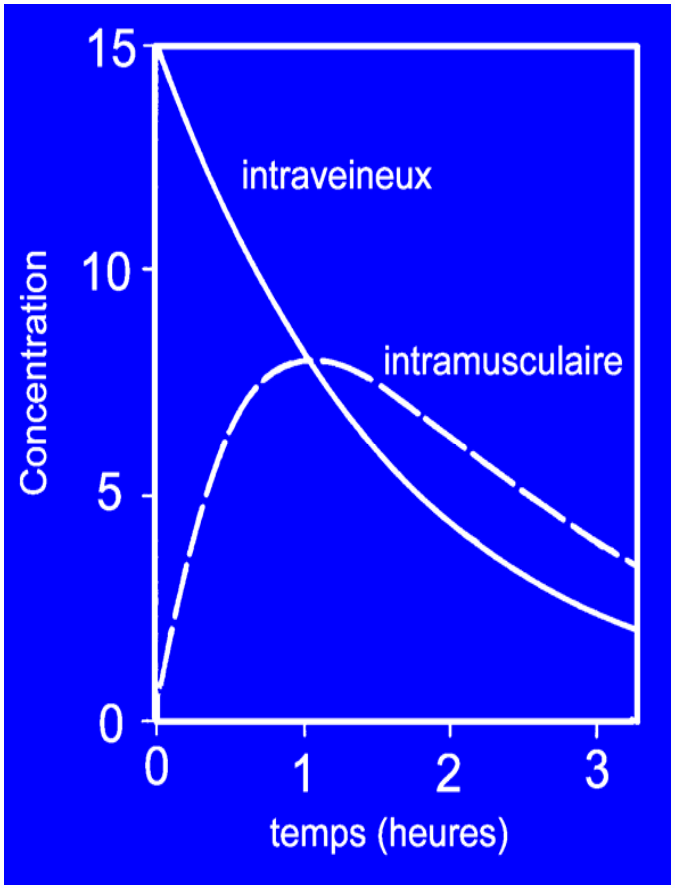
  ➔ **BEWARE:** low C_{max}/MIC and AUC/MIC ratios will lead to failures and emergence of resistance ...

After all, that was all known since 1987 ... for the good, old faithful aminoglycosides ...



Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration.

Aminoglycosides : obtain a peak !



1. adequate mode of aministration

→ **i.v. administration**

2. calculate the peak you need

→ **minimal peak = MIC / 8**

3. calculate the dose you need

peak = dose / Vd

→ **dose = peak x Vd**

PK / PD in action ...

Aminoglycosides :

increase the unit dose to get the appropriate peak !

MIC = 1 mg/L ➡ C_{max} = 8 mg/L ➡ 3 mg/kg

MIC = 2 mg/L ➡ C_{max} = 16 mg/L ➡ 6 mg/kg ⬅ **limit for G, T, N**

MIC = 4 mg/L ➡ C_{max} = 32 mg/L ➡ 15 mg/kg ⬅ **limit for A, I**

Aminoglycosides - EUCAST clinical MIC breakpoints 2006-06-20 (v 1.3)

Aminoglycosides[2] Click on antibiotic name to see wild type MIC distributions.		*Enterobac-teriaceae*	*Pseudo-monas*[3]	*Acineto-bacter*[4]	*Staphylo-coccus*
Amikacin	RD	8/16	8/16	8/16	8/16[5]
Gentamicin	RD	2/4	4/4	4/4	1/1
Netilmicin	RD	2/4	4/4	4/4	1/1
Tobramycin	RD	2/4	4/4	4/4	1/1

ak !

MIC = 2 mg/L ➡ C_{max} = 16 mg/L ➡ 6 mg/kg ← **limit for G, T, N**

MIC = 4 mg/L ➡ C_{max} = 32 mg/L ➡ 15 mg/kg ← **limit for A, I**

Fluoroquinolones: the real problem !

Related Articles, Links

1: Rev Infect Dis. 1988 Jan-Feb;10 Suppl 1:S70-6.

Comparative activity of the 4-quinolones.

Phillips I, King A.

Department of Microbiology, United Medical School, Guy's Hospital, London, United Kingdom.

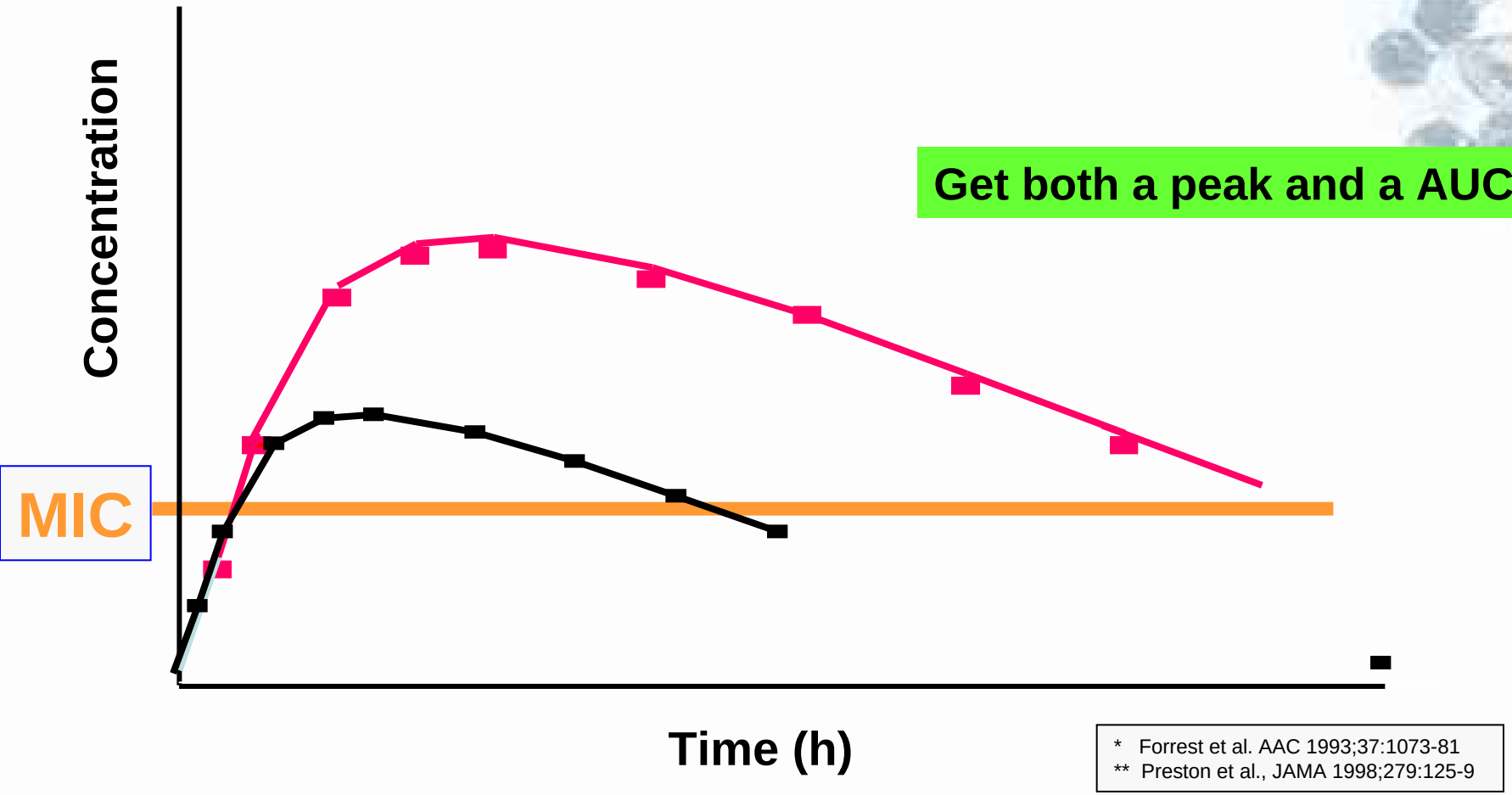
Minimal inhibitory concentrations (MICs) of the 4-quinolones ciprofloxacin, enoxacin, norfloxacin, ofloxacin, pefloxacin, difloxacin, A-56620, and CI-934 are consistent world-wide, with allowances for differences in acquired resistance. MICs of these drugs for Enterobacteriaceae correlate with those of nalidixic acid, but resistance to the quinolones is rare if a breakpoint of greater than 2 mg/L is accepted. Most intestinal pathogens are sensitive. Acinetobacter, Pseudomonas aeruginosa, and other Pseudomonas species except Pseudomonas maltophilia are usually sensitive. Ciprofloxacin is generally the most active of the 4-quinolones against these organisms. All of the new agents have antistaphylococcal activity, but that of norfloxacin and ofloxacin is borderline. Against streptococci,

with a Cmax at 1.5-2.5 mg/L ?

Fluoroquinolones: get a peak and an AUC !

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

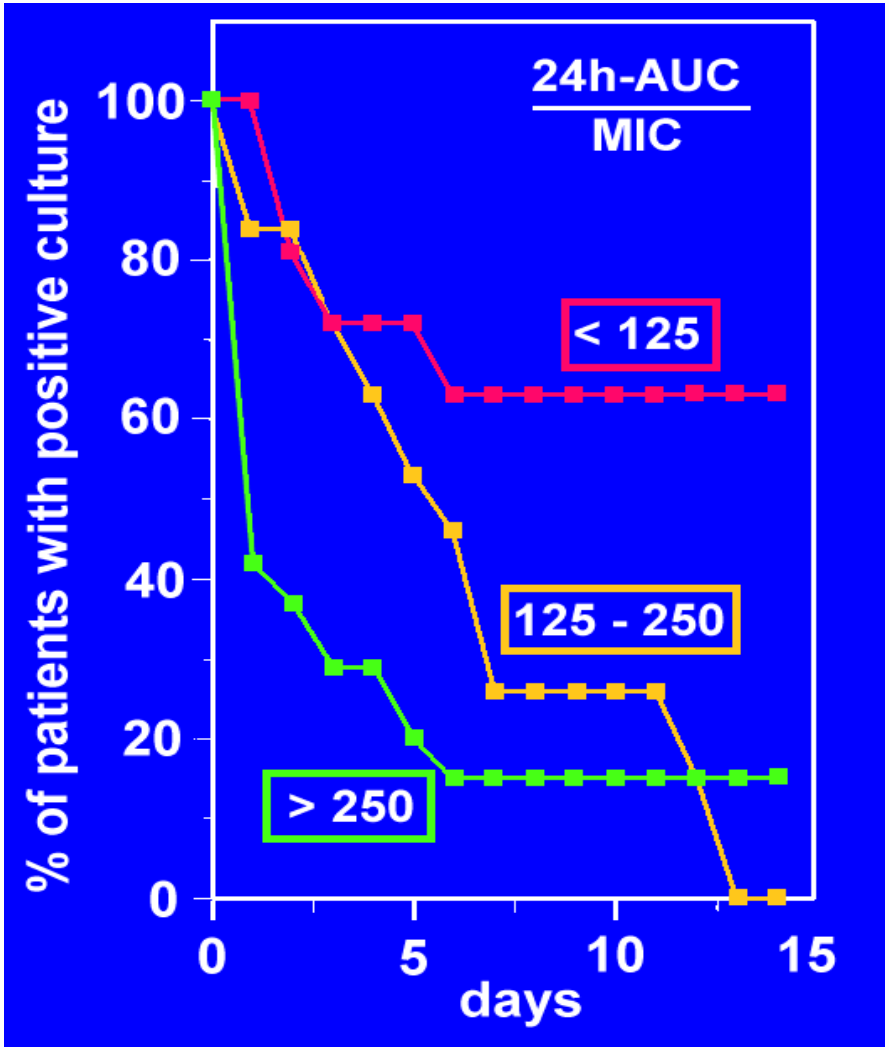
C_{max}/MIC ⇒ should be > 10 **



Get both a peak and a AUC !!

* Forrest et al. AAC 1993;37:1073-81
** Preston et al., JAMA 1998;279:125-9

AUC / MIC as the critical parameter for fluoroquinolones



Forrest et al., AAC, 1993

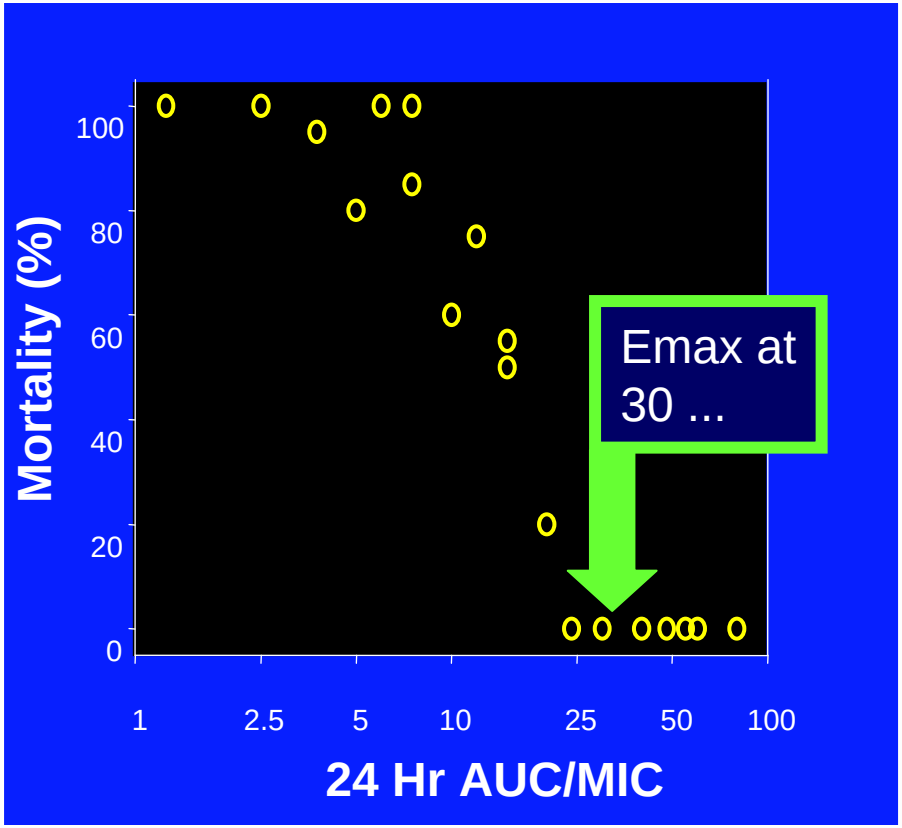
125 was the limit below which <u>clinical</u> failure rates became unacceptable because of either

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

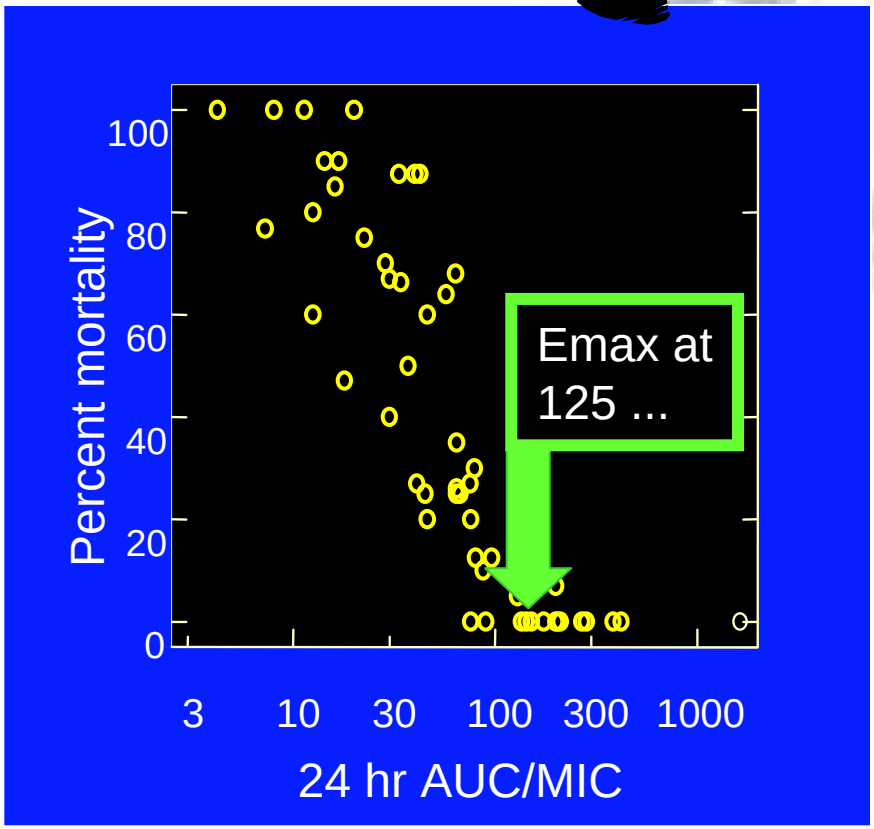
Warning: in this study, they could not really dissociate peak and AUC, and they had always low peaks, because all treatments were BID or TID

You said AUC/MIC >125 for Gram (+) ?

The saga of *S. pneumoniae* ...



non-neutropenic



neutropenic

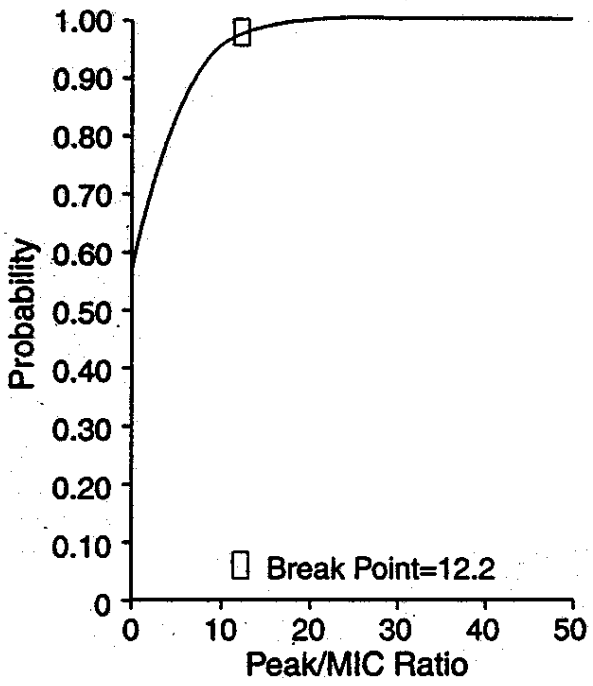
You said C_{max}/MIC ratio > 10 for Gram (+) ?

The saga of *S. pneumoniae* ...

Pharmacodynamics of levofloxacin: a new paradigm for early clinical trials. Preston et al., J.A.M.A., 1998 Jan 14;279(2):125-9

RESULTS (as presented by the authors)**:**

- 134 / 313 had both PK and MIC
- **clinical AND bacterial outcomes were related to peak/MIC**
  (logistic regression; $p < 0.001$)
- **results were favourable if peak / MIC > 12.2**



Warning: in this study, they could absolutely **not** dissociate peak and AUC, and they had always high peaks, because all treatments were QD ! Peak was chosen as key pharmacodynamic parameter arbitarily ! They also had only few true failures…

But, anyway, let us move on …

If you believe G. Drusano is telling you the truth when he says "I am a doctor"...

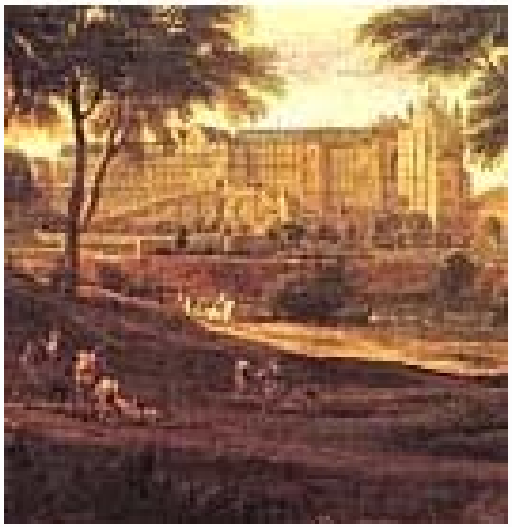
➔ peak / MIC > 10

If you believe your patient is not a healthy mouse …and can't get a high peak (as was the case in Forrest's study)

➔ AUC_{24h} / MIC > 100

If you believe that Drlica is correct in saying that you should take care of the 1st mutants
(I'd also add also efflux and QnR)

➔ get also a peak / MIC > 10



Therefore, PK/PD (… Belgian) breakpoints …

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

UCL KU LEUVEN

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 - EUCAST clinical MIC breakpoints 2008-0

Fluoroquinolone[2] Click on antibiotic name to see wild type MIC distributions		Species-related breakpoints (S≤						
		Entero-bacteriaceae[3]	*Pseudo-monas/*	*Acineto-bacter*	*Staphylo-coccus*	*Entero-coccus*	*Strepto-coccus A,B,C,G*	*S.pneu-moniae*[6]
Ciprofloxacin	RD	0.5/1	0.5/1	1/1[4]	1/1[5]	--	--	0.125/2
Levofloxacin	RD	1/2	1/2	1/2	1/2	--	1/2	2/2
Moxifloxacin	RD	0.5/1	--	--	0.5/1	--	0.5/1	0.5/0.5
Norfloxacin	RD	0.5/1	--	--	--	--	--	--
Ofloxacin	RD	0.5/1	--	--	1/1[3]	--	--	0.125/4

per limit
ml) for
ntion of
stance[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

UCL KU LEUVEN

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

So, what did EUCAST do with PK/PD ?

Meetings

1st joint EARSS-EUCAST Plenary Meeting Rome, November 23-25, 2005

Program Plenary meeting (115Kb) at the Instituto Maria SS. Babina (288Kb)

Here we are ...

Meetings

1st joint EARSS-EUCAST Plenary Meeting Rome, November 23-25, 2005

Program Plenary meeting (115Kb) at the Instituto Maria SS. Babina (288Kb)

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

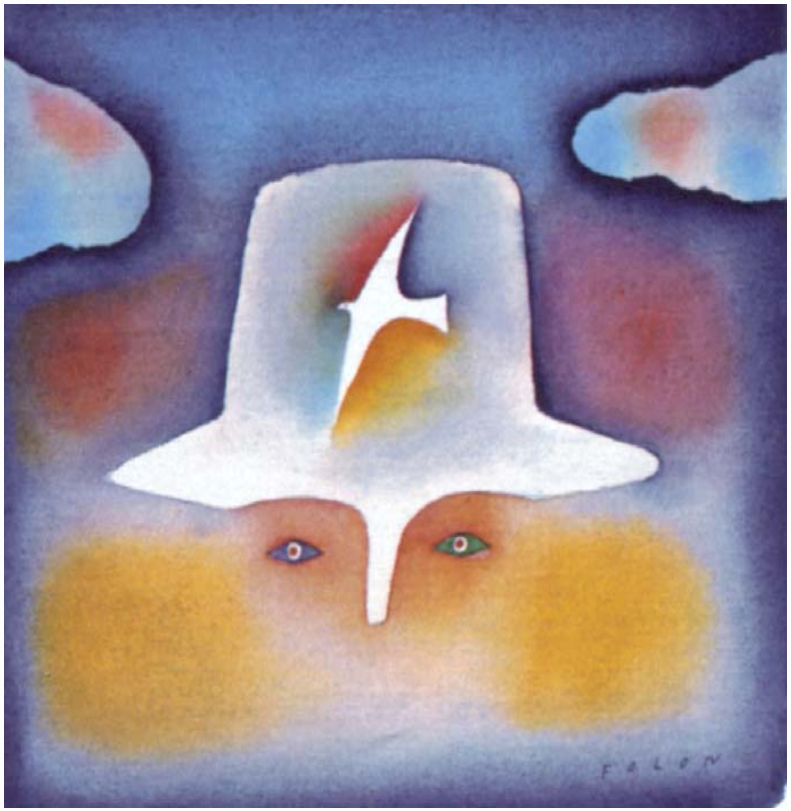
5. Pharmacodynamic data are evaluated

The PK/PD index value of the pertinent PK/PD parameter (time above MIC, AUC/MIC, C_{max}/MIC…) resulting in optimal outcome is determined from:

- in vitro data
- animal studies
- clinical trials
- The efficacy of the drugs is assessed quantitatively.

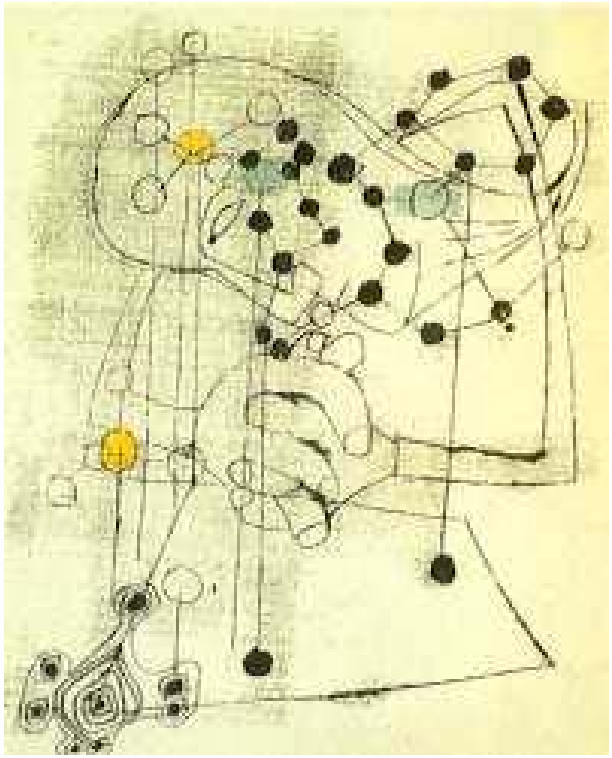
Relationships between concentration time profiles and emergence of resistance are evaluated

PK/PD, a brilliant idea …



But do not forget the problems

You said problems ?



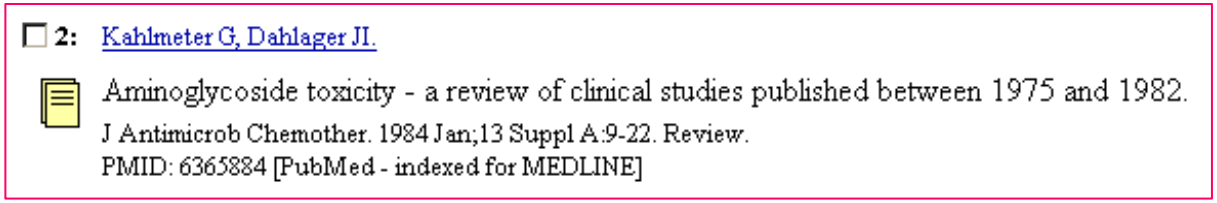
Oh, yes, they are … and many !
But think at the time when we did not even know that correct dosing of an antimicrobial could be important ...

and, please, report MICs in difficult cases, not only for your own epidemiology but also for treatment readjustment …

Conflicts of interest and Acknowledgments

- Conflicts of interest
  - Research grants from the *Fonds de la Recherche Scientifique*, Bayer, Pfizer, Wyeth, GSK, …and the Walloon and Brussels Regions
  - Honoraria for lectures from AstraZeneca, Aventis, Bayer, Lilly …
  - "Presentiegeld / Jetons de présence" from RIZIV / INAMI en FOD / SPF "Public Health"

- Acknowledgments
  - Johan Mouton (Canisius Wilhelmina Ziekenhuis, Nijmegen) for introduction to population pharamcokinetics, slides, and discussions
  - F. Van Bambeke, S. Carryn, Y. Glupczynksi, P.F. Laterre (UCL), E. De Jongh (ZOL) … for collaboration in basic and clinical studies
  - G. Kahlmeter for slides (incl. the template), discussions, and long lasting common interests…


2: Kahlmeter G, Dahlager JI.

Aminoglycoside toxicity - a review of clinical studies published between 1975 and 1982.

J Antimicrob Chemother. 1984 Jan;13 Suppl A:9-22. Review.
PMID: 6365884 [PubMed - indexed for MEDLINE]

And to conclude…

things may change

Risky situations are not far away

Will PK/PD help ?

Yes !