Hvordan benytter vi vores antibiotika: PK/PD

Niels Frimodt-Møller
Afd. For Antibiotikaresistens og Sygehushygiejne
Statens Serum Institut

Founder of PK/PD of antibiotics

Harry Eagle (1906–92)

Medical biologist, born in New York City, New York, USA. He studied medicine at Johns Hopkins, taught and researched there (1927–47), moved to the National Institutes of Health (1947–61) where he headed various sections, and then joined the faculty of the Albert Einstein College of Medicine (1961–88). Perhaps the best known achievement of his productive career was his formulation (1959) of the essential compounds needed to sustain the reproduction of human and other mammalian cells in test tubes. Known as **Eagle's growth medium**, it opened the way for new research on viruses, cancer, and genetic defects. He also made notable discoveries about the process of blood clotting, the treatment of arsenic poisoning, and a cure for African sleeping sickness.

In 1948-52 he published a series of outstanding papers on the relationship between pharmacokinetics of penicillin and effect in vivo, thereby laying the foundation for later research in PK/PD of antibiotics
(NFM´s additon)

”a night with Venus, a lifetime with Mercury…”

Effect of schedule of administration on therapeutic efficacy of penicillin on *S. pyogenes* infection in mice

	Inoculum = 100 cfu		Inoculum = 10.000 cfu		Inoculum = 1.000.000 cfu	
	Single injection	**4 x 3 h interval**	**Single injection**	**4 x 3 h interval**	**Single injection**	**4 x 3 h interval**
CD50 mg/kg	**0.35**	**0.26**	**22**	**0.43**	**50.7**	**0.53**

Eagle, Fleischman & Musselman Am J Med 1950

Calvin Kunin: Dosage schedules of antimicrobial agents: a historical review.

Rev Infect Dis, 1981; 3: 4-11

Skriver bl.a.:

”New derivatives given less frequently may thus appear to be equal in effectiveness to the parent compound given on a standard dosage schedule. Basing of dosage schedules on achievable levels and pharmacokinetic behavior may not be satisfactory.”

Konklusion: Han ved det ikke…..

The sigmoid E_{max} model

Introduceret sm m. neutrop. lårmodel i antibiotikaforskning af Herman Mattie, Leiden, Holland ca. 1980

$$E = \frac{E_{max}\, C^{n}}{EC_{50}^{n} + C^{n}}$$

E = effect

EC_{50} = Conc. 50% effect

C = concentration

n = sigmoidicity factor

~ slope of curve

The sigmoid E_{max} model

$$E = \frac{E_{max}\, C^{n}}{EC_{50}^{n} + C^{n}}$$

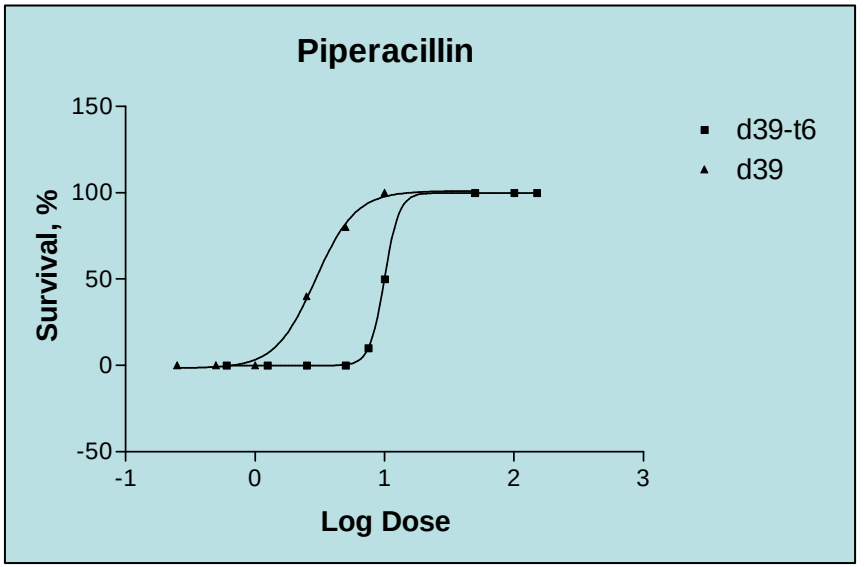
E = effect

EC_{50} = Conc. 50% effect

C = concentration

n = sigmoidicity factor

~ slope of curve



The sigmoid E_{max} model

$$E = \frac{E_{max}\, C^{n}}{EC^{n} + C^{n}}$$

Static dose = 0
vækst eller drab

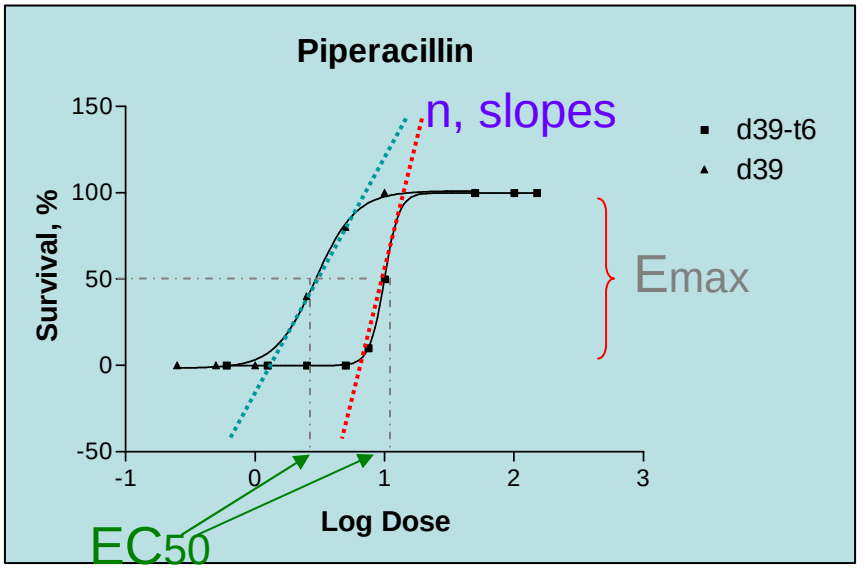
E = effect

EC_{50} = Conc. 50% effect

C = concentration

n = sigmoidicity factor

~ slope of curve



Aminoglycosides: Pharmacodynamics in vivo Gram-negative bacteraemia

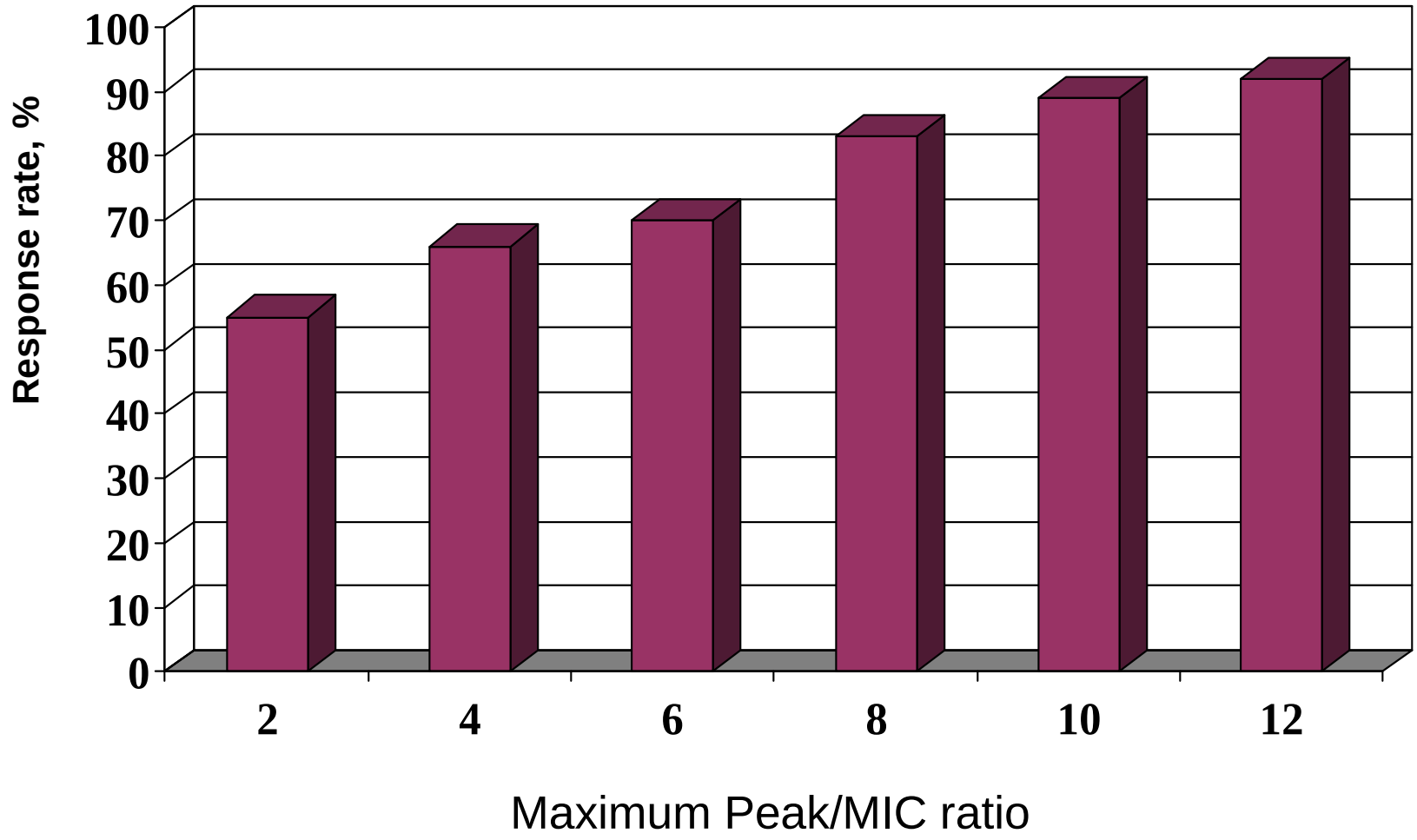
Moore et al. J Infect Dis 149: 443, 1984

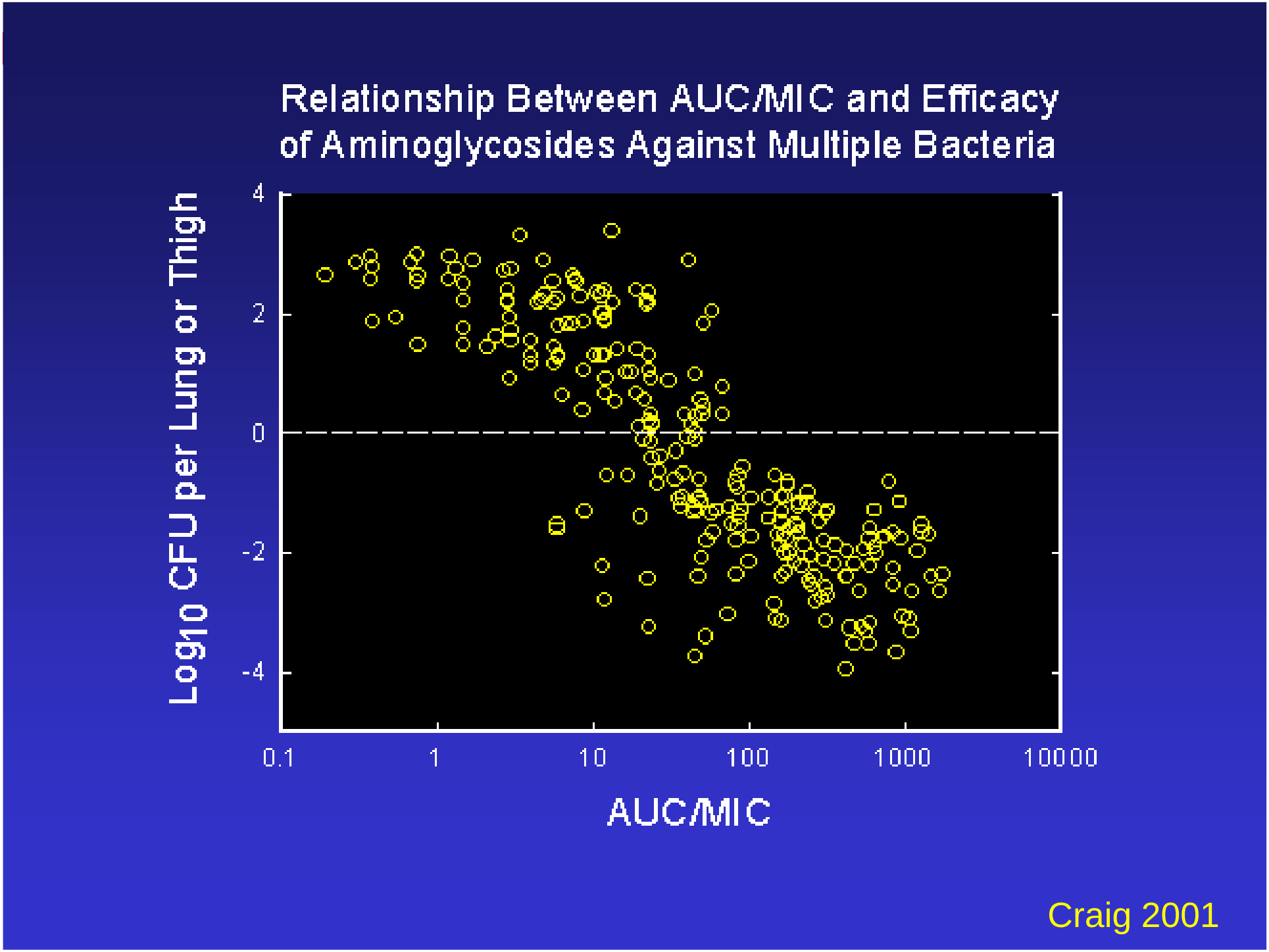
Initial serum peak level	Died	Survived
< 5 mcg/ml	9 (21%)	34 (79%)
≥ 5 mcg/ml	1 (2%)	40 (98%)

P < .01

Relationship between max. Peak/MIC ratio and the rate of clinical response for aminoglycosides

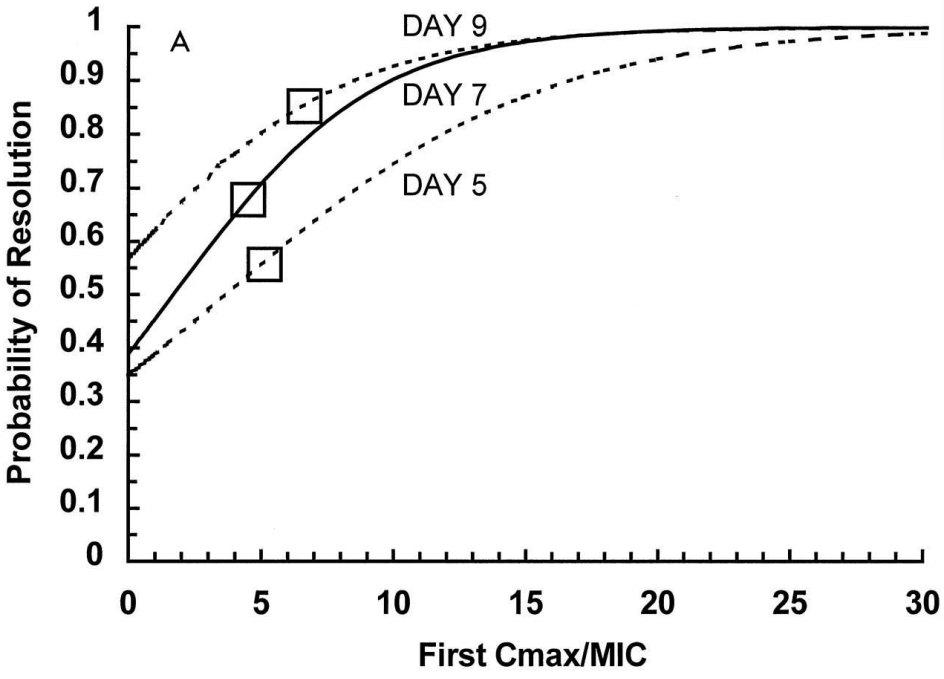
Moore et.al. J Infect Dis, 1987, 155: 93

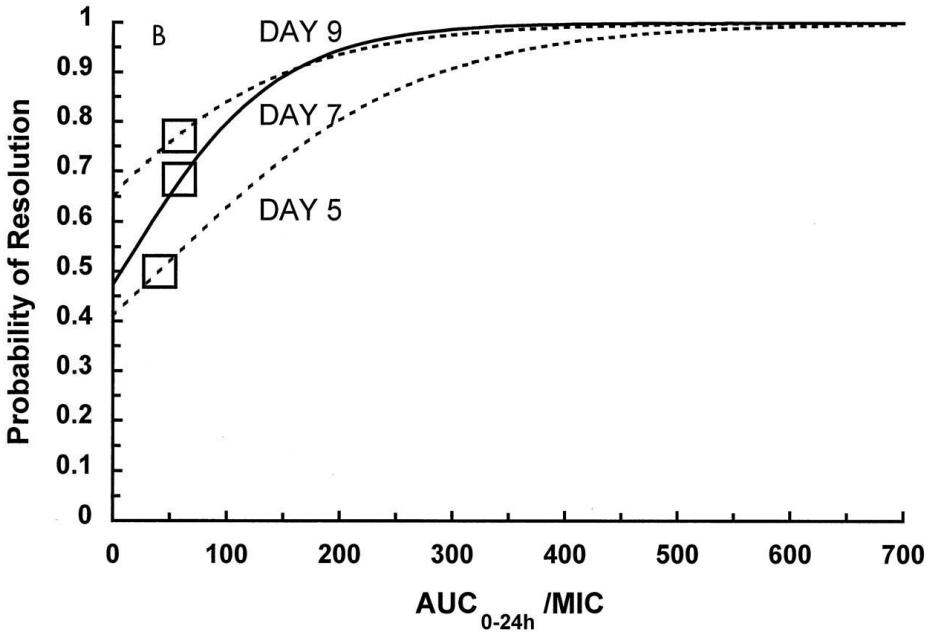



Relationship Between AUC/MIC and Efficacy
of Aminoglycosides Against Multiple Bacteria
Log10 CFU per Lung or Thigh
4
2
0
-2
-4
0.1
1
10
100
1000
10000
AUC/MIC
Craig 2001

Optimizing aminoglycoside therapy for nosocomial pneumonia caused by Gram-neg. Bacteria.
Kashuba et.al. AAC, 1999, 43: 623-29

Probability of temperature resolution by days 5, 7, and 9 of aminoglycoside therapy as determined by logistic regression analysis. (A) Use of first C_{max}/MIC as a predictor variable. (B) Use of $AUC_{0\text{-}24}$/MIC as a predictor variable.





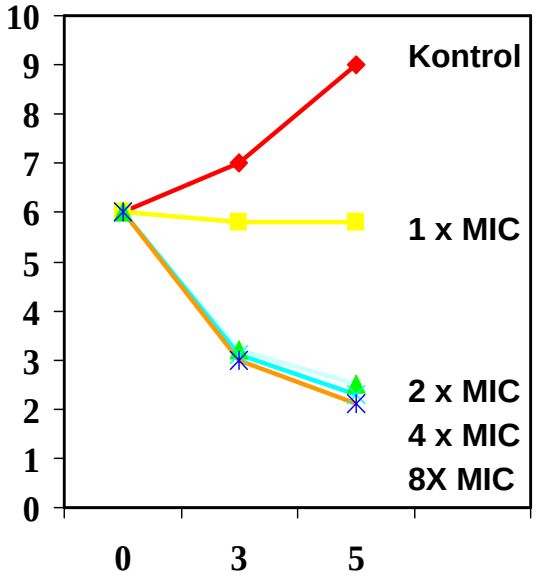
Once a day Aminoglycoside dosing : Toxicity

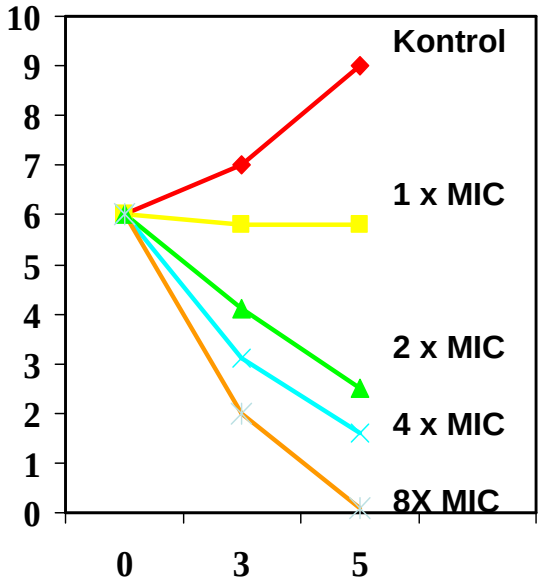
- *Nicolau et.al. AAC 1995,39: 650-655.*
- OD genta 7 mg/kg to 2.184 pts.
- **Nephrotoxicity** (def.: se-creat. > 0,5 mg/dl): 27/2.184 **(1,2 %)**
- **Ototoxicity**:
  3 ptt**.(< 0,5%)**

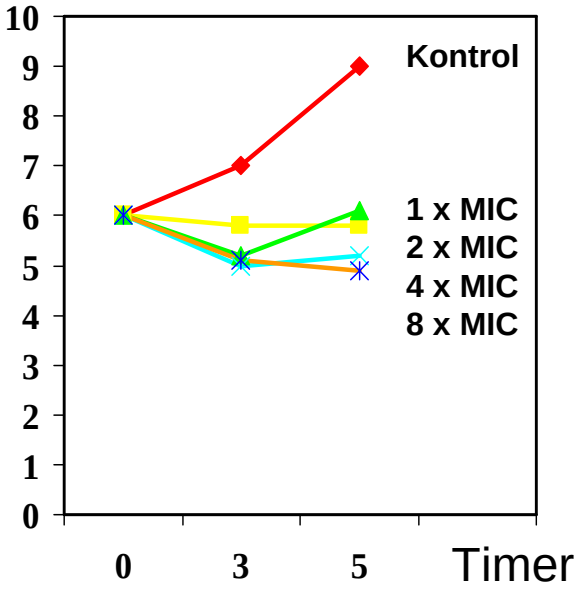
- *Christensen et.al. UfL 1997, 159: 3167-71.*
- OD genta 240 mg to 101 pts.
- **Nephrotoxicity** (def.: se-creat. > 44 umol/l): 5/101 **(5%)**
- **Ototoxicity**:
  1/101 **(1%)**

Antibakteriel drabseffekt in vitro

Log CFU/ml







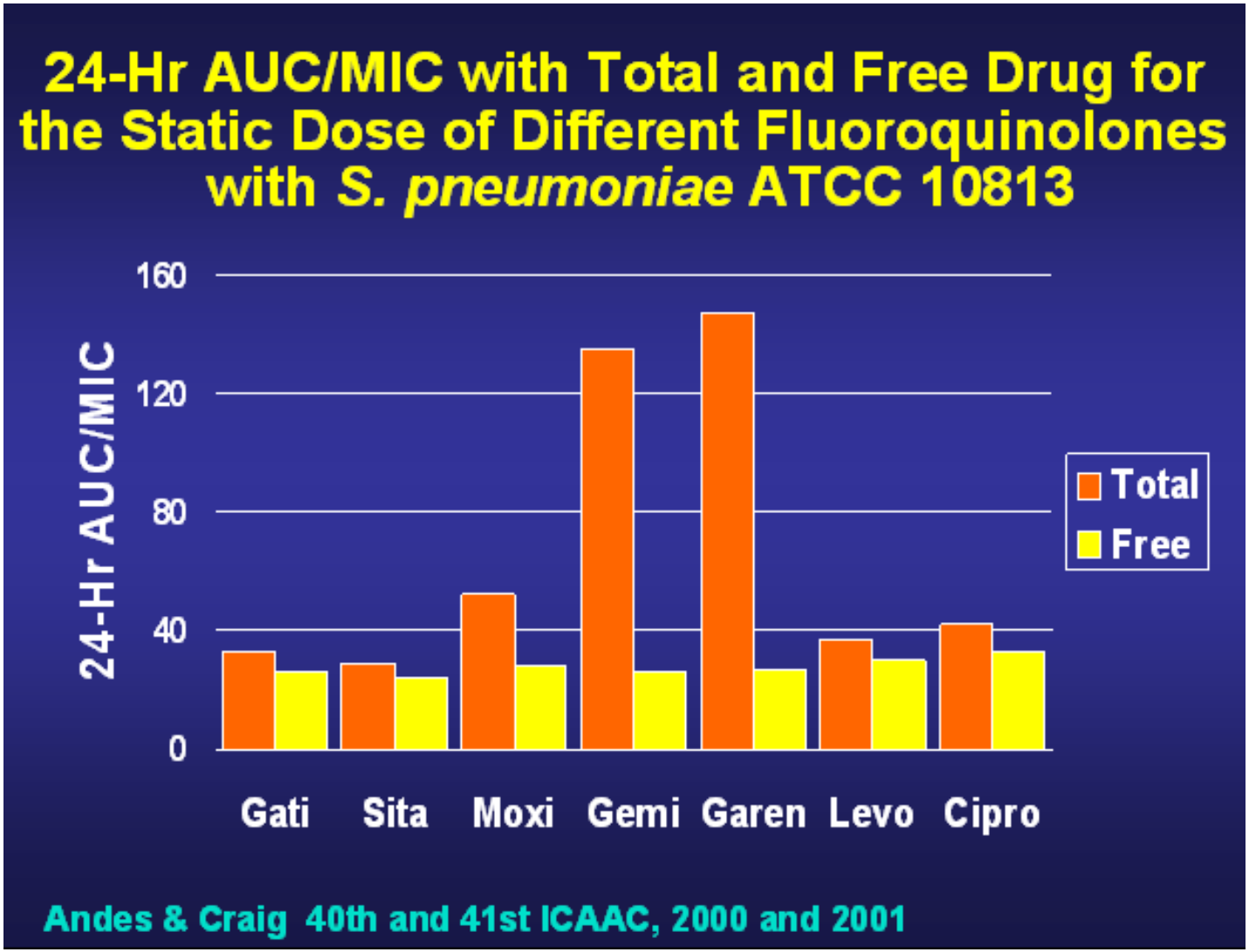
Minimal koncentrationsafhængig, tidsafhængig,
fx. beta-laktam antibiotika

Maximalt koncentrationsafhængig,
fx. fluorkinoloner og aminoglykosider

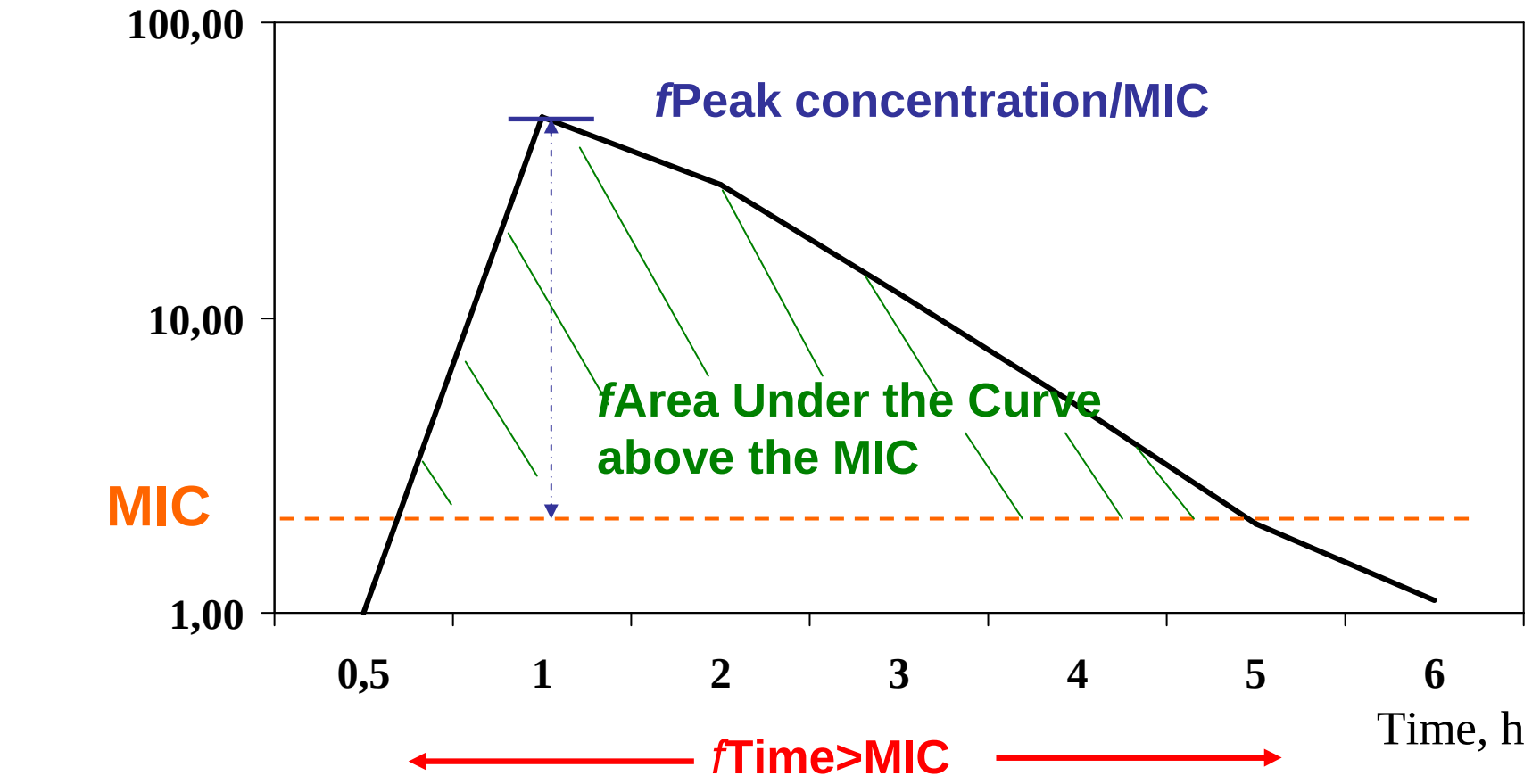
Primært bakteriostatisk
fx. makrolider, tetracykliner

Modific. efter Craig

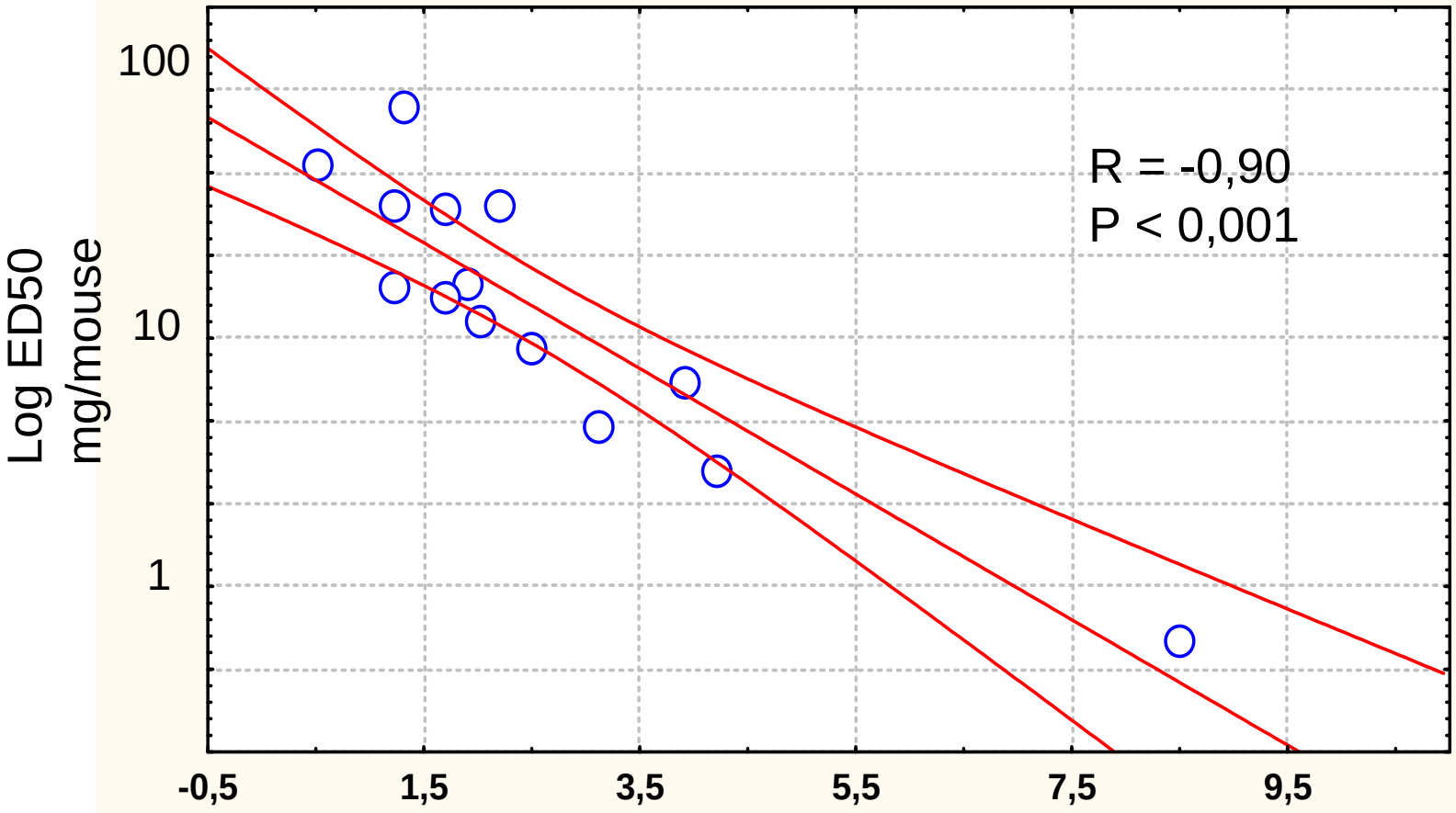
Importance of protein binding for effect of antibiotics



Pharmacokinetic/pharmacodynamic parameters



Mouse peritonitis model with *S. pneumoniae*: Correlation of in vitro activity with in vivo effect for 14 cephalosporins



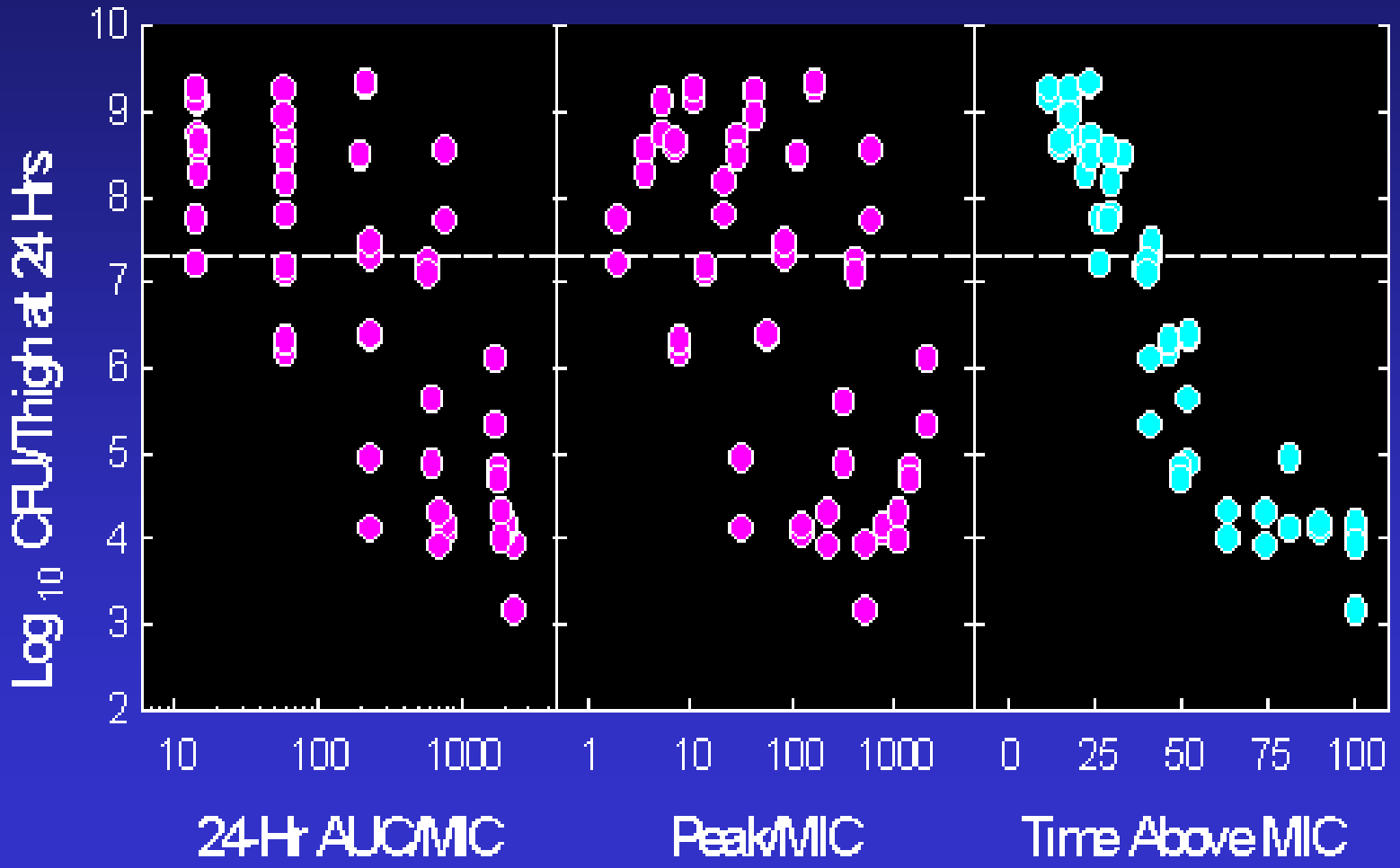
Frimodt-Møller et al. JID 1986, 154: 511-17

Mouse peritonitis model: Correlation between MIC and ED50 (single dose pen-G) for
10 pneumococci with varying penicillin MIC´s

Pk-Pd Parameter	Median (range)	Ratio high/low
T > MIC, min	42 (24-60)	2,5
C-max, mg/L	38 (0,8-70)	87,5
AUC, mg x min/L	1.794 (23-3.500)	152,2
C-max/MIC	38 (9-96)	10,7
AUC/MIC	1.616 (438-4.300)	9,8

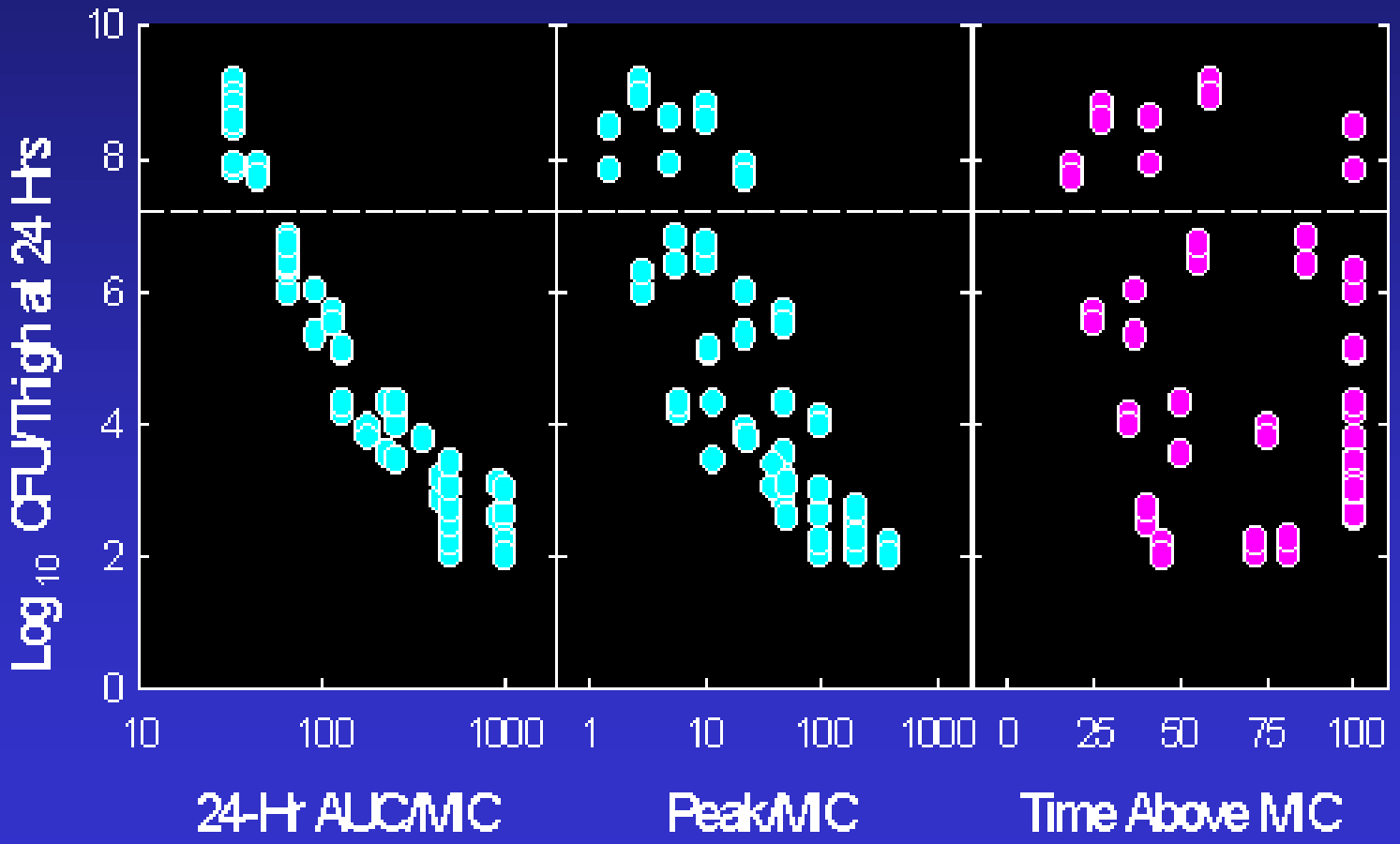
Knudsen et.al. AAC 1995;39:1253-58.

Relationship Between PK/PD Parameters and Efficacy for Ceftazidime against *Klebsiella pneumoniae* in a Murine Pneumonia Model



Craig 1999

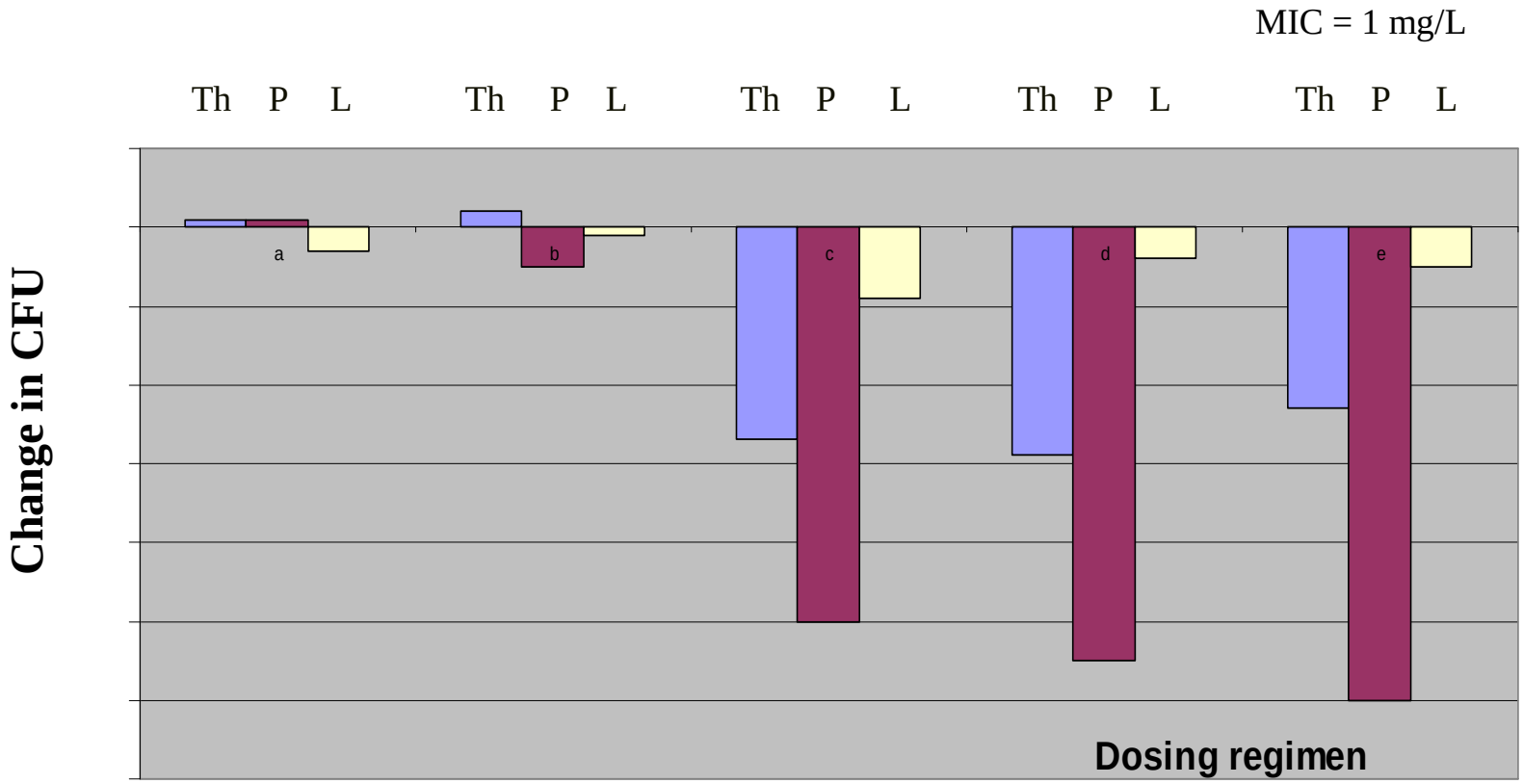
Correlation of PK/PD Parameters with Efficacy of Levofloxacin against *Streptococcus pneumoniae* in Thighs of Neutropenic Mice



Craig 1999

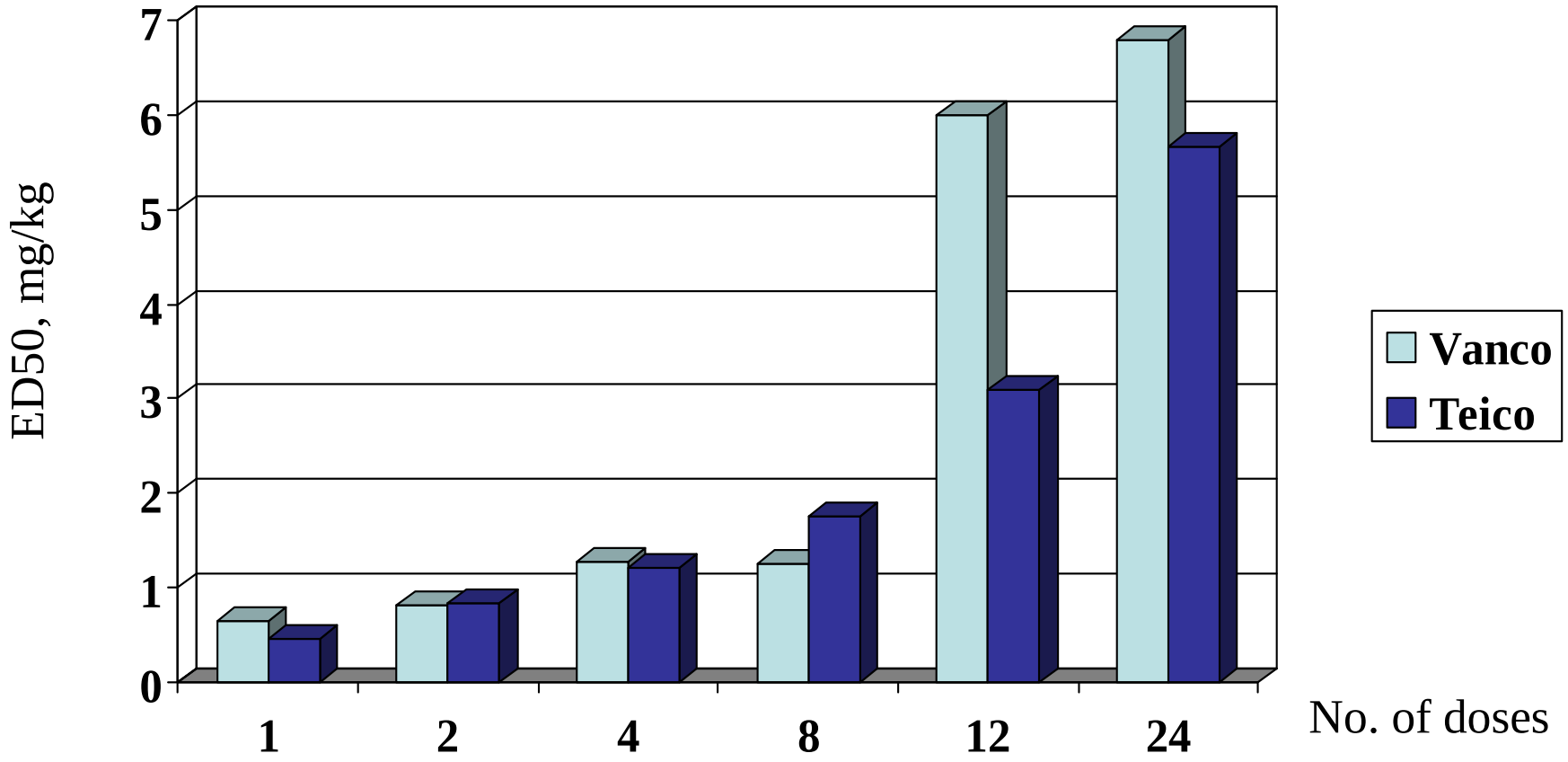
Effect of penicillin on S. pneumoniae infection in peritoneum (P), thigh (TH) and lung (L) of mice

Erlendsdottir et.al. AAC 2001.



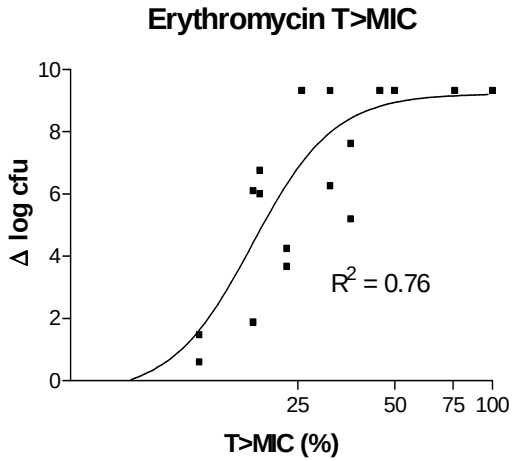
Peak/MIC	**7,4 x**	**3,7 x**	**105 x**	**47 x**	**15 x**
T>MIC	**13 %**	**16 %**	**65 %**	**71 %**	**100 %**

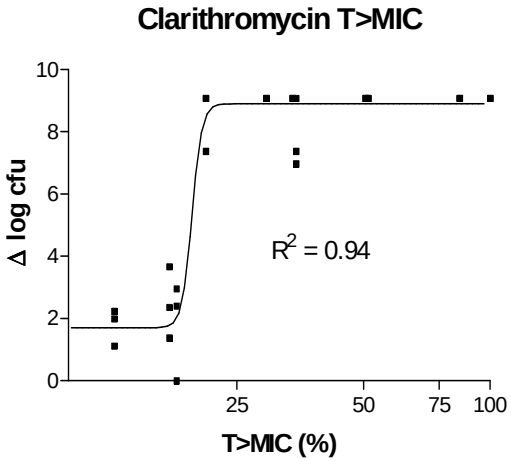
Pharmacodynamics of glycopeptides: ED50´s of different 48 h dosing regimens for vancomycin and teicoplanin against pneumococcus

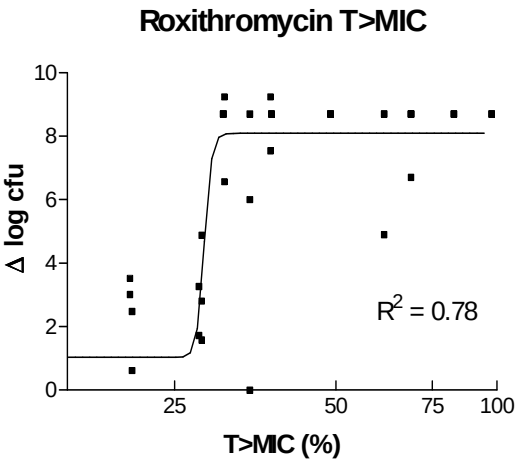


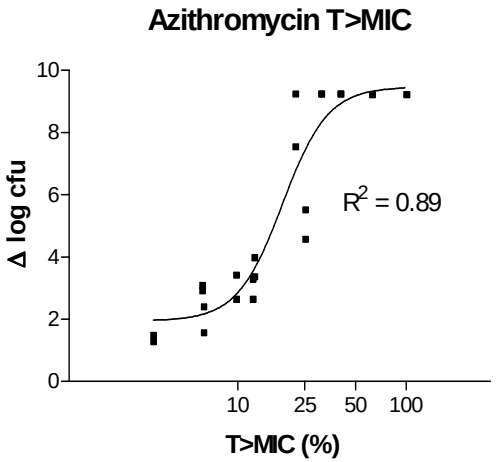
Knudsen JD et.al. AAC 2000; 44: 1247-54

Pk-Pd of macrolides against *S. pyogenes* in mouse peritonitis model: T >MIC









Each point is the result of one 24h-dosing regimen

Nielsen HU et al.

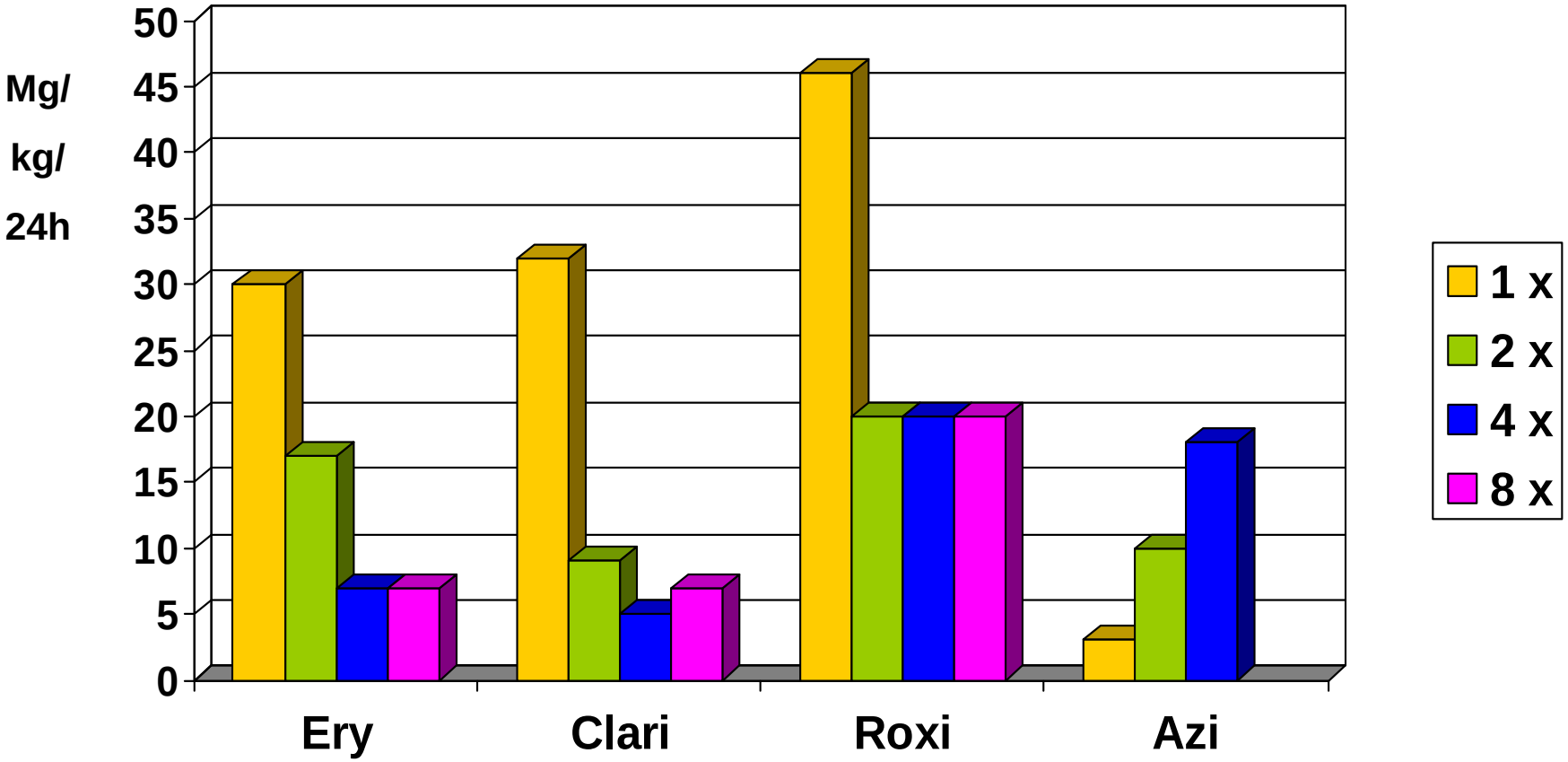
Fuursted K et al. Comparative study of bactericidal activities, PAE, and effects of bacterial virulence of Penicillin G and six macrolides against S. pneumoniae.
AAC, 1997; 41: 781–784

TABLE 3. Data calculated by logistic regression analysis of survival rates of a serotype 3 *S. pneumoniae* strain exposed to penicillin G or a macrolide at 10 times the MIC for 1 h

Drug	Slope (SE)	Intercept (SE)	LD_{50} (95% CI[a])	Relative LD_{50} (95% CI)
None (control)	2.9 (0.5)	−7.2 (1.4)	323 (216–487)	
Penicillin G	3.0 (0.9)	−7.6 (2.0)	315 (158–664)	1.0 (0.4–2.3)
Erythromycin	4.6 (1.5)	−14.0[b] (4.7)	1,916 (993–3,872)	5.9[b] (2.7–13.3)
Azithromycin	3.2 (0.6)	−10.7[b] (1.6)	2,287 (886–5,964)	7.1[b] (2.5–20.0)
Clarithromycin	3.2 (0.6)	−8.9 (1.6)	596 (228–1,537)	1.8 (0.7–5.2)
Dirithromycin	3.4 (1.4)	−10.6[b] (4.4)	1,360 (527–3,510)	4.2[b] (1.5–11.8)
Roxithromycin	2.2 (0.7)	−5.4 (1.9)	316 (154–639)	1.0 (0.4–2.21)
Spiramycin	0.8 (0.7)	−2.1[b] (2.6)	1,174 (435–3,085)	3.6[b] (1.2–10.3)

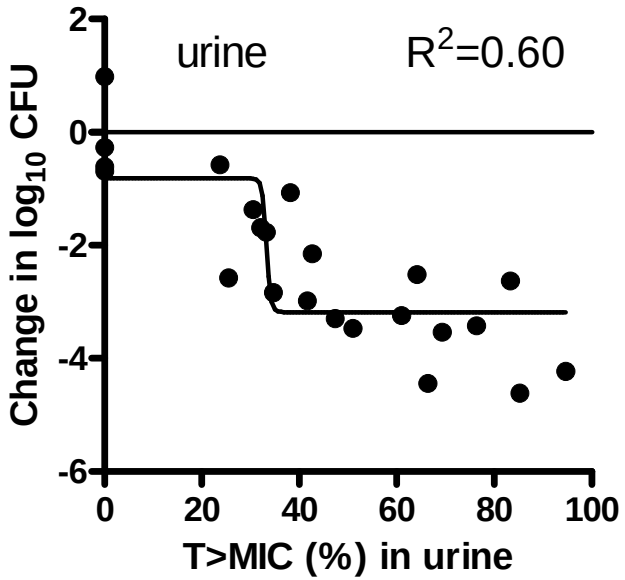
[a] CI, confidence interval.
[b] Significantly different from control at 5% test level.

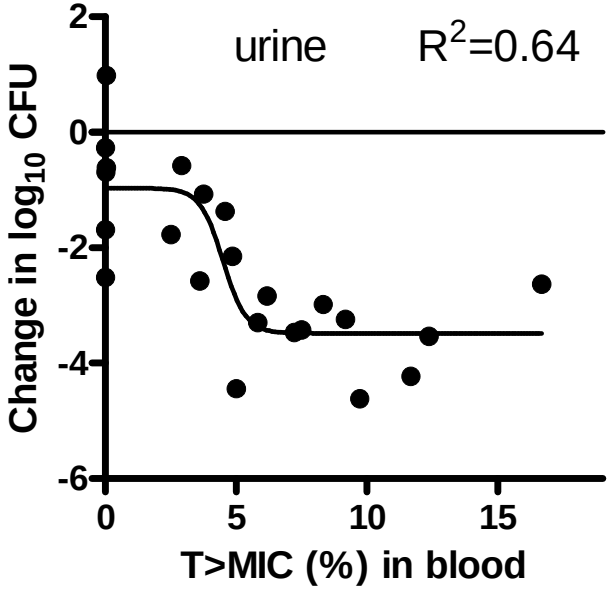
Macrolides vs. *S. pyogenes* in mouse peritonitis model: ED50 related to dosing regimen



Nielsen HU et al.

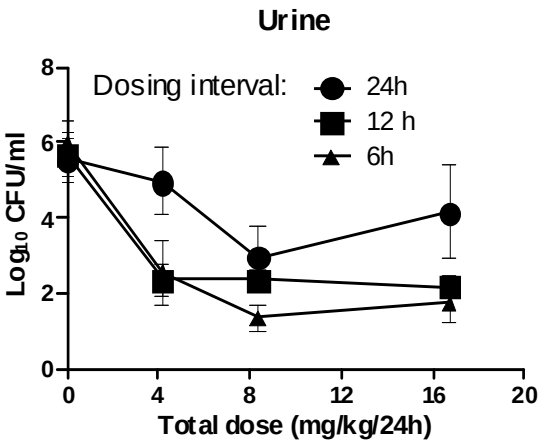
Mecillinam PKPD ved behandling af urinvejsinfektion i musemodel

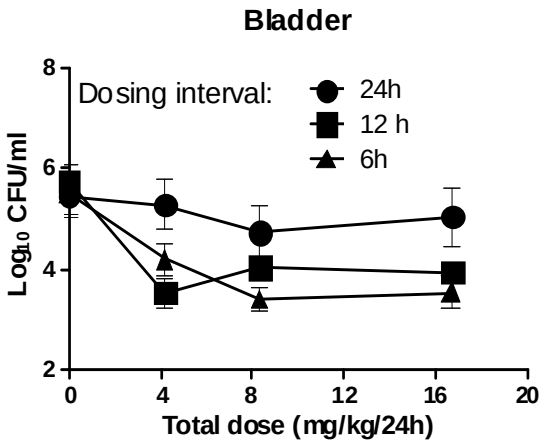


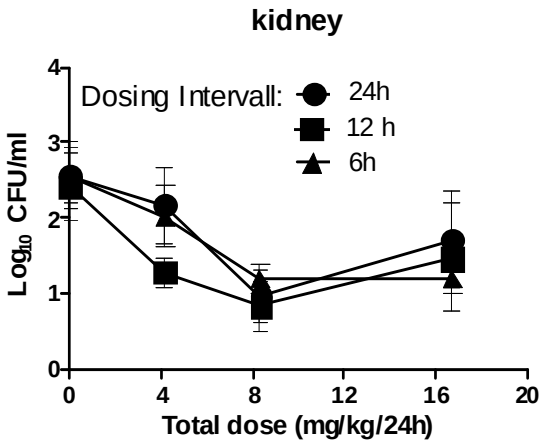


Lundberg et al. ICAAC 2009

Mecillinam PKPD ved behandling af urinvejsinfektion i musemodel

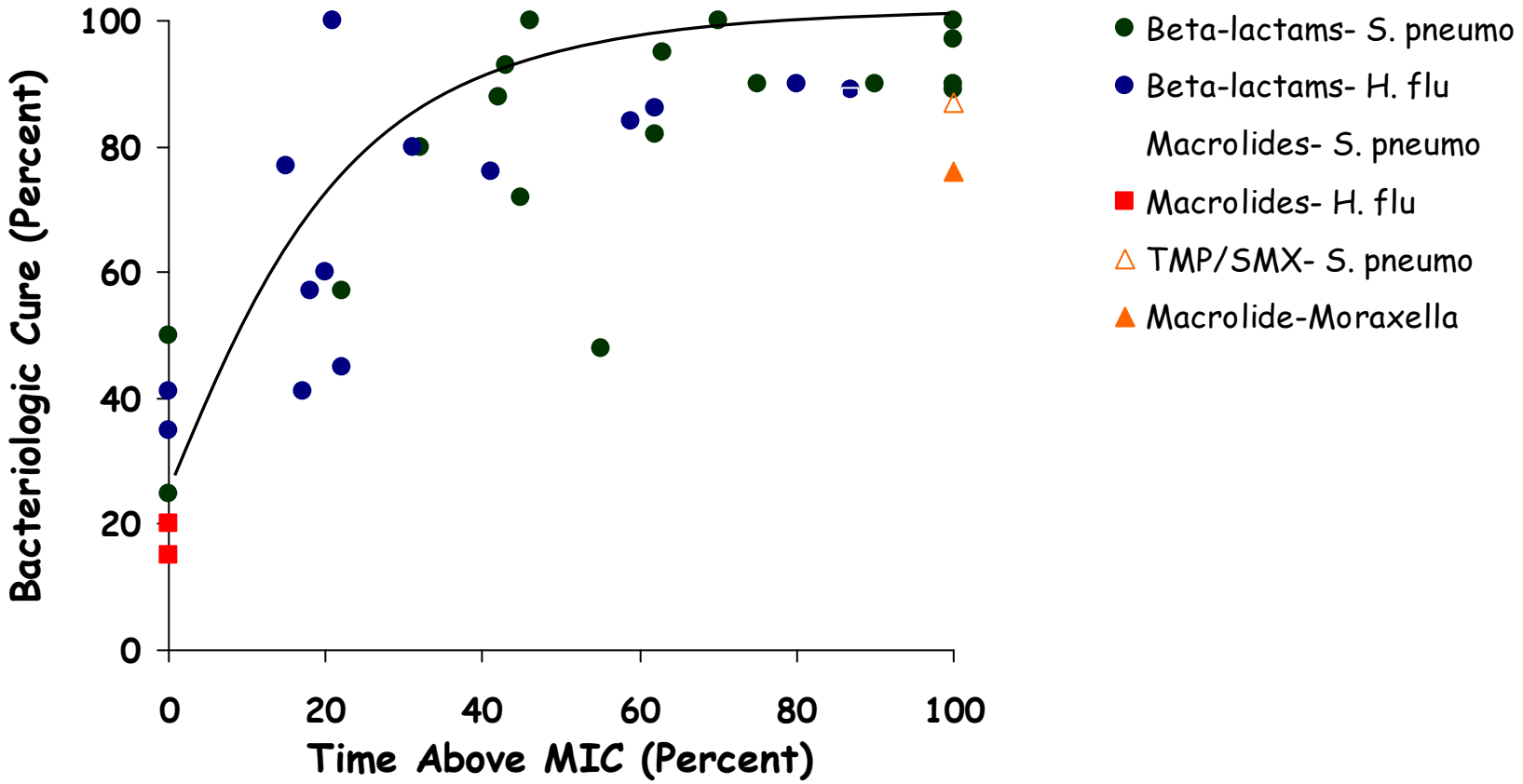






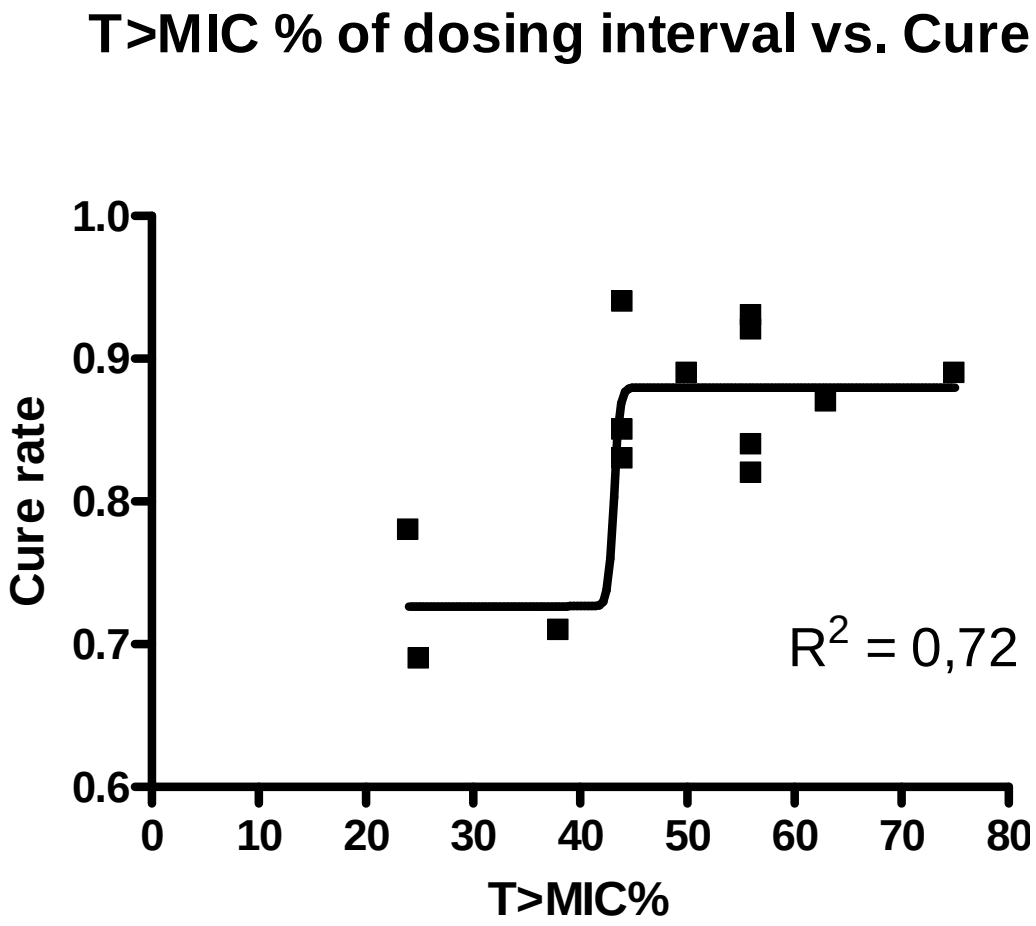
Lundberg et al. ICAAC 2009

Relationship Between T>MIC in Serum and Efficacy of Antibiotics in Treatment of Acute Otitis Media



Adapted from Craig and Andes, *Pediatr Infect Dis J* 1996;15:255-9.

Lan AJ, Colford JM. The impact of dosing frequency on the efficacy of 10-day penicillin or amoxicillin therapy for streptococcal tonsillopharyngitis: A meta-analysis.
Pediatrics 2000, 105: 19-27



Conditions:

Cmax correlated to dose

Protein binding = 70%

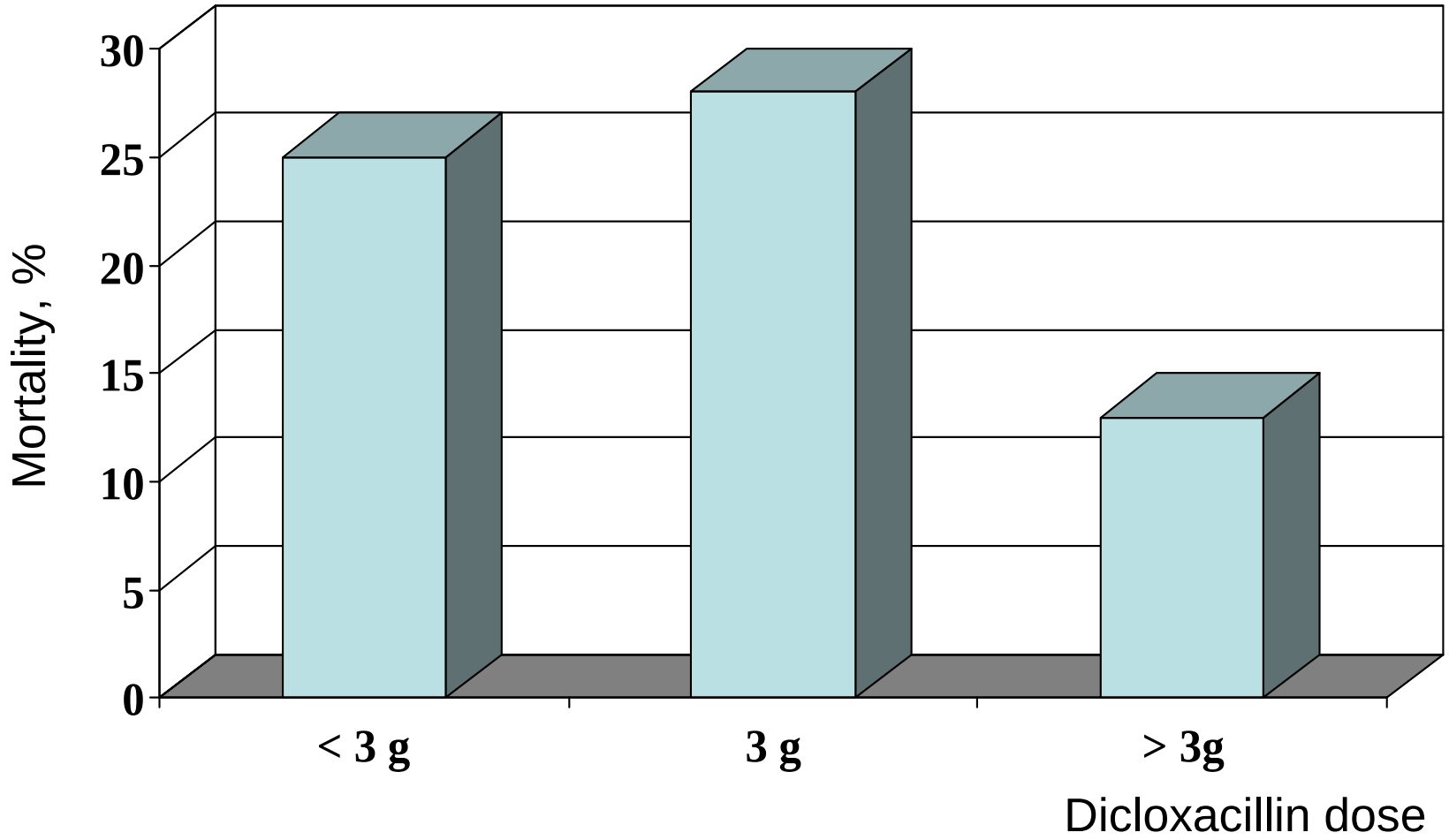
T½ = 45 min

MIC for PenV vs. *S.pyogenes*: 0,01 mg/l

F-M 2007

Mortality related to Dicloxacillin daily dose for treatment of *S. aureus* bacteremia

Jensen AG et.al. Arch Intern Med, 2002, 162: 25-32



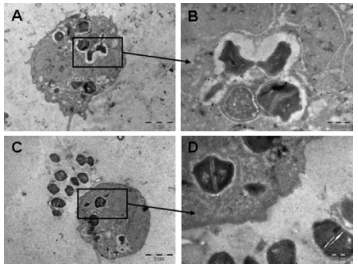
P = 0.02, > 3g vs. ≤ 3g

Dicloxacillin dose vs. Time > MIC of free (non-proteinbound) concentration

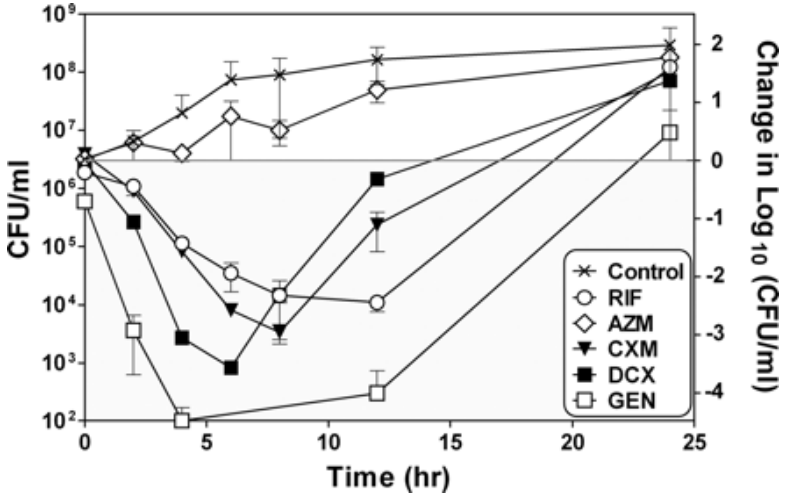
Dose	Time > MIC	
	in h	in % of dosing interval
1 g x 3	1.8 – 2.8	23 - 35 %
1 g x 4	- -	30 - 47 %
2 g x 3	2.4 – 3.6	30 - 45 %
2 g x 4	- -	40 - 60 %

T½ = 0.6-0.8 h; Vd= 0,13- 0,19 l/kg; Prot.bind.= 91-98 % MIC-s.a.= 0,4

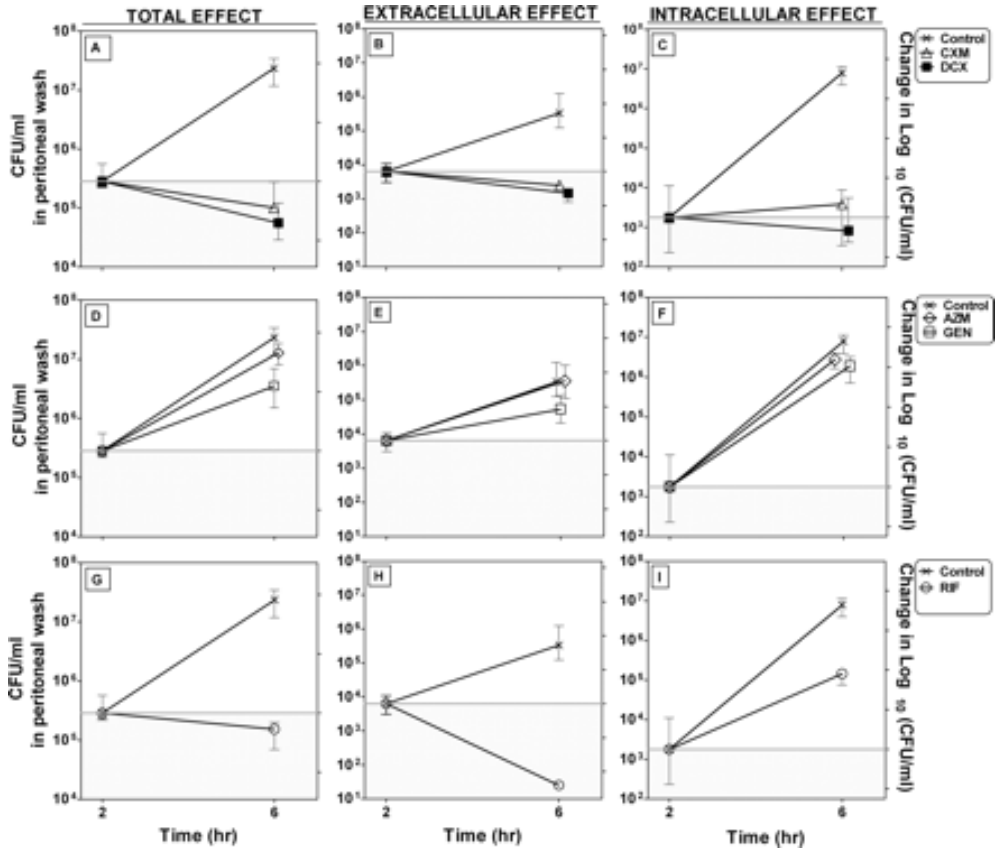
Intracellular effect of antibiotics against *S.aureus* in vitro and in vivo in the mouse peritonits model



In vitro kinetic model:

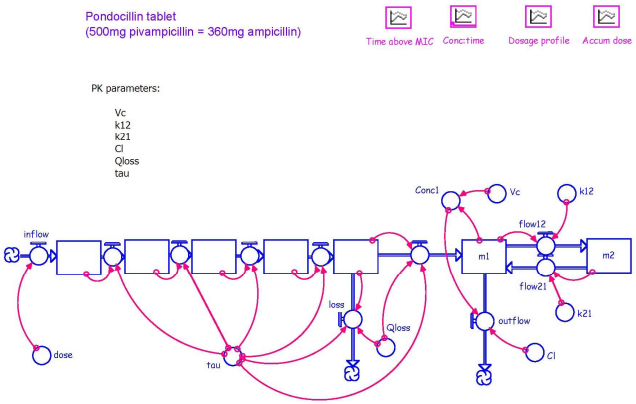


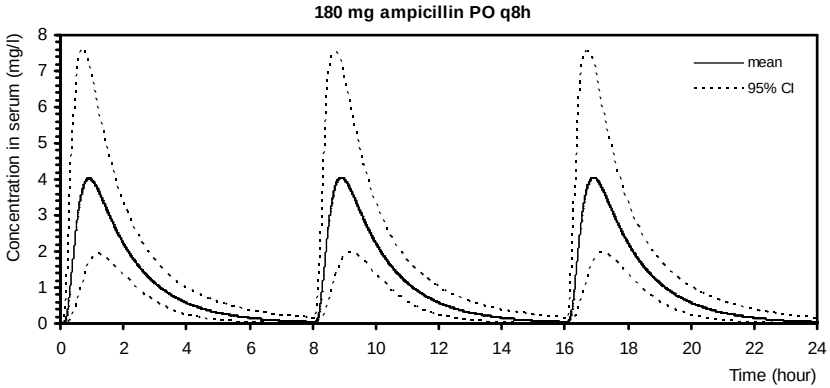
In vivo: Time kill after single dose

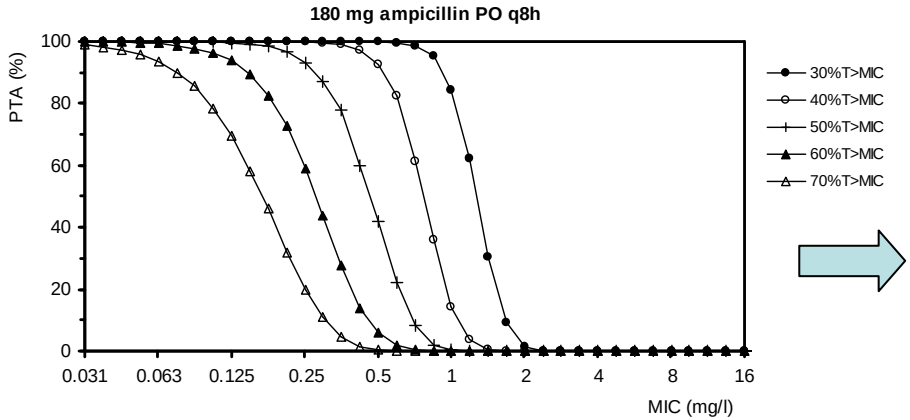


Sandberg A et al. AAC 2009, 53:1874-83

Dosering af antibiotika til mennesker: Populationsanalyse med MonteCarlo simulering: PivAmpicillin







%T>MIC = 50 :	PTA (%)	50	90	99
Scenario	Daily dose (mg)			
(a) 180 mg q8h	540	0.420	0.250	0.149
(b) 720 mg q12h	1440	0.500	0.177	0.074

Klaus Skovbo Jensen, forbedret model fra George Drusano

Journal of Antimicrobial Chemotherapy (2000) **46**, 973–980

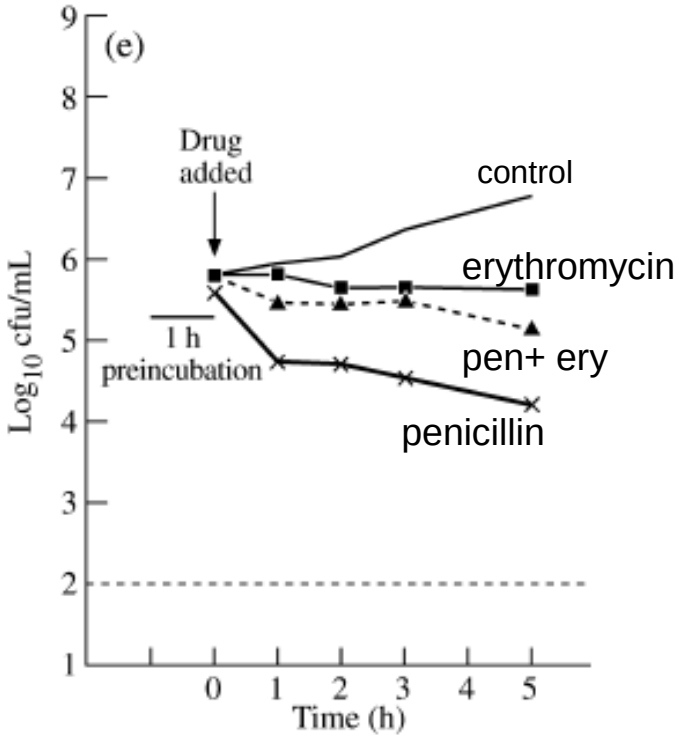
Antagonism between penicillin and erythromycin against *Streptococcus pneumoniae in vitro* and *in vivo*

Helle Krogh Johansen, Thøger Gorm Jensen, Ram Benny Dessau, Bettina Lundgren and Niels Frimodt-Møller*

Department of Clinical Microbiology, Statens Serum Institut, Artillerivej 5, DK-2300 Copenhagen S, Denmark

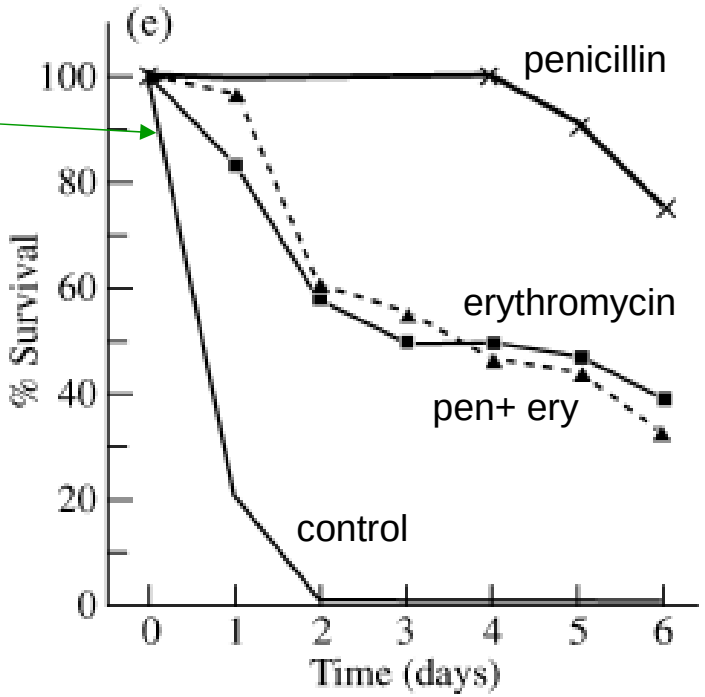
STATENS SERUM INSTITUT

In vitro



In vivo

control



Journal of Antimicrobial Chemotherapy (1998) **41**, 451–459

STATENS SERUM INSTITUT

Pharmacodynamics of penicillin are unaffected by bacterial growth phases of *Streptococcus pneumoniae* in the mouse peritonitis model

J. D. Knudsen[a]*, N. Frimodt-Møller[b] and F. Espersen[a]

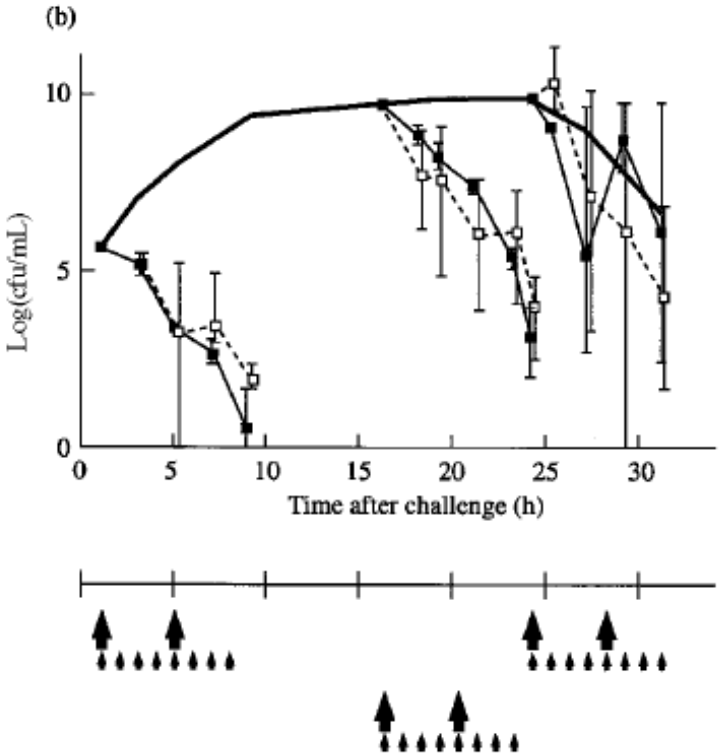
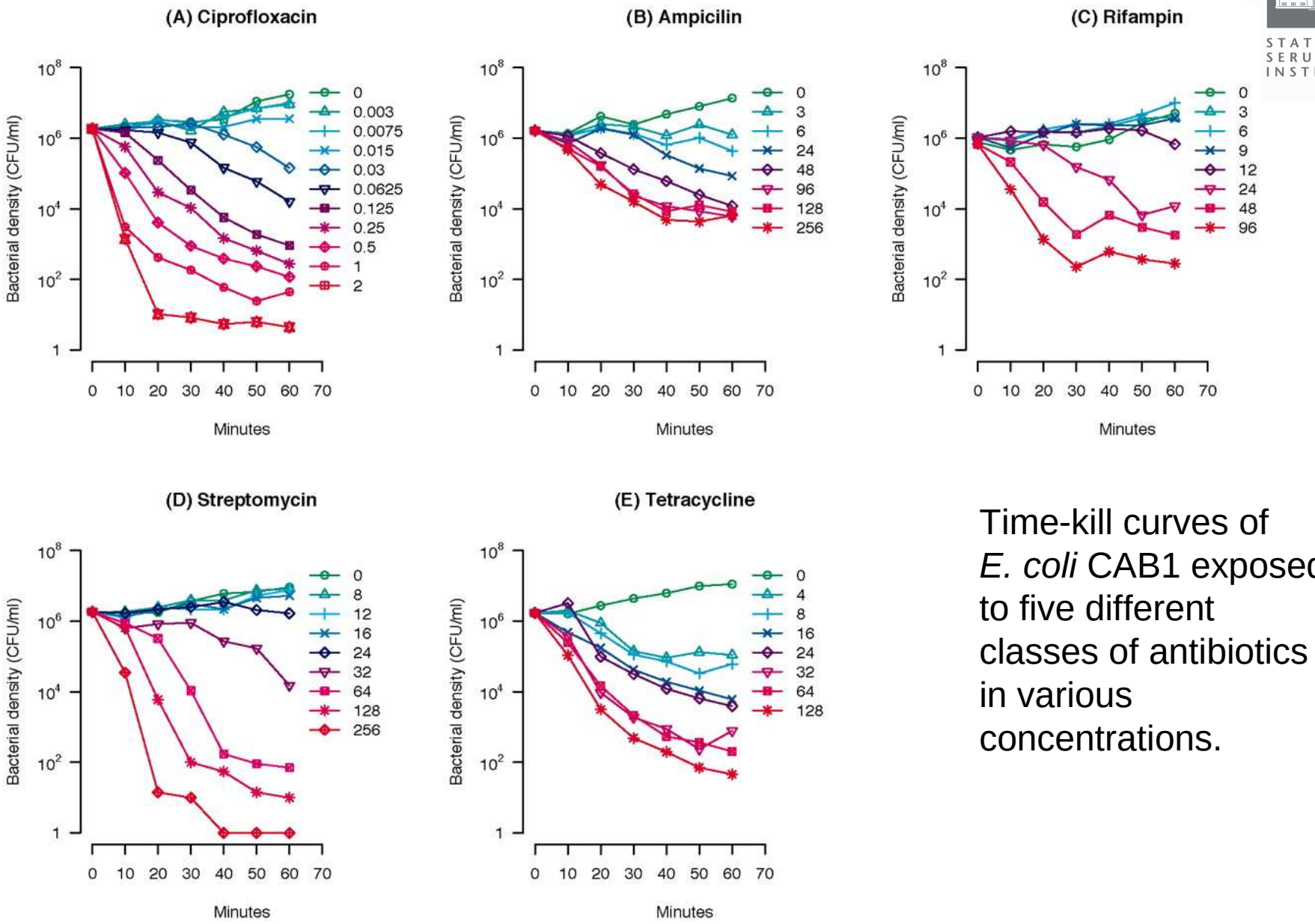


Table II. Correlation between pharmacokinetic parameters and effect achieved in nine treatment regimens initiated 1–16 h after bacterial challenge

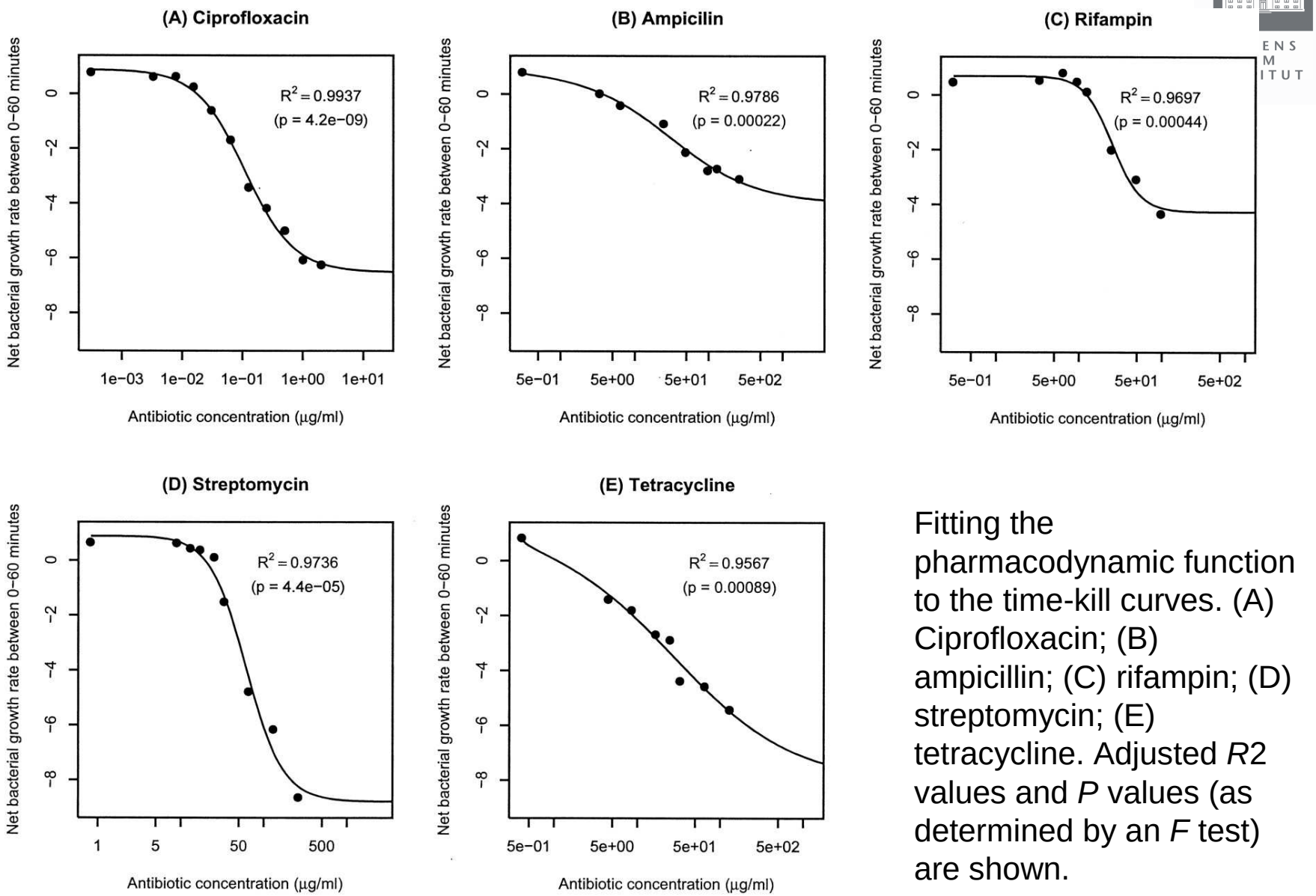
	E^a	
Pharmacokinetic parameter	Spearman's rho	*P* value
$T_{>MIC}$ as % of treatment time	–0.67	0.047
$T_{>MIC}$ after first dose	–0.72	0.027
C_{max}	–0.64	0.066
AUC	–0.72	0.027

[a]Effect *E* is the change in the mean of $\log_{10}$(peritoneal fluid cfu/mL) from the start till the finish of 8 h of treatment.



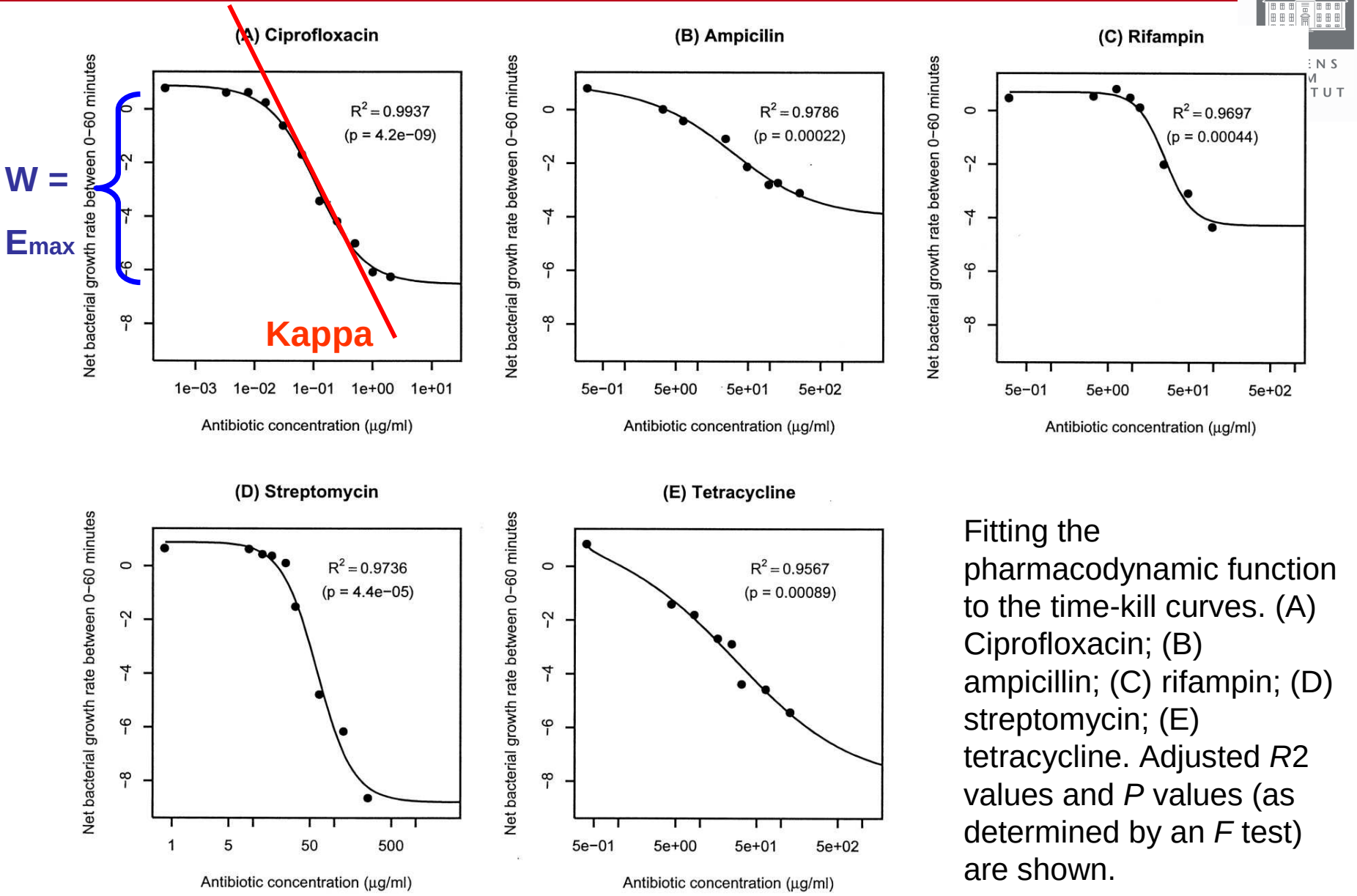
Time-kill curves of *E. coli* CAB1 exposed to five different classes of antibiotics in various concentrations.

Regoes et al. Antimicrob Ag Chemother 2004, 48: 3670-3676



Fitting the pharmacodynamic function to the time-kill curves. (A) Ciprofloxacin; (B) ampicillin; (C) rifampin; (D) streptomycin; (E) tetracycline. Adjusted *R*2 values and *P* values (as determined by an *F* test) are shown.

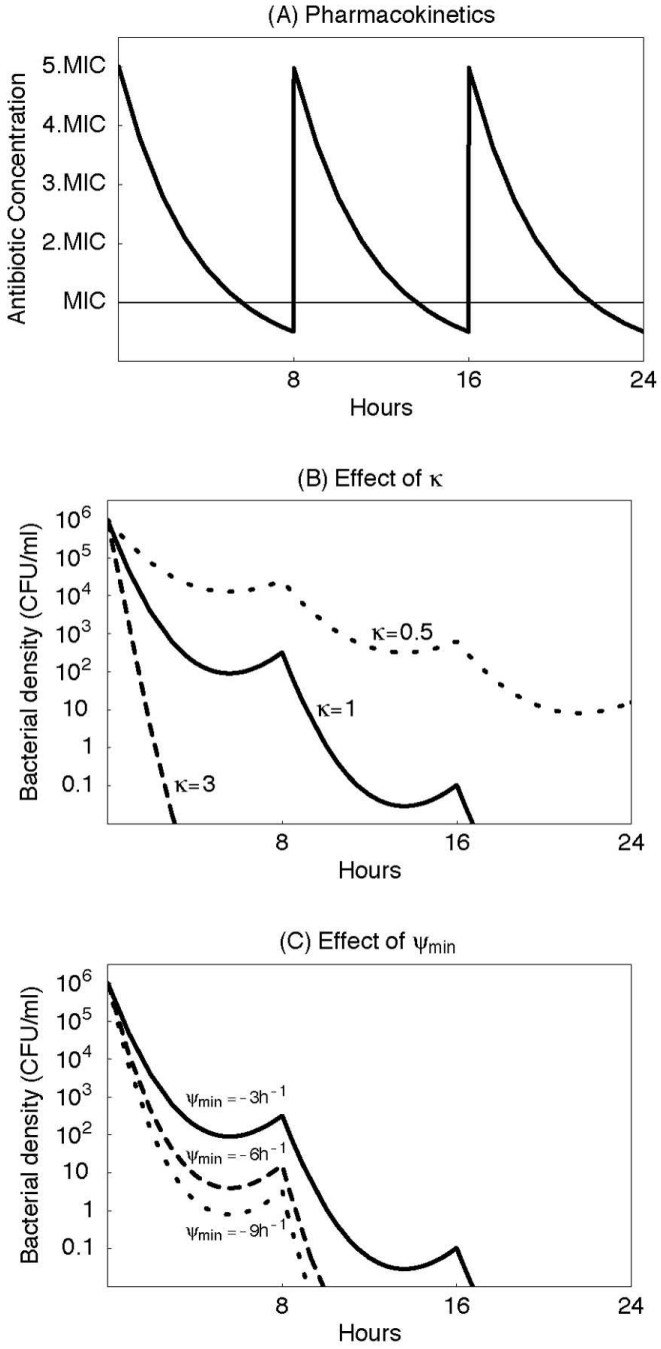
Regoes et al. Antimicrob Ag Chemother 2004, 48: 3670-3676



Fitting the pharmacodynamic function to the time-kill curves. (A) Ciprofloxacin; (B) ampicillin; (C) rifampin; (D) streptomycin; (E) tetracycline. Adjusted *R*2 values and *P* values (as determined by an *F* test) are shown.

Regoes et al. Antimicrob Ag Chemother 2004, 48: 3670-3676

N. Frimodt-Møller 2004



Simulation of the effect of treatment on the bacterial decline for three hypothetical antibiotics that differ in the shape parameter and min. (A) Pharmacokinetics which we assume to be identical for each hypothetical antibiotic. (B) Bacterial decline under treatment with an antibiotic characterized by k = 1 (solid line), k = 3 (dashed line), and K = 0.5 (dotted line). (C) Bacterial decline under treatment with an antibiotic characterized by Wmin = –3 h–1 (solid line), Wmin = –6 h–1 (dashed line), and Wmin = –9 h–1 (dotted line). It is obvious that, in addition to the MIC, the other parameters of the pharmacodynamic function (equation 3) are an important determinant of treatment efficacy.

Regoes et al. Antimicrob Ag Chemother 2004, 48: 3670-3676

Rationel antibiotikabehandling

- Hvis korrekt antibiotikum (patogen S, fokus opnåeligt) og dosis, da vil med få undtagelser (TB, endokardit) bakterierne være dræbt < 3 (1) dage
- Ergo: Hvis der ikke ses effekt efter 3 dage: Seponer behandling !
- Baktericide > bakteriostatiske

Pharmacokinetic determinants of penicillin cure of gonococcal urethritis

Jaffe et.al. AAC, 1979, 15: 587-591

- 47 male inmates of US Penitentiary, Atlanta, age > 21 years, received intraurethral inoculation with 2-mm platinum loop of 15 x 10-9 cfu of *N. gonorrhoeae* – 45 developed purulent discharge.

- 2 days after inoculation subjects were treated i.m. with penicillin in following doses: Single doses of 0.9, 1.2, or 2.4 Mill. Units or 1.0 + 0.4 Mill.Units at 3 h .

- Serum penicillin conc. measured in all subjects.

Pharmacokinetic determinants of penicillin cure of gonococcal urethritis

Jaffe et.al. AAC, 1979, 15: 587-591

RESULTS:

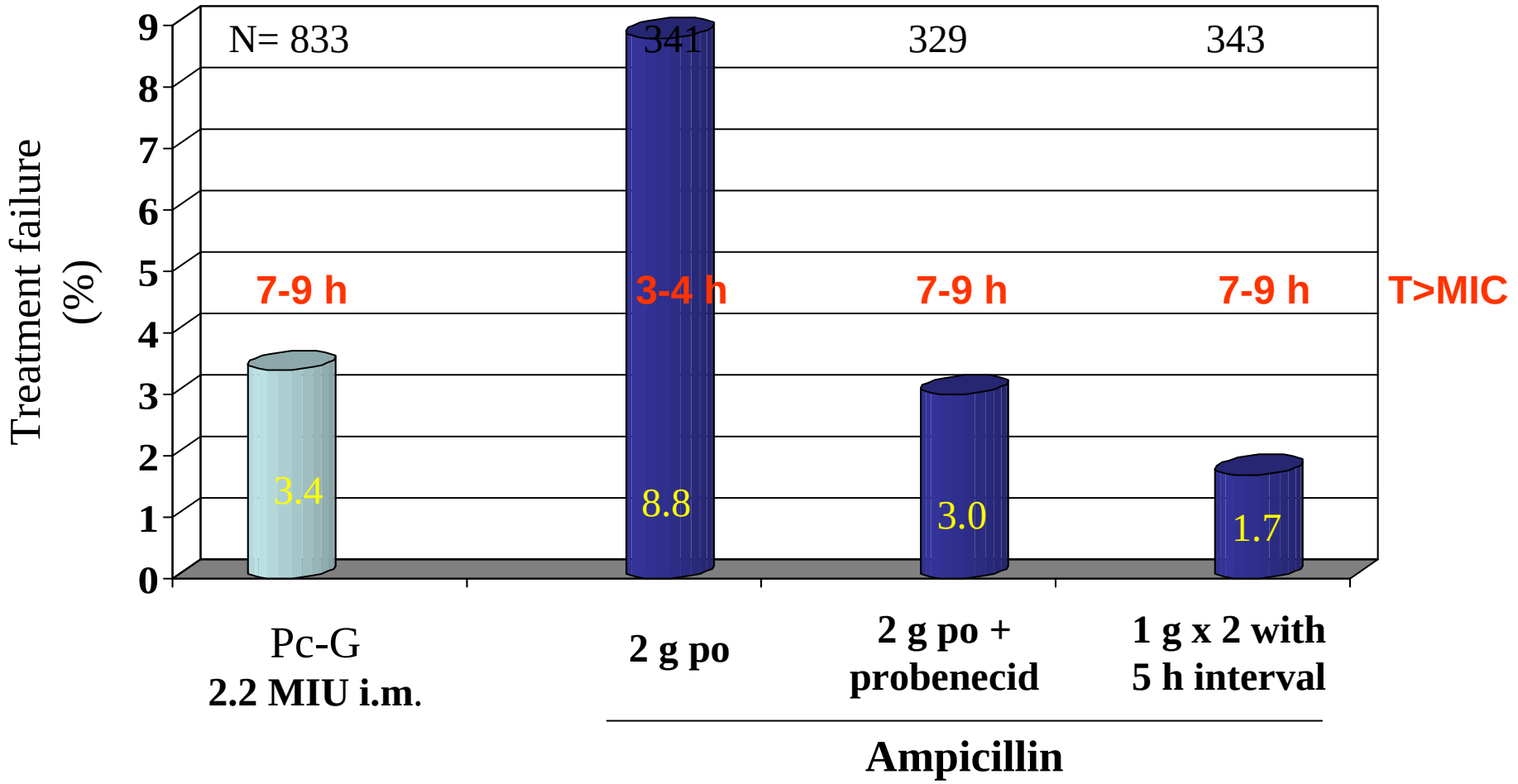
Cure was best predicted by

the time the Se-Penicillin Conc. remained above 3-4 x MIC

those cured had Se-Penicillin Conc. in this range for 7-10 h.

Treatment of gonorrhoeae in men: Comparison of Ampicillin with Penicillin-G

Eriksson, Acta Dermatovener, 1970,50: 451

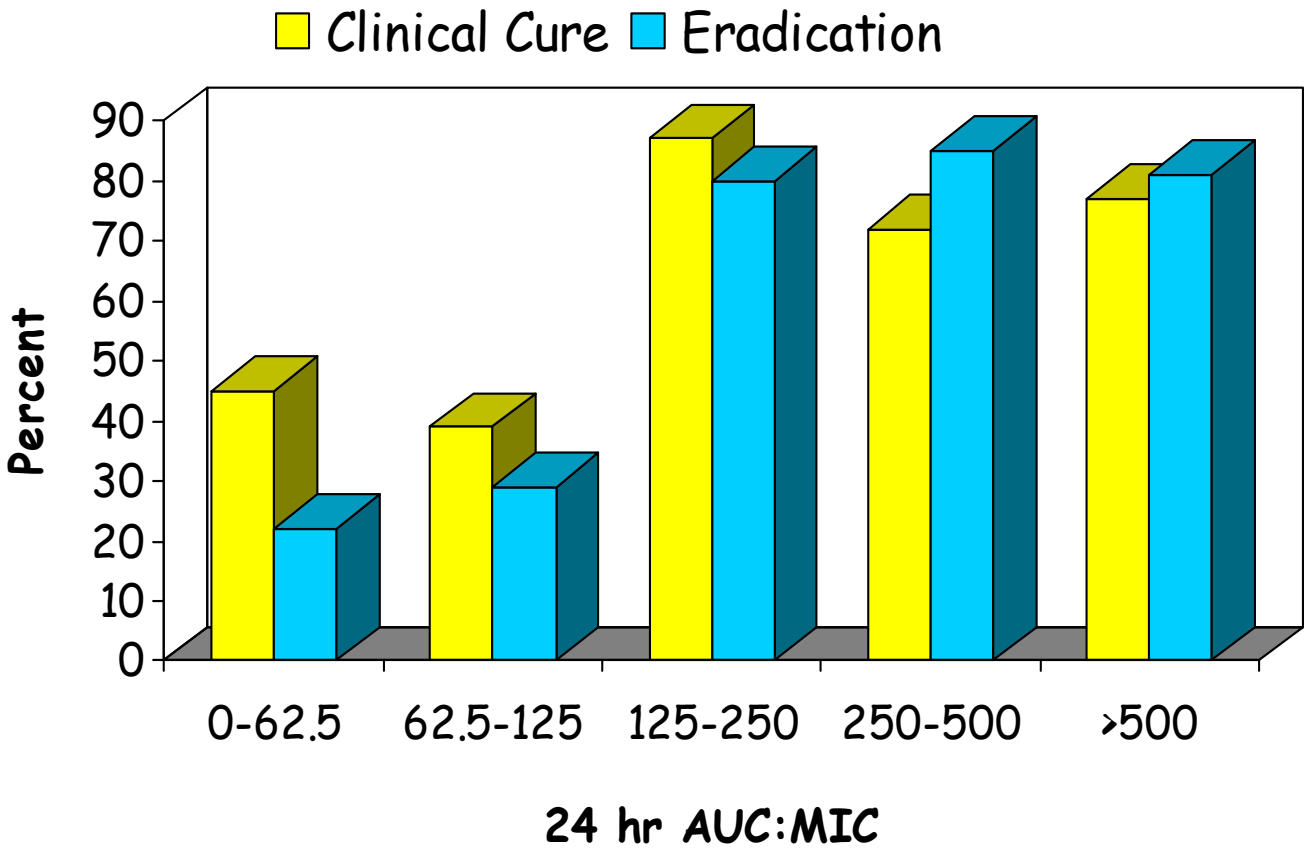


En-gangs dosering

- Gonorrhoea — beta-lactam, cipro, azithro
- Chlamydia — azithro
- Urinvejsinfektion — fosfomycin, trim/sulfa
- GAS-tonsillit — benzathin-pc, ceftriaxon, azithro
- Meningit — benzathin-pc, ceftriaxon, moxiflox

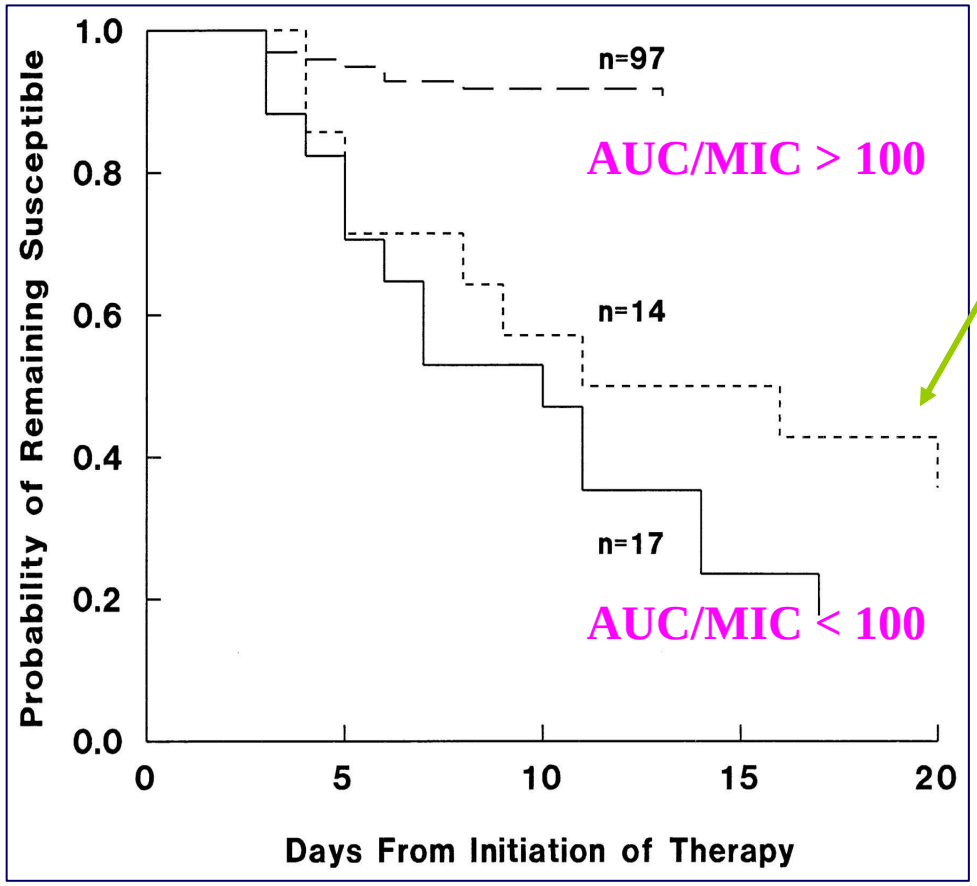
Relationship Between **Ciprofloxacin** AUC:MIC and Efficacy in Treating Bacterial Pneumonia

Forrest et al., AAC 37:1073.



Thomas JK et al. Importance of AUC/MIC ratio for development of resistance

Antimicrob Ag Chemother 1998; 42: 521-7.



- Resistance developed in β-lactamase-type-I Gram-neg. rods even when AUC/MIC > 100 after β-lactam monotherapy.
- Median time to resistance: 6 days if AUC/MIC < 100.

Sammenhæng mellem fluorkinolon forbrug på danske sygehuse og resistens hos *E. coli* fra bloddyrkninger.

NB: Standarddosis cipro er optimal mhp PKPD + res !

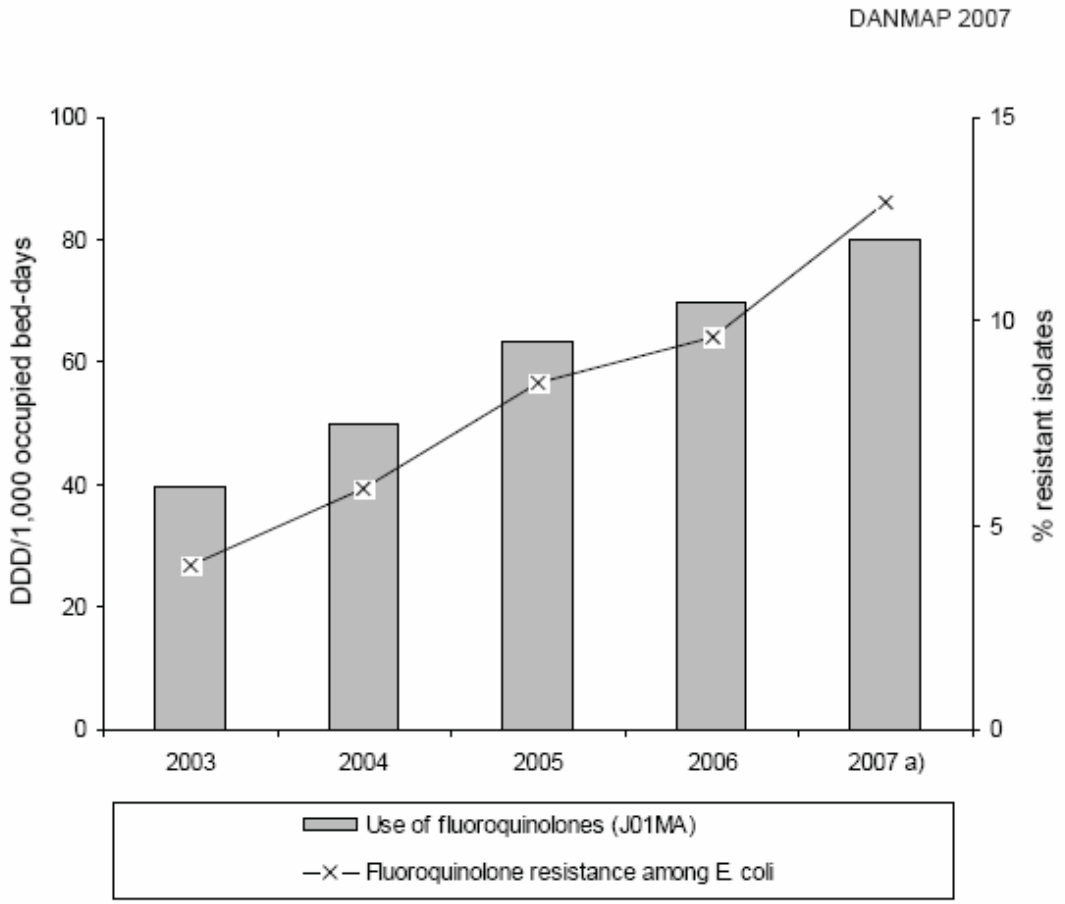
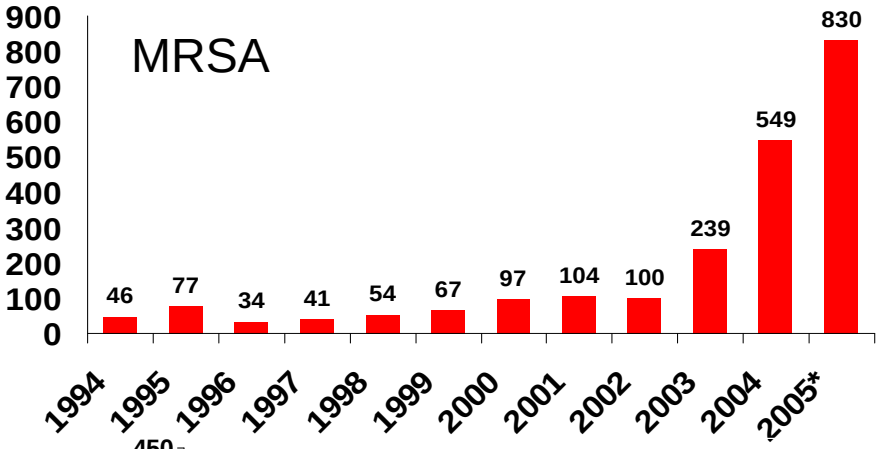
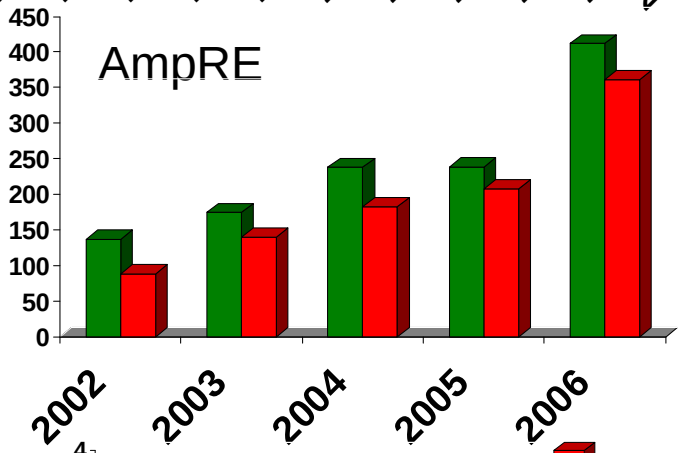
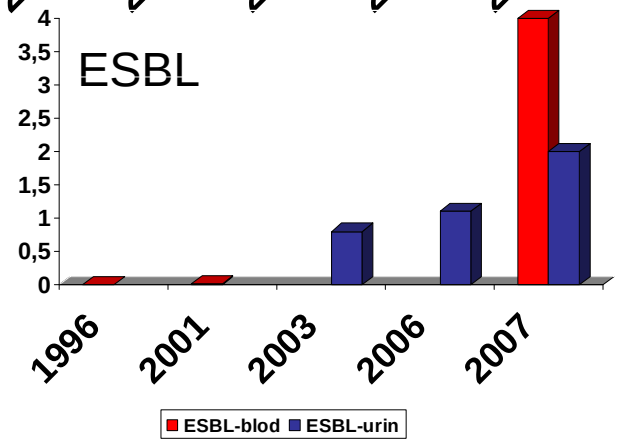


Figure 4. Trends in the use of fluoroquinolones (J01MA) and occurrence of fluoroquinolone resistance among E. coli *from blood infections*

a) Estimated number of occupied bed-days







Risikofaktorer:

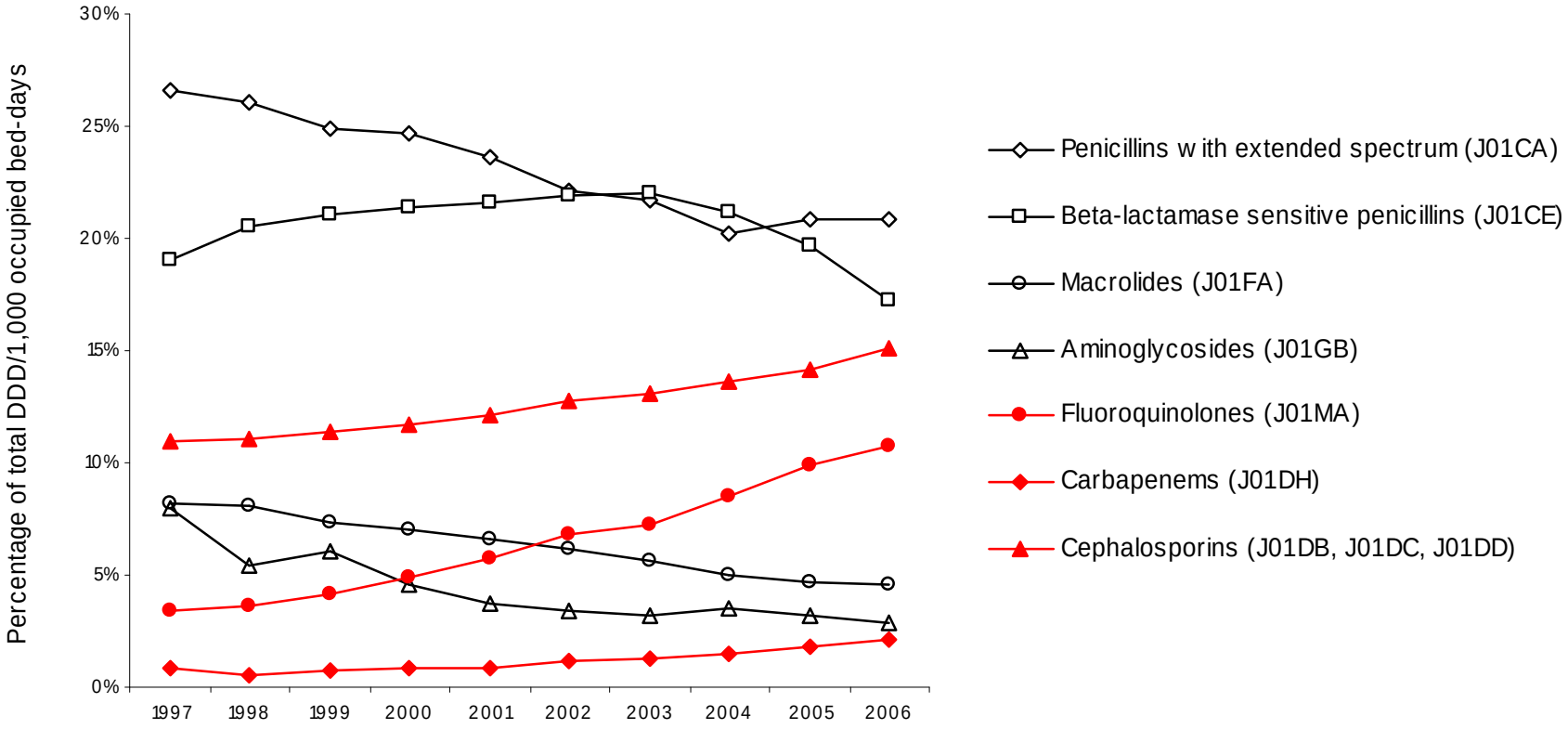
Antibiotikabehandling

0-60 dage før fund

Fluorkinoloner

Cefalosporiner

Stigende antibiotikaforbrug på danske sygehuse 1997-2007



Høiby N et al. Excretion of ciprofloxacin in sweat and multiresistant Staphylococcus epidermidis.
Lancet, 1997; 349: 167-9

- The mean concentration of ciprofloxacin in sweat increased during the 7 days of treatment-from 2.2 micrograms/mL 2.5 h after the first tablet to 2.5 micrograms/mL after the fifth tablet, and 5.5 micrograms/mL after the 13th tablet.
- All persons harboured susceptible S epidermidis (minimal inhibitory concentration [MIC] 0.25 microgram/mL) in axilla and nostrils before treatment. Four resistant strains were detected, two intermediate-level (MIC 4-12 micrograms/mL) and two high-level (MIC > 32 micrograms/mL). Three of these strains were found in all the participants, and a ciprofloxacin-sensitive variant of one of the high-level resistant strains was also found before the start of the treatment. The high-level resistant strains were also resistant to methicillin, erythromycin, gentamicin, sulphonamide, and trimethoprim.
- A mean of 2.7 days after the start of the treatment, development of ciprofloxacin resistance was detected in S epidermidis from the axilla of all persons, compared with 11 days for the appearance of resistant S epidermidis in nostrils. The resistant strains persisted for an average of 37 and 39 days in axilla and nostrils, respectively, after the end of the treatment

T>MIC ~50%

Cmax/MIC ~ 10-12

Ambrose et al.

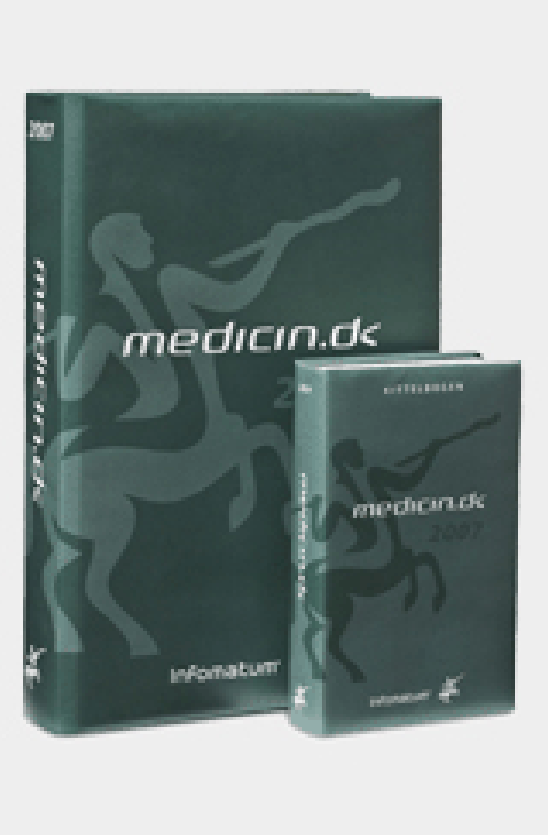
Clinical Infectious Diseases 2007; 44:79–86

Table 1. Patten of bactericidal activity in vitro and pharmacokinetic-pharmacodynamic (PK-PD) measures correlating with efficacy.

Antimicrobial agent	Bactericidal pattern of in vitro activity	PK-PD measure(s)
Aminoglycosides	Concentration dependent	AUC_{0-24}:MIC, C_{max}:MIC
β-Lactams		
Penicillins	Time dependent	T>MIC
Cephalosporins	Time dependent	T>MIC
Carbapenems	Time dependent	T>MIC
Monobactams	Time dependent	T>MIC
Clindamycin	Time dependent	AUC_{0-24}:MIC
Glycopeptides/lipopeptides		
Daptomycin	Concentration dependent	AUC_{0-24}:MIC, C_{max}:MIC
Oritavancin	Concentration dependent	T>MIC, C_{max}:MIC
Vancomycin	Time dependent	AUC_{0-24}:MIC
Macrolides and clindamycin		
Azithromycin	Time dependent	AUC_{0-24}:MIC
Clarithromycin	Time dependent	AUC_{0-24}:MIC
Teilithromycin	Concentration dependent	AUC_{0-24}:MIC
Metronidazole	Concentration dependent	AUC_{0-24}:MIC, C_{max}:MIC
Oxazolidinones		
Linezolid	Time dependent	AUC_{0-24}:MIC
Quinolones	Concentration dependent	AUC_{0-24}:MIC, C_{max}:MIC
Tetracyclines		
Doxycycline	Time dependent	AUC_{0-24}:MIC
Tigecycline	Time dependent	AUC_{0-24}:MIC

NOTE. AUC_{0-24}:MIC, the ratio of the area under the concentration-time curve at 24 h to the MIC; C_{max}:MIC, the ratio of the maximal drug concentration to the MIC; T>MIC, duration of time a drug concentration remains above the MIC.

Medicin.dk er afløseren for Lægemiddelkataloget®, og Medicin.dk/Kittelbogen for Medicinfortegnelsen



Tabel 1, p.256-8 i Medicin.dk

Stof	Dosis for PK-parame-tre	Peak-koncen-tration	Protein-binding %	Distributions-vol.	Serum halve-rings-tid	Vigtigste PK-PD parameter	Standard dosis g	Doserings-interval time
PcV Diclo Tetra						T>MIC	0,6 1 0,5	6-8 6-8 12

Antibiotika PKPD: Hvor skal vi hen ?

STATENS SERUM INSTITUT

- Viden om selektion og hvordan det undgås (type ab, dosering osv)
- Nedsætte antibiotikaforbrug:

  PKPD og dosering: Fx PenV og Amoxicillin x 4 dosering ➔ sparer 25-30 %

  Reducere varigheden af behandling

  Husk reglen om 3 dage !