Understanding antibiotic PK/PD profiles to optimize patient outcomes

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International Society of antiinfective Pharmacology

PK/PD of Anti-Infectives Study Group of the
European Society of Clinical Microbiology and Infectious Diseases

7th Asia-Pacific Respiratory Tract Infections Forum
Ho Chi Minh, Vietnam

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Disclosures

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- the Belgian *Fonds de la Recherche Scientifique* for basic research on pharmacology antibiotics and related topics
- *Université catholique de Louvain* for personal support
- Commercial Relationships:
  - AstraZeneca, GSK, Sanofi-Aventis, Bayer HealthCare, Cempra Pharmaceuticals, The Medicines Company, Northern Antibiotics, Vetoquinol
- Other relationships in relation to this talk
  - Belgian Antibiotic Policy Coordination Committee,
  - Belgian Transparency and Reimbursement Committees
  - Participation to EMA expert meetings for novel antibiotics and as Industry supporting expert for assessment of toxicity of older ones

What is an anti-infective drug ?

Paul Ehrlich and Sahachiro Hata looking for "Therapia sterilisans magna" (a treatment that could kill pathogens) and discoverers of Salvarsan®

THE LANCET, AUGUST 16, 1913.

Address in Pathology

ON

CHEMOTHERAPEUTICS:

SCIENTIFIC PRINCIPLES, METHODS, AND RESULTS.

Delivered before the Seventeenth International Congress of Medicine

BY WIRKL. GEH. OBER-MED.-RAT PROFESSOR DR. PAUL EHRLICH,

DIRECTOR OF THE ROYAL INSTITUTE FOR EXPERIMENTAL THERAPY, FRANKFURT AM M.

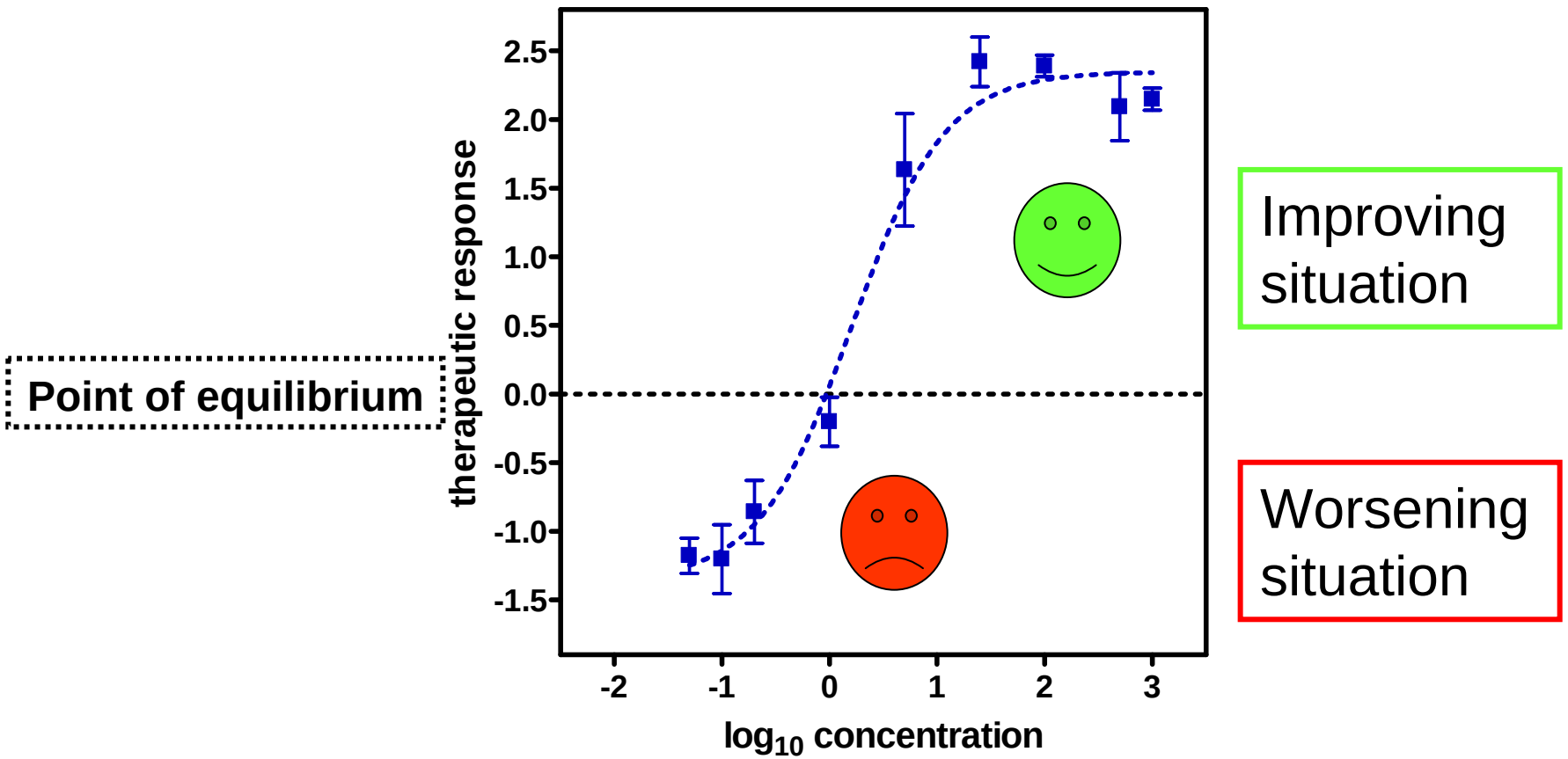
THE THERAPIA STERILISANS MAGNA.

The therapia sterilisans magna consists in this, that by means of one or at most two injections the body is freed from the parasites. In experiments on animals, and also in the case of a series of important maladies, this principle can be carried through in a clear and pure manner. Here, therefore, the old therapeutic remedy is applicable:

"*Frapper fort et frapper vite.*"

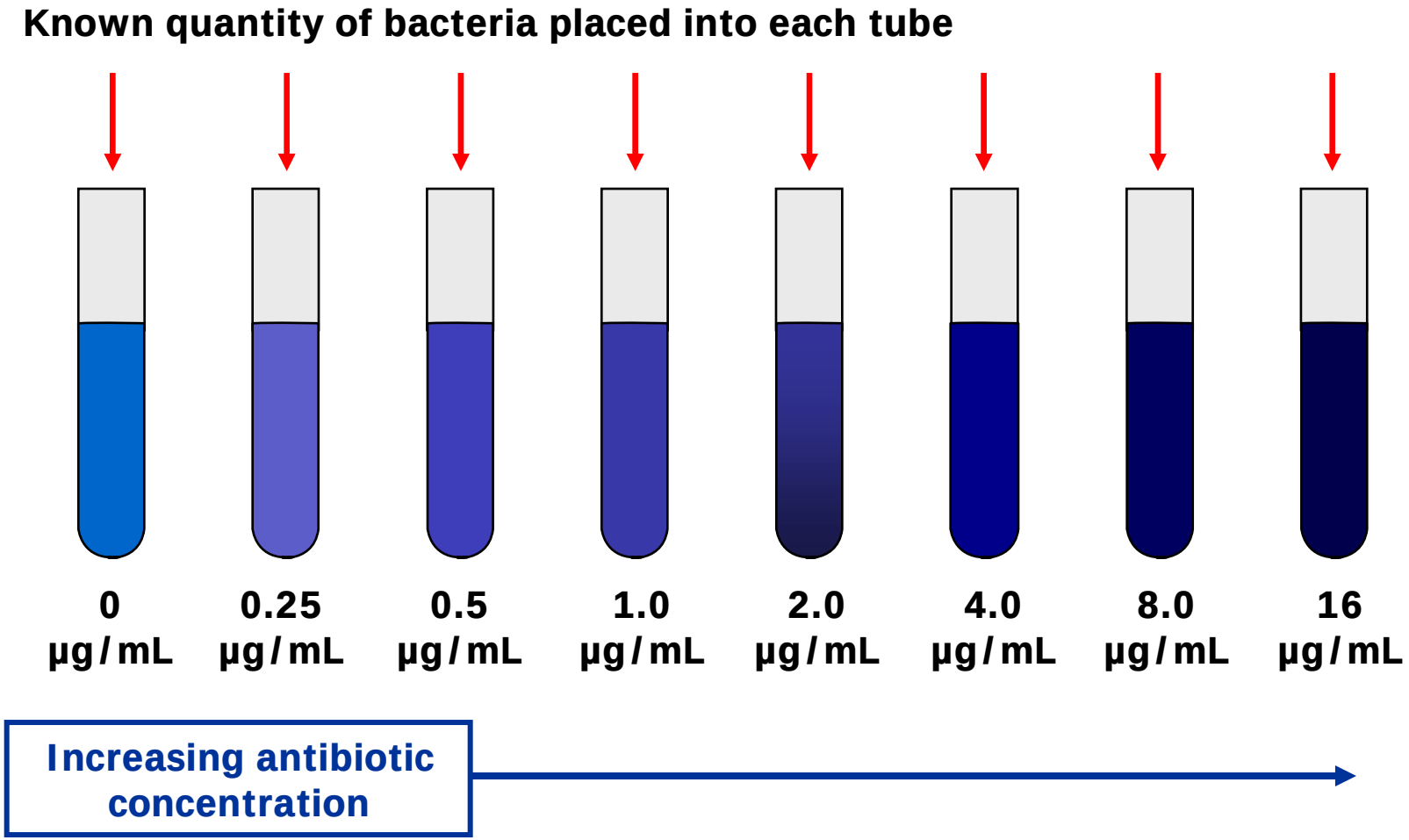
A simple pharmacological concept…

The dose must be adapted to the goal…



In a nutshell…

The target is the bacteria = MIC

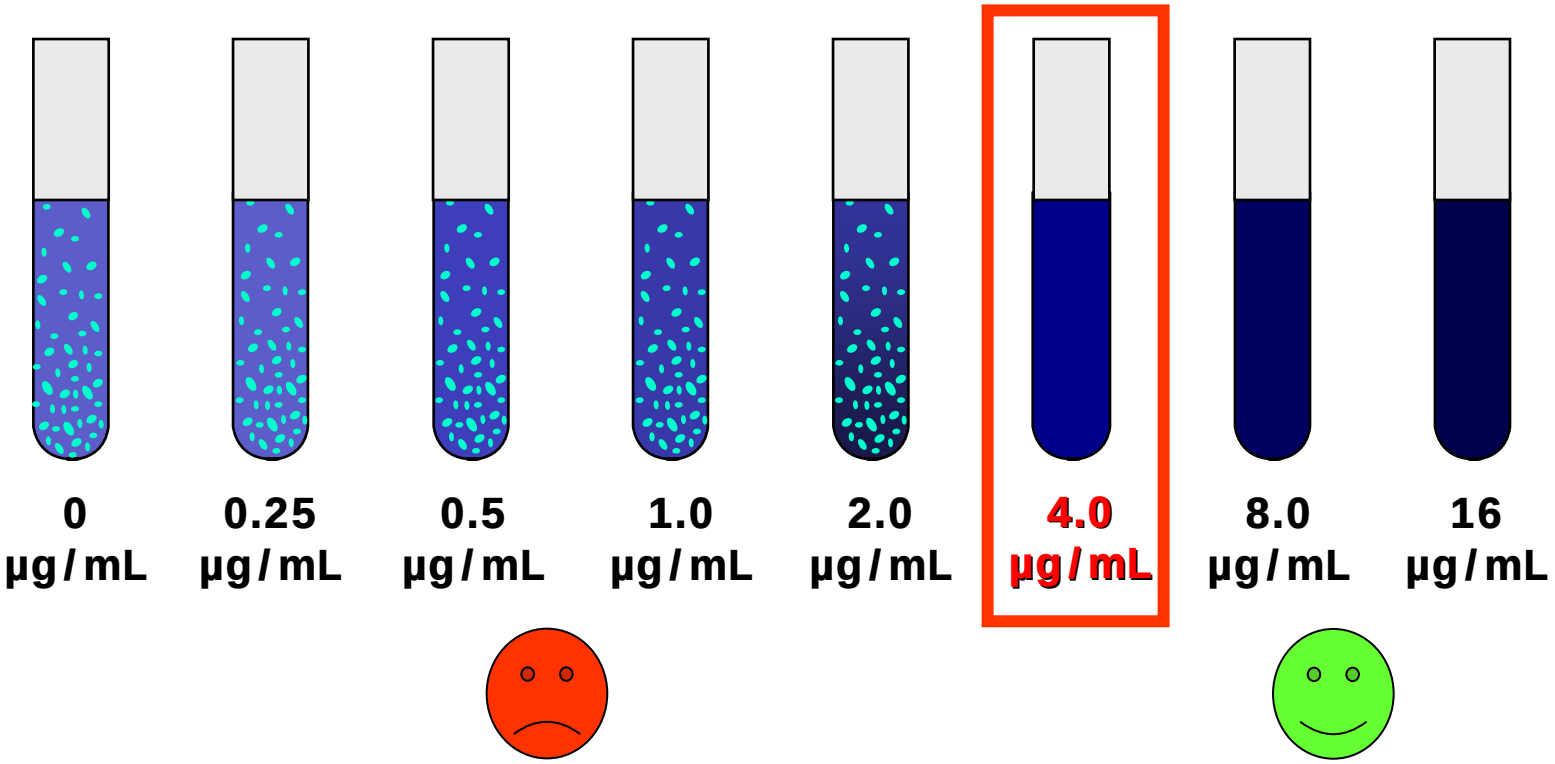


In a nutshell…

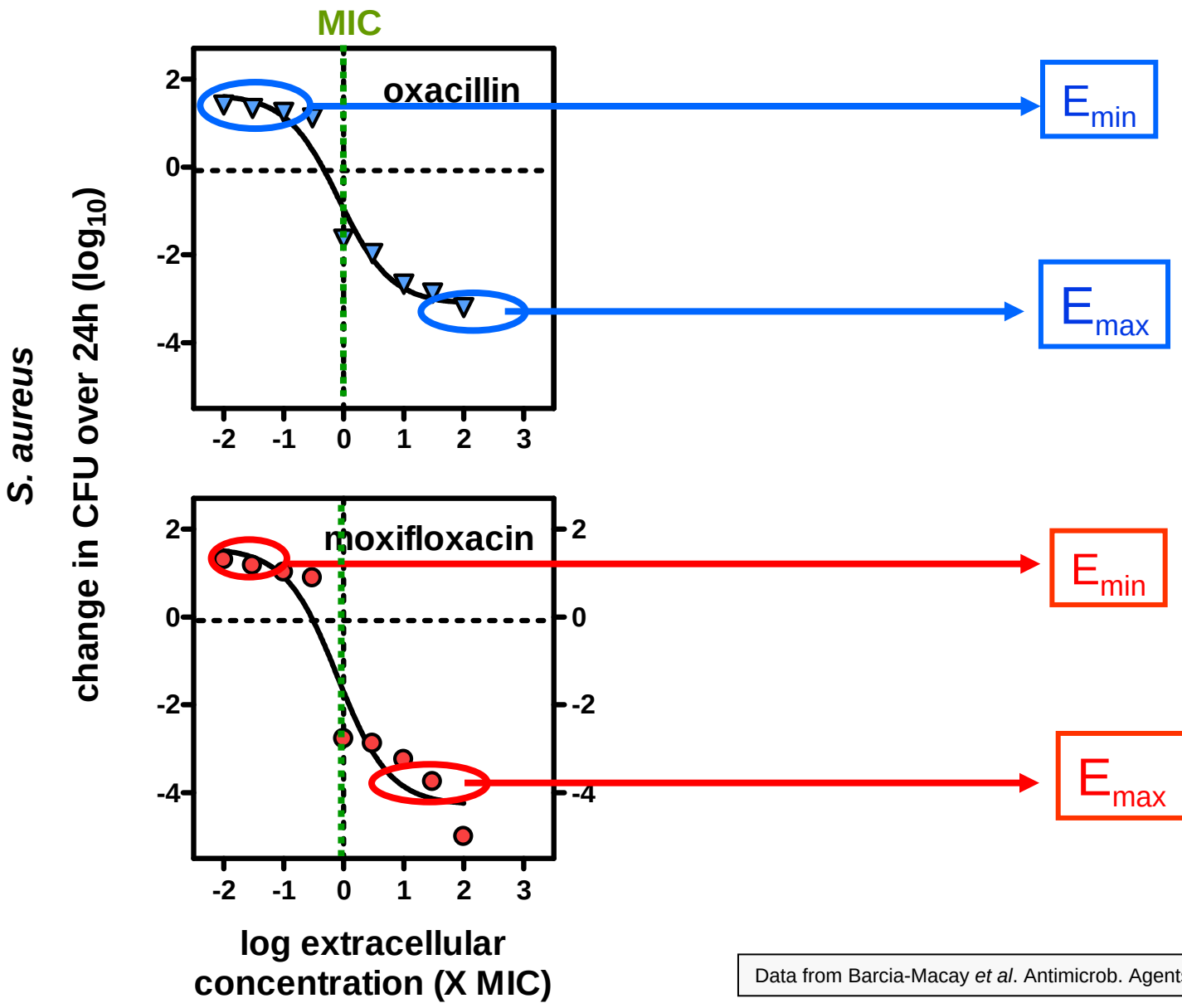
The target is the bacteria = MIC

24h later…

Lowest concentration of an antimicrobial that results in the inhibition of visible growth of a microorganism



What is the relationship between MIC and effect?



E_{min}

E_{max}

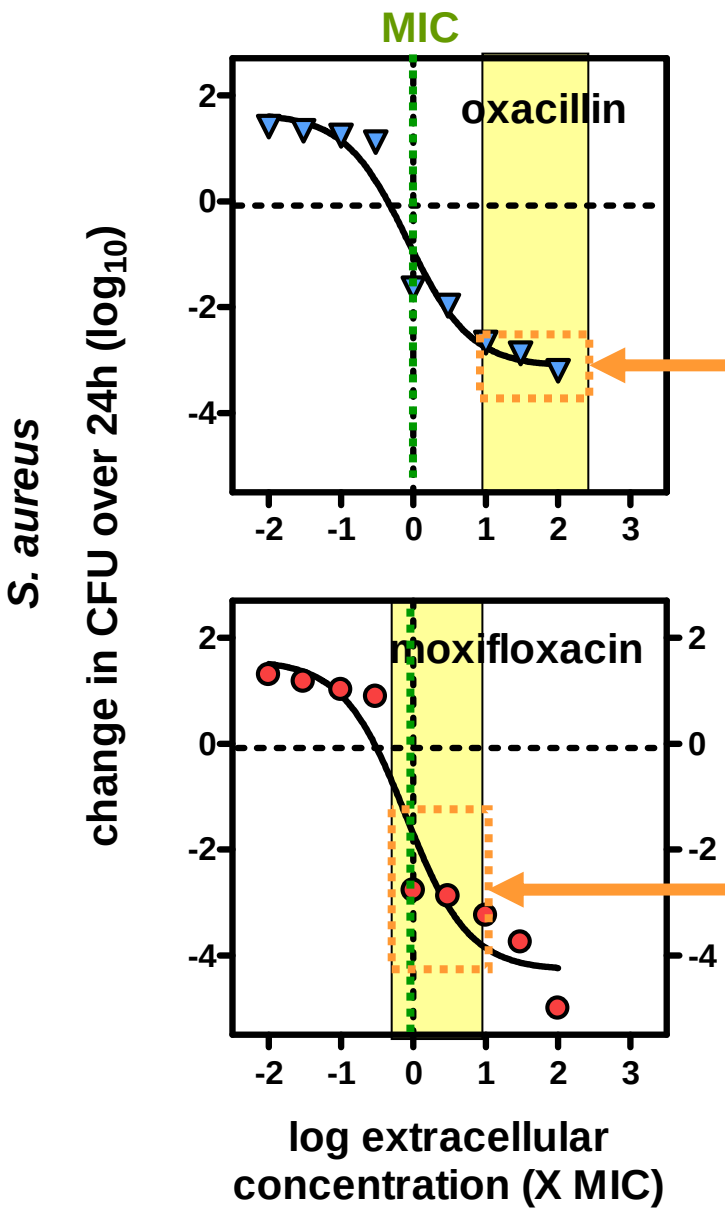
E_{min}

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 …



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}

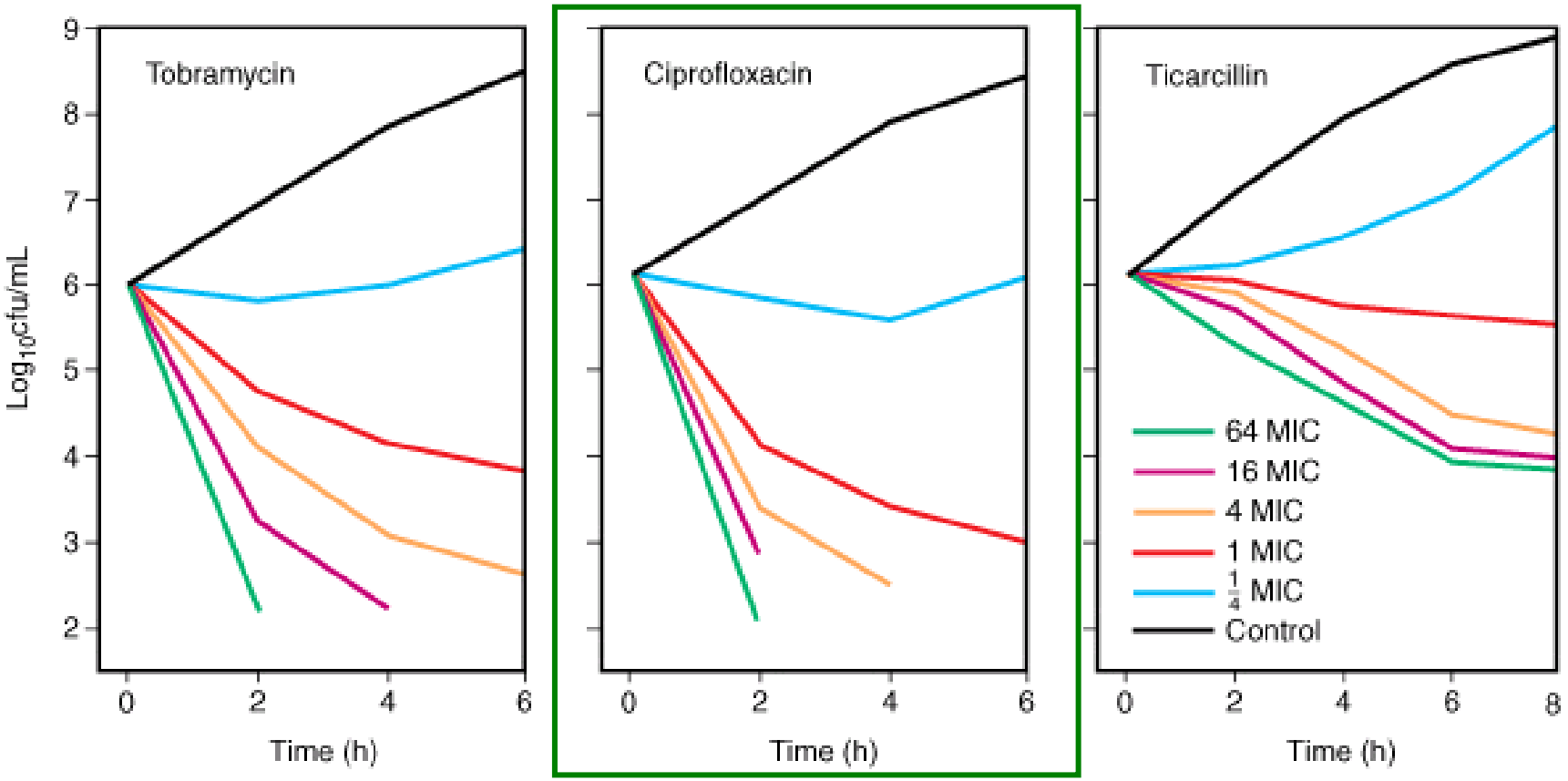
high concentration-dependence over the C_{min}-C_{max} range

➔ CONCENTRATION will emerge as an important parameter in vivo

- 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

A further comparison: in vitro kill curves

conc. dependent



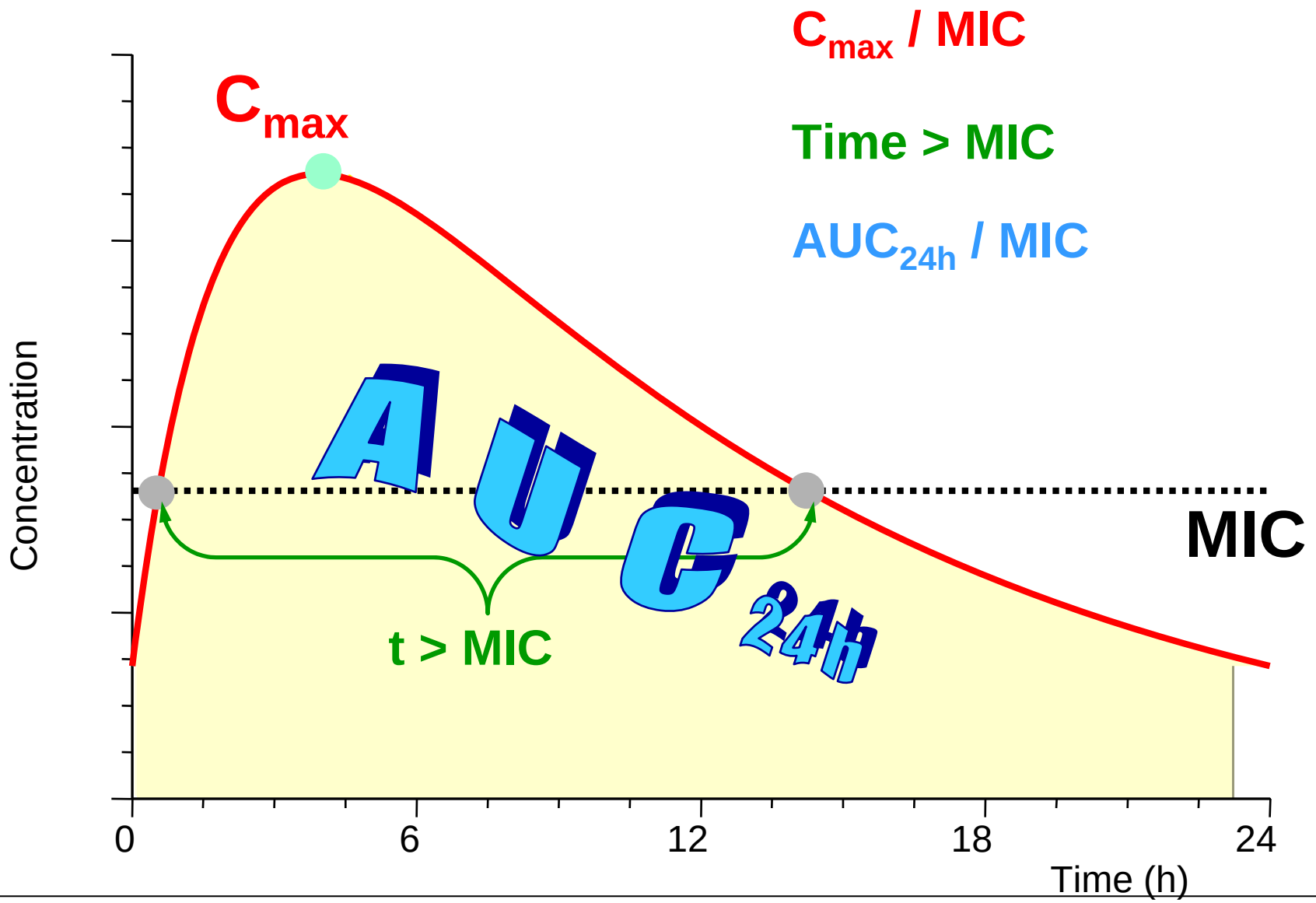
Time kill curves for *Pseudomonas aeruginosa* ATCC 27853 with exposure to tobramycin, ciprofloxacin, and ticarcillin at concentrations from one fourth to 64 times the minimum inhibitory concentration.
(From Craig WA, Ebert SC. Killing and regrowth of bacteria in vitro: A review. Scand J Infect Dis. 1990;74:63–70.)

First conclusions

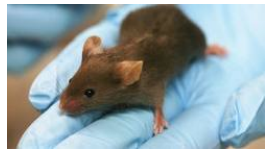
Considering their pharmacokinetics in humans

- β-lactams appear as **"time-dependent"** antibiotics because their serum concentrations is almost always > MICs …
  if you administer them several times a day (most have only short serum half-lives)
- Fluroquinolones (and aminoglycosides) are primarily **"concentration-dependent"** antibiotics as their bactericidal effect increases in proportion to their C_{max}/MIC ratio.

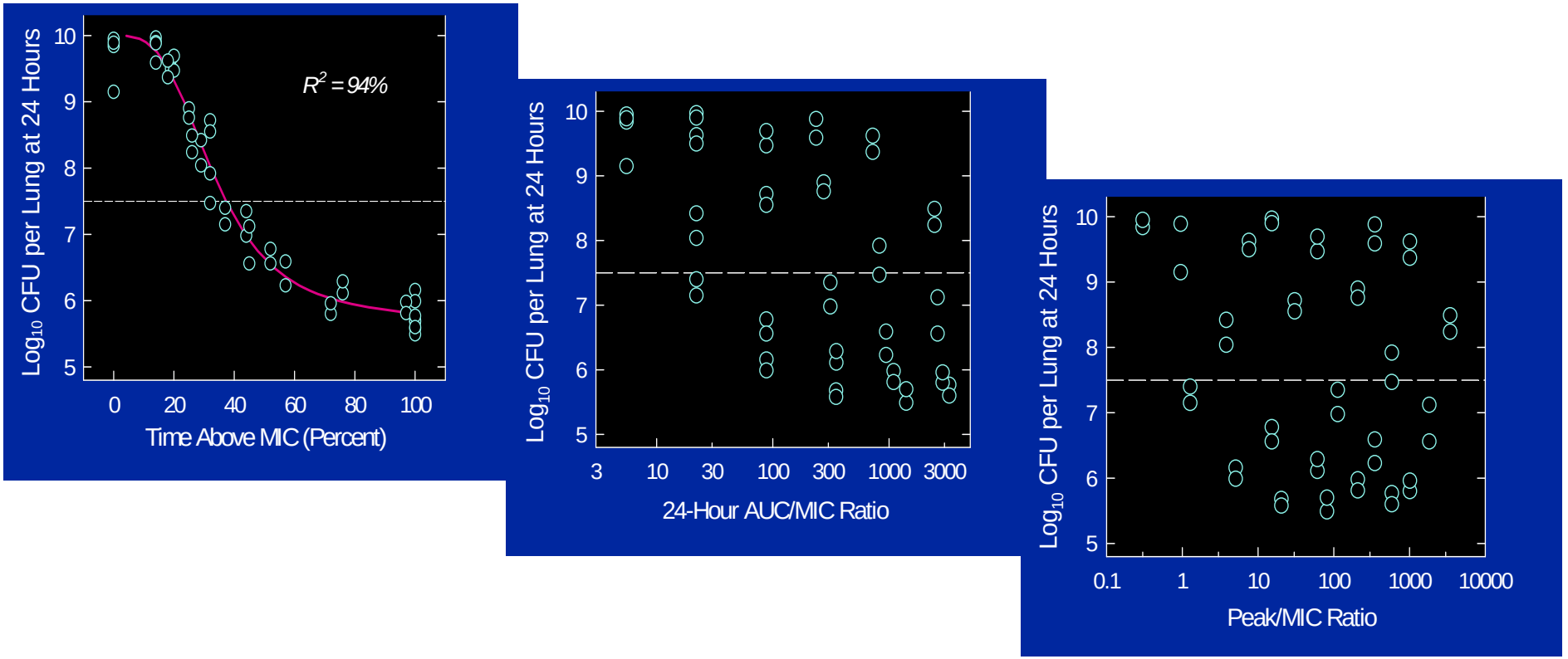
Moving to actual conditions of use



PK/PD in animals: β-lactams

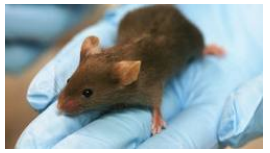


1. For β-lactams, time > MIC is the only key index for efficacy

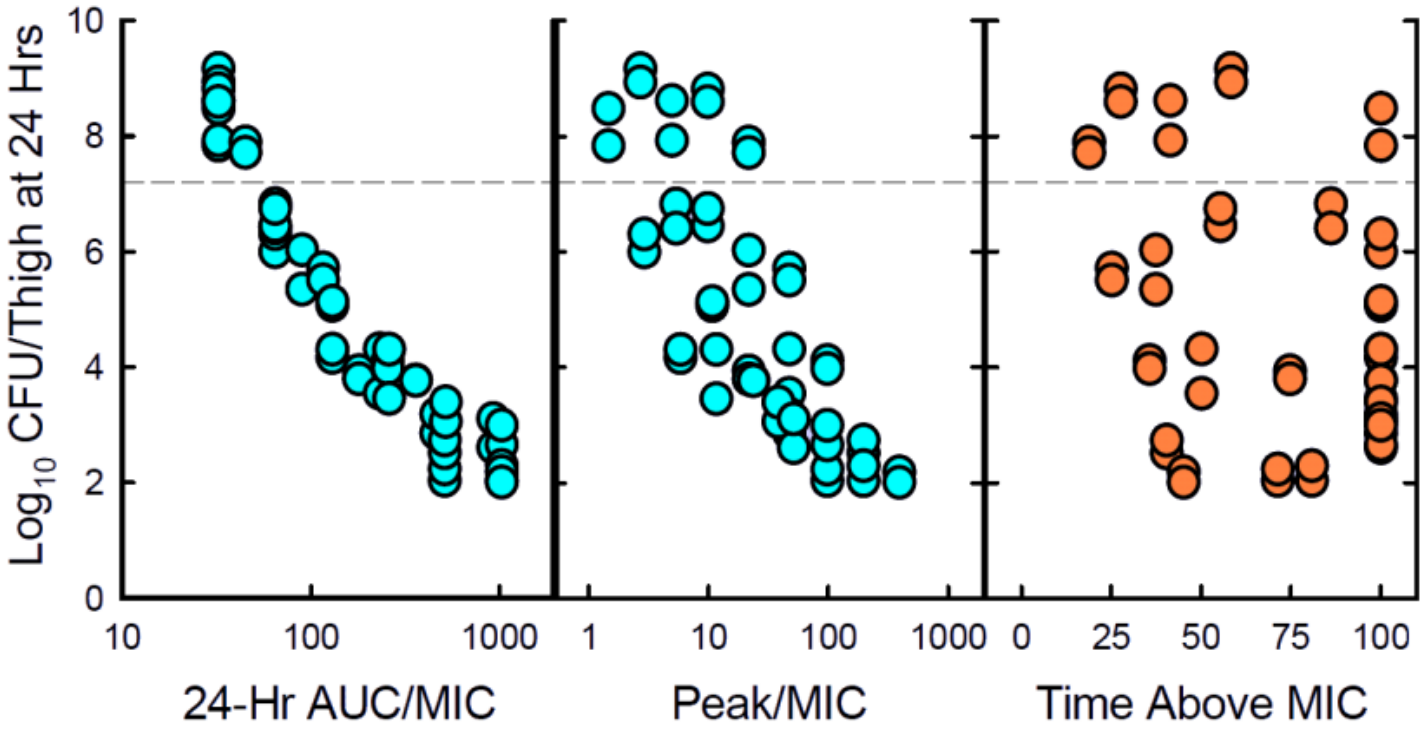


Correlation of PK/PD Indices with Efficacy of Cefotaxime against Klebsiella pneumoniae in a Murine Pneumonia Model (W.A. Craig – ISAP workshop – Stockholm, Sweden, 2000)

PK/PD in animals: fluoroquinolones

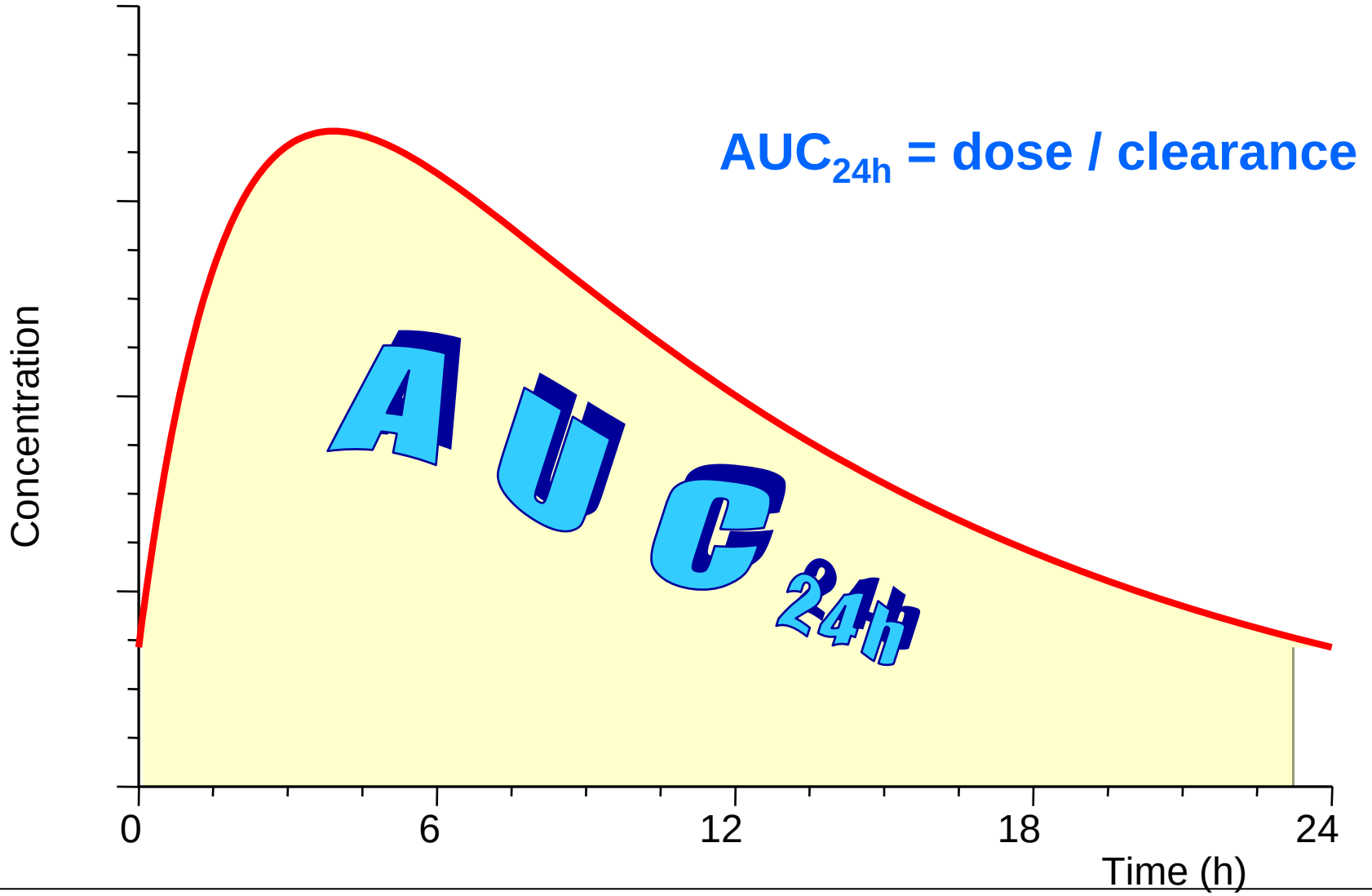


2. For fluoroquinolones, both AUC_{24h}/MIC and C_{max} emerge as key indices



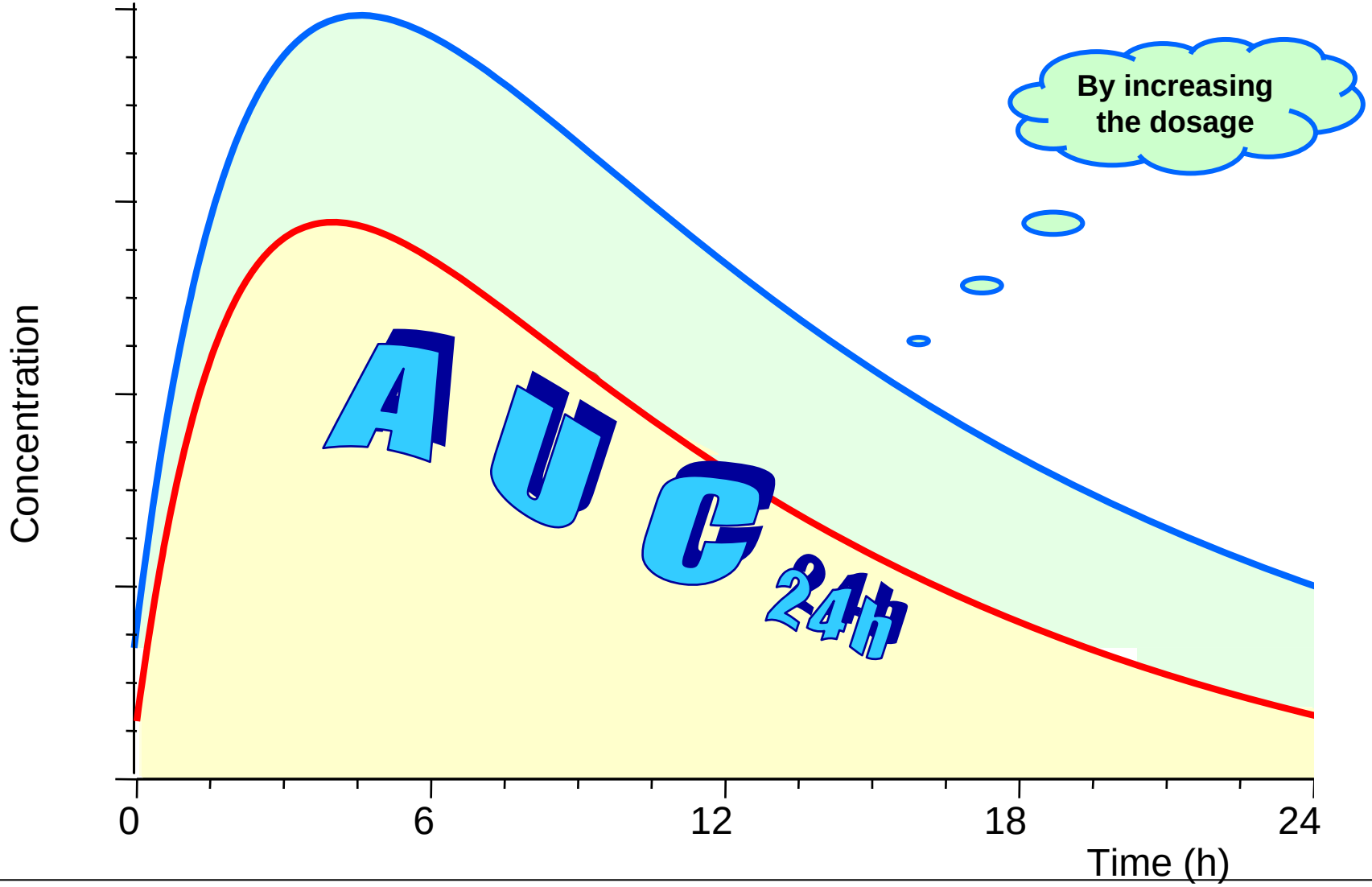
Correlation of PK/PD Indices with Efficacy of Levofloxacin against *Streptococcus pneumoniae* in Thighs of Neutropenic Mice (W.A. Craig – ISAP workshop – ICAAC 2009)

What is an AUC_{24h} ?



How do I get a larger AUC_{24h} ?

AUC_{24h} = dose / clearance



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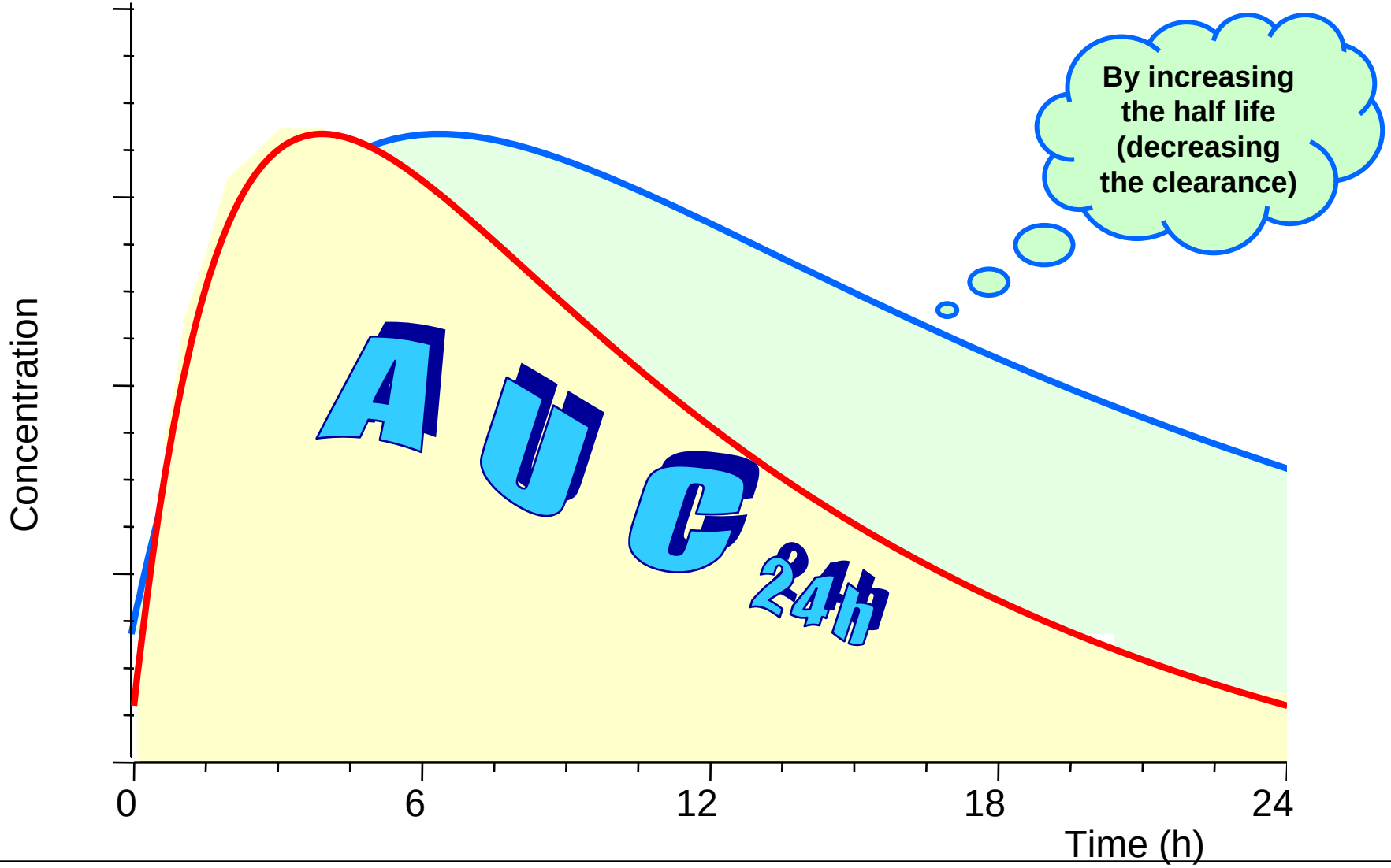
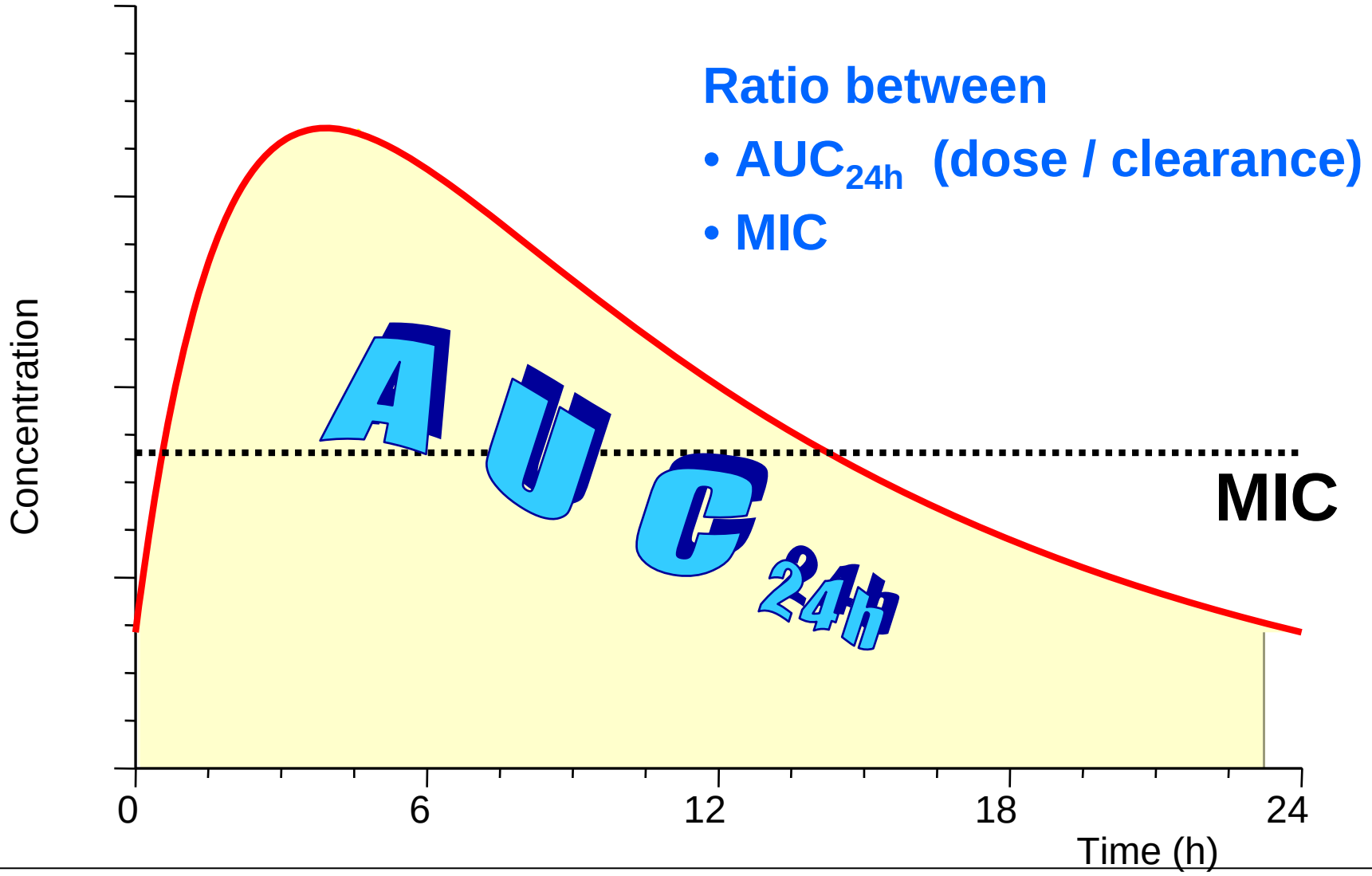


What is an AUC_{24h} / MIC ?



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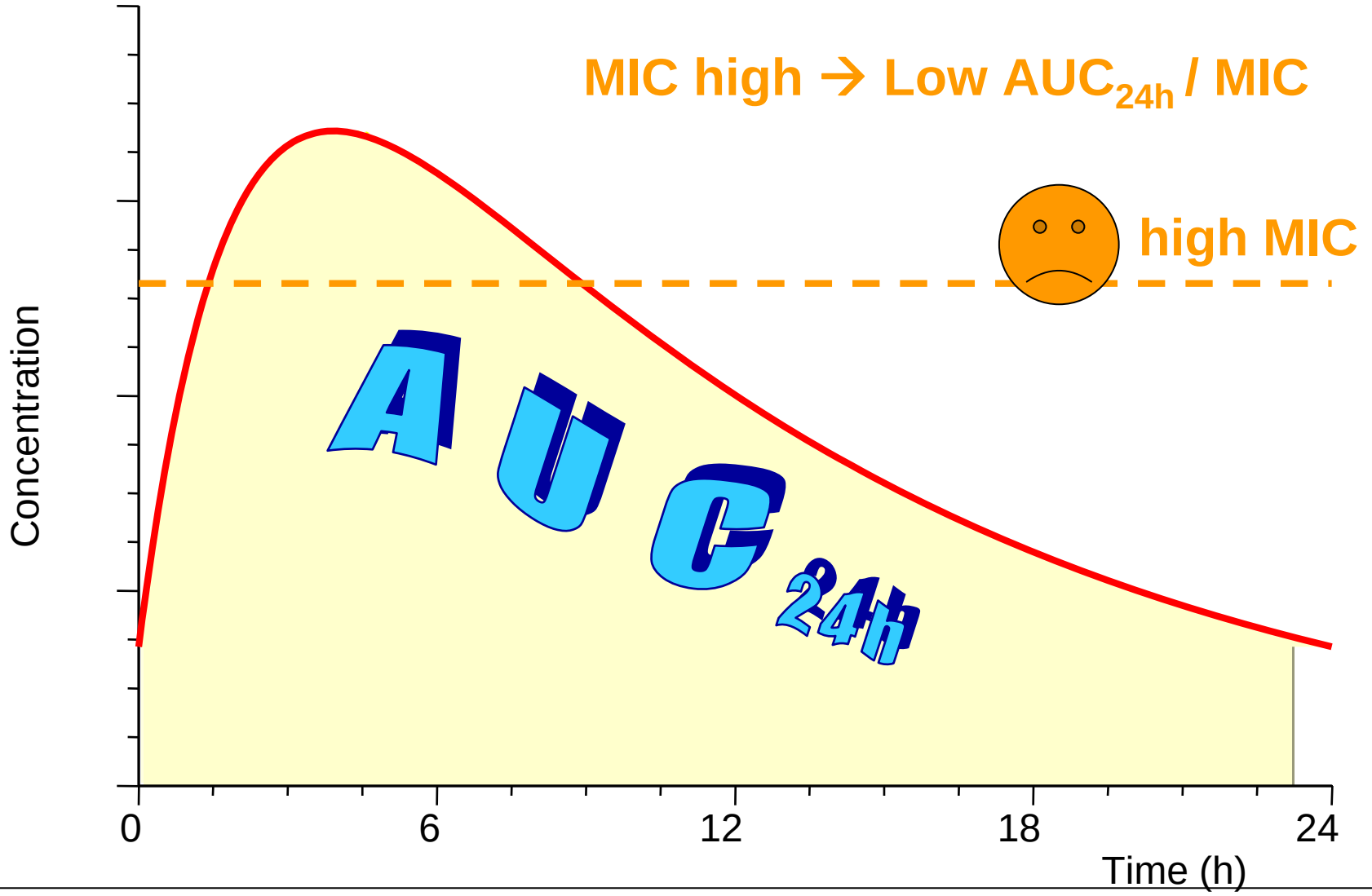
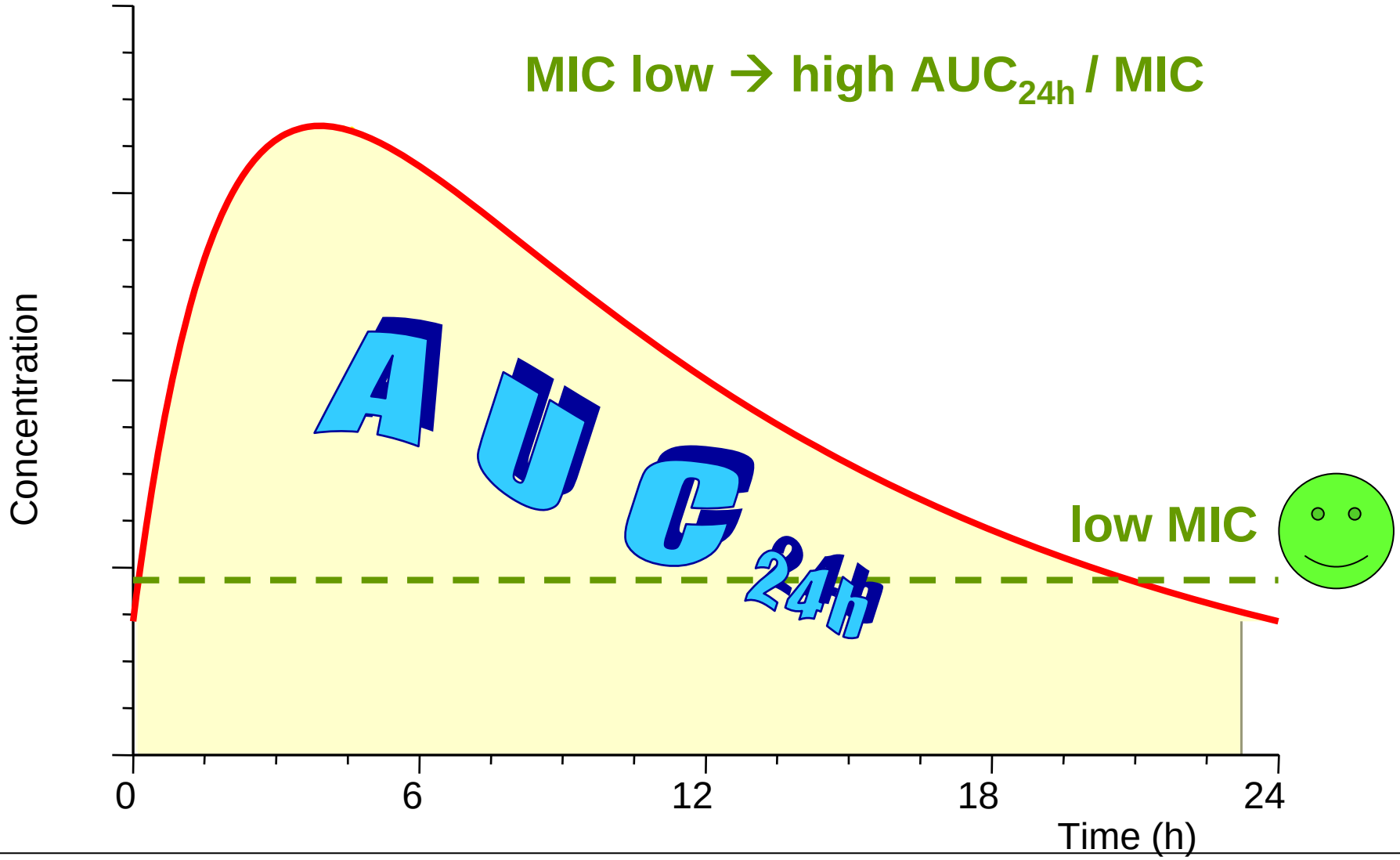
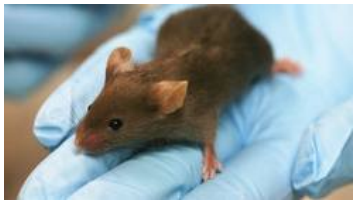


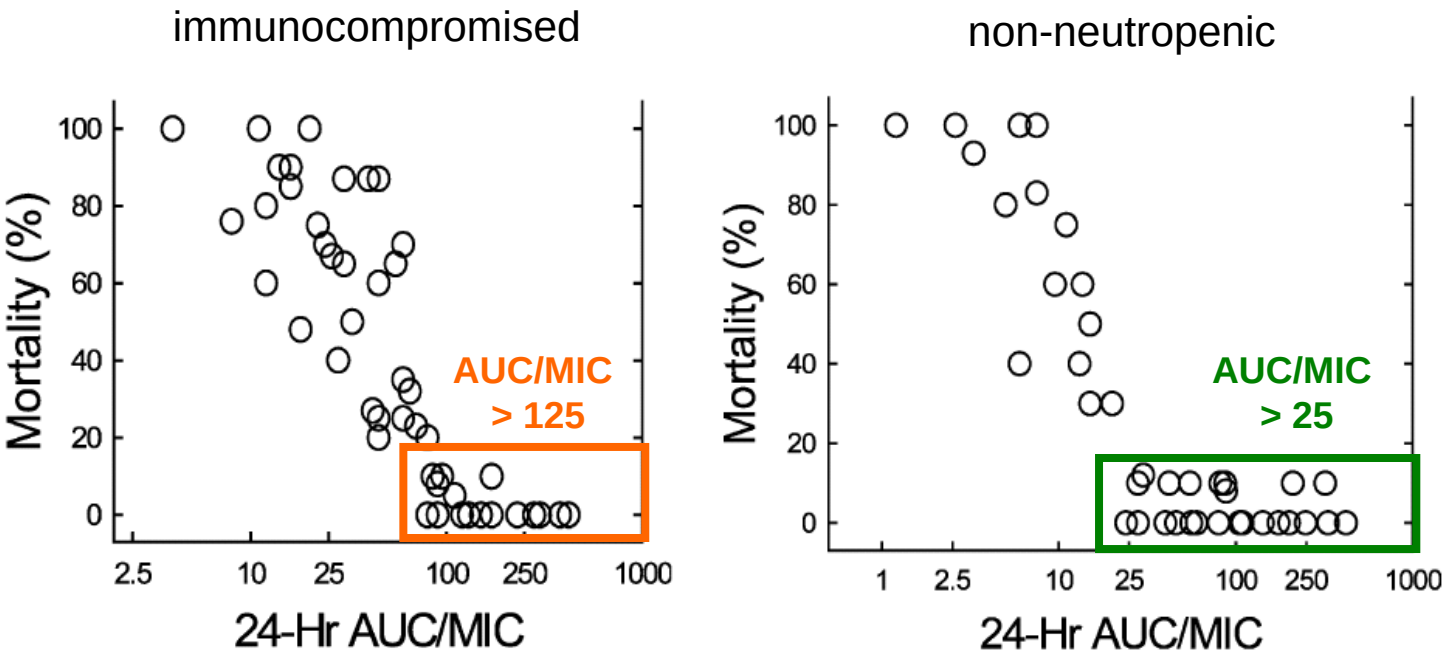
What is an AUC_{24h} ?



PK/PD in animals



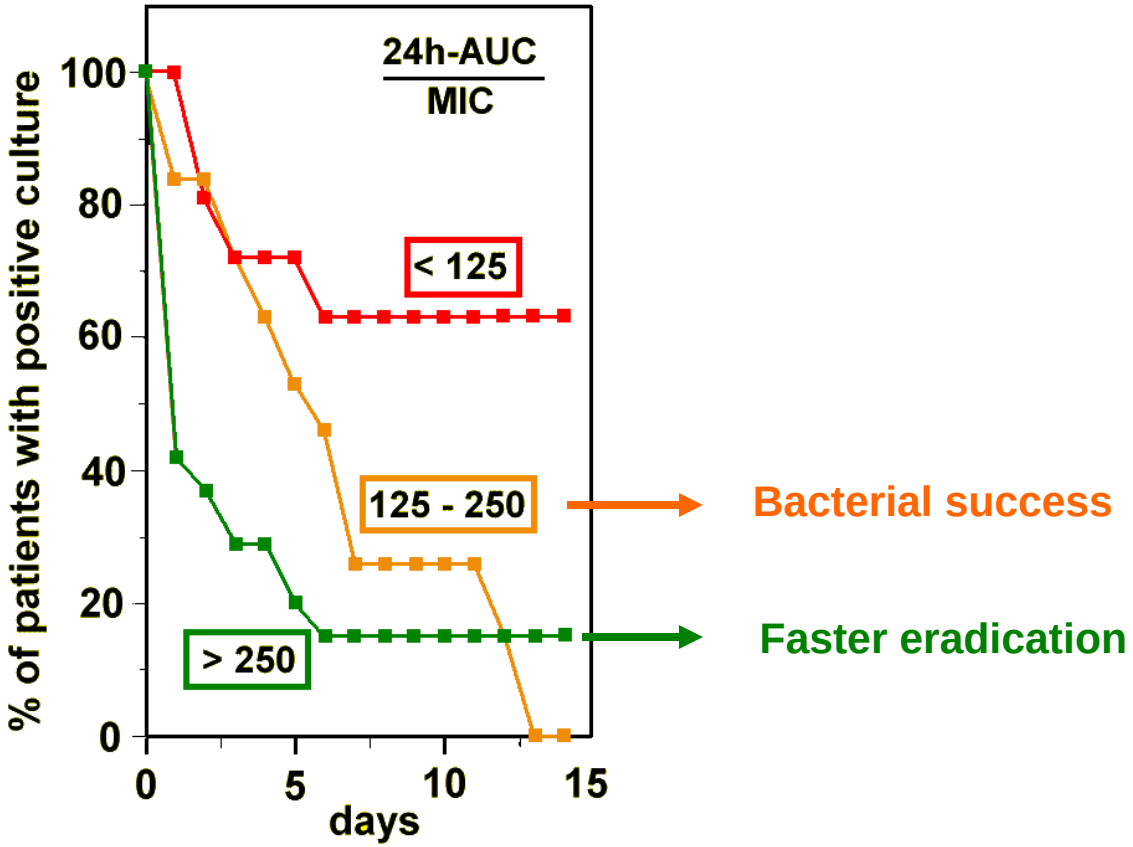
Immune status influences the magnitude of the PK/PD index required for efficacy



Relationships between mortality at the end of therapy and the 24 h AUC/MIC of fluoroquinolones with multiple pathogens (left panel) in different animal models (mostly immunocompromised) and with S. pneumoniae in non-neutropenic models (right panel).

Andes & Craig. Int. J. Antimicrob. Ag. (2002) 19: 261-68

AUC_{24h}/MIC in patients

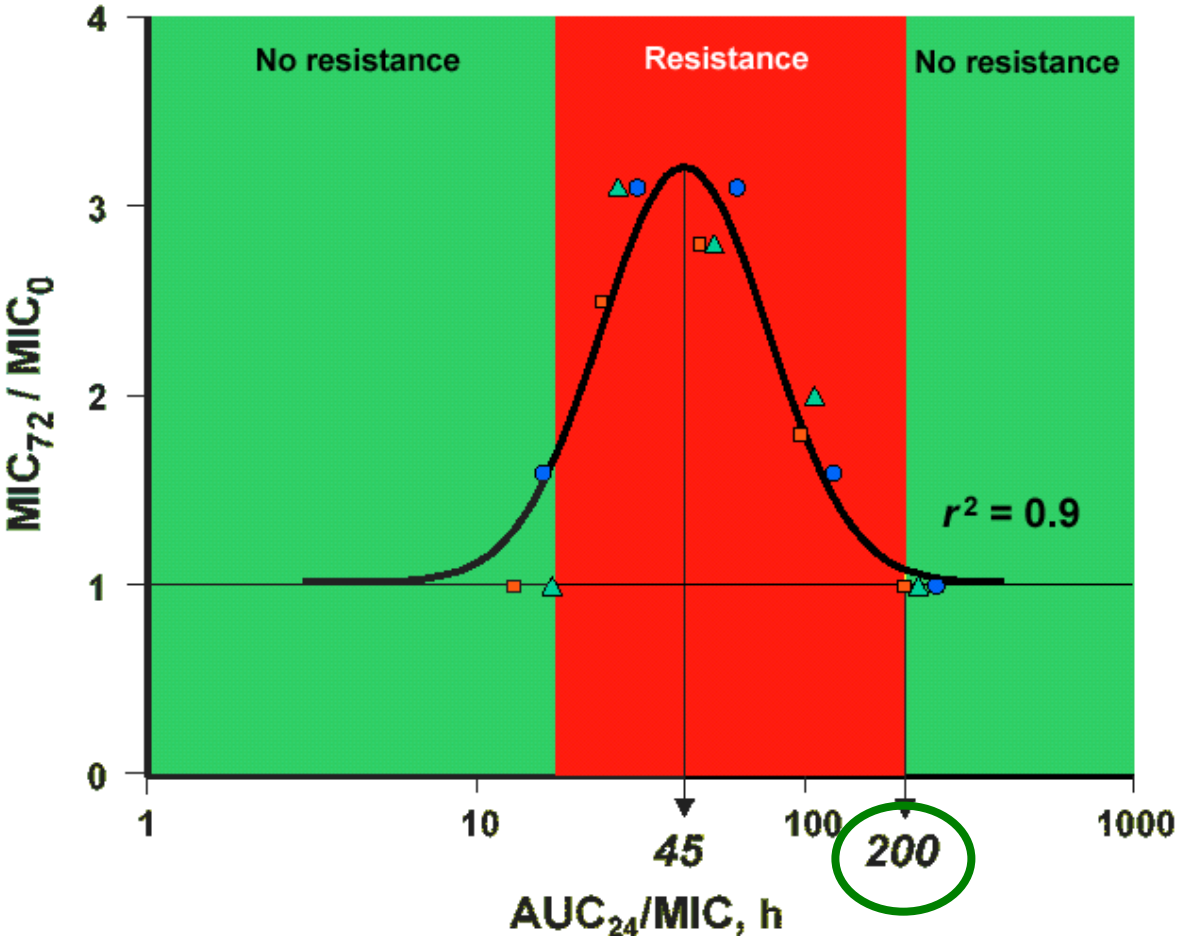


Time (days of therapy) to bacterial eradication versus AUC/MIC in severely ill patients treated with ciprofloxacin
The three groups differed significantly (P < 0.005).

Forrest et al AAC (1993) 37:1073-81

AUC_{24h}/MIC and prevention of resistance

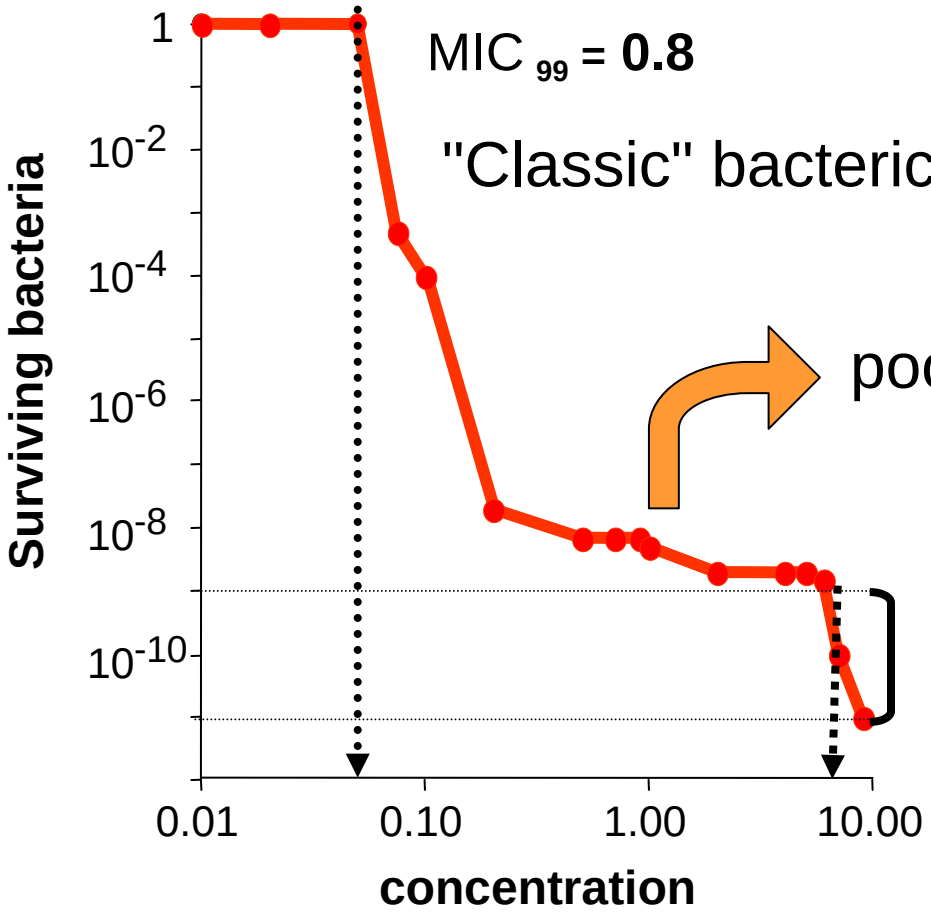
Change in susceptibility of *S. aureus* after exposure to fluoroquinolones



AUC/MIC >> 125
&
Peak/MIC > 8
to prevent resistance selection

Firsov *et al.* In vitro pharmacodynamic evaluation of the mutant selection window hypothesis using four fluoroquinolones against *Staphylococcus aureus*. Antimicrob Agents Chemother. 2003 May;47(5):1604-13.

C_{max} and the "Mutant Prevention Concentration" (MPC) …



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

"Classic" bactericidal effect

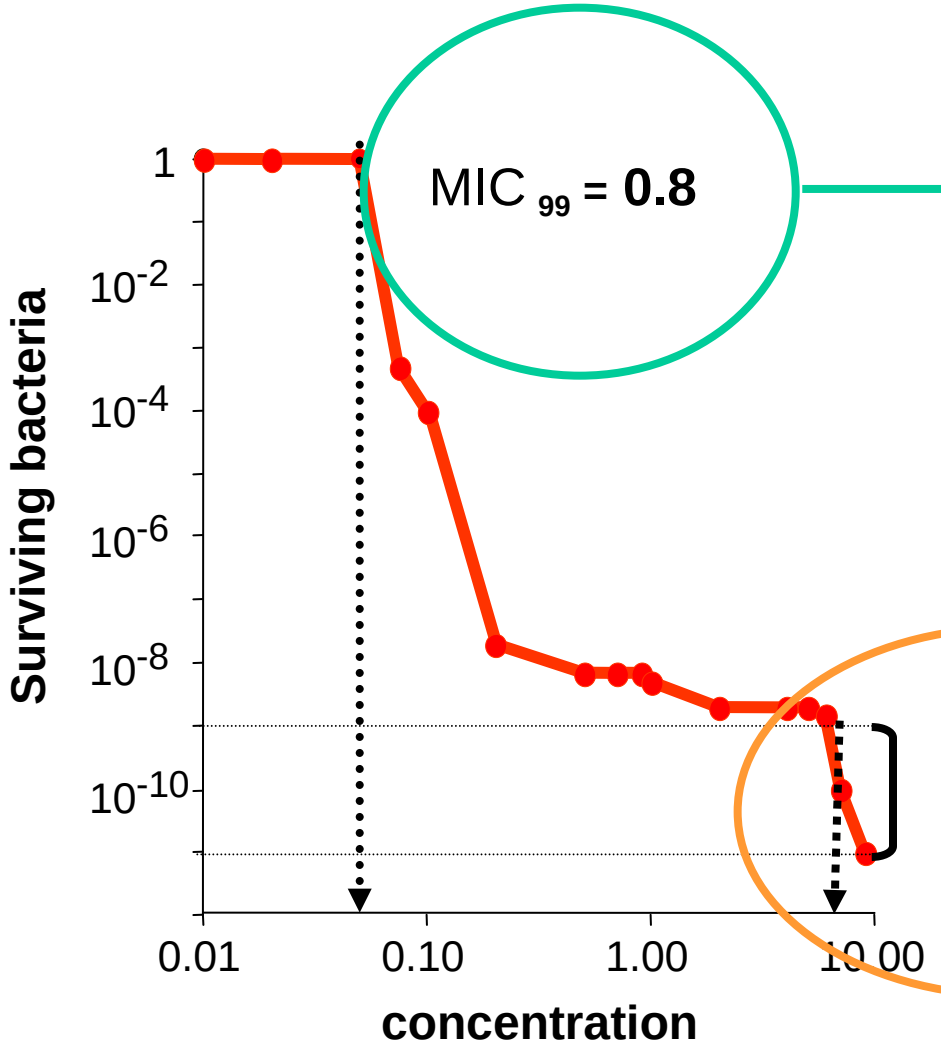
poorly sensitive organisms…

Elimination of resistant organisms

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

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

"Mutant Prevention Concentration …"

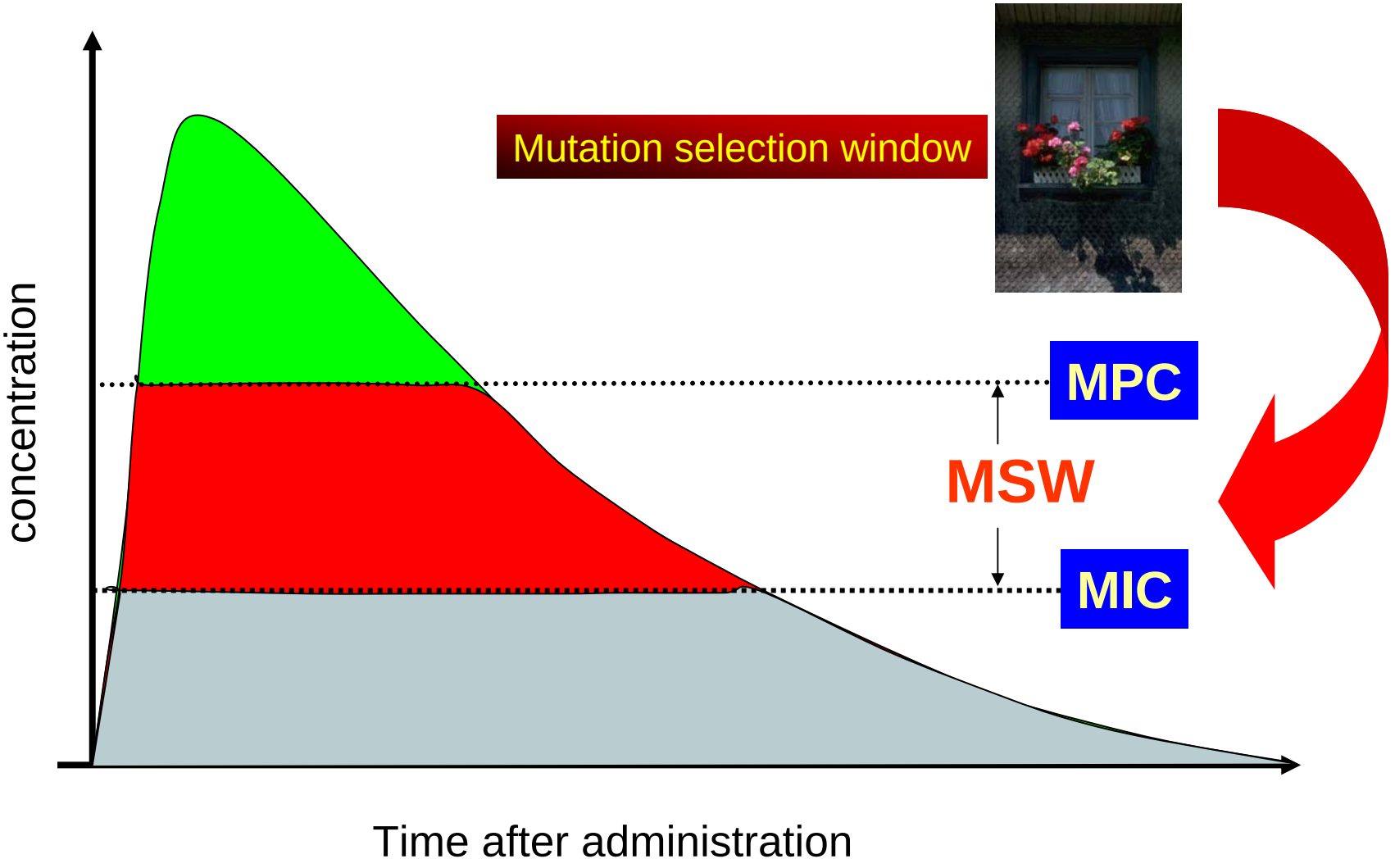


Concentration which will inhibit the majority of the organisms

Concentration needed to prevent the selection of resistant organisms

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

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



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

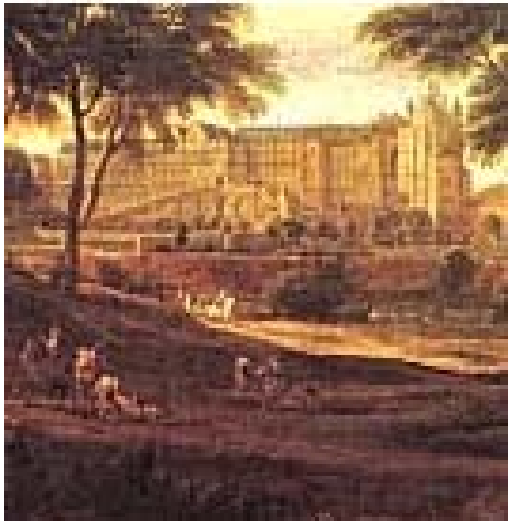
Putting all together for fluoroquinolones

If you wish to get a faster eradication and reduce emergence of resistance

➔ **peak / MIC > 10**

If you are interested in global effect …

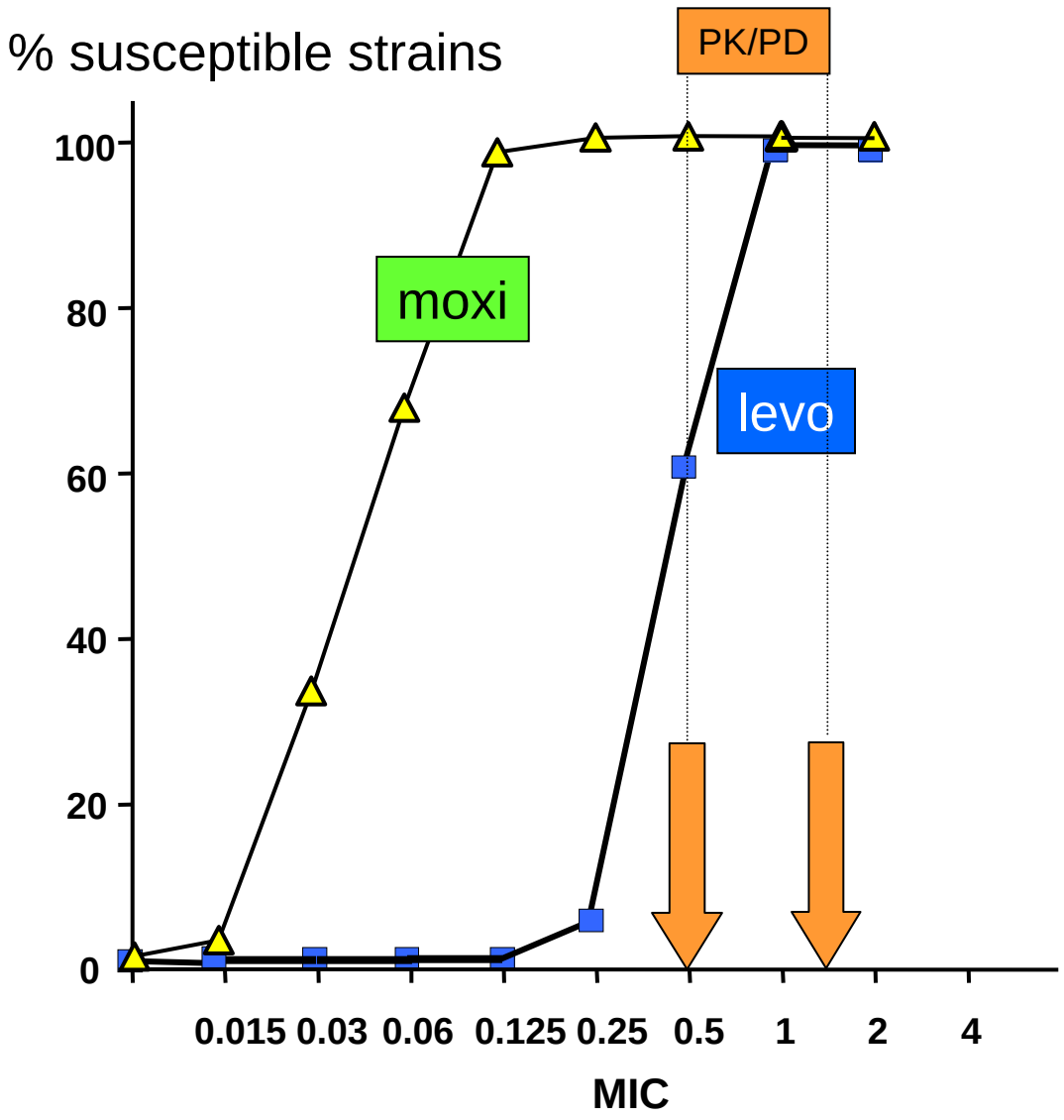
➔ **AUC_{24h} / MIC: 30 to 125**



Be practical… a short exercise

- You have two Ixacins: L-xacin and M-xacin
- They have essentially the same pharmacokinetics and tolerance
- Which one will you recommend in YOUR set-up for CAP ?

Application to pneumococci in Belgium



Moxifloxacin 400 mg 1x/d

- AUC [(mg/l)xh]: 48
  - ➢ MIC_{max}: 0.5-1.5
- peak [mg/l]: 4.5
  - ➢ MIC_{max} : ~ 0.5

Levofloxacin 500 mg 1x/d

- AUC [(mg/l)xh]: 47
  - ➢ MIC_{max}: 0.5-1.5
- peak [mg/l]: 5
  - ➢ MIC_{max} : ~ 0.5

MIC data: J. Verhaegen et al., ECCMID 2003
Similar values in 2009 (Vanhoof, ECCMID 2009)

The problem of the wrong breakpoints…

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)

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

The EUCAST breakpoints for fluoroquinolones

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
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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

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

EUCAST breakpoints

S. pneumoniae

Fluoroquinolones	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Ciprofloxacin[1]	0.12	2	5	50[A]	16[A]
Levofloxacin[2]	2	2	5	17[A]	17[A]
Moxifloxacin	0.5	0.5	5	22[A]	22[A]
Nalidixic acid (screen)	NA	NA		NA	NA
Norfloxacin (screen)	NA	NA	10	12[B]	Note[B]
Ofloxacin[3]	0.12	4	5	50[A]	13[A]

This is close to PK/PD breakpoints

These (and more) data are available at no cost from EUCAST and can be accessed freely on EUCAST website www.eucast.org.
Note: EUCAST recommendations are frequently updated but the latest versions is always available on EUCAST web site.

EUCAST breakpoints

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Levofloxacin[2]	2	2	5	17[A]	17[A]
Moxifloxacin	0.5	0.5	5	22[A]	22[A]
Nalidixic acid (screen)	NA	NA		NA	NA
Norfloxacin (screen)	NA	NA	10	12[B]	Note[B]
Ofloxacin[3]	0.12	4	5	50[A]	13[A]

1. Wild type *S. pneumoniae* are not considered susceptible to ciprofloxacin and are therefore categorised as intermediate.
A. The norfloxacin disk diffusion test can be used to screen for fluoroquinolone resistance. **See Note B.**

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EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

EUCAST breakpoints

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Norfloxacin (screen)	NA	NA	10	12[B]	Note[B]
Ofloxacin[3]	0.12	4	5	50[A]	13[A]

2. The breakpoints for levofloxacin relate to high dose therapy.

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Ofloxacin[3]	0.12	4	5	50[A]	13[A]

3. Wild type *S. pneumoniae* are not considered susceptible to ofloxacin and are therefore categorised as intermediate.

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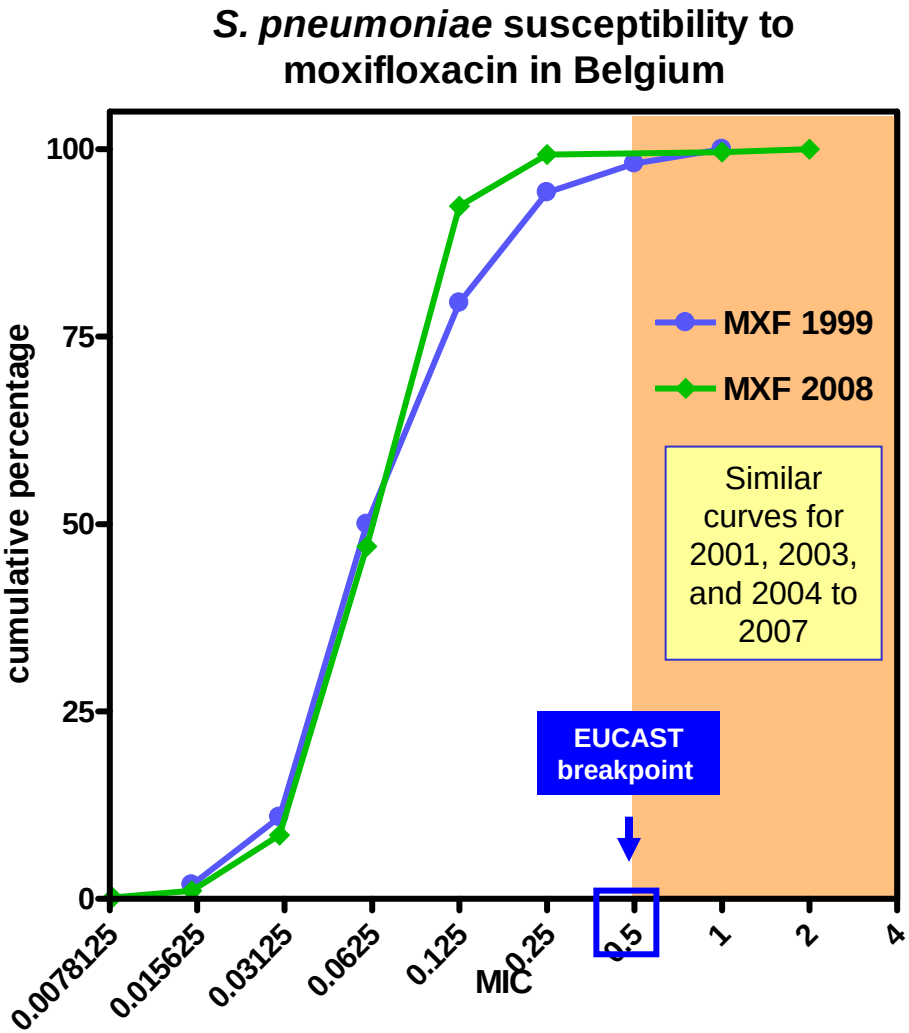
Use of PK/PD protects against resistance of *S. pneumoniae* to moxifloxacin: experience in the community in Belgium



From data of a <u>national</u> collection

- Non invasive respiratory tract infections
- similar results in 2008 for a collection of *S.pneumoniae* from clinically-confirmed CAP)

- Surveys from the Belgian Scientific Institute for Public Health for *S. pneumoniae* from community isolates (n=156 in 1999 and 448 in 2008)
- Data available yearly for 1999 through 2008
- http://www.iph.fgov.be

Vanhoof RLM, et al. 19th European Congress of Clinical Microbiology and Infectious Diseases. May, 16-19 2009, Helsinki.
Lismond et al. Antimicrobial susceptibility of Streptococcus pneumoniae isolates from vaccinated and non-vaccinated patients with a clinically confirmed diagnosis of community-acquired pneumonia in Belgium. Int J Antimicrob Agents. 2012; ;39:208-16.

But you can (and must) use your own data…

C. Zhao et al. / Diagnostic Microbiology and Infectious Disease 73 (2012) 174–181

Table 1
Susceptibility to 18 antimicrobial agents of clinical Gram-positive isolates in China, 2005–2010.

Organisms	Antimicrobial agents	2005		2006		2007		2008		2009		2010	
		%S[a]	MIC_{90}	%S[a]	MIC_{90}	%S[a]	MIC_{90}	%S[a]	MIC_{90}	%S[a]	MIC_{90}	%S[a]	MIC_{90}
S. pneumoniae		$n = 95$		$n = 100$		$n = 152$		$n = 225$		$n = 227$		$n = 232$	
	Levofloxacin	89.9	2	97	1	98.7	1	97.8	1	93.8	2	98.6	1
	Moxifloxacin	93.3	0.38	98	0.125	100	0.25	98.2	0.125	95.2	0.5	98.6	0.25

Youning Liu et al.
BMC Infectious Diseases 2009, **9**:31 doi:10.1186/1471-2334-9-31

Table 4: Antimicrobial susceptibility of 63 *S. pneumoniae* isolates obtained in the study

Antimicrobial agent	% of isolates			MIC (μg/ml)		
	Susceptible	Intermediate	Resistant	MIC_{50}	MIC_{90}	Range
Levofloxacin	93.7	0.0	6.3	1	2	0.5–16
Gatifloxacin	93.7	0.0	6.3	0.25	0.5	0.125–4
Moxifloxacin	95.2	3.2	1.6	0.125	0.25	0.064–4

I was not alone…

not too long ago …

G. Drusano **W.A. Craig**

J.J. Schentag

1998

since 1999

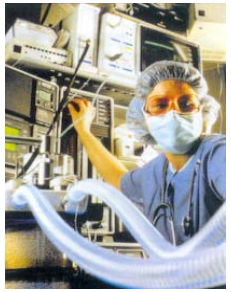
… and again this year

ICAAC 2012

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

1999

EMA



and to clinical practice

Questions ?


3X3=6
4X4=16
22
There are
NO STUPID QUESTIONS
or stupid answers.