Nijmegen Institute for Infection, Inflammation & Immunity

What are PK/PD breakpoints?

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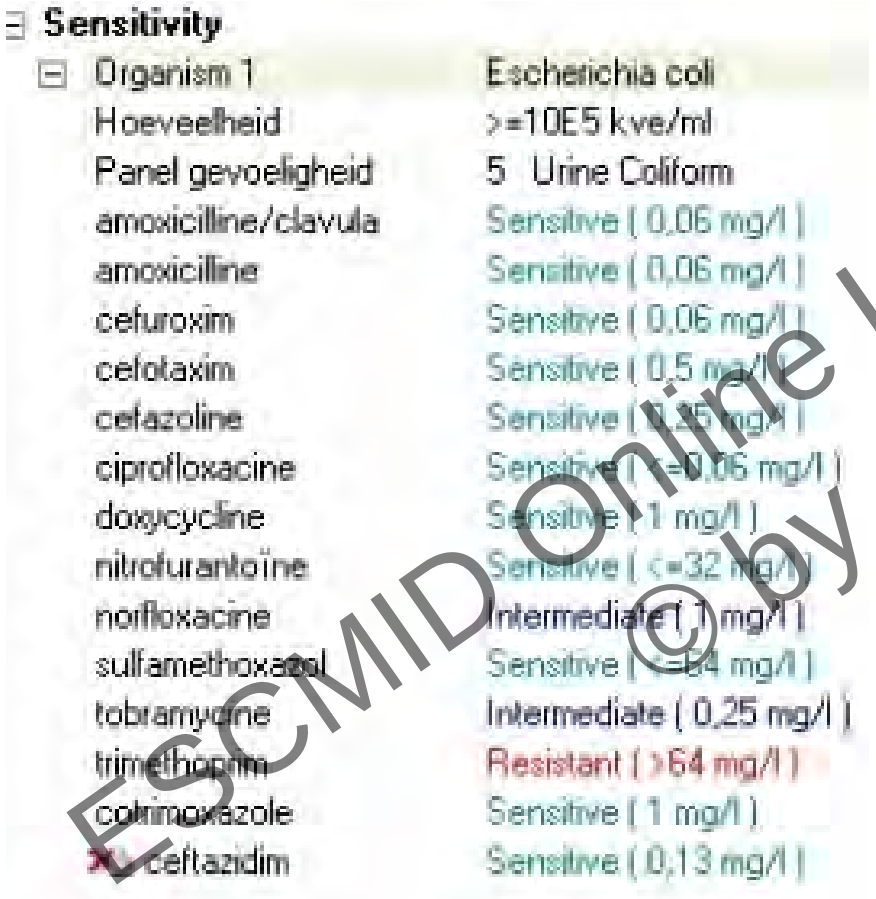
Professor pharmacokinetics and pharmacodynamics

LAB REPORT



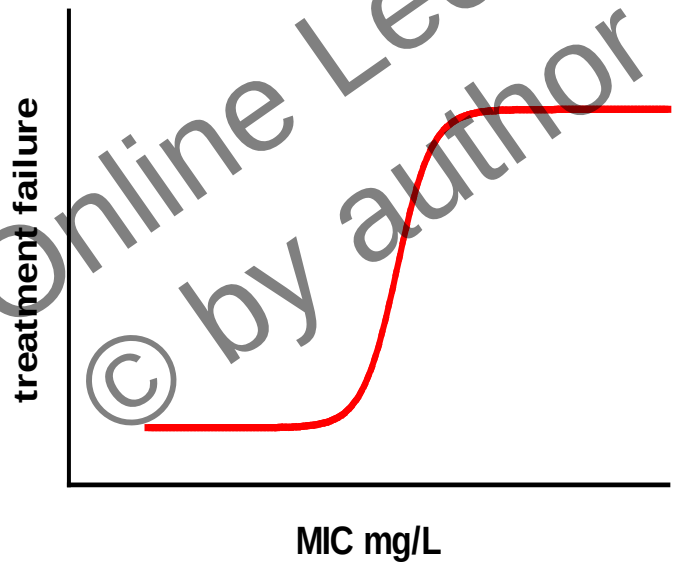
Sensitivity	
Organism 1	Escherichia coli
Hoeveelheid	>=10E5 kve/ml
Panel gevoeligheid	5 Urine Coliform
amoxicilline/clavula	Sensitive (0,06 mg/l)
amoxicilline	Sensitive (0,06 mg/l)
cefuroxim	Sensitive (0,06 mg/l)
cefotaxim	Sensitive (0,5 mg/l)
cefazoline	Sensitive (0,25 mg/l)
ciprofloxacine	Sensitive (<=0,06 mg/l)
doxycycline	Sensitive (1 mg/l)
nitrofurantoïne	Sensitive (<=32 mg/l)
norfloxacine	Intermediate (1 mg/l)
sulfamethoxazol	Sensitive (<=64 mg/l)
tobramycine	Intermediate (0,25 mg/l)
trimethoprim	Resistant (>64 mg/l)
cotrimoxazole	Sensitive (1 mg/l)
ceftazidim	Sensitive (0,13 mg/l)

- Provides Clinician/Consultant guidelines how to optimally treat a patient (Freely translated from EUCAST guideline)

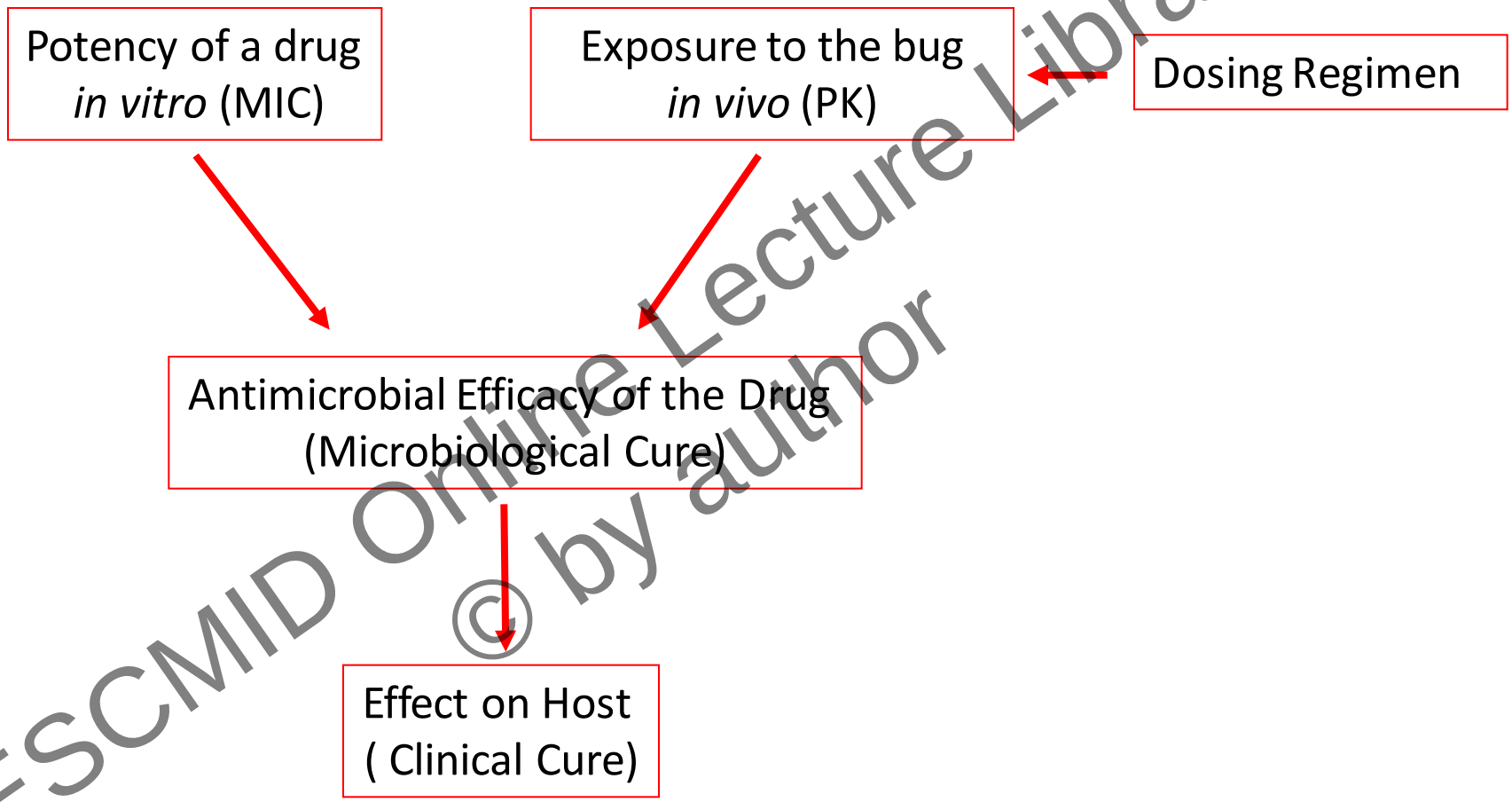
Susceptible can be interpreted as:

a. The micro-organism does not have a resistance mechanism
b. If the patient is treated he/she will likely respond to therapy
c. If the patient is treated the micro-organism is likely to be eliminated
d. The drug can safely be used for therapy

Is susceptibility (MICs) related to (clinical) outcome?



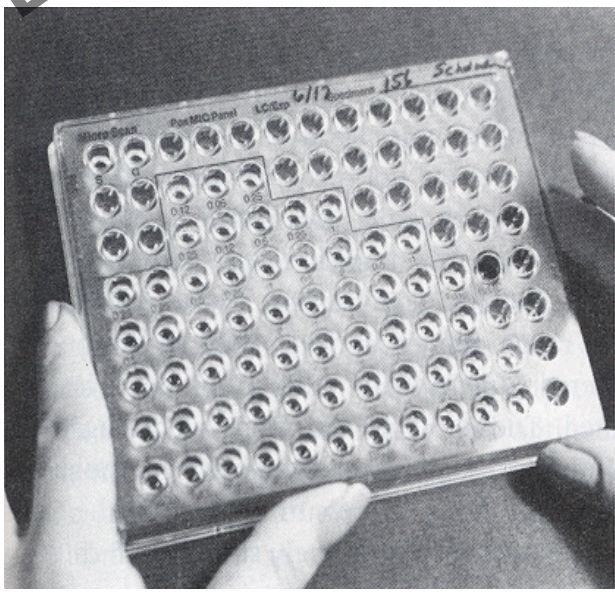
If yes, which values (breakpoints) make the difference?

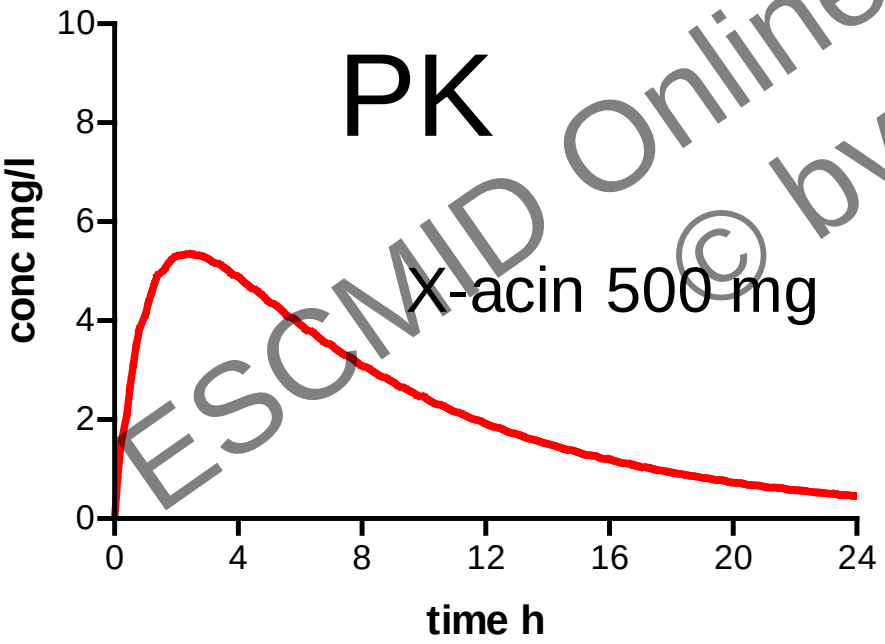


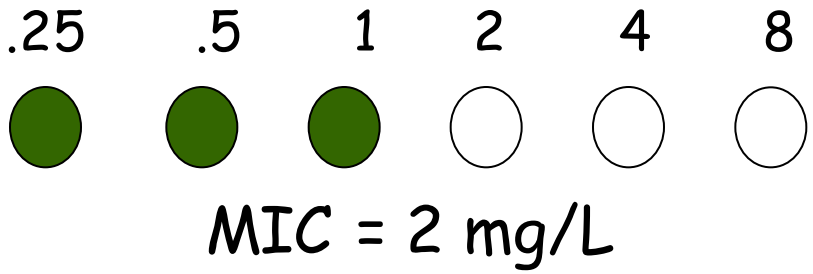
Mouton et al., *Drug Resistance Updates 2011*

MIC

Lowest concentration with no visible growth after 18 hour incubation

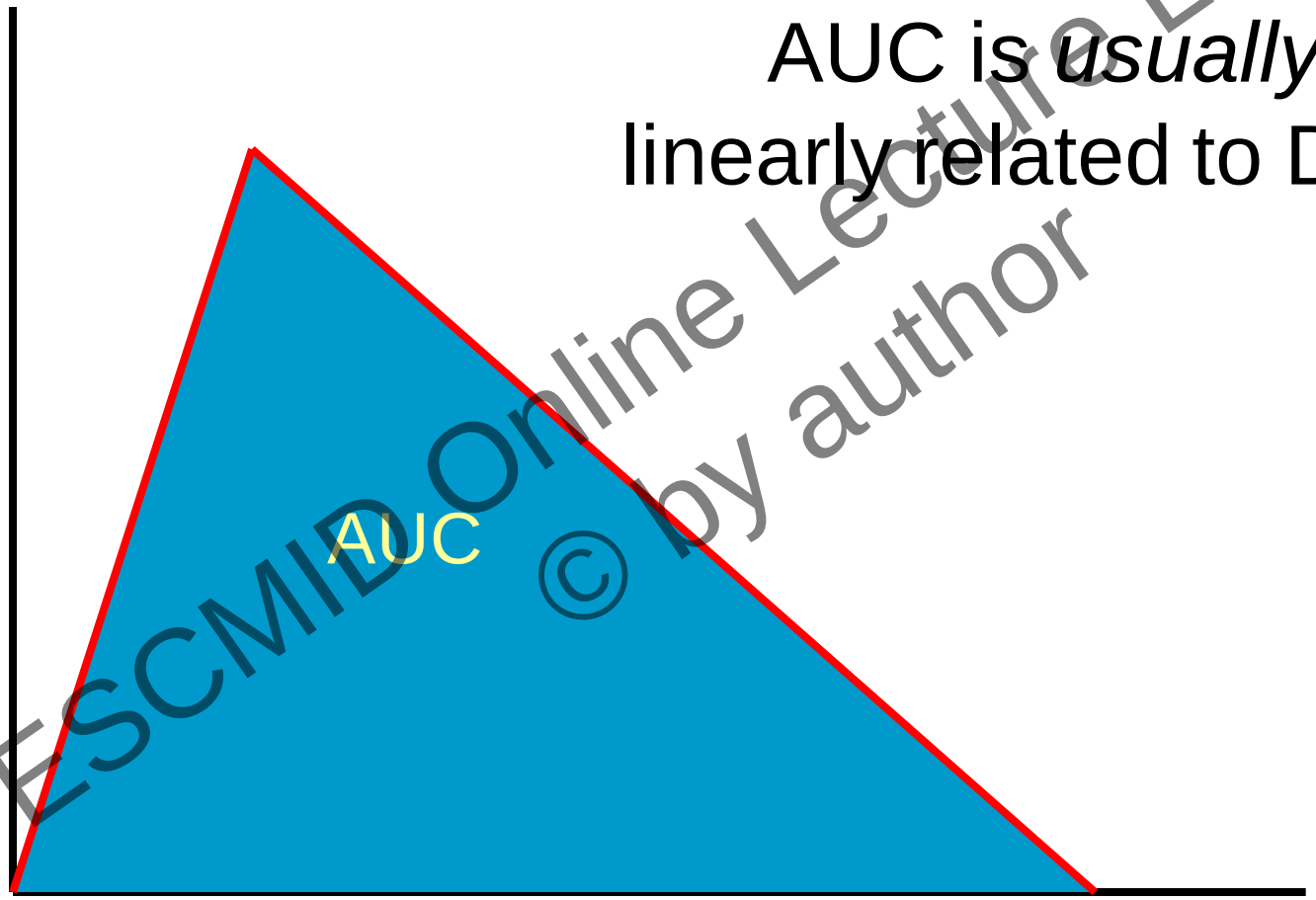






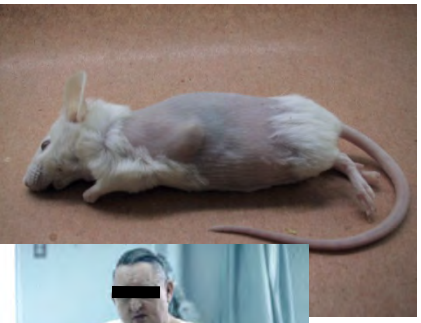
Pharmacokinetic parameters : Measures of Exposure

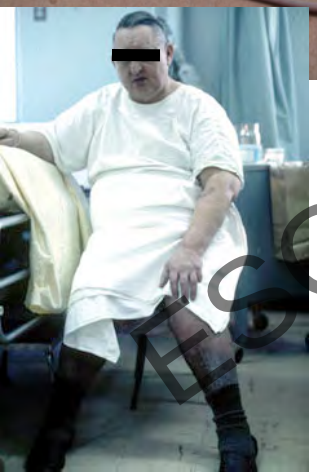
AUC is *usually* linearly related to Dose

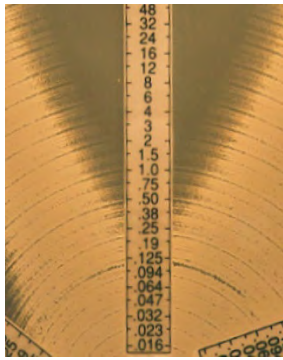


Pharmacokinetic parameter

MIC



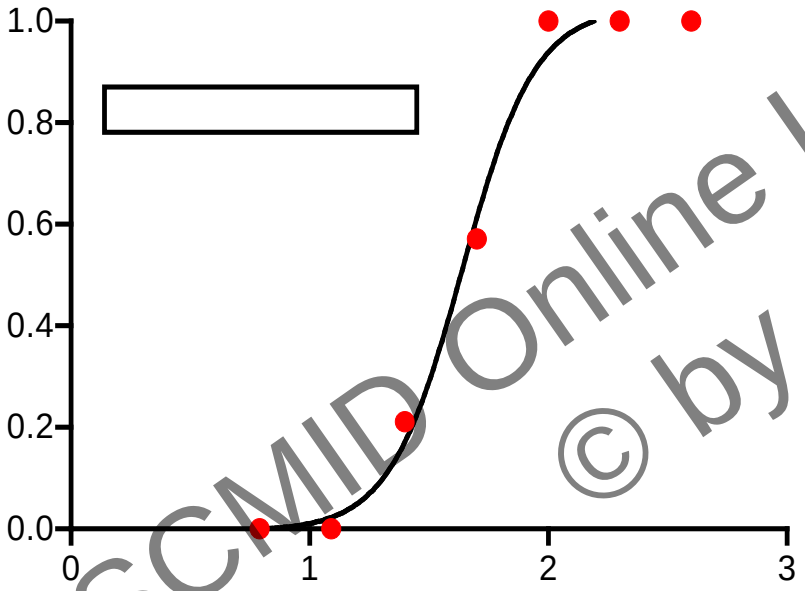




Pharmacodynamic index

(AUC/MIC, Peak/MIC, T>MIC)

Probability of cure after treatment with fluconazole Oropharygeal Candidiasis n=132

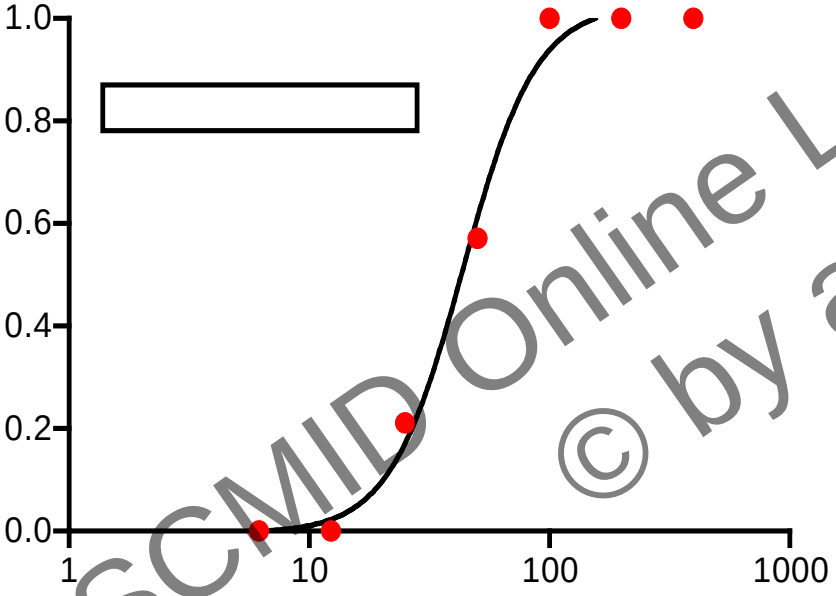


- Prob cure correlates with AUC/MIC
- POSITIVE correlation with EXPOSURE
- INVERSE correlation with MIC

Pharmacodynamic index (AUC/MIC)

Rodriguez- Tudela et al, AAC 2007

Probability of cure after treatment with fluconazole Oropharygeal Candidiasis n=132



- If AUC is known because of the standard dose
  e.g. 400 mg ~ 400 mg.h/L
- And an AUC/MIC of 100 is required
- It follows that the breakpoint is 400/100 = 4 mg/L

Rodriguez- Tudela et al, AAC 2007

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

Susceptible (S)

A micro-organism is defined as susceptible by a level of antmicrobial activity associated with a high likelihood of therapeutic success. A micro-organism is categorized as susceptible by applying the appropriate breakpoint in a defined phenotypic test system.

Note: This breakpoint may be altered with legitimate changes in circumstances

Intermediate (I)
A micro-organism is defined as intermediate by a level of antimicrobial activity associated with indetermiate therapeutic effect. A micro-organism is categorized as intermediate by applying the appropriate breakpoints in a defined phenotypic test system.
Note: This breakpoints may be altered with legitimate changes in circumstances.

Resistant (R)
bacteria are defined as resistant by a level of antimicrobial activity associated with a high likelihood of therapeutic failure. A micro-organism is categorized as resistant by applying the appropriate breakpoint in a defined phenotypic test system.
Note: This breakpoint may be altered with legitimate changes in circumstances

WE AIM FOR:

A high likelyhood of success for every one (S)

Hitting the PK/PD target

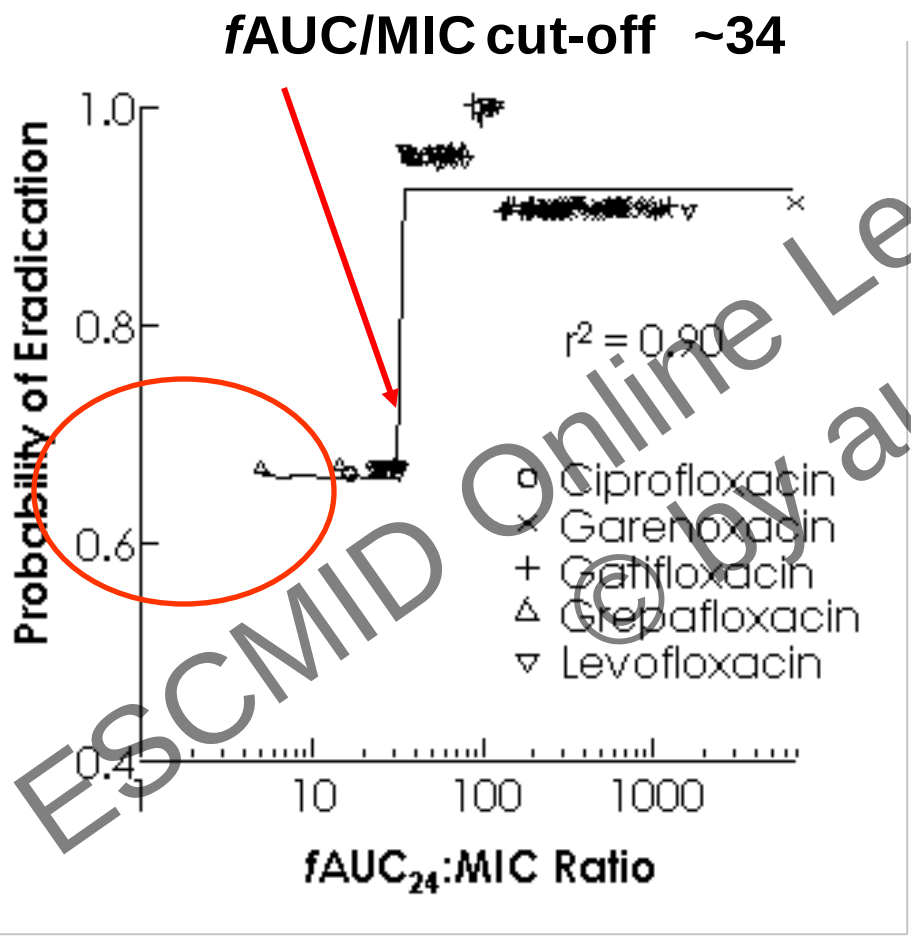
SETTING A BREAKPOINT –PK/PD (example 1)

DETERMINE THE PK/PD TARGET e.g. *value of the PK/PD Index*

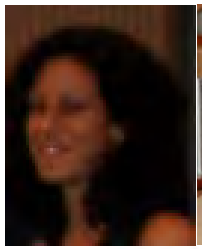
ESTIMATE EXPOSURE from the dosing regimen and PK, including population variability

CALCULATE PK/PD BREAKPOINT from *PK/PD target = PK/PD Index*

Relationship between *f*AUC/MIC and Effect
121 patients with *S. pneumoniae* respiratory infection



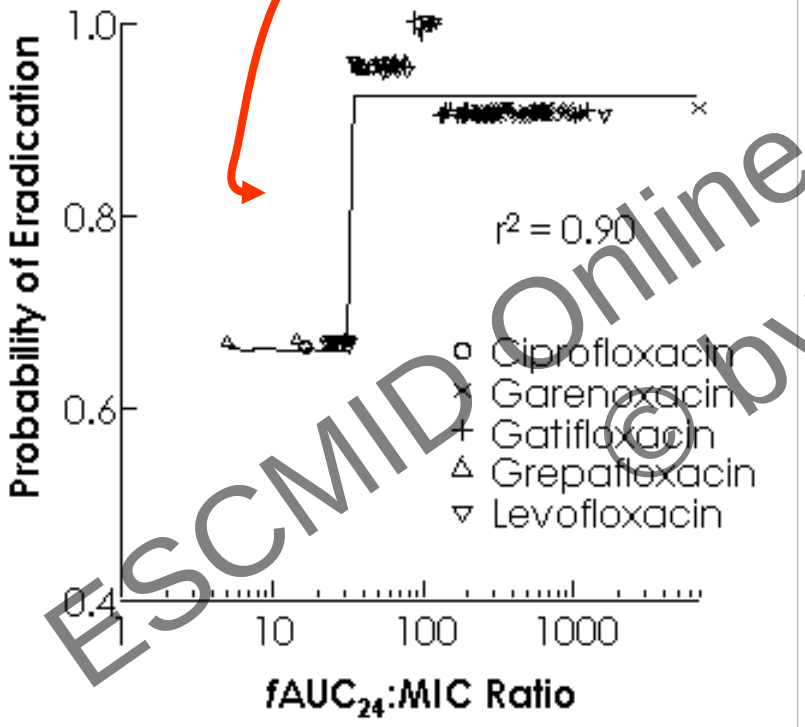
- Relationship between *f*AUC:MIC ratio & microbiological response from a total 121 patients with respiratory tract infection involving *S. pneumoniae*.
- *f*AUC:MIC > 34 had 92.6% response rate.
- *f*AUC:MIC < 34 had 66.7% response rate.



Ambrose PG, Bhavnani SM, Owens RC. Infect Dis Clin N Amer. 2003;17:529-543.

UMC St Radboud

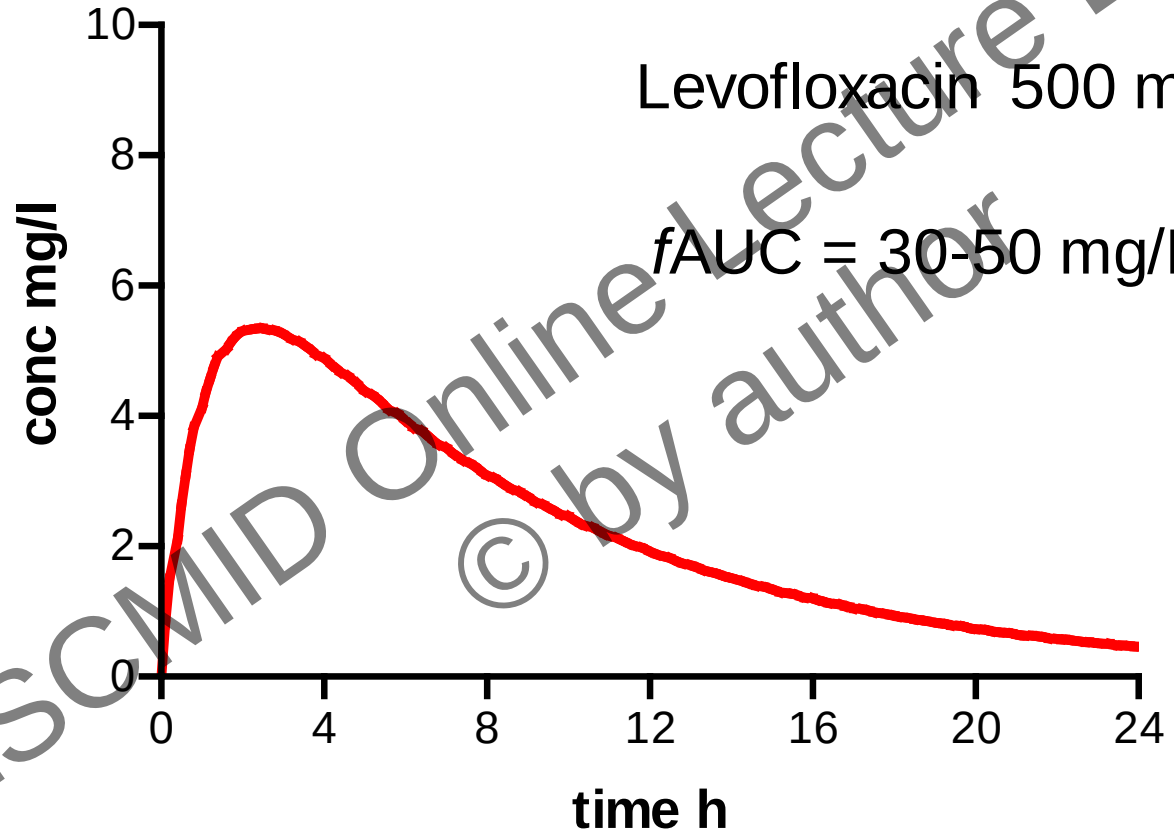
GOOD Clinical Practice



Be sure that the *f*AUC/MIC ratio is at least appr. 34 in every patient

AUC

MIC



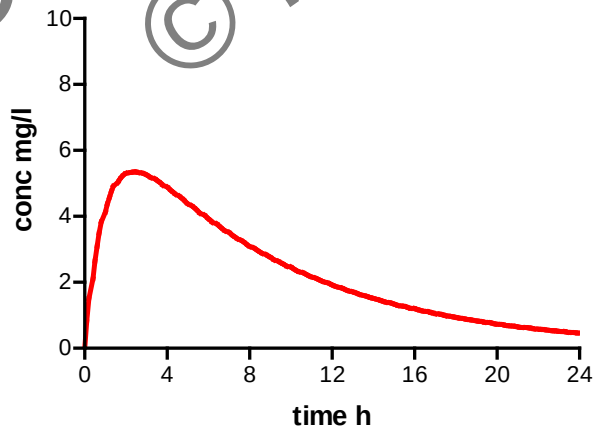
Levofloxacin 500 mg

*f*AUC = 30-50 mg/L

Clinical practice :

When starting treatment, we do not know :

- the AUC in the individual patient

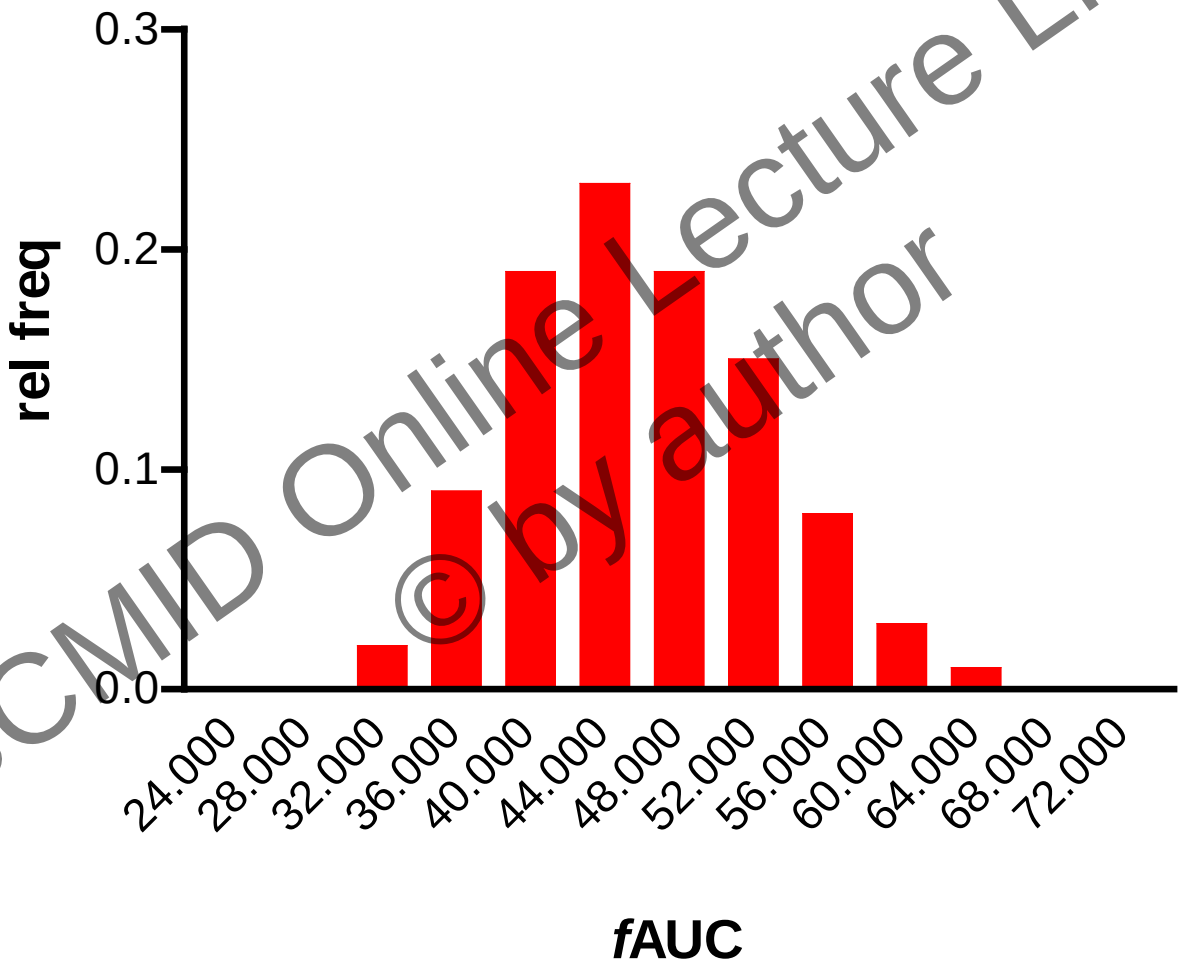


Pharmacokinetics

Some people are more equal than others…

fAUC distribution levofloxacin

(monte carlo simulation)



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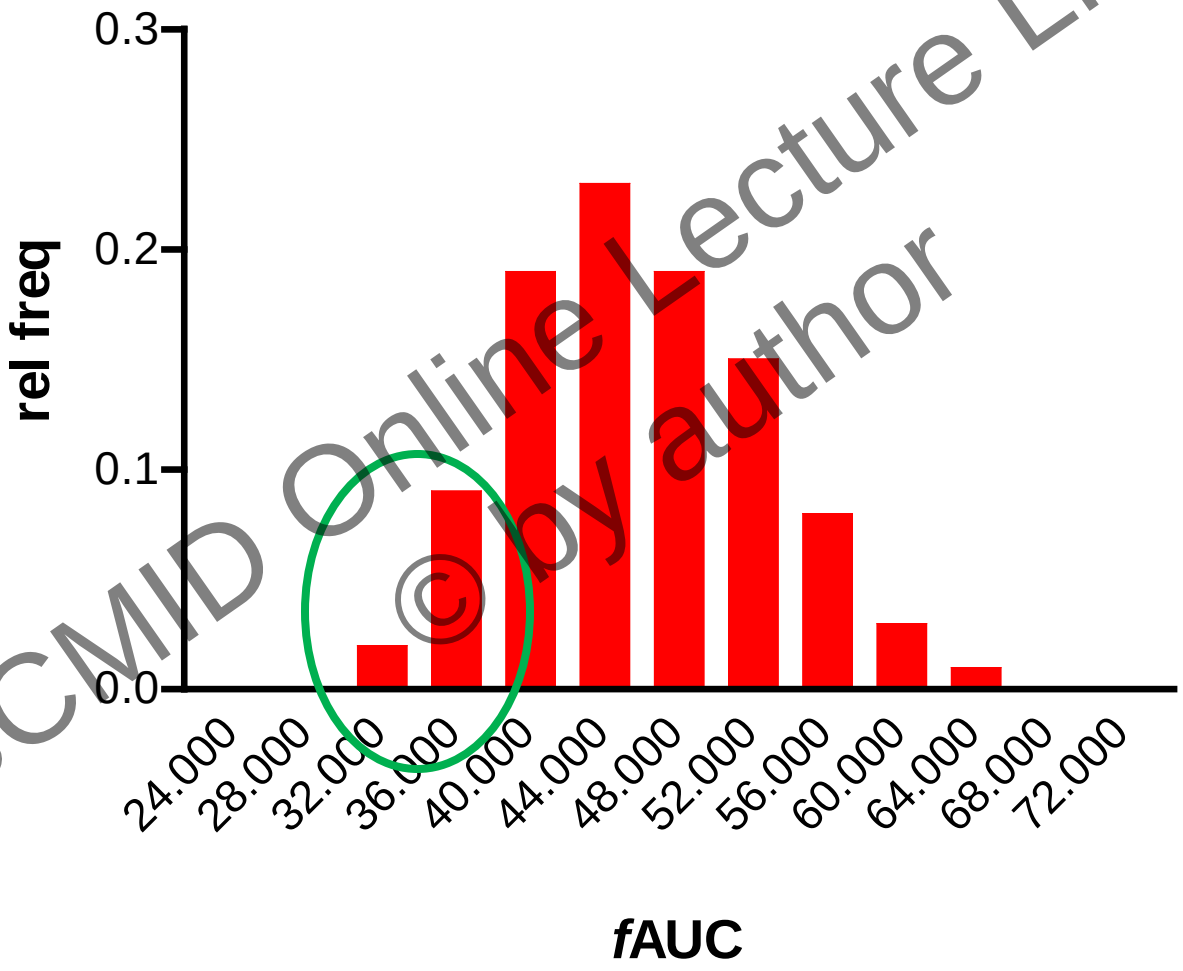
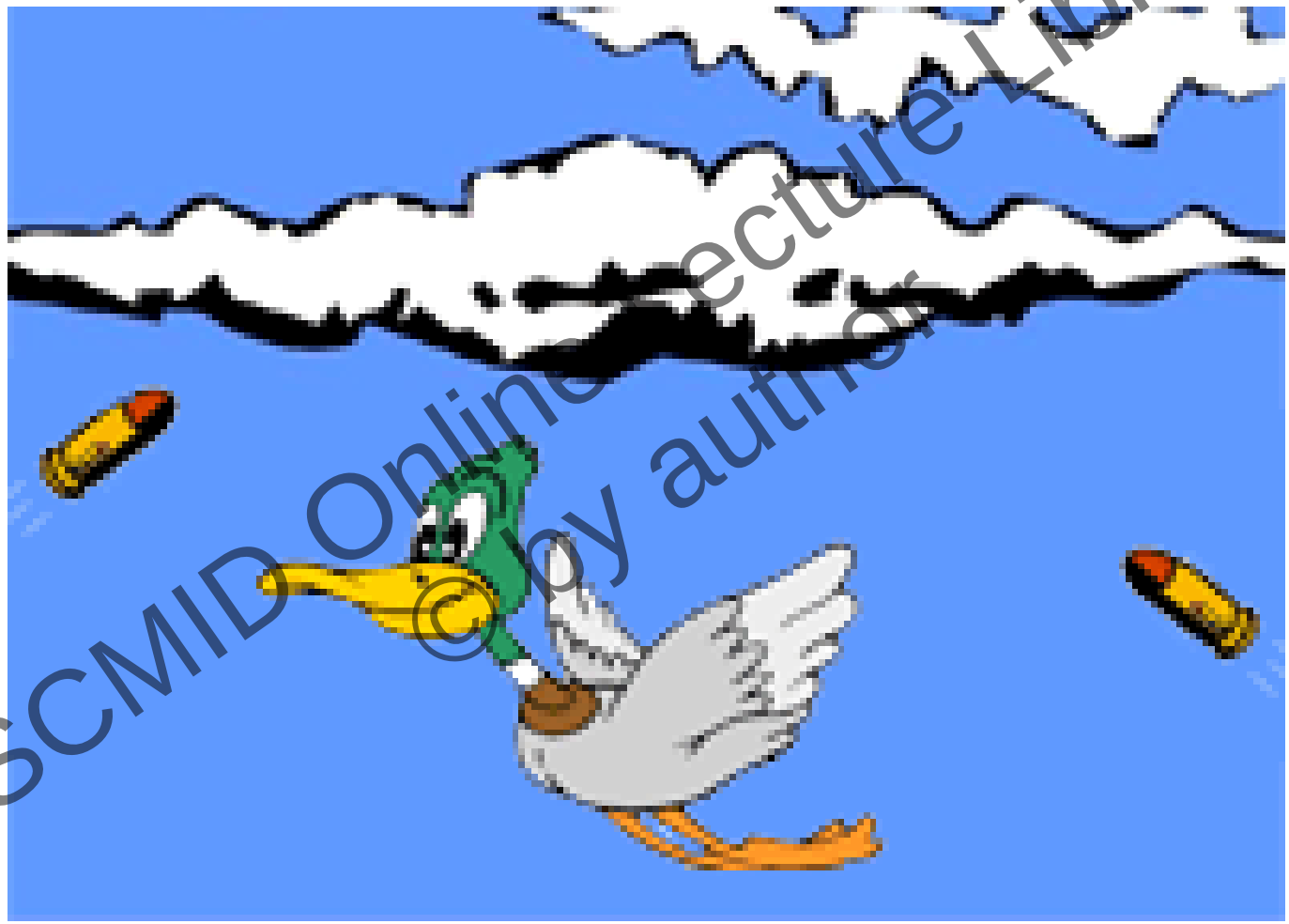
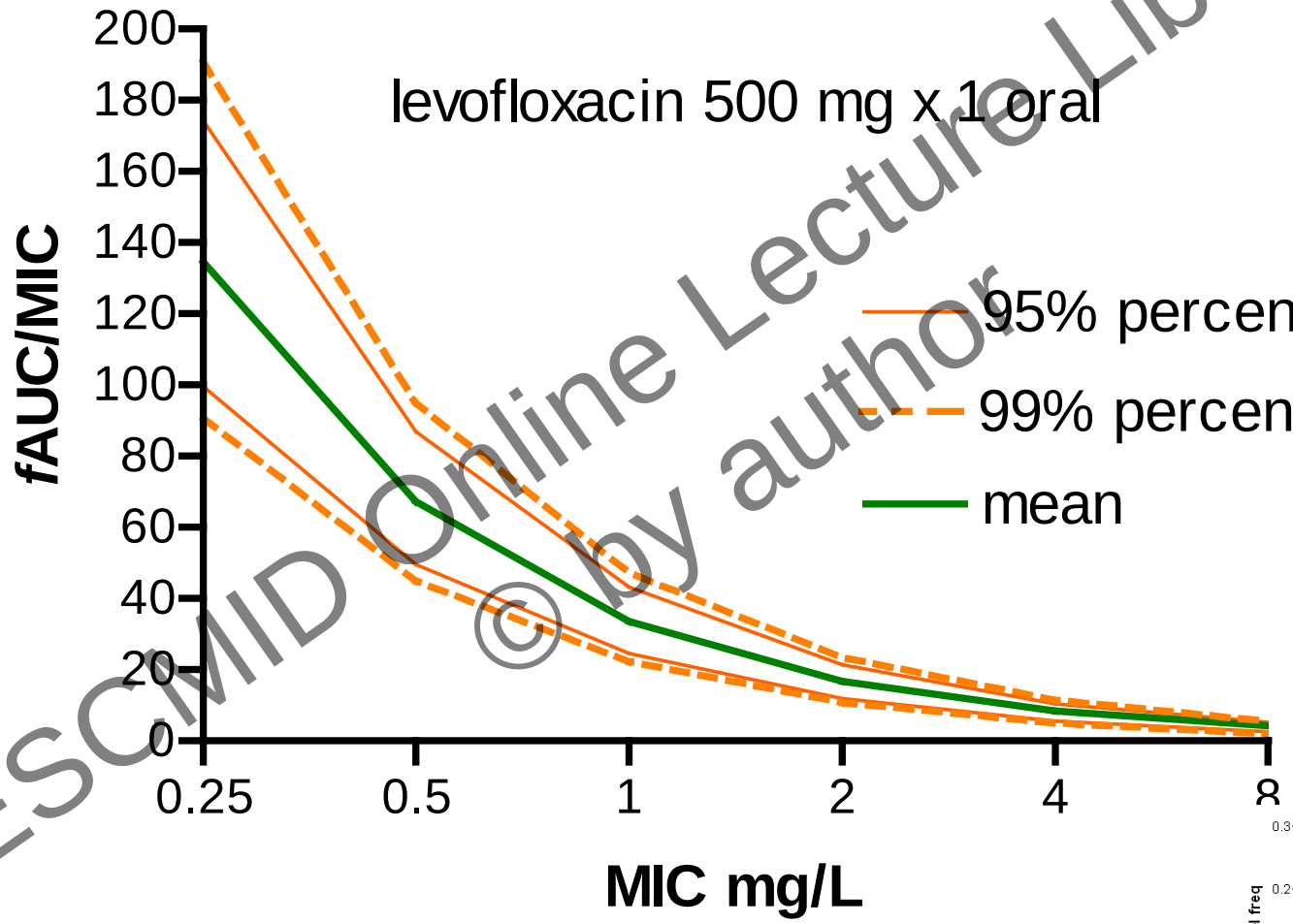
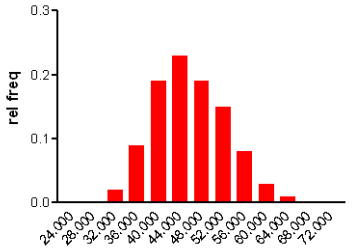




On the average, this duck is dead

The fAUC is calculated for 10.000 patients using MCS
This results in a probability distribution of AUCs
The *f*AUC/MIC is calculated for each MIC





Mouton et al., 2004

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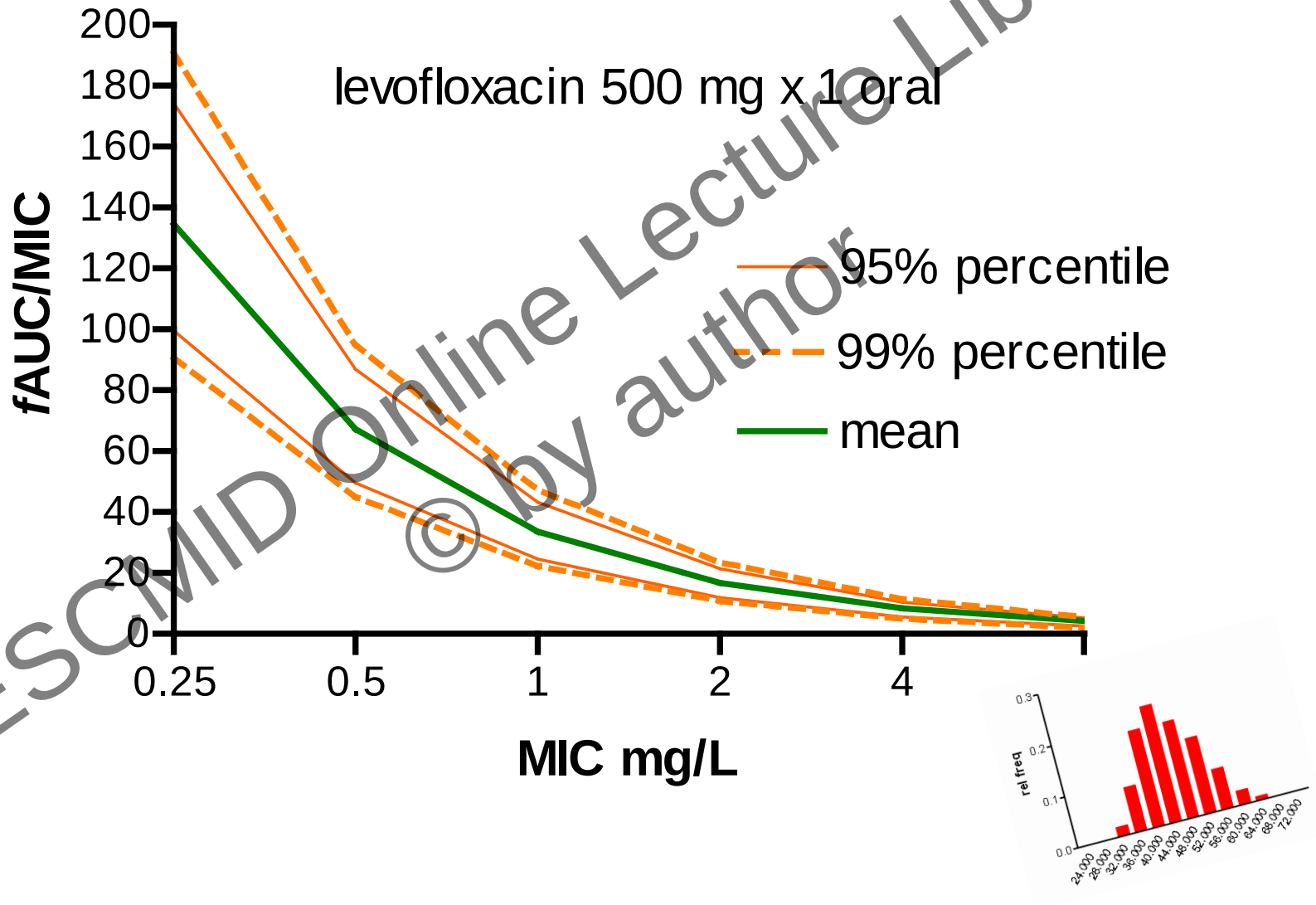

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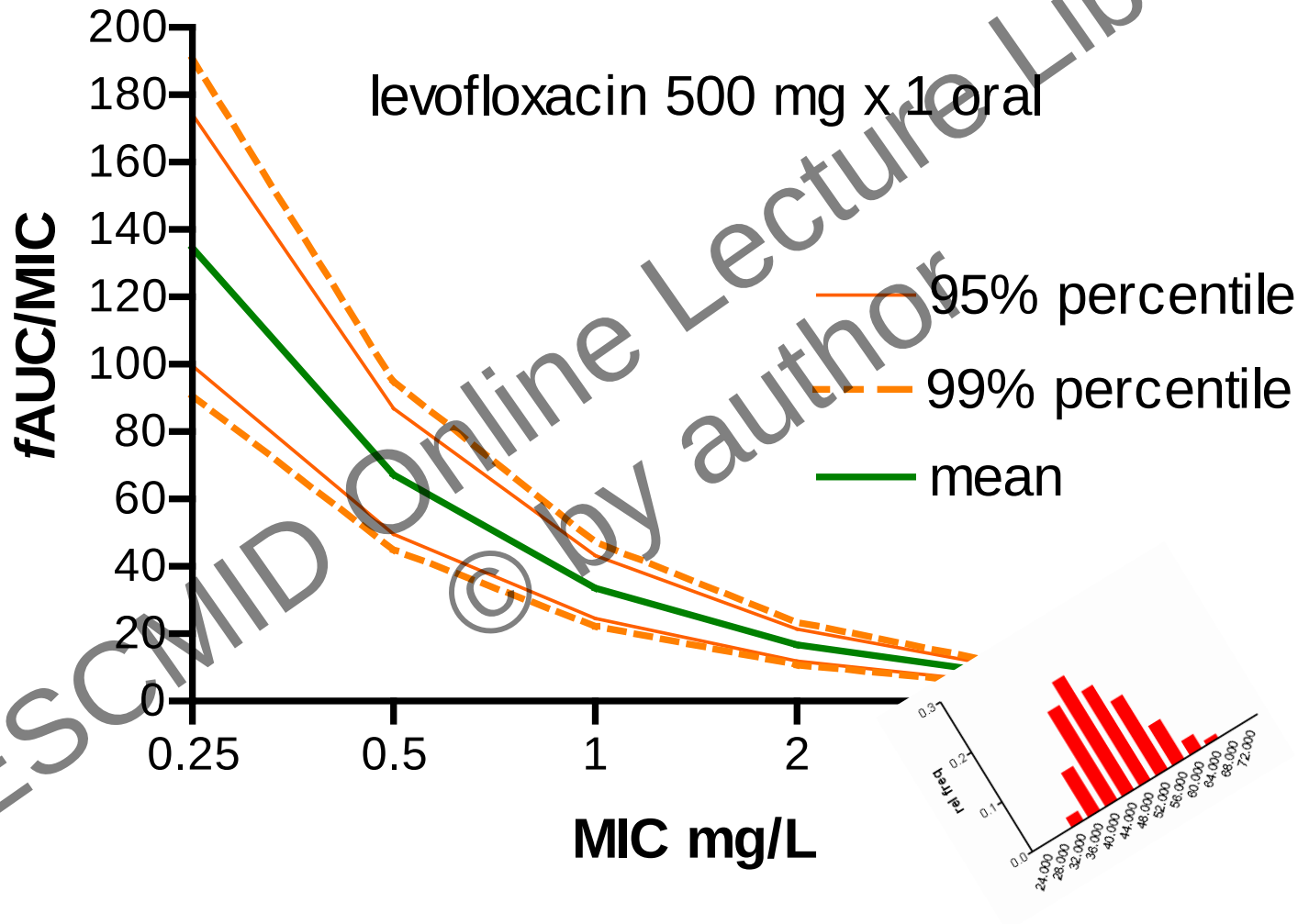

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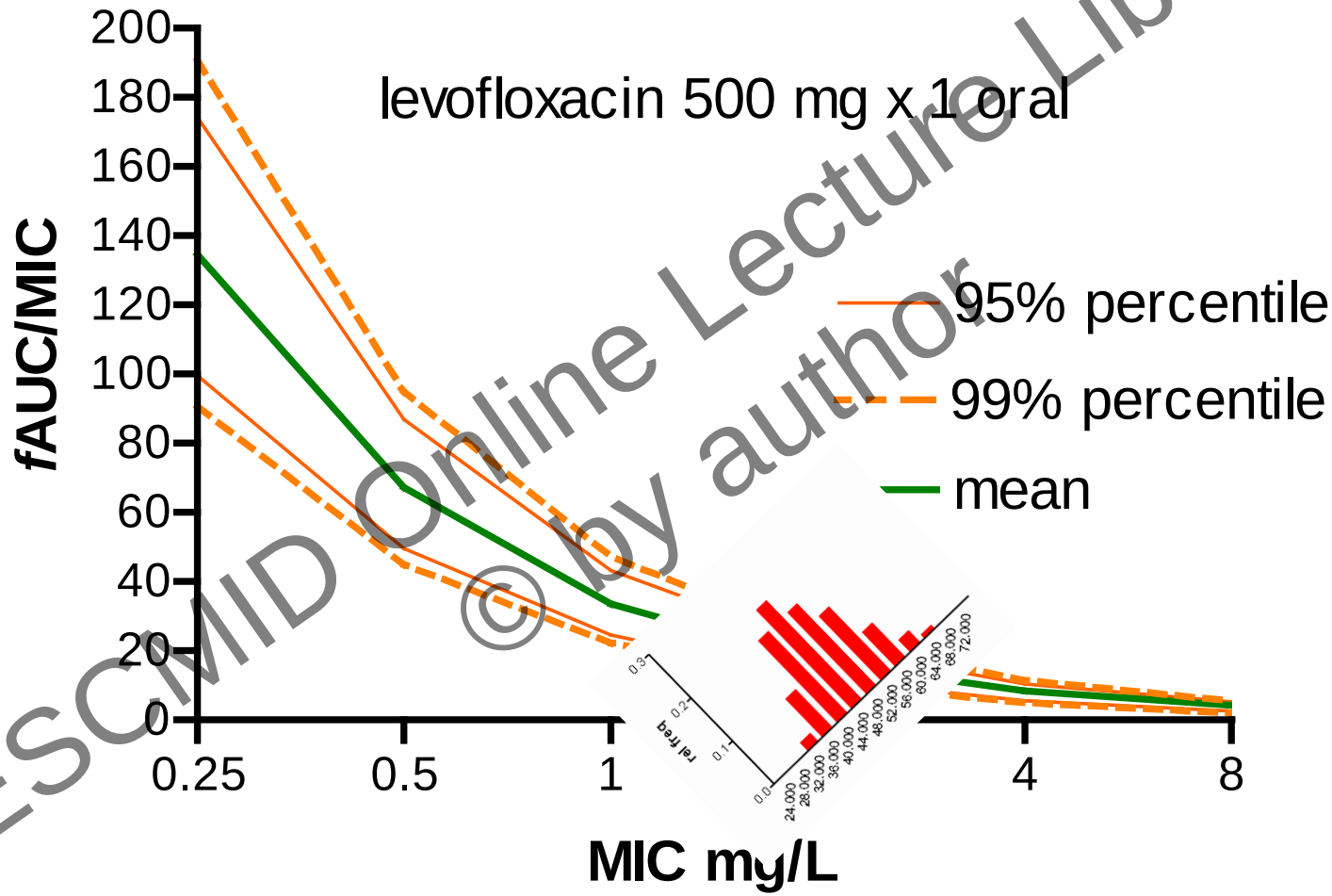

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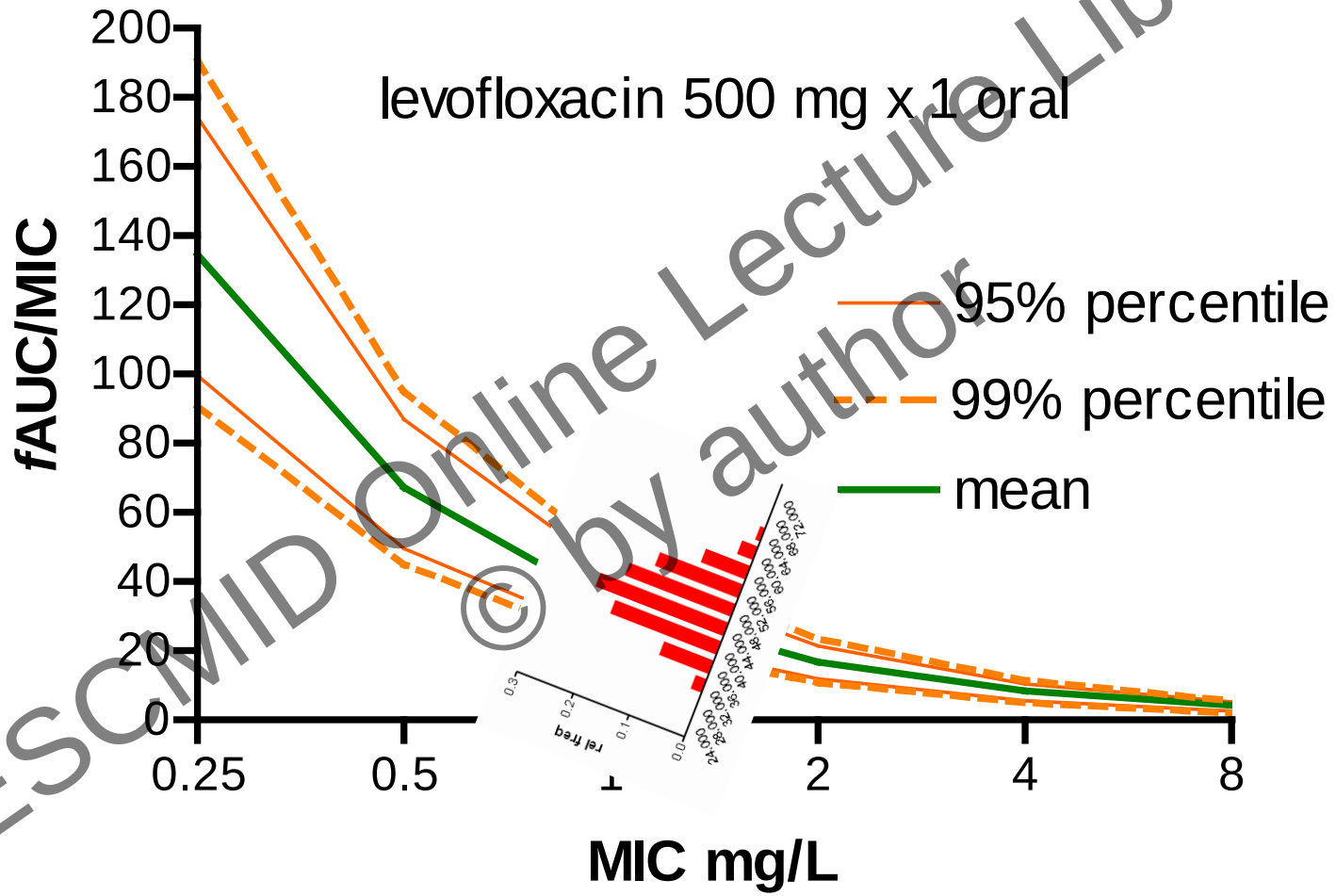

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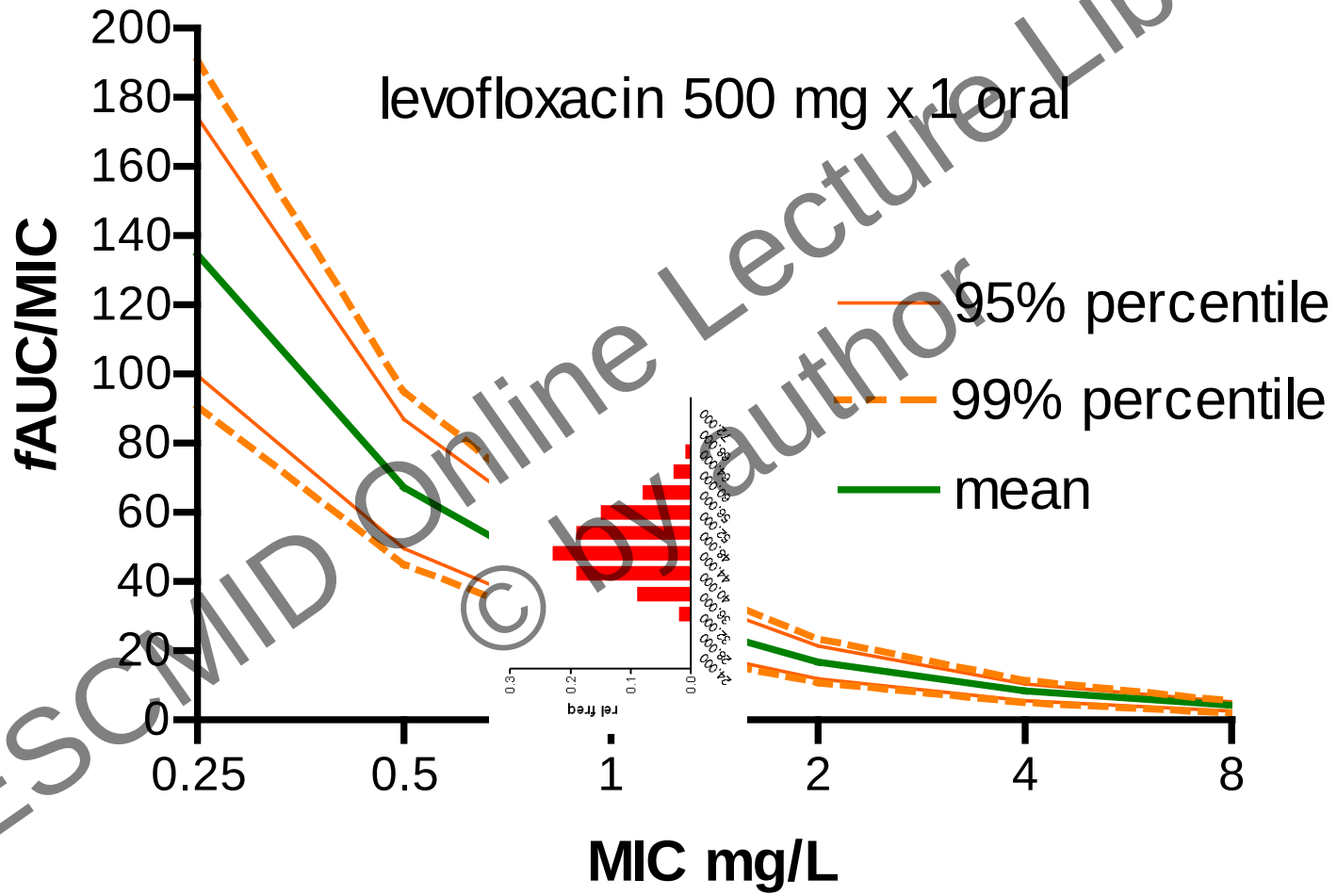

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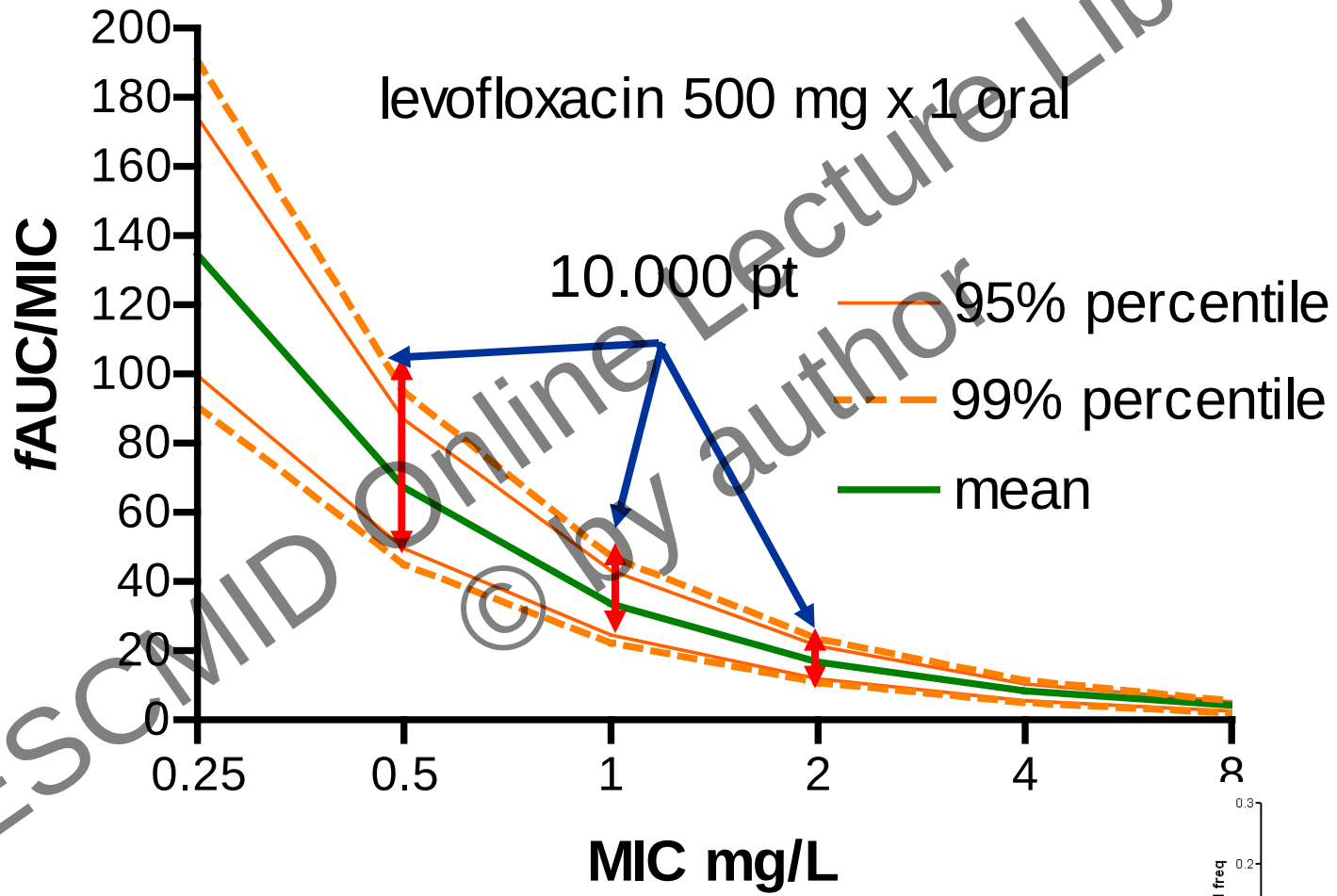

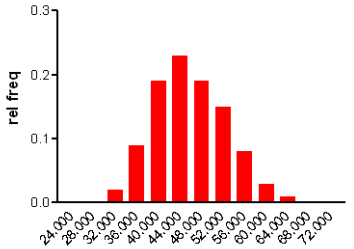

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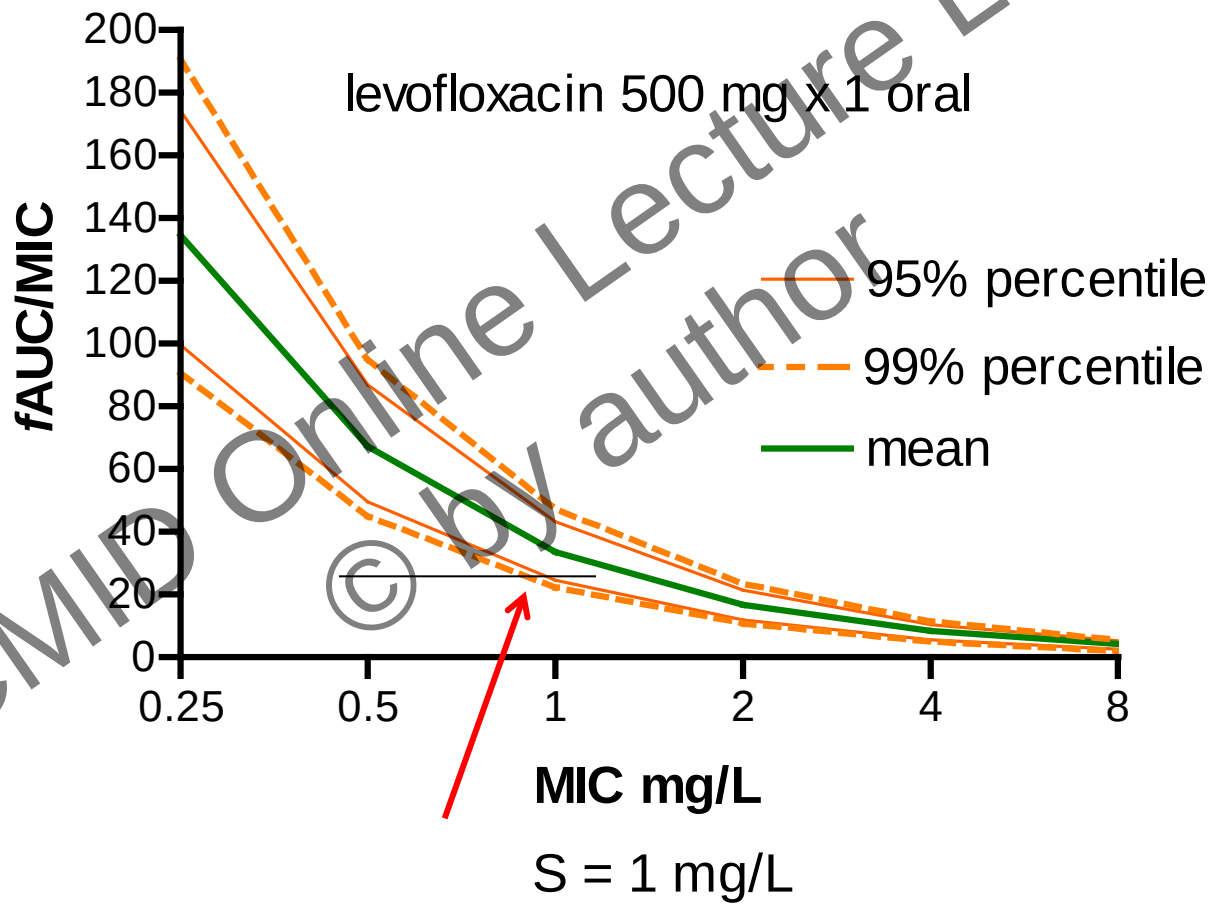
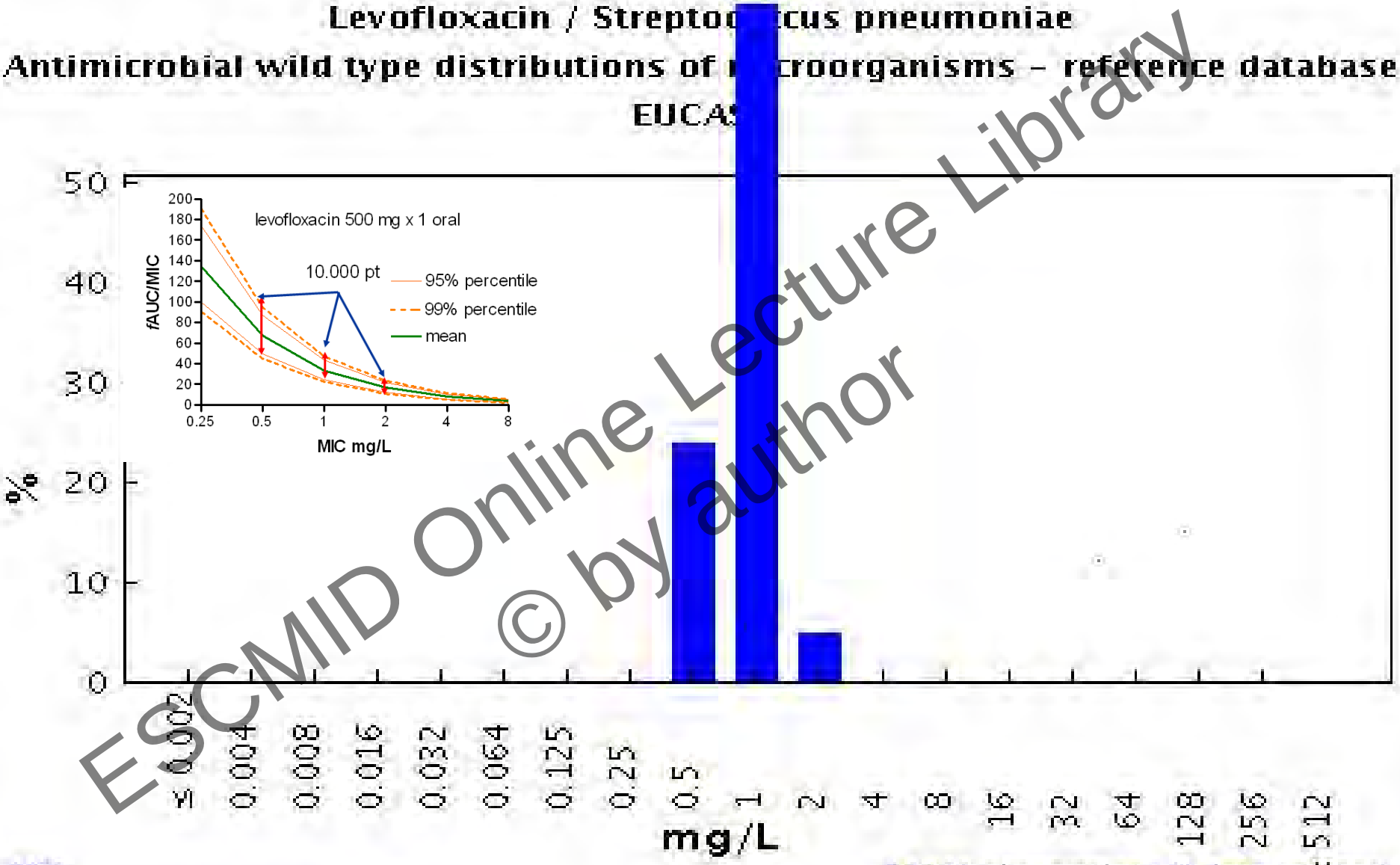
UMC St Radboud



EUCAST., 2004

Levofloxacin / Streptoc cus pneumoniae

Antimicrobial wild type distributions of r croorganisms – reference database EUCAS

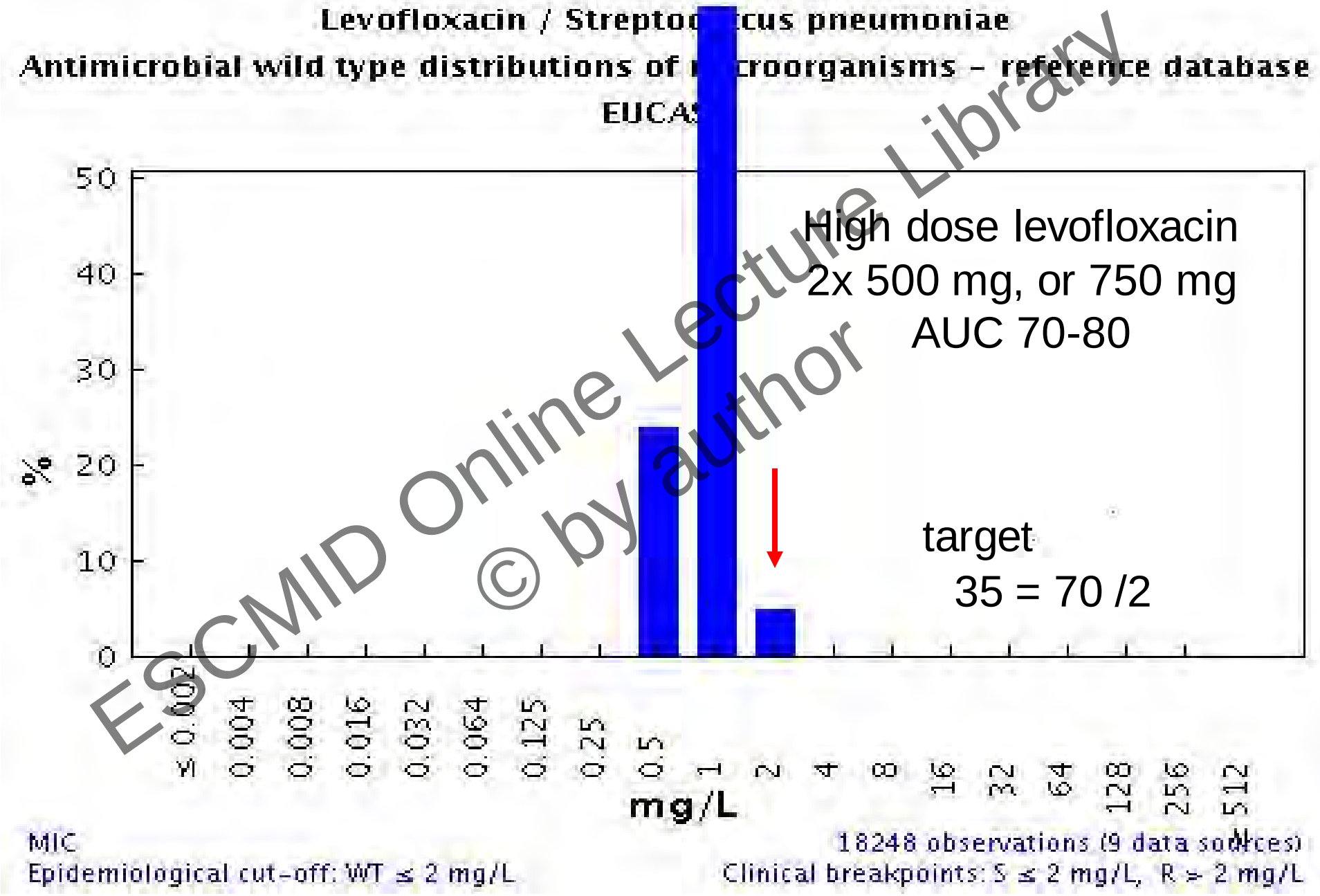


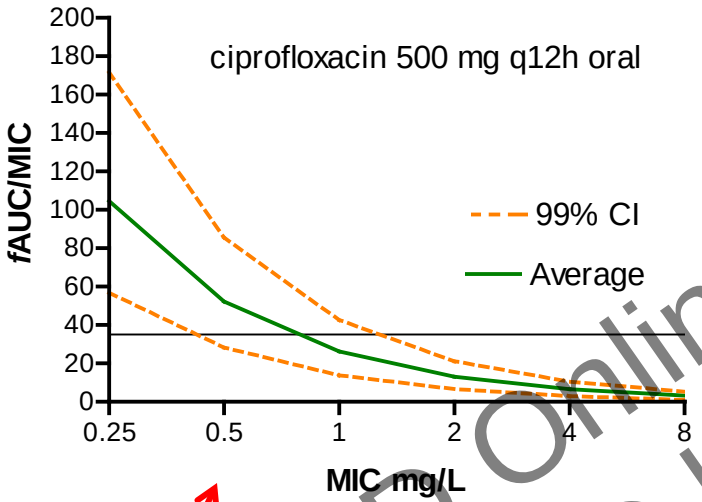
MIC

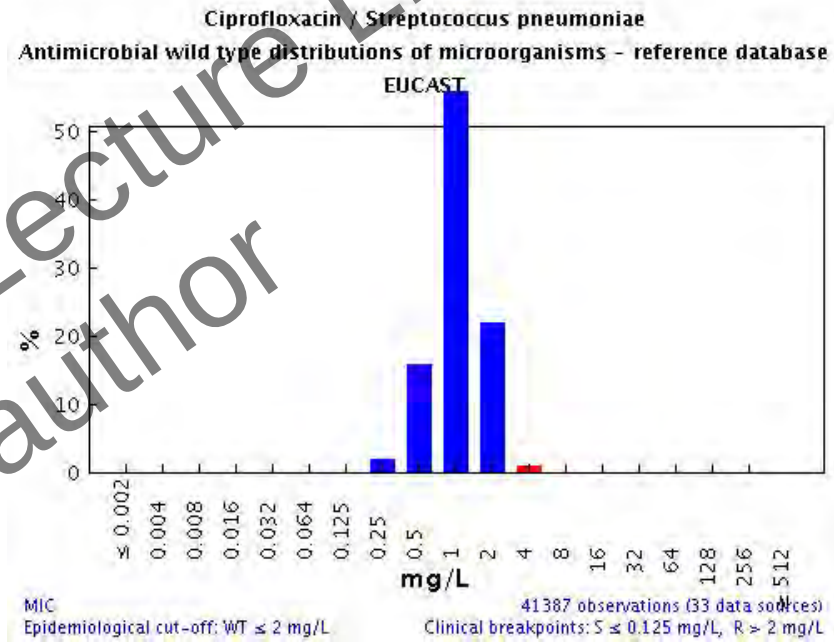
Epidemiological cut-off: WT ≤ 2 mg/L

18248 observations (9 data sources)

Clinical breakpoints: S ≤ 2 mg/L, R > 2 mg/L





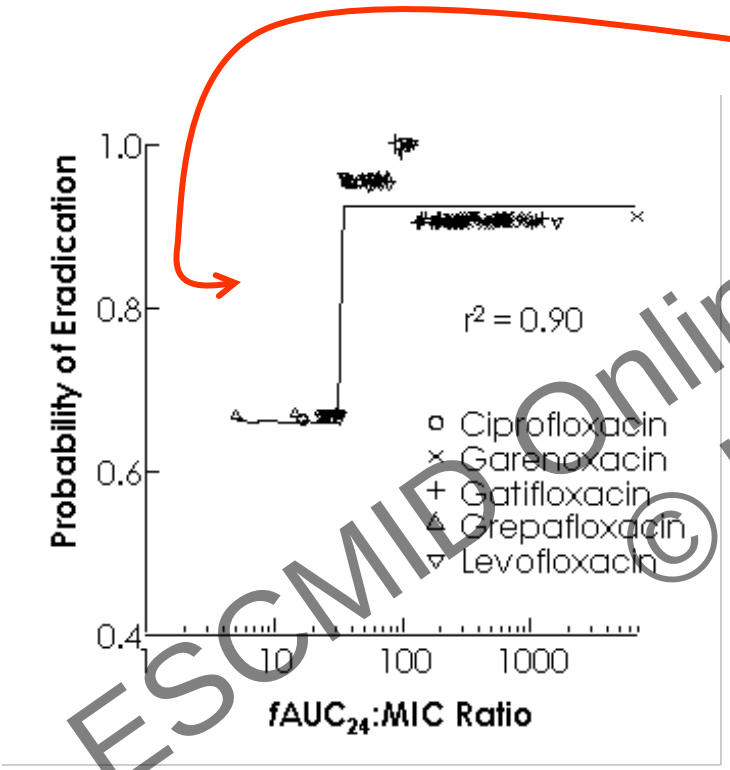


Pk/Pd S = 0.5 mg/L

"He chose poorly"

-Knight from Indiana Jones: The Last Crusade

GOOD Clinical Practice



Be sure that the *f*AUC/MIC ratio is at least appr. 34 in every patient

This includes patients with a high clearance

Bugs with MICs that can be expected

SETTING A BREAKPOINT –PK/PD (example 2)

DETERMINE THE PK/PD TARGET e.g. *value of the PK/PD Index*

ESTIMATE EXPOSURE from the dosing regimen and PK, including population variability

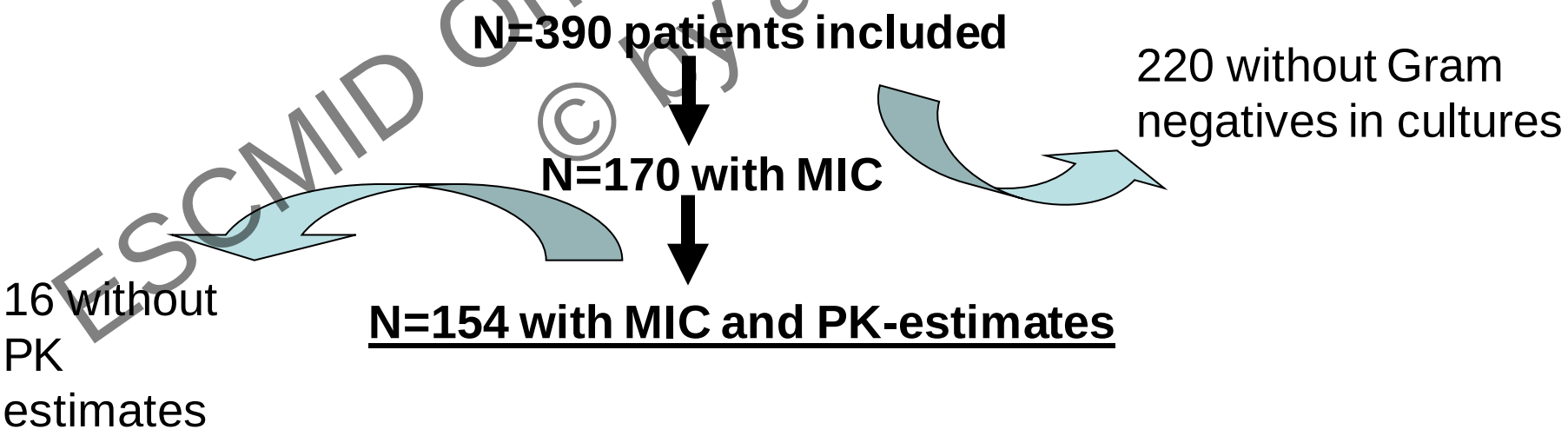
CALCULATE PK/PD BREAKPOINT from *PK/PD target = PK/PD Index*

What is the benefit of antimicrobial treatment?
(how much does antimicrobial treatment add to clinical cure)

a. 0%
b. 25%
c. 50%
d. 75%
e. 100%

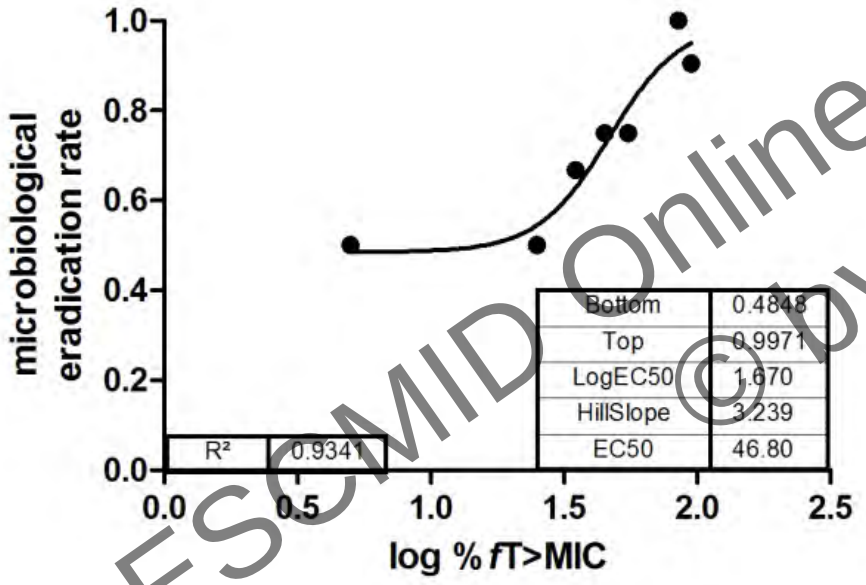
Ceftazidime in patients with nosocomial pneumonia

- randomized, double-blind phase 3 clinical trial (NCT00210964):
  - comparing the efficacy of ceftobiprole with the combination CAZ and linezolid
  - Ceftazidime 3dd 2 gr 2h infusion
  - Extensive and sparse sampling of ceftazidime



Muller et al, JAC 2013 68:900-906

Exposure-response Emax model

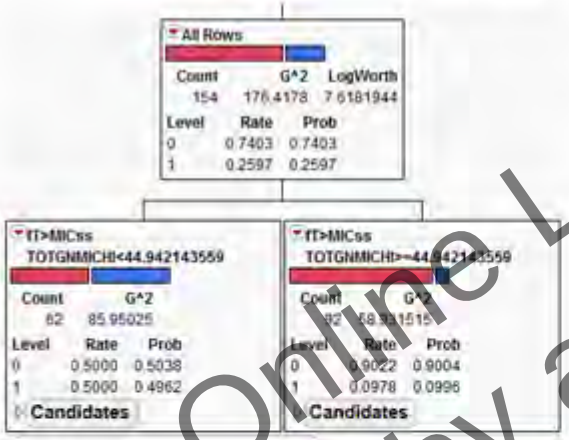


- Individual exposures to CAZ
- Categorised (%*f*T>MIC per 10%)
- Eradication rate per group
- 154 patients

Muller et al, JAC 2013 68:900-906

Ceftazidime in patients with nosocomial pneumonia

CART analysis



- to differentiate between lower and higher response rate

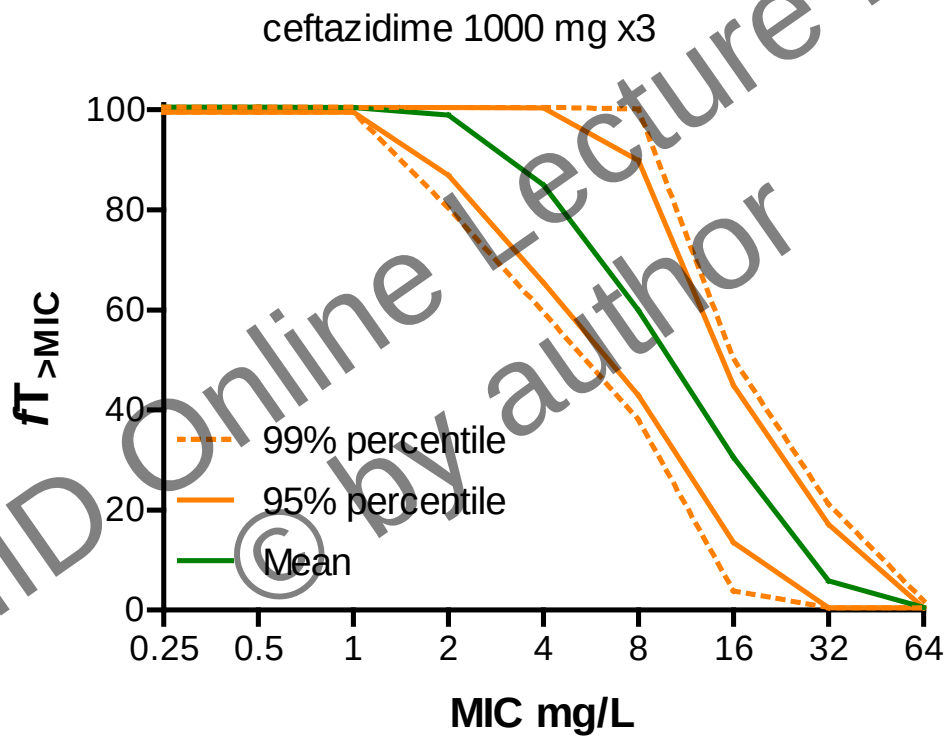
%*f*T>MIC breakpoint = 44.9 %

P< 0.0001

%*f*T>MIC	Success	Failure
≥44.9	83 (90.2%)	9 (9.8%)
<44.9	31 (50%)	31 (50%)

Muller et al, JAC 2013 68:900-906

Probability of Target Attainment - Ceftazidime



BP = 4 mg/L

EUCAST rationale document

EUCAST

EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Susceptible (S)

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Note: This breakpoint may be altered with legitimate changes in circumstances

Intermediate (I)

A micro-organism is defined as intermediate by a level of antimicrobial activity associated with indetermiate therapeutic effect. A micro-organism is categorized as intermediate by applying the appropriate breakpoints in a defined phenotypic test system.

Note: This breakpoints may be altered with legitimate changes in circumstances.

Resistant (R)

bacteria are defined as resistant by a level of antimicrobial activity associated with a high likelihood of therapeutic failure. A micro-organism is categorized as resistant by applying the appropriate breakpoint in a defined phenotypic test system.

Note: This breakpoint may be altered with legitimate changes in circumstances

UMC St Radboud

The role of pharmacokinetics/pharmacodynamics in setting clinical MIC breakpoints: the EUCAST approach

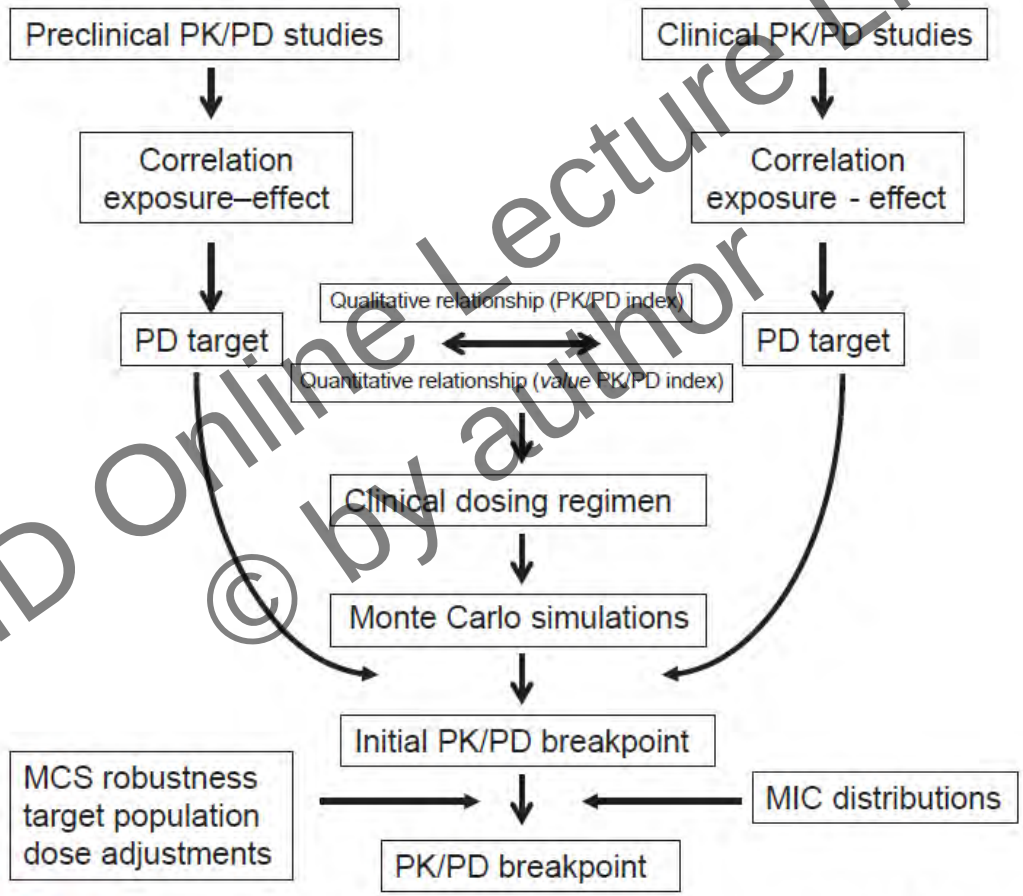
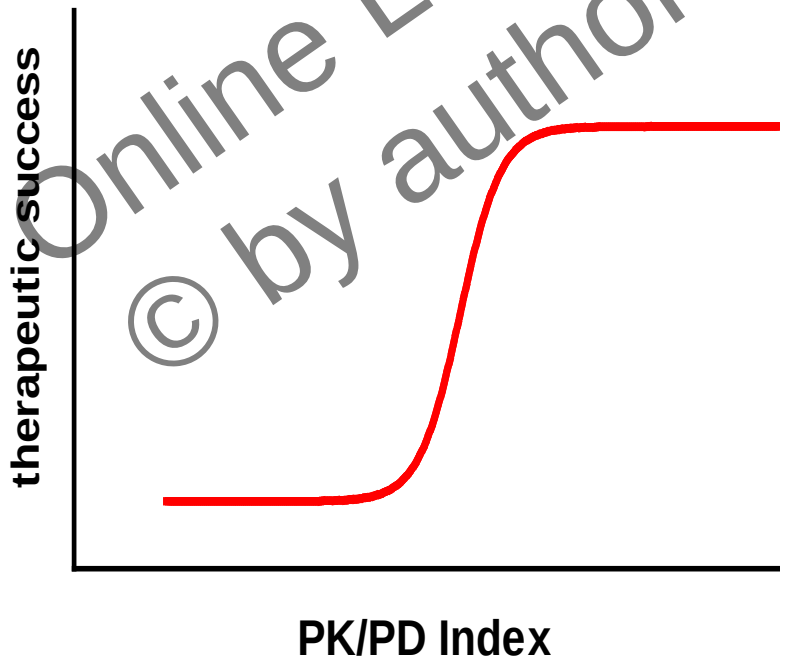


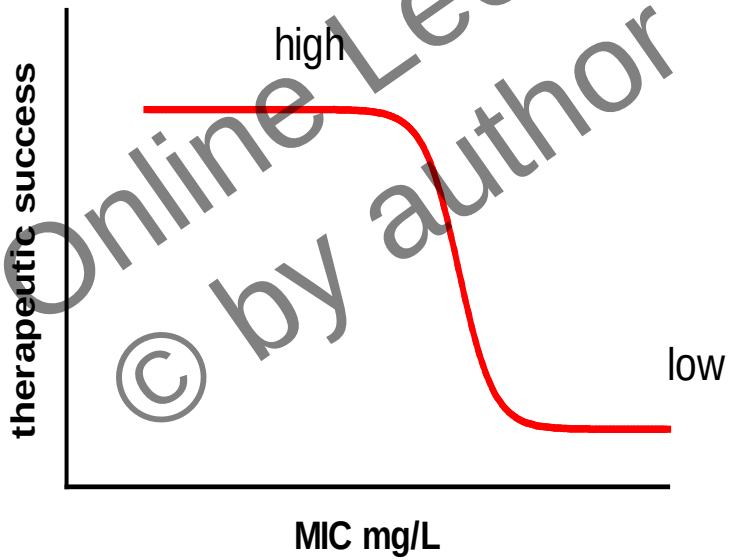
FIG. 7. Summary of the process of setting pharmacokinetic/pharmacodynamic (PK/PD) breakpoints by EUCAST.

Mouton et al, CMI 2012

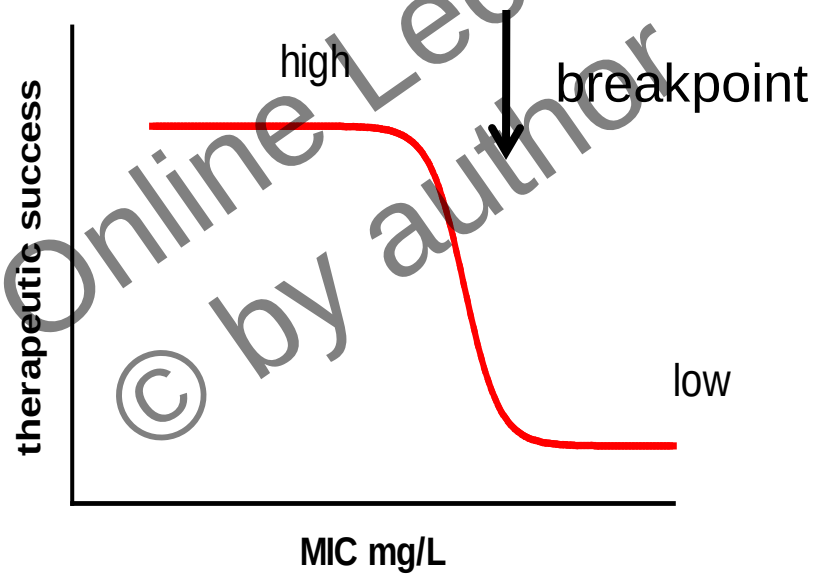
Implications for breakpoints



Susceptibility (MICs) are related to (clinical) outcome



Susceptibility (MICs) are related to (clinical) outcome?



Breakpoint values
make the difference –but include PK!!!

Conclusions

- PK/PD breakpoints reflect the relationship between exposure and clinical outcome
- PK/PD breakpoints are dependent on dose (!), pharmacokinetic profile and pharmacodynamic target
- The pharmacodynamic target MAY differ by species (e.g. Gram- vs Gram+)
- EUCAST PK/PD breakpoints are based on clinical data if available and otherwise on animal data and other data. Rationale documents describe the background.