Pharmacokinetics, pharmacodynamics and toxicodynamics: how to boost efficacy, reduce toxicity, and mitigate resistance (with focus on aminoglycosides and oxazolidinones)

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Disclosures

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- Non-profit Institutions (grants):
  - the Belgian *Fonds de la Recherche Scientifique* for basic research on pharmacology antibiotics and related topics
  - The European Union (MON4STRAT [7th Framework programme] – CO-ACTION [JPIAMR])
  - *Université catholique de Louvain* for past personal support

- Industry (grants, PPPs, and honoraria):
  - AstraZeneca, Bayer, Cempra, Debiopharm, Eumedica, GSK, Melinta, Merlion, MSD, Northern Antibiotics, Trius …

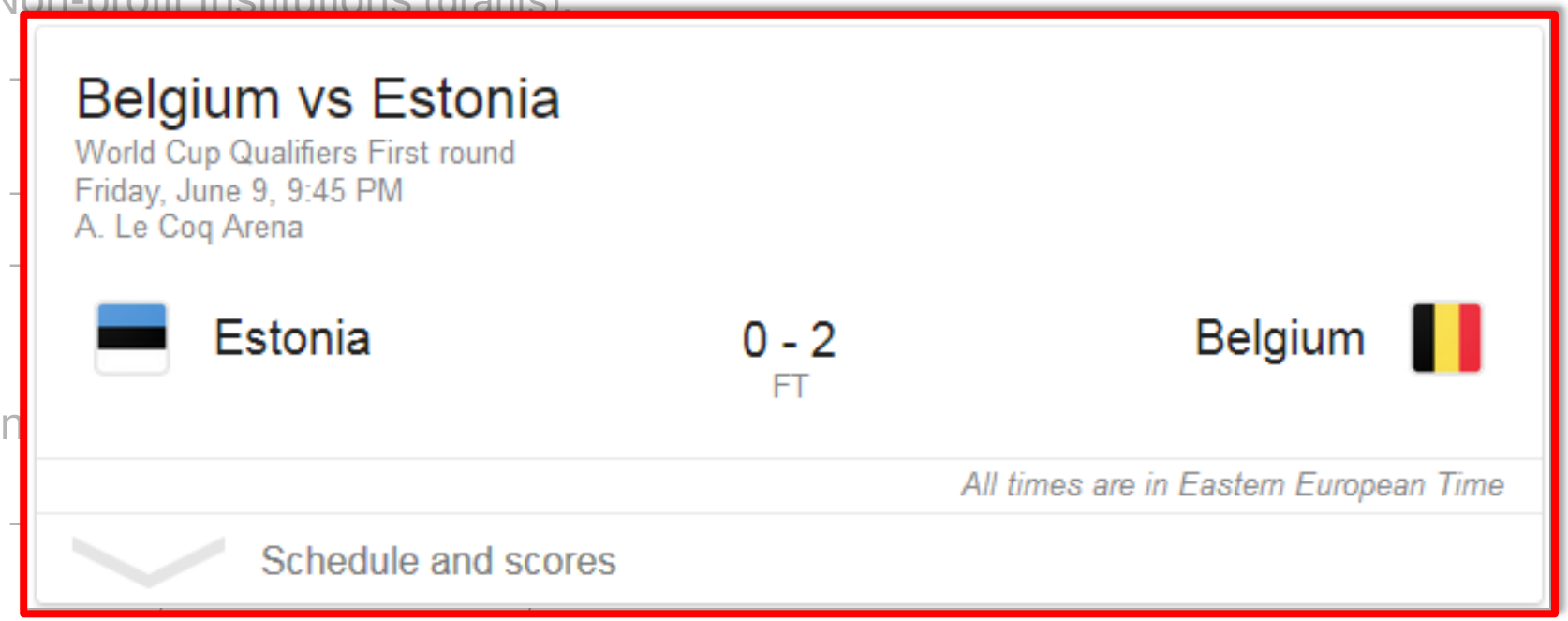
Slides: http://www.facm.ucl.ac.be → Lectures

Disclosures

Financial support from

major conflict of interest

- Non-profit Institutions (grants):
- In



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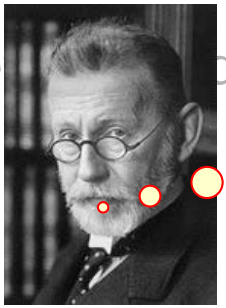
Slides:

The programme…

- Why pharmacokinetics/pharmacodynamics/toxicodynamics ?
- The main PK/PD indices and the main methods to discover them
- The breakpoints … and what they mean
- What about toxicity ?
- What about resistance ?

The programme…

- **Why pharmacokinetics/pharmacodynamics/toxicodynamics ?**
- The main PK/PD indices and the main me… dis…
- The breakpoints … and what they mean
- What about toxicity ?
- What about resistance ?



what the hell is this ?

The programme…

- **Why pharmacokinetics/pharmacodynamics/toxicodynamics ?**
- Th PK/PD indices and the main methods to discover them
- Th points … ?
- W t toxicity ?
- What about resistance ?

"Frapper vite et frapper fort"

Moving from discovery to clinical use…

- find a target… and the chemical entity that inhibits it…
- check for specificity (*vs*. eukaryotic cells… or other predictive model)
- look for MICs against target organisms (should usually be similar or lower than available drugs) including resistant strains…
- run preliminary animal general toxicity (to avoid surprises) and organ-specific toxicity (if known or guessed)

Moving from discovery to clinical use…

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- check for specificity (*vs*. eukaryotic cells… or other predictive model)
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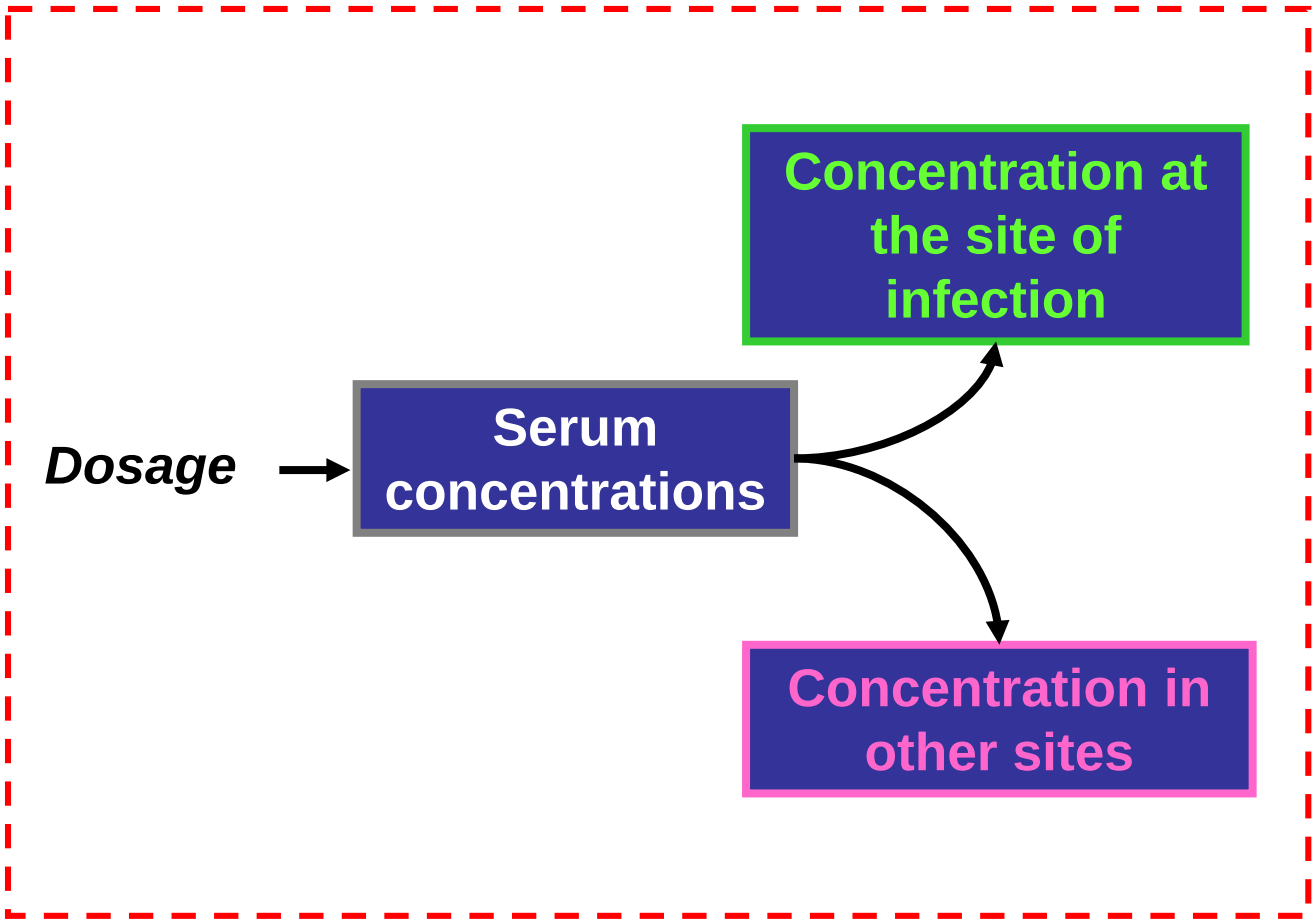
- run preliminary animal general toxicity (to avoid surprises) and organ-specific toxicity (if known or guessed)

- **NOW, what will be the correct dose and schedule ?**
  - for efficacy … MIC ? above ? how much ? how long ?
  - to prevent emergence of resistance … MIC ? sub-populations ?
  - to avoid toxicity… C_{max}, C_{min}, AUC ?

When you administer a drug…

pharmacokinetics *

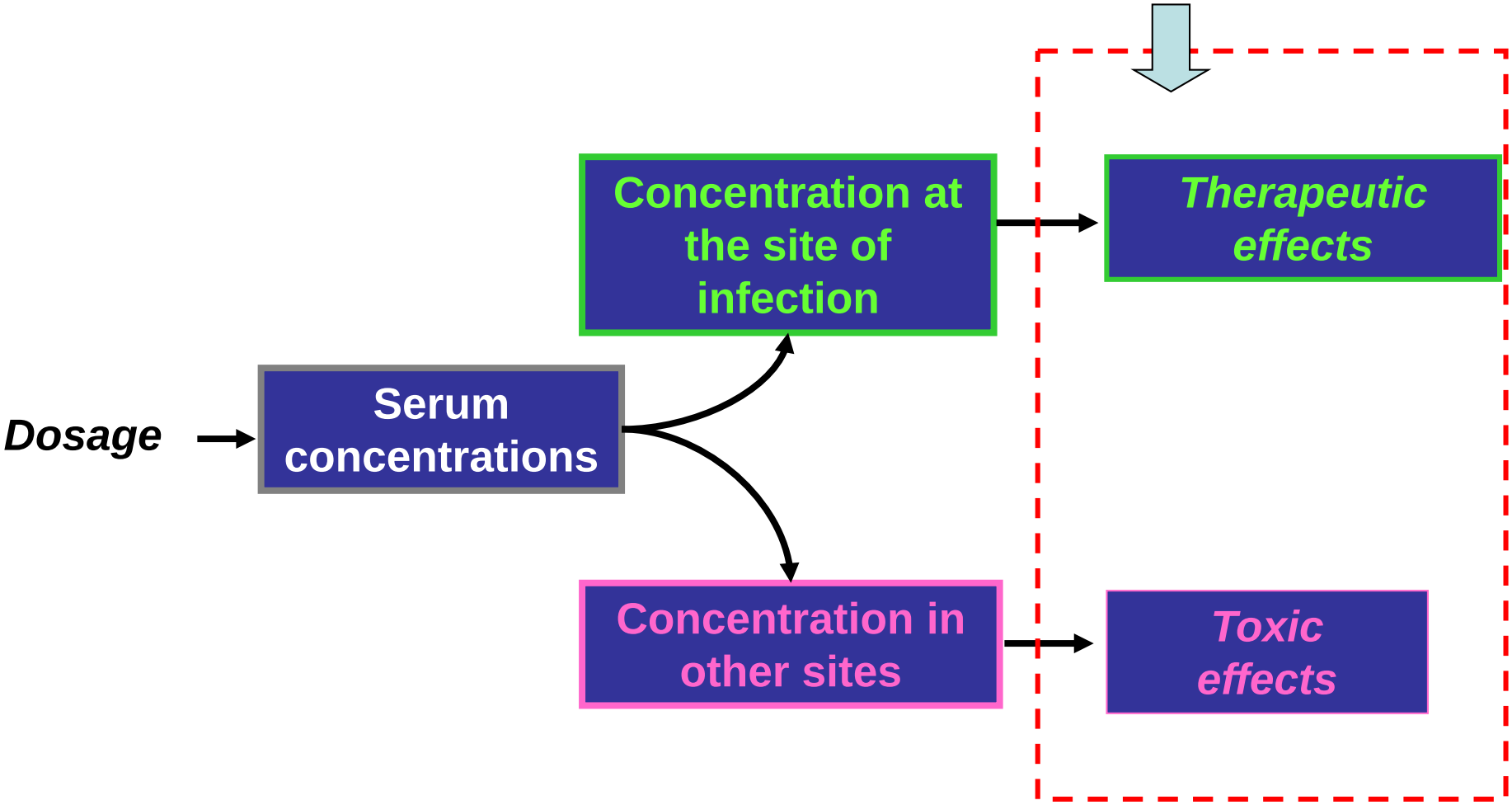
*** what the body does to the drug**



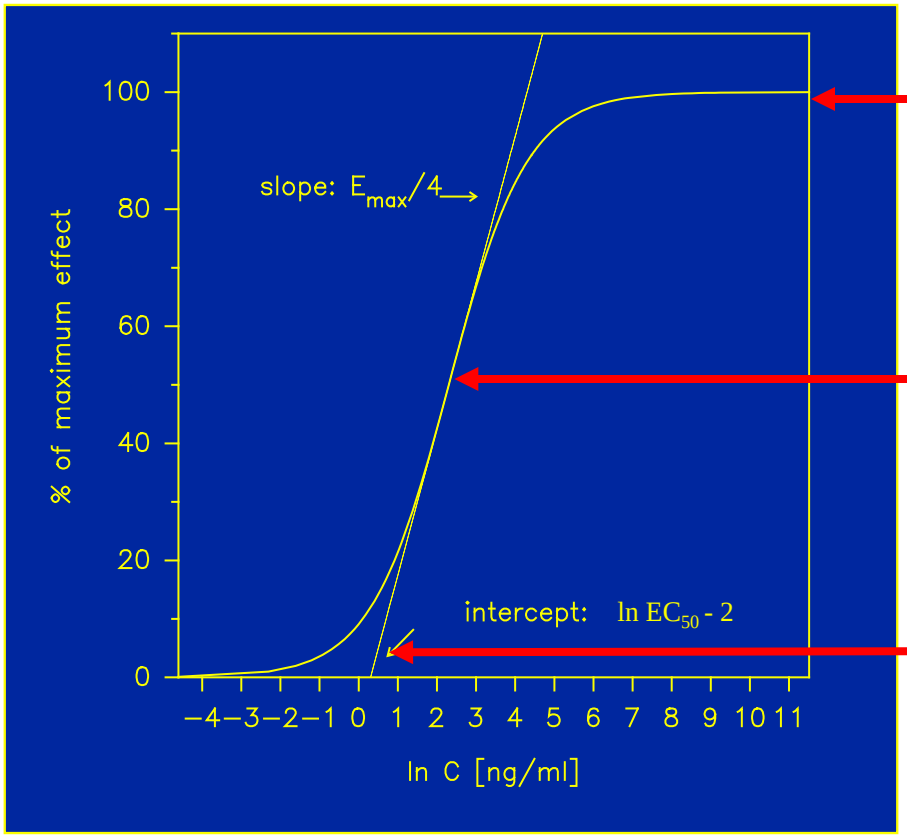
When you administer a drug…

pharmacodynamics
toxicodynamics *

*** what the drug does to the body**



Let us first concentrate on dynamics…



E_{max}

$E_{50\%}$

E_{min}

Maximal effect

this is your goal of efficacy

this is your goal of toxicity

Minimal effect

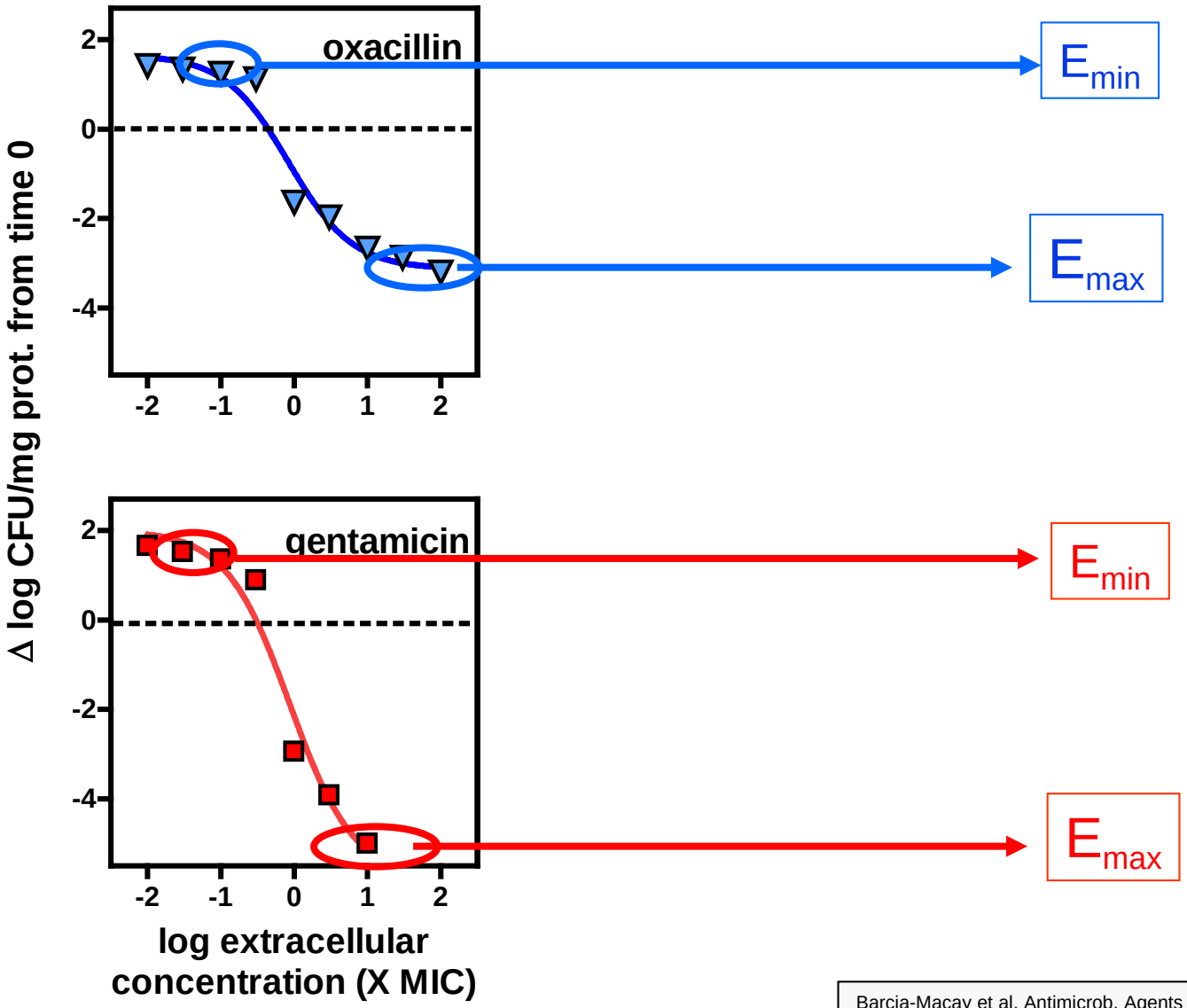
$$E = \frac{E_{max} \times C^n}{EC_{50}^n + C^n}$$

The programme…

- Why pharmacokinetics/pharmacodynamics/toxicodynamics ?
- **The main PK/PD indices and the main methods to discover them**
- The breakpoints … ar[illegible]pan
- What about toxicity
- What about resistance ?

who were those guys ?

Here is what you (apparently) get for all antibiotics…



Barcia-Macay et al. Antimicrob. Agents Chemother. 2006; 50(3):841-51

But there are differences …

Within a 1/8 to 64 x MIC concentration range

- **β-lactams** (ticarcillin, e.g.) show **limited dose-dependence…**
- **aminoglycosides** (tobramycin, e.g.) show **marked dose-dependence**

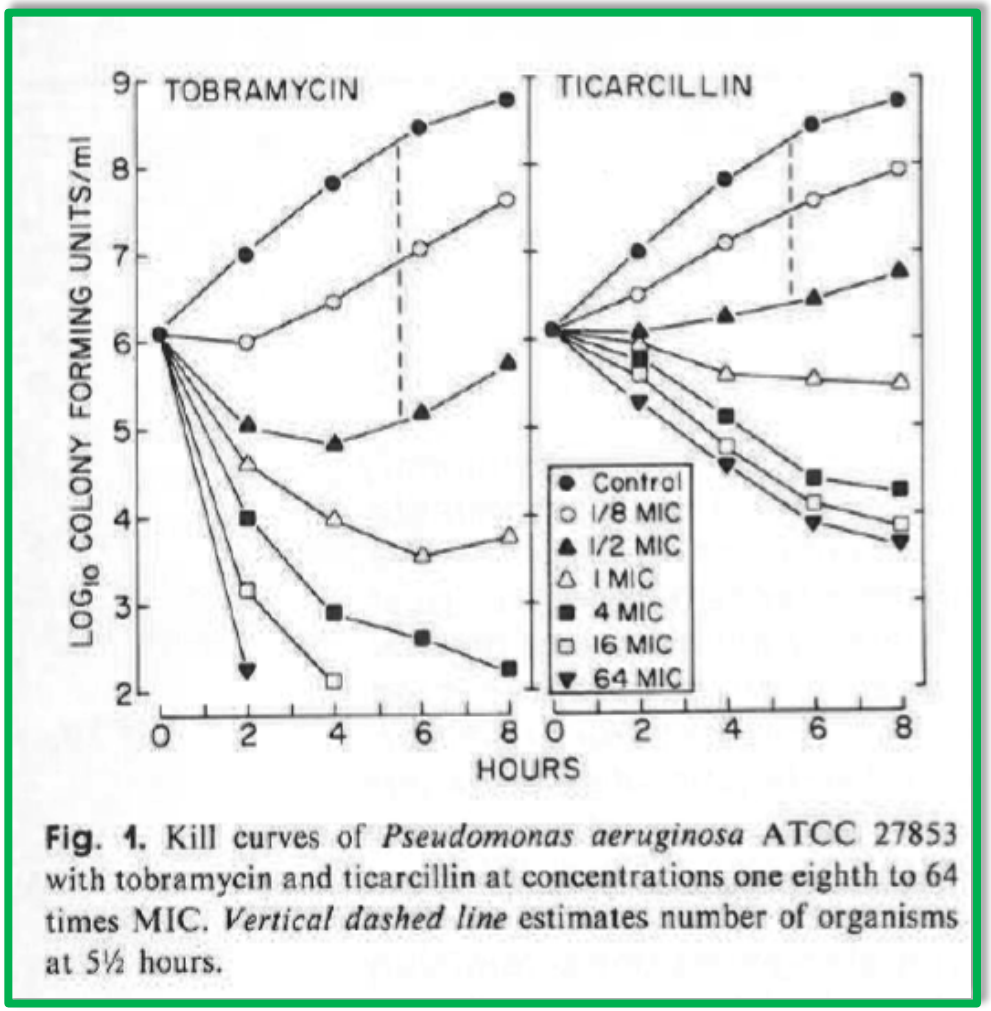
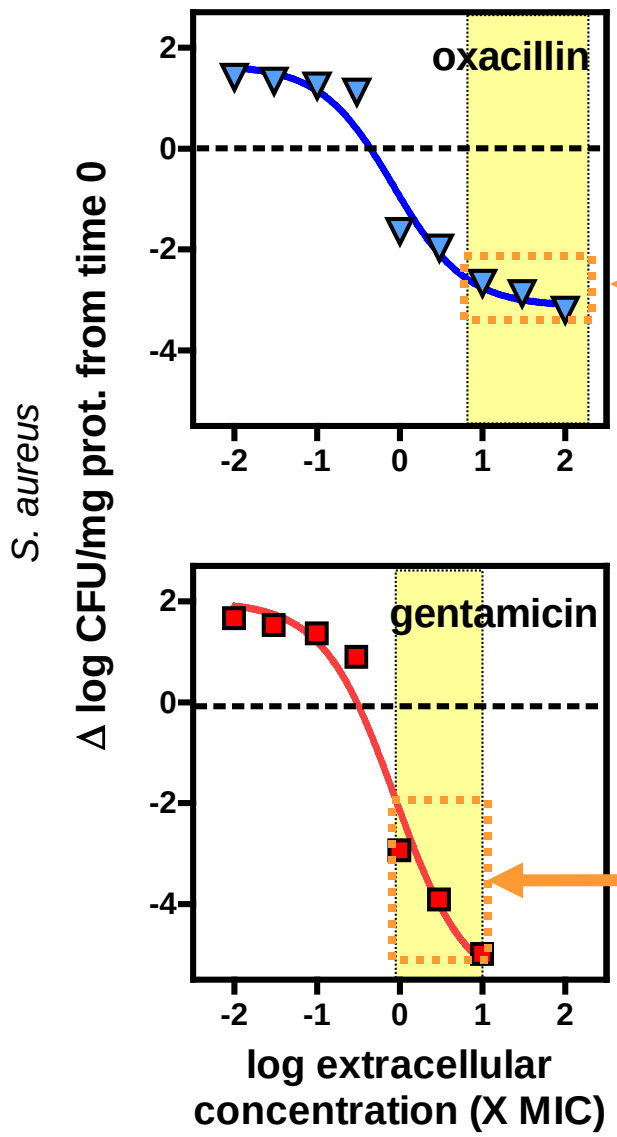


Fig. 1. Kill curves of *Pseudomonas aeruginosa* ATCC 27853 with tobramycin and ticarcillin at concentrations one eighth to 64 times MIC. *Vertical dashed line* estimates number of organisms at 5½ hours.

Vogelman & Craig (1986) Jounal of Pediatrics 108:835-840

Introducing pharmacokinetics…



weak concentration-dependence over C_{min}-C_{max}

➔ **time (above the MIC) becomes the predominant predicting index in the clinics**

C_{min}-C_{max}

marked concentration dependence over C_{min}-C_{max}

➔ **concentration (above the MIC) becomes the predominant index in the clinics**

A first additional factor: the post-antibiotic effect

A. *in vitro*

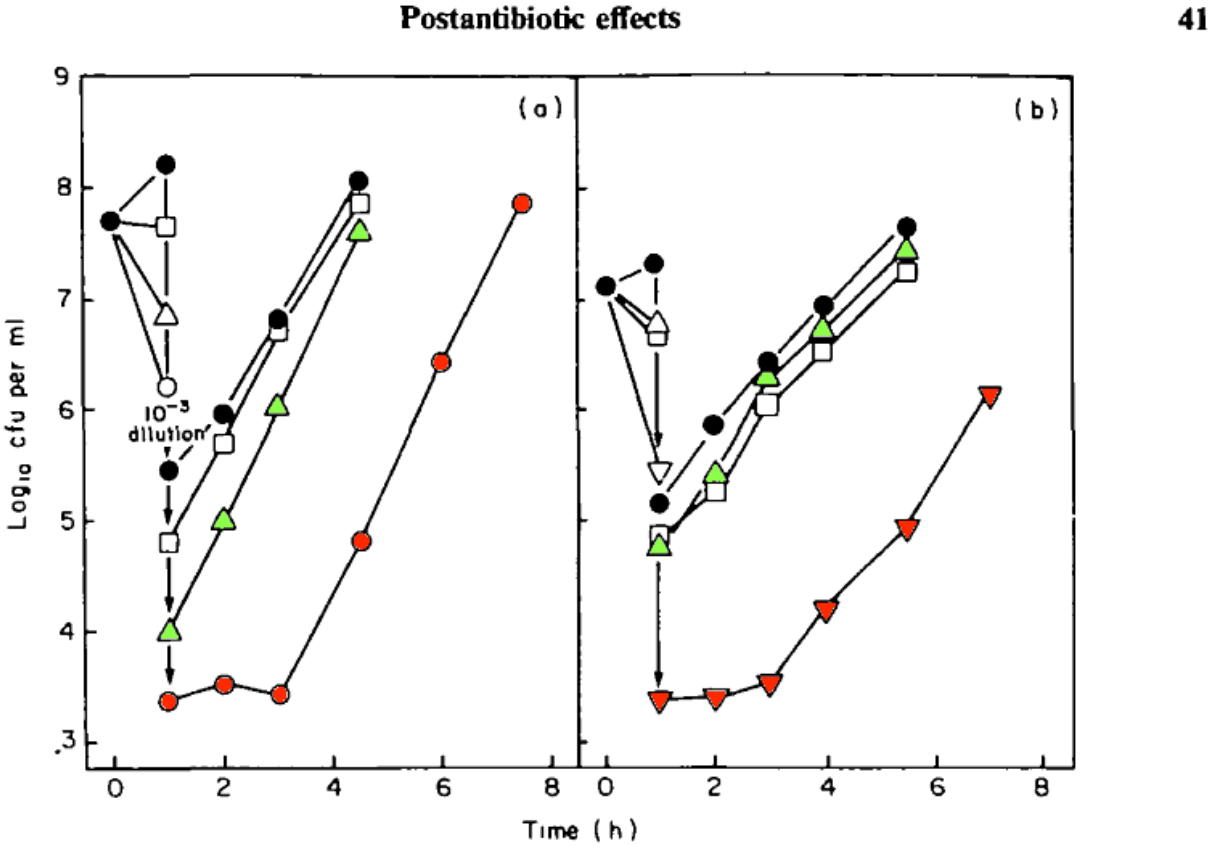


Figure 3. Growth curves for *K pneumoniae* UCLA 5166 (a) and a clinical strain of *Ps aeruginosa* (b) following 1-h exposures to β-lactam and aminoglycoside antibiotics at 4– times the MIC ●, Control, □, cefoperazone, △, moxalactam; ●, tobramycin, ▽, gentamicin

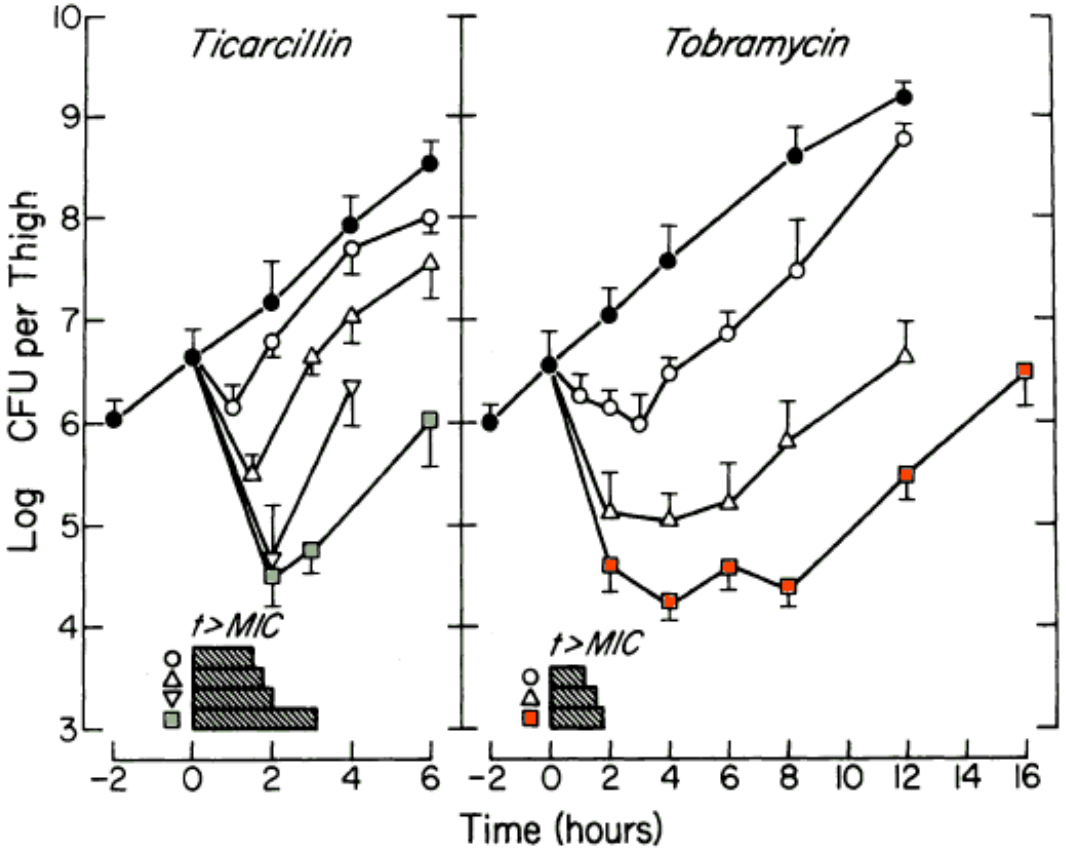
Vogelman & Craig, Journal of Antimicrobial Chemotherapy (1985) 15, Suppl. A, 37-46

A first additional factor: the post-antibiotic effect

B. *in vivo*

In Vivo PAE

Figure 1. Growth curves of control (●) and antibiotic-exposed *P. aeruginosa* ATCC 27853 in mouse thighs after a single dose of ticarcillin at 300 (○), 600 (△), 1200 (▽), or 2400 (■) mg/kg and tobramycin at 4 (○), 12 (△), or 20 (■) mg/kg. Data are mean ± SD (*bars*) values from four thighs. *Cross-hatched bars* denote the interval that serum levels exceeded the MIC ($t >$ MIC).



Vogelman et al. J Infect Dis 1988;157:287-298

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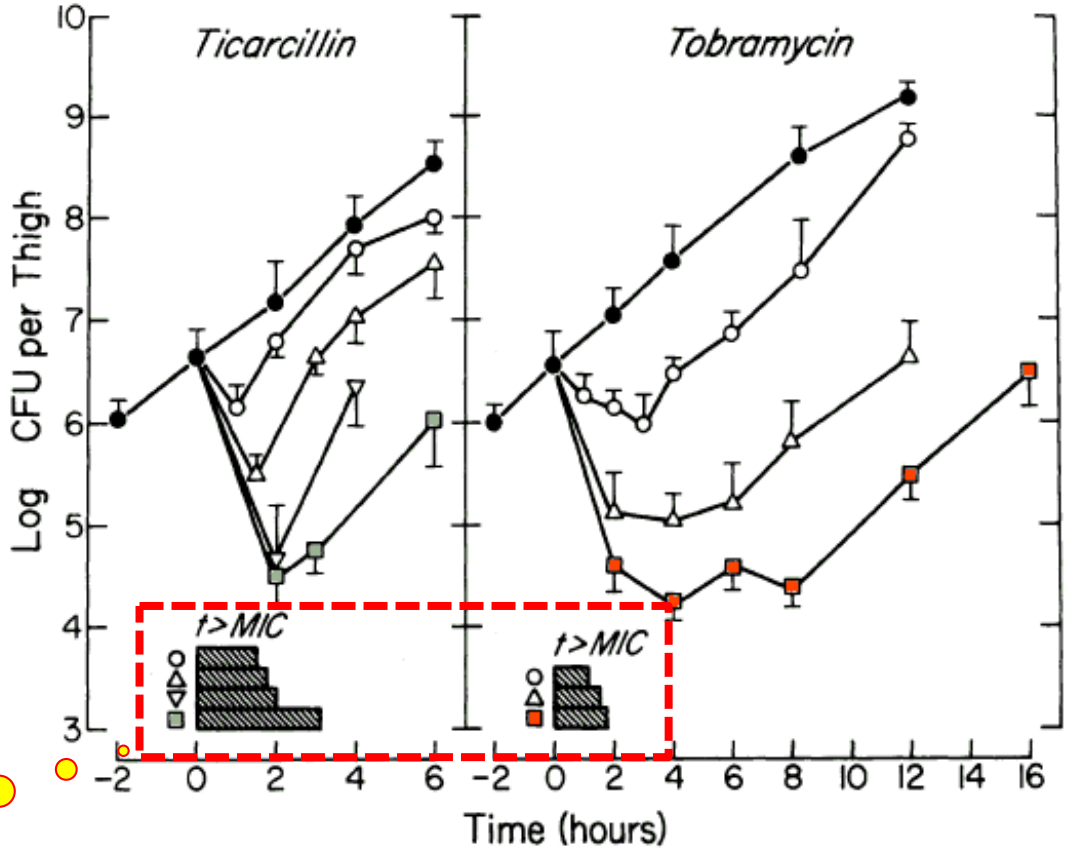


Pay attention to this !

Vogelman et al. J Infect Dis 1988;157:287-298

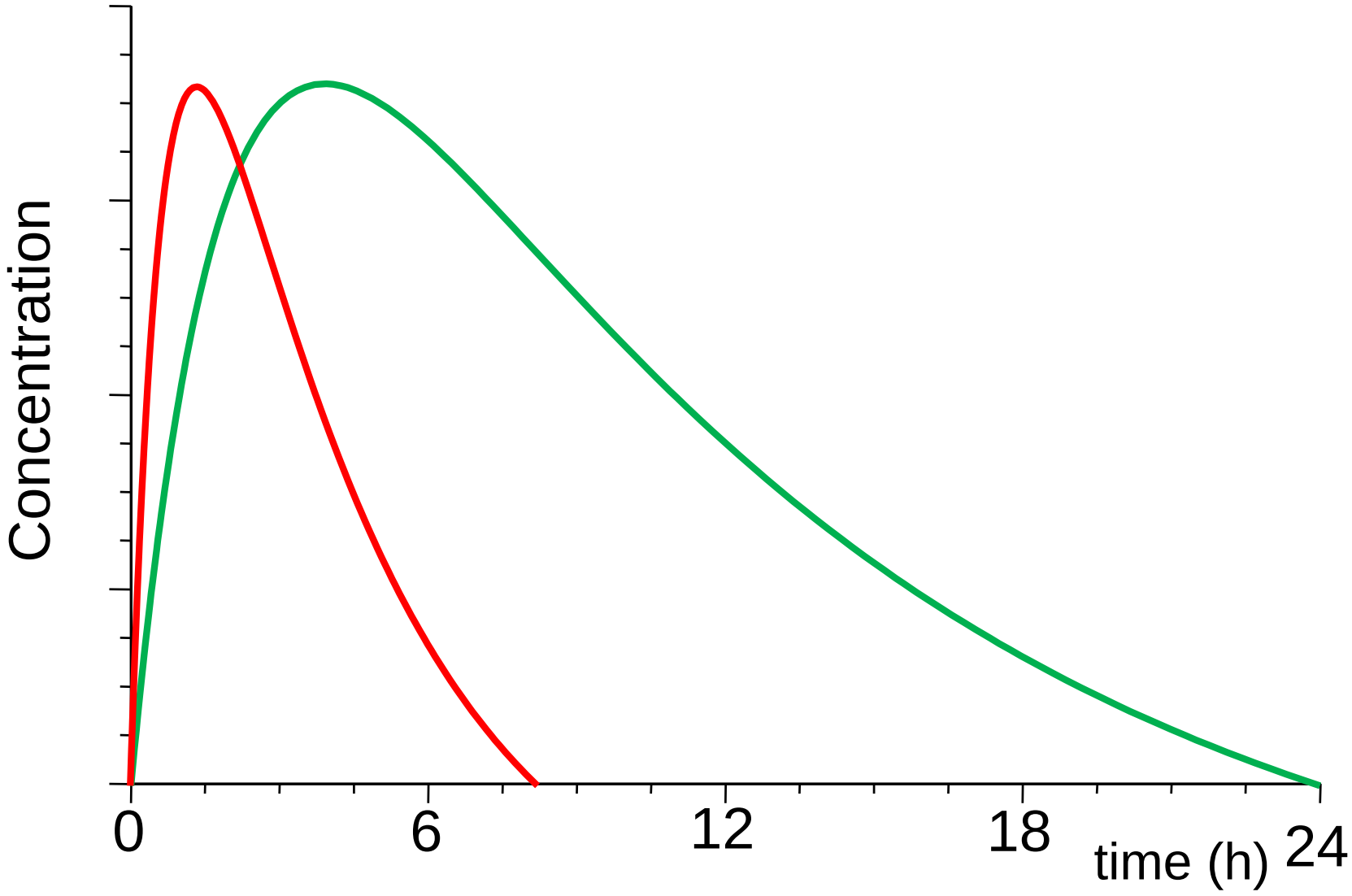
As a result: two (first) main PK/PF patterns for efficacy

- Pattern #1: antibiotics that are primarily time-dependent
  - β-lactams (all)
  - goal: maintain concentration above the MIC as long as needed…
  - advice to clinicians: frequent administrations (or even continuous infusion)

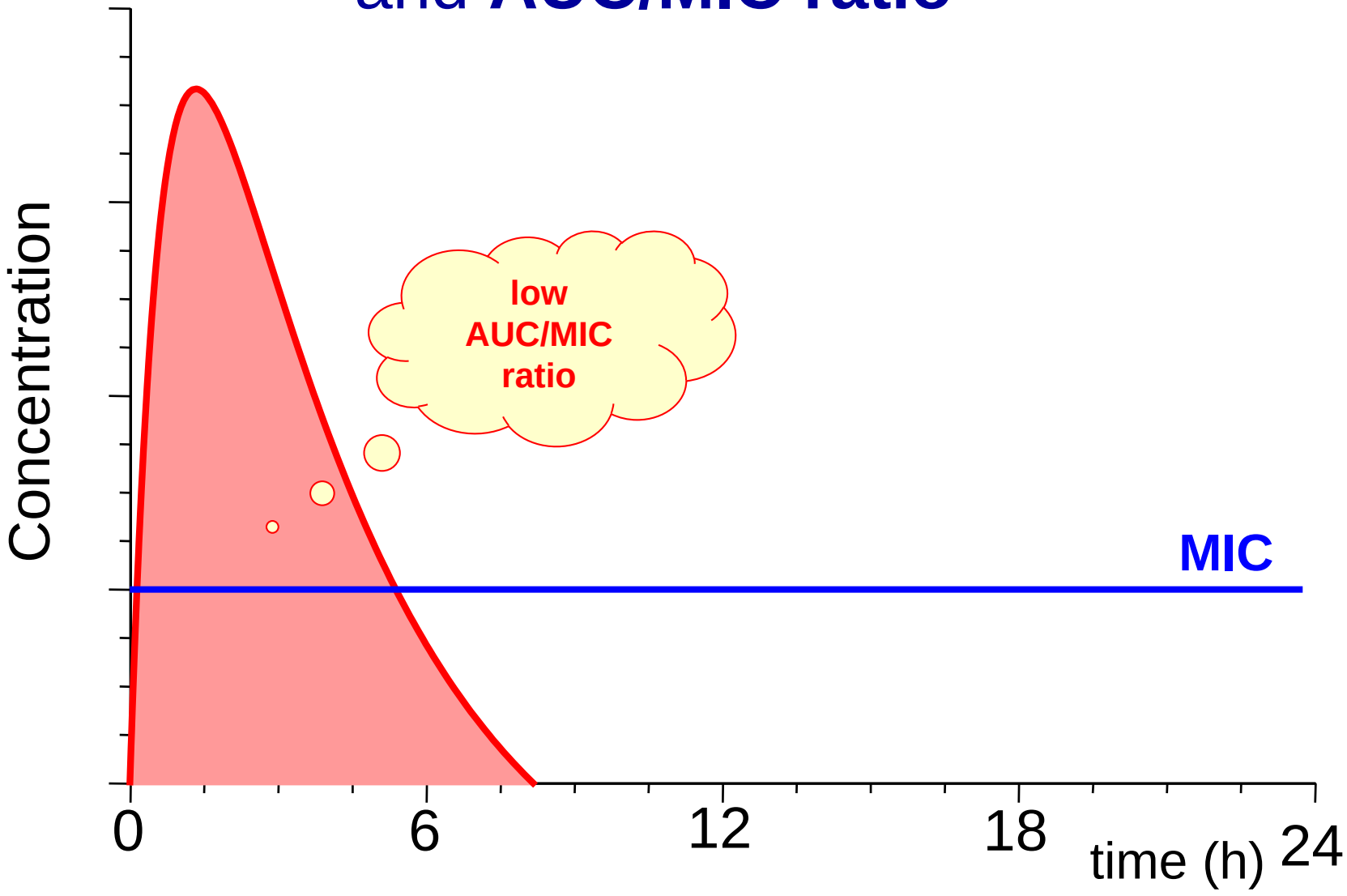
- Pattern #2: antibiotics that are primarily concentration-dependent
  - aminoglycosides
  - goal: reach a sufficient C_{max}/MIC ratio (8-10 x)
  - advice to clinicians: use discrete IV administration … and infrequently if post-antibiotic effect …

more explanations soon…

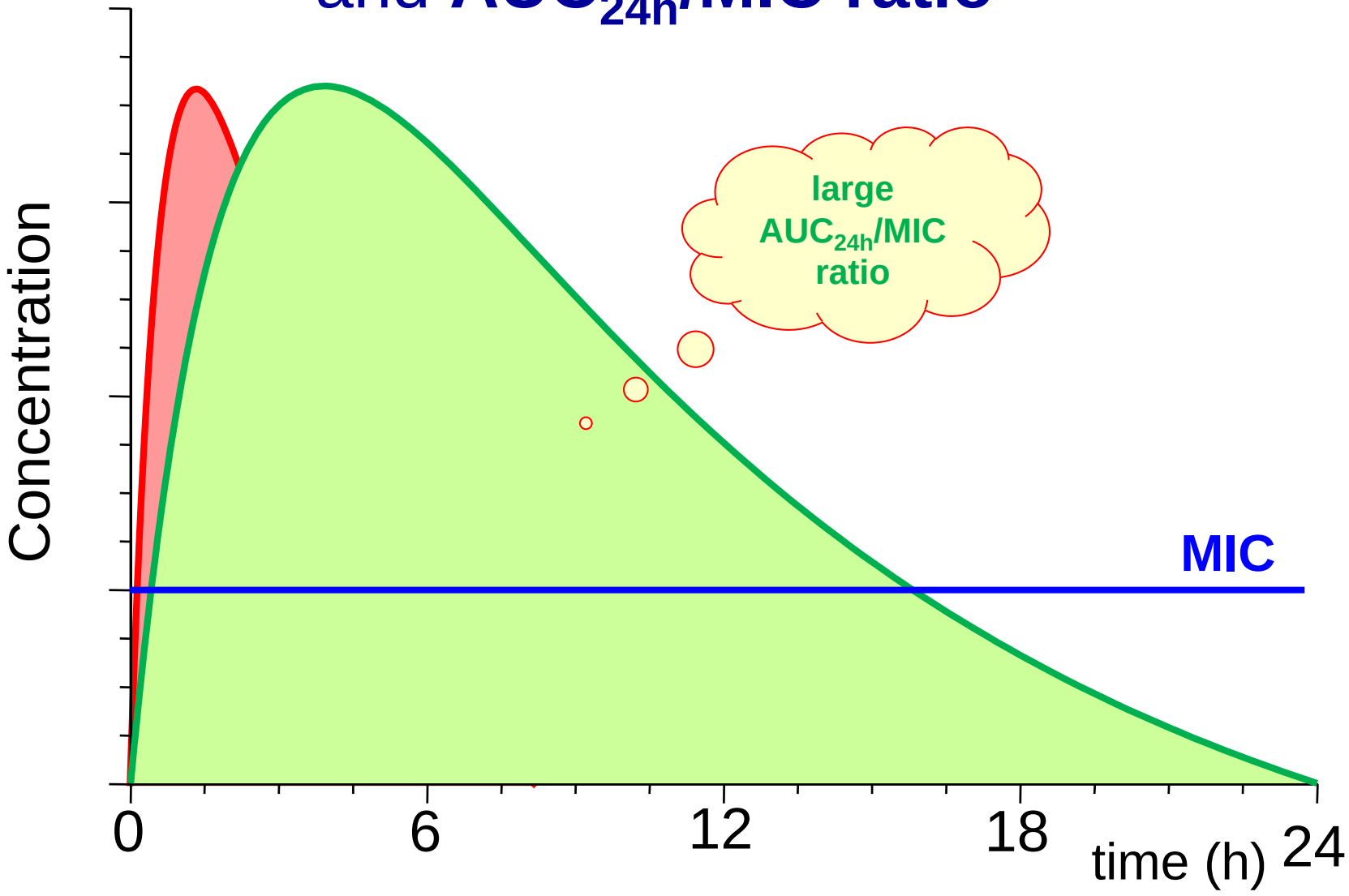
A second additional factor: antibiotic half-life



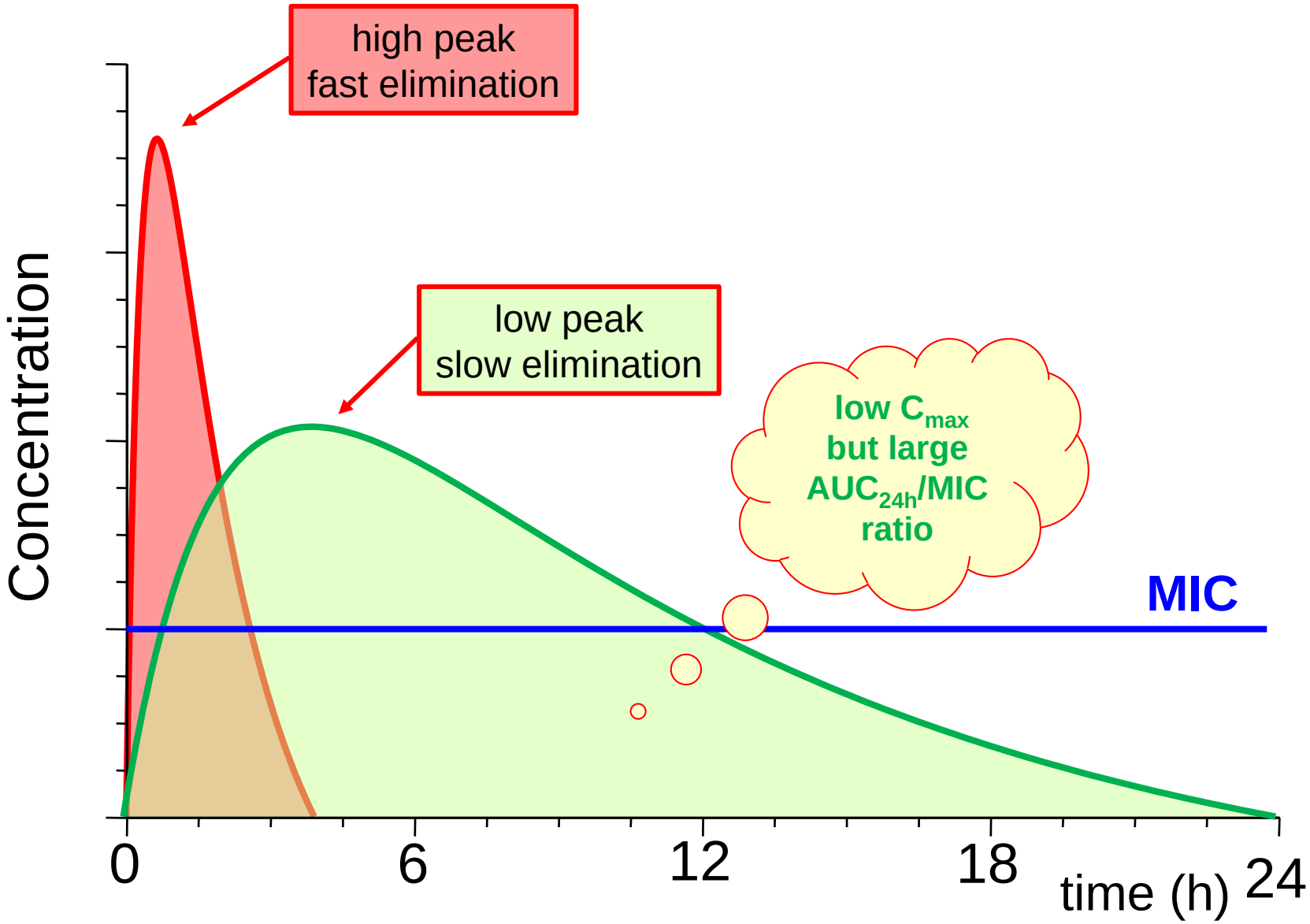
A second additional factor: antibiotic half-life and **AUC/MIC ratio**



A second additional factor: antibiotic half-life and **AUC_{24h}/MIC ratio**

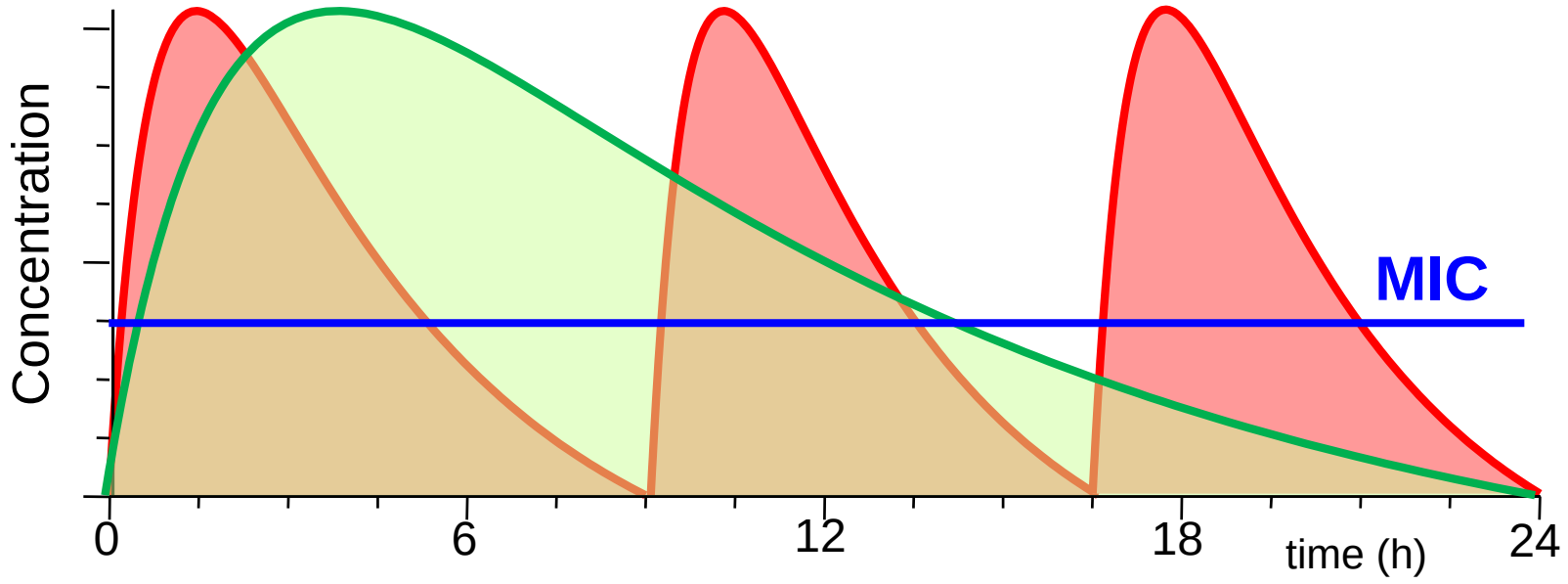


AUC_{24h}/MIC ratio may become predominant !



As a result: the third (and most frequent) PK/PD patterns for efficacy

- Pattern #3: antibiotics that are primarily AUC_{24h}/MIC- dependent
  - most clinically-approved antibiotics (others than β-lactams and aminoglycosides)
  - goal: adjust the total daily dose to obtain the needed AUC_{24h}/MIC ratio…
  - **advice to clinicians:** it is the **<u>total daily dose</u>** that matters (frequency of administration depends on the half-life)



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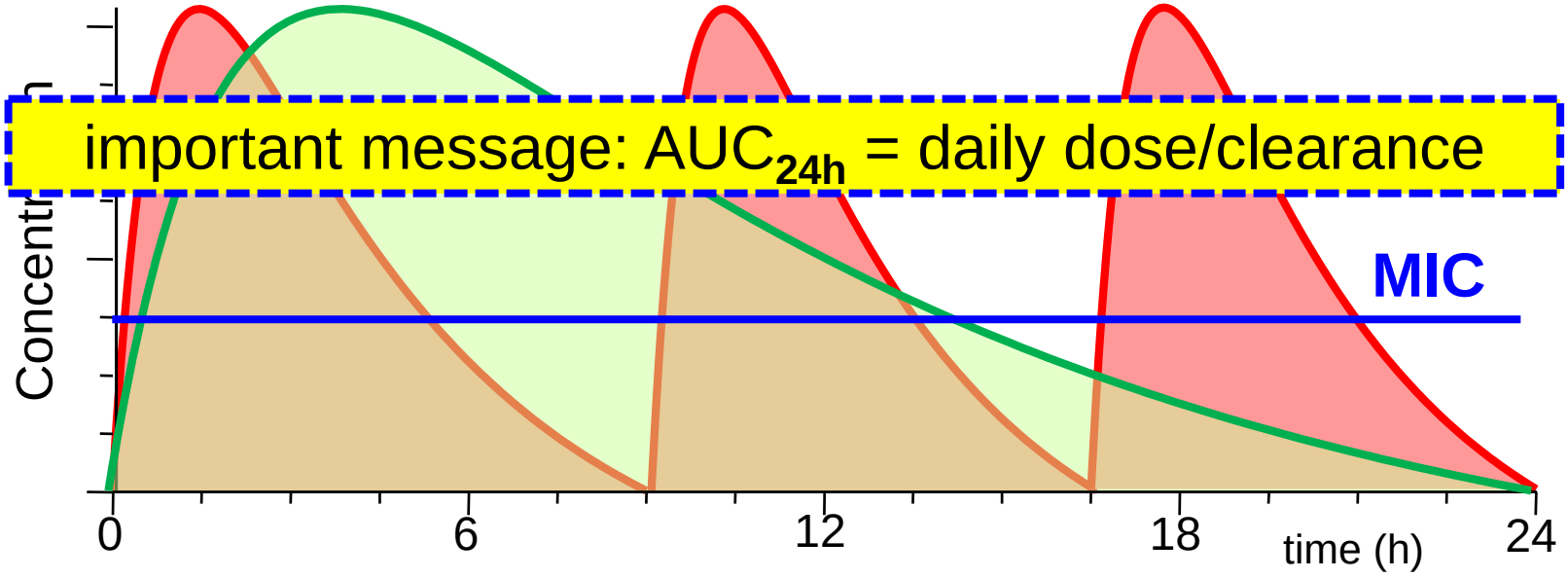
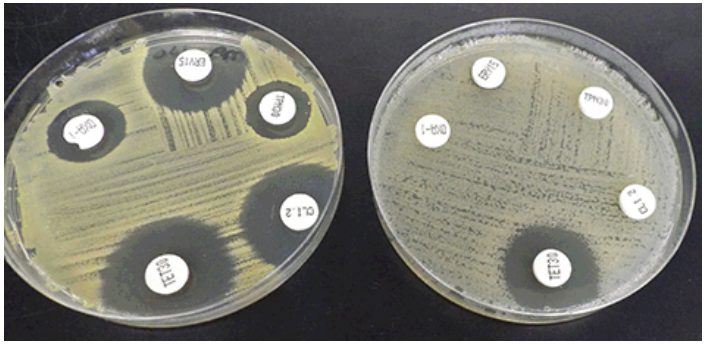


How do you find which antibiotic follow which pattern ?

- **Main experimental models**
  - *In vitro* dynamic models
  - Animal models
- **Complementary approaches** (not really covered here)
  - Modelling of therapeutic response(s), resistance emergence and development of toxicity
  - Monte-Carlo simulations
  - Target attainment rates (quick illustration)

In vitro dynamic models…



moving from static to dynamic …

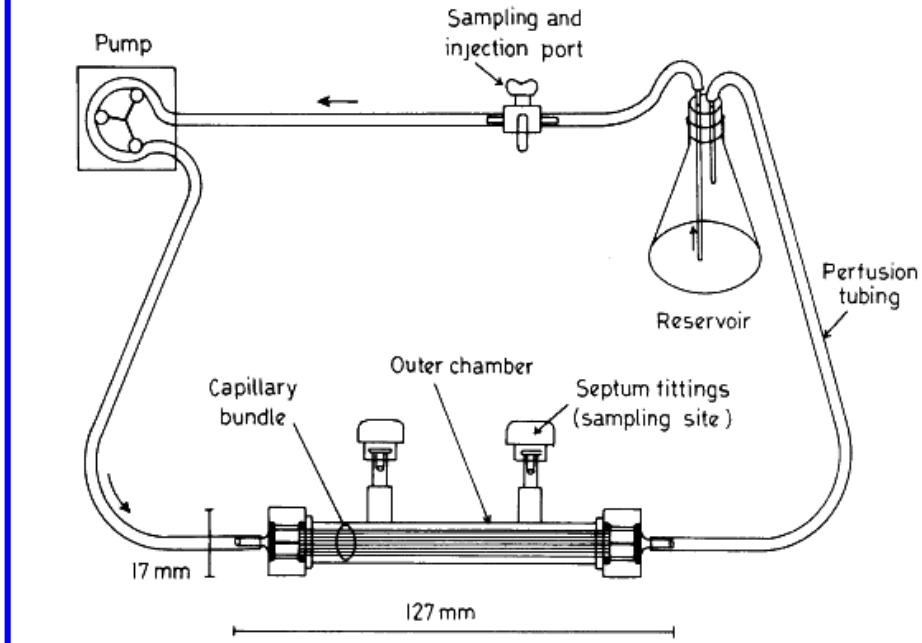
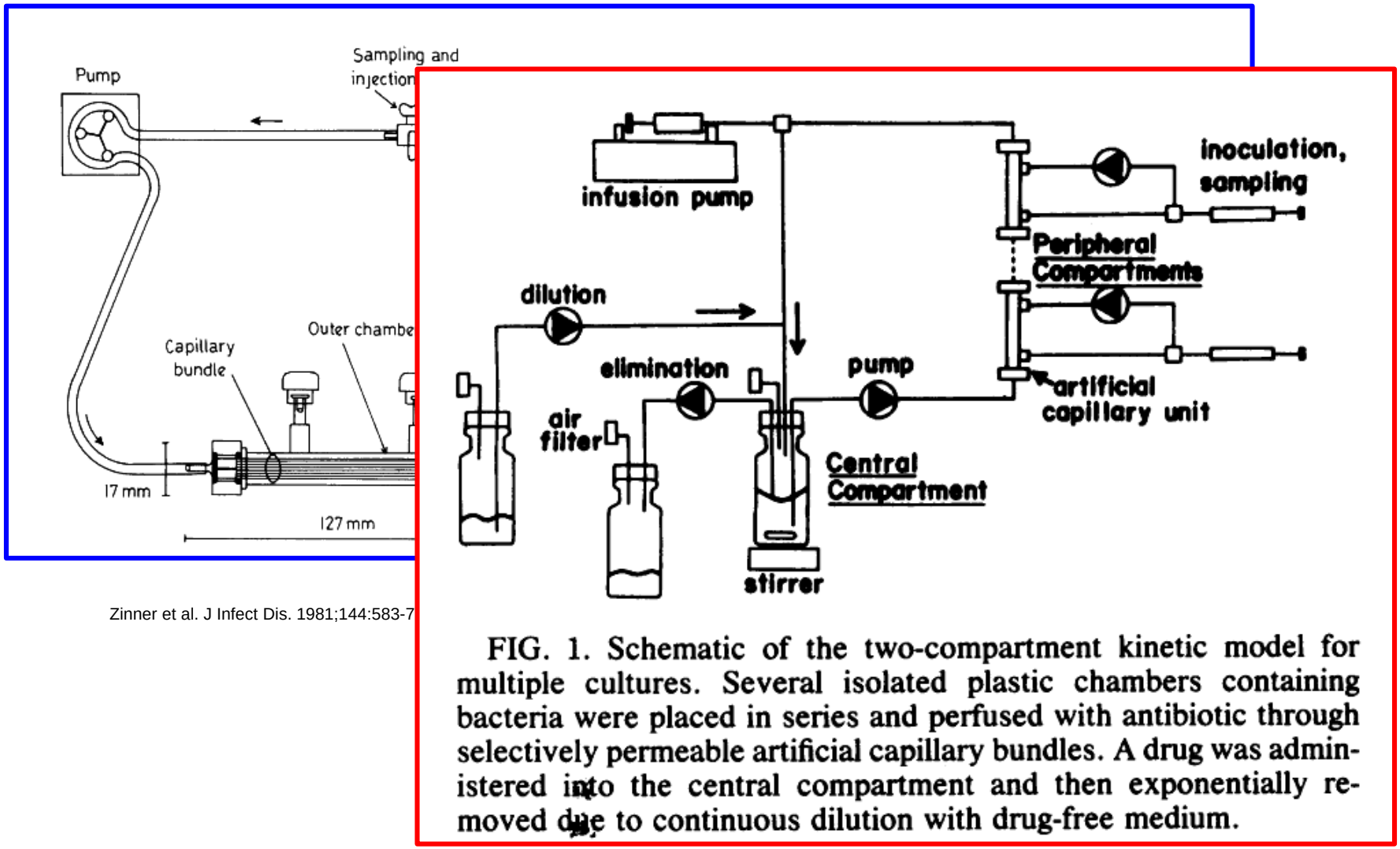


Figure 1. Schematic of an artificial capillary unit and perfusion system to simulate serum and tissue levels of antibiotic. The tubing, reservoir, and pump are not drawn to scale.

Ziinner et al. J Infect Dis. 1981;144:583-7 - PMID 6799585

In vitro dynamic models



Zinner et al. J Infect Dis. 1981;144:583-7

FIG. 1. Schematic of the two-compartment kinetic model for multiple cultures. Several isolated plastic chambers containing bacteria were placed in series and perfused with antibiotic through selectively permeable artificial capillary bundles. A drug was administered into the central compartment and then exponentially removed due to continuous dilution with drug-free medium.

Blaser et al. Antimicrob Agents Chemother. 1985;27:343-9 - PMID 3922294

In vitro dynamic models: an aminoglycoside…

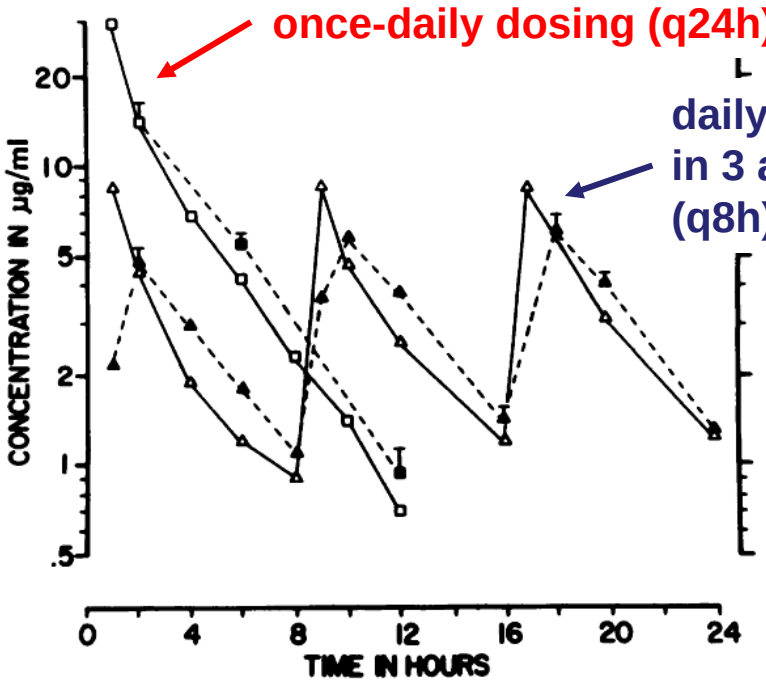
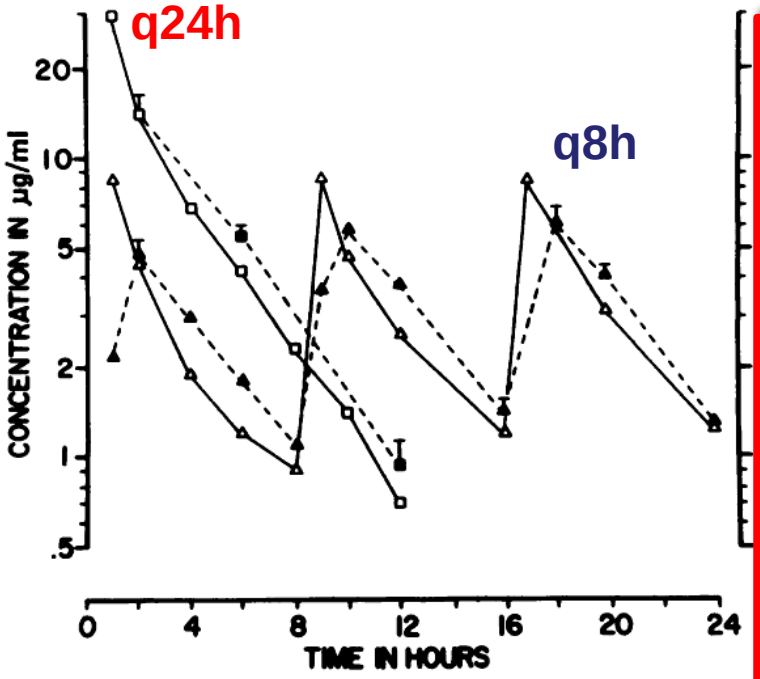


FIG. 2. Netilmicin concentrations in the central (solid line) and peripheral (broken line) compartments during the administration of the same daily dose given either in one or in three 60-min infusions. Standard deviations of fourfold replications are shown.

Blaser et al. Antimicrob Agents Chemother. 1985;27:343-9 - PMID 3922294

In vitro dynamic models: an aminoglycoside…



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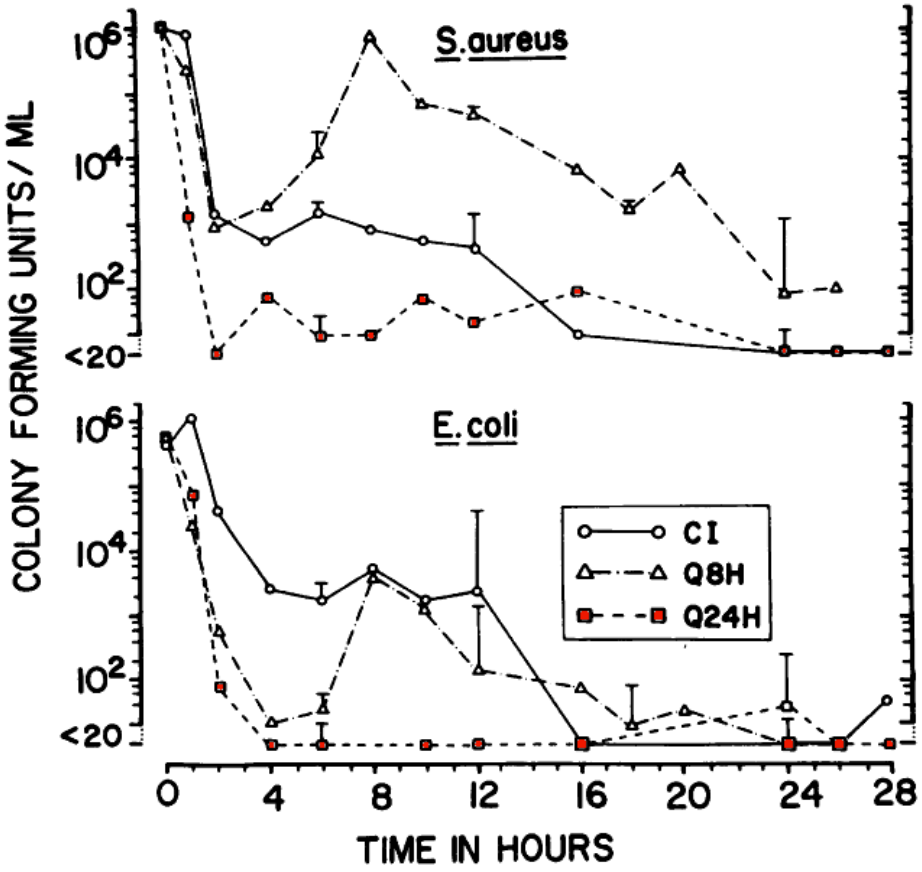

FIG. 4. Bactericidal effect of netilmicin on *S. aureus* (top panel) and *E. coli* (bottom panel). The same daily dose was administered either as a CI or as 60-min infusions q8h or q24h. Geometric means of duplicate experiments were plotted. For clarity, range is shown only for every 6 h.

Blaser et al. Antimicrob Agents Chemother. 1985;27:343-9 - PMID 3922294

Animal models…

- Neutropenic mice *
  - to allow bacterial growth…
  - to examine the activity of the antibiotic disregarding immune responses (pharmacological investigation)
  - to explore the conditions of both success and <u>failures</u> *

- Dose fractionation approach
  - to fully dissociate the covariables ** (C_{max}, t > MIC, AUC_{24h})

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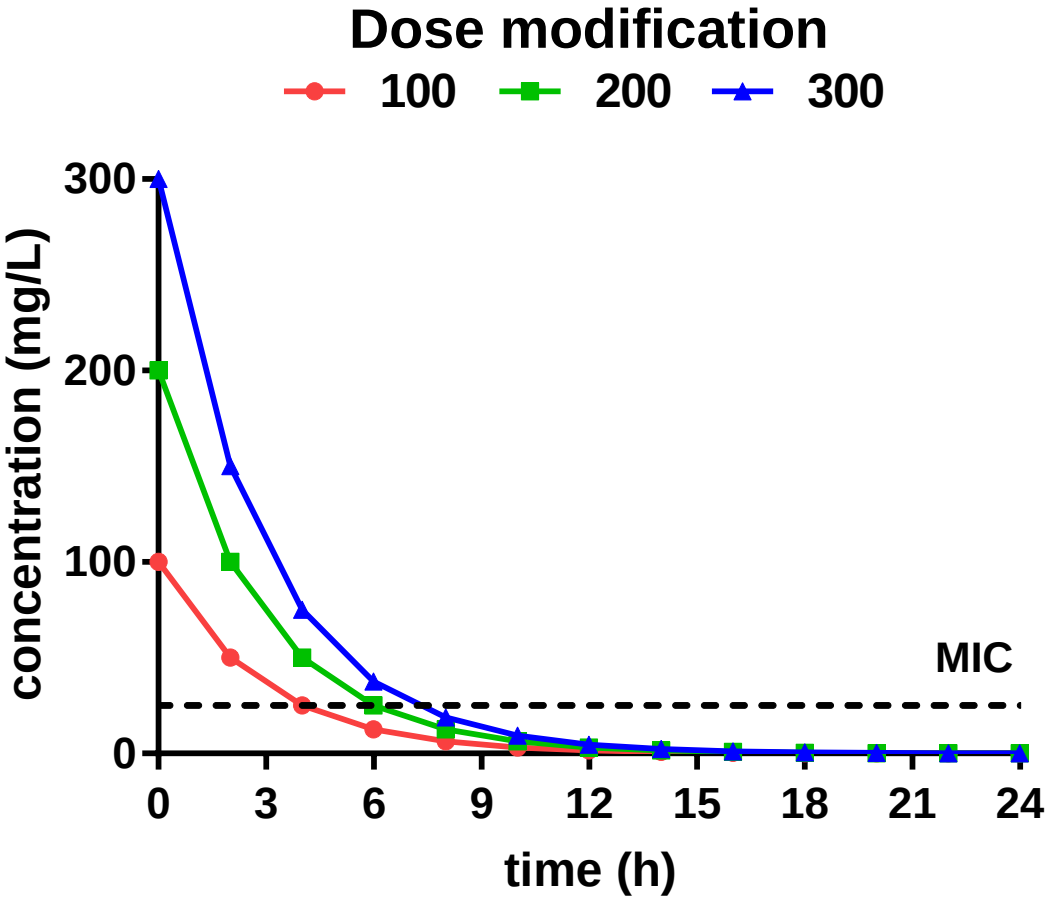
* non-neutropenic is some situations

** difficult to study in clinical trials

Dissociating the covariables

modifying the dose is not enough !



Dissociating the covariables

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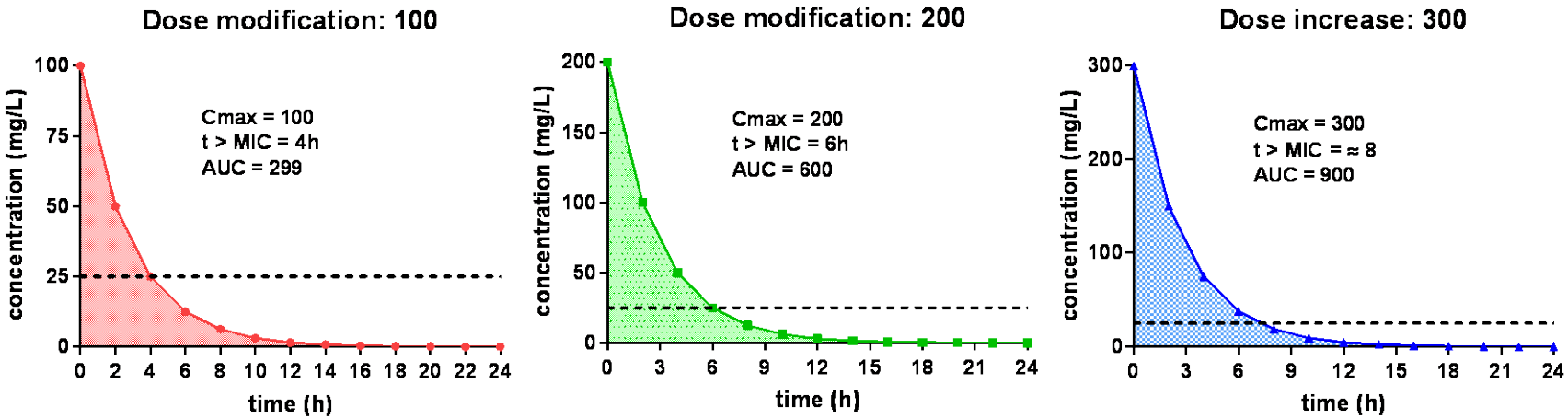
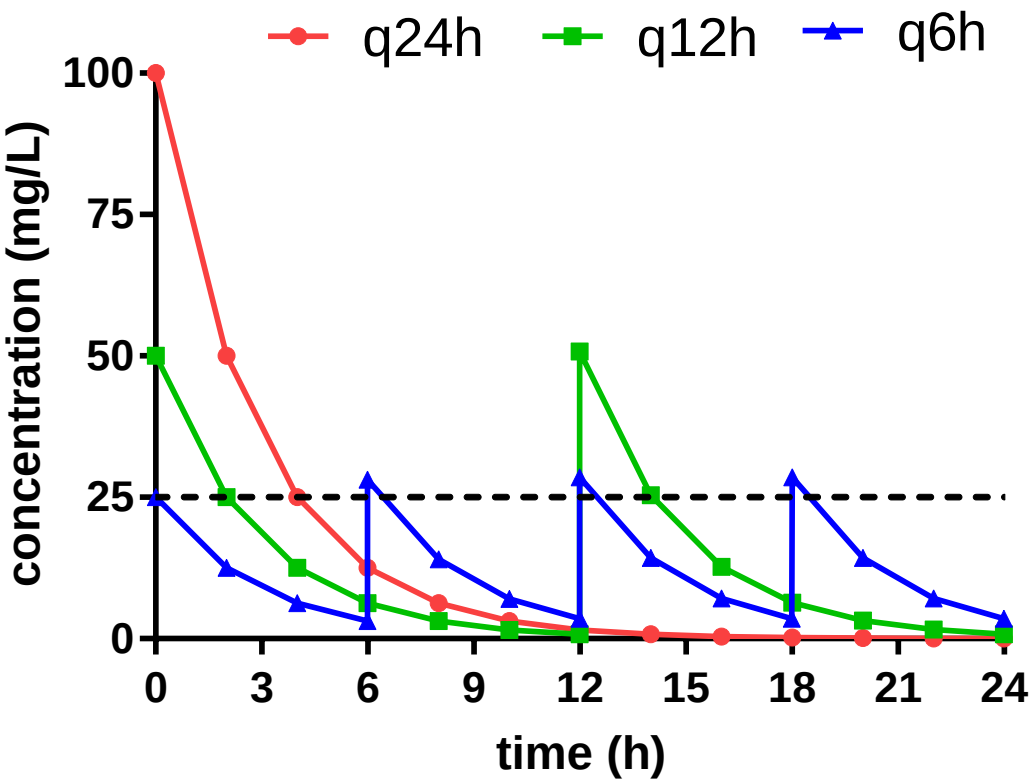


you increase all 3 parameters !

Dissociating the covariables

You must modify the schedule (daily dose fractionation)

Dose fractionation of the same daily dose



Dissociating the covariables

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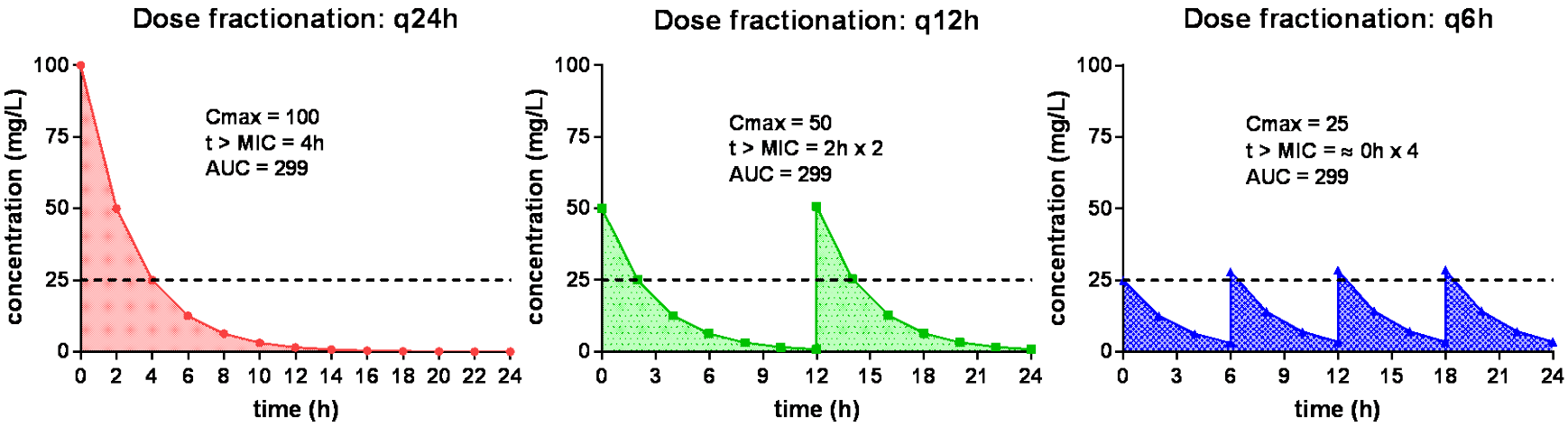


Cmax ↘
t > MIC = and ↘
AUC =

Animal models…

Looking for the index-driving activity

5

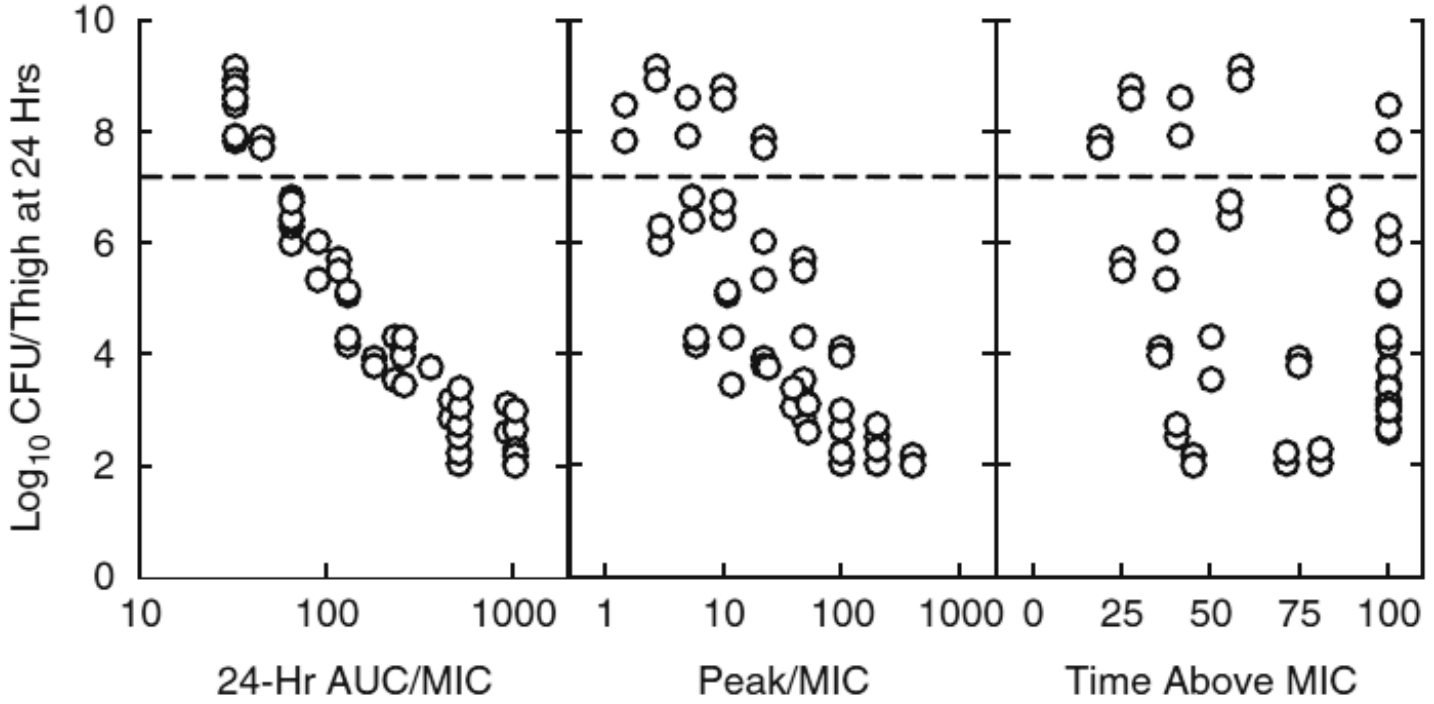
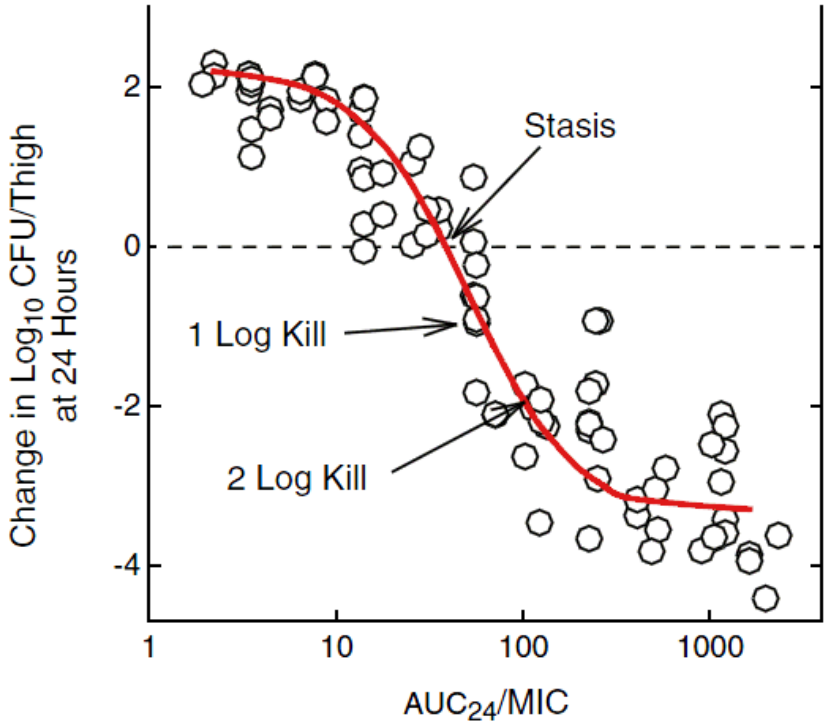


Fig. 1.1 Relationship between three PK/PD indices for total drug of levofloxacin and the $\log_{10}$ CFU/thigh at 24 h for *Streptococcus pneumoniae* ATCC 10813 in the thighs of neutropenic mice. Reproduced with permission from Andes and Craig (2002)

Andes & Craig WA Int J Antimicrob Agents 2002;19:261–268

Animal models: what can you measure…

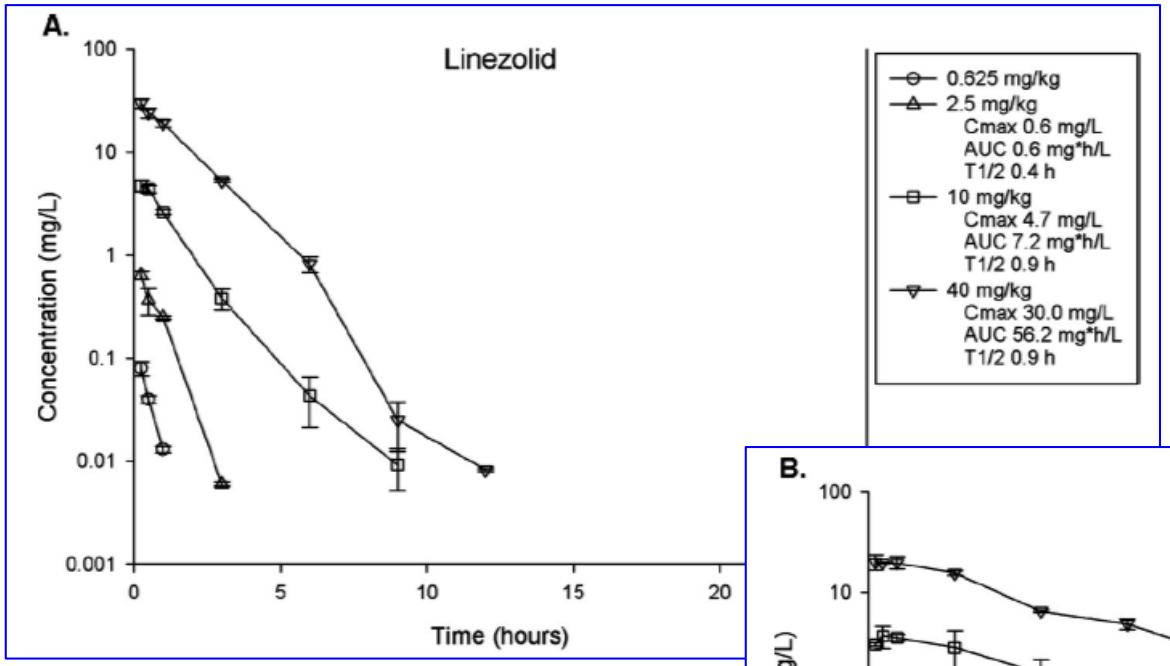
Fig. 2.6 Change in $\log_{10}$ CFUs/thigh over 24 h for various Enterobacteriaceae following treatment with multiple fluoroquinolones in neutropenic mice. Redrawn from data in Andes and Craig (2002)



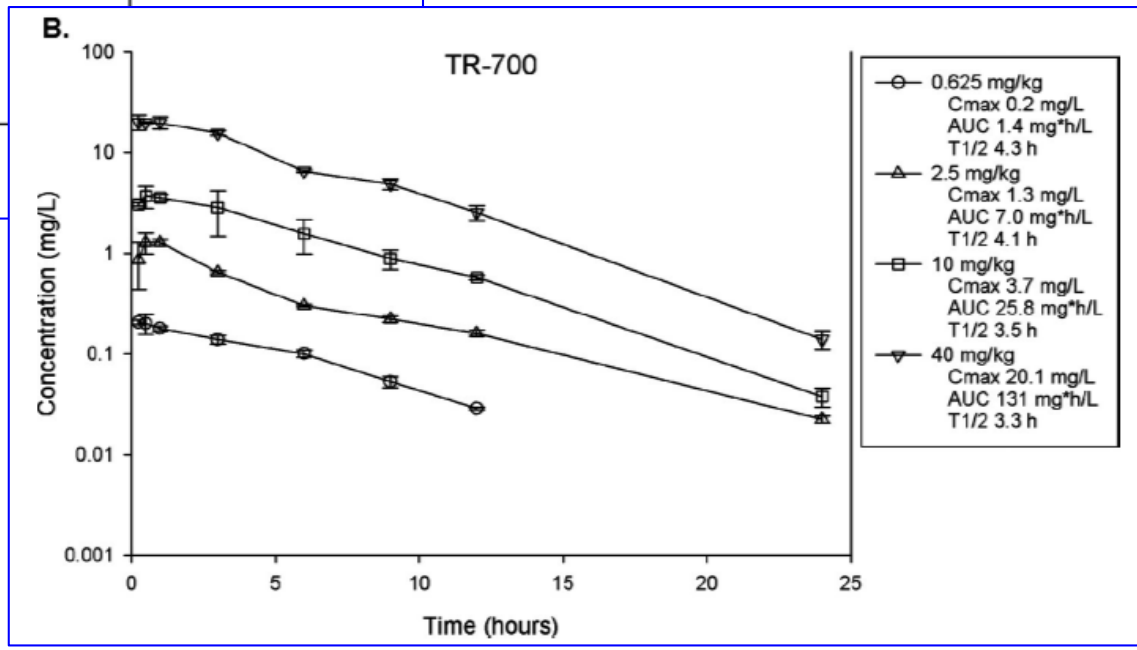
Andes & Craig WA Int J Antimicrob Agents 2002;19:261–268

Animal models: application to two oxazolidinones

1. pharmacokinetics



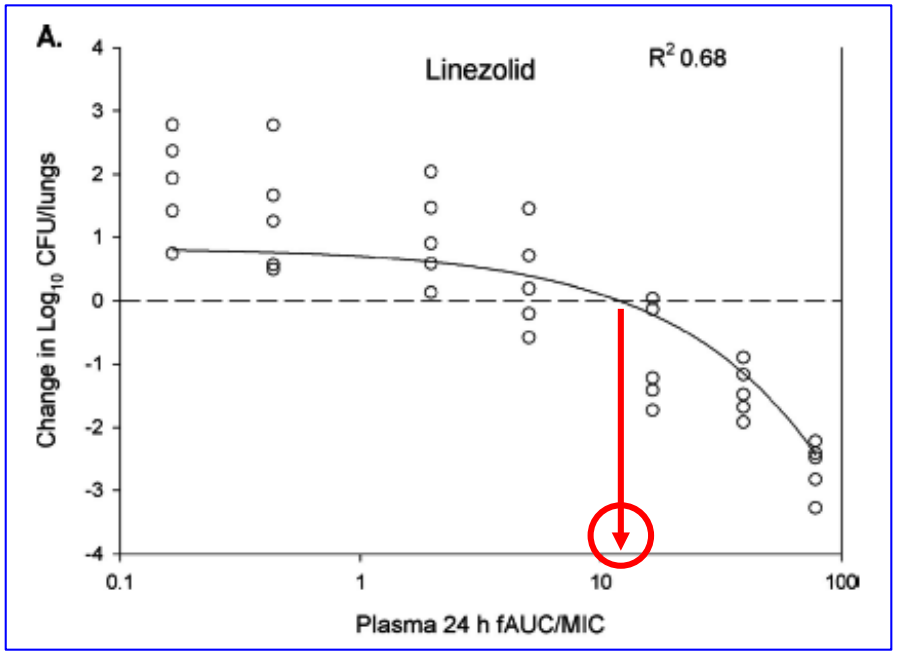
major differences in pharmacokinetics and in MICs



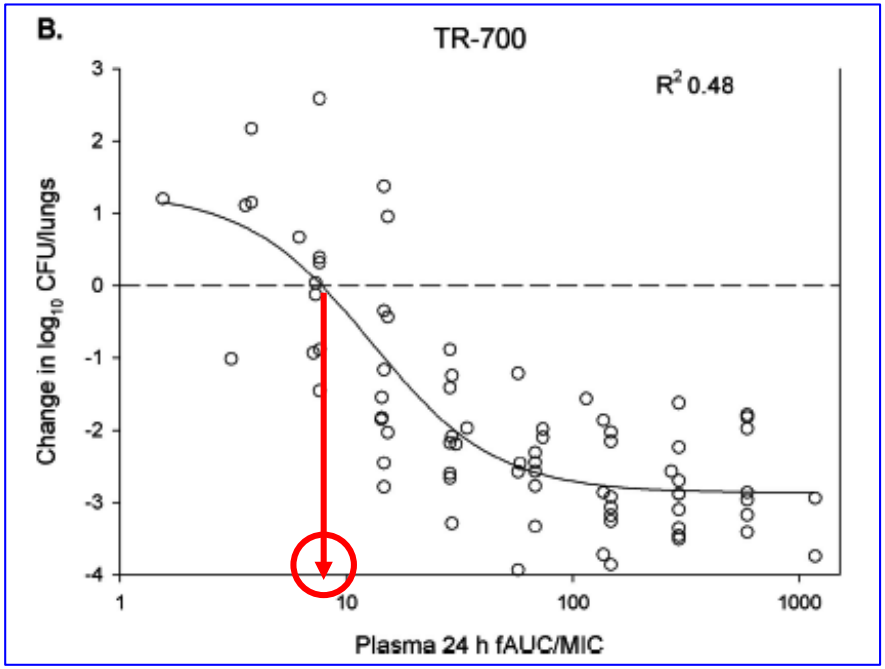
	modal EUCAST MIC
linezolid	2 mg/L
TR700	0.25 mg/L

Animal models: application to two oxazolidinones

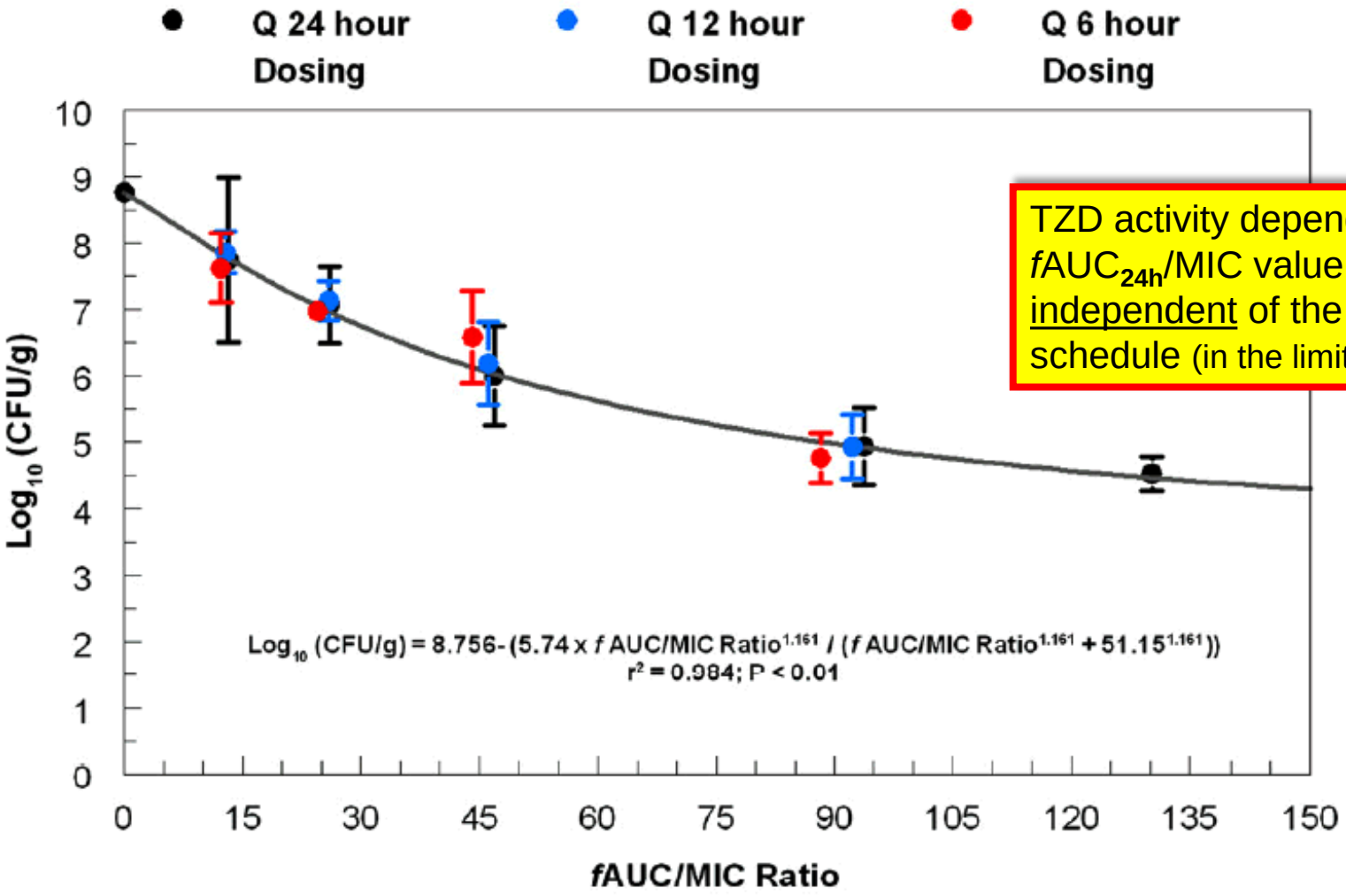
2. pharmacodynamics



similar AUC_{24h}/MIC
for static effect !



AUC_{24h} and activity tedizolid



TZD activity depends on actual *f*AUC_{24h}/MIC value, and is <u>independent</u> of the dosing schedule (in the limits investigated)

Louie *et al* Antimicrob Agents Chemother 2011;55:3453-3460 – PMID 21502615

You can use different environments…

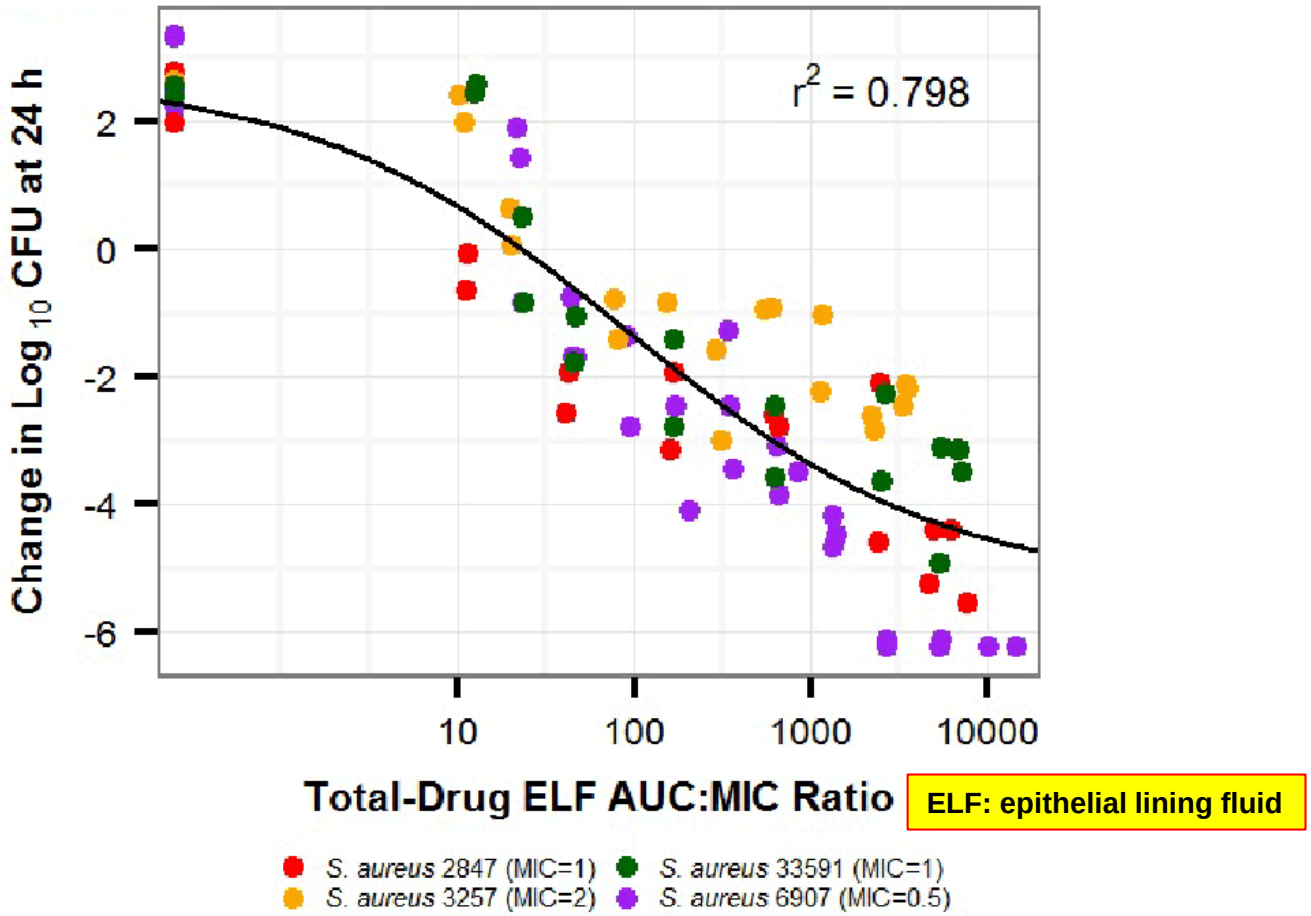


Figure 2. Relationship between change in $\log_{10}$ CFU from baseline and arbekacin total-drug ELF AUC:MIC ratio based on data for four MRSA isolates

Van Scoy et al. ASM Microbe 2017 – poster SUNDAY 197

The programme…

- Why pharmacokinetics/pharmacodynamics/toxicodynamics ?
- The main PK/PD indices and the main methods to discover them
- **The breakpoints … and what they mean**
- What about toxicity ?
- What about resistance ?

What are breakpoints ?

- a magic number obtained from *in vitro* susceptibility testing, which the clinical microbiologists use to determine if the antibiotic will or will not be active *in vivo* against a given pathogen;
- this number is usually a given diameter [1] of growth inhibition in an agar plate around a disk loaded with a standard amount of antibiotic;
- while this system yields *per definition* a continuous variable (i.e. a diameter of any size [from 0 mm to the limit of the dish…), microbiologists and authorities like to cut the results it in 3 discrete categories
  - less than x mm[1] ➔ RESISTANT
  - larger than y mm[1] ➔ SUSCEPTIBLE
  - between x and y mm[1]➔ INTERMEDIATE

which is what the clinician will get…

[1] diameters must be converted into an MIC by using previously validated regression lines with the ISO method (the ISO method is microdilution…which , by definition, yields an MIC)

An example of breakpoints… (EUCAST)

Streptococcus pneumoniae

Macrolides, lincosamides and streptogramins	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Azithromycin	0.25[1]	0.5[1]		Note[A]	Note[A]
Clarithromycin	0.25[1]	0.5[1]		Note[A]	Note[A]
Erythromycin	0.25[1]	0.5[1]	15	22[A]	19[A]
Roxithromycin	0.5[1]	1[1]		Note[A]	Note[A]
Telithromycin	0.25	0.5	15	23	20
Clindamycin[2]	0.5	0.5	2	19[B]	19[B]
Quinupristin-dalfopristin	-	-		-	-

Notes

Numbered notes relate to general comments and/or MIC breakpoints.

Lettered notes relate to the disk diffusion method.

1/A. Erythromycin can be used to determine susceptibility to azithromycin, clarithromycin and roxithromycin.

2. Inducible clindamycin resistance can be detected by antagonism of clindamycin activity by a macrolide agent. If not detected, then report as susceptible. If detected, then report as resistant.

B. Place the erythromycin and clindamycin disks 12-16 mm apart (edge to edge) and look for antagonism (the D phenomenon) to detect inducible clindamycin resistance.

http://www.eucast.org/clinical_breakpoints/

EUCAST definitions of clinical breakpoints

Clinically Susceptible (S)

- level of antimicrobial activity associated with a high likelihood of therapeutic success

Clinically Intermediate (I)

- level of antimicrobial activity associated with indeterminate therapeutic effect

Clinically Resistant (R)

- level of antimicrobial activity associated with a high likelihood of therapeutic failure.

a microorganism is categorized as S, I or R by applying the appropriate breakpoint in a defined phenotypic test system

Clinical breakpoints may be altered with legitimate changes in circumstances

Clinical breakpoints are presented as S≤ x mg/L ; I >x, ≤ y mg/L ; R >y mg/L

For long, breakpoints have been set too high…

Drug	Typical daily dosage[a]	Typical PK values: C_{max} in mg/L total/free (dose)	Typical PK values: $AUC_{24\,h}$ (mg × h/L) total/free	Proposed PK/PD upper limit: Efficacy[b]	Proposed PK/PD upper limit: Prevention of resistance[c]	Breakpoints (mg/L)[d]: NCCLS (S/I/R)
Norfloxacin	800 mg	1.4/1.1 (400 mg PO)	14/11	0.1–0.4	0.1	≤4/8/>16[j]
Ciprofloxacin	1000 mg	2.5/1.75 (500 mg PO)	24/18	0.2–0.8	0.2	≤1/2/>4[k]
Ofloxacin	400 mg	4/3 (400 mg PO)	40/30	0.3–0.9	0.4	≤2/4/8[l]
Levofloxacin	500 mg	4/2.8 (500 mg PO)	40/28	0.3–0.9	0.3	≤2/4/8[l]
Moxifloxacin	400 mg	3.1/1.8 (400 mg PO)	35/21	0.2–0.7	0.2	≤1/2/4[m]

NCCLS, National Committee for Clinical Laboratory Standards (Clinical and Laboratory Standards Institute) (http://www.ncc

Van Bambeke F, Michot JM, Van Eldere J, Tulkens PM.
Quinolones in 2005: an update. Clin Microbiol Infect. 2005 Apr;11(4):256-80. PMID: 15760423

Breakpoint setting: the EUCAST way

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

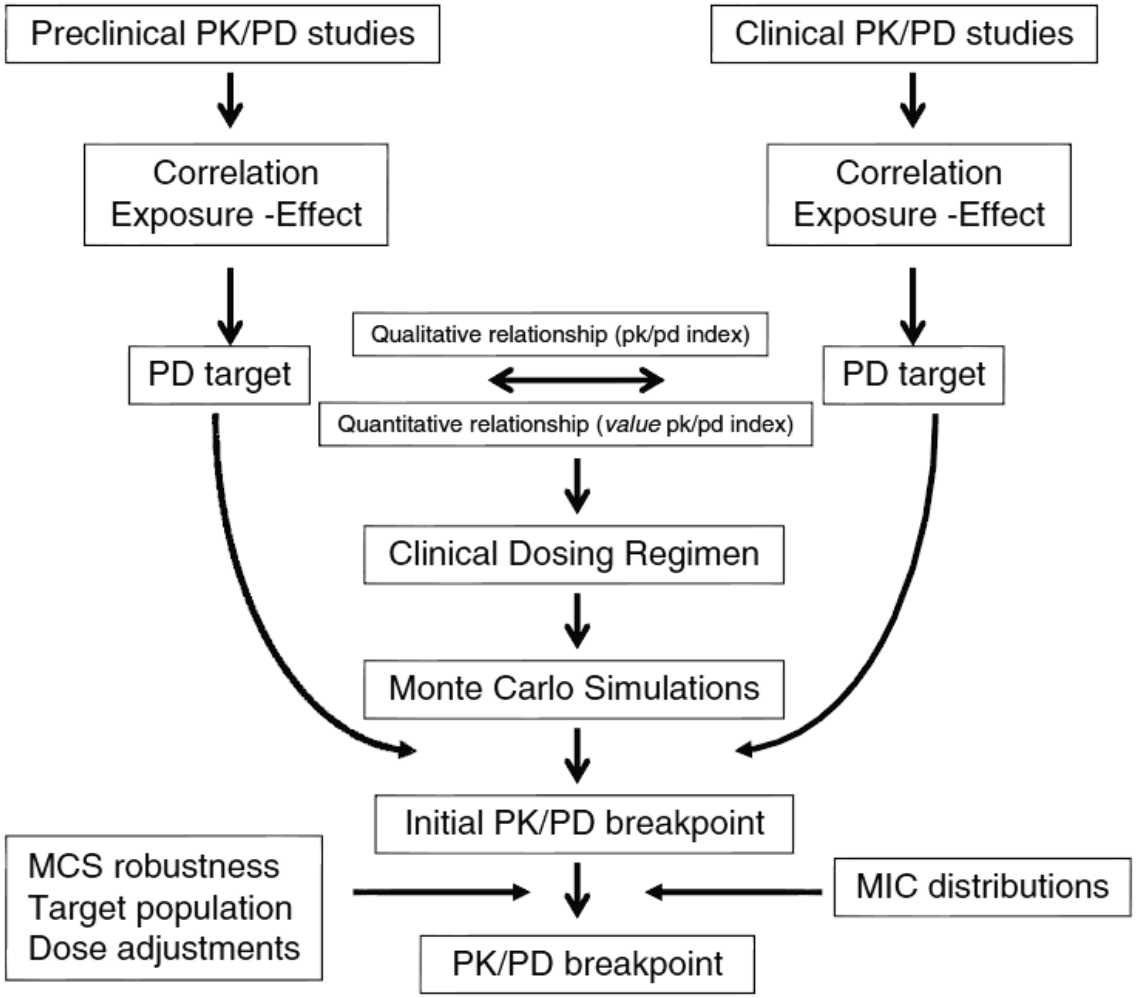
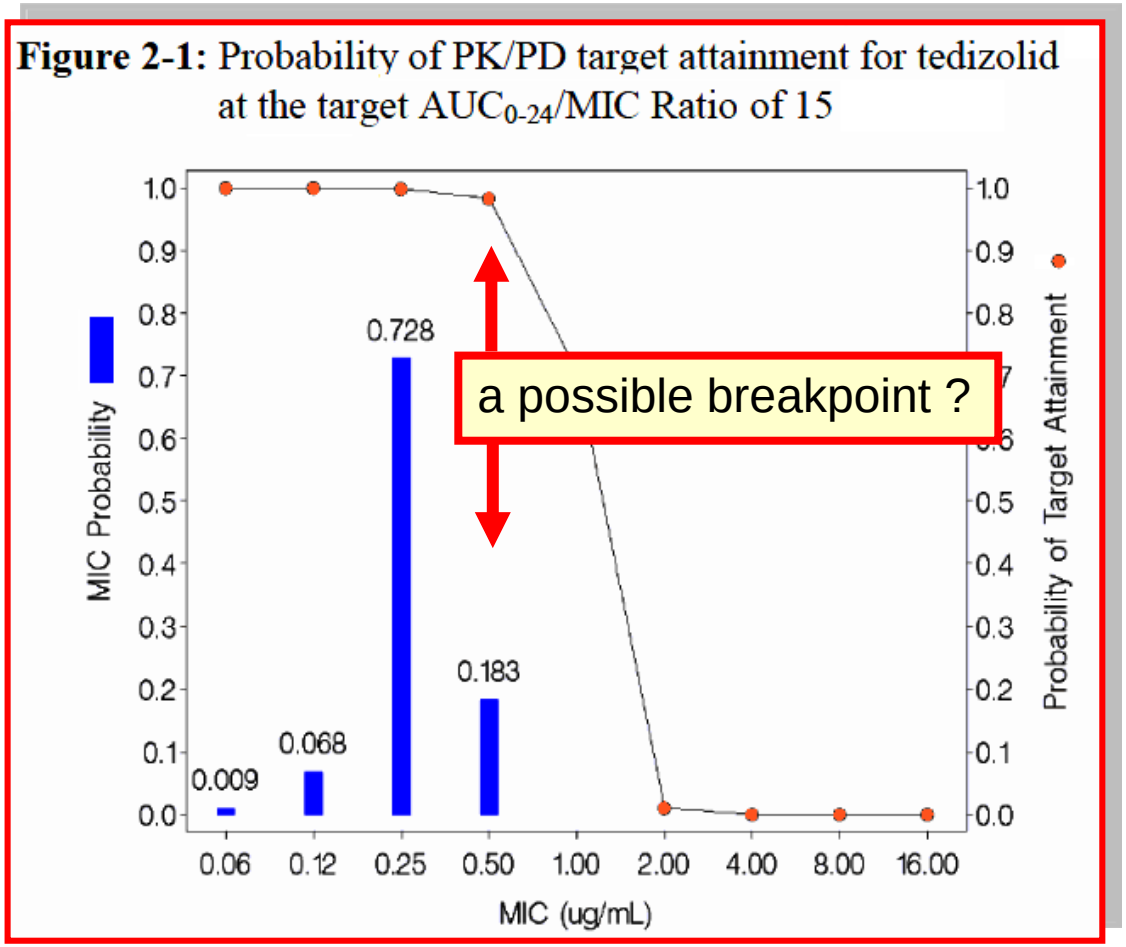


Fig. 3.4 Summary of the process of setting PK/PD breakpoints by EUCAST (Mouton et al. 2012)

Towards a breakpoint… probability of target attainment rate

- A tedizolid free $AUC_{0\text{-}24h}$/MIC ratio of 15 was determined as the PK/PD target associated with the activity of tedizolid against *S. aureus* in the non-neutropenic mouse thigh model of infection…[1]

Calculation of the probability of reaching the necessary *f*AUC_{24h}/MIC ratio for increasing MICs in humans…



[1] FDA briefing document: anti-infective drug advisory committee meeting
March 31, 2014
http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/anti-infectivedrugsadvisorycommittee/ucm390789.pdf
Last accessed: May 17, 2015

Tedizolid breakpoints… a matter of dispute ?

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

Tedizolid

Organism group	Breakpoint (mg/L)	
	S ≤ (mg/L)	R > (mg/L)
Staphylococcus spp.	0.5	0.5
Enterococcus spp.	IE	IE
Streptococcus groups A,B,C,G	0.5	0.5
Viridans group streptococci (*Streptococcus anginosus* group only)	0.25	0.25
PK/PD breakpoints	IE	IE

1 mg/L for *S. aureus* is resistant

1 mg/L for *S. aureus* is intermediate

Table 5 Susceptibility Test Interpretive Criteria for SIVEXTRO

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)		
	S	I	R
Staphylococcus aureus (methicillin-resistant and methicillin-susceptible isolates)	≤0.5	1	≥2
Streptococcus pyogenes	≤0.5	-	-
Streptococcus agalactiae	≤0.5	-	-
Streptococcus anginosus Group*	≤0.25	-	-
Enterococcus faecalis	≤0.5	-	-

S=susceptible, I=intermediate, R=resistant
* Includes *S. anginosus*, *S. intermedius*, *S. constellatus*

The programme…

- ThWhy pharmacokinetics/pharmacodynamics/toxicodynamics ?
- e main PK/PD and PK/TD indices and the main methods to discover them
- The breakpoints … and what they mean
- **What about toxicity ?**
- What about resistance ?

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This is where unanticipated observations shake you …

But before we begin: Types of toxicity (in very short)…

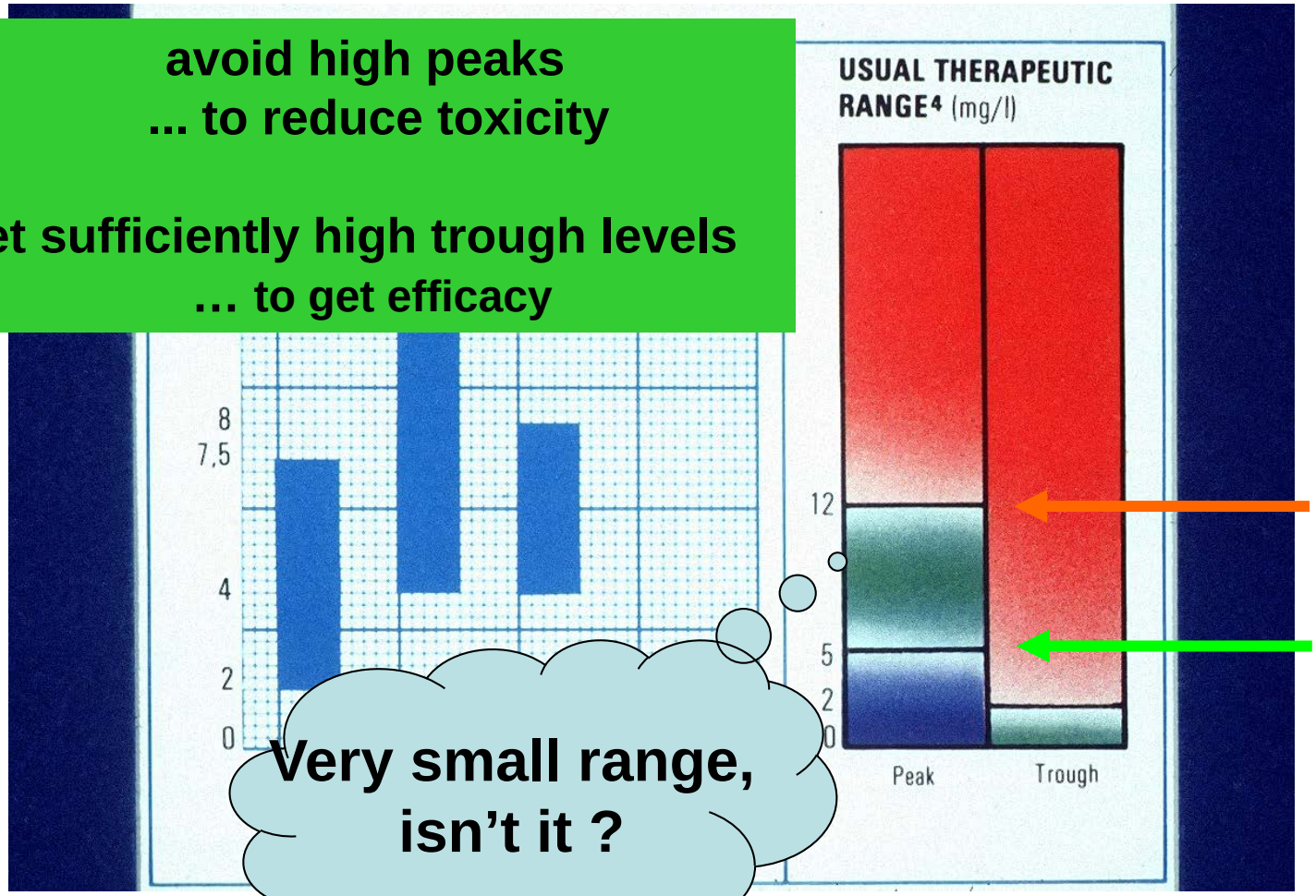
- related to the mode of therapeutic action
  - ➢ titrate the dosage (if possible)

- unrelated to the therapeutic effect
  - drug and drug/drug interactions
    - ➢ prevention / mitigation (pharmacokinetics)
  - action on non-therapeutic target organ(s)
    - non dose-related (idiosyncratic)
      - ➢ epidemiological and registry studies leading to general withdrawal/change of label if not-acceptable (e.g. telithromycin)
    - <u>dose-related</u> (somehow)
      - ➢ **open to pharmacokinetic/toxicodynamic studies susceptible to lead to mitigation approaches**

Aminoglycosides monitoring in the 80's ...

avoid high peaks
... to reduce toxicity

get sufficiently high trough levels
… to get efficacy

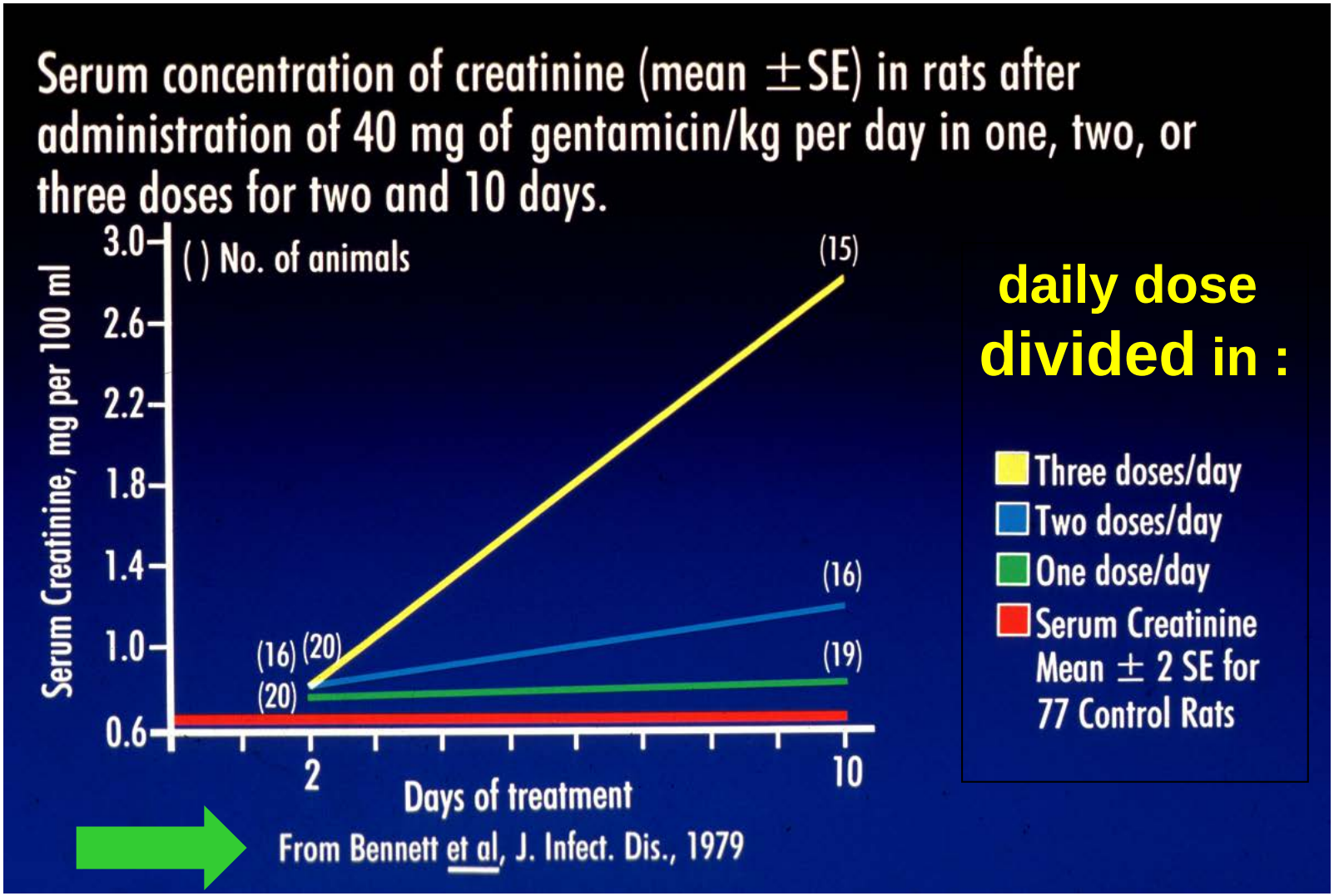


toxicity !!

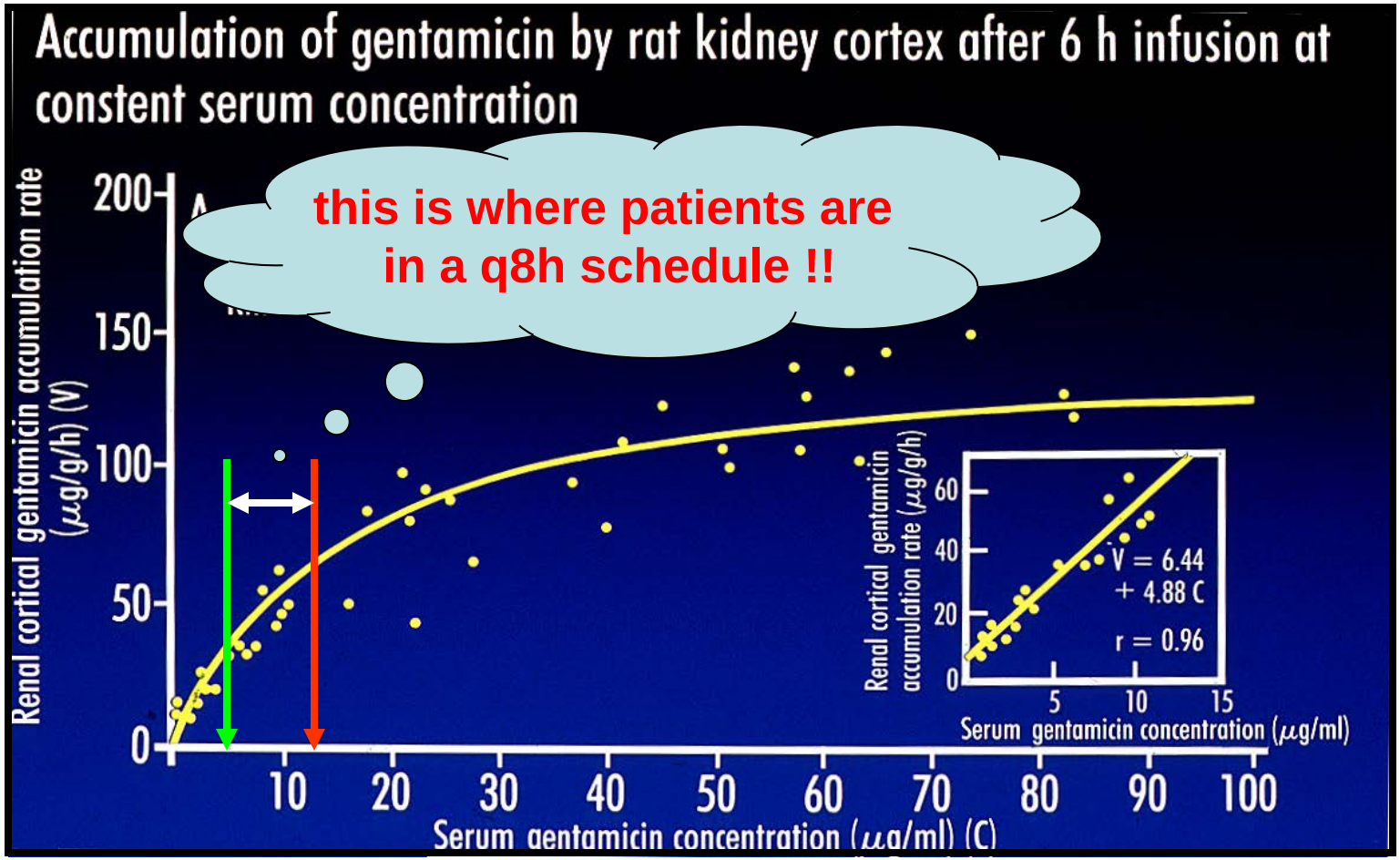
lack of efficacy

Abott TdX manual, 1986

But aminoglycoside toxicity is **not** linked to peak ...



Aminoglycoside accumulation is kidney is saturable at clinically meaningful concentrations * ...



* Giuliano *et al.*, J. Pharm. Exp. Ther., 1986

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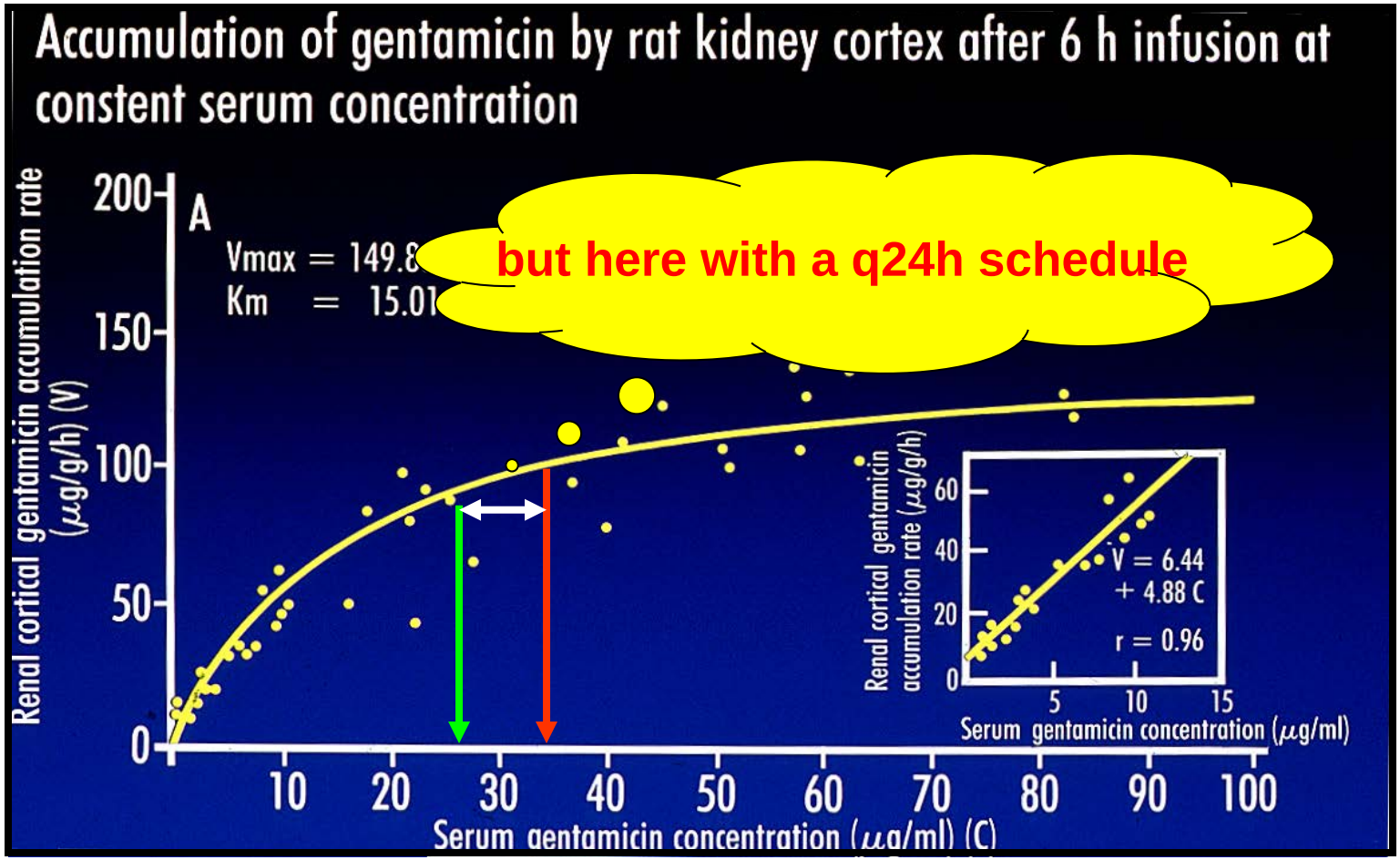
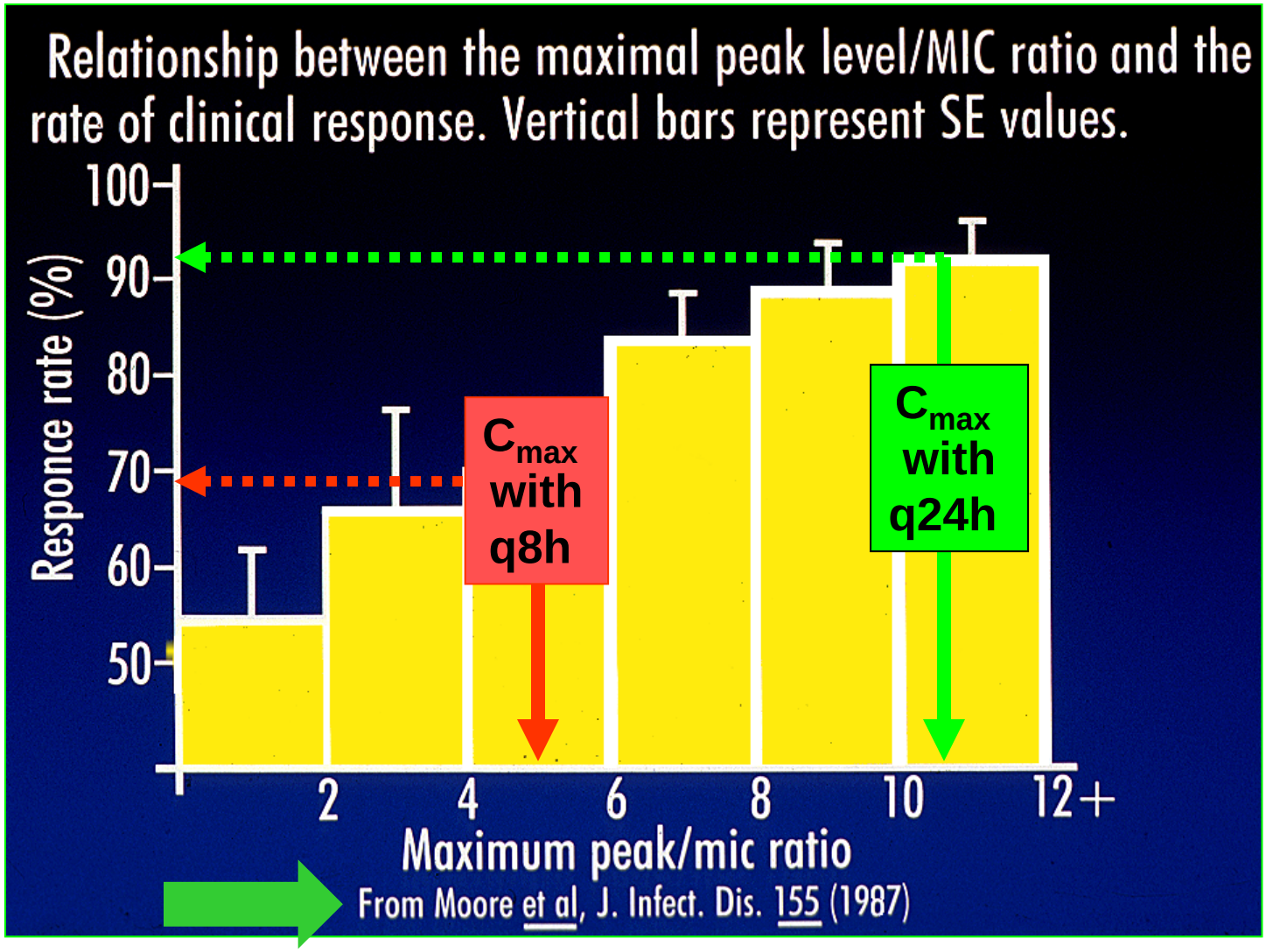


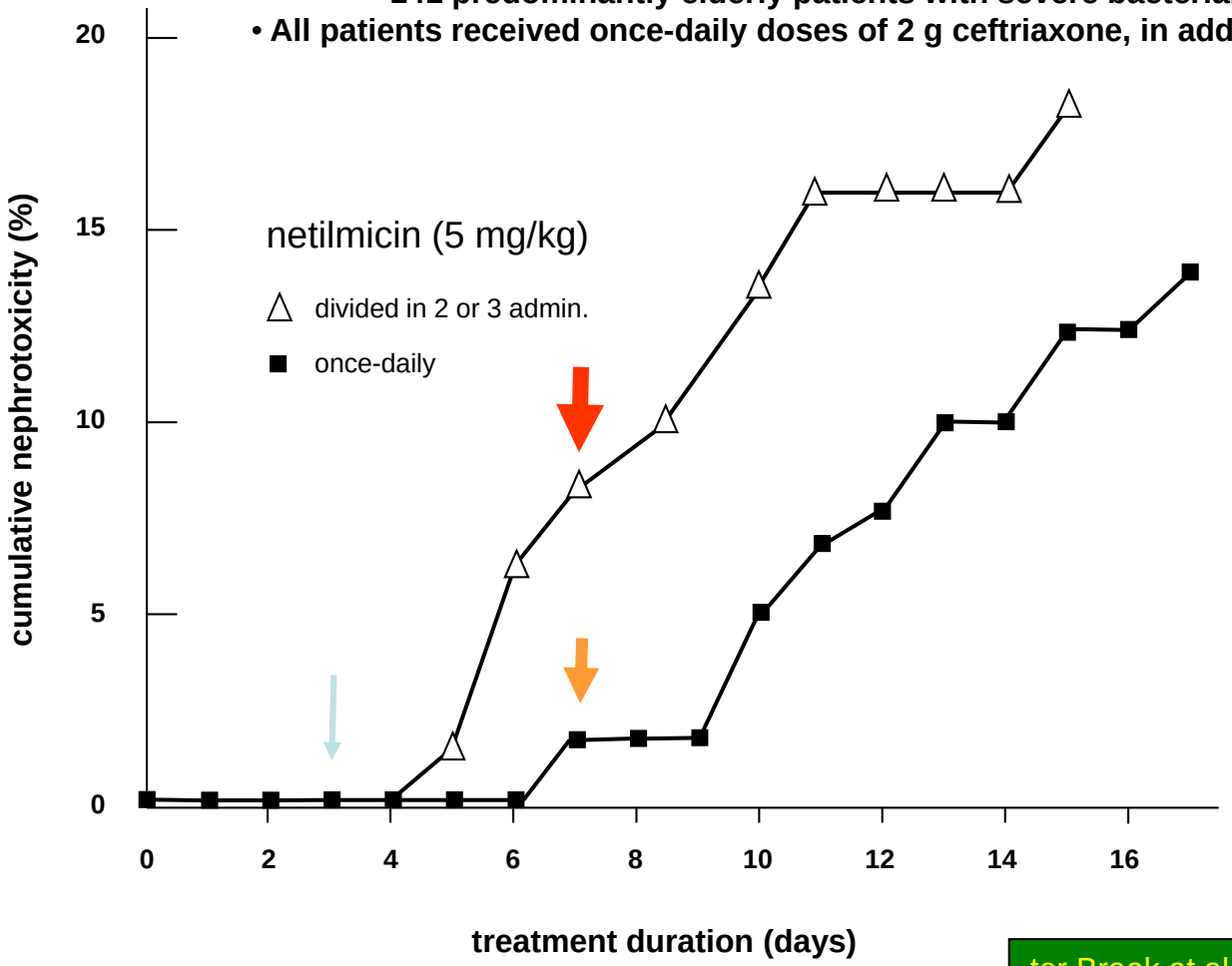
* Giuliano *et al.*, J. Pharm. Exp. Ther., 1986

Aminoglycoside peak /MIC ratio is predictive of clinical efficacy



Nephrotoxicity and schedule of administration … the first large scale clinical trial

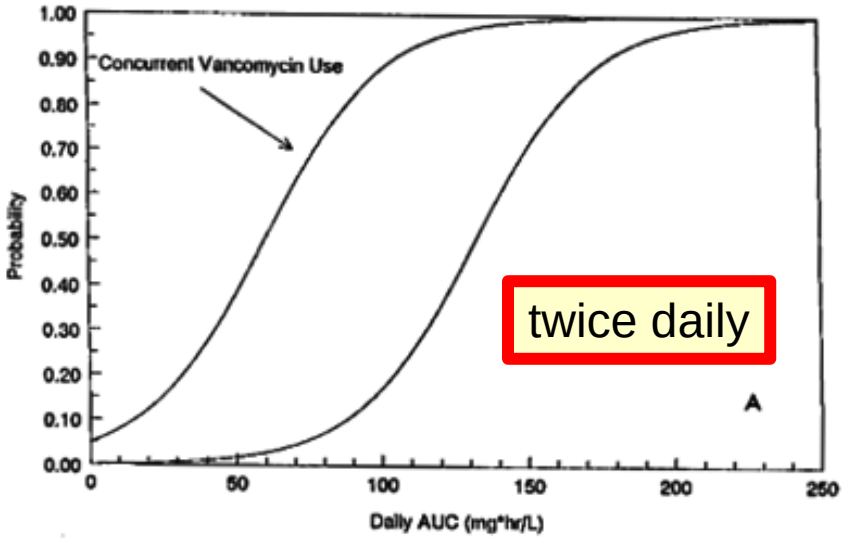
• 141 predominantly elderly patients with severe bacterial infections.
• All patients received once-daily doses of 2 g ceftriaxone, in addition to netilmicin.



"Netilmicin-induced toxicity may be reduced by using once-daily dosing regimens and limiting the duration of treatment."

ter Braak et al., Am J Med. 1990 Jul;89(1):58-66.

Aminoglycoside nephrotoxicity when combined with vancomycin: influence of schedule



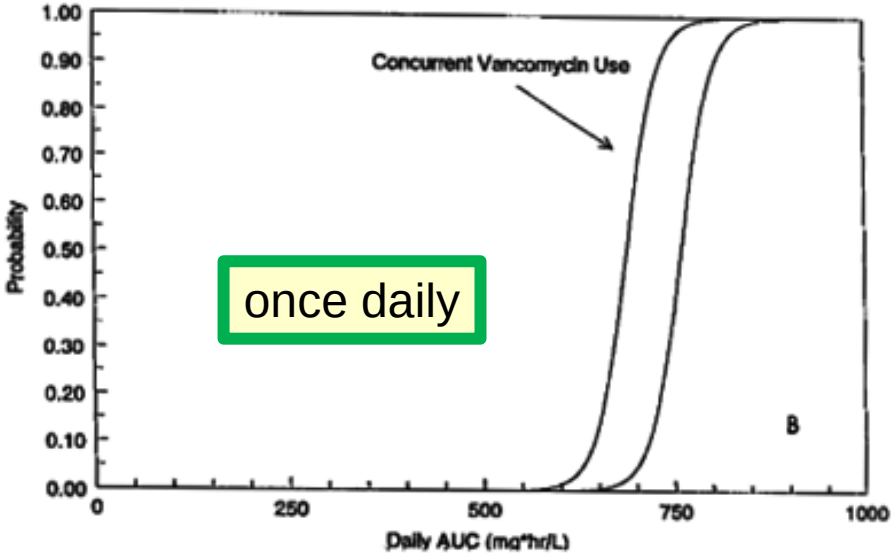


FIG. 1. (A) Curve of probability of development of aminoglycoside nephrotoxicity for patients receiving the drug on a twice-daily basis as estimated by multivariate logistic regression analysis. The probability rises as a function of increasing daily exposure to aminoglycoside, as indexed to the AUC. Concurrent vancomycin use provides a marked increase in the probability of nephrotoxicity for equivalent exposure to aminoglycosides, as indexed to the daily AUC. (B) Once-daily administration shifts the curves of probability of nephrotoxicity as influenced by daily aminoglycoside AUC to the right.

Toxicodynamics of linezolid

Modelling of linezolid toxicity

Clinical Population Pharmacokinetics and Toxicodynamics of Linezolid

Lauren M. Boak,[a]* Craig R. Rayner,[a,b] M. Lindsay Grayson,[c,d] David L. Paterson,[e]* Denis Spelman,[f] Sharmila Khumra,[c,h] Blair Capitano,[e]* Alan Forrest,[g] Jian Li,[a] Roger L. Nation,[a] Jurgen B. Bulitta[a,g,h]

Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University (Parkville campus), Parkville, Australia[a]; d3 Medicine LLC, Parsippany, New Jersey, USA[b]; Department of Medicine, Austin Hospital, Melbourne, Australia[c]; Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia[d]; University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA[e]; Department of Infectious Diseases, Alfred Hospital and Monash University, Melbourne, Australia[f]; School of Pharmacy and Pharmaceutical Sciences, SUNY at Buffalo, Buffalo, New York, USA[g]; Centre for Medicine Use and Safety, Monash University (Parkville campus), Parkville, Australia[h]

Antimicrob Agents Chemother 2014;58:334–2343

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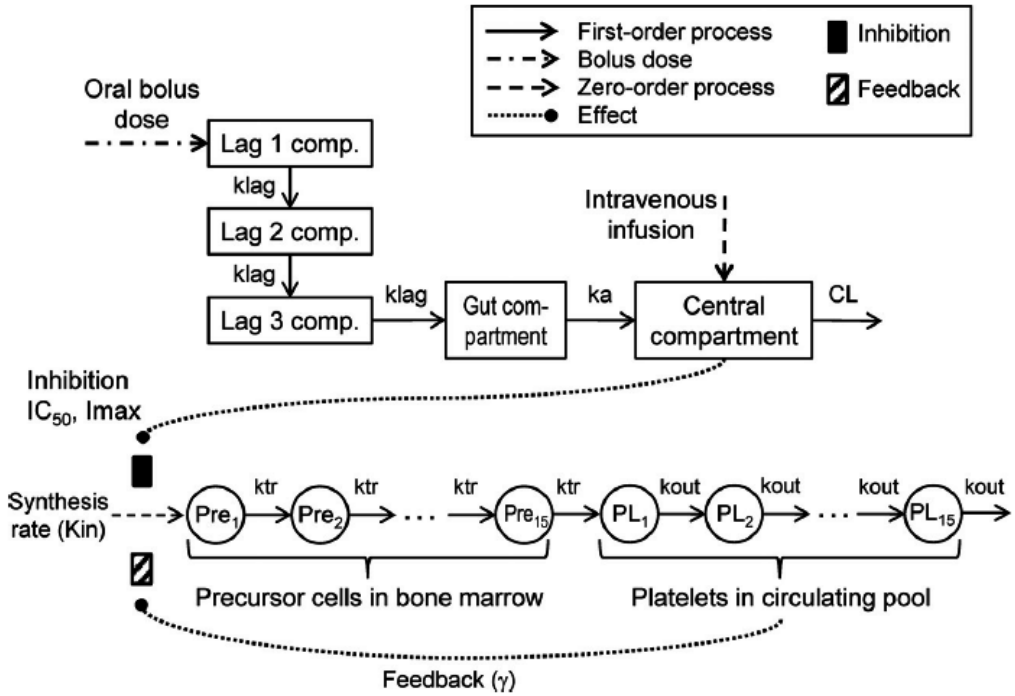

FIG 1 Structure of the final mechanism-based population pharmacokinetic/toxicodynamic model. The pharmacokinetic model is comprised of three absorption lag compartments, a gut compartment, and a central compartment. One series of 15 transit compartments was used to describe platelet precursor cells in the bone marrow, and another series of 15 transit compartments to describe platelets in the circulating pool. Platelets displayed a feedback effect on the synthesis of platelet precursor cells. A lack of platelets in the circulating pool compared to the platelet count at steady state caused a stimulation of platelet precursor synthesis, and an excess of platelets in the circulating pool caused an inhibition of platelet precursor synthesis.

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AAC Journals.ASM.org

Clinical Popula
Linezolid

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Blair Capitano,[e]* Alan Forres

Drug Delivery, Disposition and Dyna
Parsippany, New Jersey, USA[b]; Depa
University, Melbourne, Australia[d]; Un
Monash University, Melbourne, Aust
Monash University (Parkville campus

Antimicrob Agents Chemot

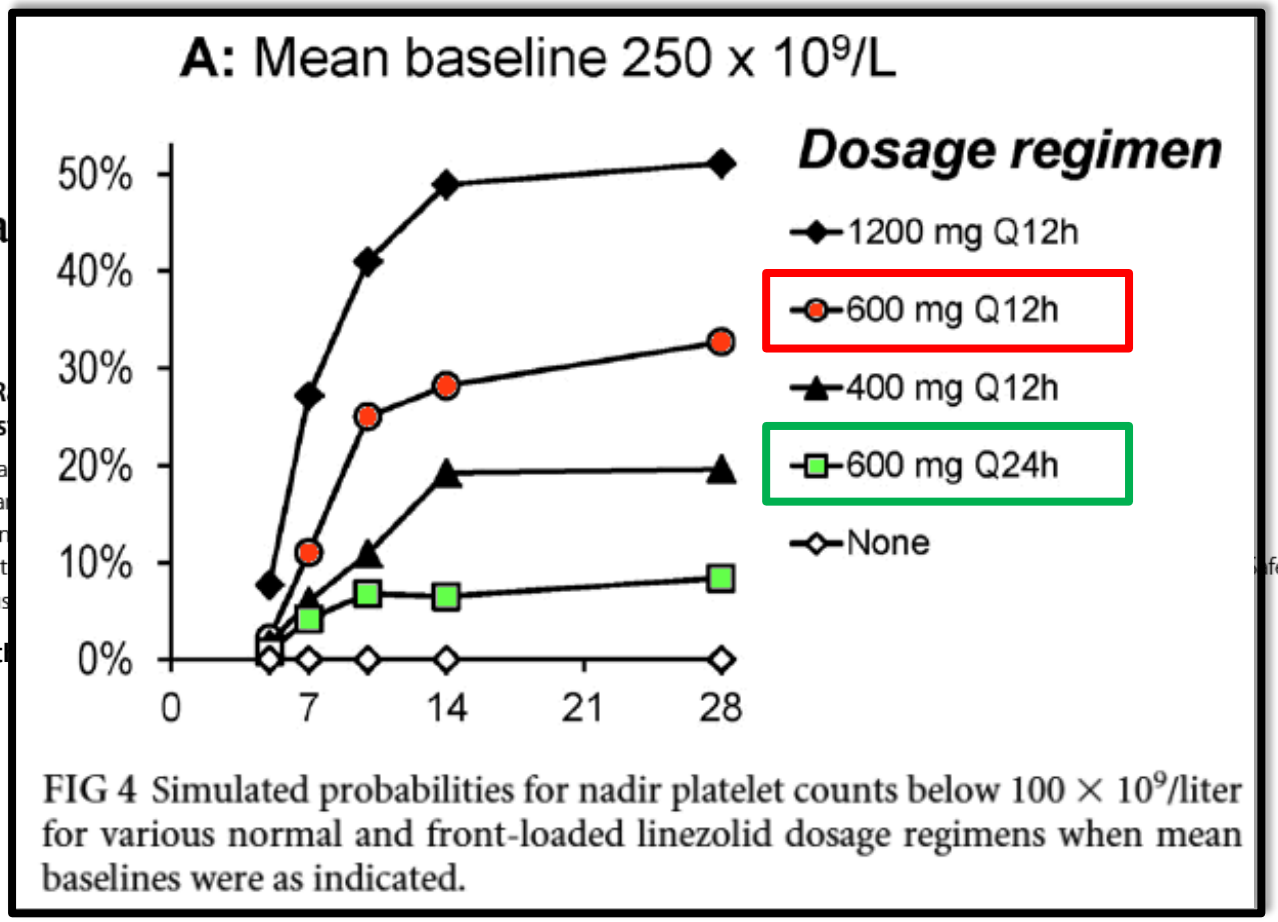

FIG 4 Simulated probabilities for nadir platelet counts below 100 × 10^9/liter for various normal and front-loaded linezolid dosage regimens when mean baselines were as indicated.

Toxicodynamics: avoid the elevated C_{min}…

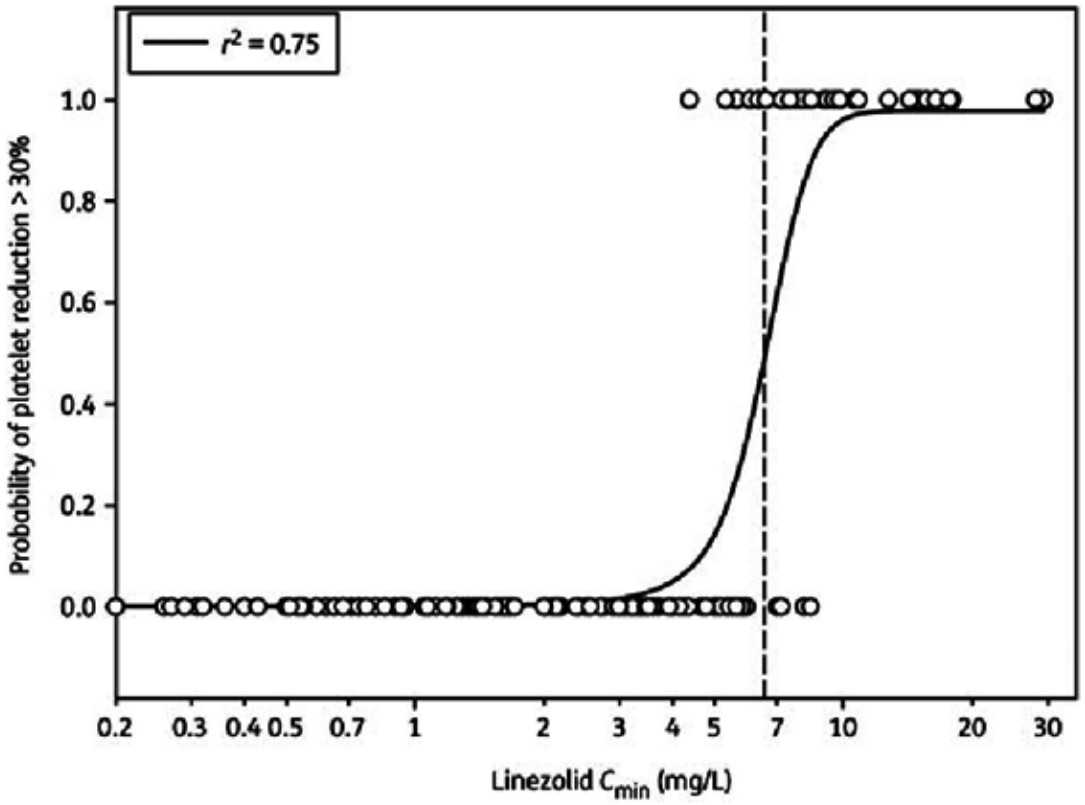

Fig. 16.13 Linezolid C_{min} and logistic regression model for thrombocytopenia (Pea et al. 2012), reproduced with permission. The symbols refer to the C_{min} observed over time in each patient with (*top*) or without (*bottom*) thrombocytopenia. The *continuous line* represents the result of the logistic regression model. The *vertical broken line* identifies the C_{min} value predicting 50 % probability of thrombocytopenia

Theuretzbacher U, PK/PD of Oxazolidinones In: Fundamentals of Antimicrobial Pharmacokinetics and Pharmacodynamics, AA. Vinck, H. Derendorf & JW Mouton eds, Springer, 2014, p 401-443

Linezolid and tedizolid impairment of mitochondrial protein synthesis and impact of pharmacokinetics

1. Impairment of mitochondrial protein synthesis may explain linezolid-induced lactic acidosis and neuropathies
2. Both linezolid and tedizolid impair mitochondrial protein synthesis …. but this is reversible…[1]
3. Plasma free concentrations of linezolid remain always > IC_{50} (twice daily administration) → permanent inhibition [2]
4. Plasma free tedizolid free through concentrations fall < IC_{50} for part of the dosing interval (once-daily administration) → partial daily recovery [2]

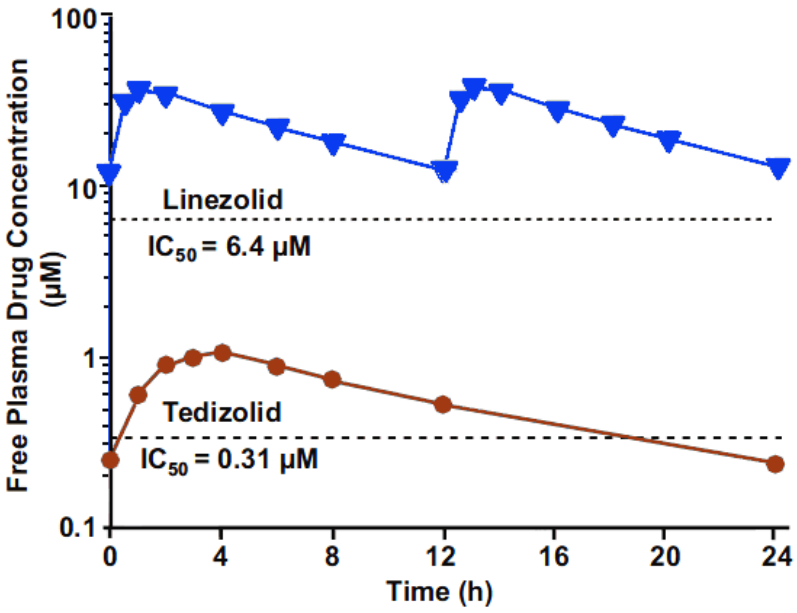

FIG 4 Mean free (unbound) drug plasma exposure concentrations at steady state for therapeutic-dose tedizolid (200 mg once daily; circles) and linezolid (600 mg twice daily; triangles) over the course of the dosing interval, based on published values (25, 41), in relation to the MPS IC_{50} of each agent.

[25] Pharmacia and Upjohn Co. 2014. Zyvox (linezolid) prescribing information.Pfizer, Inc, New York, NY.
[41] Flanagan et al. 2013;23d ECCMID - poster 921. 2

[1] Milosevic *et al.* 55th ICAAC & 25th ICC, 2015: poster 1008 (available from http://www.facm.ucl.ac.be/posters.htm)

[2] Flanagan *et al.* Antimicrob Agents Chemother 2015; 59:178-185 – PMID 25331703

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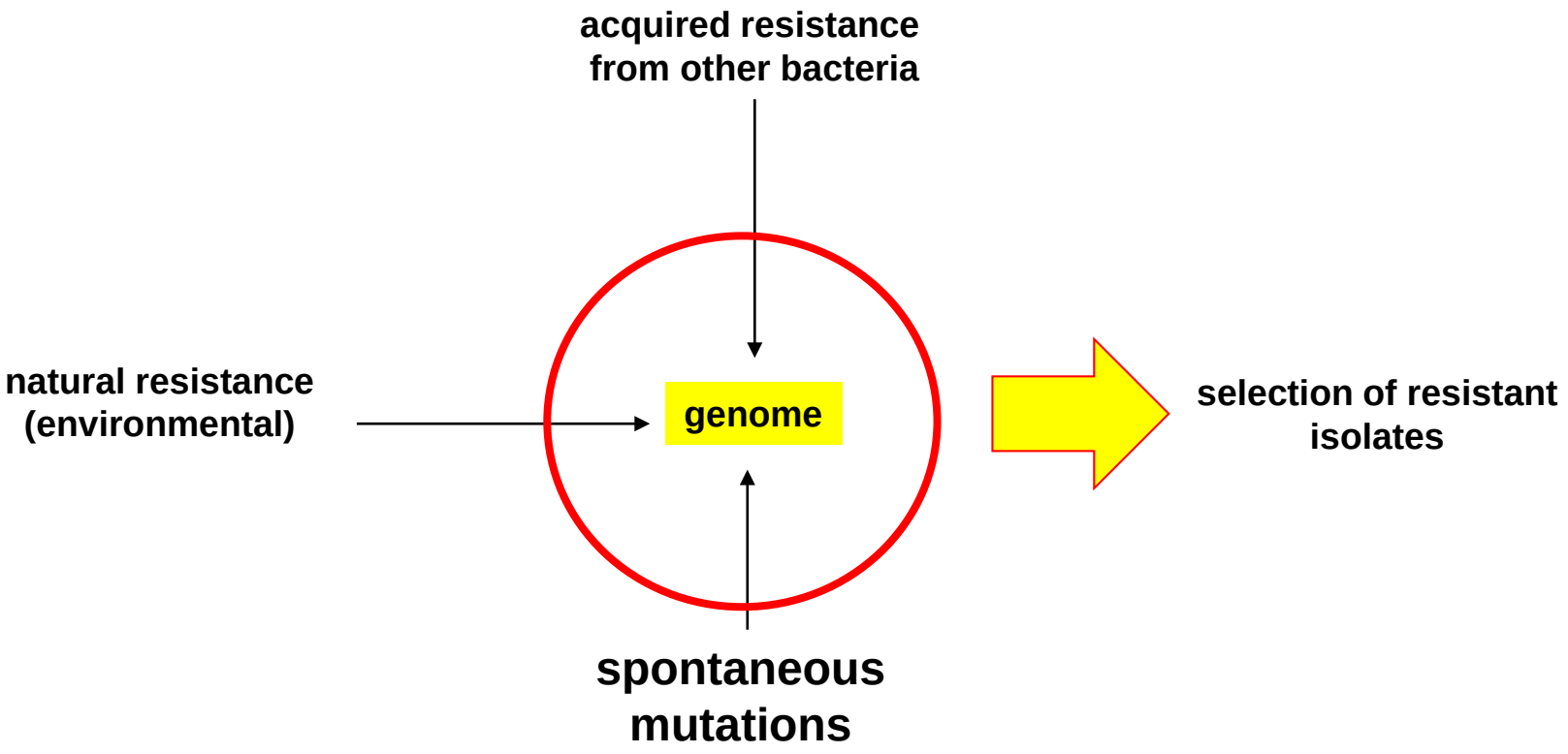
- What about toxicity ?
- **What about resistance ?**

Why so much resistance ?



A process linked to exposure to antibiotics

A direct visualization…

ANTIBIOTIC RESISTANCE

Spatiotemporal microbial evolution on antibiotic landscapes

Michael Baym,[1] Tami D. Lieberman,[1]* Eric D. Kelsic,[1] Remy Chait,[1]† Rotem Gross,[2] Idan Yelin,[2] Roy Kishony[1,2,3]‡

A key aspect of bacterial survival is the ability to evolve while migrating across spatially varying environmental challenges. Laboratory experiments, however, often study evolution in well-mixed systems. Here, we introduce an experimental device, the microbial evolution and growth arena (MEGA)–plate, in which bacteria spread and evolved on a large antibiotic landscape (120 × 60 centimeters) that allowed visual observation of mutation and selection in a migrating bacterial front. While resistance increased consistently, multiple coexisting lineages diversified both phenotypically and genotypically. Analyzing mutants at and behind the propagating front, we found that evolution is not always led by the most resistant mutants; highly resistant mutants may be trapped behind more sensitive lineages. The MEGA-plate provides a versatile platform for studying microbial adaption and directly visualizing evolutionary dynamics.

Baym *et al*. Science. 2016; 353:1147-51

A direct visua

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Baym *et al*. Science. 2016; 353:1147-5

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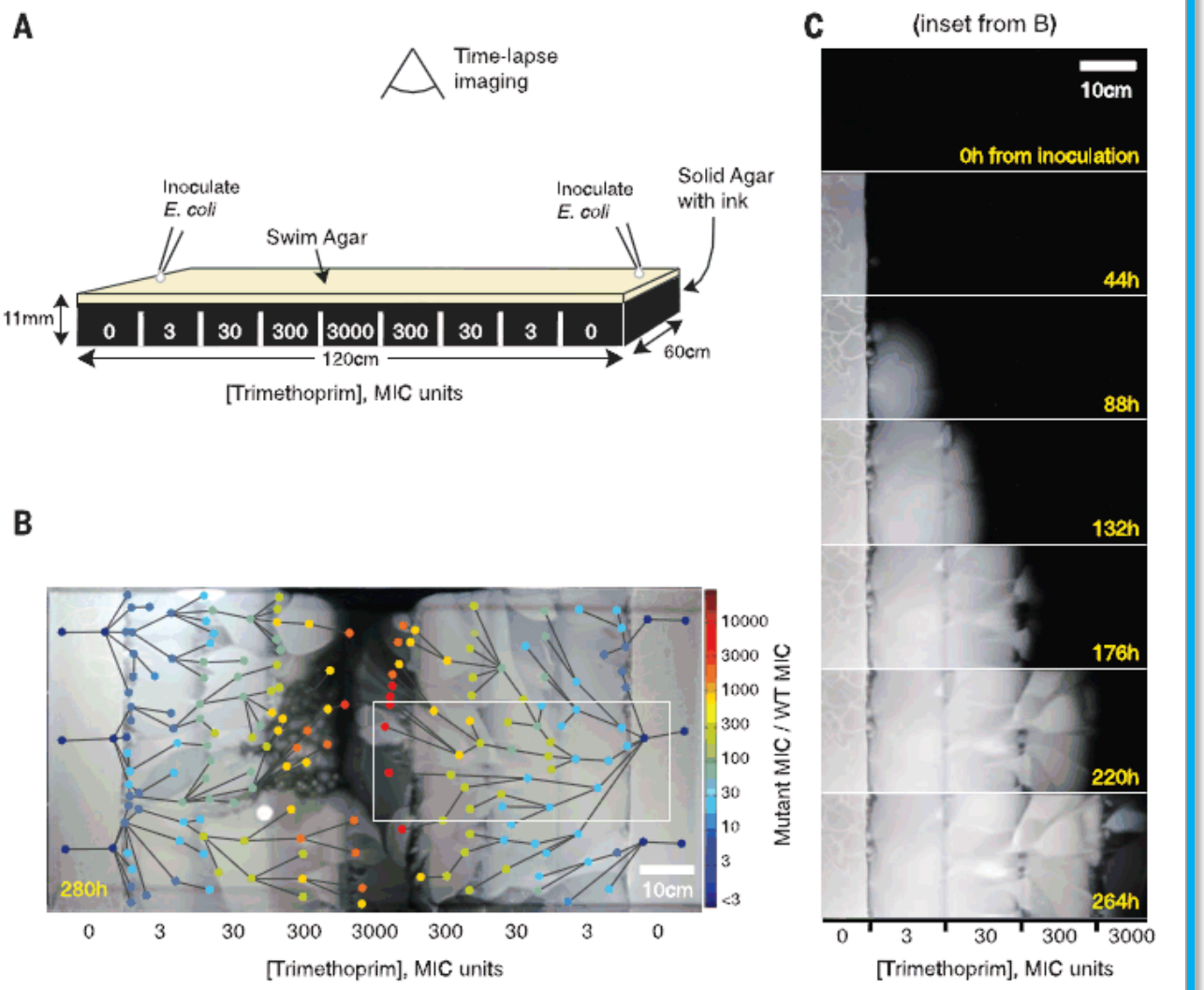

Fig. 1. An experimental device for studying microbial evolution in a spatially structured environment. (**A**) Setup of the four-step gradient of trimethoprim (TMP). Antibiotic is added in sections to make an exponential gradient rising inward. (**B**) The four-step TMP MEGA-plate after 12 days. *E. coli* appear as white on the black background. The 182 sampled points of clones are indicated by circles, colored by their measured MIC. Lines indicate video-imputed ancestry. (**C**) Time-lapse images of a section of the MEGA-plate. Repeated mutation and selection can be seen at each step. Images have been aligned and linearly contrast-enhanced but are otherwise unedited.

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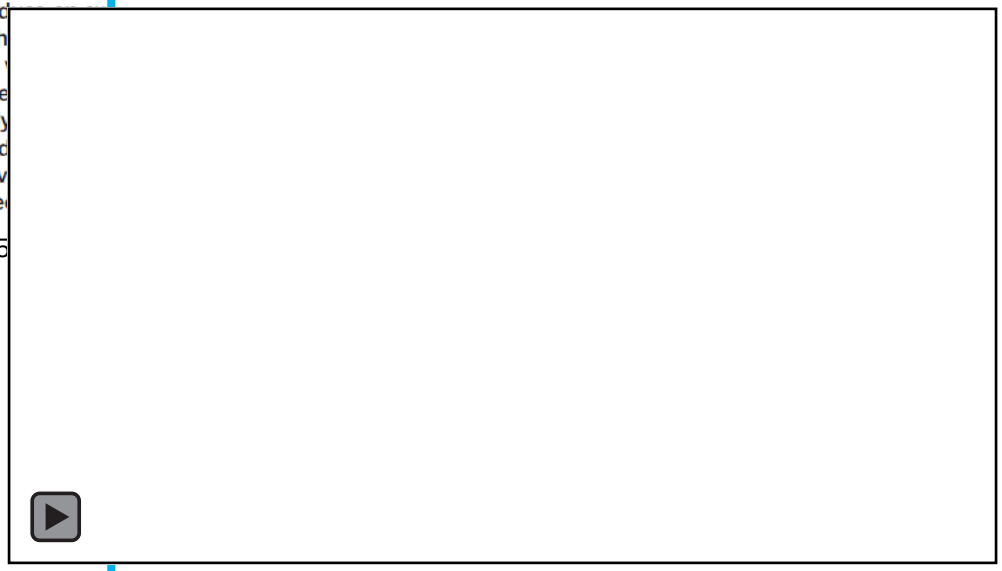
Baym *et al*. Science. 2016; 35



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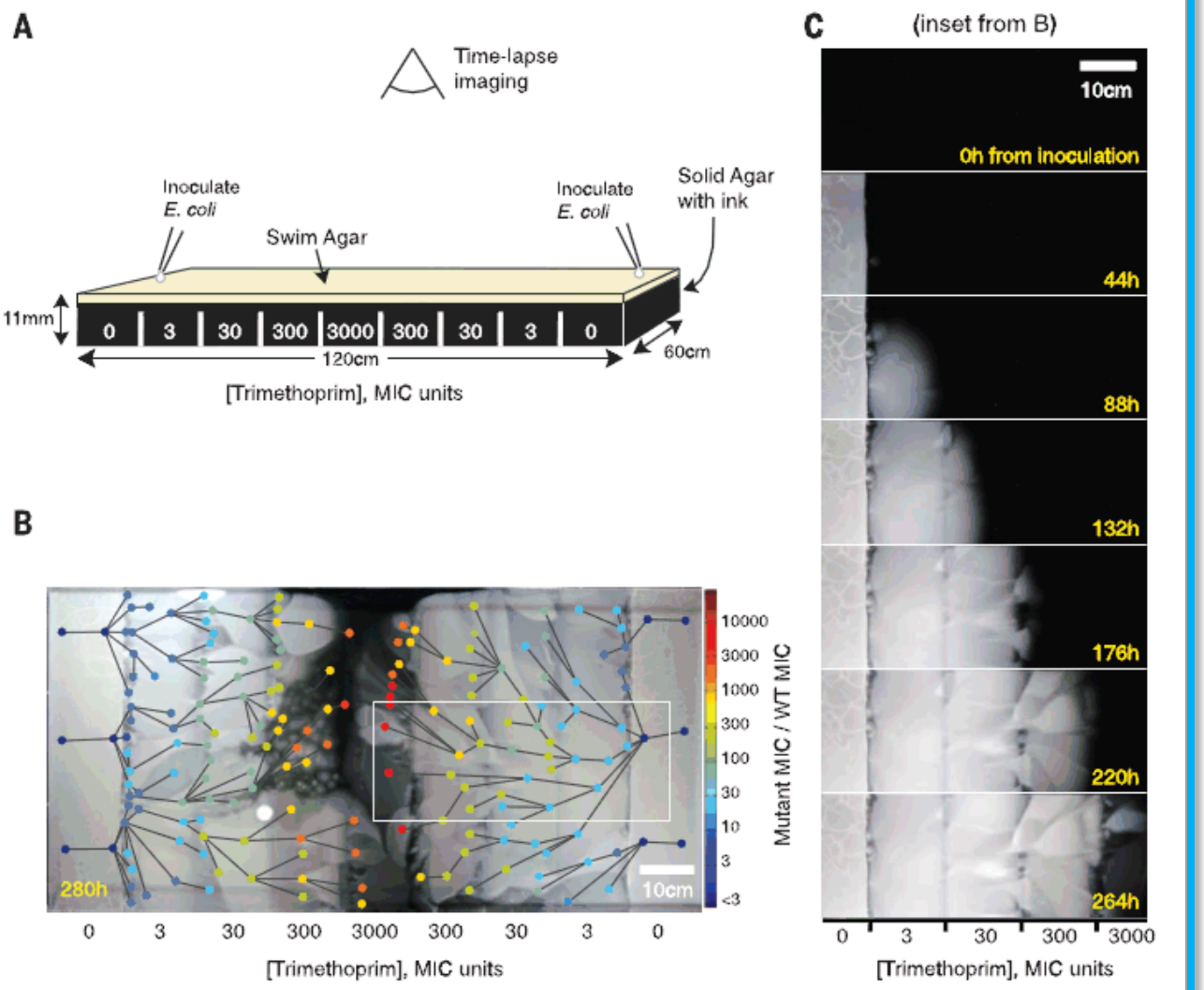

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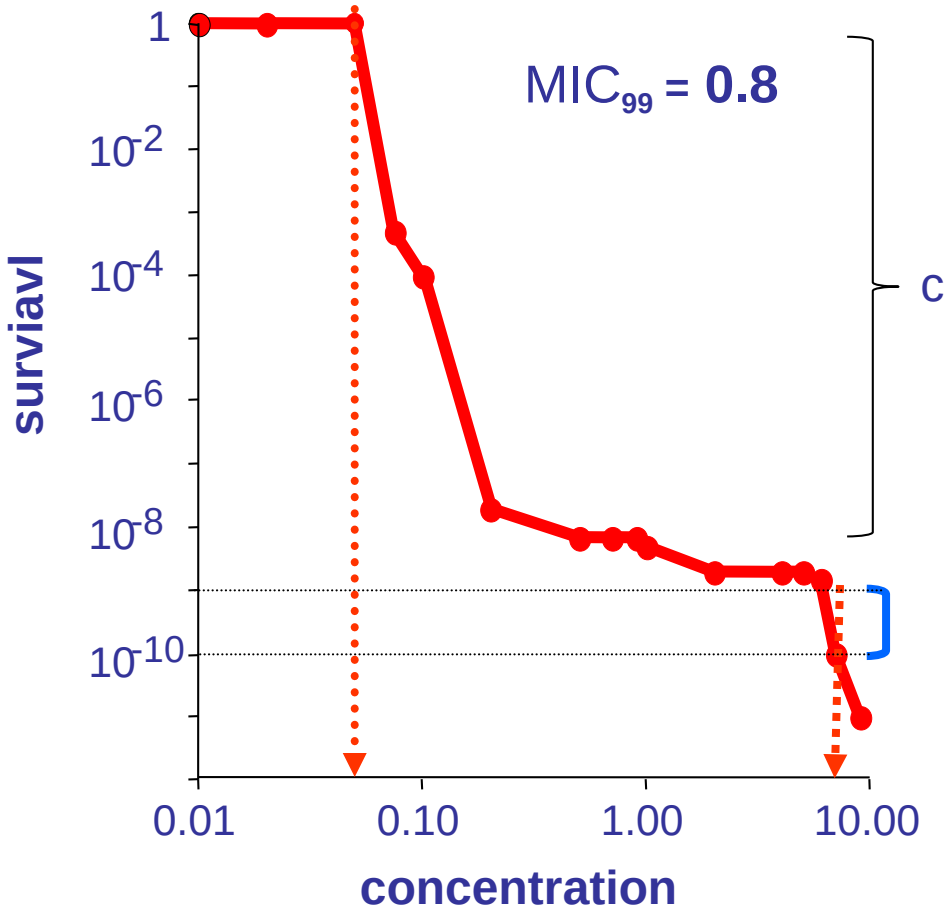
Concentration that prevent mutations / efflux

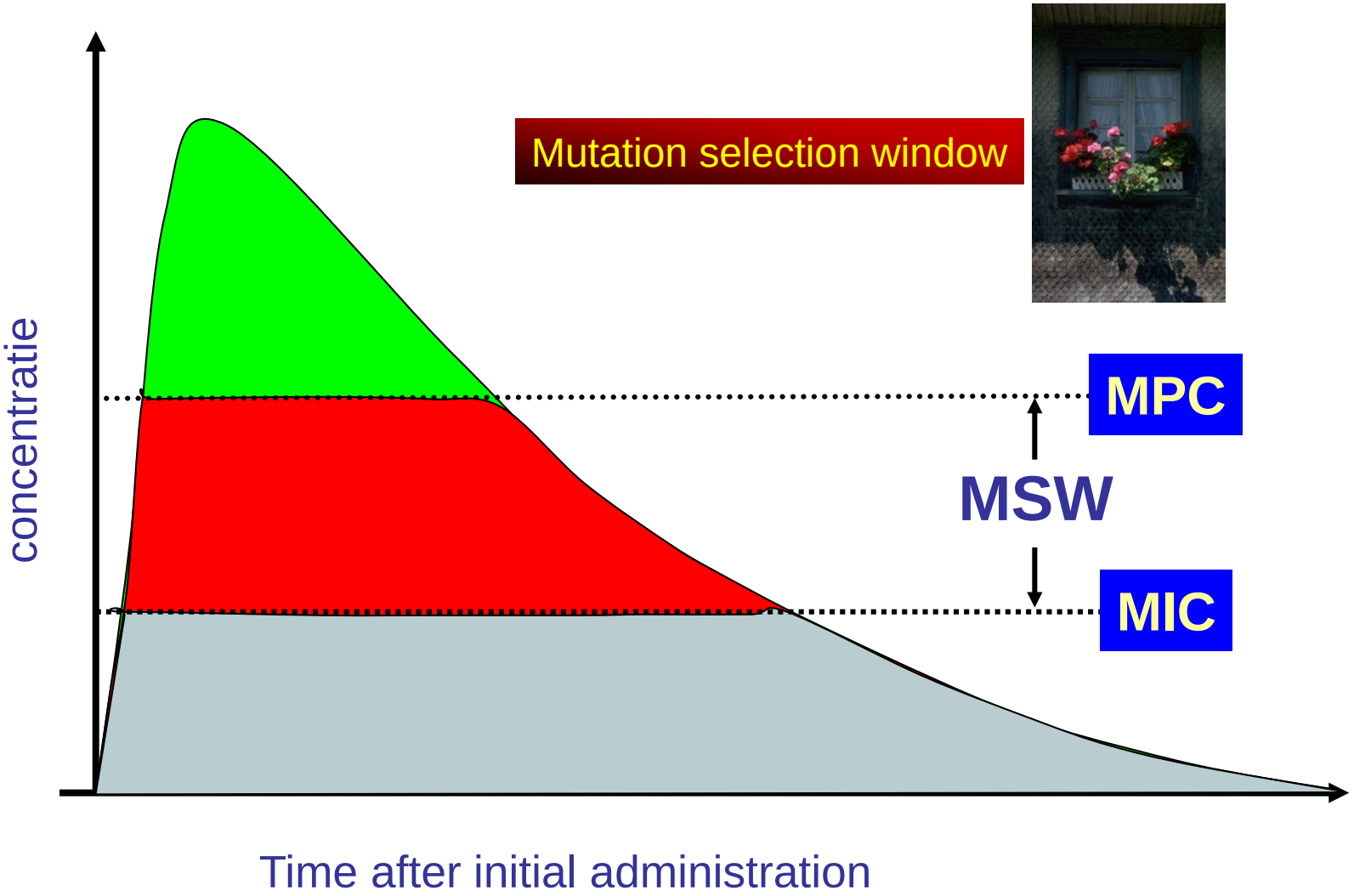
Mutation Preventing Concentration [MPC])

Illustration with *Mycobacterium bovis* and fluoroquinolones



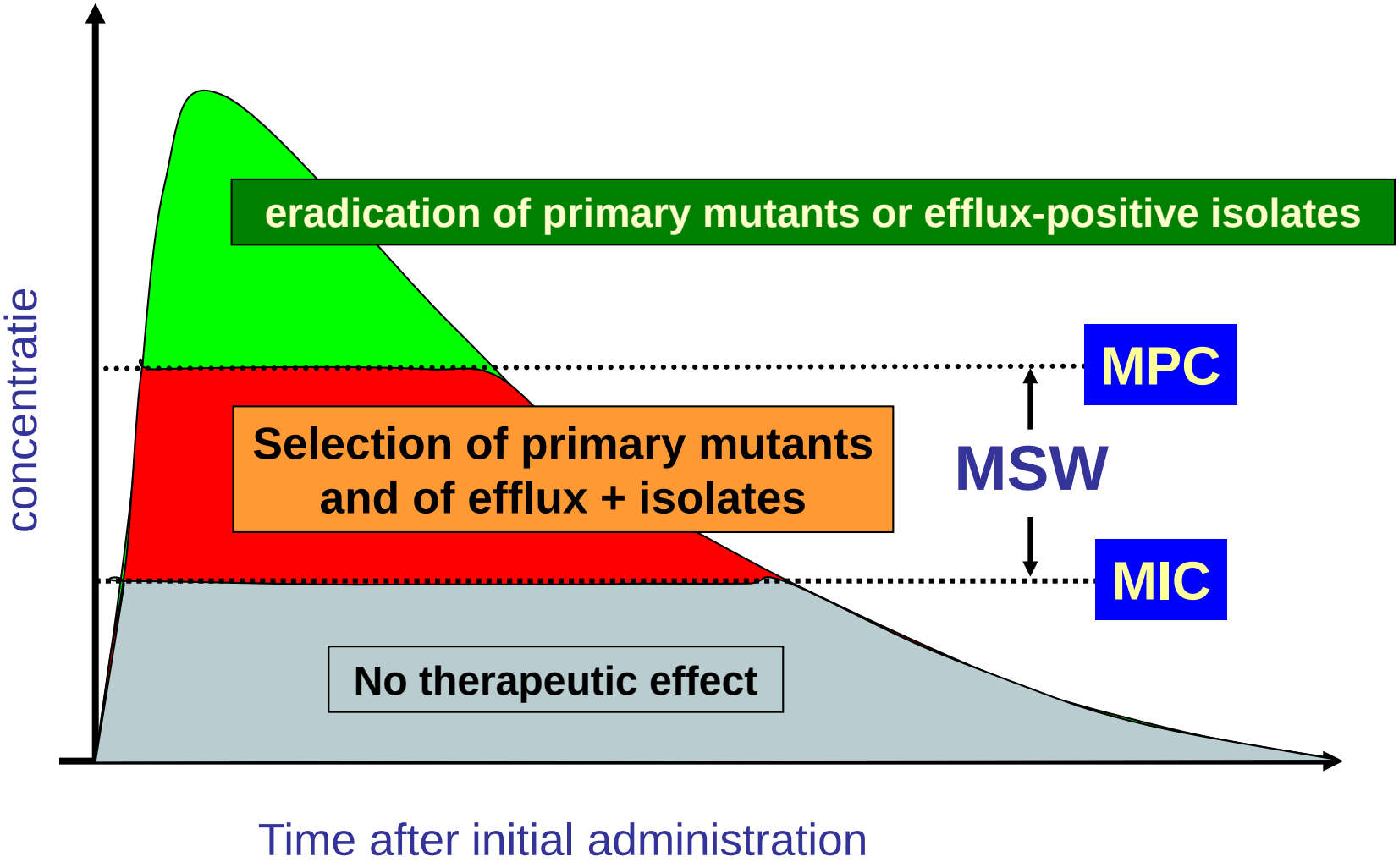
Dong *et al.* Antimicrob Agents Chemother 1999; 43:1756-1758

Window for selection of resistance



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

Window for selection of resistance



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Mutant prevention concentration: an example with linezolid

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In Vitro Resistance Studies with Bacteria That Exhibit Low Mutation Frequencies: Prediction of "Antimutant" Linezolid Concentrations Using a Mixed Inoculum Containing both Susceptible and Resistant *Staphylococcus aureus*

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Antimicrob Agents Chemother 2015;59:1014 –1019.

Mutant prevention concentration: an example with linezolid

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Mutant prevention concentration: an example with linezolid

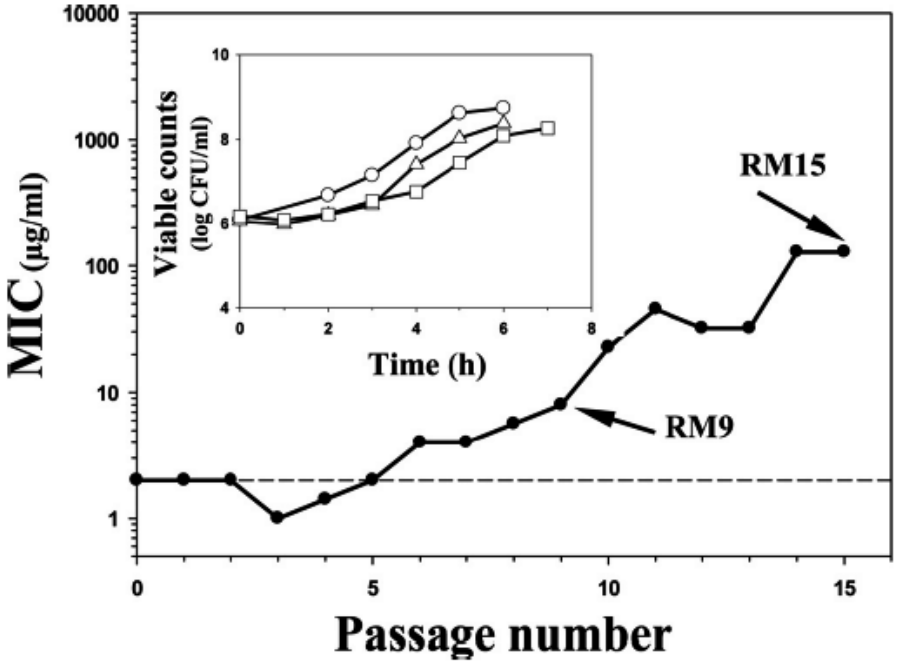

FIG 1 Loss in susceptibility of *S. aureus* 10 passaged on linezolid-containing MHB. The inset graph shows *S. aureus* growth in antibiotic-free MHB. Symbols: ○, *S. aureus* 10; Δ, RM9; □, RM15. The linezolid MIC for the parent strain is indicated by a dotted line.

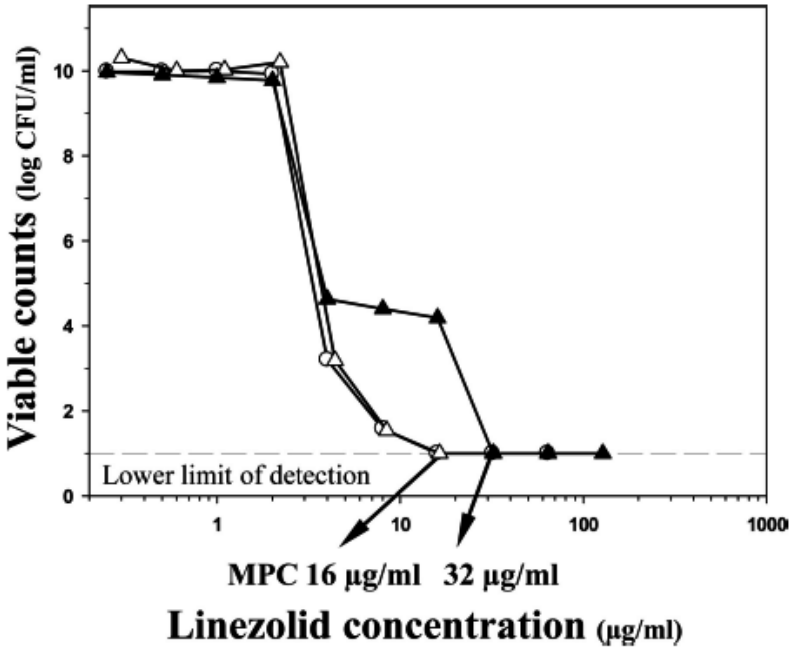

FIG 2 Linezolid MPC determination with *S. aureus* 10 alone and supplemented by RM. Symbols: ○, parent strain; Δ, parent strain (10^{10} CFU/ml) plus RM9 (10^{2} CFU/ml); ▲, parent strain (10^{10} CFU/ml) plus RM9 (10^{4} CFU/ml).

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Mutant prevention concentration: an example with linezolid

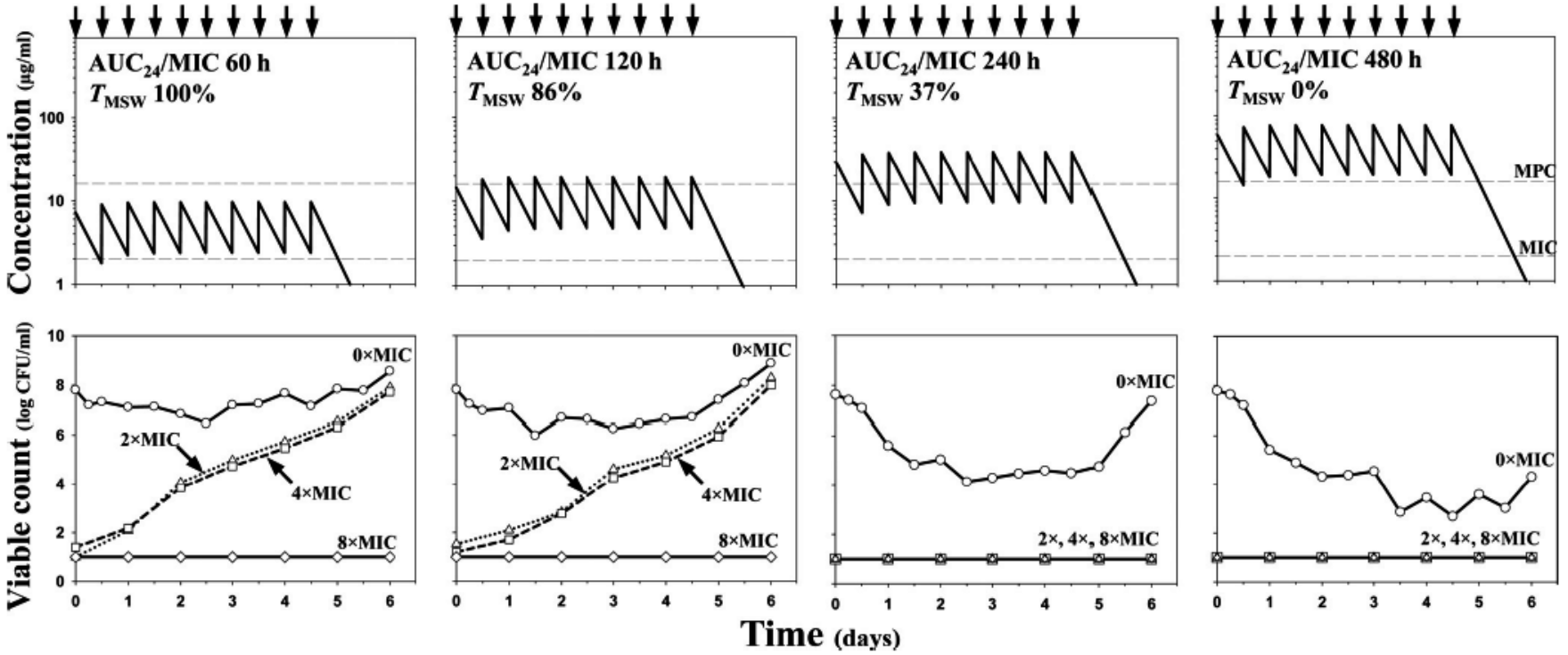

FIG 3 Simulated pharmacokinetics of linezolid and time courses of susceptible (0× the MIC) and resistant (2×, 4×, and 8× the MIC) subpopulations of antibiotic-exposed *S. aureus* supplemented with its RM. The arrows reflect antibiotic dosing.

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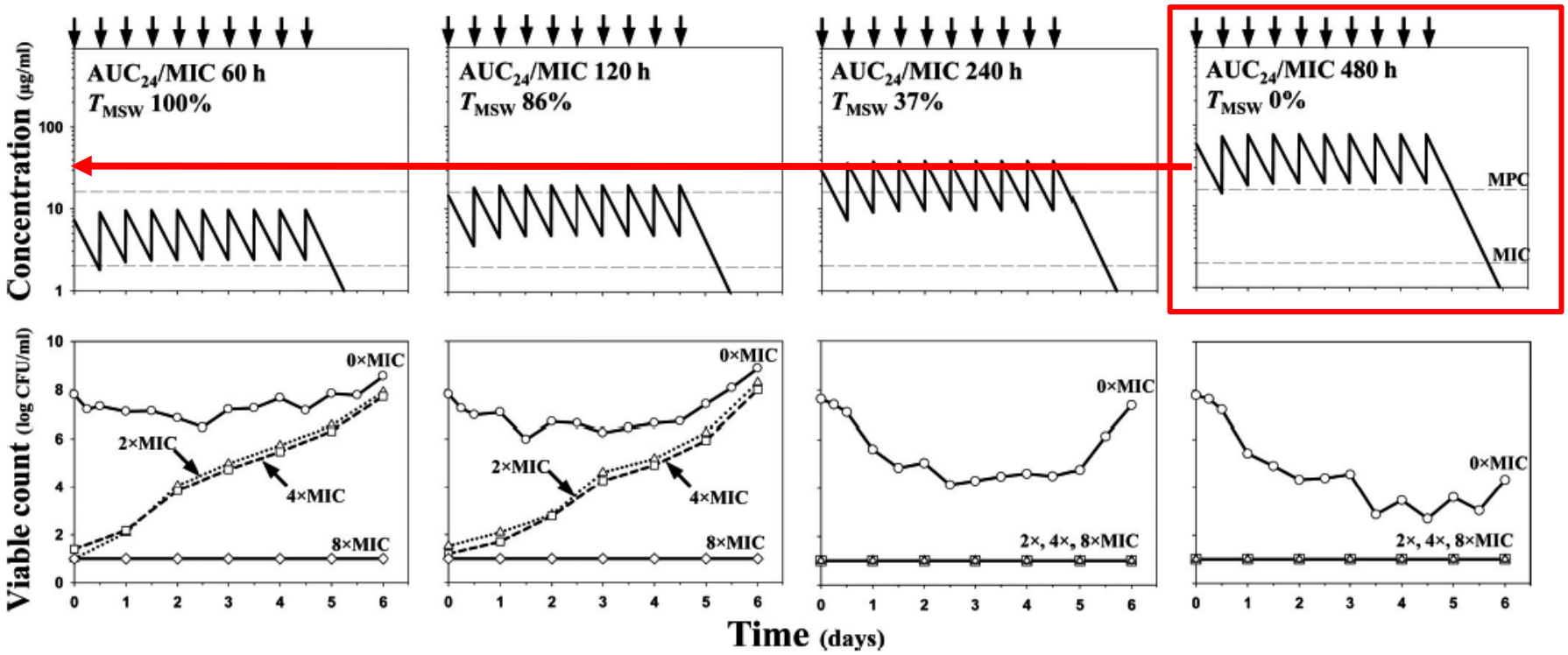
Mutant prevention concentrations:
impossible to obtain concentrations in a patient …



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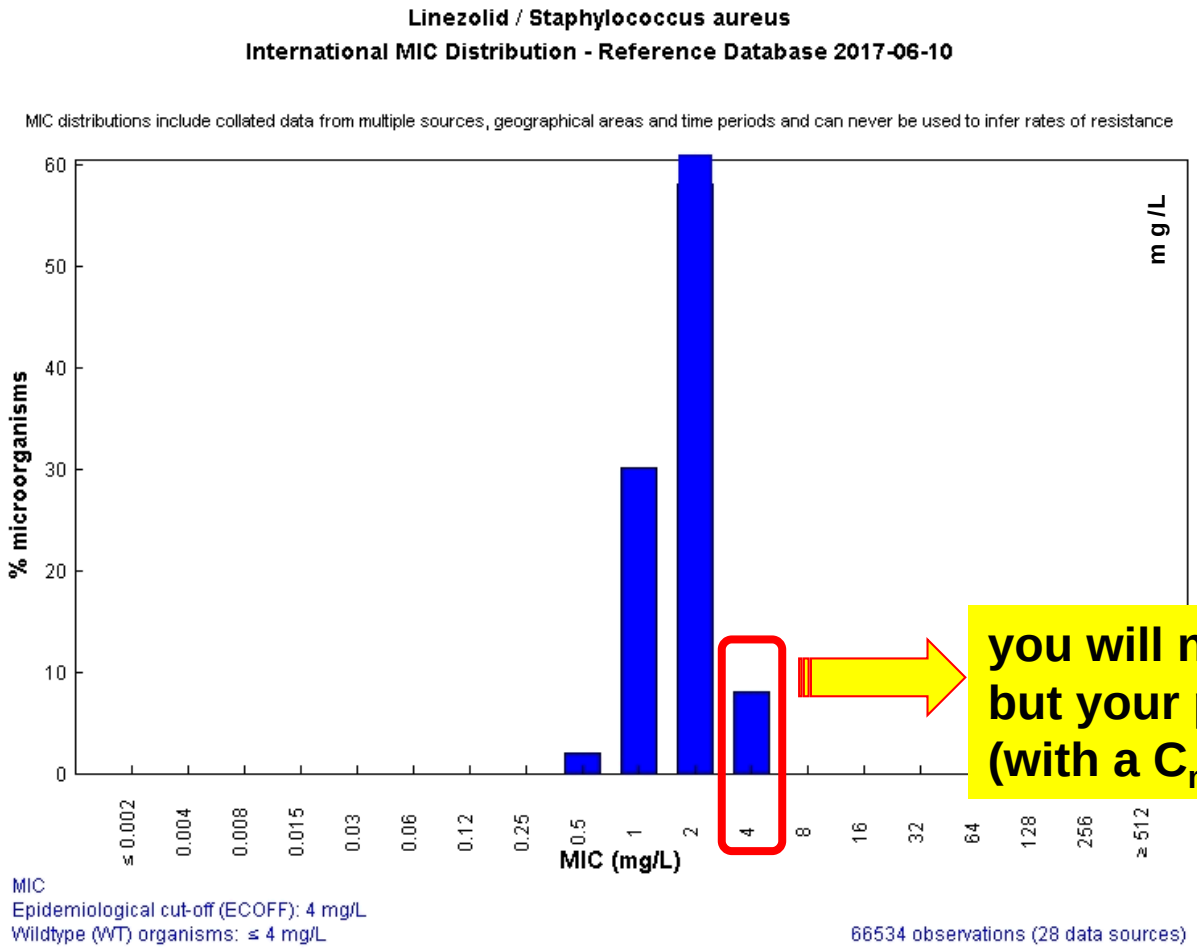
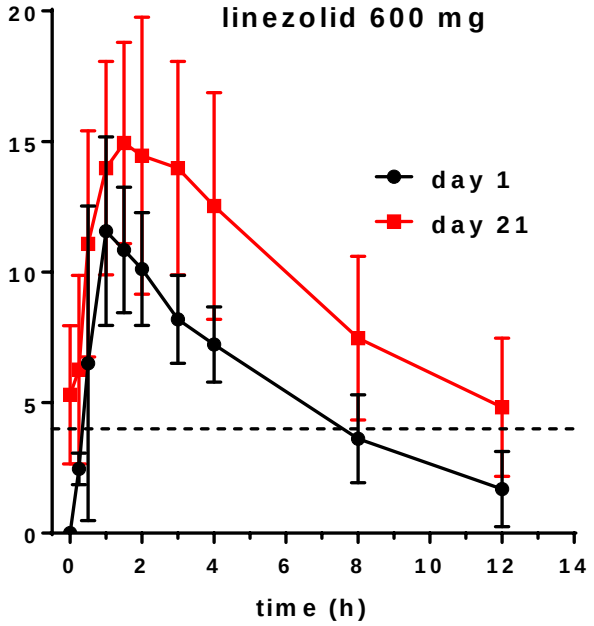
The impossible concentration …

MPC is often ~ 10 x the MIC…

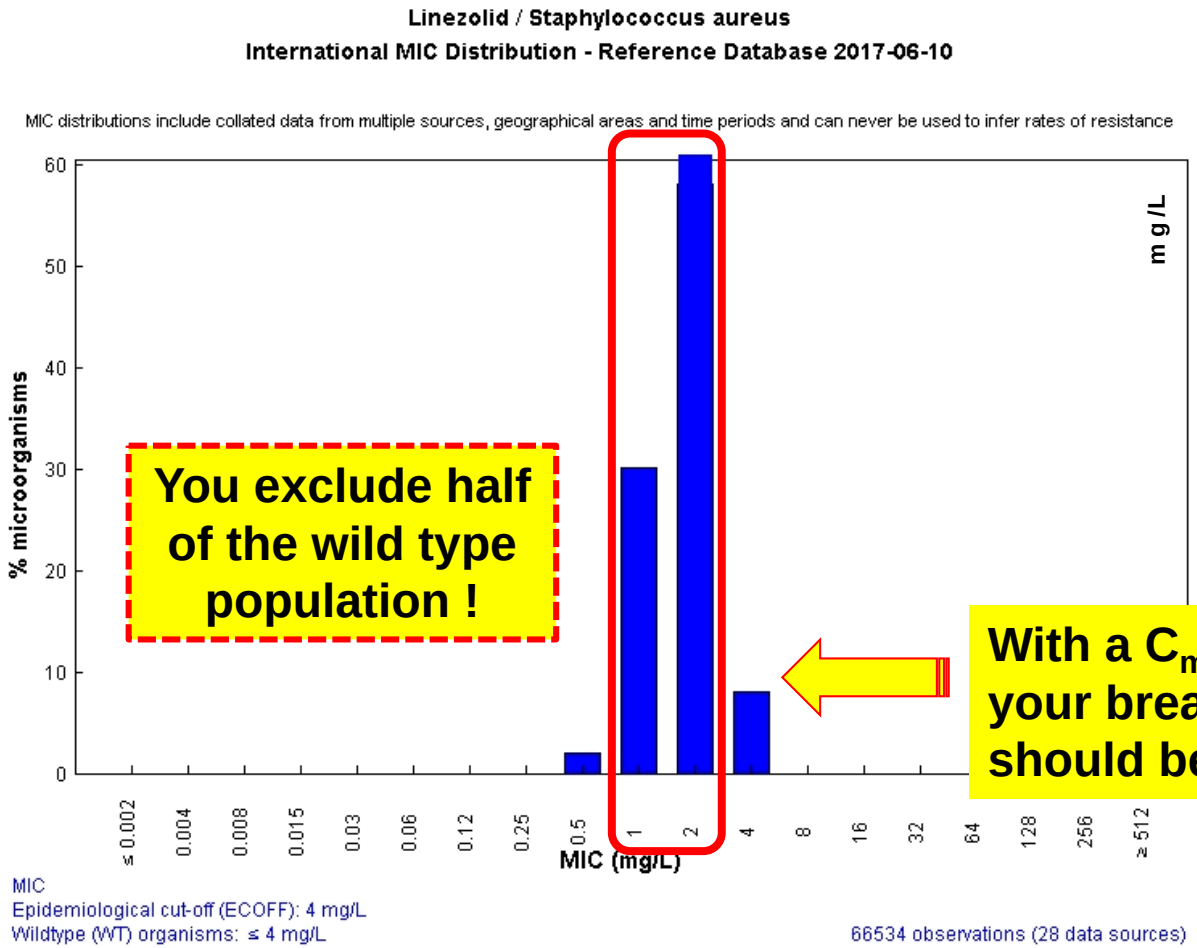




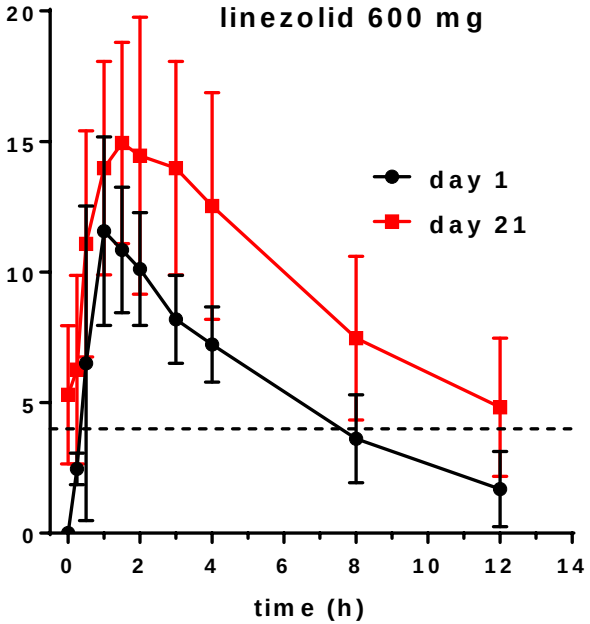
you will need a C_{max} of 40 mg/L … but your peak is only 10-15 mg/L (with a C_{min} at ~ 5 mg/L)

The impossible breakpoint …

MPC is often ~ 10 x the MIC…



You exclude half of the wild type population !



With a C_{max} at 15 mg/L, your breakpoints (for MPVC) should be 1.5 mg/L

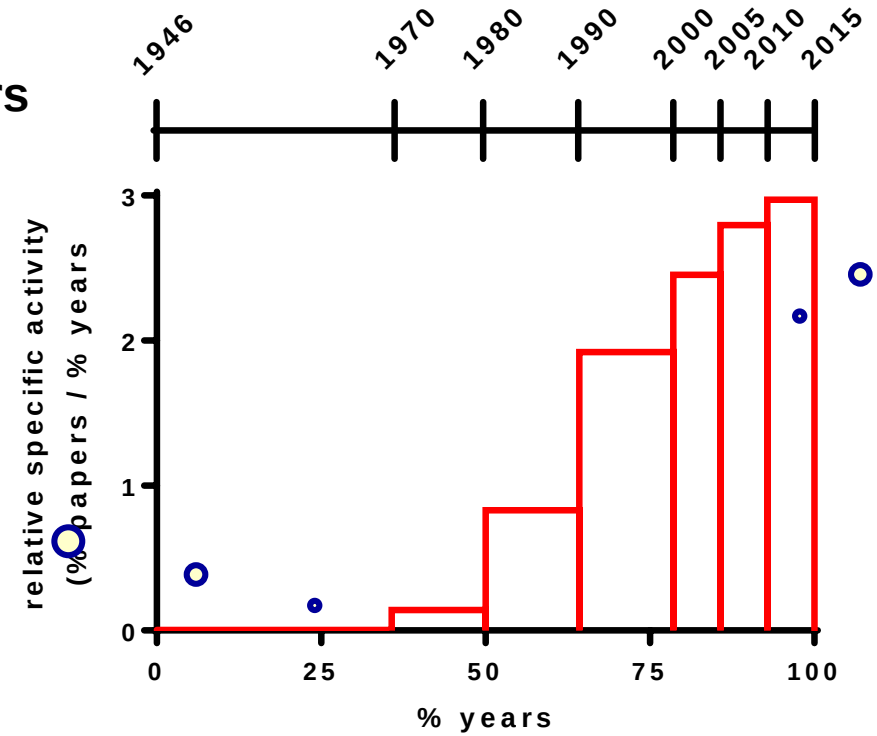
In summary…

- PK/PD helps (successfully) to define the conditions of administration (doses, schedules) associated with efficacy
  - **now a requirement for registration of new antibiotics (and old ones are being revisited)**
- PK/TD approaches may also help do mitigate toxicity if dose-related (directly of indirectly)…
  - **will be increasingly used for defining safe use of antibiotics … but will not solve all toxicity problems…**
- PK/PD and MPC show the current limits of currently available antibiotics and why we may have always emergence of resistance by selection of less susceptible subpopulations (via tolerance/persistence)
  - **we DO need new, more innovative ideas…**

Who did that ?

http://www.isap.org

but also many others



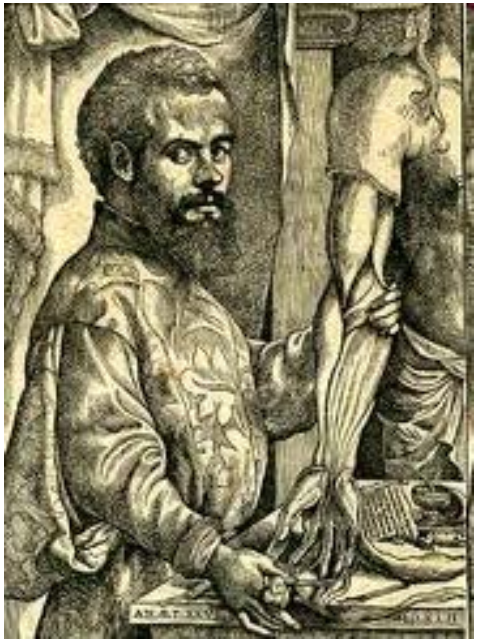
911 papers /year

20 papers /year

1219 papers in 2016-2017 …

* PubMed search using (pharmacokinetic* OR pharmacodynamics*) AND (antibiotic* OR antiviral* OR antifungal*)

Please, ask questions …



be critical,
ask for facts !

Vesalius - anatomy

Slides will be available on http://www.facm.ucl.ac.be → Lectures