PK/PD for antibiotics: an overview

Pierre-Louis Toutain,

INRA & National veterinary School of Toulouse, France

Wuhan 05/10/2015

1-What is PK/PD approach for antibiotics?

What is the main goal of PK/PD for antibiotics

- It is an alternative to dose-titration studies to discover an optimal dosage regimen:
  - For efficacy
  - For prevention of resistance

Why PK/PD approach is an attractive alternative to the dose-titration to determine a dosage regimen

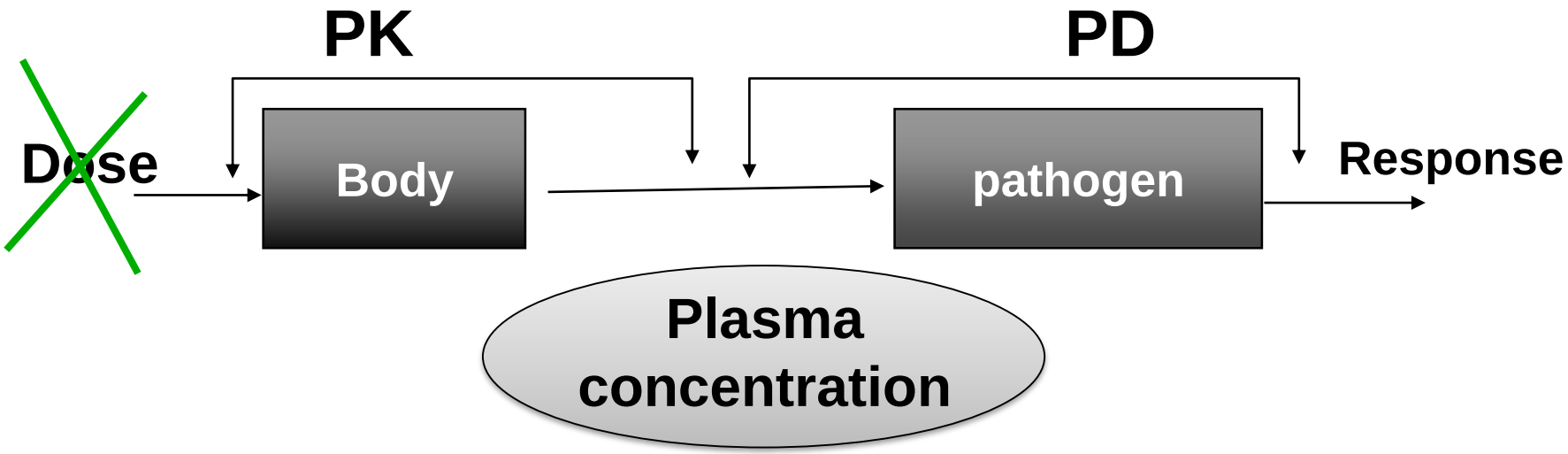
- Dose titration, not the PK/PD approach, require an experimental infectious model,
  - Severe
  - not representative of the real world
  - Prophylaxis vs. metaphylaxis vs. curative
  - power of the design generally low for large species
- The pivotal PD parameter (MIC) is easily obtained in vitro

2-An overview on the concept of PK/PD

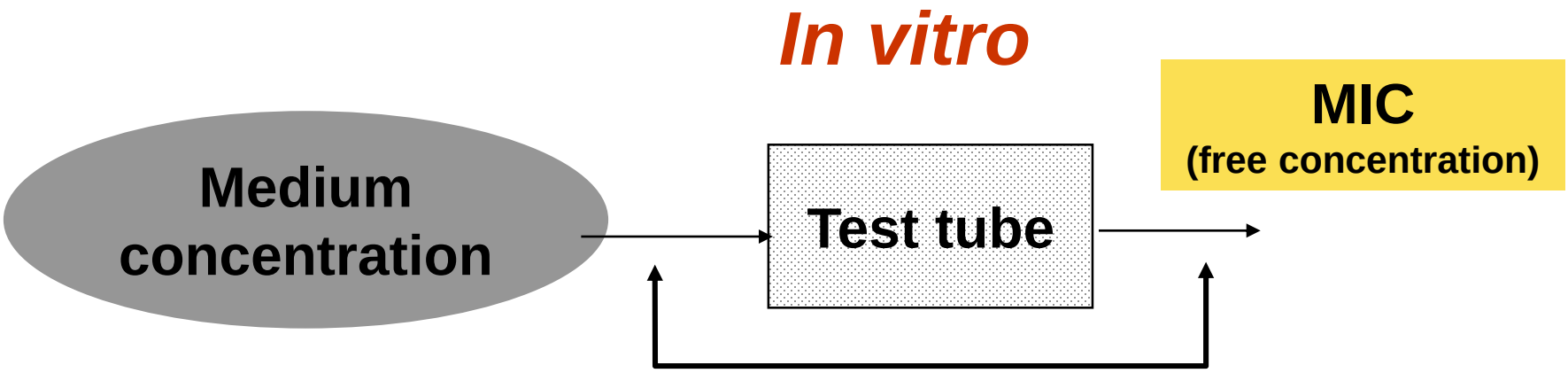
Dose titration

Dose titration for antibiotic using infectious model

PK/PD



For antibiotics drug efficacy/potency is *a priori* known from *in vitro* investigation



The idea at the back of the PK/PD approach for antibiotics was to develop surrogates able to predict clinical success by scaling a PK variable by the MIC

- **MIC is a reasonable approximate of the order of magnitude of concentration of free drug needed at the site of infection to treat an animal**

Where are located the pathogens?

Where are located the pathogens

Extra Cellular Fluid

Most bacteria of clinical interest

- respiratory infection

- wound infection

- digestive tract inf.

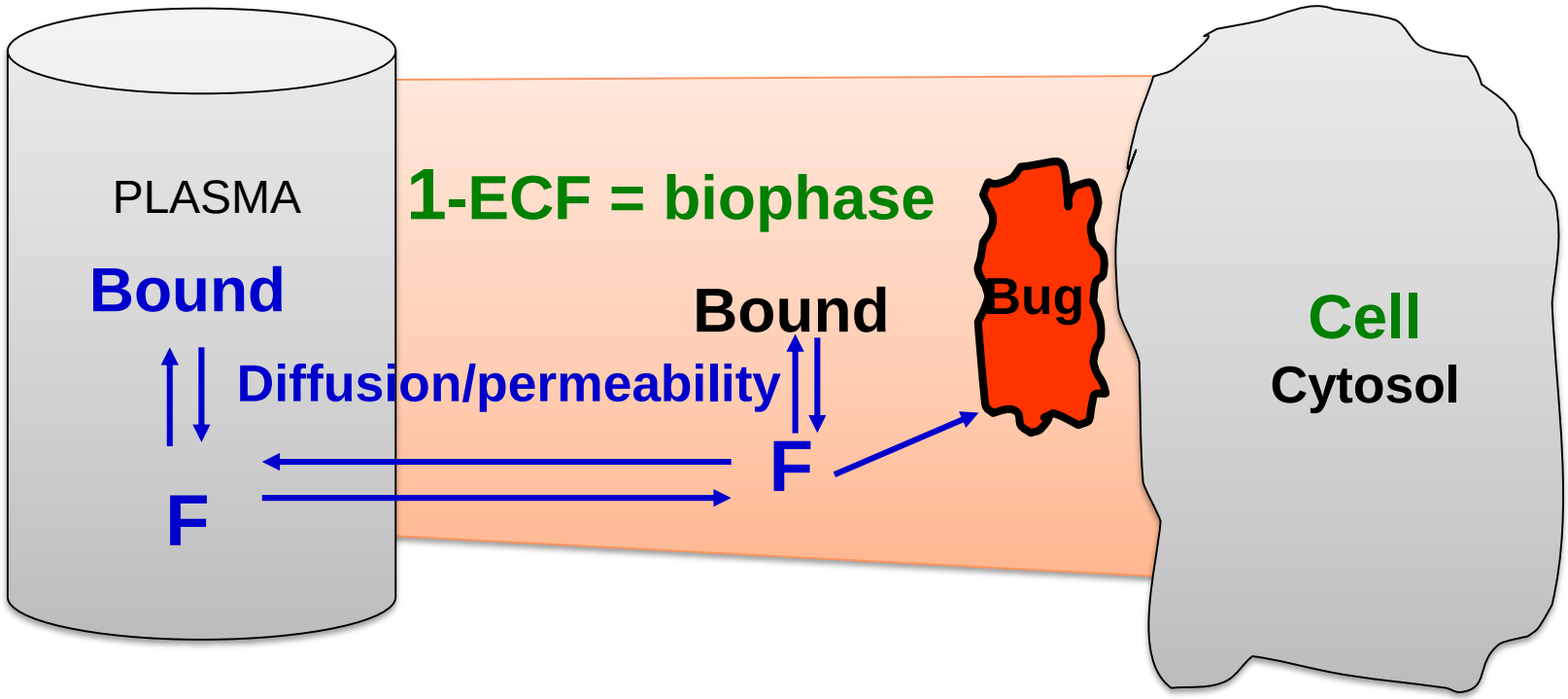
Cell

(in phagocytic cell most often)

- **Legionnella spp**
- **mycoplasma (some)**
- **chlamydiae**
- **Brucella**
- **Cryptosporidiosis**
- **Listeria monocytogene**
- **Salmonella**
- **Mycobacteria**
- **Meningococci**
- **Rhodococcus equi**

Most pathogens of veterinary interest are extracellular

Free drug concentration is the driving force controlling AB concentrations at the biophase level



$AUC_{free\ plasma} = AUC_{free}$ ECF (biophase)

Free serum concentrations is the best predictor of AB effect

When there is no barrier to penetration, free antibiotic plasma concentration reflects antibiotic concentration at the site of infection

Journal of Antimicrobial Chemotherapy Advance Access published December 6, 2007

Journal of Antimicrobial Chemotherapy
doi:10.1093/jac/dkm476

JAC

Tissue concentrations: do we ever learn?

Johan W. Mouton[1]*, Ursula Theuretzbacher[2], William A. Craig[3], Paul M. Tulkens[4], Hartmut Derendorf[5] and Otto Cars[6]

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Over the last decades, numerous papers have appeared—and still are appearing—that describe concentrations in tissues in an effort to predict the efficacy of an antimicrobial agent based on these concentrations and MICs for microorganisms. A common method is to use measurements of concentrations in tissue homogenates, comparing these with values derived from the corresponding blood samples and on that basis draw conclusions with respect to the potential clinical use of the drug. This approach is not justifiable for a number of reasons that includes both pharmacokinetic as well as pharmacodynamic causes. This way of presenting data with the derived conclusions is often misleading and may ultimately be harmful in patient care.

3-How integrate PK and PD data (MIC) for antibiotics to find a dose

A fundamental PK/PD relationship

$$Dose = \frac{Body \quad Clearance \times Therapeutic \quad concentration}{Bioavailability}$$

For all antibiotics, the in vivo MIC is directly related to Therapeutic concentrations

A dose can be determined rationally using a PK/PD approach but the MIC is not the best candidate to be "*the* " therapeutic concentration

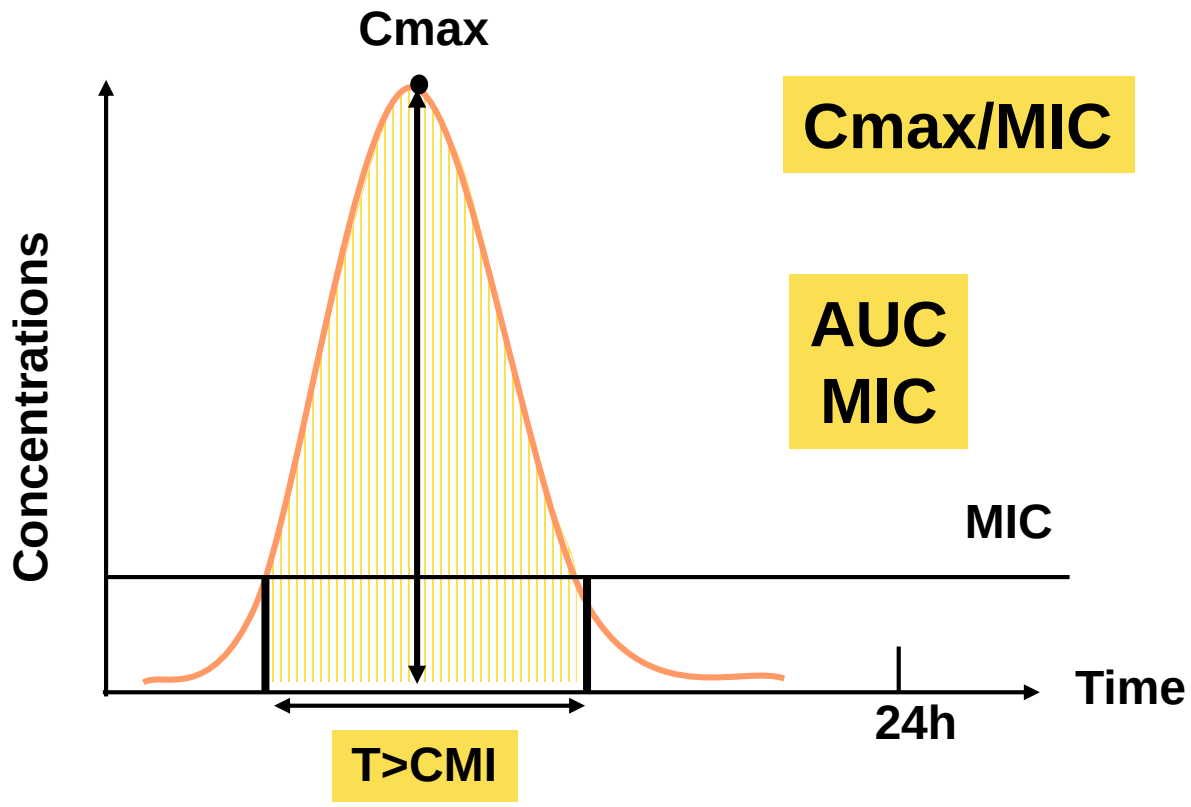
In order to use the MIC to determine a dose, It has been developed 3 surrogates indices (predictors) of antibiotic efficacy taking into account MIC (PD) and exposure antibiotic metrics (PK)

Practically, 3 indices cover all situations:

- ***A*UC/MIC**
- **Time>MIC**
- **Cmax/MIC**

PK/PD predictors of efficacy

- **Cmax/MIC : aminoglycosides**
- **AUC/MIC : quinolones, tetracyclines, azithromycins,**
- **T>MIC : penicillins, cephalosporins, macrolides,**



Appropriate PK/PD indices for the different antibiotics according to their bactericidal properties

Bactericidal pattern	Antibiotics	Therapeutic goal	PKPD indices
Type I Concentration dependant & persistent effect	Aminoglycosides Fluoroquinolones	To optimize plasma concentrations	Cmax/MIC 24h-AUC/MIC
Type II Time-dependent and no persistent effect	Penicillins Céphalosporins	To optimize duration of exposure	T>MIC
Type III Time-dependent and dose-dependent persistent effect	Macrolides Tétracyclines	To optimize amount (doses)	24h-AUC/MIC

4-Why these indices are termed PK/PD

Why these indices are termed PK/PD

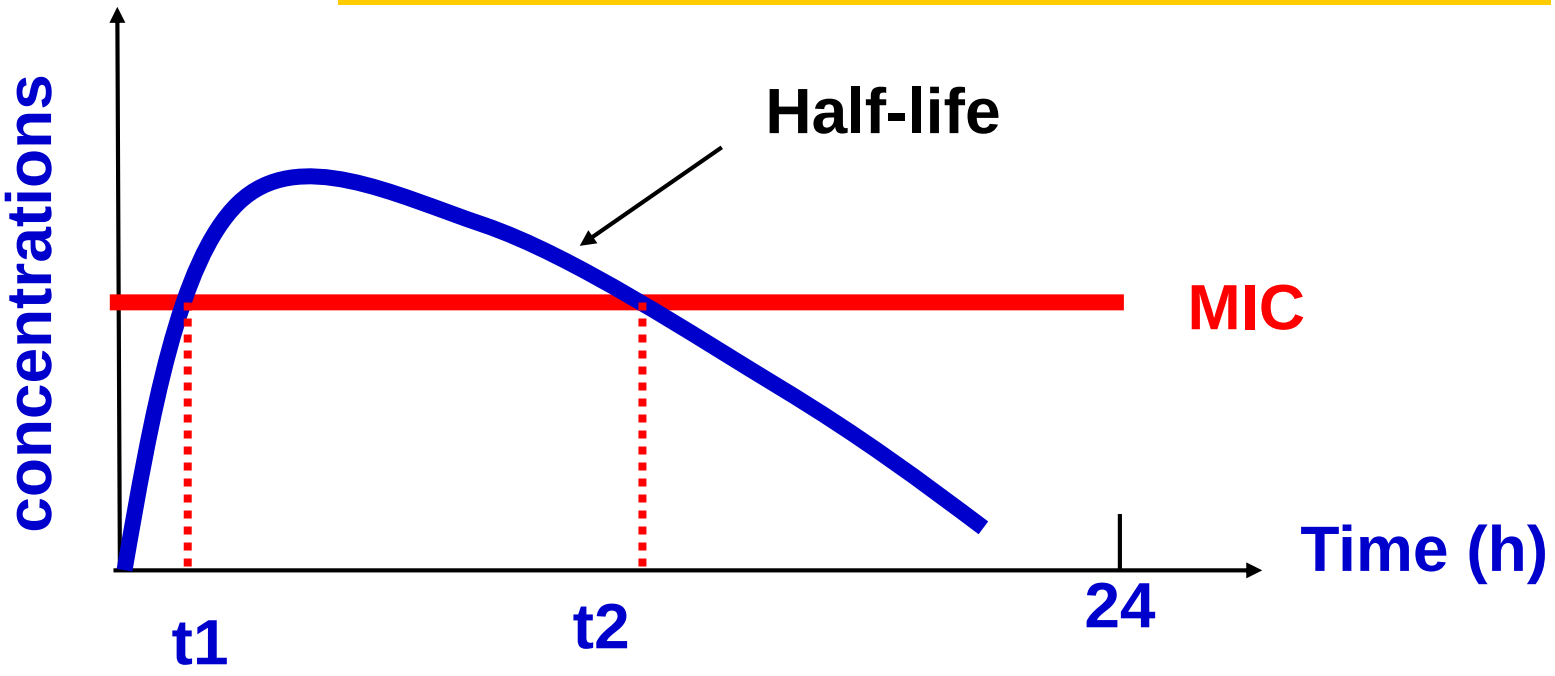
PK parameter expressing capacity of the body to eliminate the antibiotic

$$\frac{AUC}{MIC} = \frac{F \times Dose / Clearance}{MIC_{90}}$$

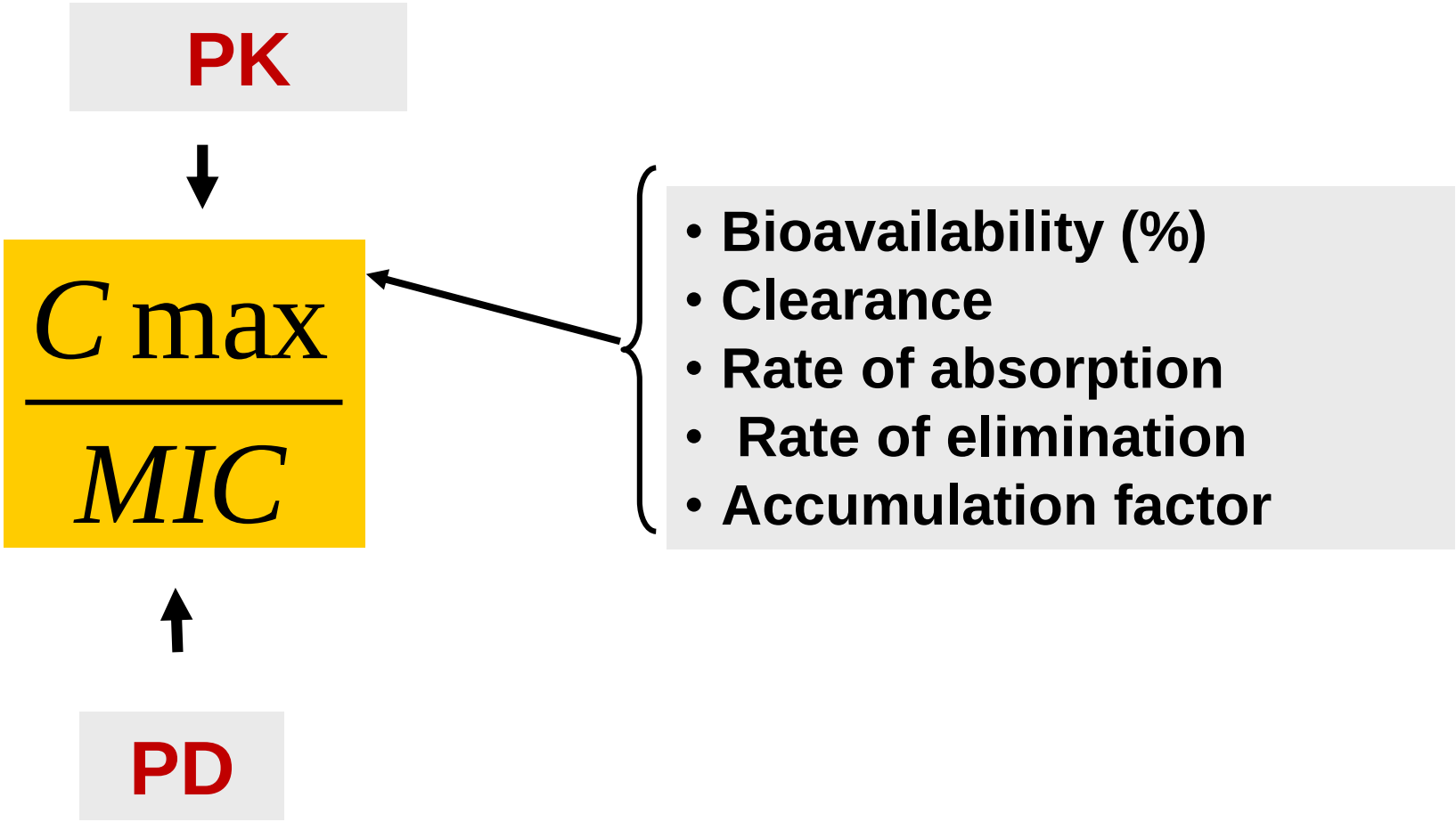
PD parameter expressing antibiotic potency

Time > MIC

$$\%Time > MIC \approx Ln\frac{Dose}{Vd \times MIC} \times \frac{T_{1/2}}{Ln2} \times \frac{100}{\tau}$$



Cmax / MIC


PK
$\frac{C\,\max}{MIC}$
PD
• Bioavailability (%)
• Clearance
• Rate of absorption
• Rate of elimination
• Accumulation factor

PK/PD indices are hybrid parameters

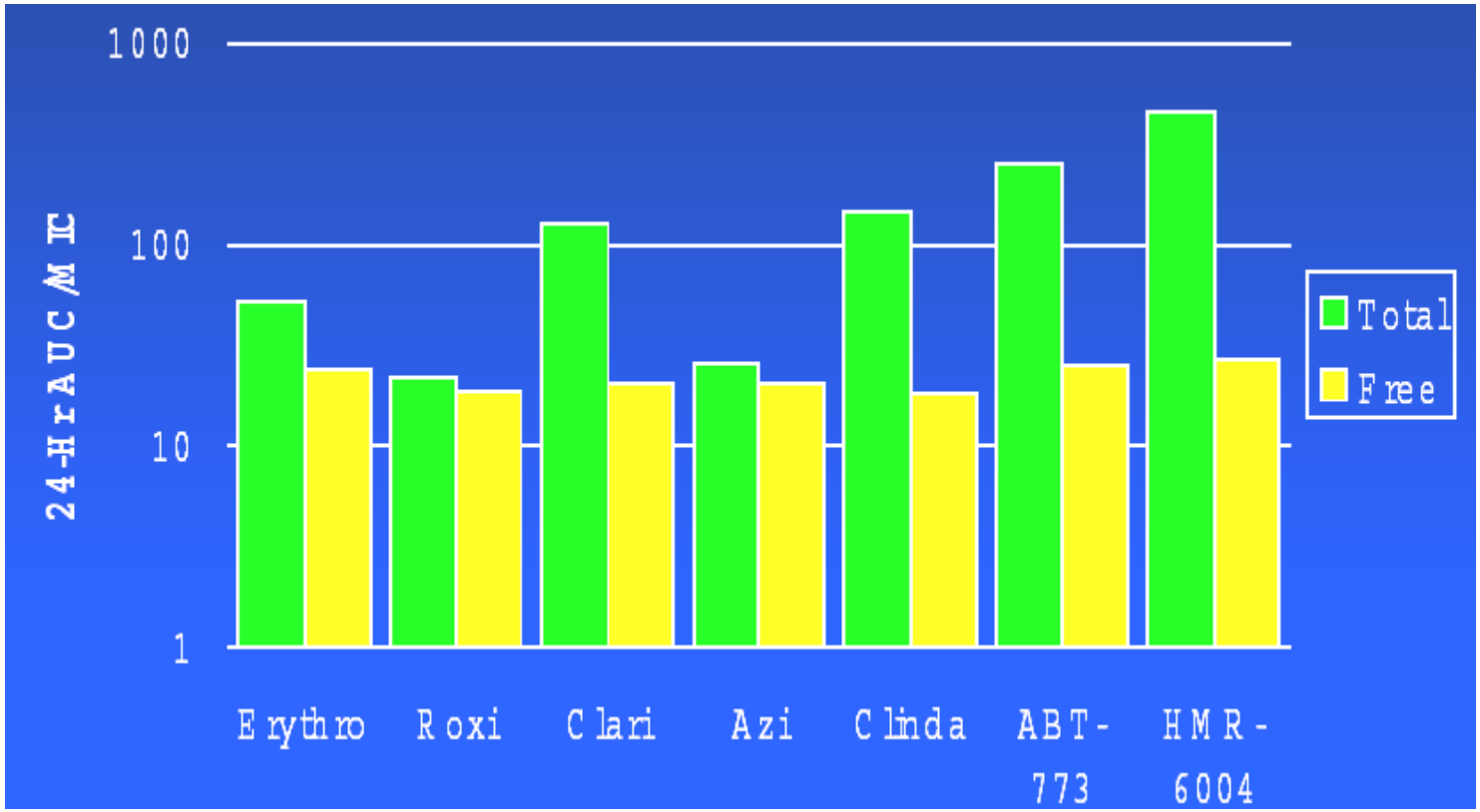
- **For all indices**:
  - **the PD input is the MIC**
  - **the PK input is associated to the free plasma concentration**

The PK input is associated to the *free* plasma: concentration and because MIC is homogeneous to a free plasma concentration, an *f for free* is often added to write the indices as

- ***f*AUC/MIC**
- ***f*Time>MIC**
- ***f*Cmax/MIC**

Comparative AUC/MIC computed with free and total concentrations for different macrolides, kétolides and clindamycin for*S. pneumoniae*

All free AUC/CMI are very similar



Craig et al. 42nd ICAAC, 2002

PK/PD indices have a dimension (units)

- **AUC/MIC=h**
  - Not very appealing
  - Often units are deleted
  - AUC/MIC divided by 24h give a scaling factor without units
    - E.g AUC/MIC=125h is equivalent to say that in steady state condition, the average plasma concentration should be equal to 125h/24h=5.2 times the MIC
- **Cmax/MIC: ratio (scalar)**
- **Time>MIC: expressed as a % over the 24h dosage interval**

To know more on the dimension of AUC/MIC and its consequences in veterinary medicine

Journal of Antimicrobial Chemotherapy Advance Access published October 11, 2007

Journal of Antimicrobial Chemotherapy
doi:10.1093/jac/dkm360

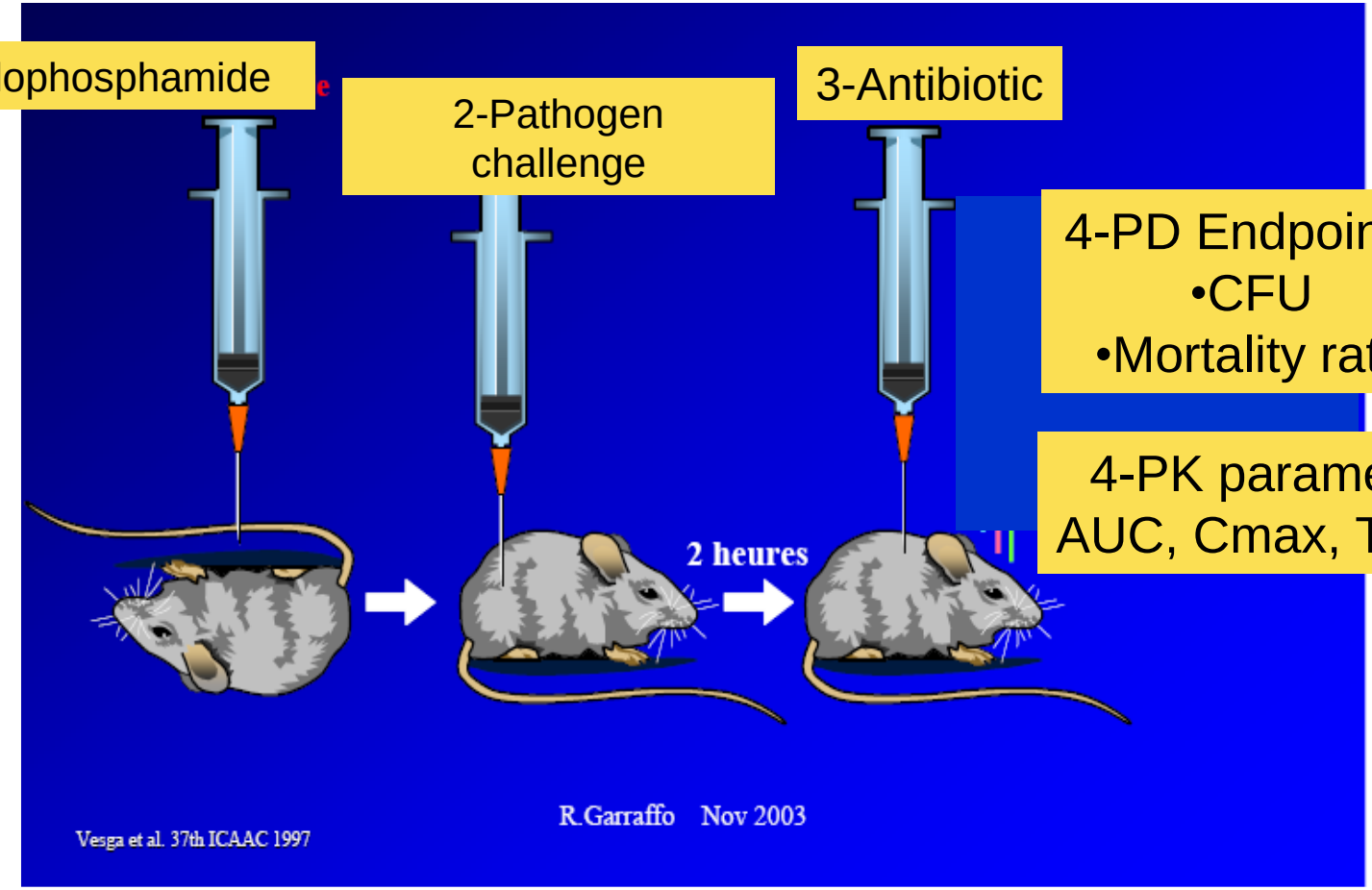
JAC

AUC/MIC: a PK/PD index for antibiotics with a time dimension or simply a dimensionless scoring factor?

Pierre-Louis Toutain[1]*, Alain Bousquet-Mélou[1] and Marilyn Martinez[2]

5-How were established these indices?

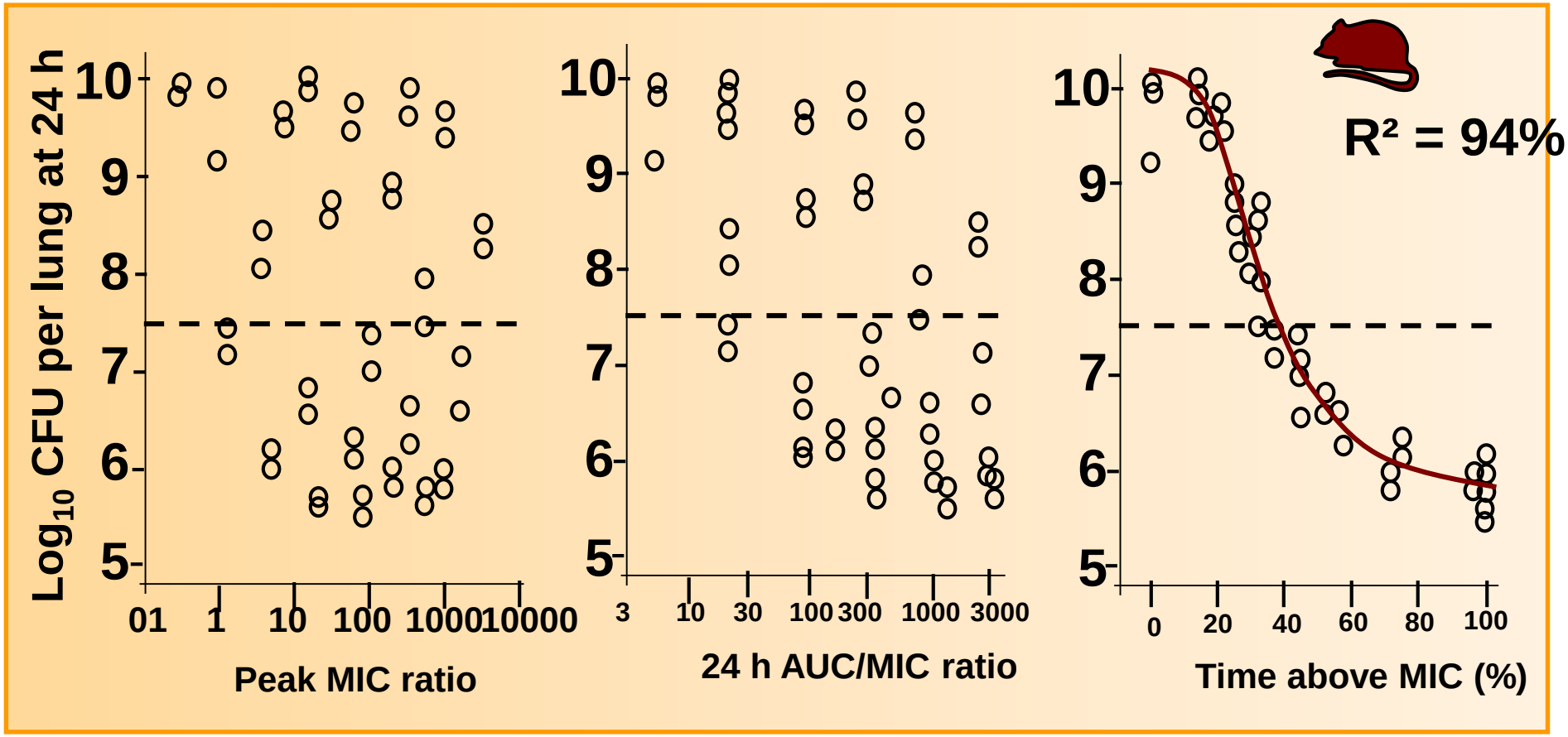
How were established these indices?



Search for the best correlation between the shape of the plasma antibiotic exposure and efficacy

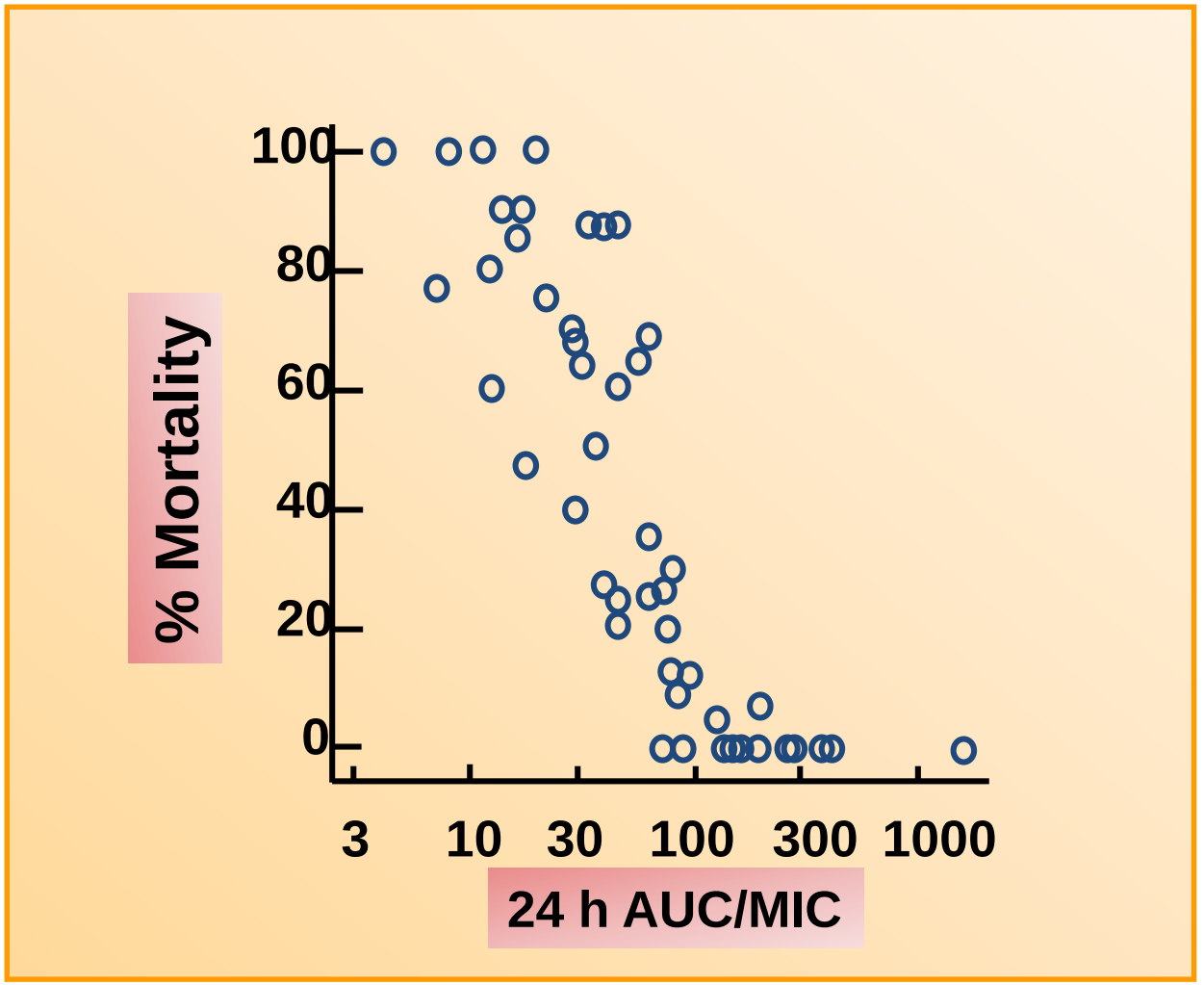
- A lung or thigh infectious challenge in neutropenic mouse
- From 20 to 30 different dosage regimens (5 doses levels and 4-6 intervals of administration) are tested
- Efficacy is measured in terms of reduction of Log10 CFU (bacteriological endpoint) or mortality (clinical endpoint) after 24h
- Plot of results and computation of correlation between each putative PK/PD index (T>CMI, Cmax/CMI, AUC/CMI) and the outcome

Relationship between the different PK/PD indices and the effect of Cefotaxim against *Klebsiella pneumoniae* in a murine lung infectious model



Craig CID, 1998

Relationship between AUC/MIC and mortality rate for a fluoroquinolone against a Gram positive bacillus



6-What is the appropriate magnitude (size) of PK/PD indices to guarantee efficacy i.e. how establish PK/PD breakpoint values

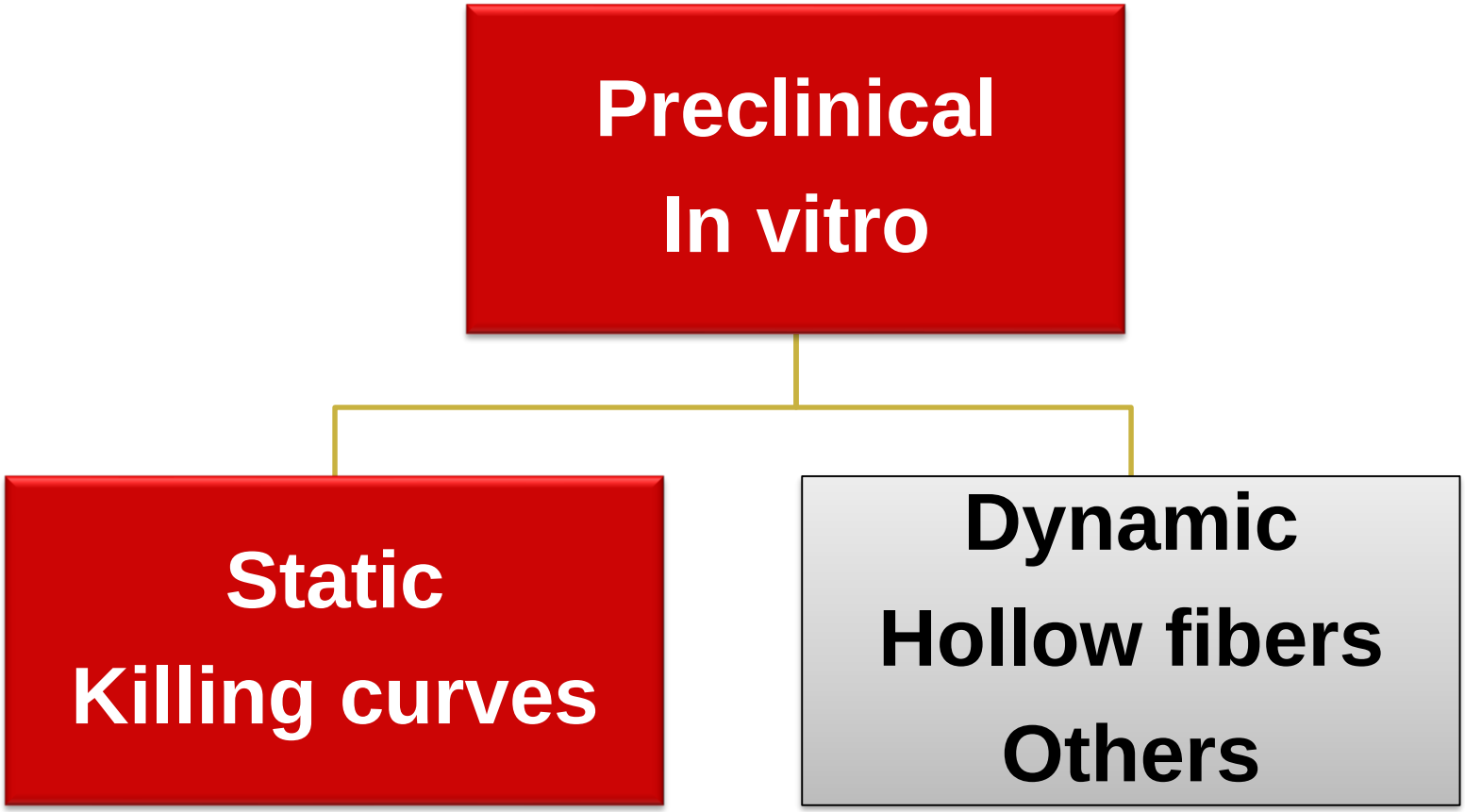
1. To optimize efficacy
2. To minimize resistance

Determination of breakpoint value of PK/PD indices

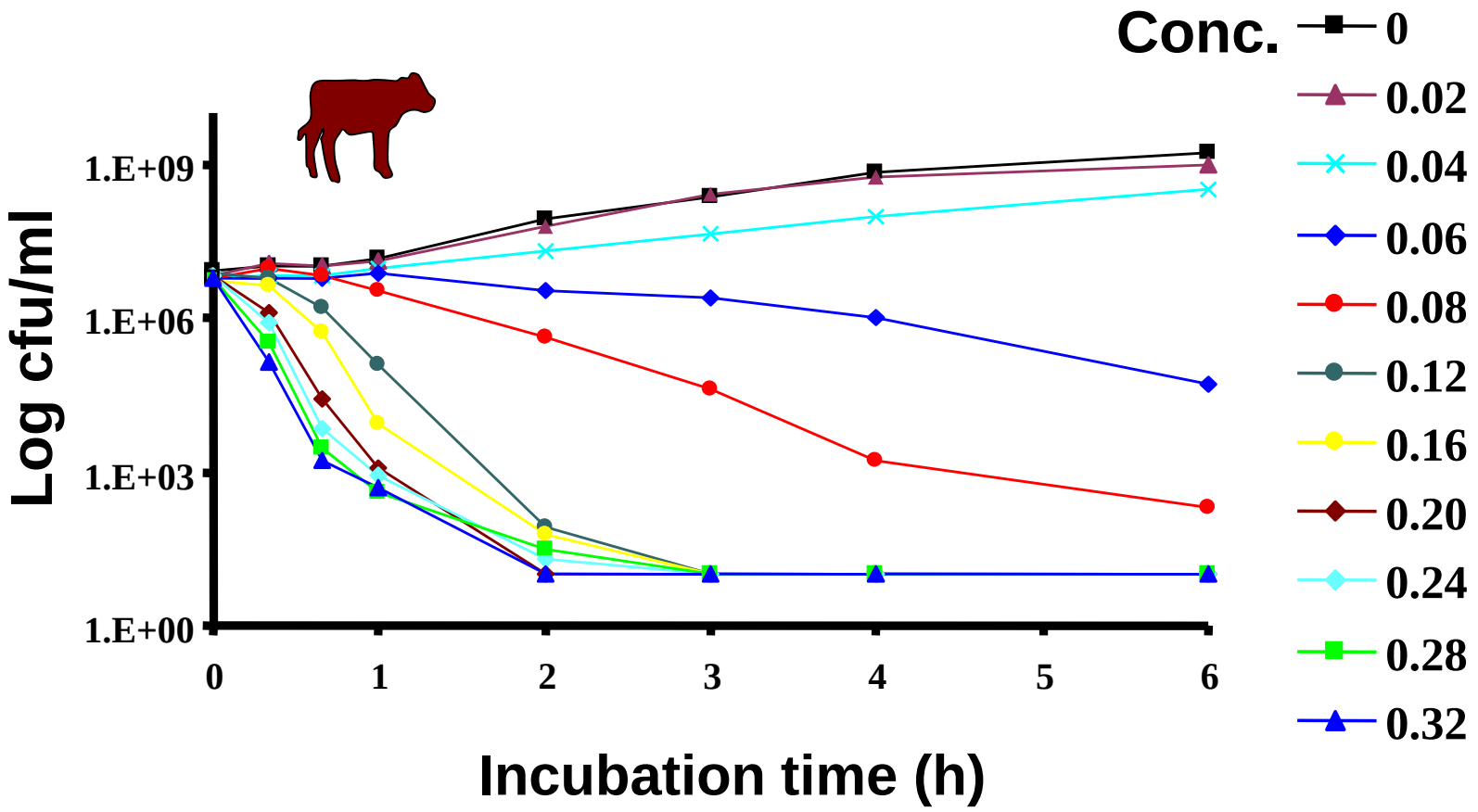
1. ***In vitro or ex vivo*** **(tissue cage)**
2. ***in vivo***
   - **Prospectively from dose-titration**
   - **Retrospectively from meta-analysis of clinical trials**

7-Preclinical determination of the magnitude of the PK/PD indices

Preclinical determination of the PK/PD size



Bacterial growth in serum containing danofloxacin for incubation periods of 0.25 to 6h

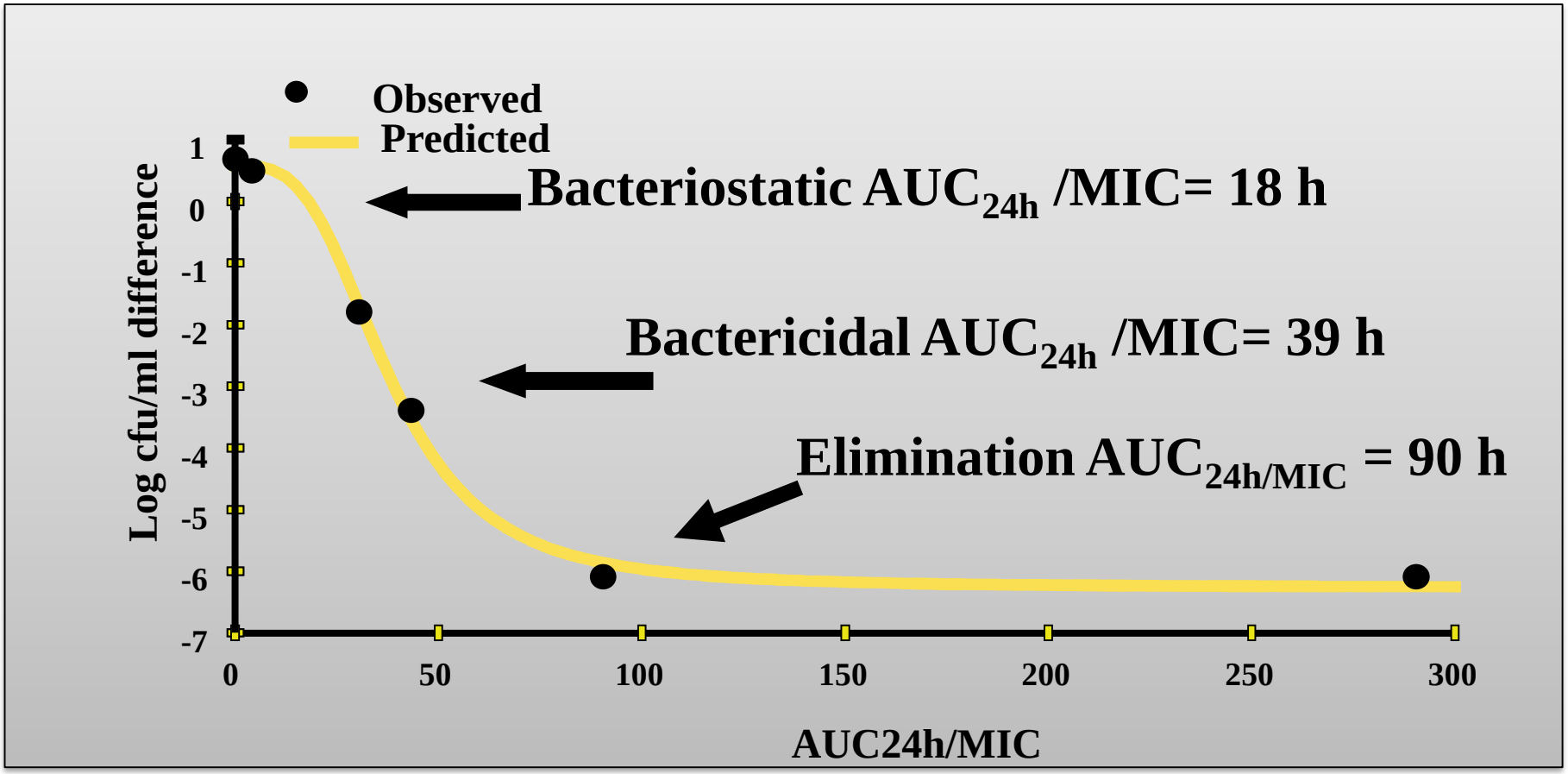


P. Lees

In vitro Data modelling for AUC/MIC

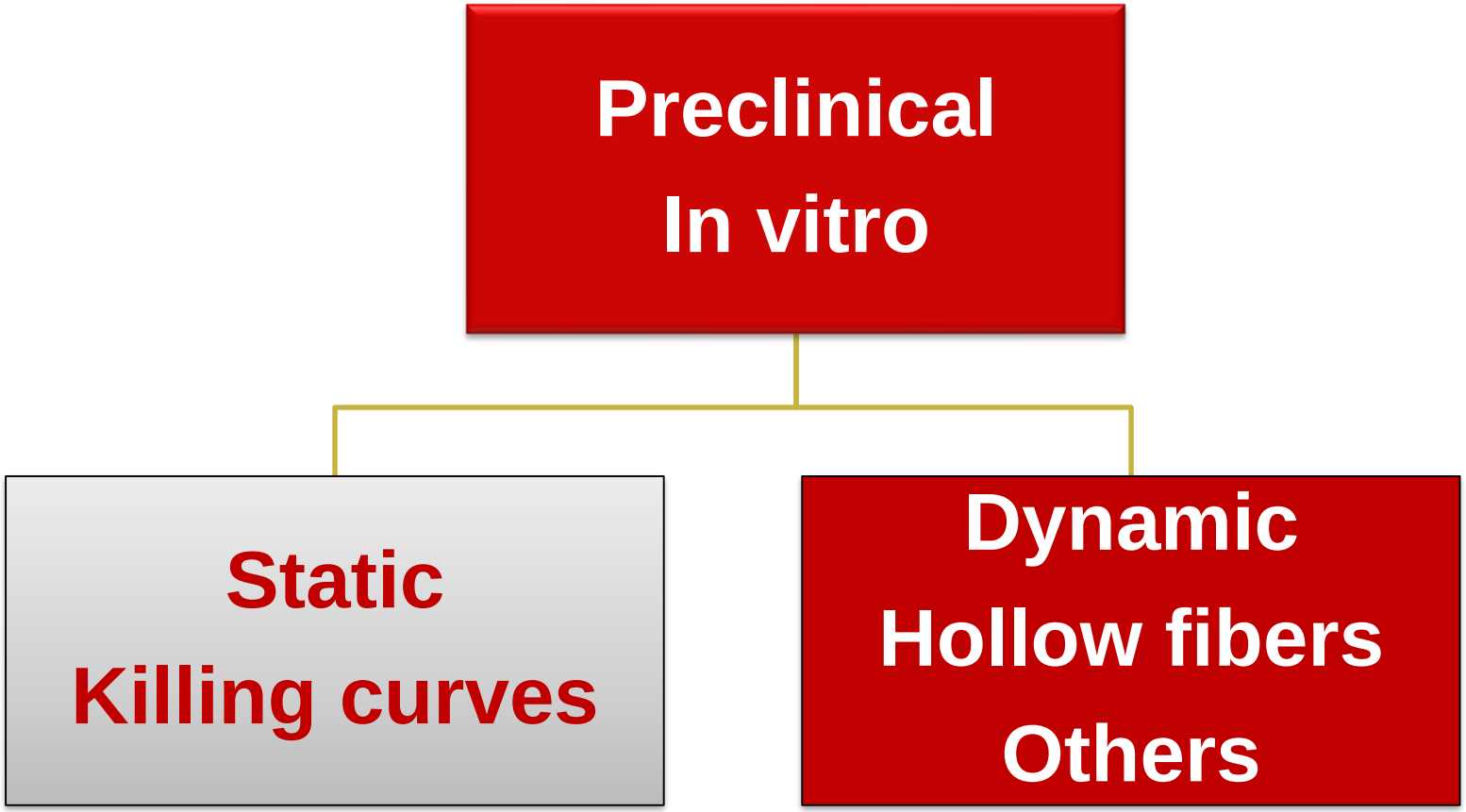
- **A classical Emax model**
- $$E = E_0 + \frac{E_{max} \times X^N}{EC_{50}^N + X^N}$$
  - **E_0** is the bacterial growth after 24 h incubation in the absence of drug, expressed as $\log_{10}$ cfu/mL subtracted from the initial inoculum $\log_{10}$ cfu/mL;
  - **E_{max}** is the maximum growth inhibition determined as the change from the initial count in $\log_{10}$ cfu/mL over 24 h incubation with the antibiotic;
  - **X** is the concentration term (expressed as $AUC_{(0\text{-}24h)}$/MIC)
  - N is the Hill coefficient, which describes the slope of the $AUC_{(0\text{-}24h)}$/MIC-effect curve;
  - **EC_{50}** is the $AUC_{(0\text{-}24h)}$/MIC value providing 50% of the maximum antibacterial effect.
- **Solving the model to compute AUC//MIC to achieve bacteriostatic , bactericidal or eradication**

Sigmoidal Emax relationship for bacterial count vs. ex vivo AUC_{24h}/MIC

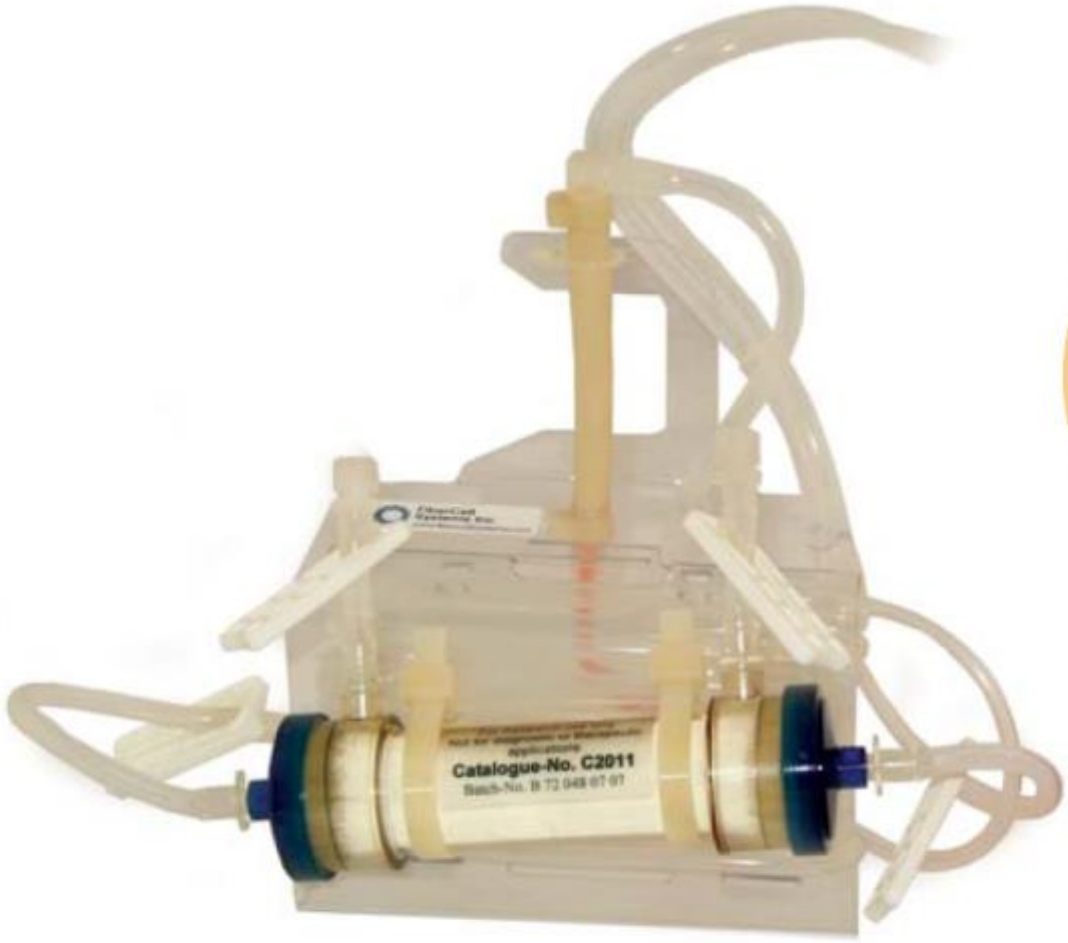


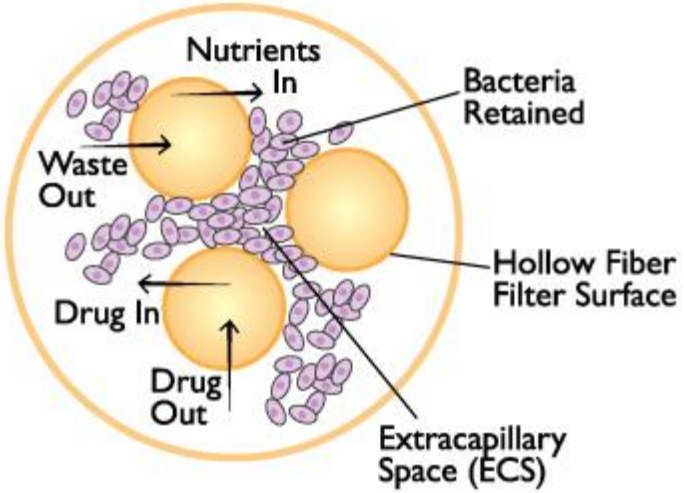
P. Lees

Preclinical determination of the PK/PD size



The hollow fiber





Hollow fiber cartridge two-compartment models (I)

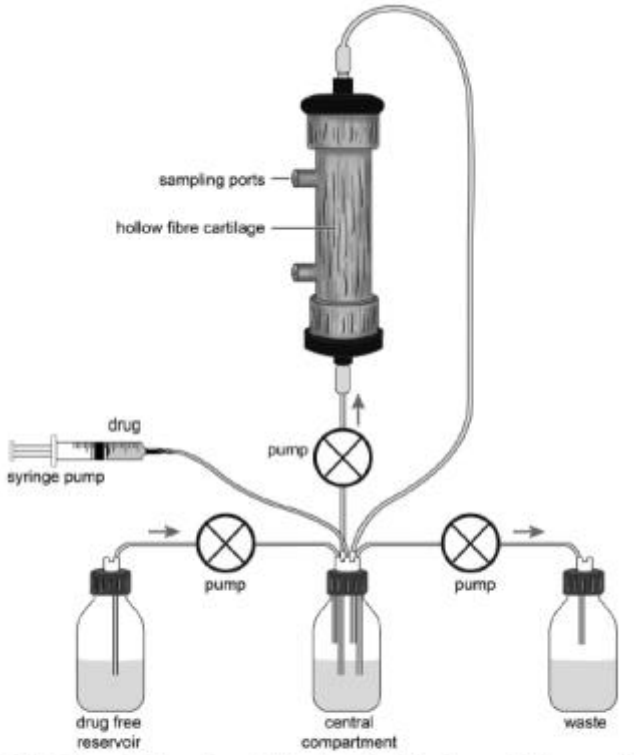


FIG 1 Schematic illustration of the hollow-fiber infection model. The central compartment is connected to the hollow-fiber cartridge, a drug-free reservoir of media, and the waste. Drug may be added to the central compartment via a programmable syringe driver. Courtesy of Helen Carruthers; reproduced with permission.

- **Hollow fiber bioreactors are modules containing thousand of hollow fibers; small tubular filters 200 microns in diameter.**
- **The fibers are sealed at each end so that liquid entering the ends of the cartridge will necessarily go through the insides of the fibers.**
- **The pore size of the fibers is selected to retain the organisms while allowing drugs and other small molecule to freely cross the fiber.**

Advances in Pharmacoepidemiology & Drug Safety

Cadwell, Adv Pharmacoepidem Drug Safety 2012, S1
http://dx.doi.org/10.4172/2167-1052.S1-007

Review Article Open Access

The Hollow Fiber Infection Model for Antimicrobial Pharmacodynamics and Pharmacokinetics

John J.S. Cadwell*

Advantages of the two-compartment hollow fiber infection model

1. The target bacteria are contained within a very small volume, 10-20 mL, so they are at a similar concentration to *in vivo* infections and the drug can equilibrate rapidly within the compartment.
2. Representative samples can be taken easily without significantly affecting the bacteria population.
3. Large numbers of organisms can be tested in one experiment so the emergence of drug resistance is easily quantified.
4. Both absorption and elimination kinetics of the drug being testing can be controlled.
5. The kinetics of multiple drugs can also be controlled so drug/drug interactions and combination therapies can readily be examined.
6. Long duration of experiment to predict development of resistance

8- PK/PD: semi-mechanistic models

A major review

1521-0081/65/3/1053–1090$25.00
PHARMACOLOGICAL REVIEWS

http://dx.doi.org/10.1124/pr.111.005769
Pharmacol Rev 65:1053–1090, July 2013

ASSOCIATE EDITOR: DAN ANDERSSON

Pharmacokinetic-Pharmacodynamic Modeling of Antibacterial Drugs

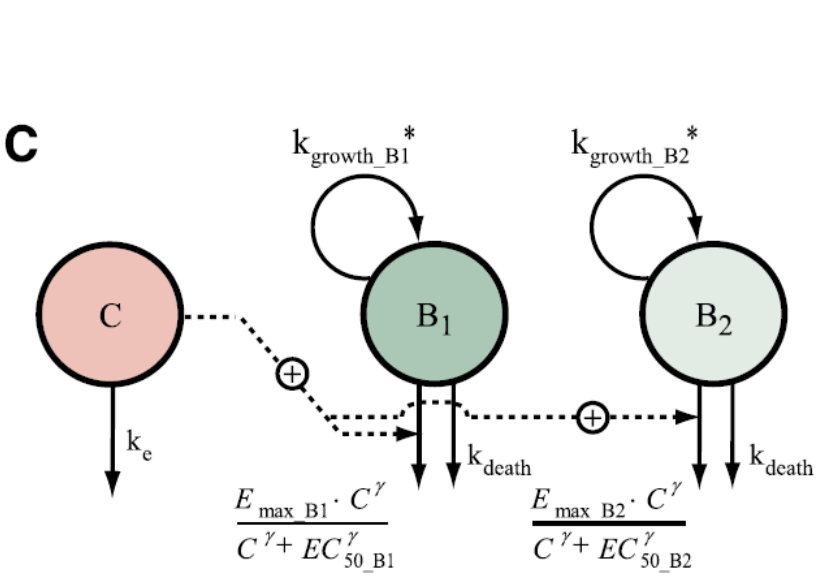
Elisabet I. Nielsen and Lena E. Friberg

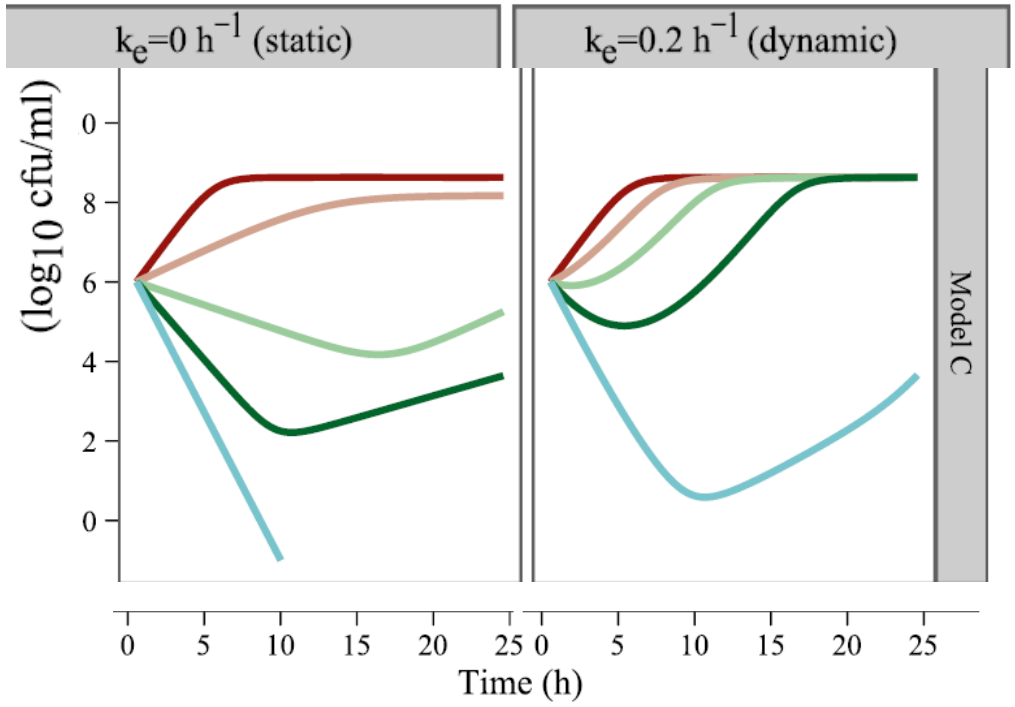
Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden

Mechanism-based model of antimicrobials

- A mechanism-based AM PK/PD model should include equations to describe:
  - Microorganisms growth (microorganisms submodel)
    - Net growth rate or Replication and death rate
  - Changing drug concentration (PK model)
  - Effect of AM drug (AM submodel) to describe the interaction between the two preceeding submodel
  - They can also include a sub-model for the host defenses.

PK/PD model for resistance and predicted bacterial time-kill curves

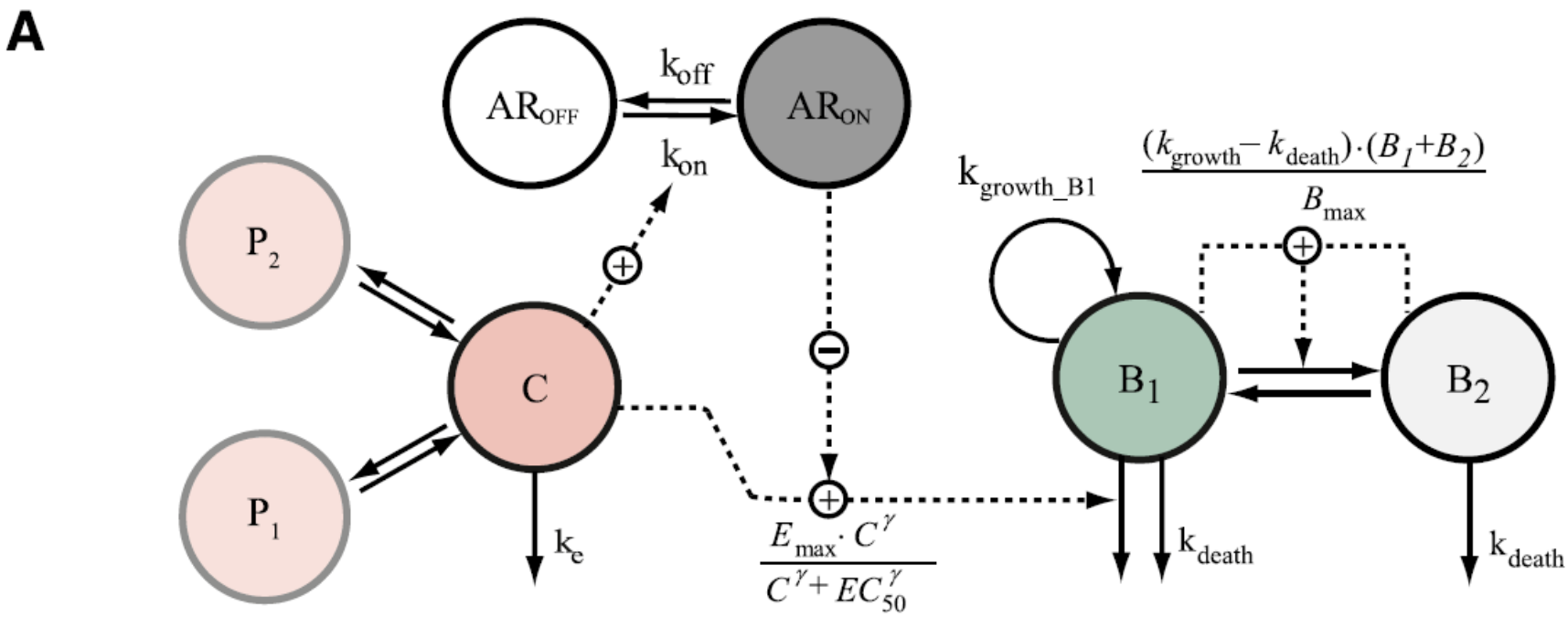




B1, compartment with drug sensitive bacteria;
B2, compartment with less drug-sensitive bacteria;

PK/PD model structure describing adaptive resistance

Nielsen and Friberg



B1, cpt with growing drug-sensitive bacteria; B2, cpt with non growing drug insensitive bacteria;

AROFF and ARON, cpt describing adaptive resistance being off and on, respectively; kon and koff, rate constants for development and reversal of adaptive resistance, respectively;

Classical PK/PD indices vs. semi-mechanistic models

- These semi-mechanistic models are able to predict the classical PK/PD indices and their breakpoint values.
- They are able to predict time development of resistance

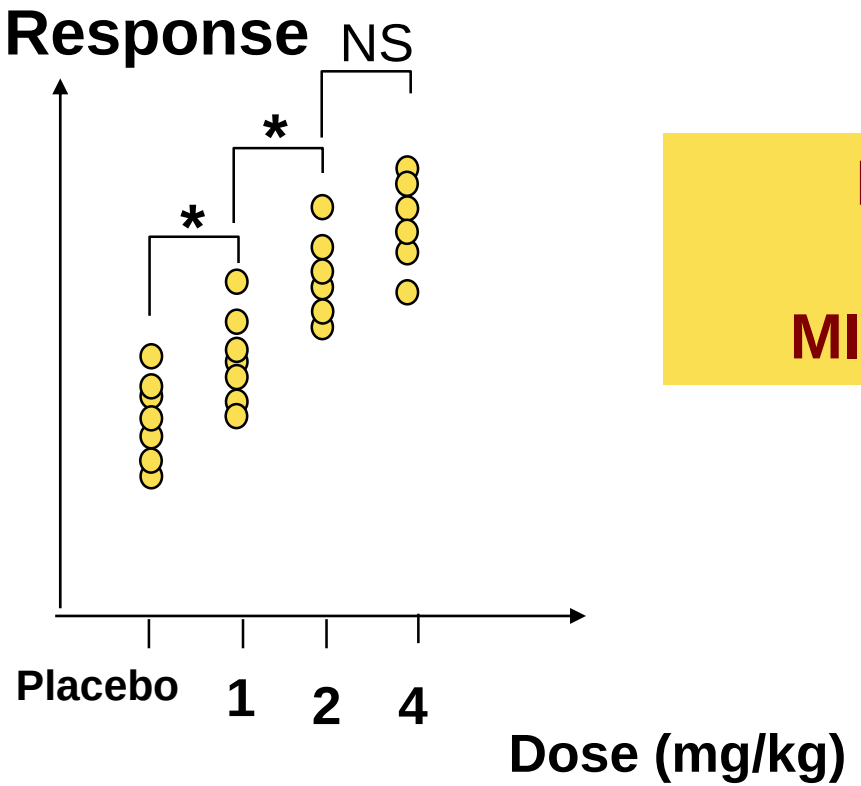
Classical PK/PD indices vs. semi-mechanistic models

- However, they also predict that when the AM half-life is short, the best predictor is always T>MIC and when the half-life is long, the best predictor is always AUC/MIC whatever the antibiotic.

- These kind of results are very important for veterinary medicine that uses many long-acting formulations and the use of AUC/MIC as a universal PK/PD index would greatly facilitate many tasks such as finding an optimal dosage regimen and fixing sound clinical breakpoints for susceptibility testing.

9-Prospective determination of the breakpoint of PK/PD indices from a dose –titration trial by establishing the relationship between AUC/MIC and the clinical success

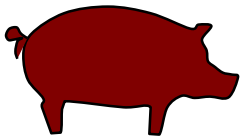
Determination of the PK/PD clinical breakpoint value from the dose titration trial using an infectious model

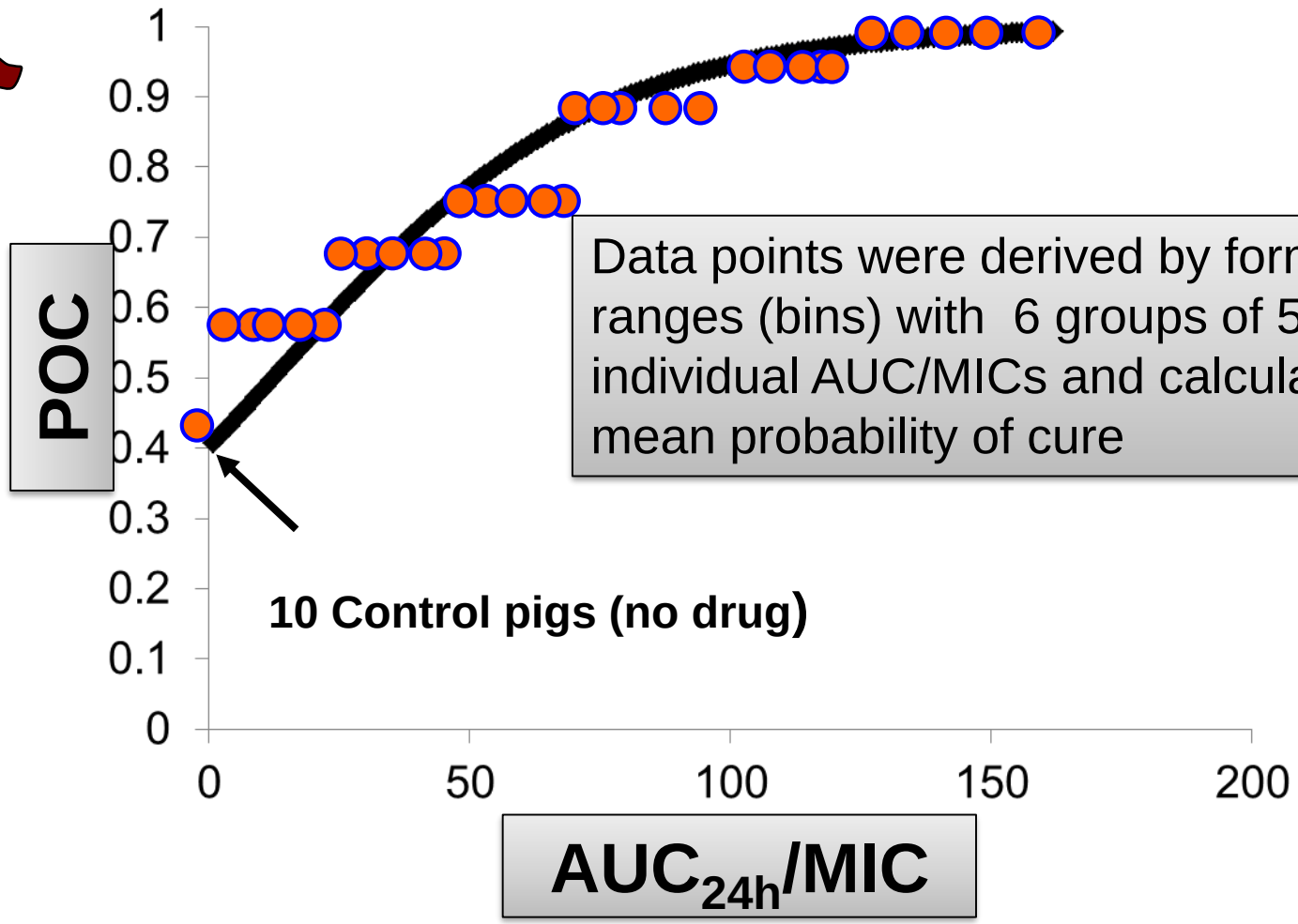


Blood samples should be collected and MIC of the pathogen is known

- **Parallel design**
- **4 groups of 10 animals**

AUC/MIC vs. Probability of Cure (POC)





Probability of cure (POC)

- **Logistic regression was used to link measures of drug exposure to the probability of a clinical success**

$$POC = \frac{1}{1 + e^{a - bf(AUC/MIC)}}$$

Dependent variable

Placebo effect

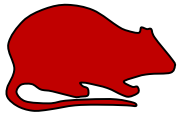
sensitivity

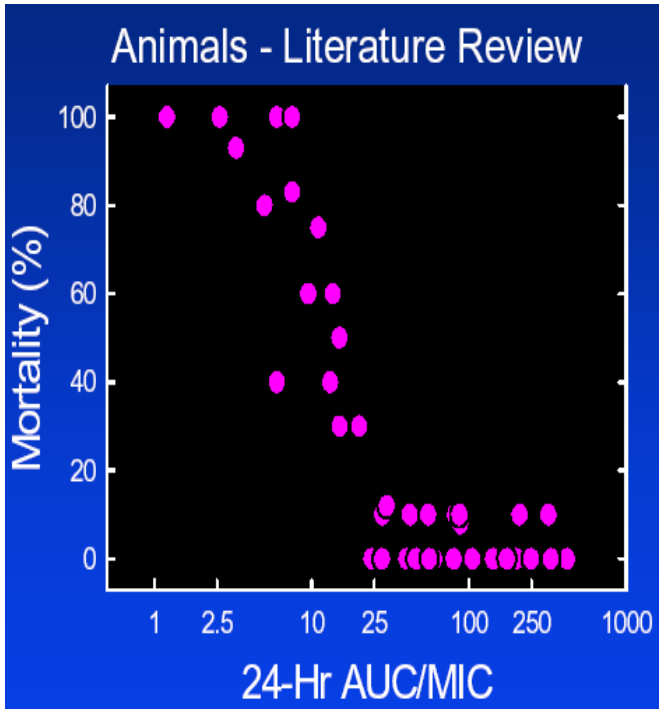
Independent variable

2 parameters: **a** (placebo effect) & **b** (slope of the exposure-effect curve)

10-Retrospective determination of the breakpoint of PK/PD indice from (human) clinical trials

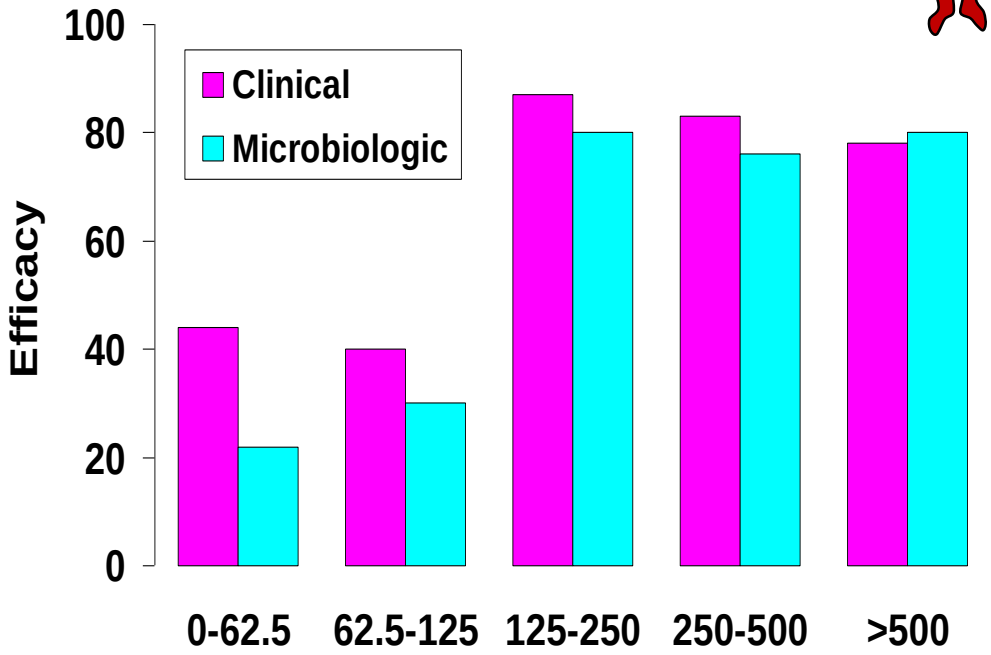
Comparison of the relationships between efficacy and 24-hr AUC/MIC for fluoroquinolones in animal models and infected patients





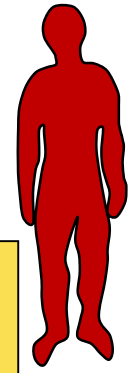
AUC/MIC

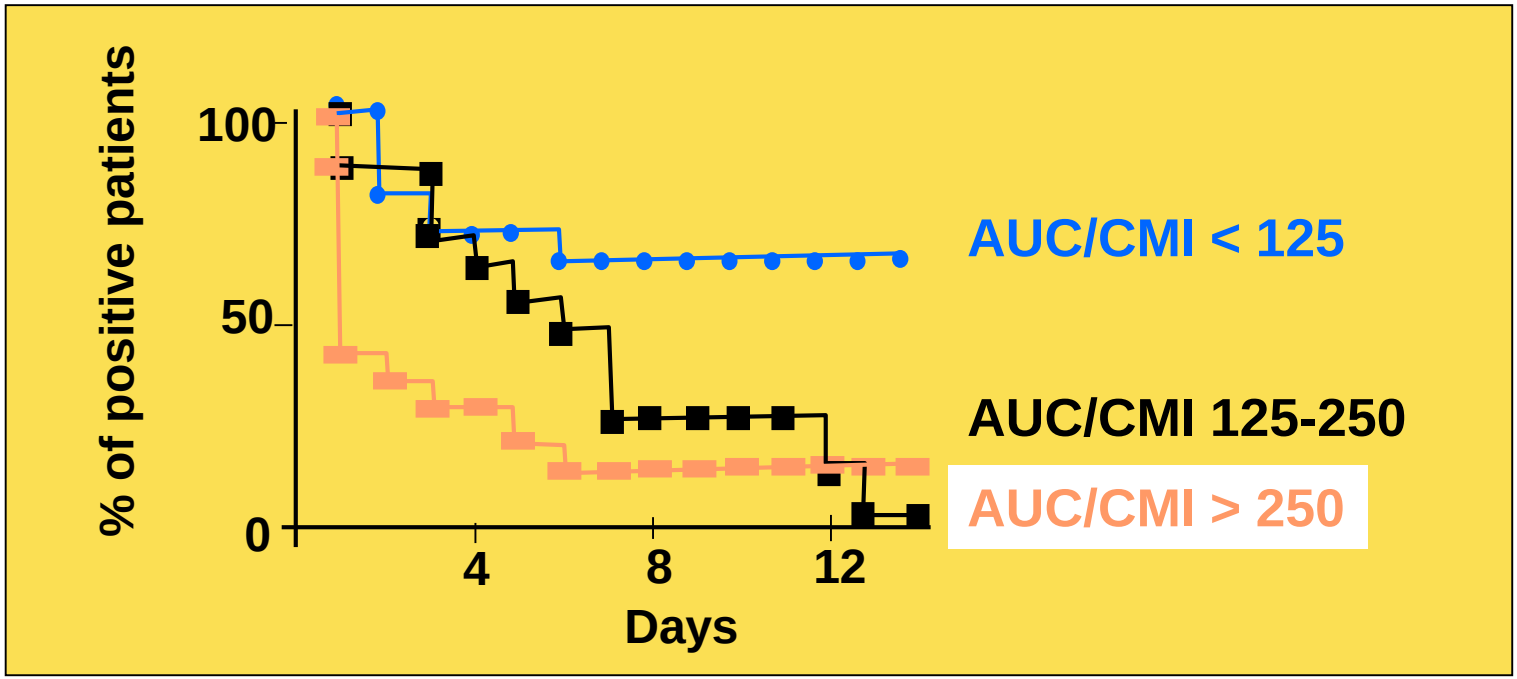
Seriously ill patients+Ciprofloxacin



24-Hr AUC/MIC

AUC/CMI and bacterial eradication for ciprofloxacin in nosocomial pneumonia



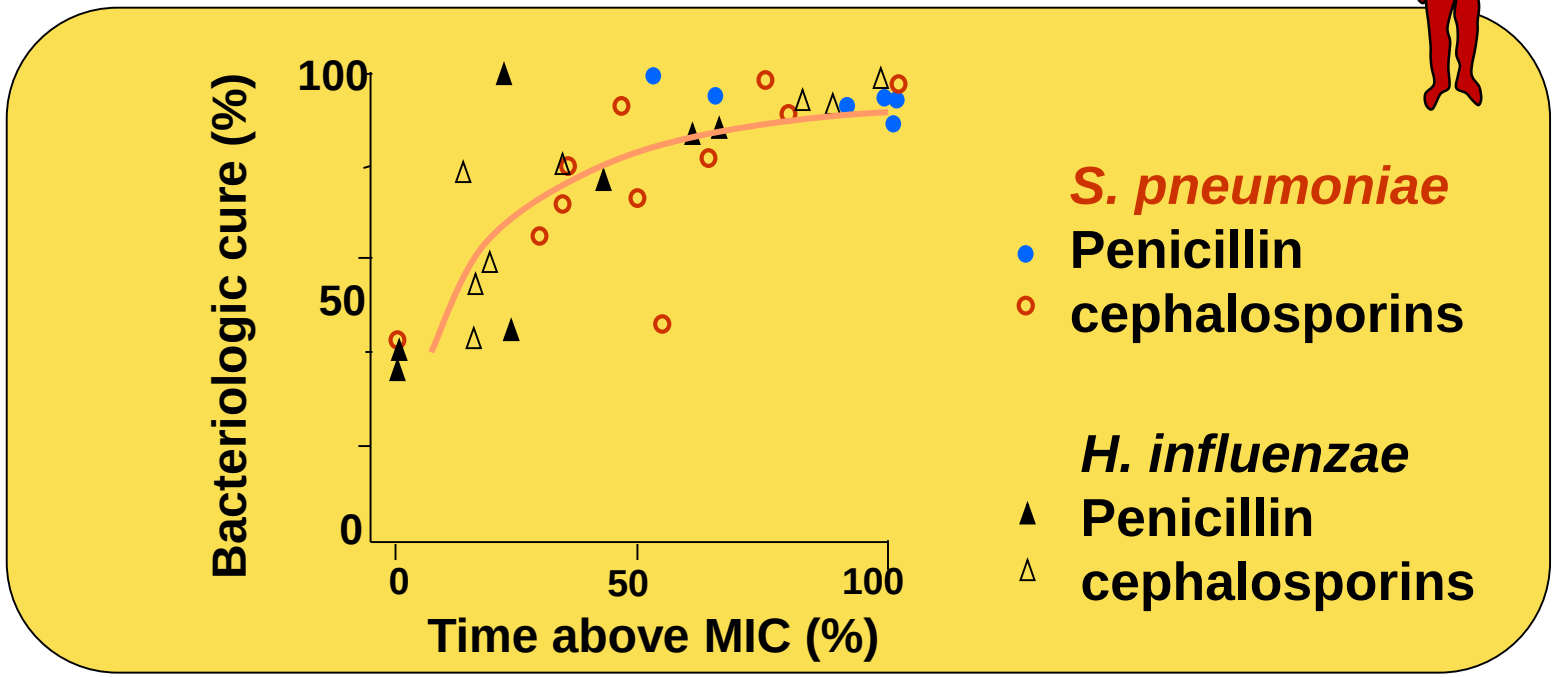


All

Schentag Symposium, 1999

Efficacy index: clinical validation

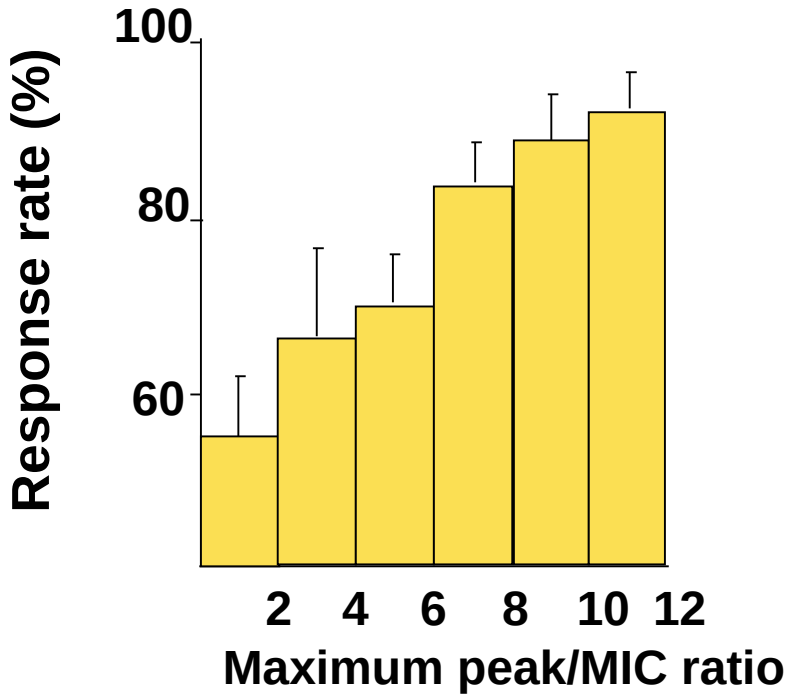
Bacteriological cure versus time above MIC in otitis media (from Craig and Andes 1996)



- **Free serum concentration need to exceed the MIC of the pathogen for 40-50% of the dosing interval to obtain bacteriological cure in 80% of patients**

Efficacy index: clinical validation

Relationship between the maximal peak plasma level to MIC ratio and the rate of clinical response in 236 patients with Gram-negative bacterial infections treated with aminoglycosides (gentamicin, tobramycin, amikacin)



Moor et al. 1984 J. Infect. Dis.

Breakpoint values for PK/PD indices

PK/PD indices	Pathogens	Breakpoint values
24h-AUC/MIC	Gram positive	~50h
24h-AUC/MIC	Gram negative	~125-250h
T>MIC	Gram positive	~40-50% of the dosage interval
T>MIC	Gram negative	~100% of the dosage interval
Cmax/MIC	All pathogens	10

Universality of PK/PD breakpoint

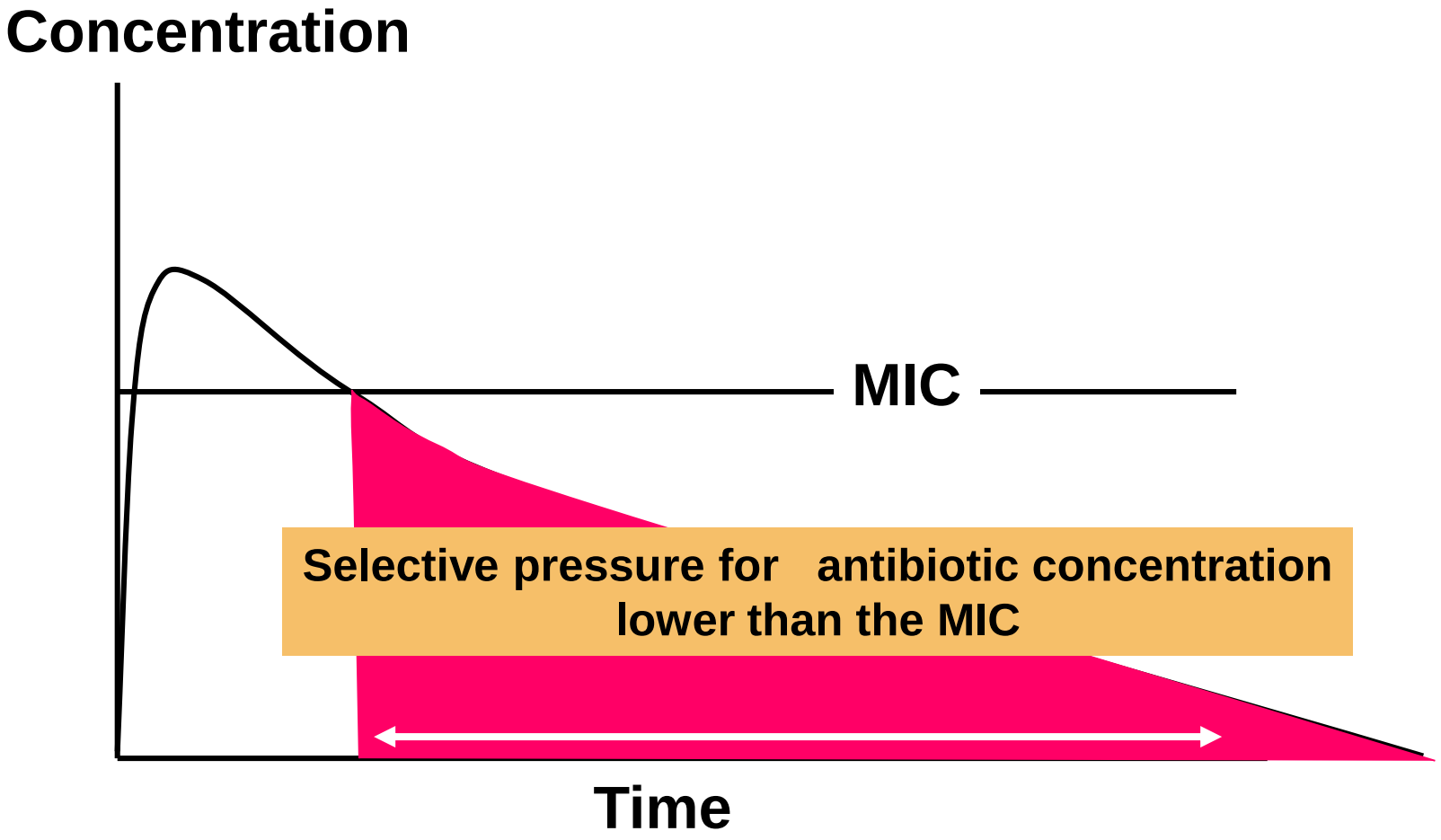
- **Likely (because PK & PD)**
- **Allow interspecific extrapolation**

11-PK/PD indices and the development of resistance

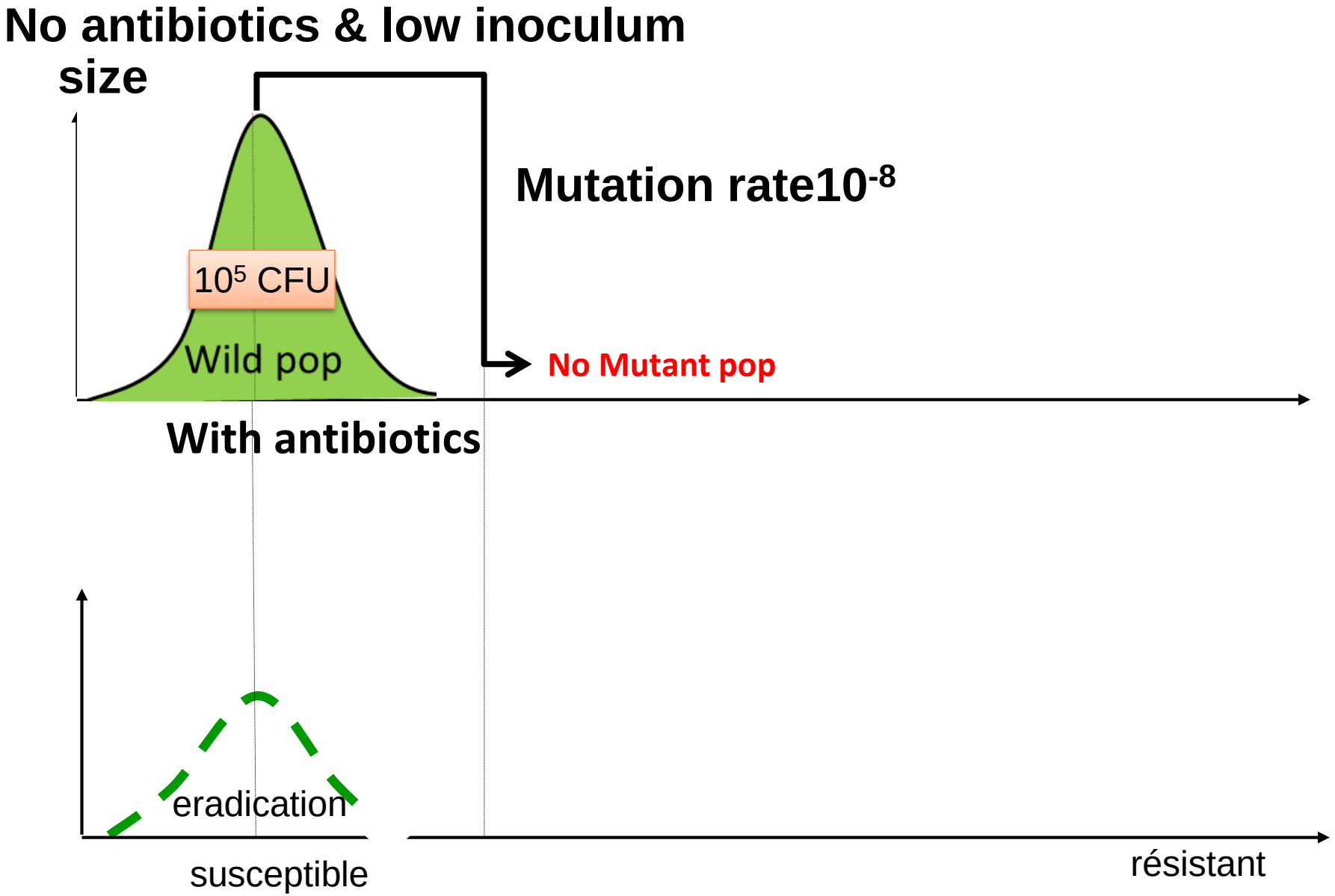
The mutant Selective Window (MSW)

Currently the MSW is the only PK/PD index that is use to mitigate the emergence of resistance

Traditional hypothesis on emergence of AMR

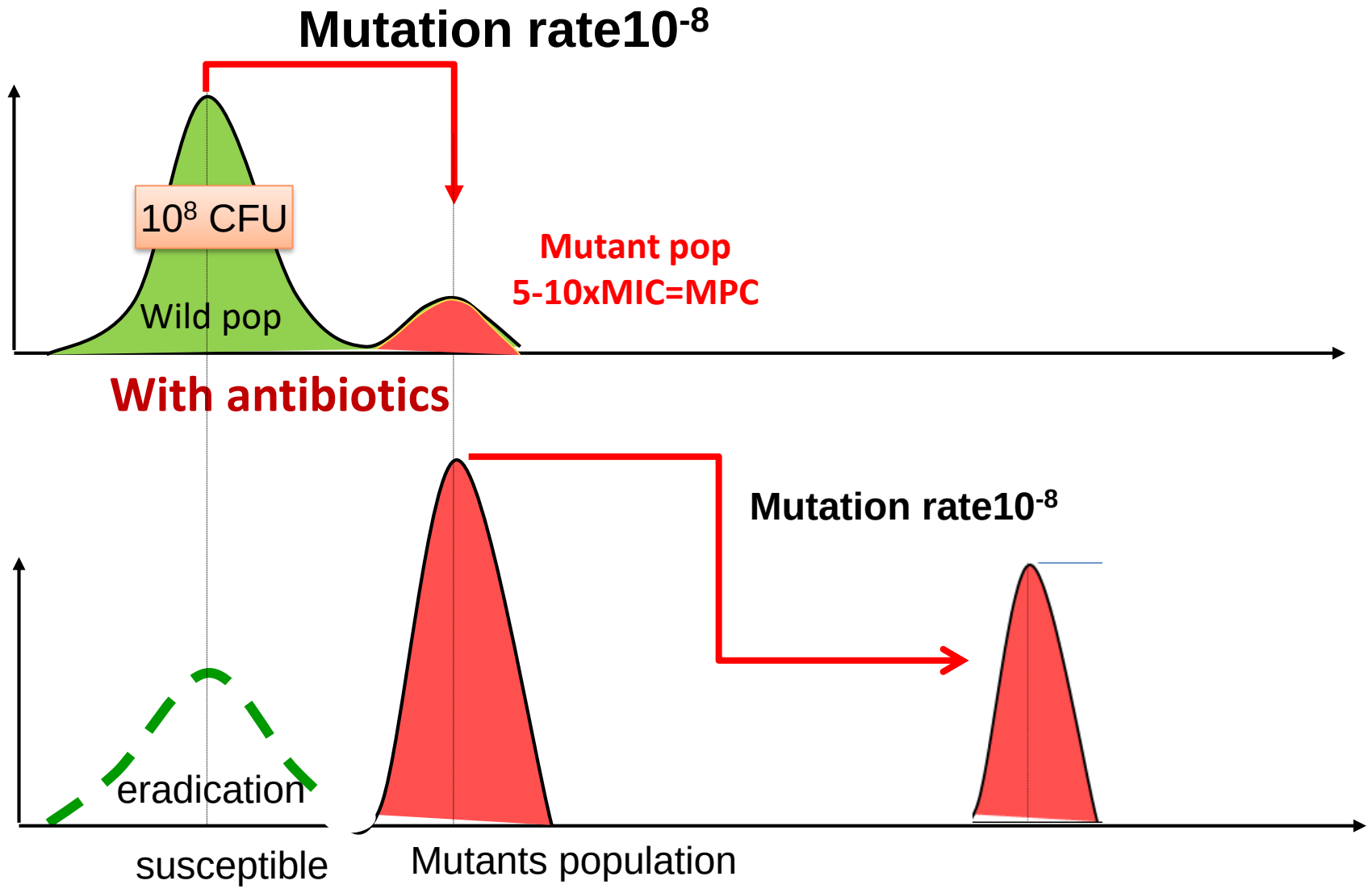


Current view for the emergence and selection of resistance : situation II

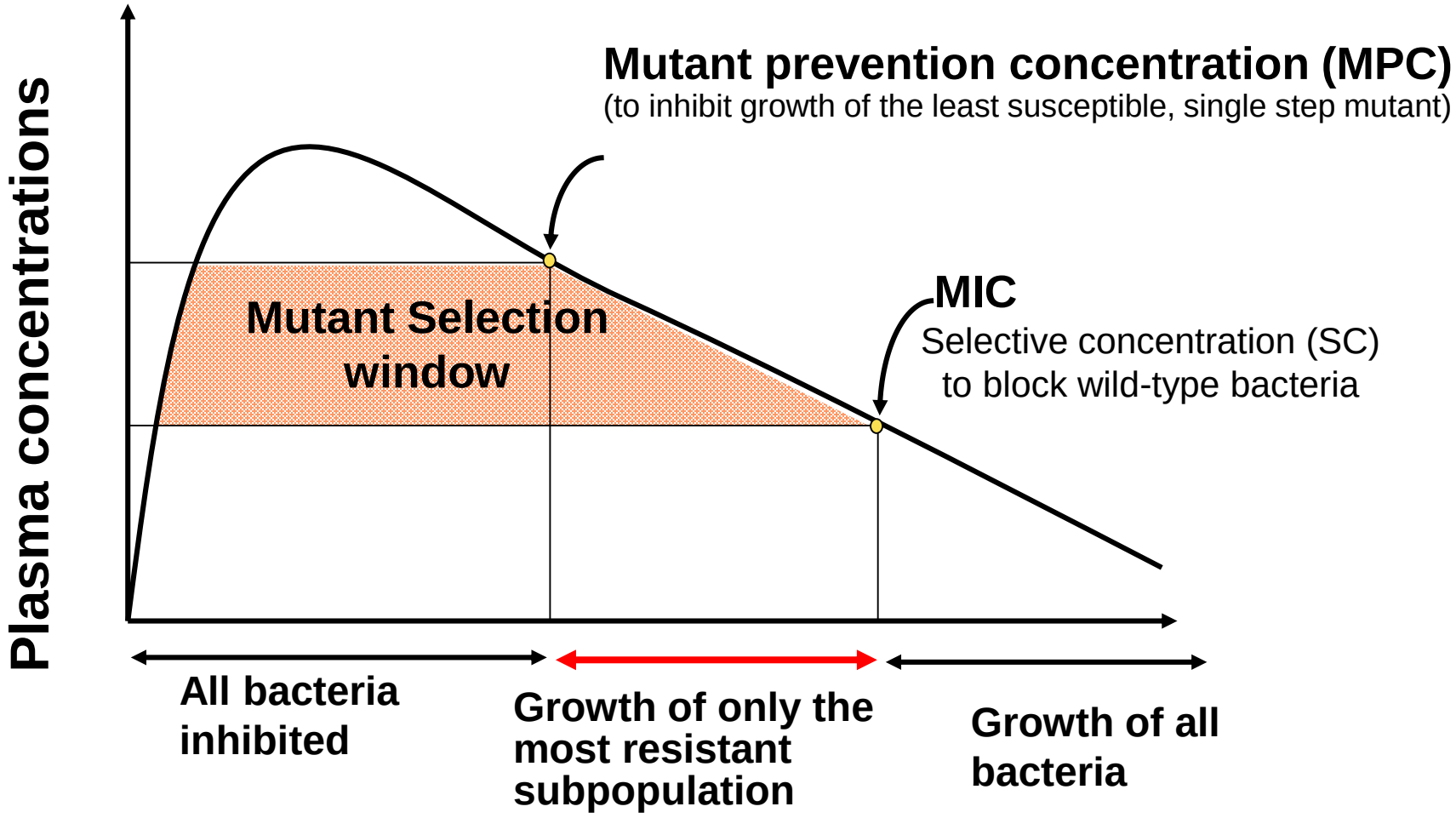


Current view for the emergence and selection of resistance : situation II

No antibiotics & high inoculum



The selection window hypothesis



MIC & MPC for the main veterinary quinolones for *E. coli* & *S. aureus*

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Oct. 2005, p. 4166–4173 Vol. 49, No. 10
0066-4804/05/$08.00+0 doi:10.1128/AAC.49.10.4166–4173.2005

Comparative Mutant Prevention Concentrations of Pradofloxacin and Other Veterinary Fluoroquinolones Indicate Differing Potentials in Preventing Selection of Resistance†

H.-G. Wetzstein*

Bayer HealthCare AG, Animal Health Division, 51368 Leverkusen, Germany

TABLE 1. Potencies of veterinary fluoroquinolones expressed in terms of MICs and MPCs[a]

Compound	*E. coli* ATCC 8739			*S. aureus* ATCC 6538		
	MIC (μg/ml)	MPC (μg/ml)	MPC/MIC	MIC (μg/ml)	MPC (μg/ml)	MPC/MIC
Pradofloxacin	0.015–0.03^{++}	0.2–0.25	9.4	0.03–0.06^{++}	0.5–0.6**	12
Danofloxacin	0.06	0.5–0.55	8.8	**0.125**–0.25	10–11*	56
Difloxacin	0.125–**0.25**	1.5–1.6	8.3	0.125	16–18*	136
Enrofloxacin	**0.03**–0.06^{+}	0.3–0.35	7.8	0.06–0.125^{++}	3–3.5*	35
Marbofloxacin	0.03	0.25–0.3	9.2	0.25–0.5	3–3.5	9
Orbifloxacin	0.125	1–1.25	9.0	0.5	8–9	17
Sarafloxacin	0.03–**0.06**	0.5–0.6	12.2	**0.125**–0.25	8–9	45
Ciprofloxacin	0.015–**0.03**	0.1–0.15	5.6	0.25–0.5^{+}	6	16
Moxifloxacin	0.06–**0.125**	0.5–0.6	6.0	0.03–0.06	0.8–1	20

[a] MICs have been compiled from three, six, or seven ($^{+}$) and 10 to 14 ($^{++}$) independent experiments; the more frequent result is printed in bold. MPCs were determined in three, five (*), or nine (**) experiments. In calculations, mean values were employed.

Comparative MIC and MPC values for 285 *M. haemolytica* strains collected from cattle

	MIC_{50}	MIC_{90}	MPC_{50}	MPC_{90}	MPC/MIC
Ceftiofur	0.016	0.016	1	2	125
Enrofloxacine	0.016	0.125	0.25	1	8
Florfenicol	2	2	4	8	4
Tilmicosine	2	8	16	>32	≈8
Tulathromycine	1	2	4	8	4

Vet Microbiol 2012 Blondeau JM

The size of the PK/PD index and emergence of resistance for FQ

MAJOR ARTICLE

Impact of Drug-Exposure Intensity and Duration of Therapy on the Emergence of *Staphylococcus aureus* Resistance to a Quinolone Antimicrobial

V. H. Tam,[1,a] A. Louie,[1] T. R. Fritsche,[2] M. Deziel,[1,b] W. Liu,[1] D. L. Brown,[1] L. Deshpande,[2] R. Leary,[2,a] R. N. Jones,[2] and G. L. Drusano[1]

What is the concentration needed to prevent mutation and/or selection of bacteria with reduced susceptibility?

- **Beta-lactams:**
  - **stay always above the 4xMIC**
- **Aminoglycosides:**
  - **achieve a peak of 8x the MIC at least**
- **Fluoroquinolones:**
  - **AUC/MIC > 200 and peak/MIC > 8**

12-Limits of the PK/PD indices

Classical PK/PD indices

- **However, the PK/PD indices have several drawbacks associated with assumptions made when neglecting information on the time-course of PK and PD.**
- **All indices rely on MIC, and drawbacks associated to MIC are thus propagated into the PK/PD indices,**

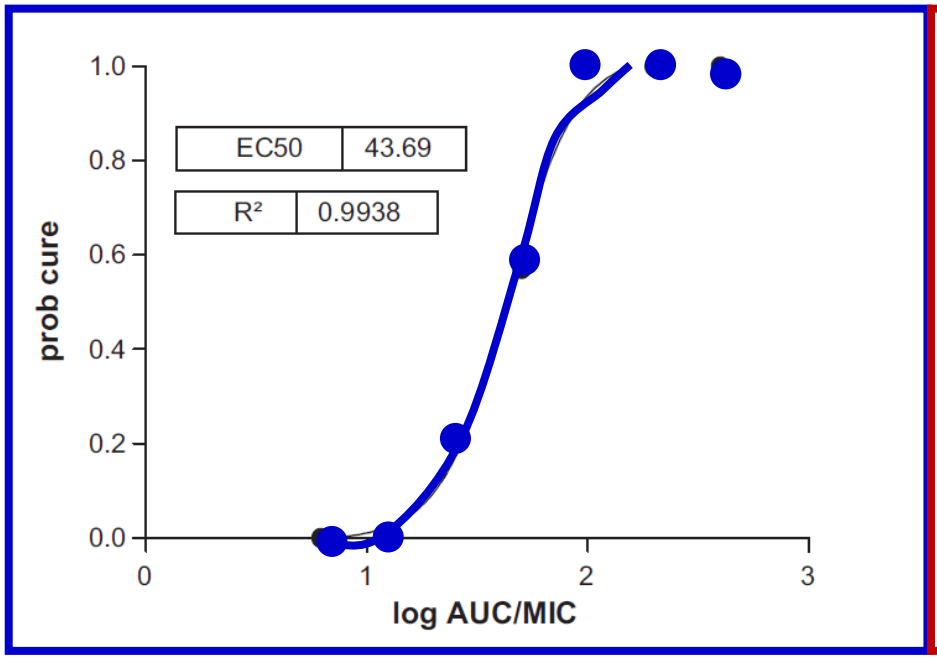
The limit of PK/PD indices

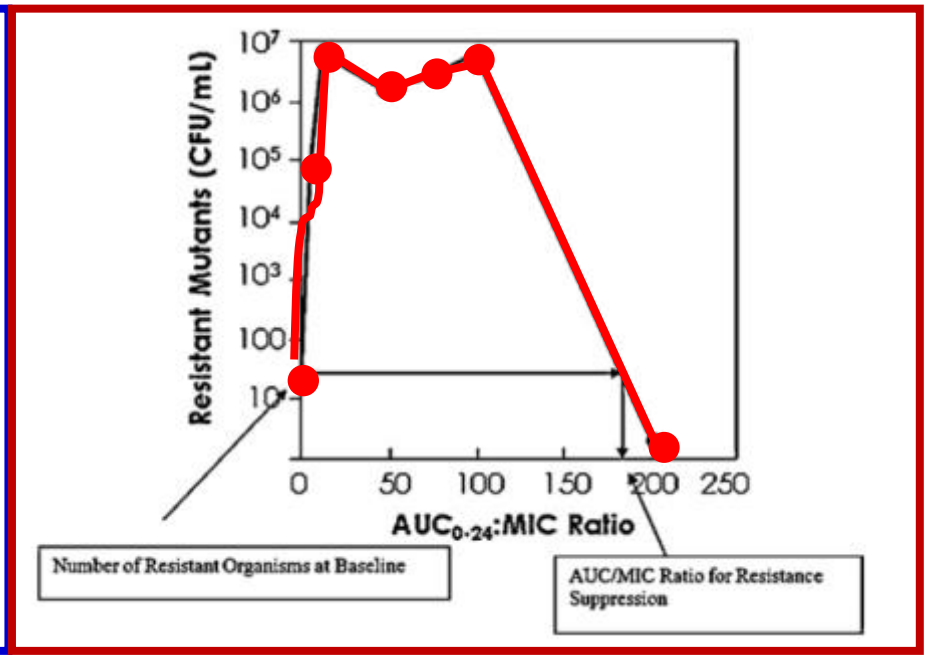
- **it is known that the breakpoint values required for these indices to guarantee an optimal efficacy may also amplify resistant subpopulations.**

Limits of the PK/PD indices

- the use of the PK/PD indices have several drawbacks.
- most often is restricted to a single 24-hour observation time point,
- 24 hours is generally a relatively short period to study the adaptation of the bacteria to antibiotic drug exposure and selection of resistant bacterial subpopulations.
- Therefore, the PK/PD indices ignore essential parts needed to achieve an optimal antibacterial dosing regimen.

Exposure–response relationships and emergence of resistance





- **For efficacy, the PKPD relationship is sigmoid and monotonic**

For resistance selection, the PK/PD relationship is distinctly non-monotonic and has the shape of an inverted “U”

Conclusions

- PK/PD is a powerful tool allowing to arrive very quickly to a appropriate dosage regimen recommendation
- PK/PD cannot replace confirmatory clinical trials of efficacy
- Classical PK/PD indices as obtained over 24h are not enough to predict resistance