Pharmacology of Anti-Infective Agents in 2005: The Basics and Beyond

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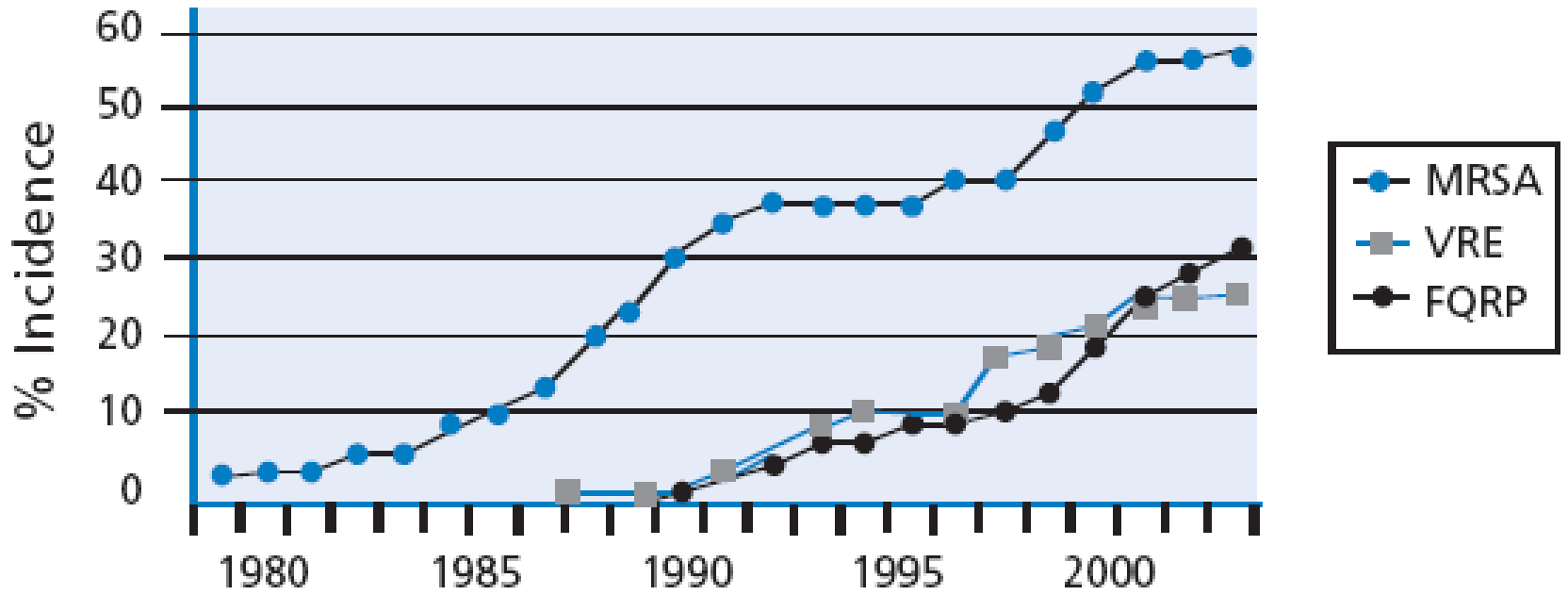
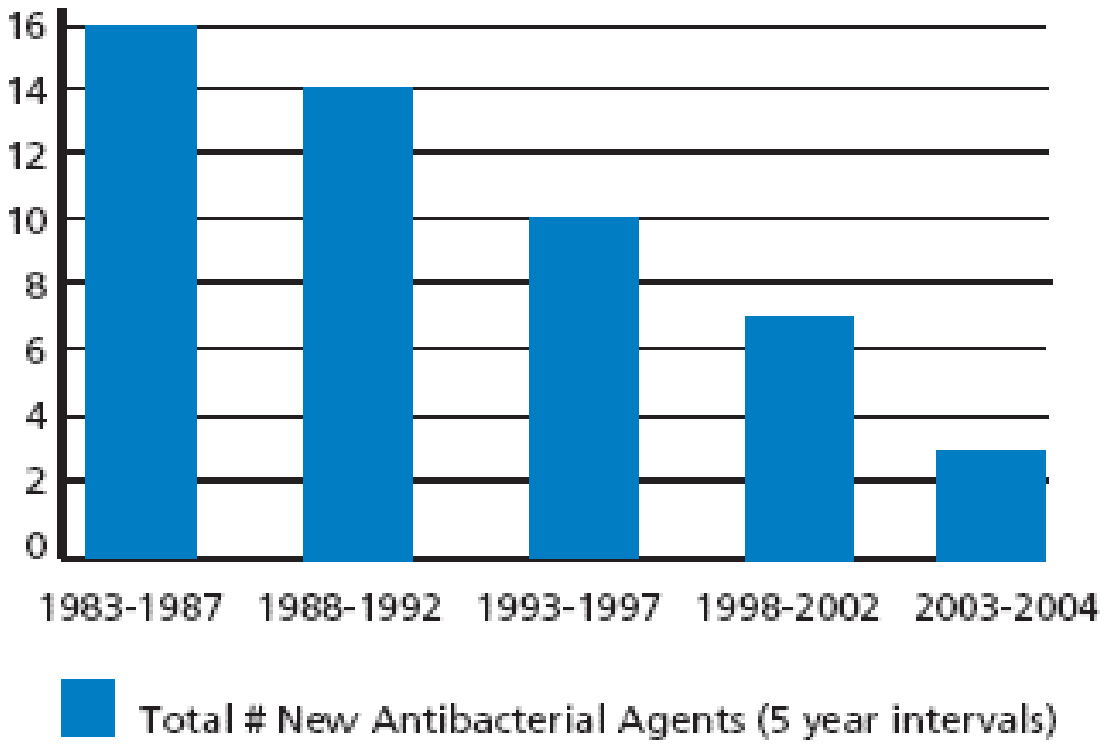
Resistance Development



Source: Centers for Disease Control and Prevention

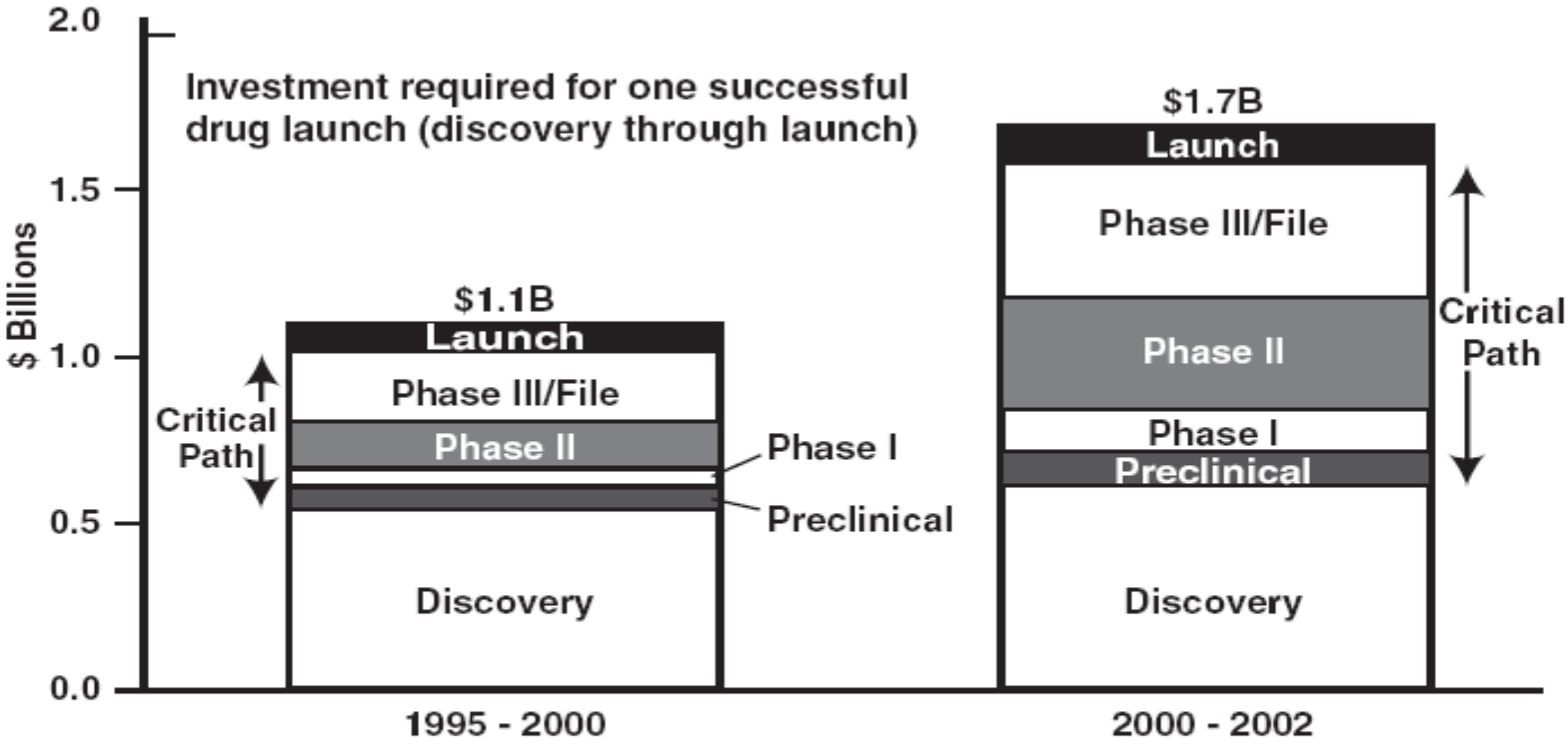
This chart shows the increase in rates of resistance for three bacteria that are of concern to public health officials: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and fluoroquinolone-resistant *Pseudomonas aeruginosa* (FQRP). These data were collected from hospital intensive care units that participate in the National Nosocomial Infections Surveillance System, a component of the CDC.

Approved Antibacterial Agents
1983-2004



Source: Spellberg et al., *Clinical Infectious Diseases*, May 1, 2004 (modified)

Figure 3: Investment Escalation per Successful Compound

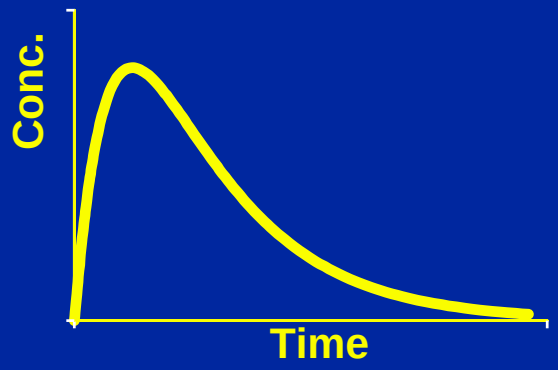


SOURCE: Windhover's In Vivo: The Business & Medicine Report, Bain drug economics model, 2003

The figure shows one estimate of the total investment required to "launch" (i.e., market) a successful drug in two time periods. Most of the recent cost increases are within the "critical path" development phase, between discovery and launch.

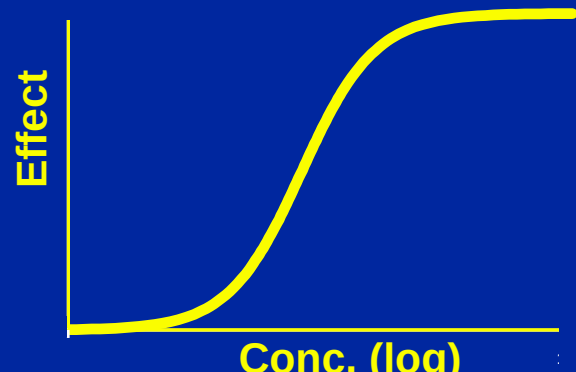
Pharmacokinetics

conc. vs time



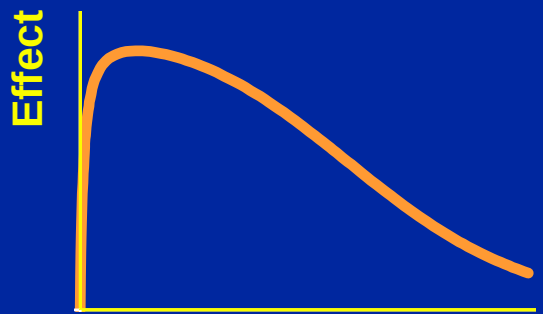
Pharmacodynamics

conc. vs effect

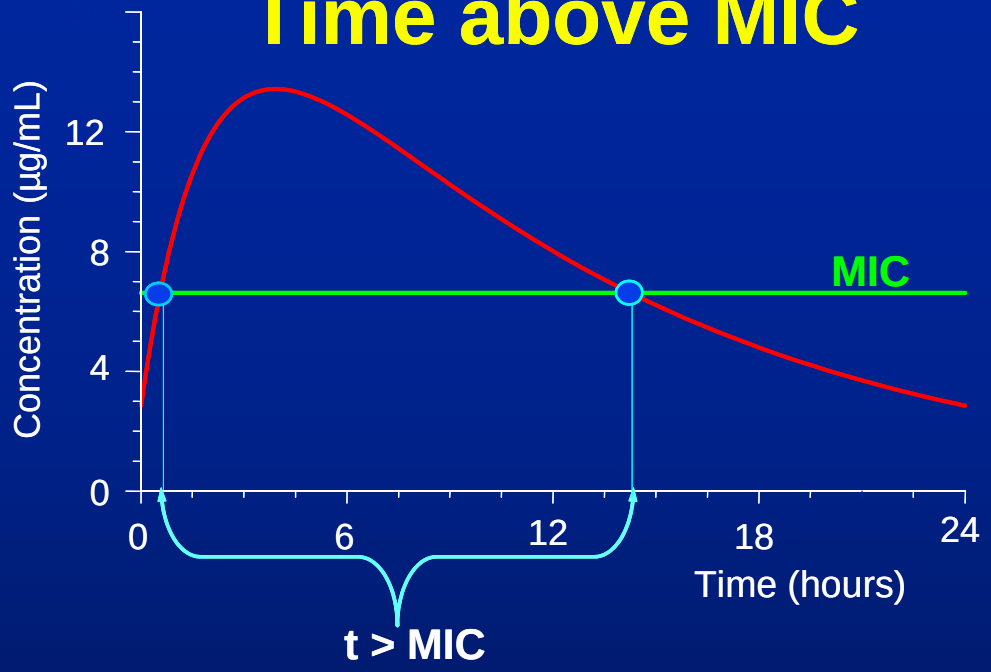


PK/PD

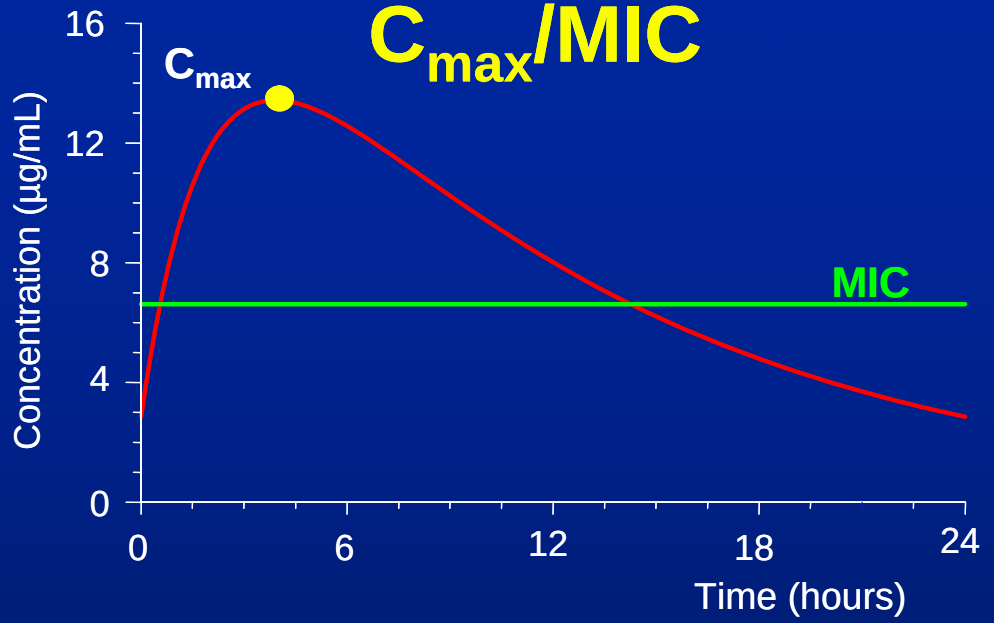
effect vs time



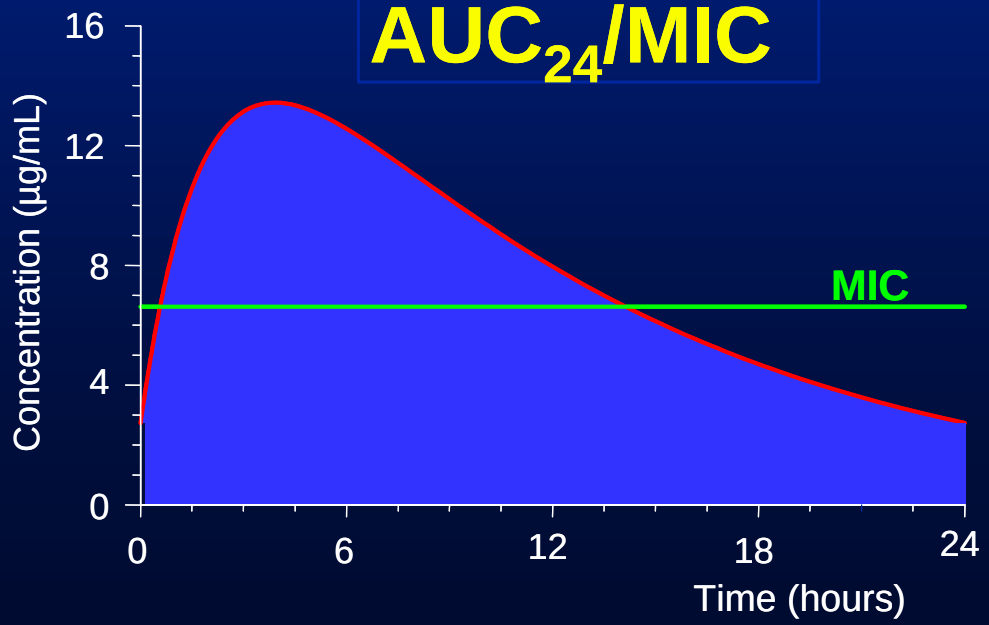
Time above MIC



C_{max}/MIC



AUC_{24}/MIC



PK

PD

Serum

MIC

Pharmacokinetics

Problems:

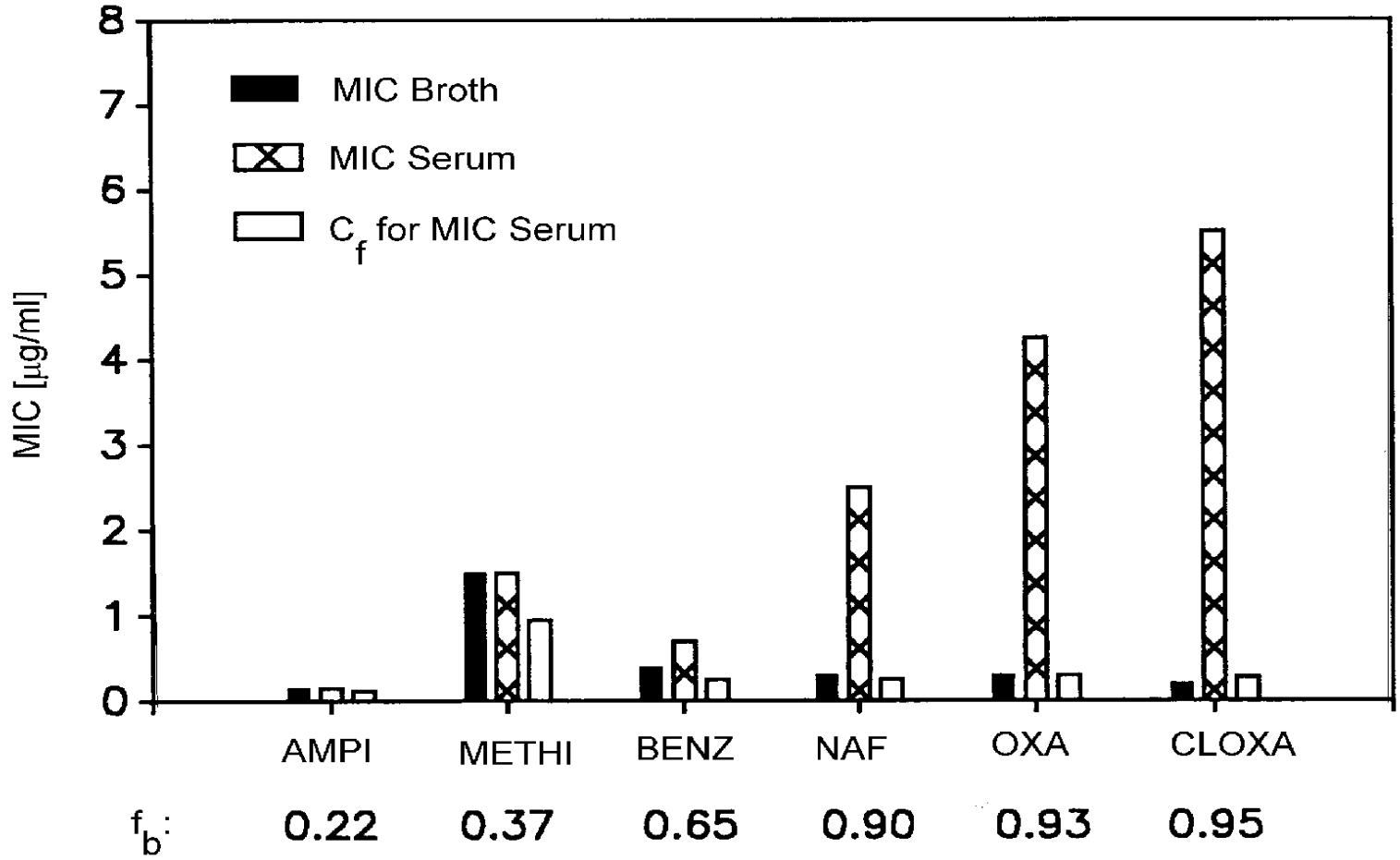
- **Protein Binding**
- **Tissue Distribution**

Protein Binding of Cephalosporines

Cefonicid	98
Ceftriaxone	90-95
Cefoperazone	89-93
Cefazolin	89
Cefotetan	85
Ceforanide	80-82
Cefamandole	74
Cefoxitin	73
Cephalothin	71
Cefmetazole	70
Cefixime	65
Cephapirin	62
Moxalactam	53-67
Cefprozil	40
Cefotaxime	36
Cefpodoxime	25

Effect of Protein Binding on Antimicrobial Activity

MICs of Staphylococcus aureus (Data from Kunin et al. (1973))

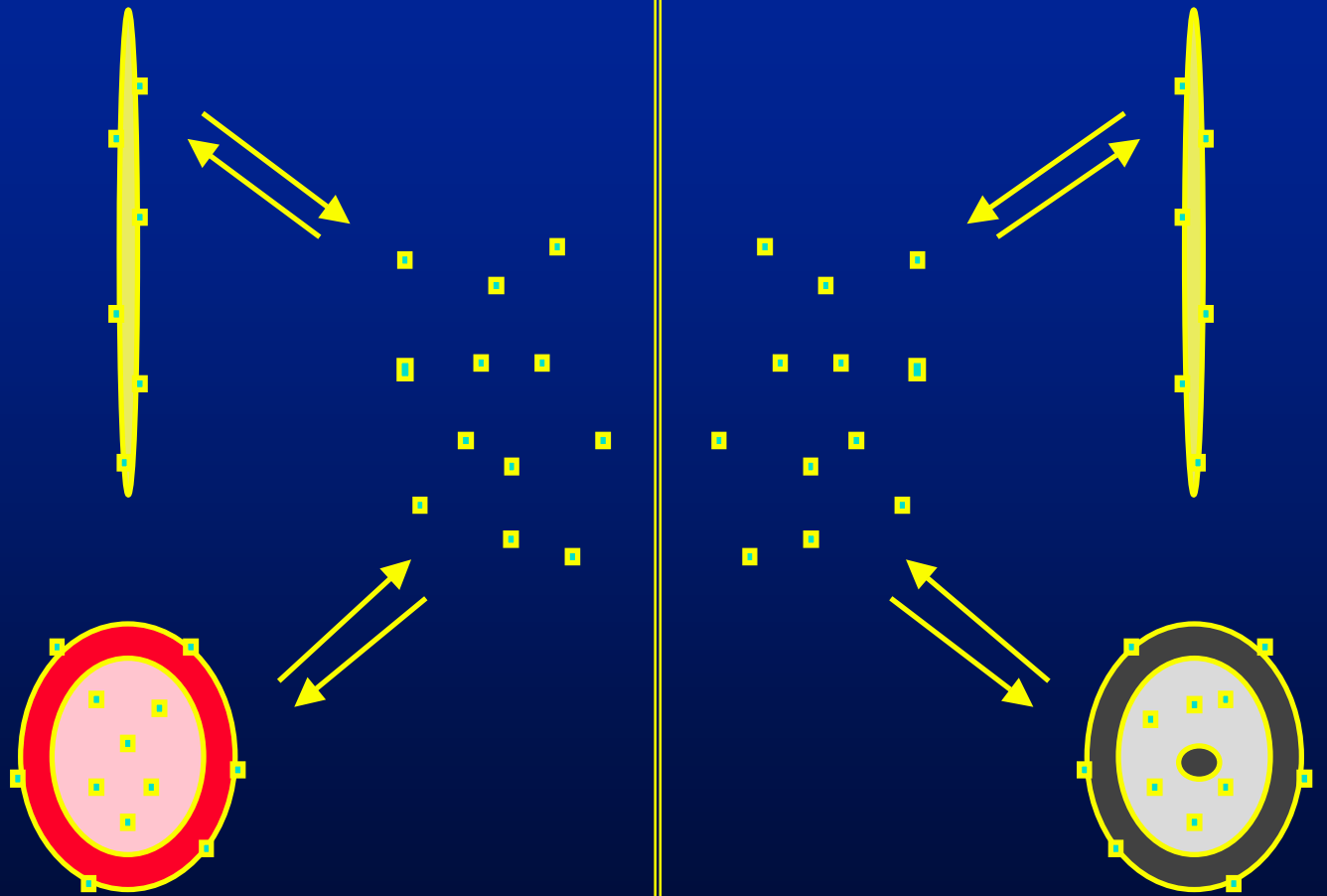


vascular space

extravascular space

plasma protein binding

binding to extracellular biological material



blood cell binding,

diffusion into blood cells,

binding to intracellular biological material

tissue cell binding,

diffusion into tissue cells,

binding to intracellular biological material

Tissue Concentrations

Tissue can be looked at as an aqueous dispersed system of biological material. It is the concentration in the water of the tissue that is responsible for pharmacological activity.

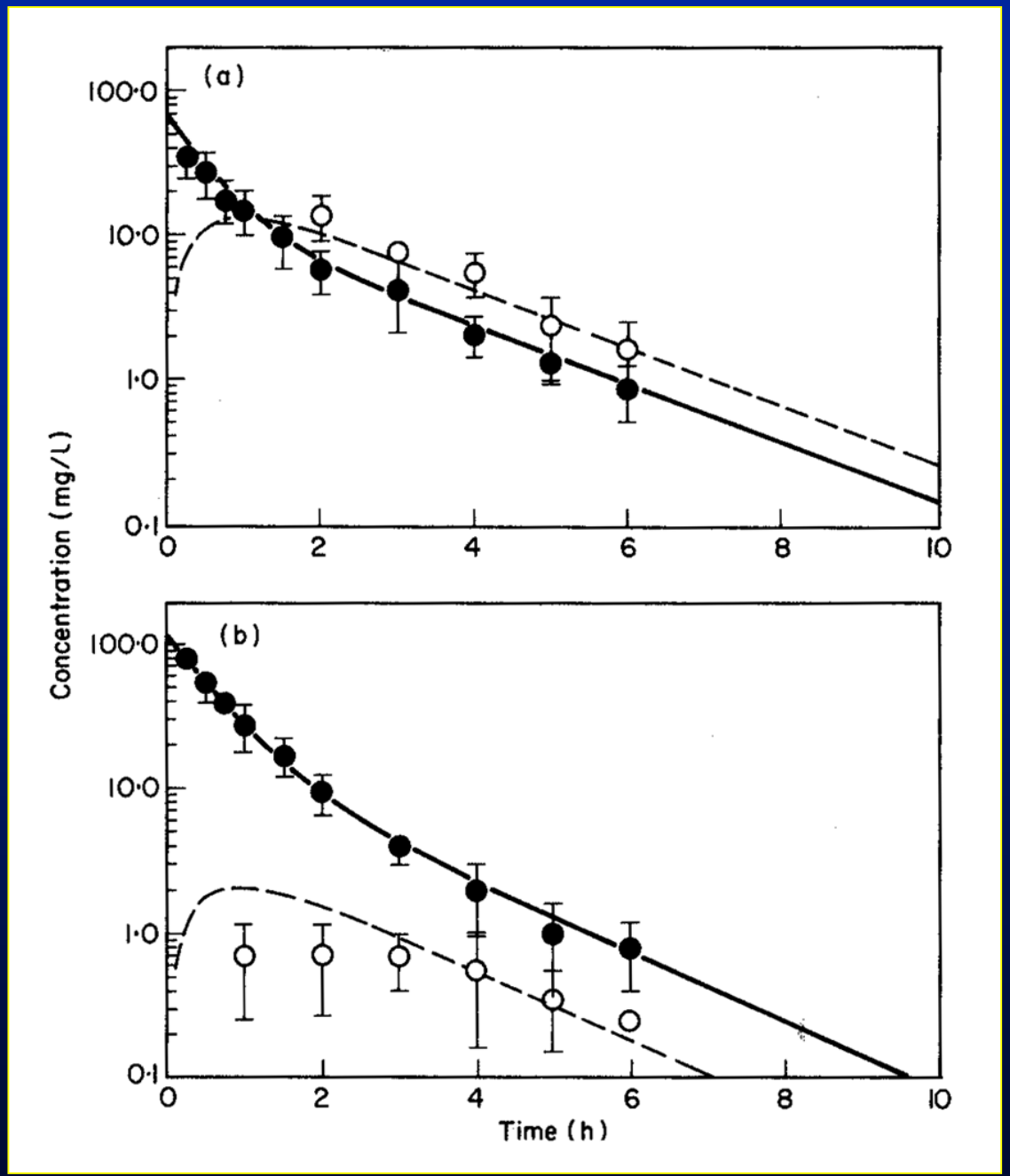
Total tissue concentrations need to be interpreted with great care since they reflect hybrid values of total amount of drug (free + bound) in a given tissue

‘Tissue-partition-coefficients’ are not appropriate since they imply homogenous tissue distribution

The free (unbound) concentration of the drug at the receptor site should be used in PK/PD correlations to make prediction for pharmacological activity

Blister Fluid

- Blister fluid is a ‘homogenous tissue fluid’
- Protein binding in blister fluid needs to be considered

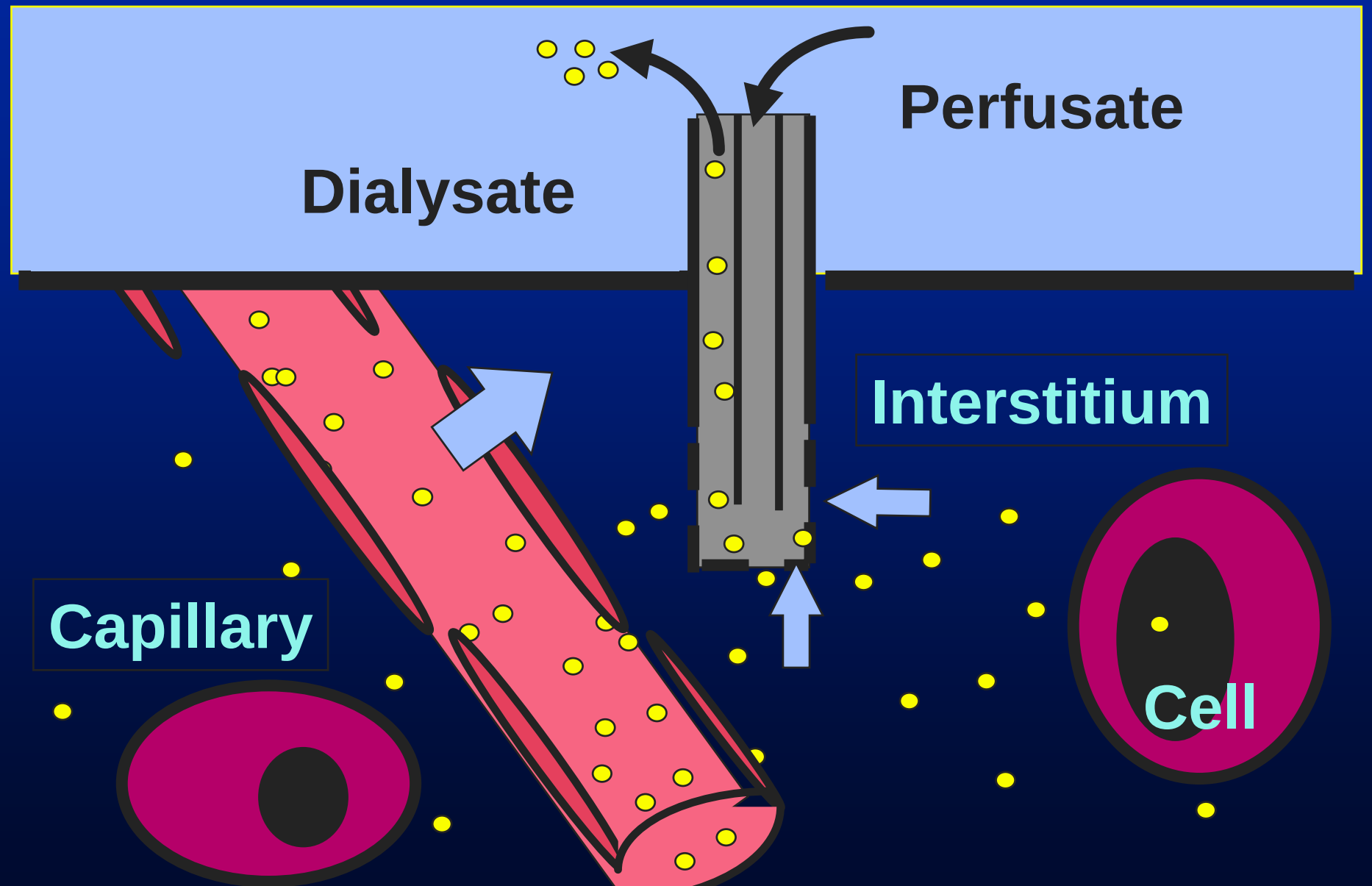


Ampicillin

Cloxacillin

● Serum
❍ Free blister fluid

Microdialysis

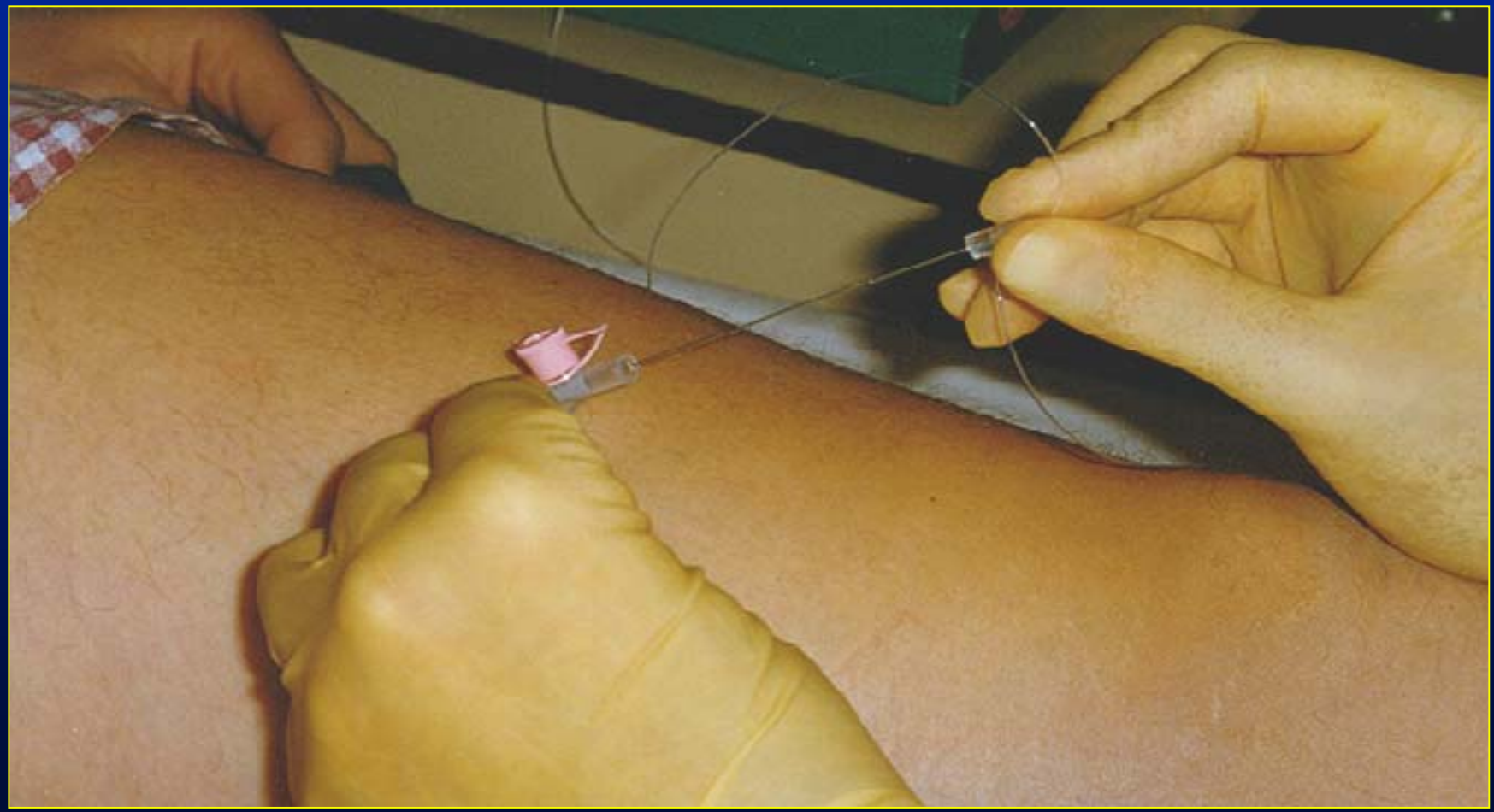


Clinical study
Cefpodoxime and Cefixime

- To compare the soft tissue distribution of these two antibiotics after 400mg oral dose in healthy male volunteers by microdialysis

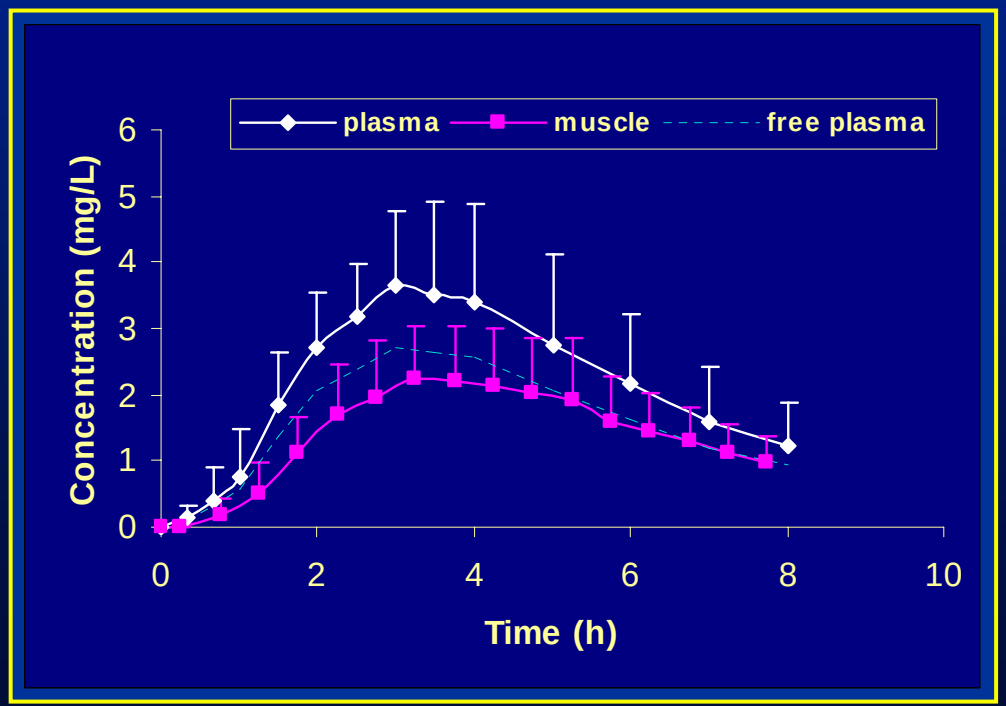
- Two way cross-over, single oral dose study

Microdialysis

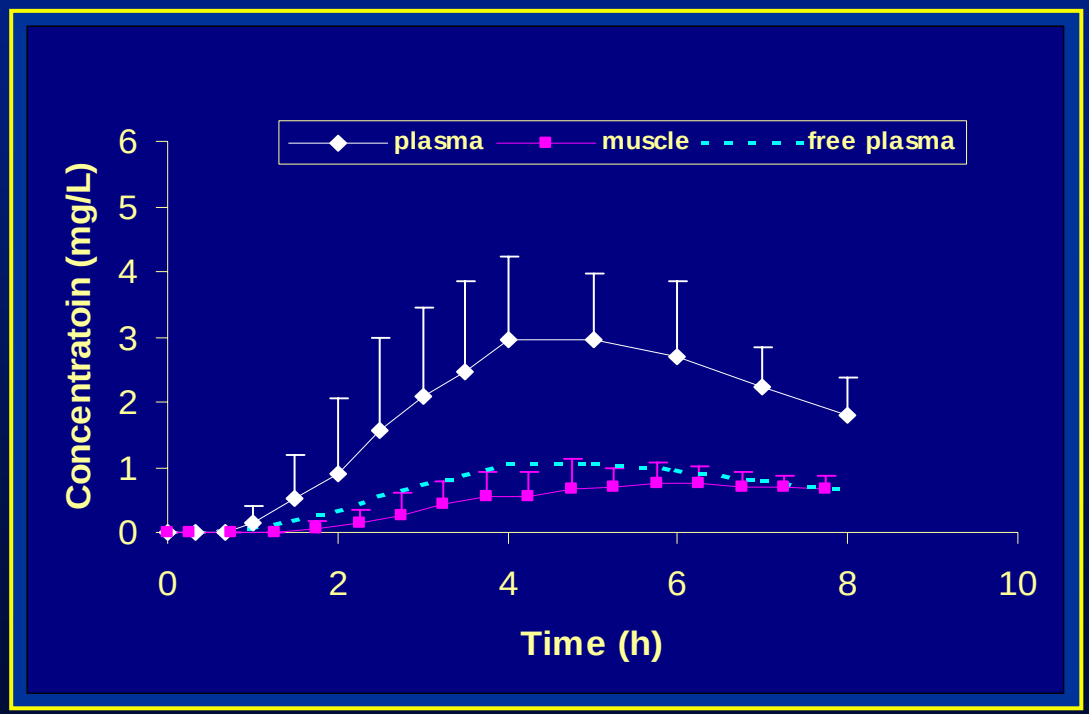


Clinical Microdialysis

Cefpodoxime
400 mg po



Cefixime
400 mg po



Liu & Derendorf, JAC 50, 19 (2002)

Pharmacokinetics

	Cefpodoxime	Cefixime
AUC_P [mg*h/L]	22.4 (8.7)	25.7 (8.4)
AUC_T [mg*h/L]	15.4 (5.2)	7.4 (2.1)
$C_{max,\,P}$ [mg/L]	3.9 (1.2)	3.4 (1.1)
$C_{max,T}$ [mg/L]	2.1 (1.0)	0.9 (0.3)

Conclusion

Microdialysis has opened the door to get better information about the drug concentrations at the site of action.

This, in combination with appropriate PK/PD-models, will allow for better dosing decisions than traditional approaches based on blood concentrations and MIC.

Pharmacodynamics

Problems:

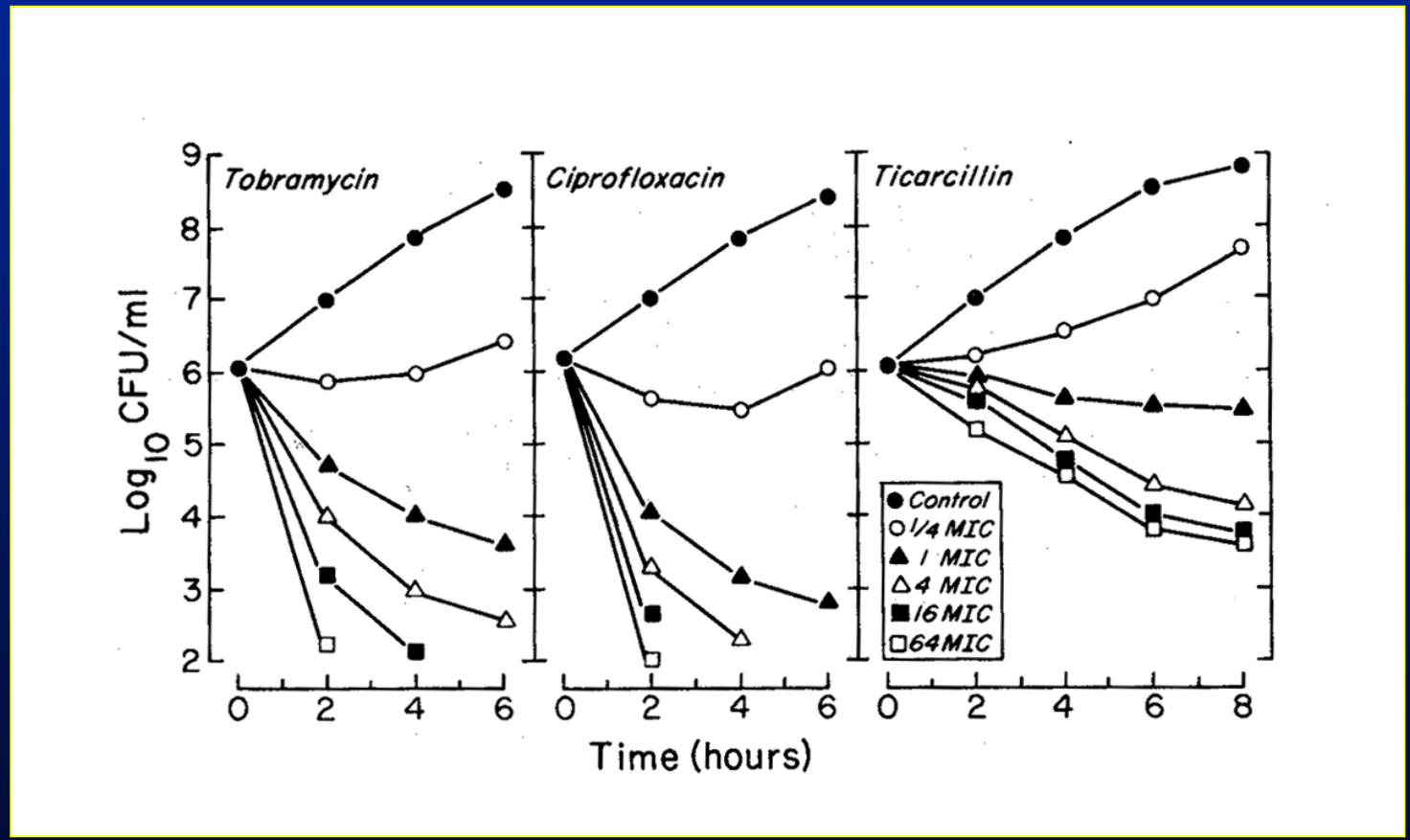
- **MIC is imprecise**
- **MIC is monodimensional**
- **MIC is used as a threshold**
- **When MIC does not explain the data, patches are used (post-antibiotic effect, sub-MIC effect)**

MIC
The Current Paradigm

MIC is poison for the mind.

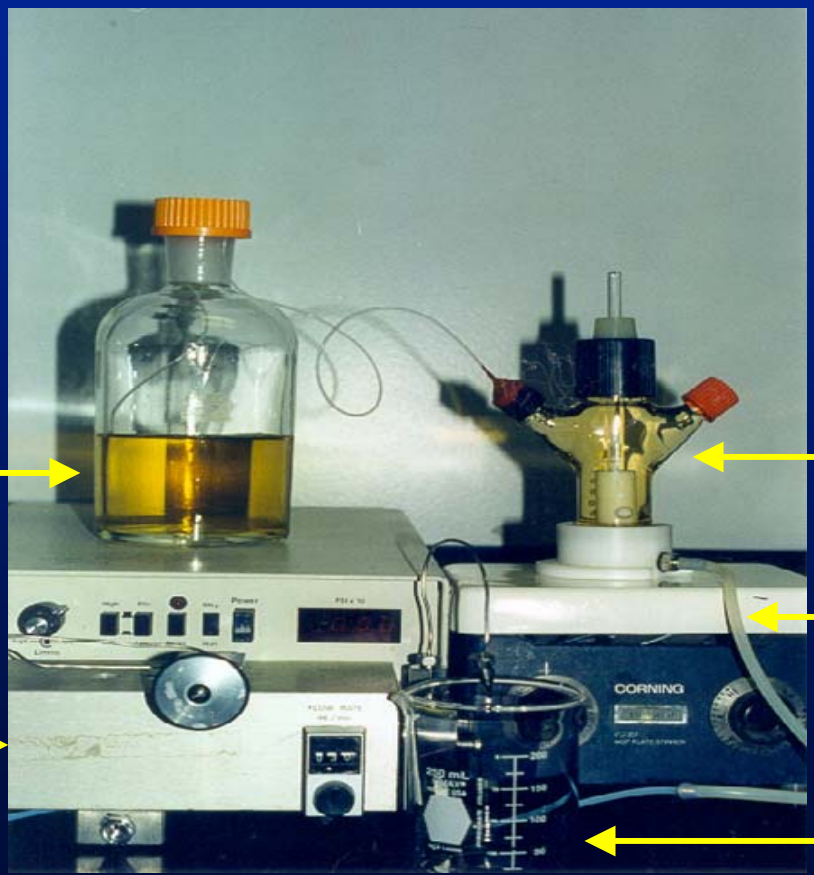
H. Mattie (1994), after a long after-dinner discussion

Concentration-dependent vs. Time-dependent



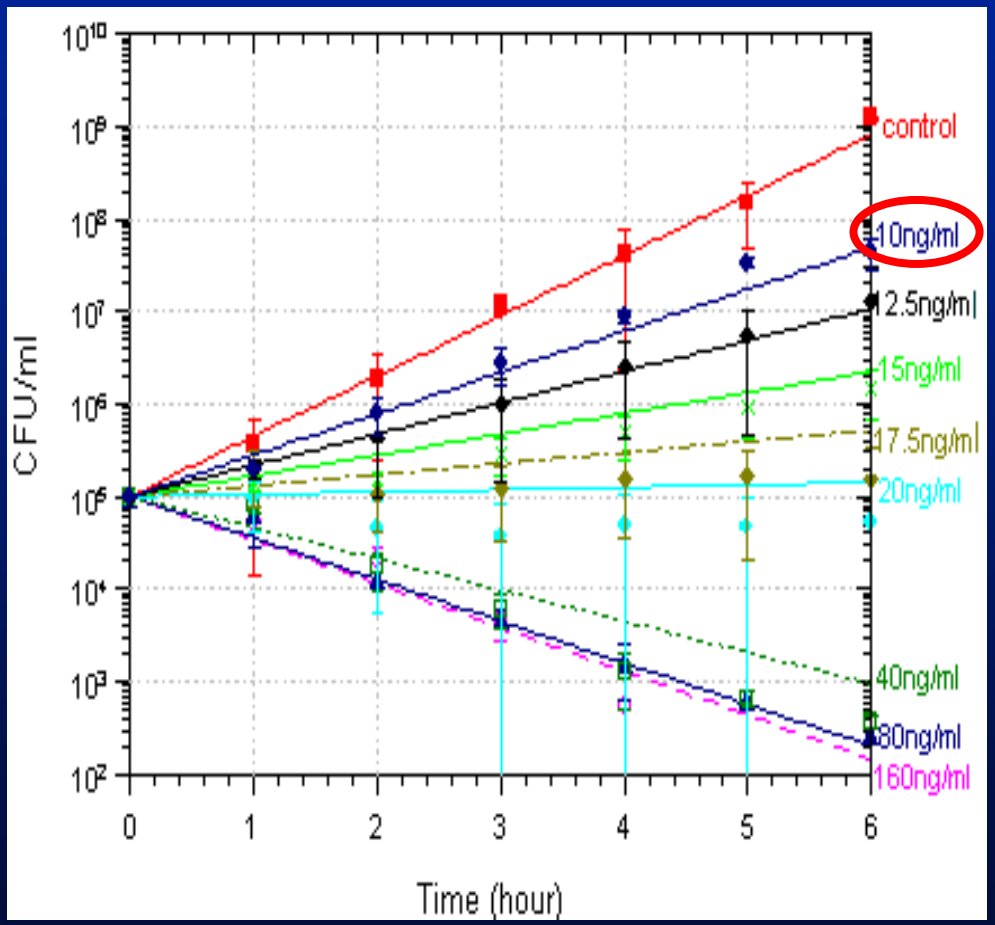
Craig 1991

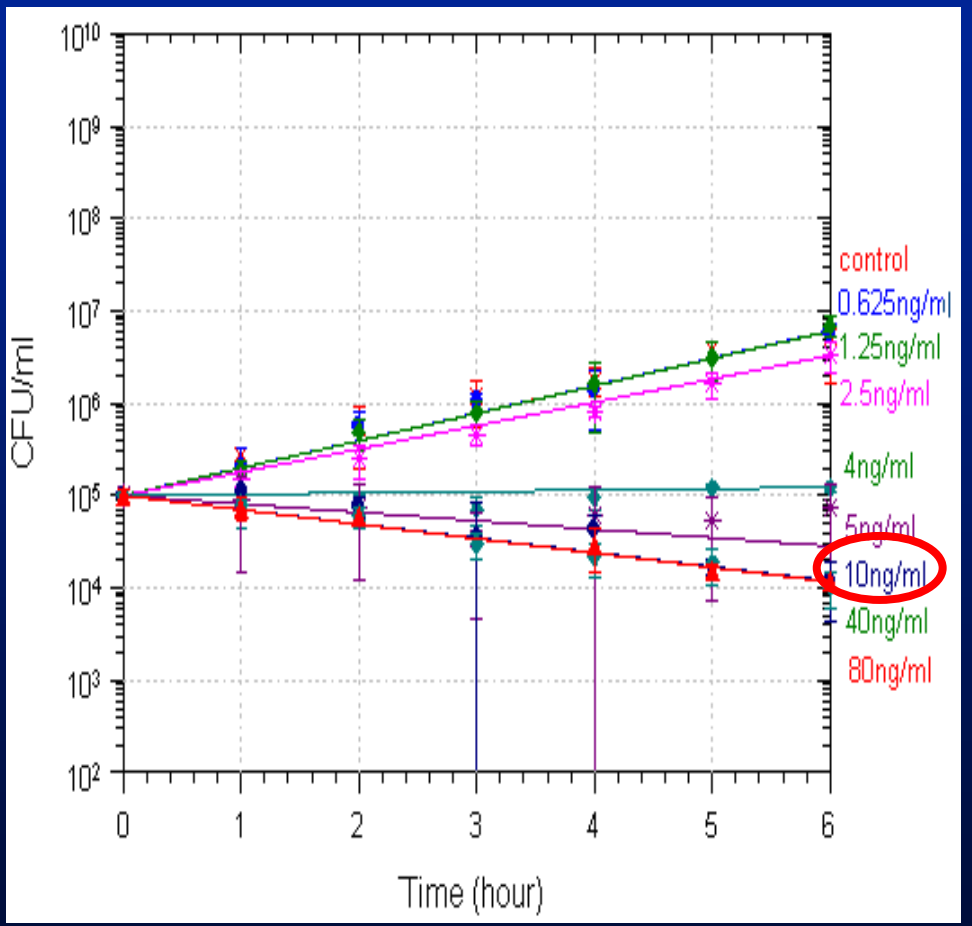
Kill Curves



Auto-dilution system

Kill Curves of Ceftriaxone

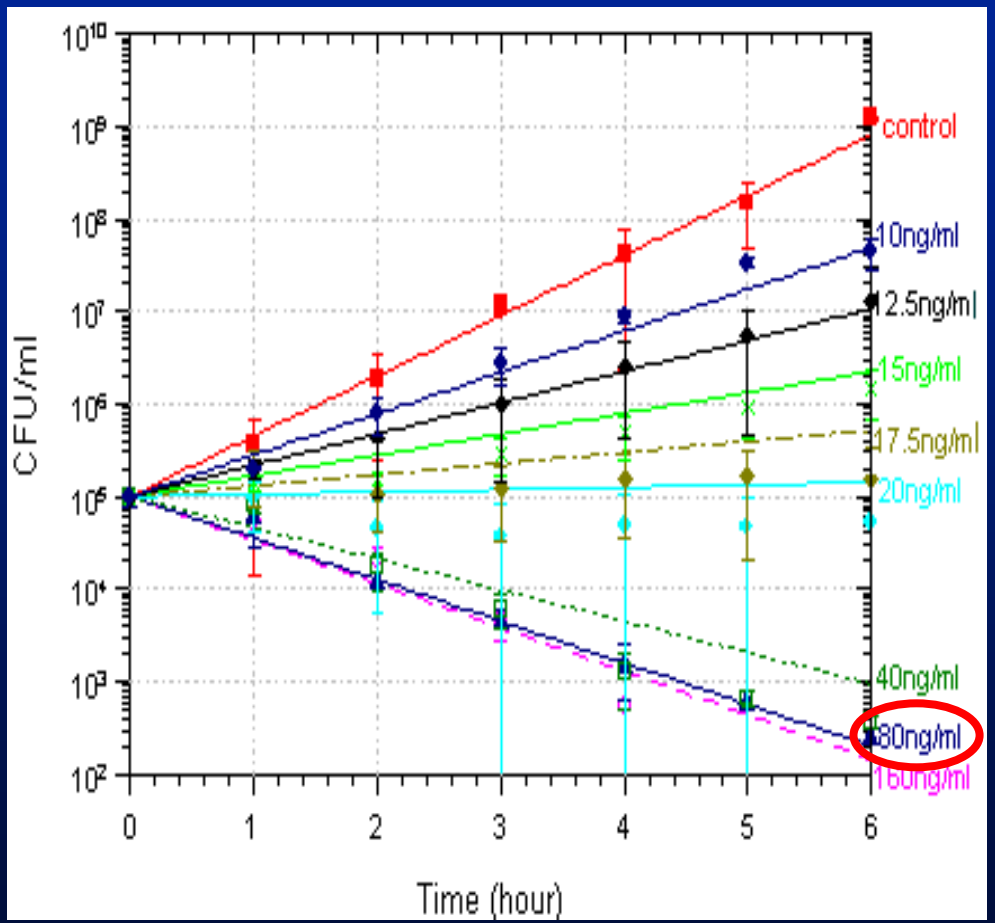


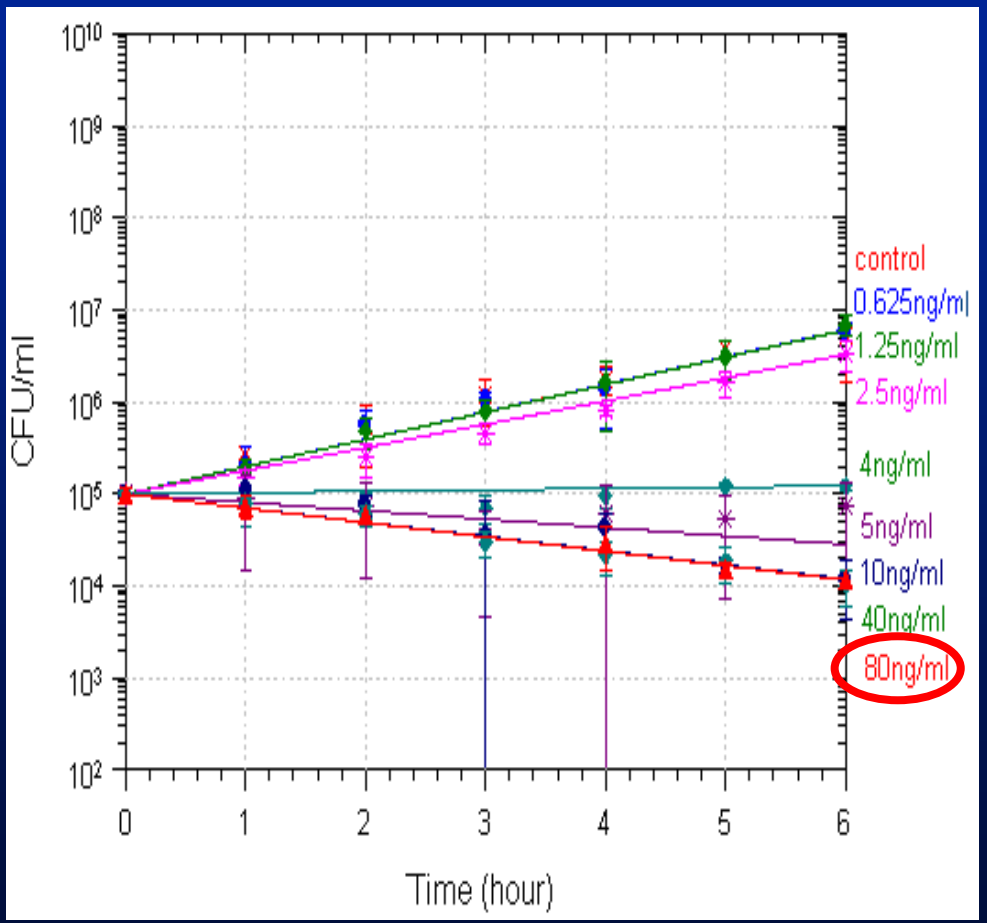


***S. pneumoniae* ATCC6303**
MIC: 20 ng/mL

***H. influenzae* ATCC10211**
MIC: 5 ng/mL

Kill Curves of Ceftriaxone





***S. pneumoniae* ATCC6303**
MIC: 20 ng/mL

***H. influenzae* ATCC10211**
MIC: 5 ng/mL

PK-PD Model

$$\frac{dN}{dt} = \left(k - \frac{k_{\max} \cdot C_f}{EC_{50} + C_f} \right) \cdot N$$

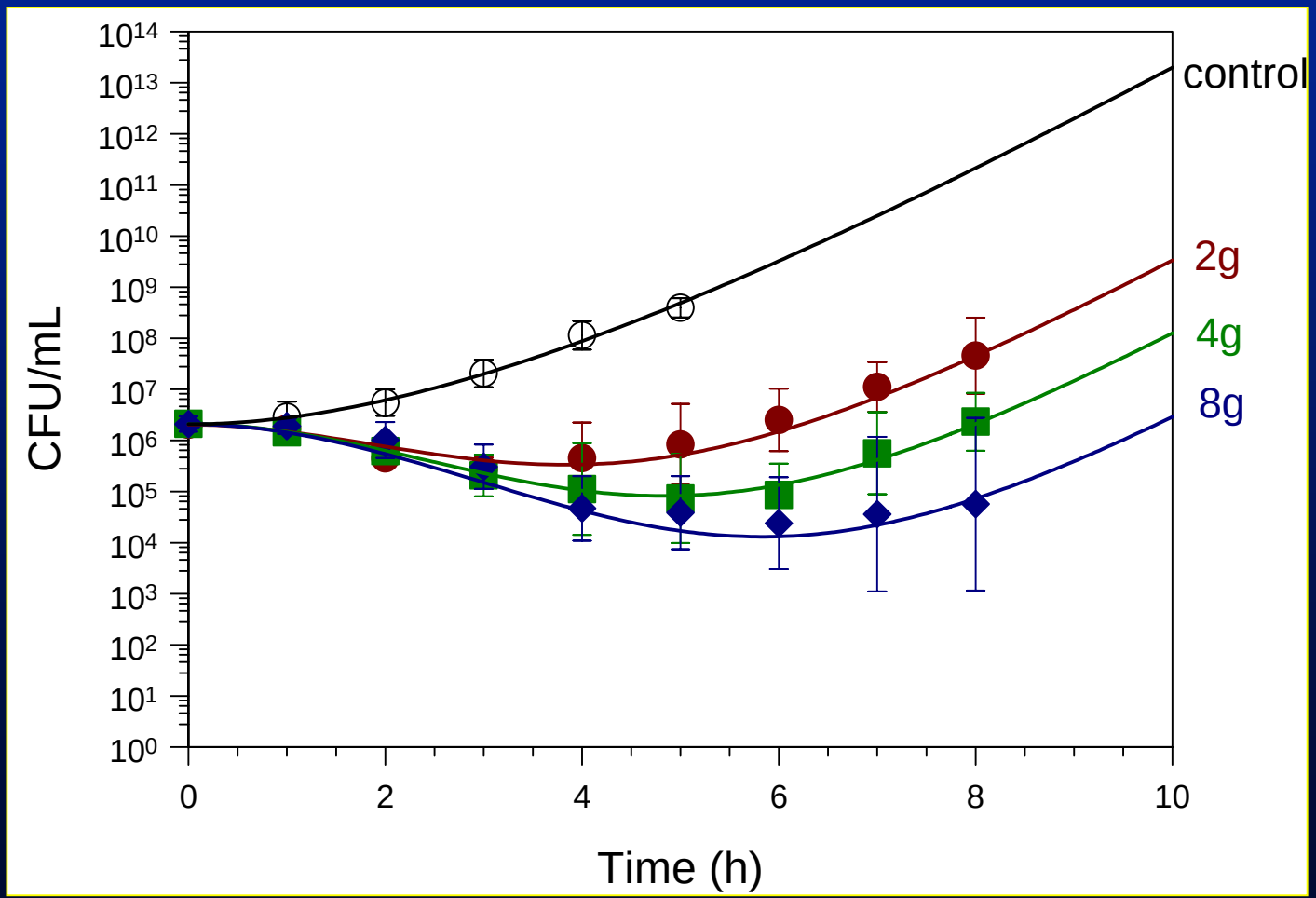
Maximum Growth Rate Constant **k**

Maximum Killing Rate Constant **$k\text{-}k_{max}$**

Initially, bacteria are in log growth phase

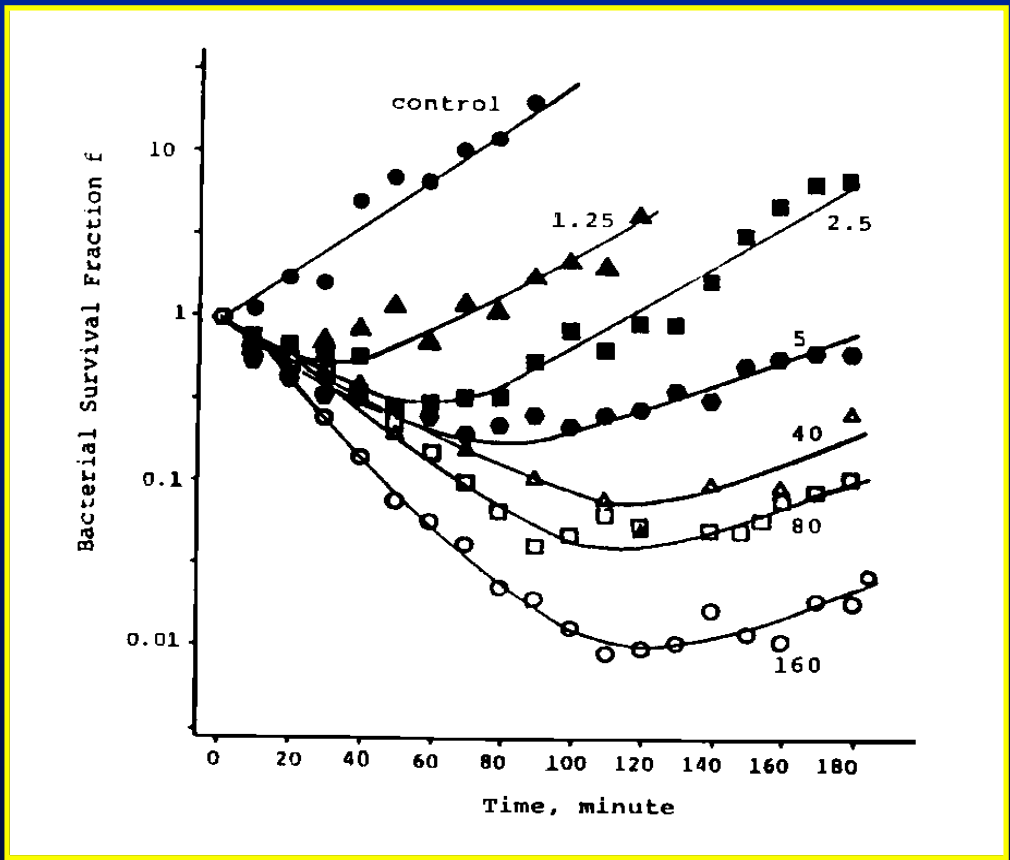
Single Dose

Piperacillin vs. E. coli



PK-PD Model

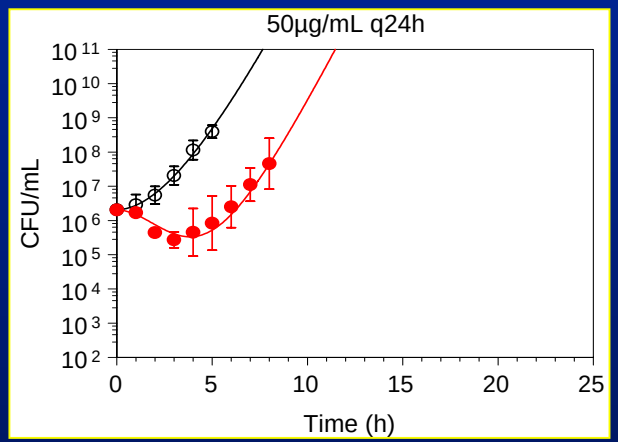
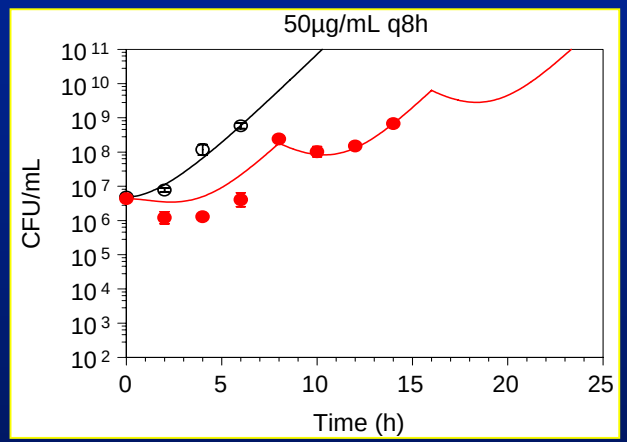
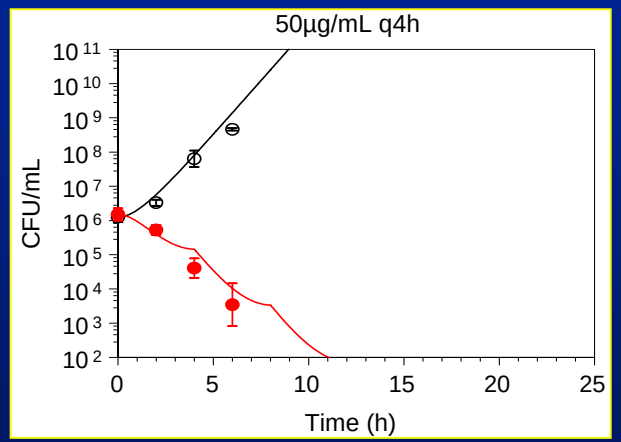
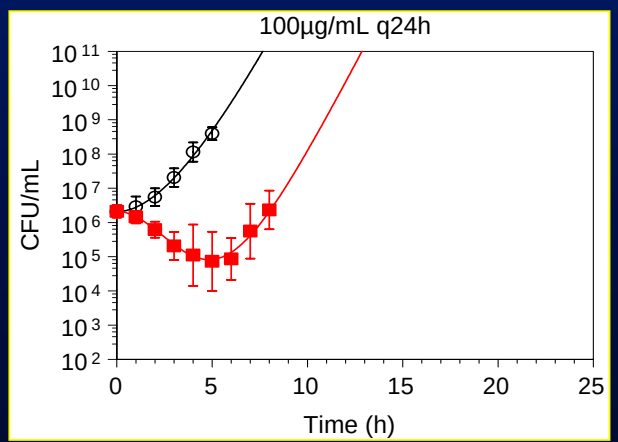
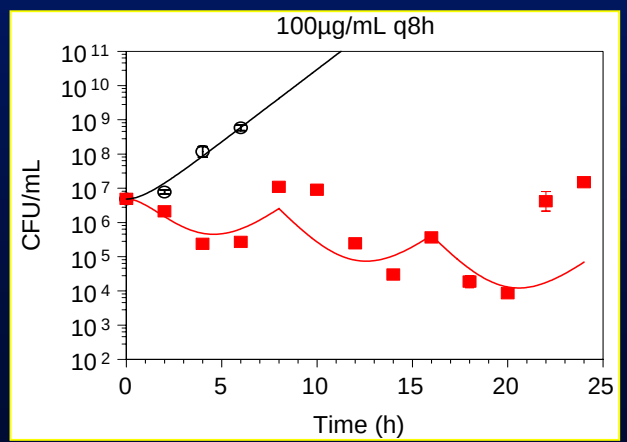
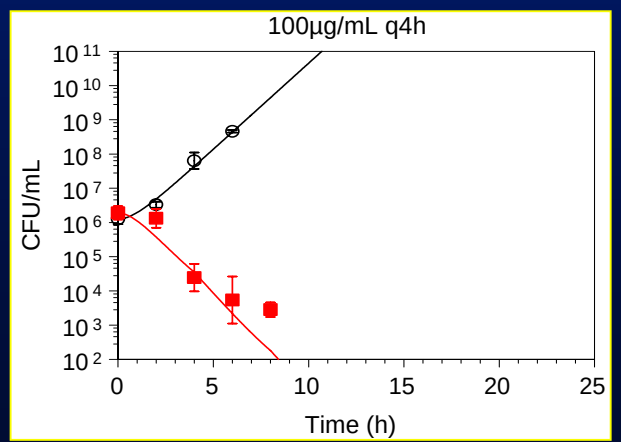
In animals



Bacterial survival fraction of P. aeruginosa in a neutropenic mouse model at different doses (mg/kg) of piperacillin (Zhi et al., 1988)

Dosing Interval

Piperacillin (2g and 4g) vs. E. coli

q24h	q8h	q4h
		
		

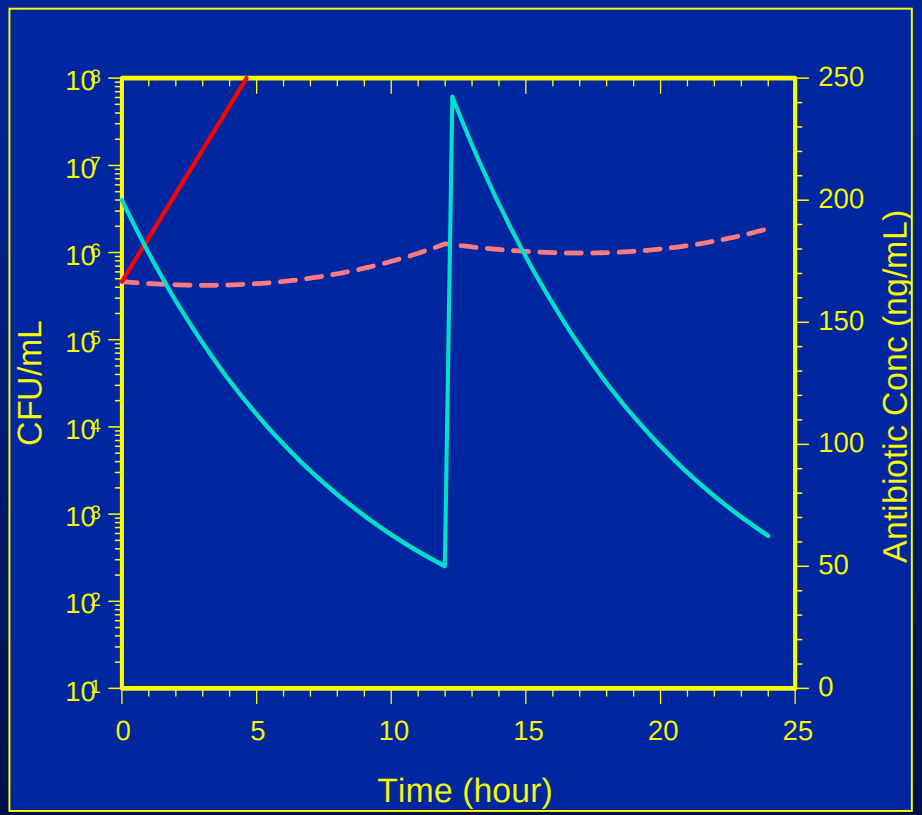
Example 1

- Same PK
- Same MIC
- Same t>MIC
- Same AUC/MIC
- Same C_{max}/MIC
- Same k (Growth Rate)

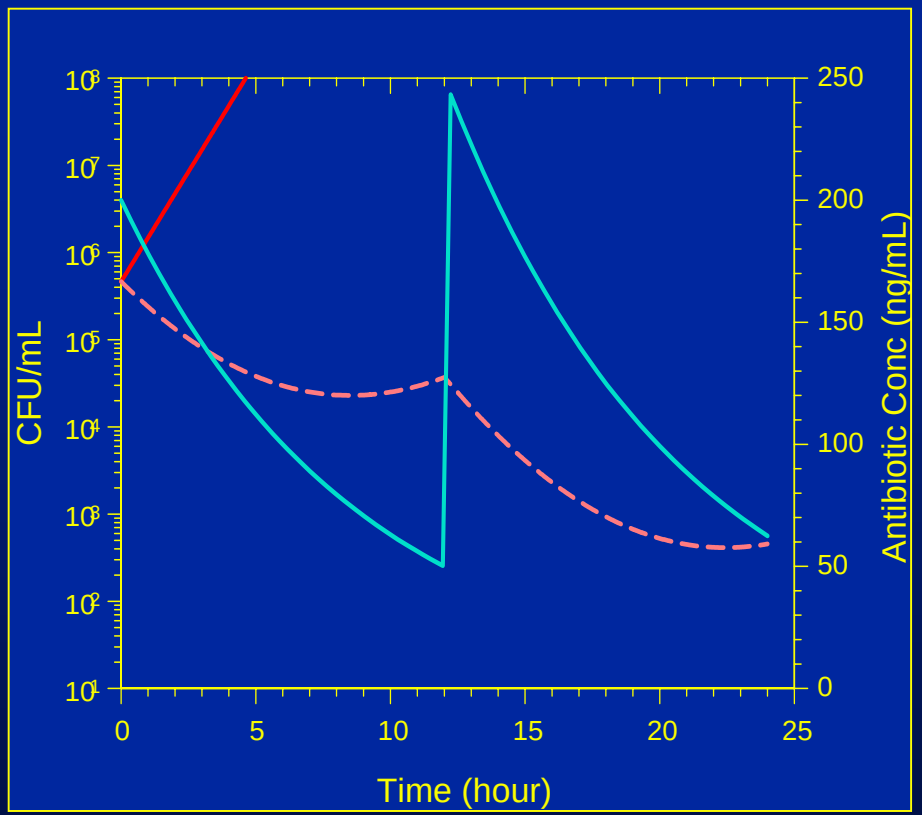
- Different EC_{50} (Sensitivity)
- Different k_{max} (Maximum Kill Rate)

PK-PD modeling based on Kill Curves

Condition 1



Condition 2



Control (CFU/mL)
Treated (CFU/mL)
Antibiotic concentration

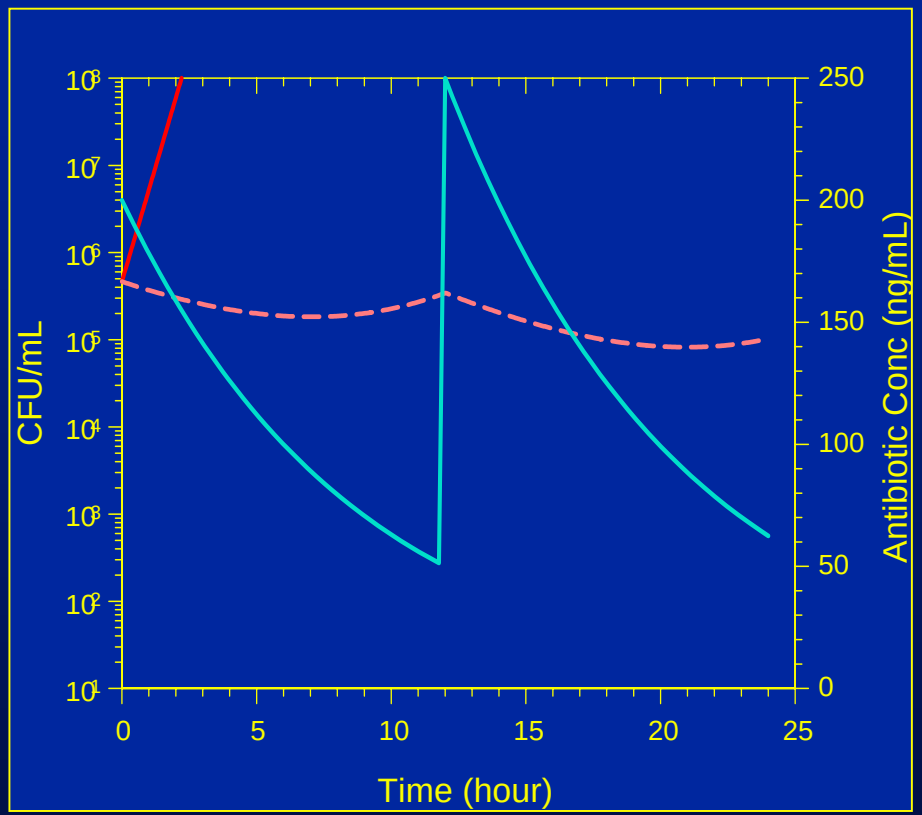
Example 2

- Same PK
- Same MIC
- Same t>MIC
- Same AUC/MIC
- Same C_{max}/MIC
- Same k_{max} (Maximum Kill Rate)

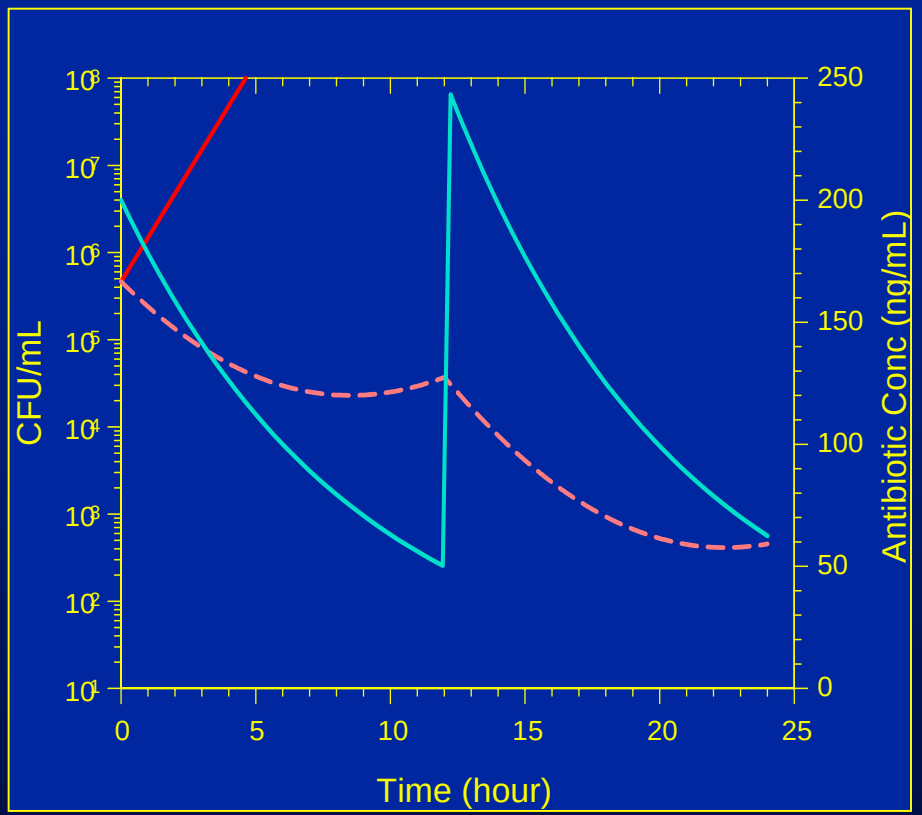
- Different EC_{50} (Sensitivity)
- Different k (Growth Rate)

PK-PD modeling based on Kill Curves

Condition 1



Condition 2

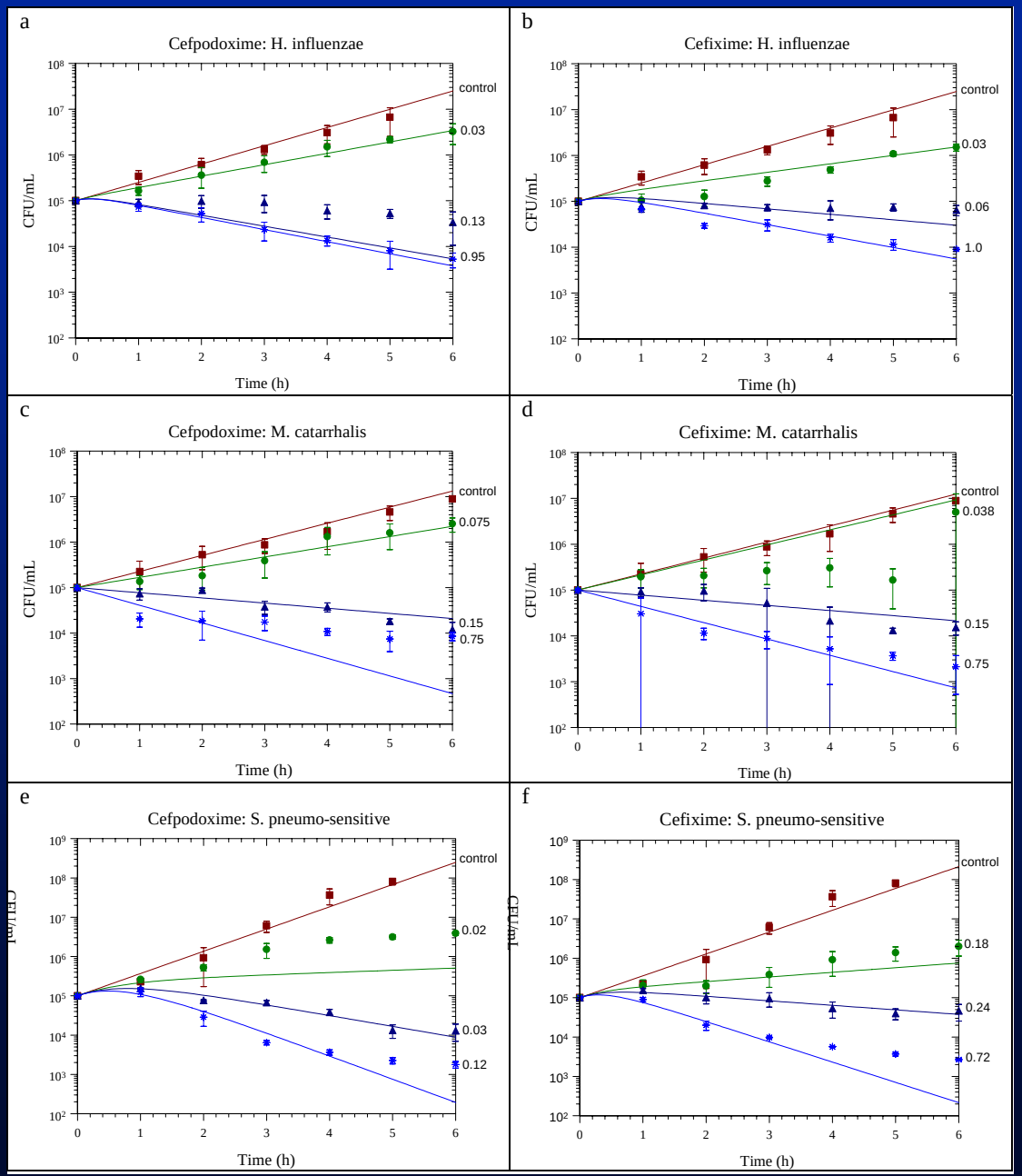


Control (CFU/mL)
Treated (CFU/mL)
Antibiotic concentration

	MIC (mg/L) Cefpodoxime	MIC (mg/L) Cefixime
Haemophilus influenzae	0.06-0.12	0.06
Moraxella catarrhalis	0.12-0.25	0.12
Streptococcus pneumoniae (penicillin-sensitive)	0.03	0.25
Streptococcus pneumoniae (penicillin-intermediate)	0.12	1.0

Cefpodoxime

Cefixime

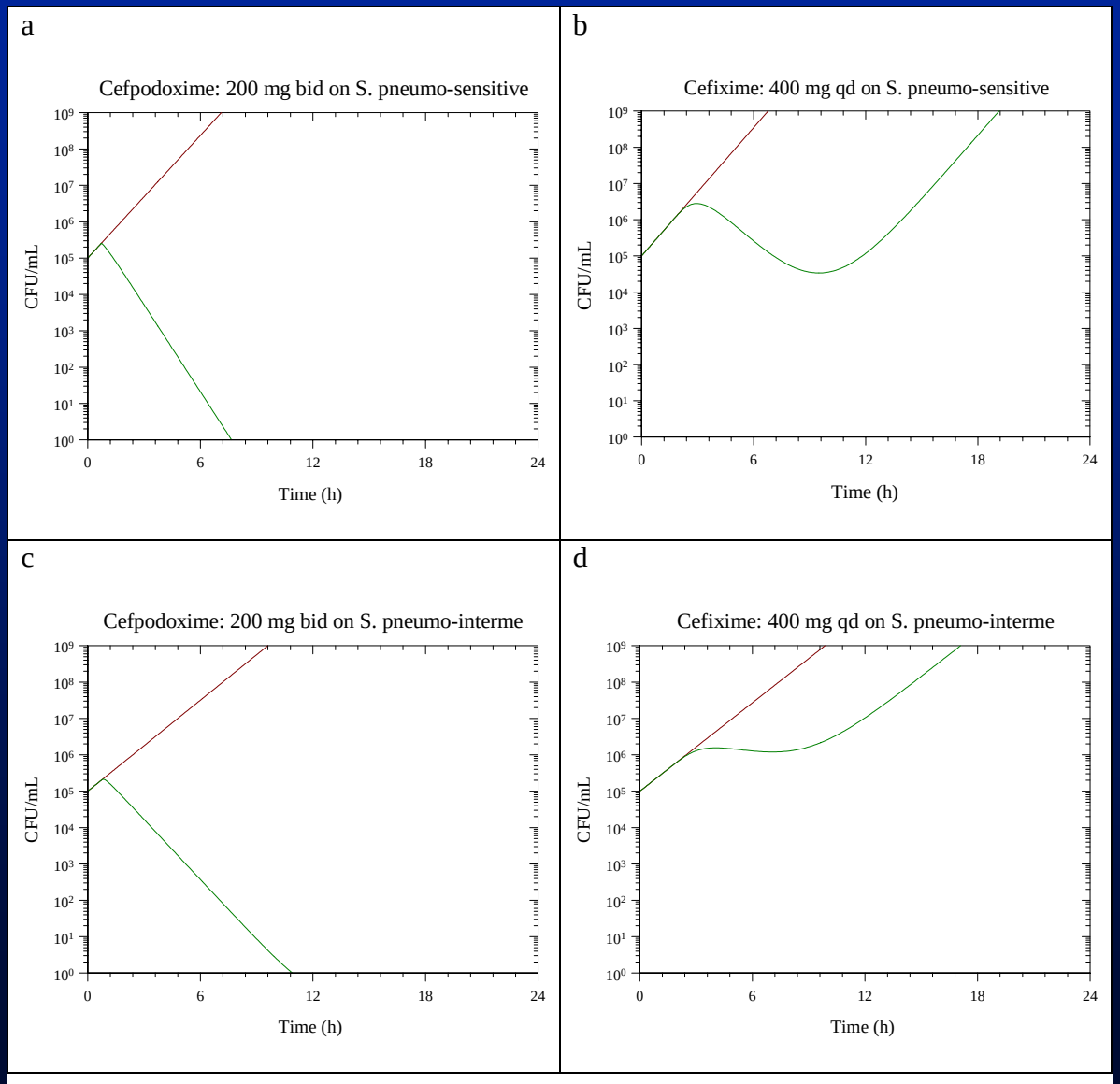


H. influenzae

M. catarrhalis

S. pneumococci

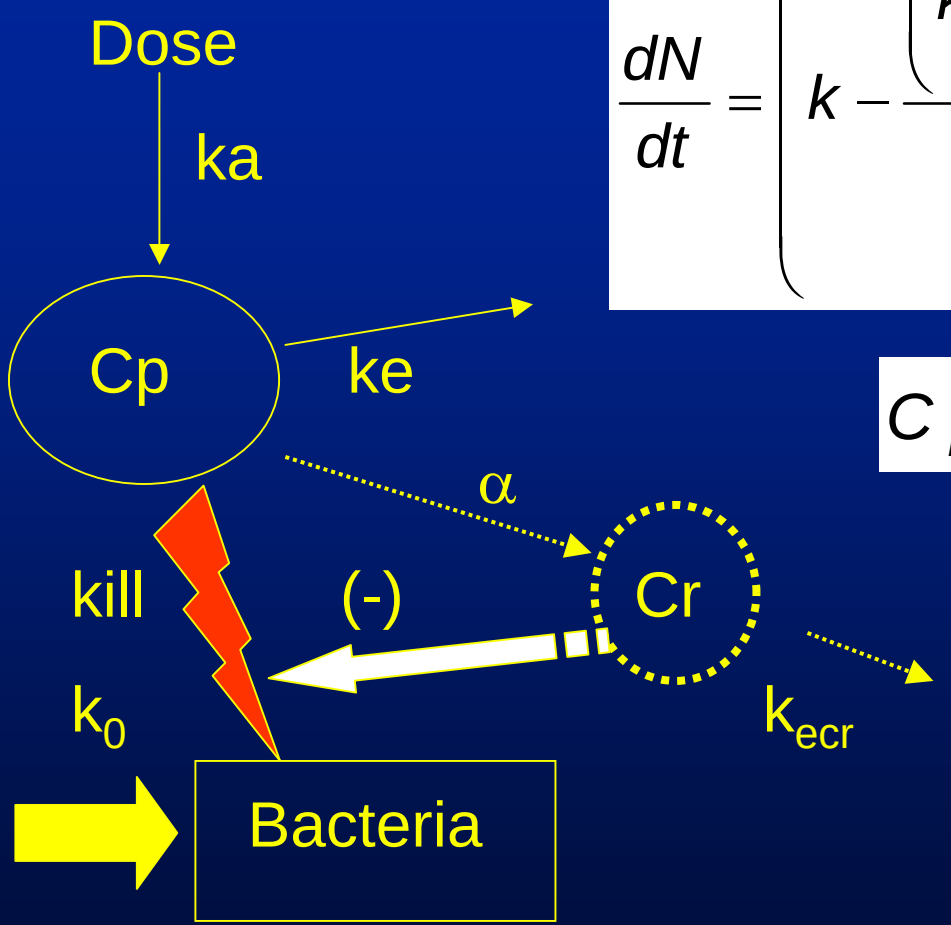
200 mg Cefpodoxime bid vs. 400 mg Cefixime qd



S. pneumococci-penS

S. pneumococci-penI

Modified E_{max} Model:



$$\frac{dN}{dt} = \left(k - \frac{\left(k_1 \cdot \left(1 - \frac{C_r}{IC_{50} + C_r} \right) + k_2 \right) \cdot C}{EC_{50} + C} \right) \cdot N \cdot \left(1 - e^{-z \cdot t} \right)$$

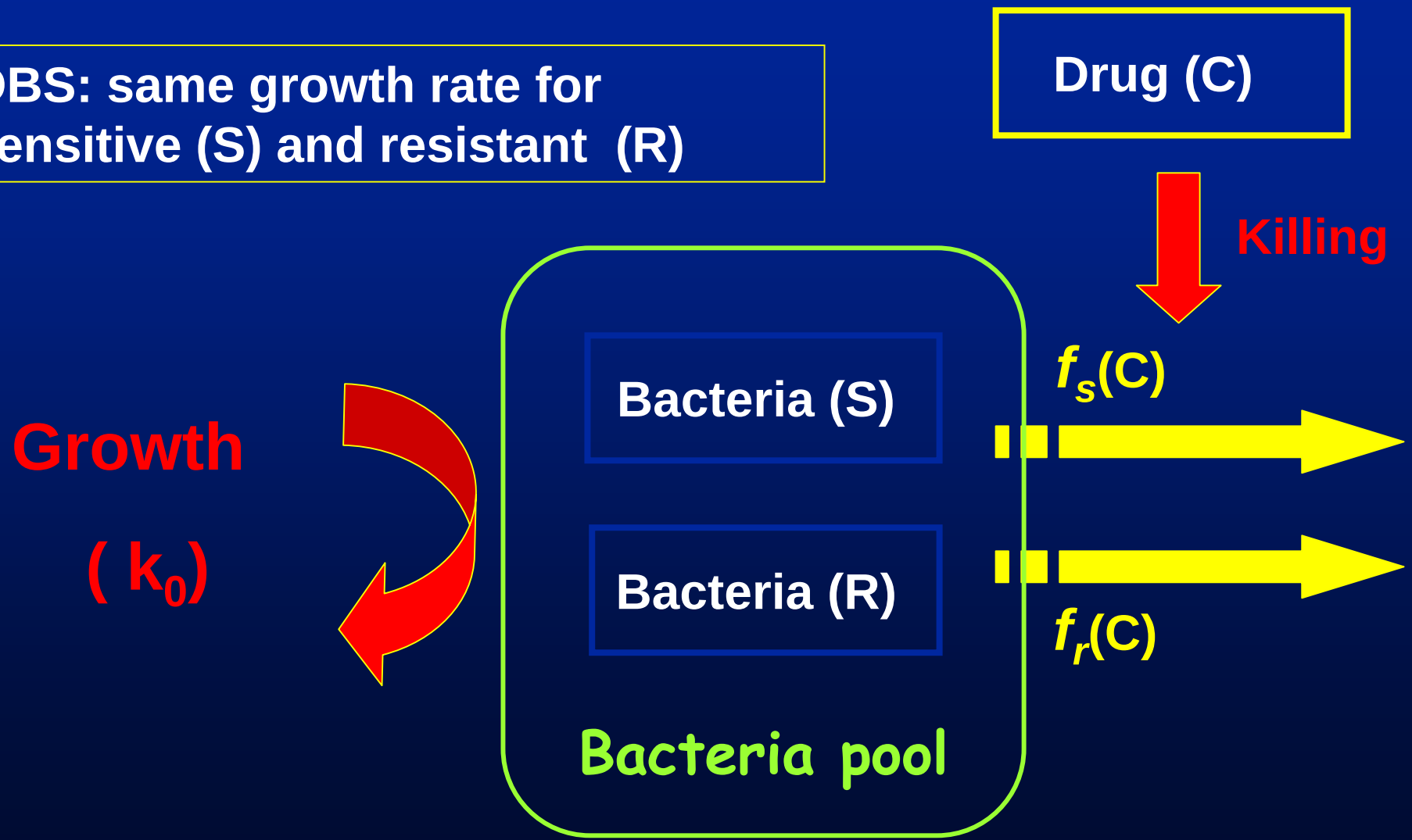
$$C_r = C_0 \cdot \left(e^{-k_e \cdot (t - t_{lag})} - e^{-\alpha \cdot (t - t_{lag})} \right)$$

Comparing to E_{max} model:

$$K_{\max} = k_1 \left(1 - \frac{Cr}{IC_{50} + Cr} \right) + k_2$$

Two sub-population model

OBS: same growth rate for sensitive (S) and resistant (R)



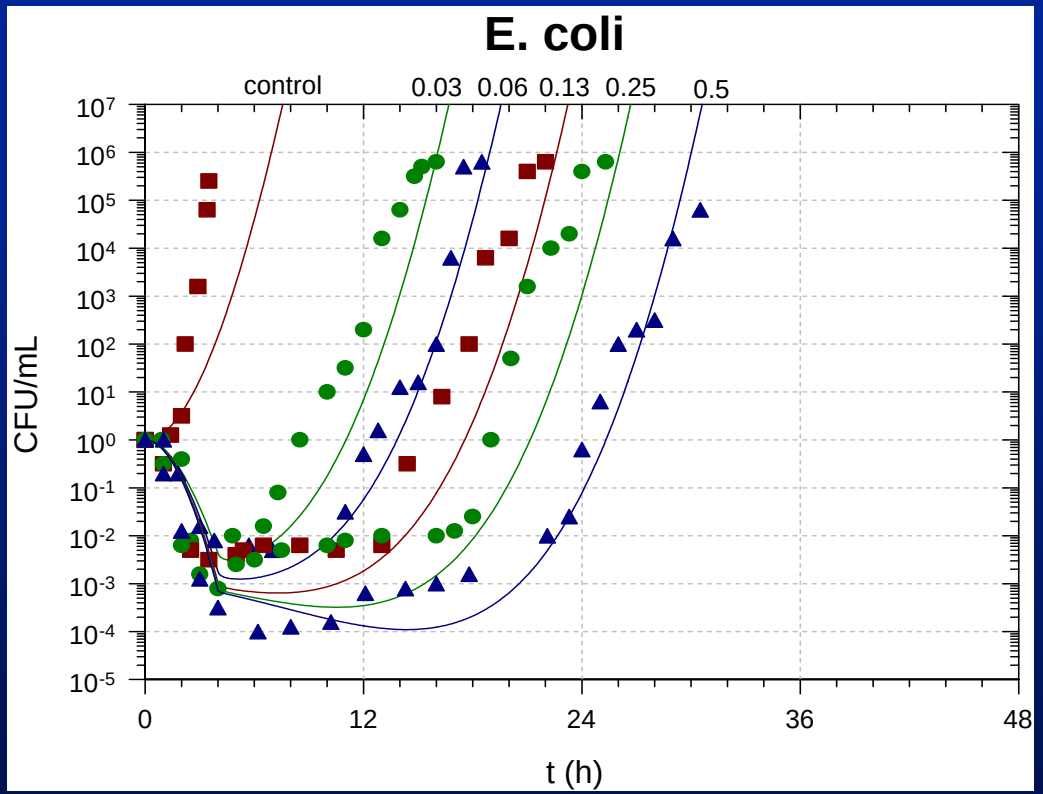
Two sub-population E_{max} model

$$\frac{dNr}{dt} = \left[k_0 - \frac{K_{\max\ r} \cdot C}{EC_{50\ r} + C} \right] \cdot Nr \cdot \left(1 - e^{-z \cdot t}\right)$$

$$\frac{dNs}{dt} = \left[k_0 - \frac{K_{\max\ s} \cdot C}{EC_{50\ s} + C} \right] \cdot Ns \cdot \left(1 - e^{-z \cdot t}\right)$$

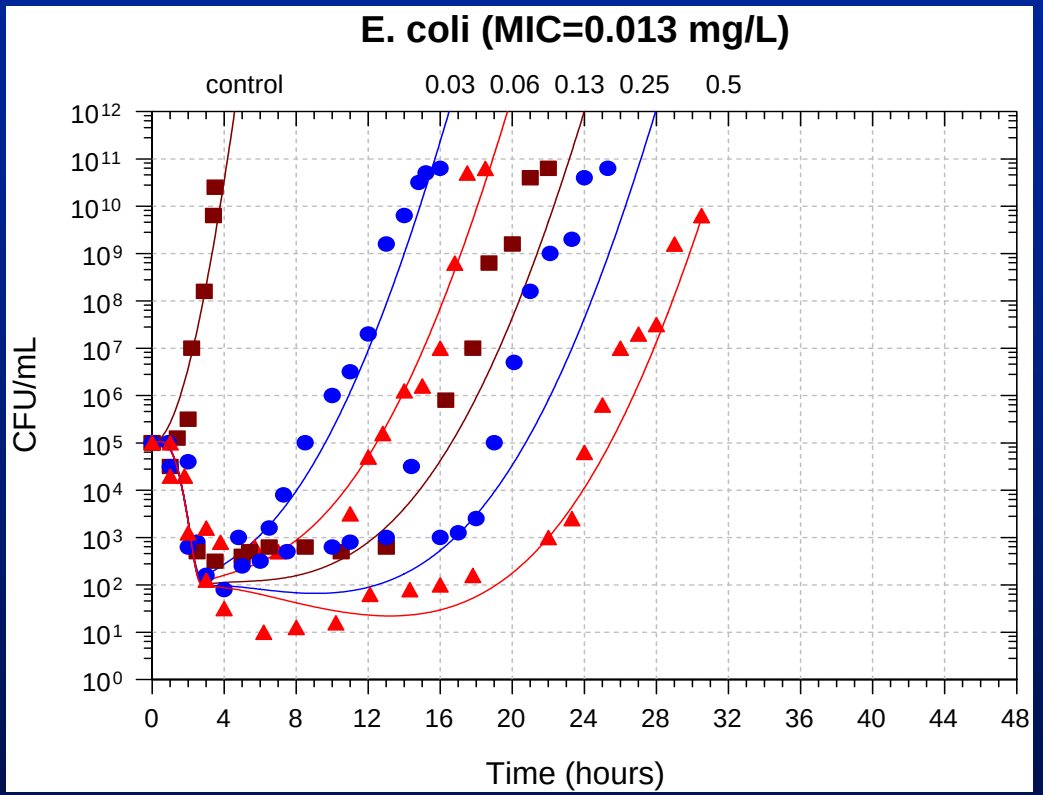
$$N_t = Nr + Ns$$

Model Comparison – *E. coli*



Modified E_{max} model

(simultaneous fit)



Two sub-population model

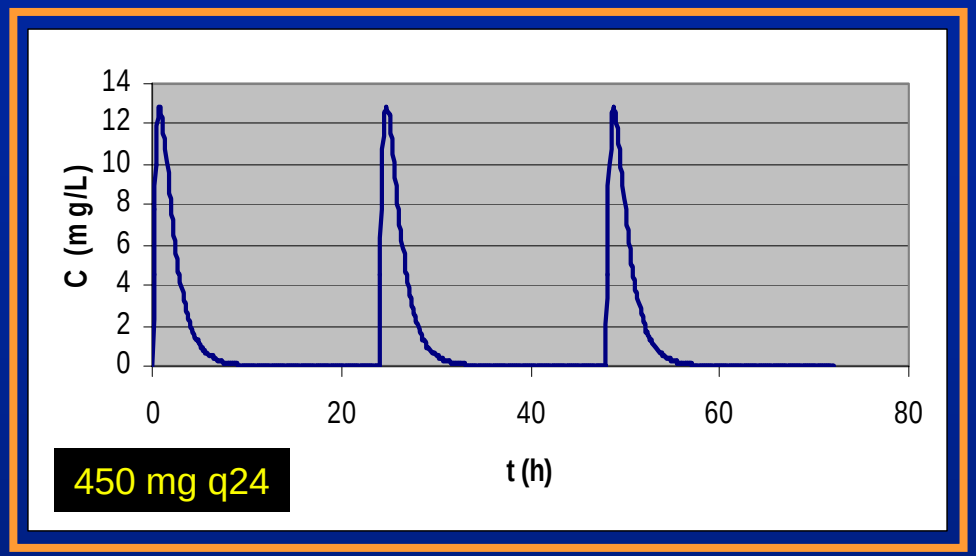
(simultaneous fit)

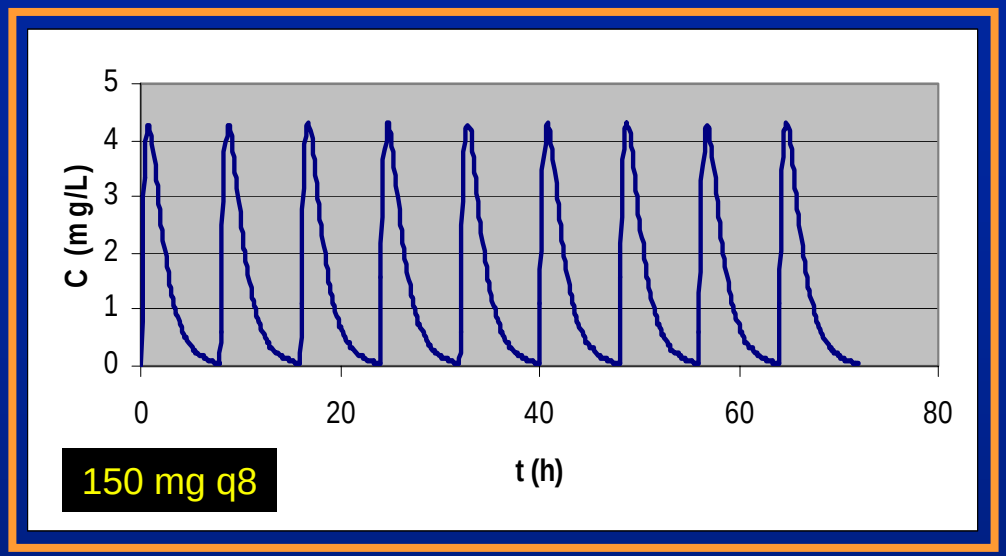
Faropenem Daloxate

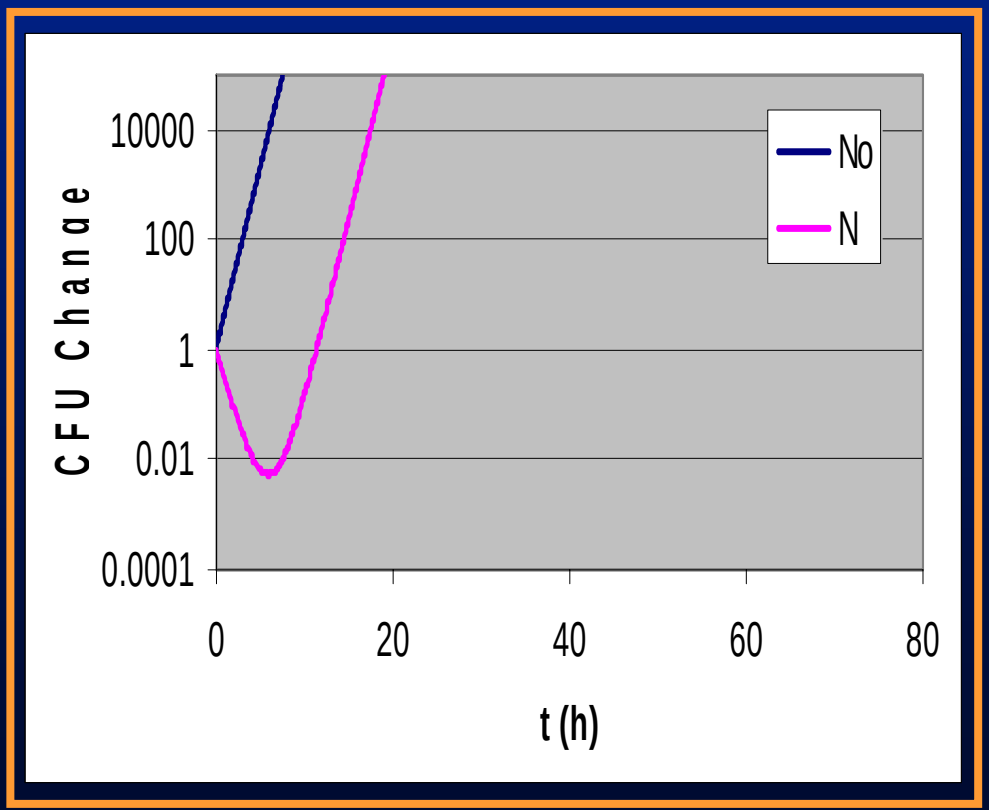
After oral administration, faropenem daloxate is rapidly absorbed and immediately converted in plasma to its active moiety faropenem

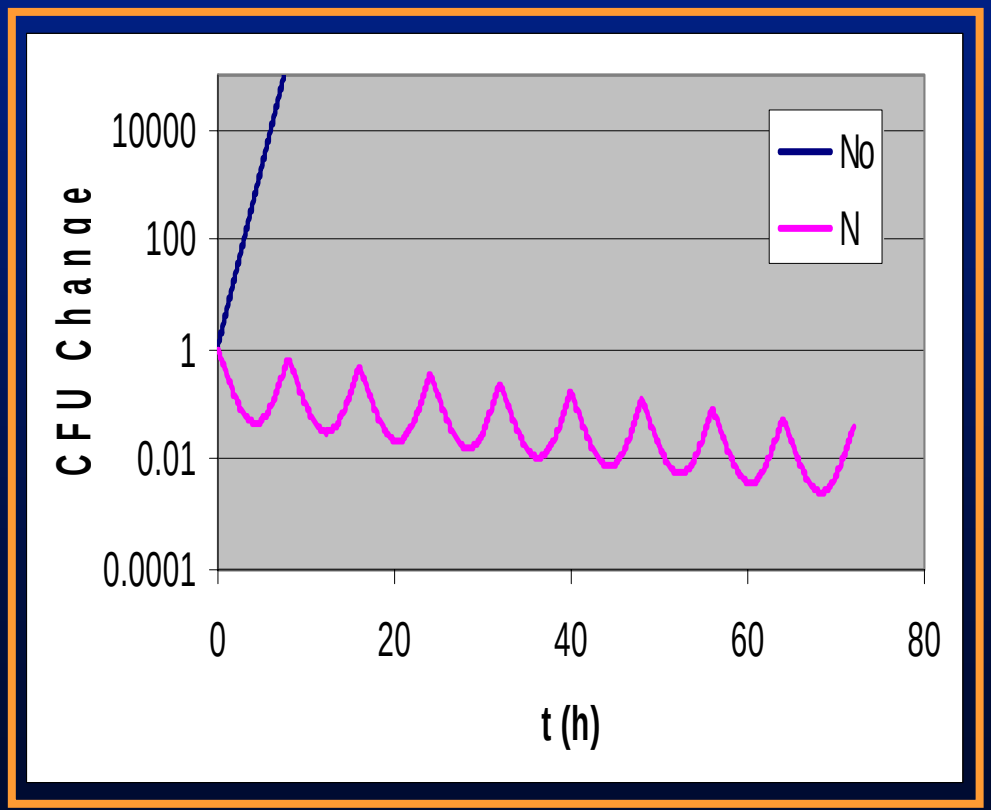
Advantages of using the pro-drug instead of faropenem sodium:

- higher oral bioavailability (70-80%)
- less gastrointestinal side effects


C (mg/L)
14
12
10
8
6
4
2
0
0
20
40
60
80
t (h)
450 mg q24


C (mg/L)
5
4
3
2
1
0
0
20
40
60
80
t (h)
150 mg q8


CFU Change
10000
100
1
0.01
0.0001
0
20
40
60
80
t (h)
No
N


CFU Change
10000
100
1
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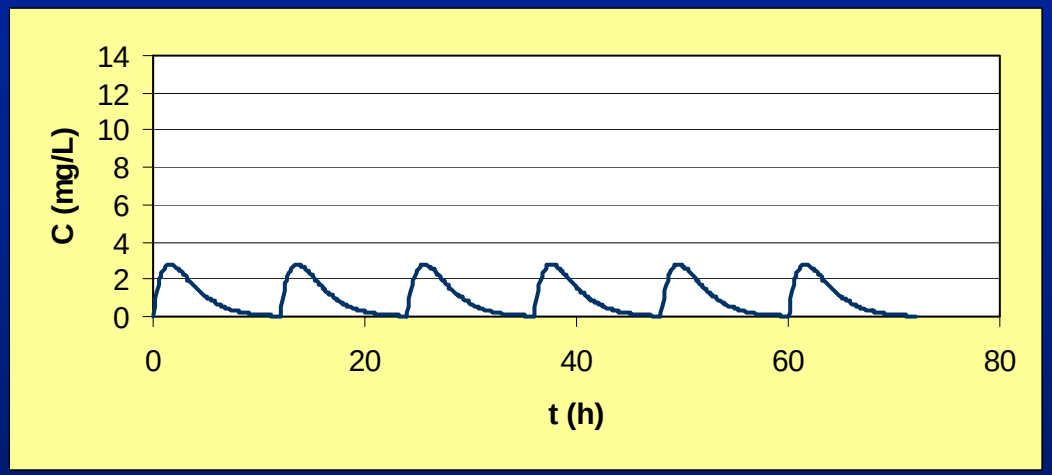
0.0001
0
20
40
60
80
t (h)
No
N

Faropenem daloxate 300 mg q12h

Fed



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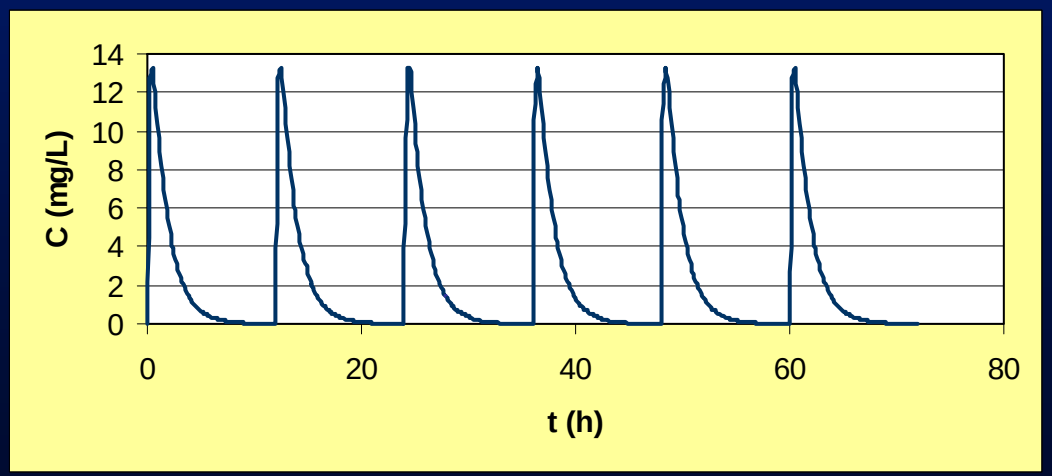
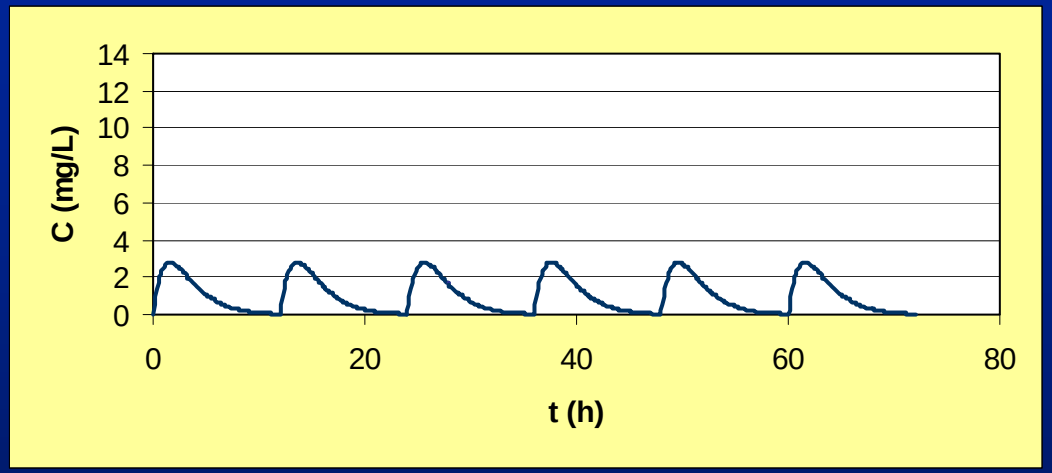


Faropenem daloxate 300 mg q12h

Fed



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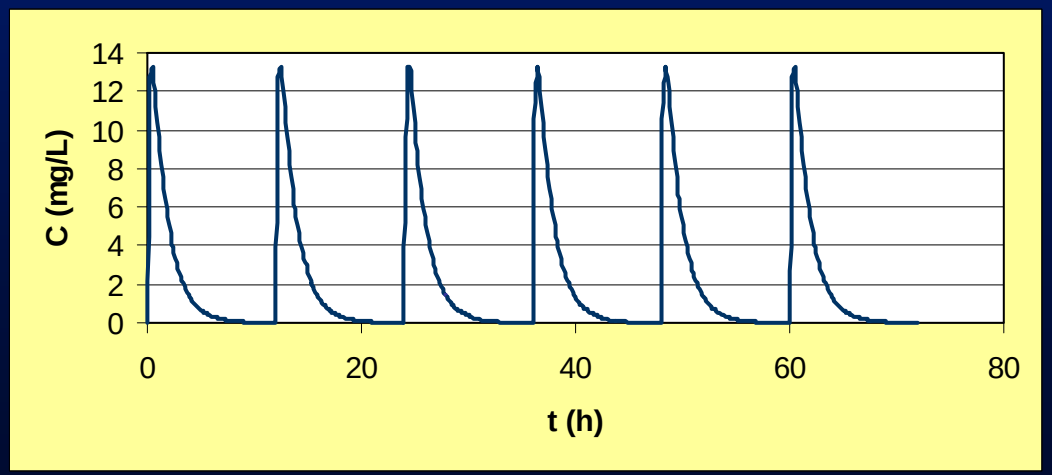
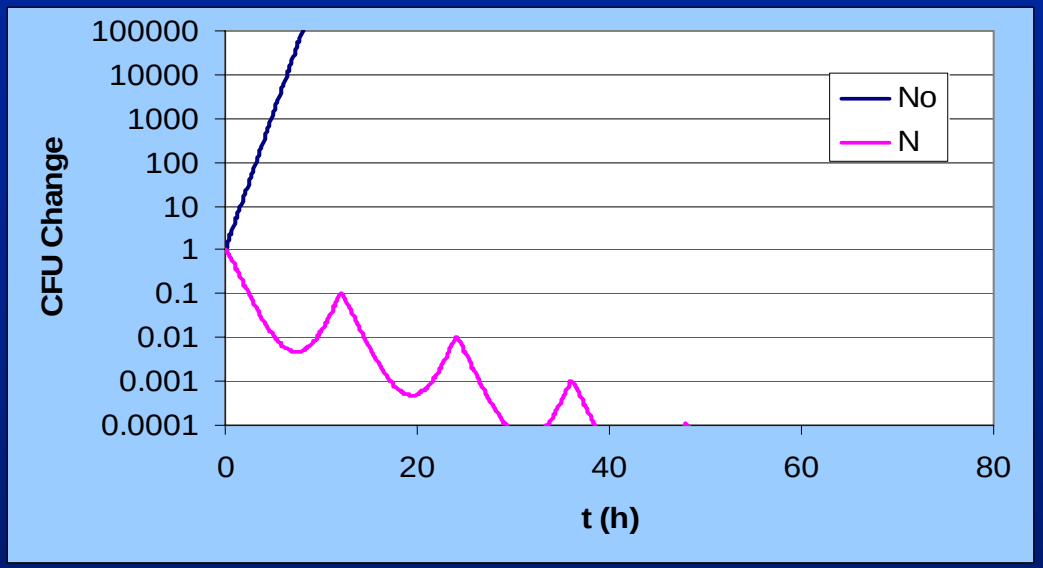
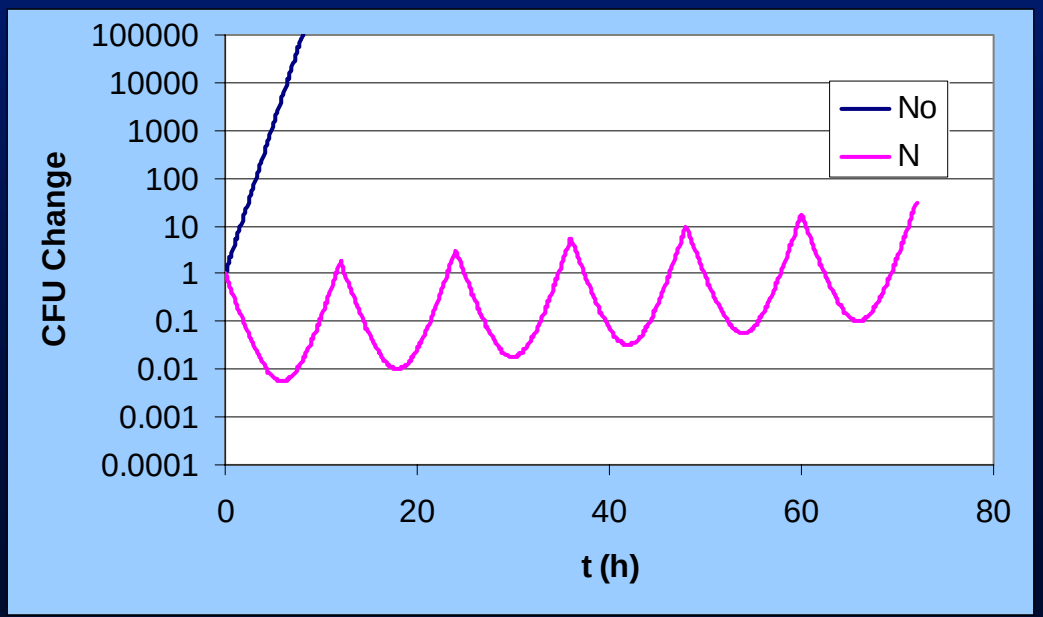
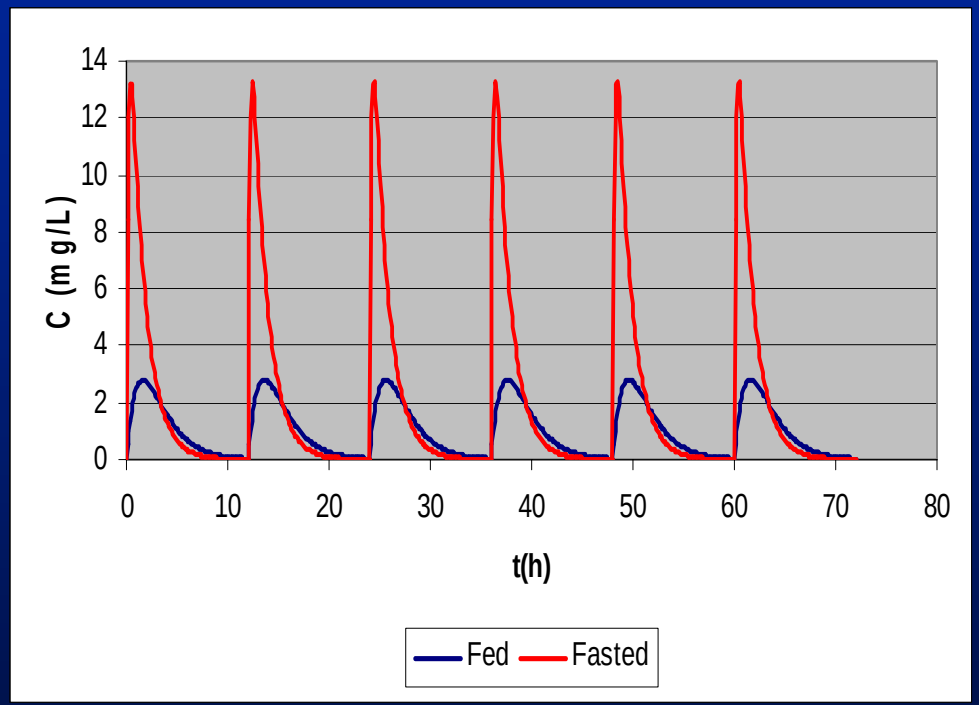


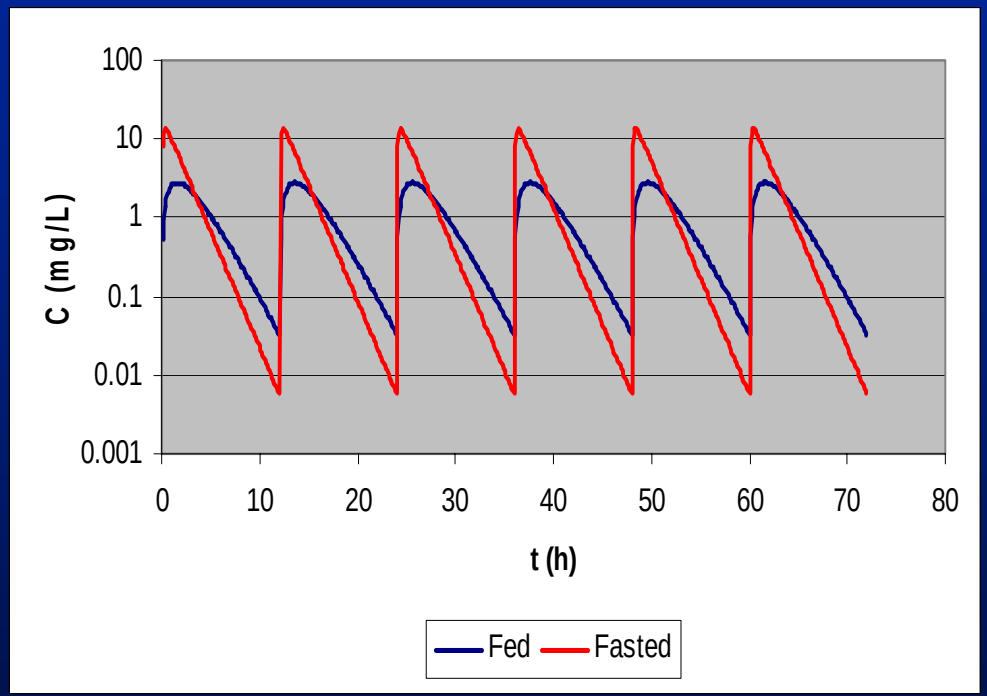
S. pneumo. #49619





Faropenem daloxate
300 mg q12h



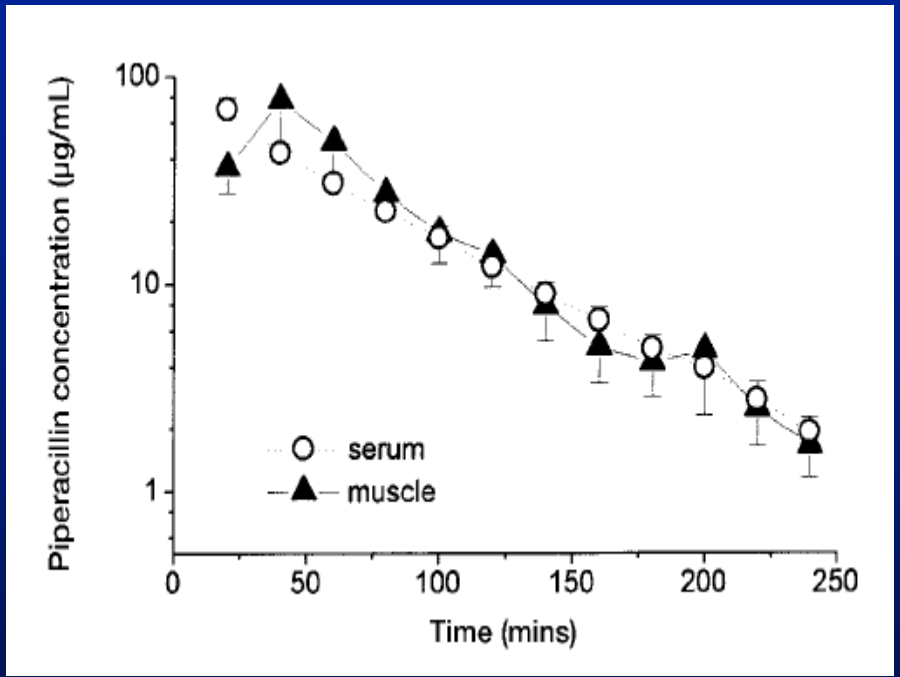


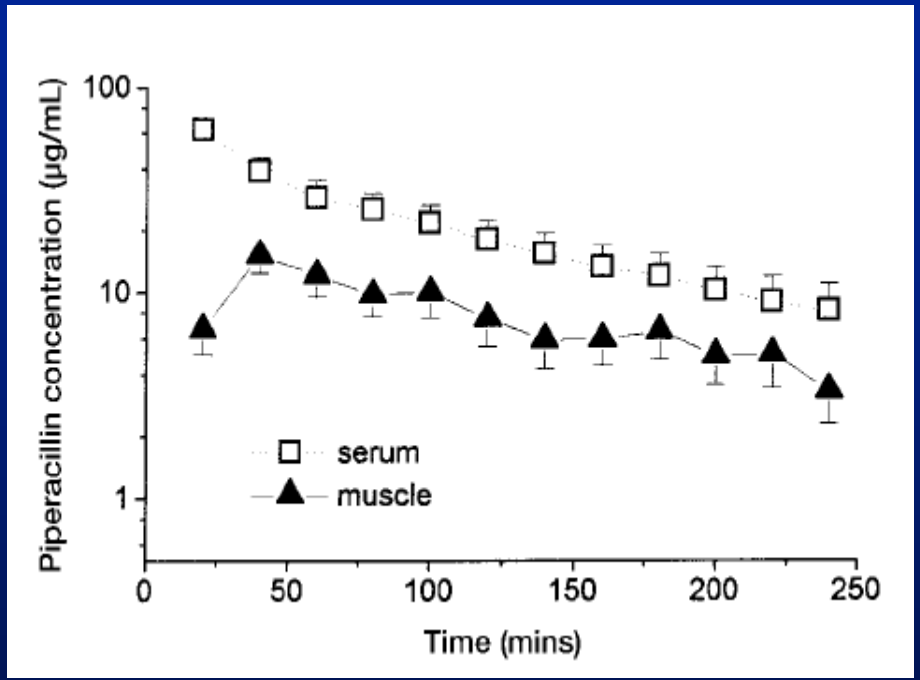
Normal scale

Semilogarithmic scale

EC_{50} 0.026 mg/L

Piperacillin in patients



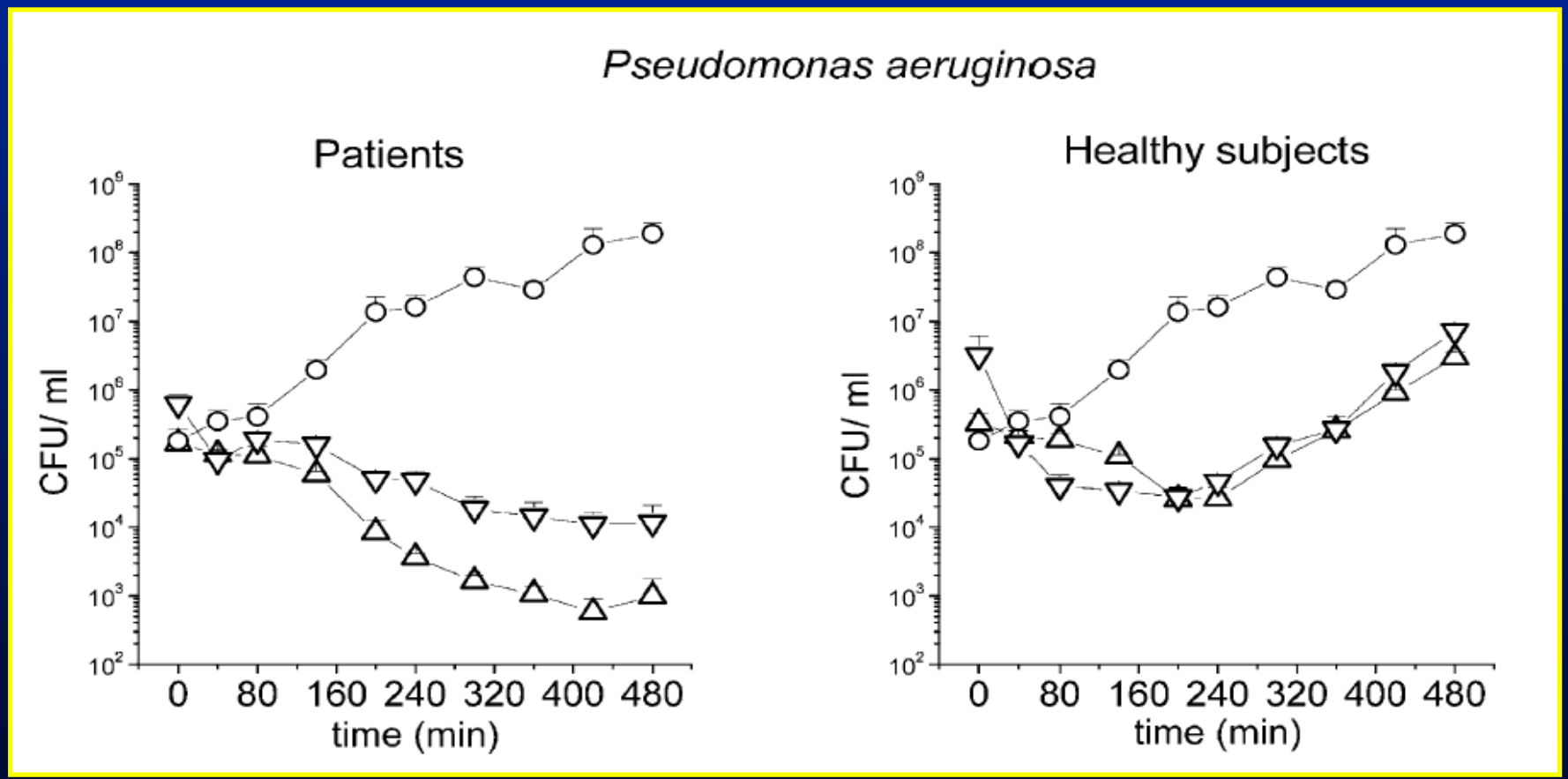


Piperacillin serum and muscle levels in healthy patients and intensive care patients after single iv dose of 4g

Brunner et al, 2000

Piperacillin in patients

Piperacillin kill curves (MIC: △ = 2 mg/l and ▽=4 mg/l)



Sauermann et al, 2003

Summary

- A simple comparison of serum concentration and MIC is usually not sufficient to evaluate the PK/PD-relationships af anti-infective agents.
- Protein binding and tissue distribution are important pharmacokinetic parameters that need to be considered. Microdialysis can provide information on local exposure.
- PK-PD analysis based on MIC alone can be misleading.
- Microbiological kill curves provide more detailed information about the PK/PD-relationships than simple MIC values.

Proposal

Wild Card Patent Extension

A company that receives approval for a new antibiotic, or a new indication for an existing antibiotic, that treats a targeted pathogen would be permitted to extend the market exclusivity period for another of the company's FDA-approved drugs.

ISAP

International Society of Anti-Infective Pharmacology

- Workshops at ECCMID and ICAAC
- Symposia at ECCMID and ICAAC
- Spring 2004: Joint Symposium with FDA and IDSA
- Website with slides, presentations and tons of information

www.isap.org

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