

# Φαρμακοκινητικοί – Φαρμακοδυναμικοί Δείκτες (PK/PD index)

Διαμαντής Πλαχούρας  
Λέκτορας Παθολογίας – Λοιμώξεων  
Δ' Παθολογική Κλινική

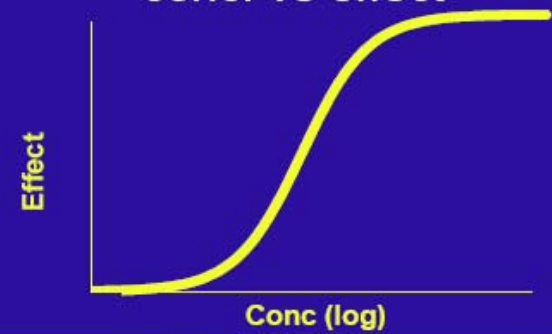
## Pharmacokinetics

conc. vs time



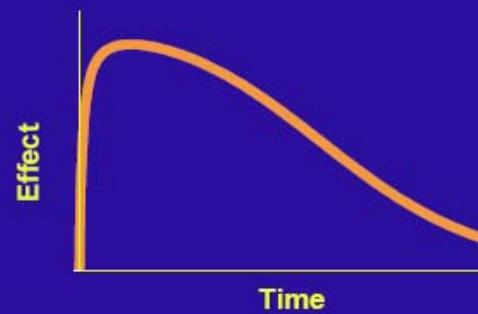
## Pharmacodynamics

conc. vs effect



## PK/PD

effect vs time



# Στόχος αντιμικροβιακής θεραπείας

Αποτελεσματική αντιμετώπιση της λοίμωξης

?

Συγκέντρωση του αντιμικροβιακού >  
MIC



Παράμετροι που σχετίζονται  
ποσοτικά με την  
αποτελεσματικότητα

# PK/PD δείκτες

$$T > MIC$$

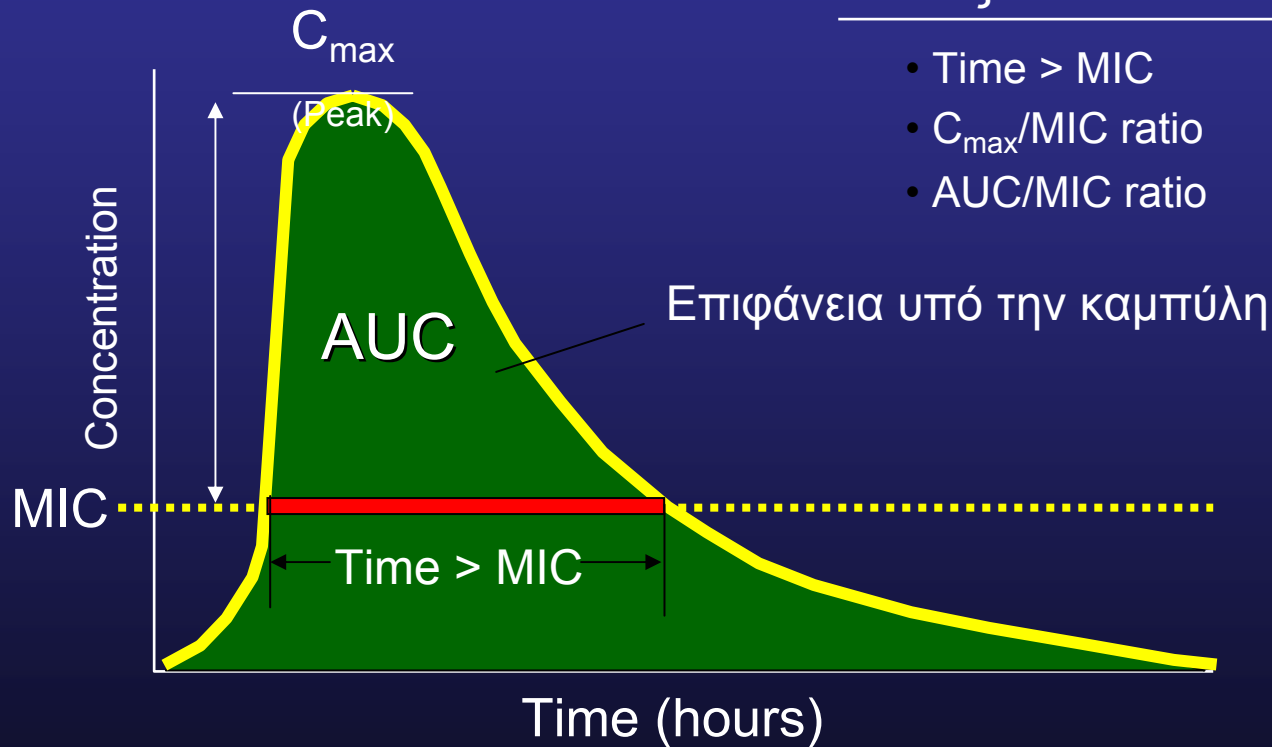
$$AUC / MIC$$

$$C_{max} / MIC$$

# Φαρμακοκινητική

## Δείκτες PK/PD

- Time > MIC
- $C_{max}/MIC$  ratio
- AUC/MIC ratio



# Μοντέλο μηρού ουδετεροπενικού ποντικού

- Λοίμωξη στον μηρό ουδετεροπενικού ποντικού
- Διάφορα δοσολογικά σχήματα
- Υπολογισμός φαρμακοκινητικών παραμέτρων
- Μέτρηση αποικιών μικροβίου (cfu / ml) στις 24 ώρες
- Γράφημα PD παραμέτρων προς αποτέλεσμα



## Neutropenic Mouse Thigh-Infection Model



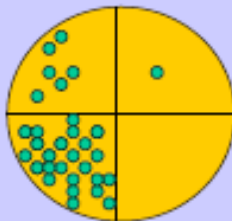
1. Neutropenia induced by 2 injections of cyclophosphamide on days -4 and -1



2. Bacteria injected into thighs on day 0 ( $10^{4-7}$ )

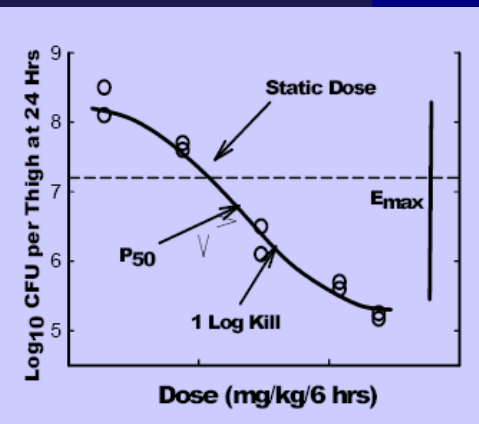
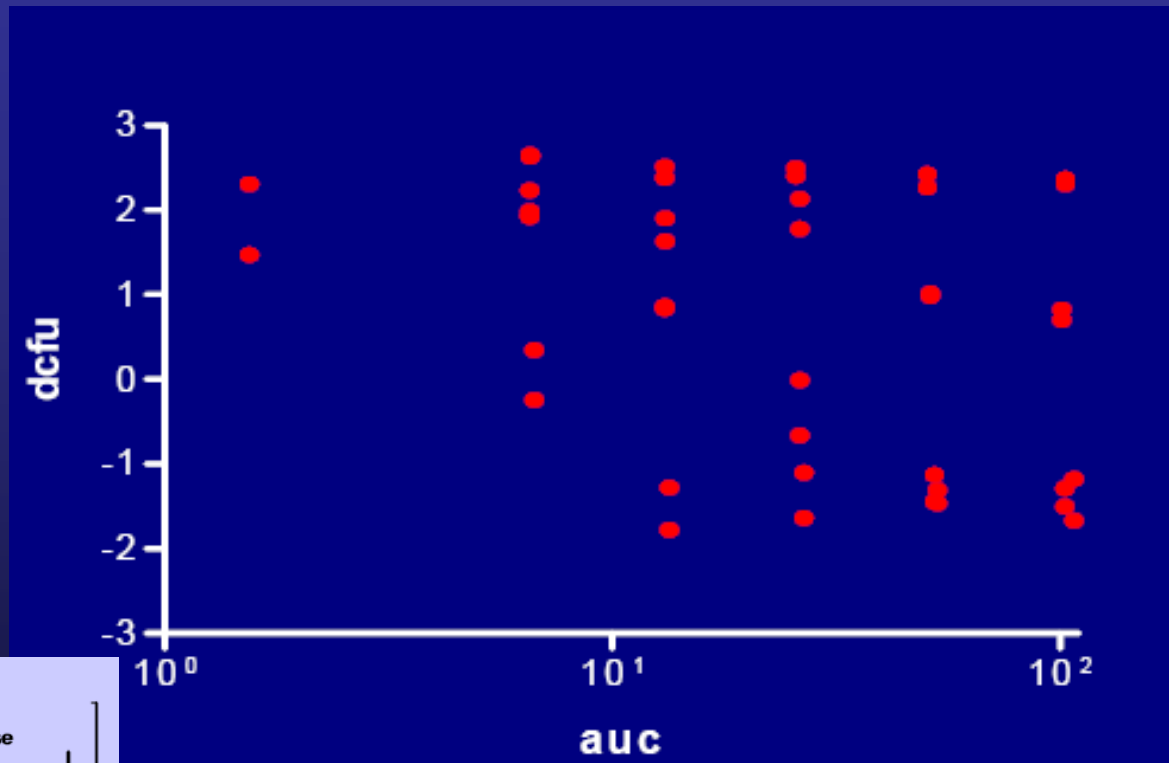


3. Treatment (usually given SQ) started 2 hr after infection and continued for 1-5 days



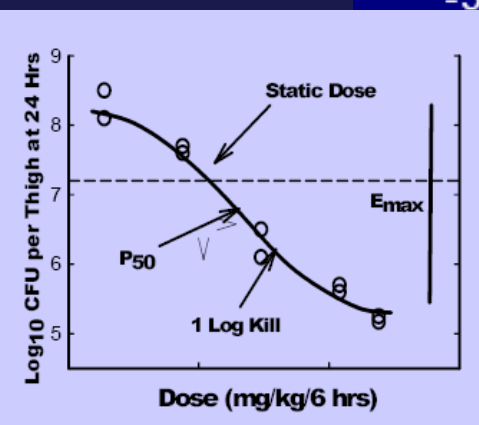
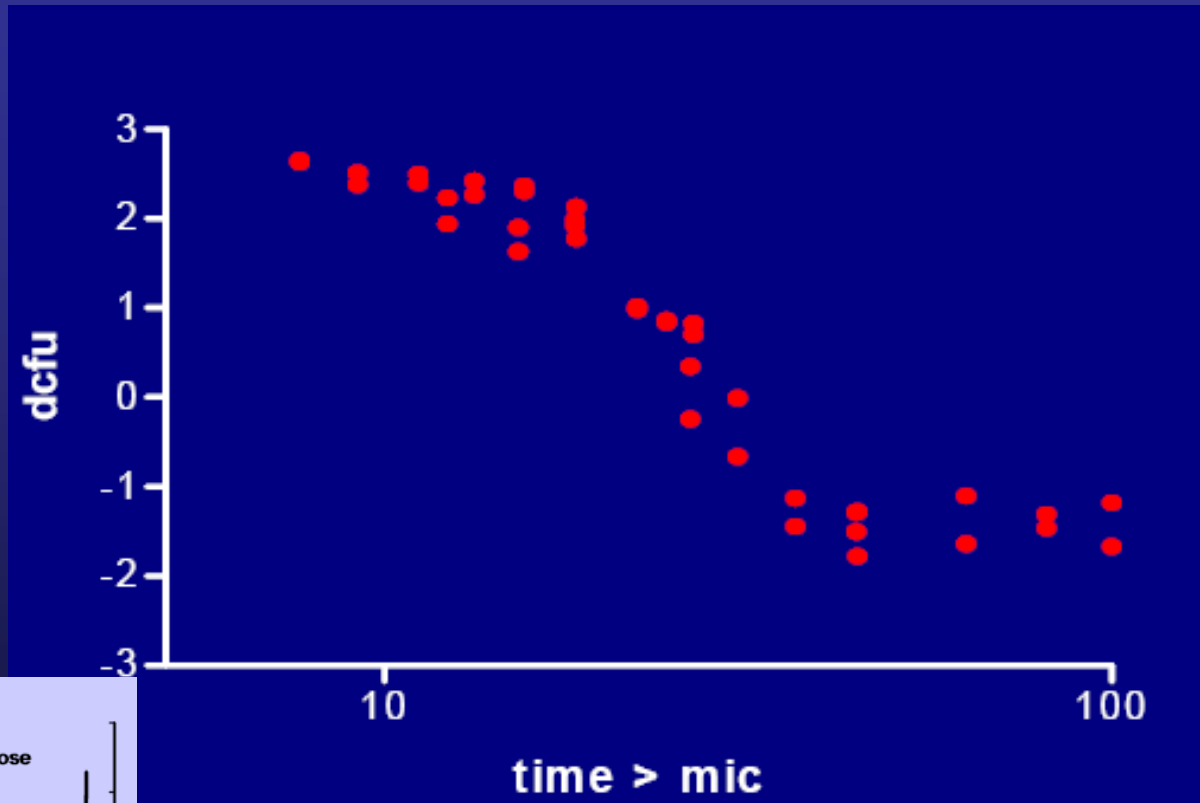
4. Thighs removed, homogenized, serially diluted and plated for CFU determinations

# Meropenem vs. Klebsiella

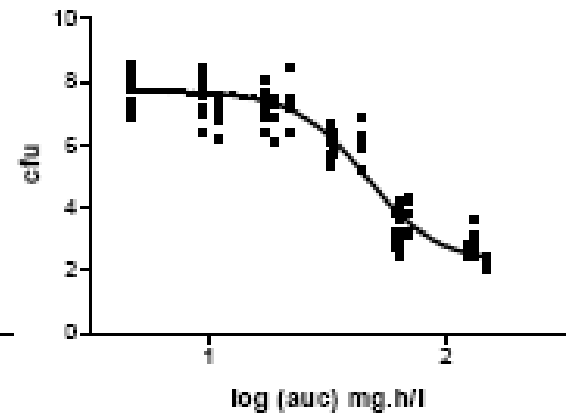
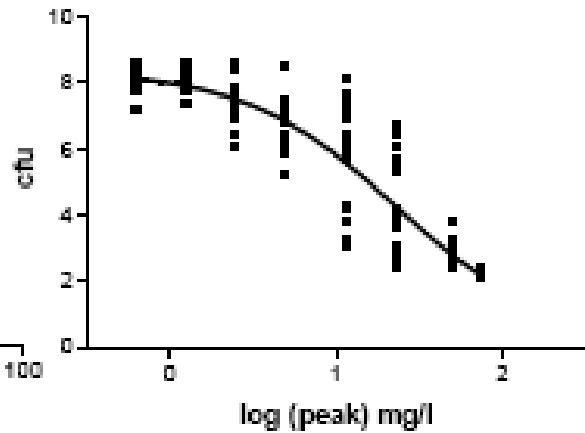
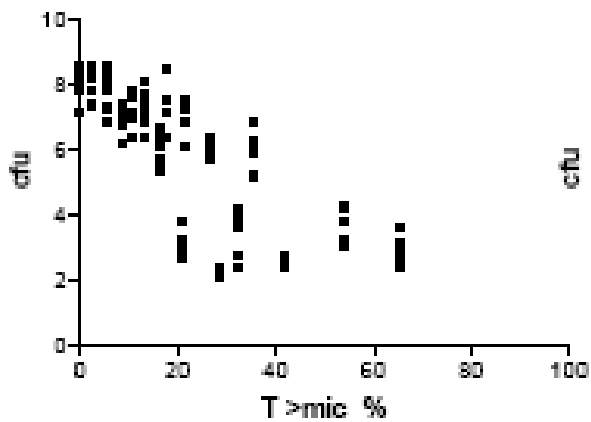




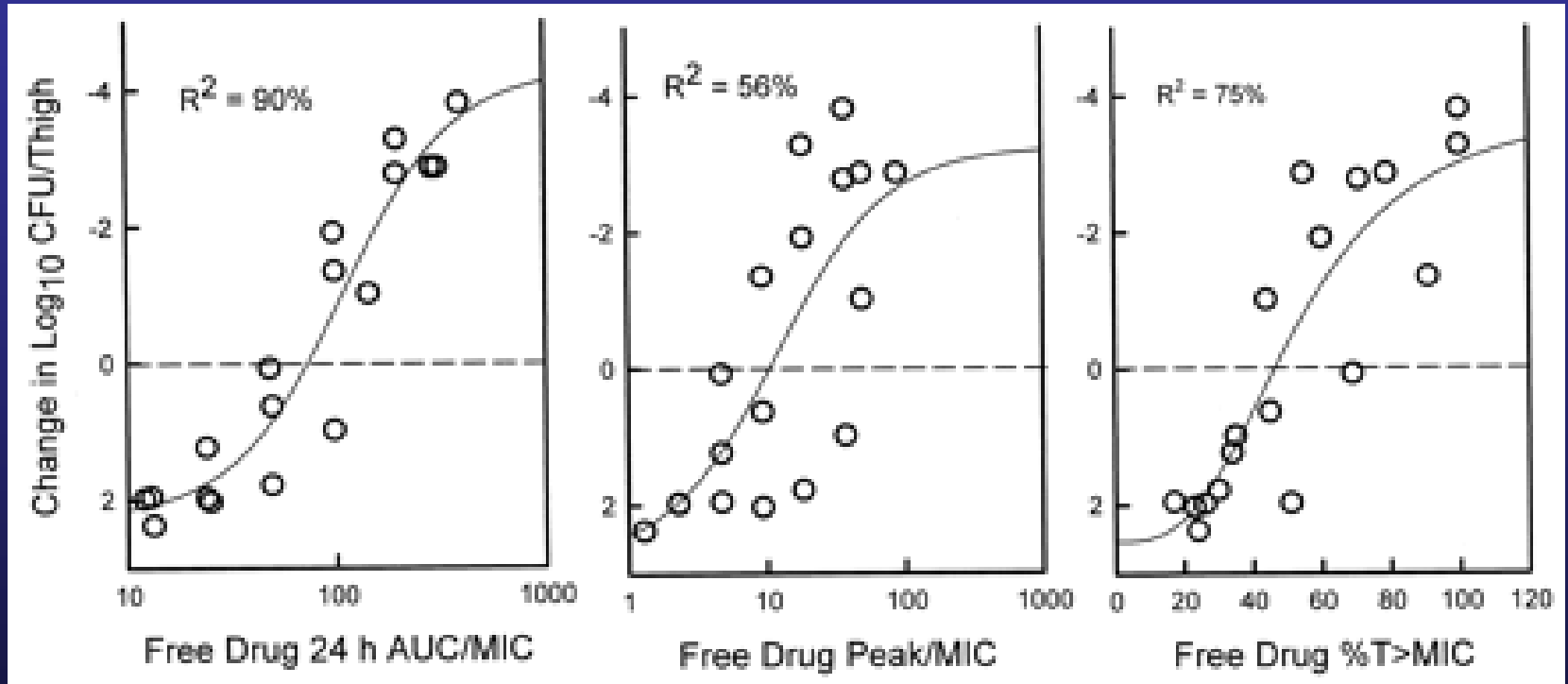
# Meropenem vs. Klebsiella

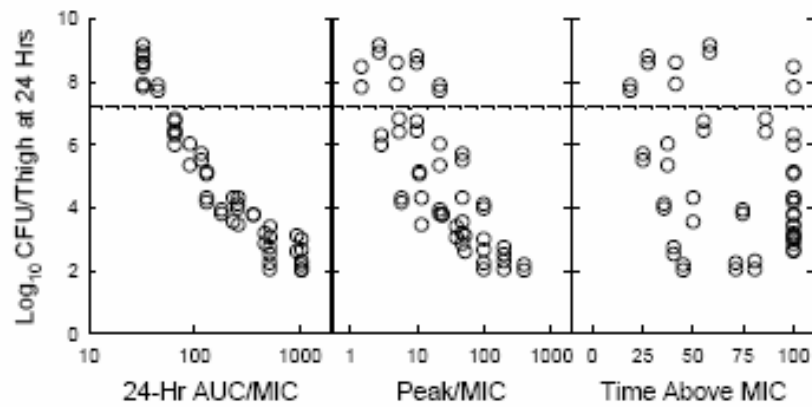


# Λεβοφλοξασίνη vs *Streptococcus pneumoniae*

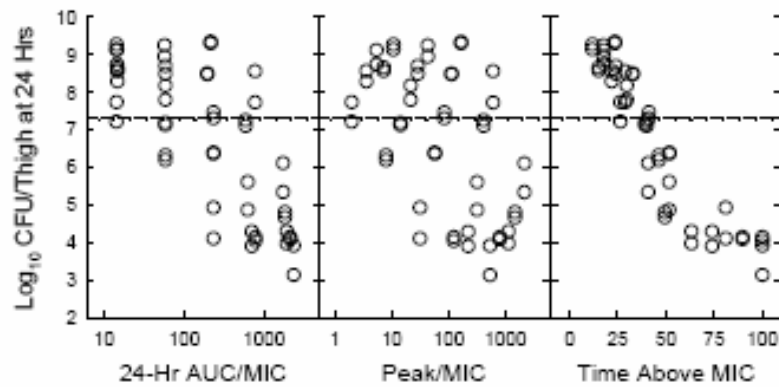


# Garenoxacin vs *Str. pneumoniae*



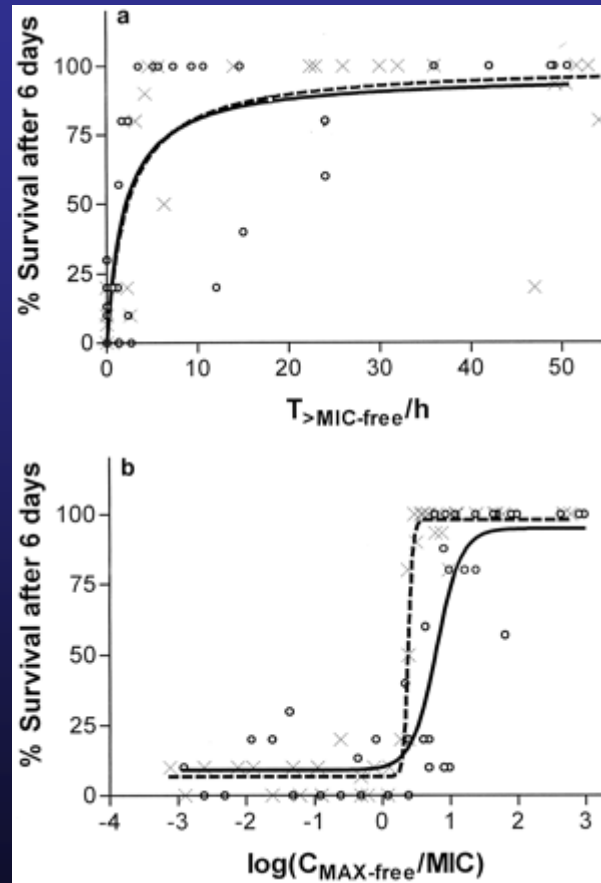


levofloxacin



ceftazidim

# PK/PD δείκτες και γλυκοπεπτίδια



## T>MIC

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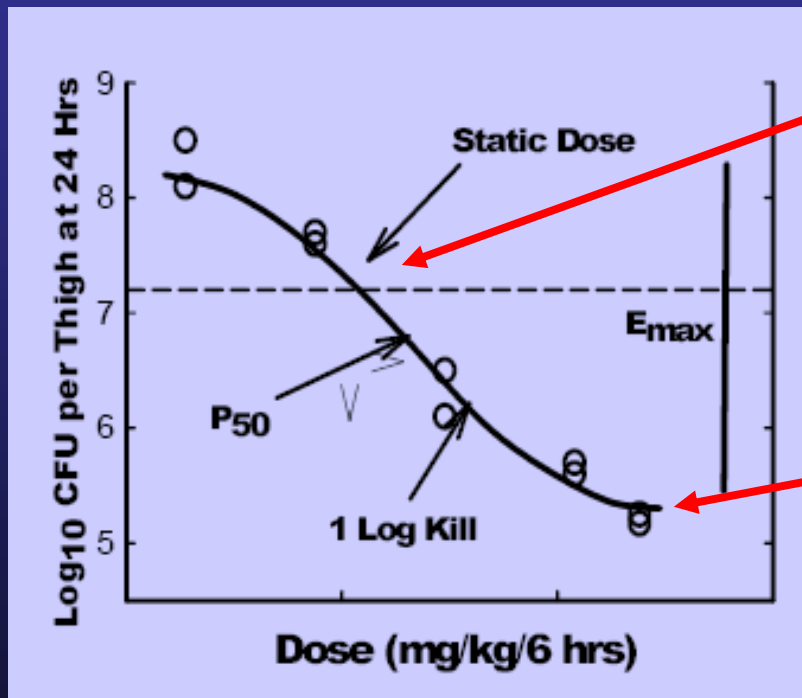
Penicillins  
Cephalosporins  
Carbapenems  
Monobactams  
Tribactams

## AUC

Aminoglycosides  
Fluoroquinolones  
Metronidazole  
Lipopeptides  
Ketolides  
Macrolides  
Clindamycin  
Streptogramins  
Glycopeptides  
Glycylcyclines  
Oxazolidinones  
Tetracyclines  
Azoles

# Μέγεθος δείκτη PK/PD

- Αντιμικροβιακό
- Μικροοργανισμός
- Ανοσολογική επάρκεια ξενιστή
  - Φυσιολογικός
  - Ουδετεροπενικός
- Θέση λοίμωξης
- Πρωτεΐνοδέσμευση
- Μικροβιακό inoculum



### Βακτηριοστατικό αποτέλεσμα

- Ανοσοεπαρκείς
- Λοιμώξεις σε «εύκολα» διαμερίσματα

### Βακτηριοκτόνο αποτέλεσμα

- Ουδετεροπενικοί
- Ασθενείς ΜΕΘ
- Ενδοκαρδίτιδα, μηνιγγίτιδα



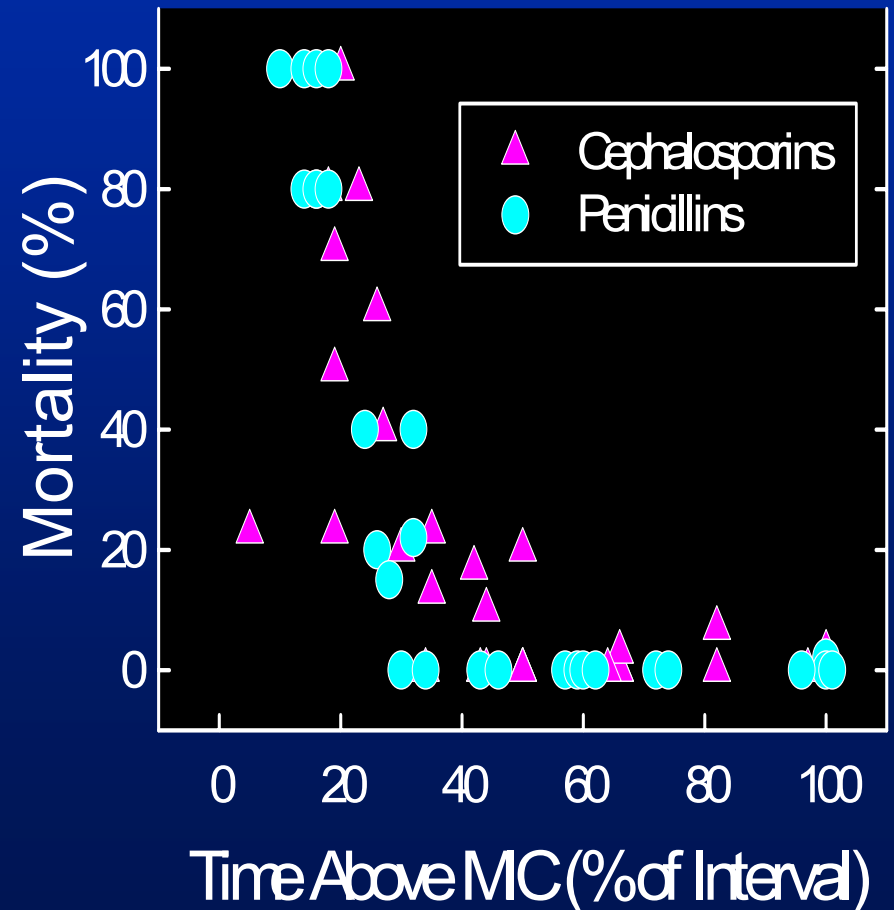
# Pharmacodynamic Goals (T>MIC as percent of Interval) with Beta-Lactams

<u>Class</u>	<u>Organism</u>	<u>Stasis</u>	<u>Killing</u>
Cephalosporins	GNR, pneumo	40-50	70-80
	Staph	20-30	40-50
Penicillins	GNR, pneumo	30-40	60-70
	Staph	20-30	40-50
Carbapenems	GNR, staph	20-30	40-50
	Pneumo	10-20	25-40

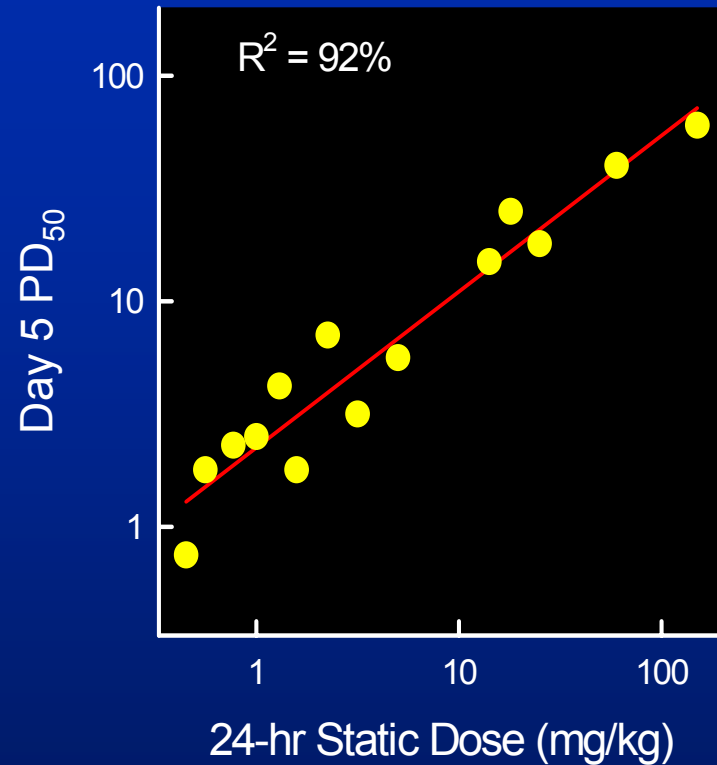
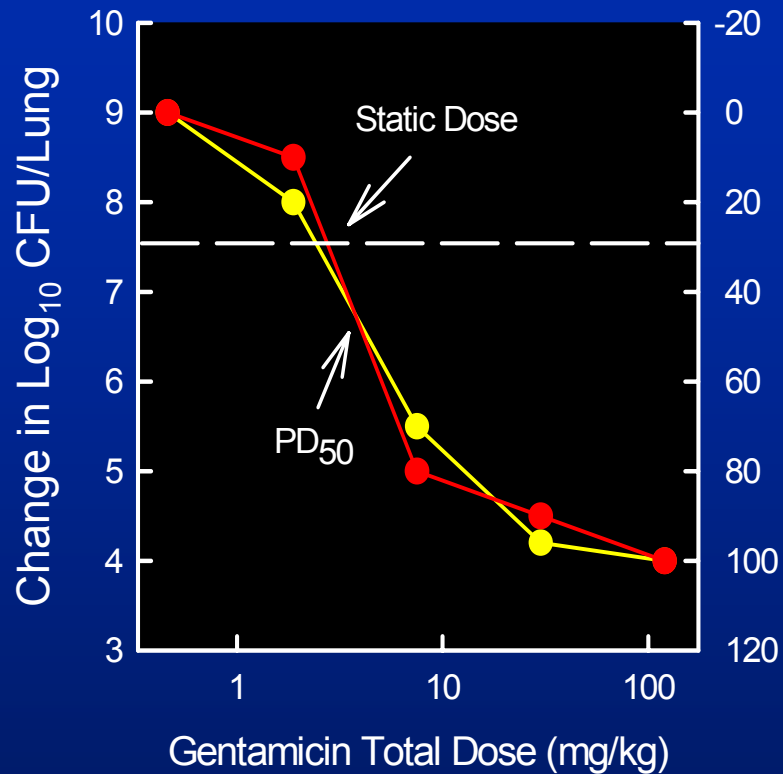
# Literature Review for $T > MIC$ for Beta-Lactams Versus Mortality in Animal Models

- At least 48 hours of treatment
- Mortality 80-100% in untreated controls
- Pharmacokinetics provided to calculate magnitude of PK/PD parameter
- Mortality recorded within 24 hrs after last dose of drug
- Data from 3 animal species and 4 sites of infection

## *Streptococcus pneumoniae*



# Correlation Between Bacterial Numbers After 24-hr of Therapy and Survival After 4-5 Days of Therapy

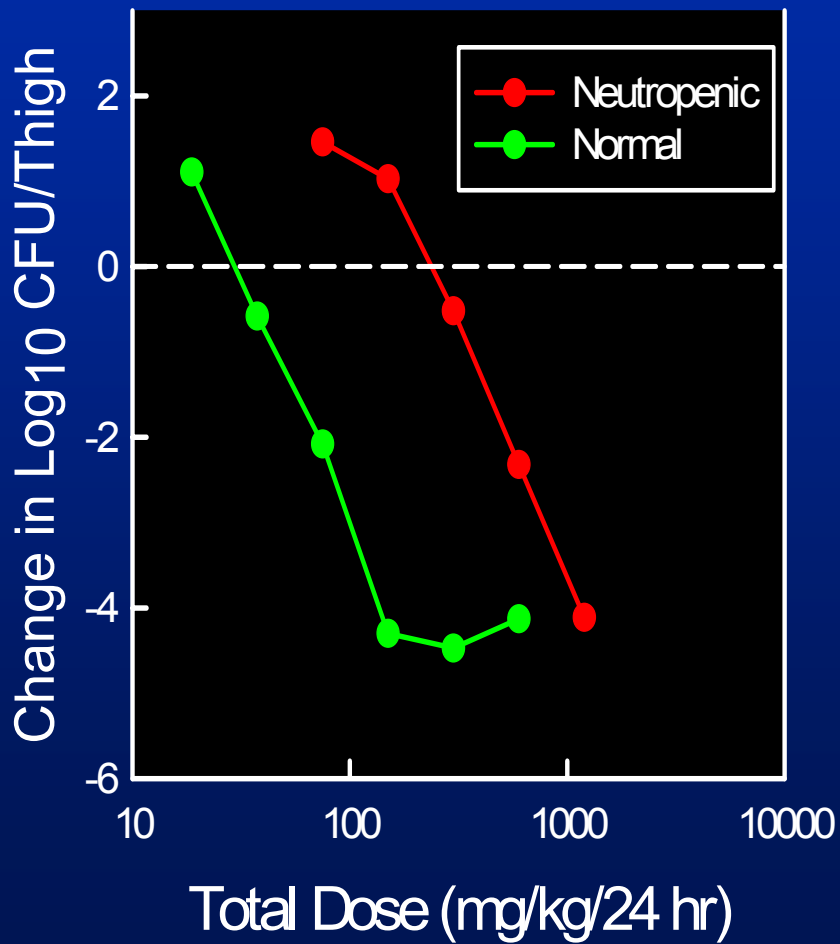


**3 Quinolones**  
**2 Aminoglycosides**  
**4 B-lactams**

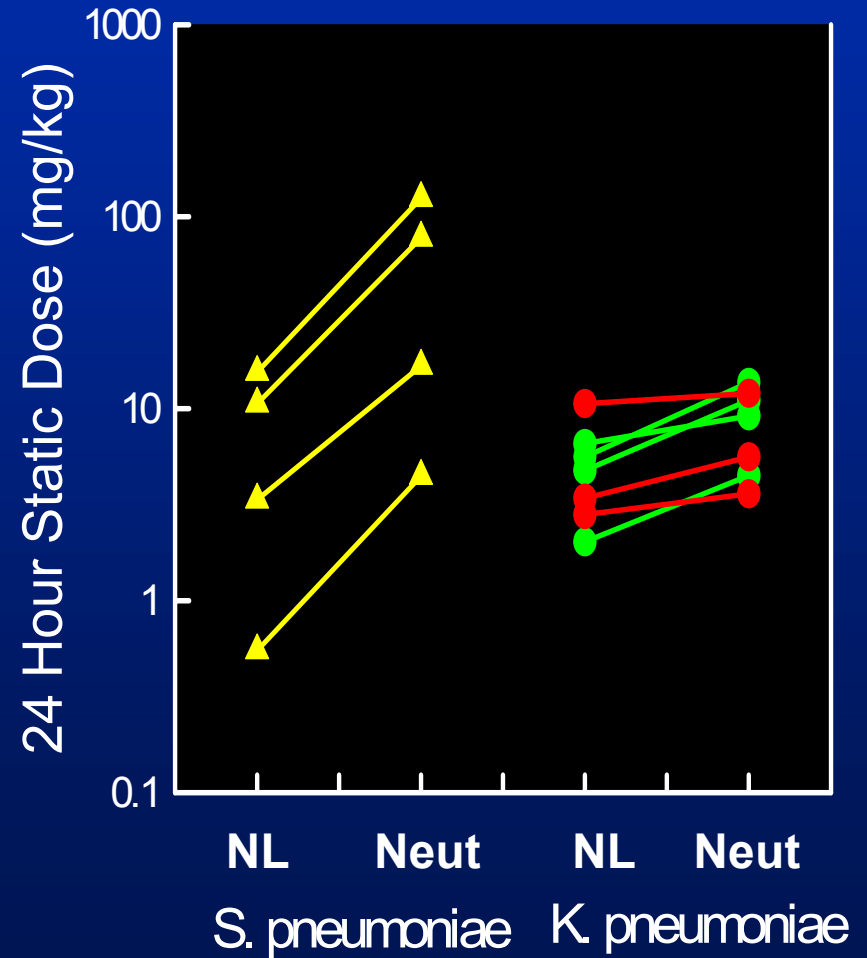
**K. pneumoniae**  
**P. aeruginosa**  
**S. pneumoniae**

**Thigh**  
**Lung**

Ciprofloxacin Dose-Response Relationship Against *S. pneumoniae* in Both Normal and Neutropenic Mice

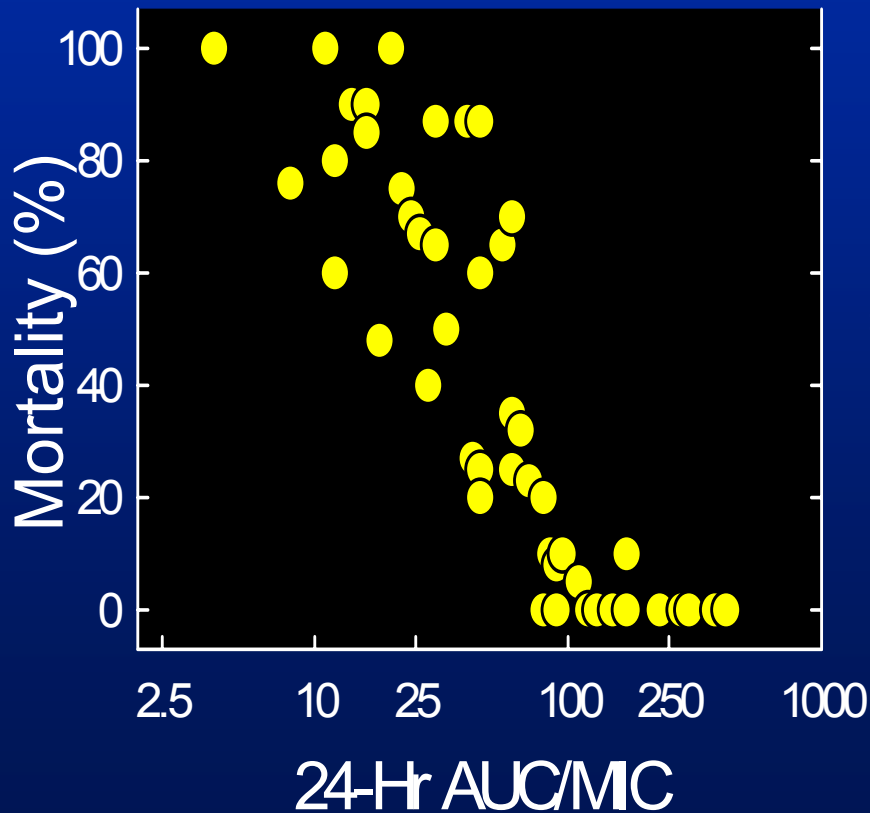


Impact of Neutrophils on the 24 hr Static Dose of Selected Quinolones Against *S. pneumoniae* and *K. pneumoniae*

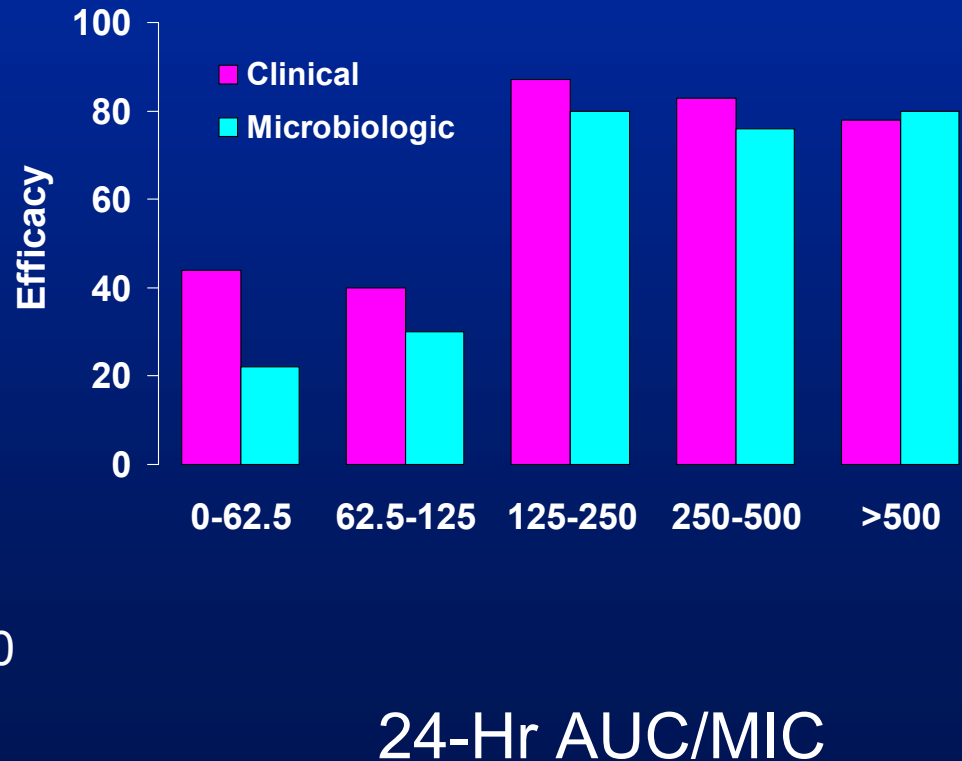


# Comparison of the Relationships Between Efficacy and 24-Hr AUC/MIC for Fluoroquinolones in Animal Models and Infected Patients

Animals - Literature Review



Seriously ill patients + Ciprofloxacin



# Inoculum effect

## Impact of Inocula on Static Dose against Staphylococci for Different Antibacterials

<u>Drug</u>	<u>Increase in Static Dose for Inocula from <math>10^5</math> to <math>10^7</math></u>
Vancomycin	13- to 25-fold
Linezolid	2- to 8-fold
Daptomycin	3- to 7-fold
Ceftobiprole	2- to 5-fold

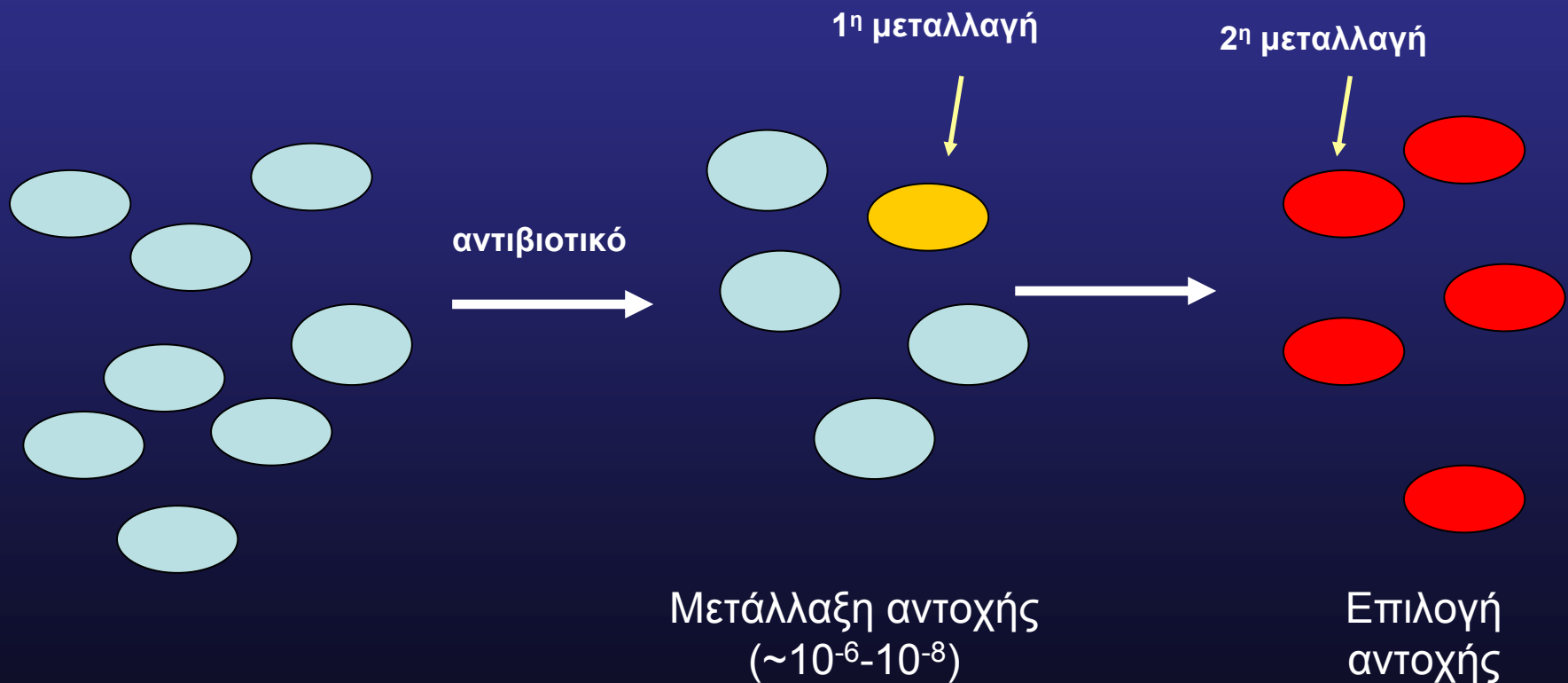
PK PD και αντοχή

Μπορούμε να χρησιμοποιήσουμε  
τις αρχές PK/PD με σκοπό να  
προλάβουμε την

ΑΝΑΠΤΥΞΗ **ΑΝΤΟΧΗΣ**;



# Μοντέλο ανάπτυξης αντοχής



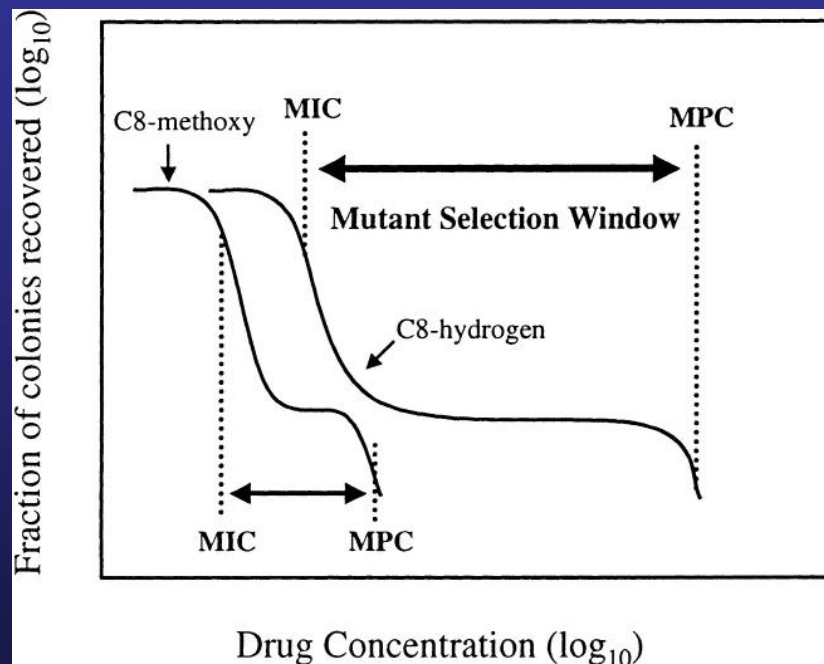
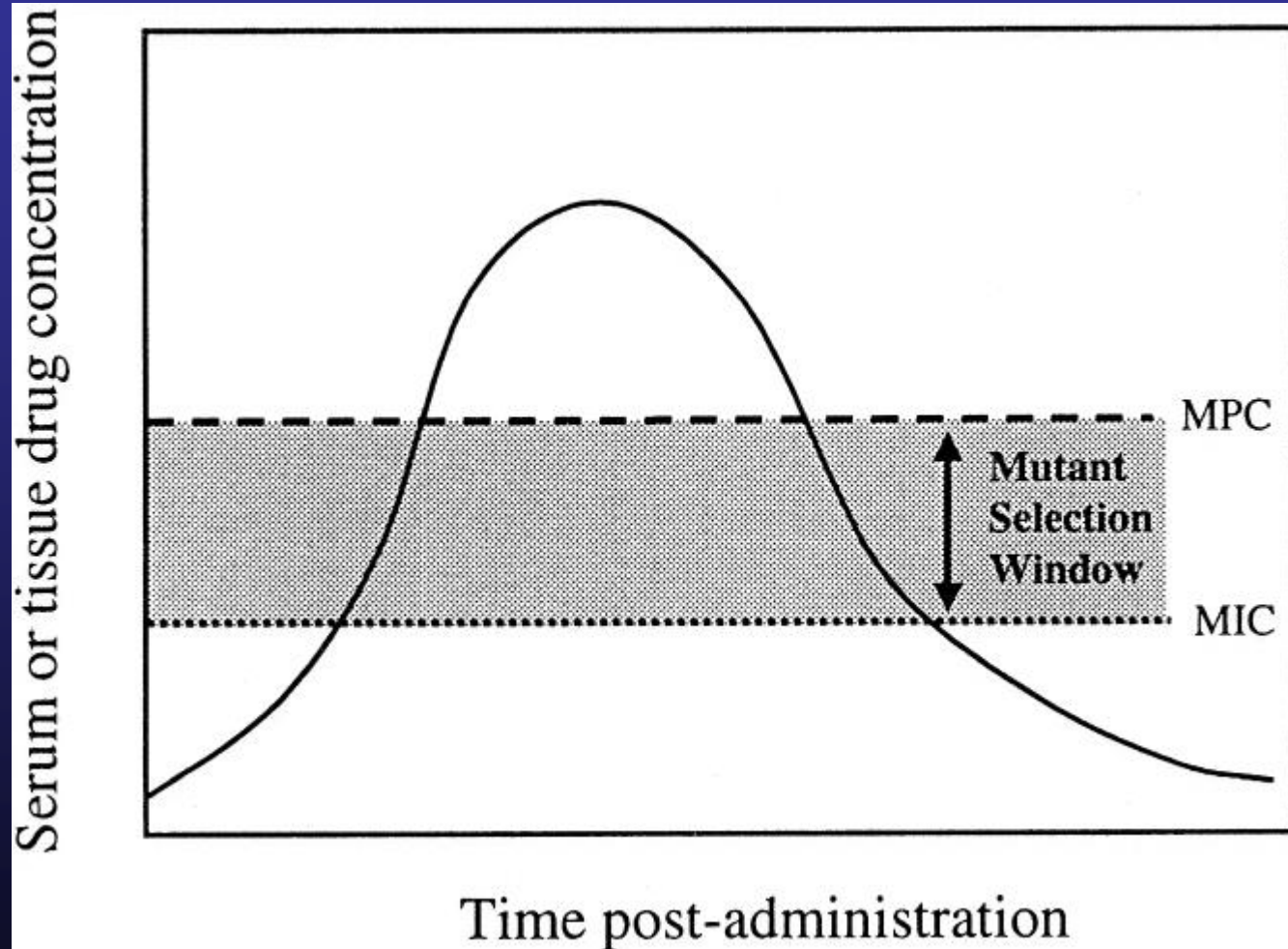
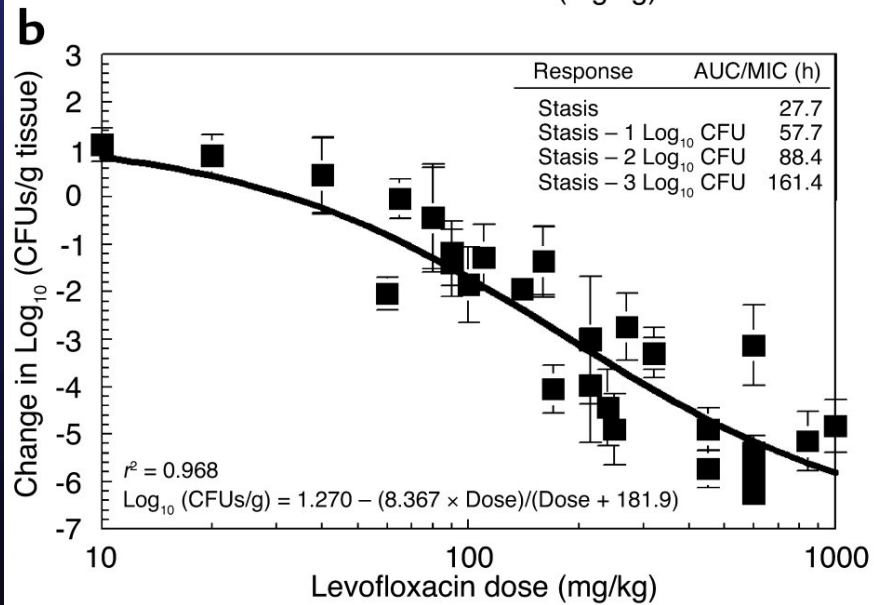
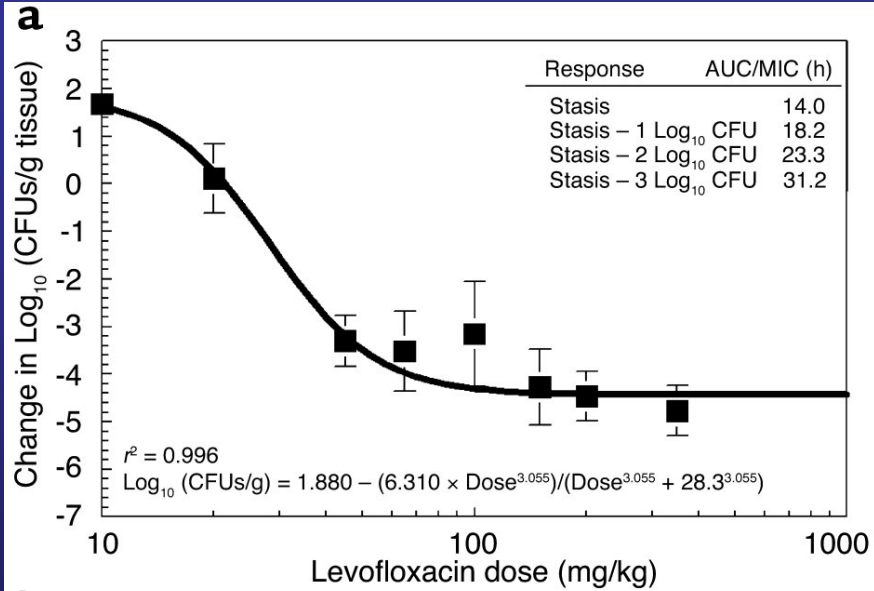
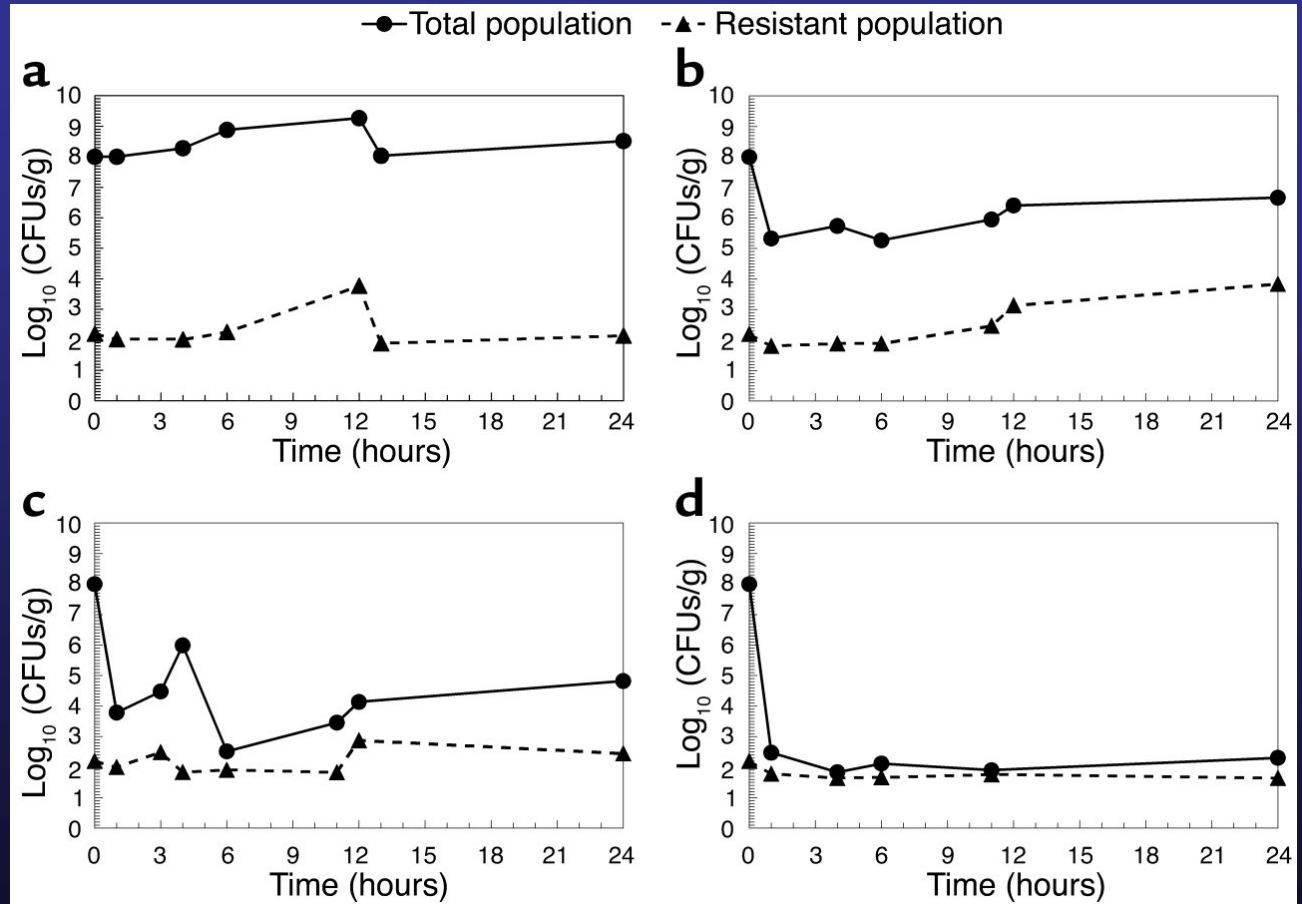


Figure 2. Effect of fluoroquinolone concentration on selection of resistant mutants. *Mycobacterium bovis* BCG was applied to agar plates containing various concentrations of fluoroquinolone, and, after suitable incubation, colonies were counted. The figure is stylized from data in [24], and the fraction of cells recovered at the plateaus was about 1 in 108. MIC and mutant prevention concentration (MPC) are indicated by dotted lines, and the mutant selection windows are indicated by the double-headed arrows. In principle, the lower boundary of the window occurs at the drug concentration where growth inhibition of susceptible cells begins, a concentration that is difficult to determine. We use MIC for inhibition of 99% of the cells in a population to approximate this limit. MICs determined according to the NCCLS standards can also be used for approximation of the lower limit.

# Mutant selection window







# MPC κινολονών

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	Δόση	MIC	MPC	Cmax	t 1/2
Λεβοφλοξασίνη	500 mg	1	8	5.7	8
Μοξιφλοξασίνη	400 mg	0.25	2	4.5	12

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Brief Report

RESISTANCE TO LEVOFLOXACIN  
AND FAILURE OF TREATMENT  
OF PNEUMOCOCCAL PNEUMONIA

ROSS DAVIDSON, PH.D., RODRIGO CAVALCANTI, M.D.,  
JAMES L. BRUNTON, M.D., DARRIN J. BAST, PH.D.,  
JOYCE C.S. DE AZAVEDO, PH.D., PAMELA KIBSEY, M.D.,  
CHRISTINE FLEMING, M.L.T., AND DONALD E. LOW, M.D.

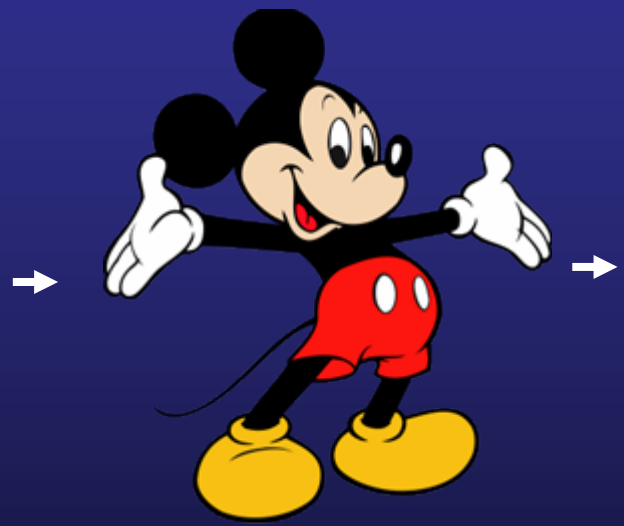
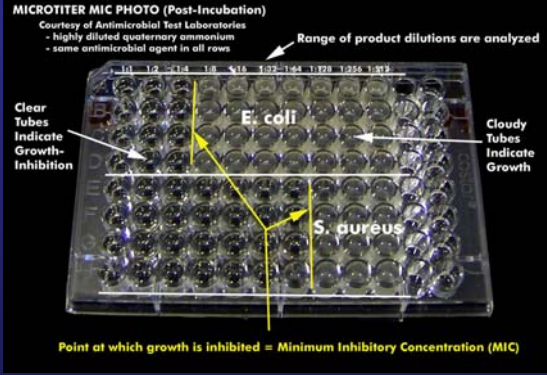
N Engl J Med, Vol. 346, No. 10 · March 7, 2002

MAJOR ARTICLE

Emergence of Levofloxacin-Resistant  
Pneumococci in Immunocompromised  
Adults after Therapy for Community-Acquired  
Pneumonia

Kevin B. Anderson,<sup>1</sup> James S. Tan,<sup>1</sup> Thomas M. File, Jr.,<sup>1</sup> Joseph R. DiPersio,<sup>1</sup> Barbara M. Willey,<sup>2</sup>  
and Donald E. Low<sup>2</sup>

<sup>1</sup>Summa Health System, Akron, Ohio; and <sup>2</sup>Toronto Medical Laboratories/Mount Sinai Hospital Department of Microbiology, University of Toronto, Toronto, Ontario, Canada





Ευχαριστώ