Modelling in Clinical Microbiology : Basic Concepts and Why do we Need it

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Predicting the Future...

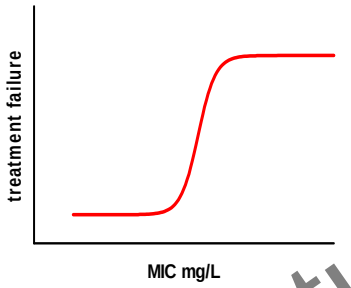
This Patient Needs Antibiotics.
But Which Ones, And Which Dose?

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)

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



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

Efficacy of the drug

Potency of a drug (MIC)

Exposure to the bug *In vivo* (PK)

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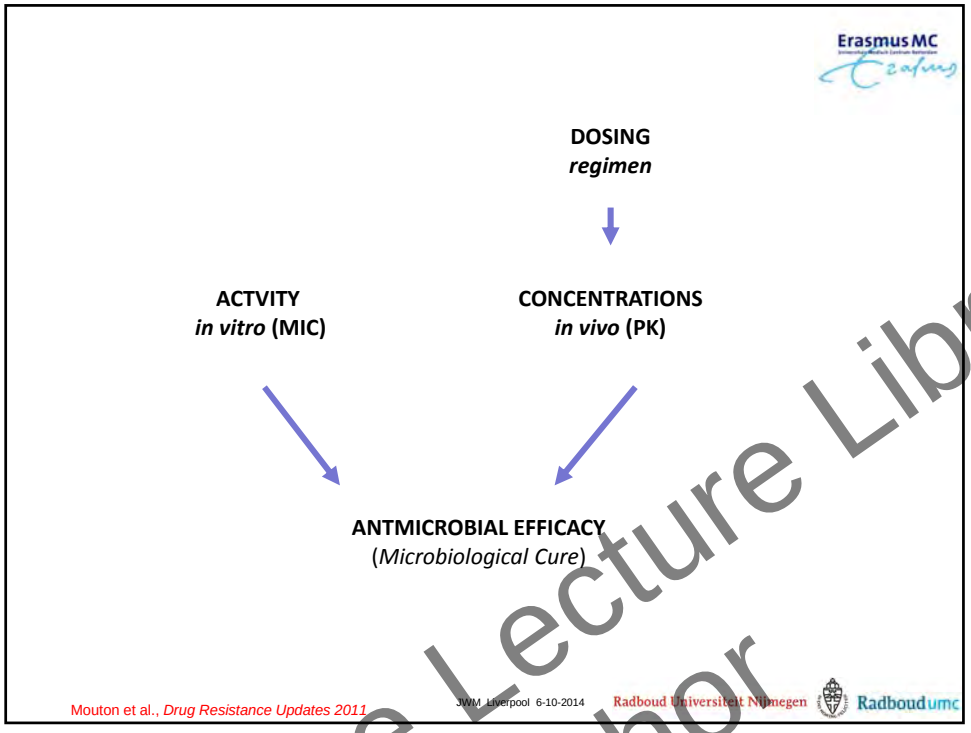
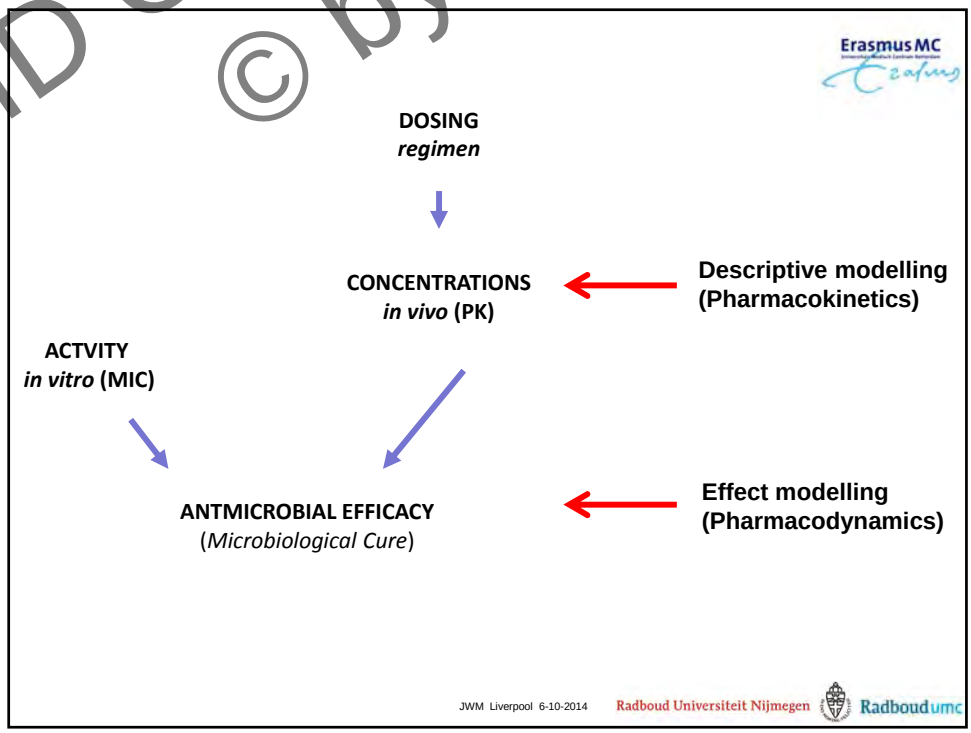
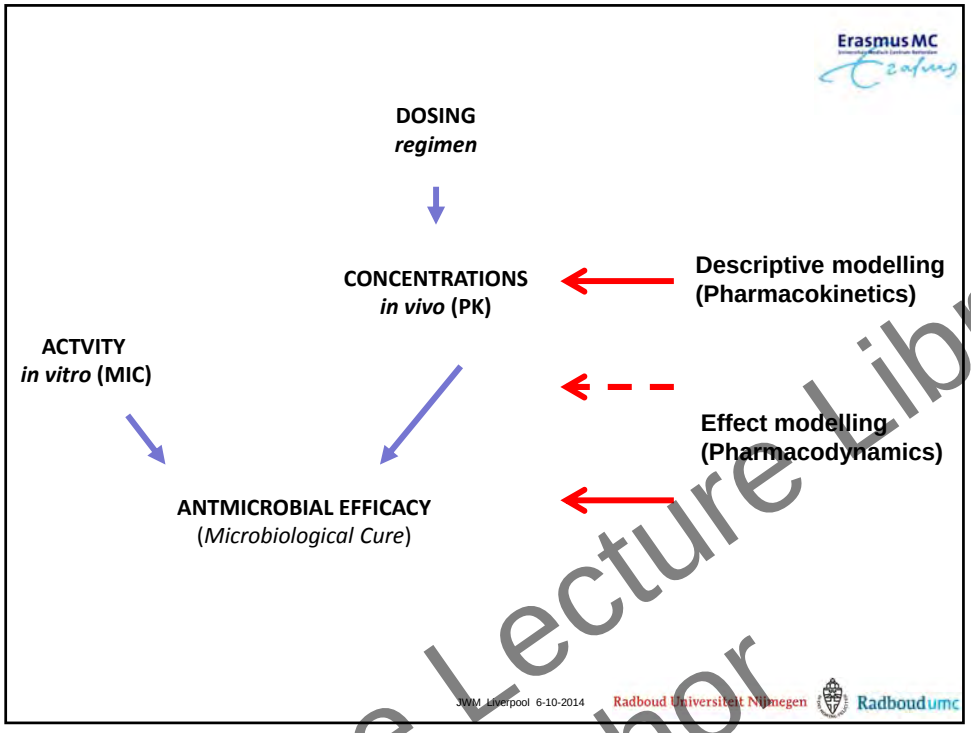
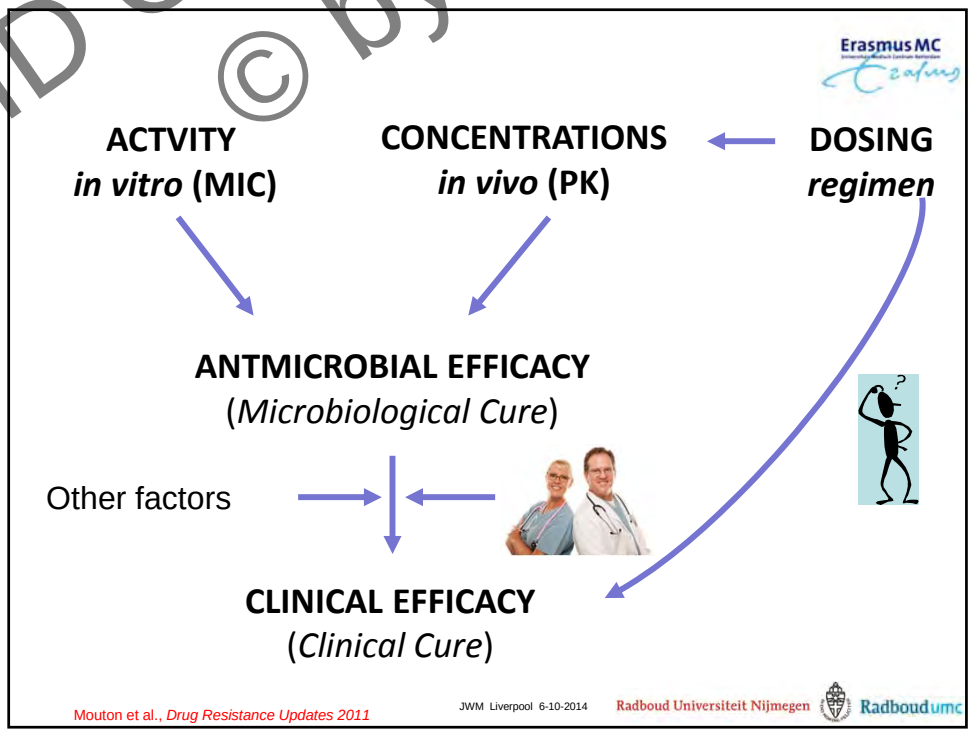
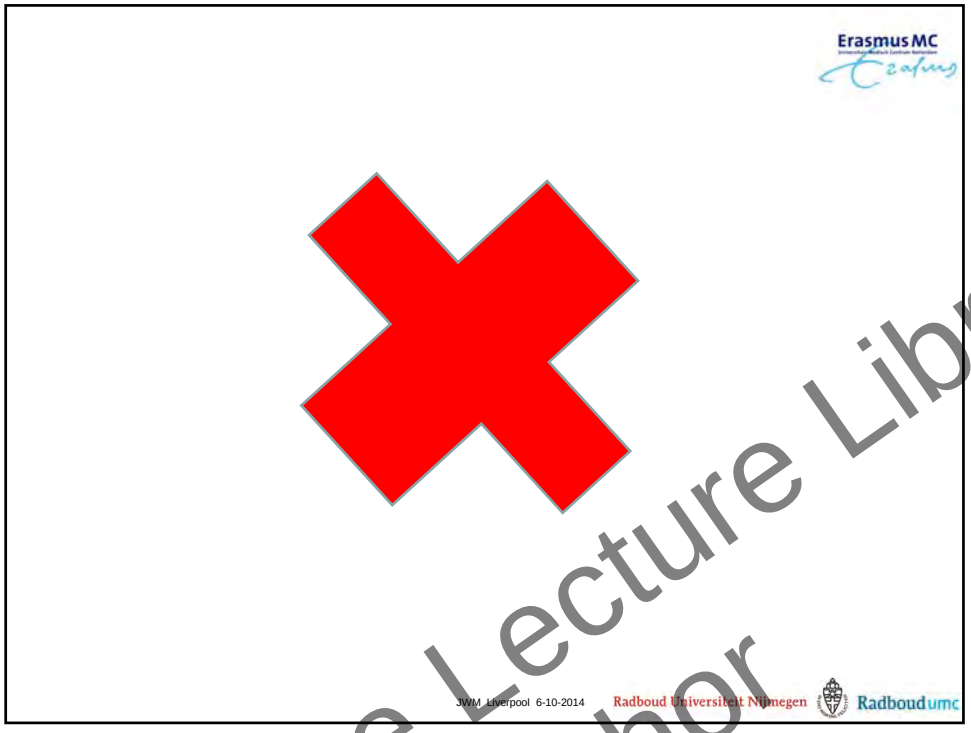
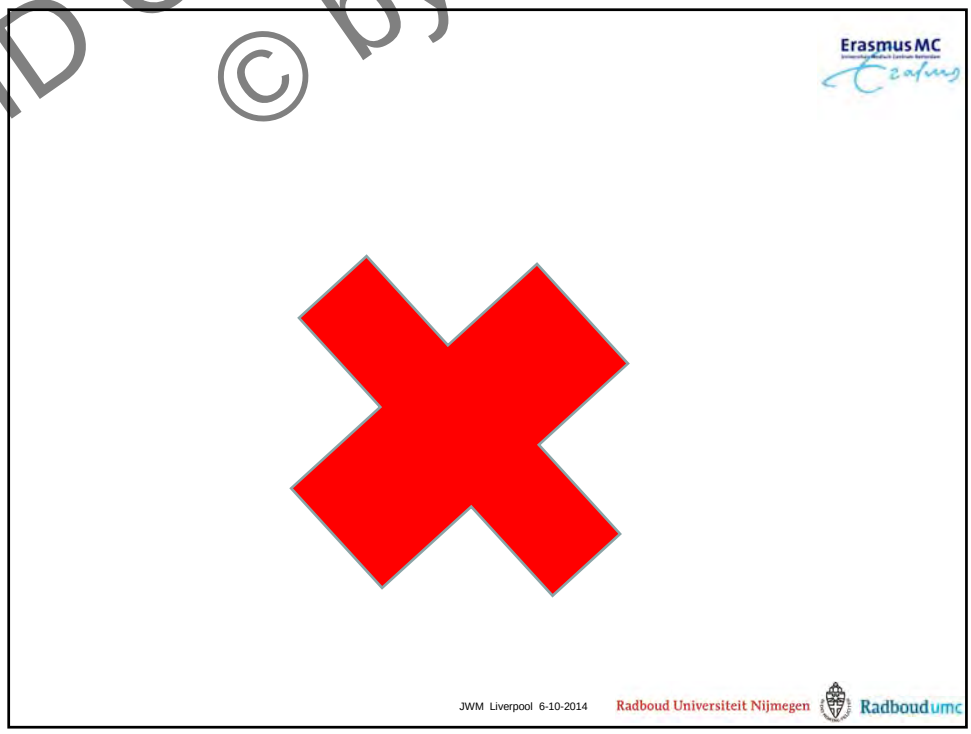








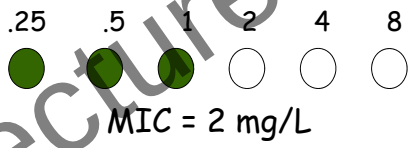




MIC
Measure of Potency

MIC

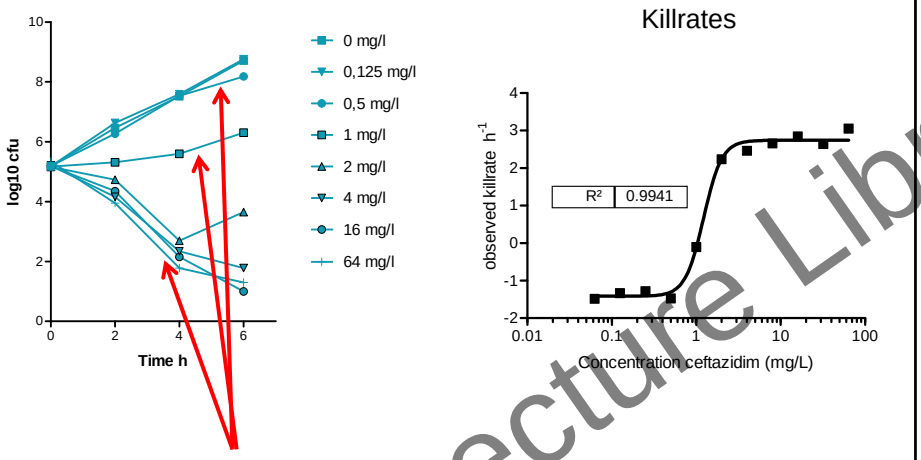
Lowest concentration
with no visible growth
after 18 hour incubation



What happens in the test tube?

Pharmacodynamic Modelling

Modelling Kill Kinetics



Kill rates

Mouton et al AAC 2007

CHANGE IN NUMBER OF BACTERIA OVER TIME

Growth Kill

$$\frac{dN}{dt} = \{\lambda \bullet (1 - \frac{N}{N_{max}}) - \varepsilon \bullet \frac{C^{\gamma}}{C^{\gamma} + EC_{50}^{\gamma}}\} \bullet N \quad (1)$$

Growth rate Max kill rate

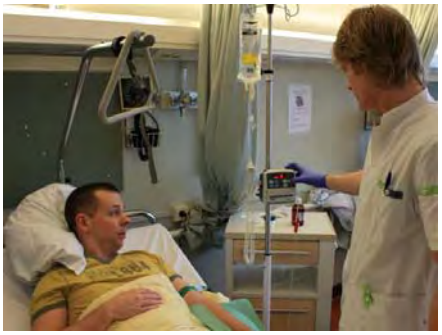
Mouton et al AAC 1997

Predicted *f*T>MIC needed for in vivo static effect -- Mice

	Mouse[1]	
regimen	mg/kg	%*f*T>MIC
q2	2.12	37.3
q3	4.60	38.1
q4	9.29	37.6
q6	35.6	36.5
q8	129.7	35.7
q12	-	-

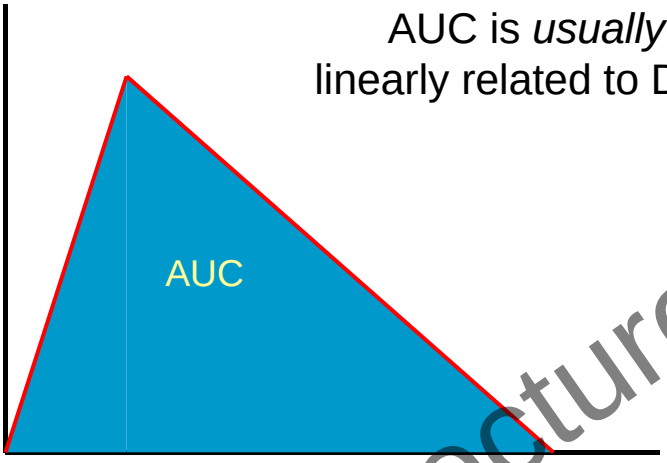
Mouton et al AAC 2007

Antimicrobial Treatment



Pharmacokinetic parameters : Measures of Exposure

AUC is *usually* linearly related to Dose



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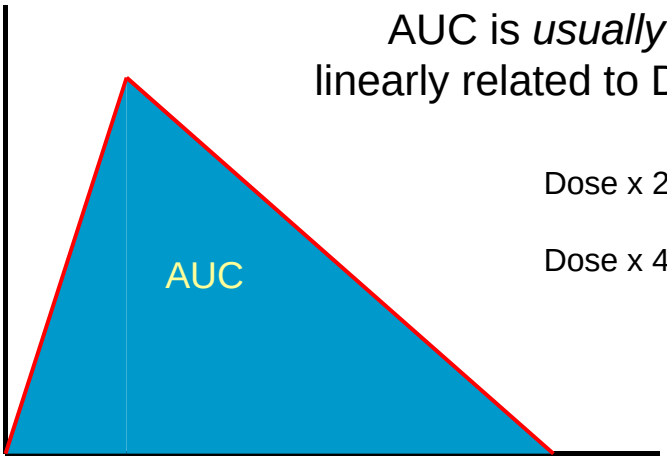


Dose x 2 = AUC x 2

Dose x 4 = AUC x 4

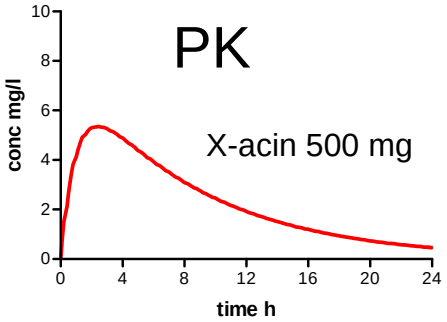
How to determine the AUC?

- Pharmacokinetic Modelling
  - Noncompartmental
  - Classical compartmental
  - Population modelling

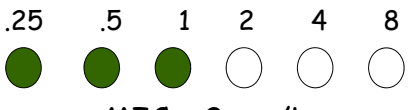
MIC

Lowest concentration with no visible growth after 18 hour incubation

PK



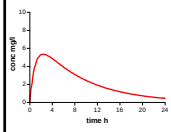
X-acin 500 mg



MIC = 2 mg/L

Pharmacokinetic Parameter (and Dose)

MIC



- Thus, we have to:
  - Establish a relationship between the MIC in vitro and concentrations in vivo (thus, dosing regimens)
  - Determine which dosing regimens are optimal for Treatment in relation to the MIC

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* (animal studies, clinical studies)

↓

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

↓

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

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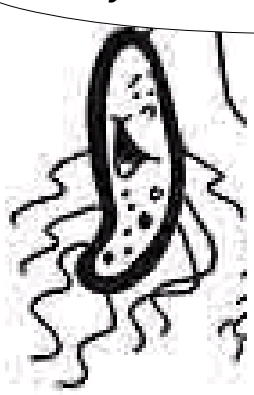
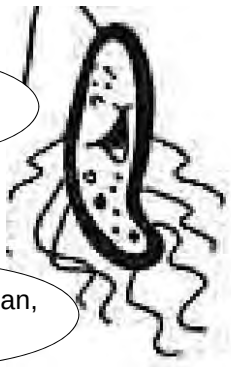
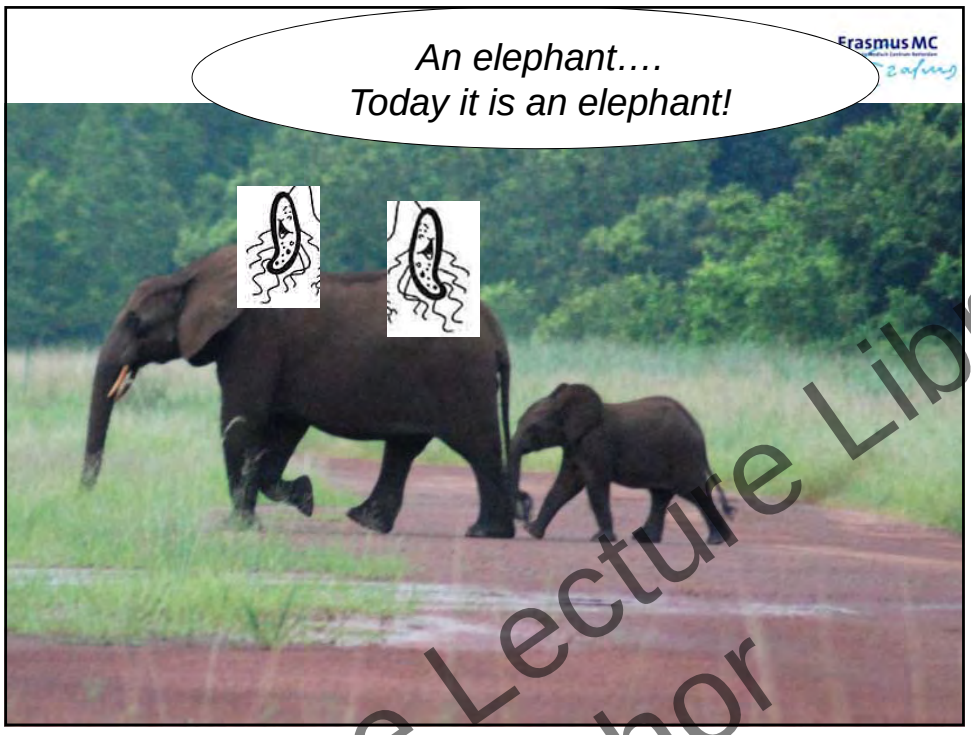
Any idea where we are today?



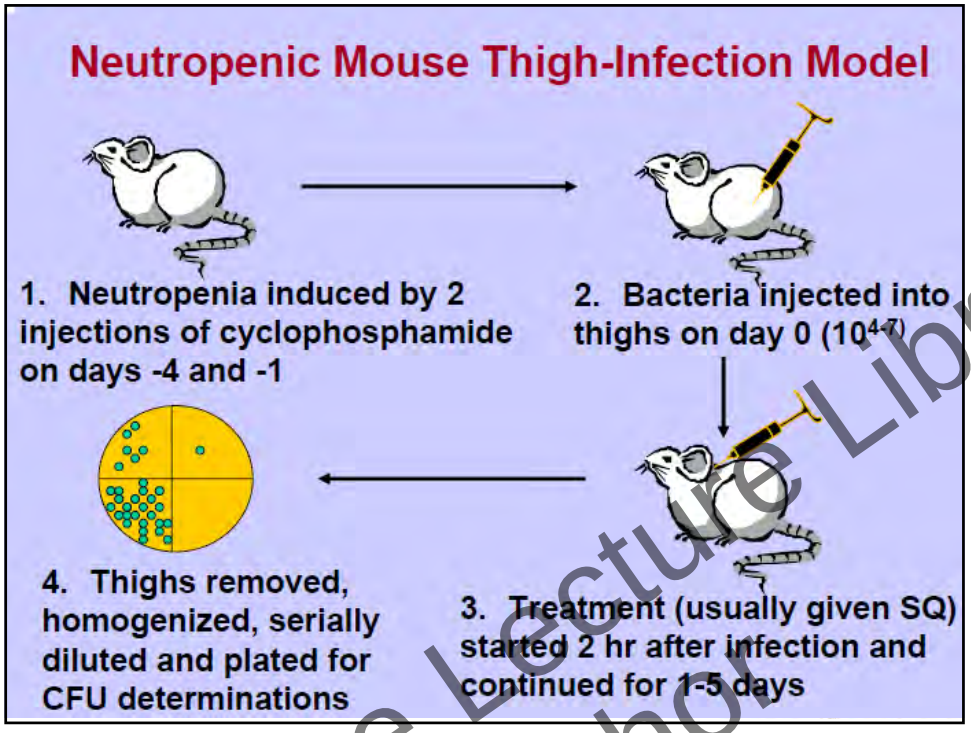
No idea…
may be a mouse?

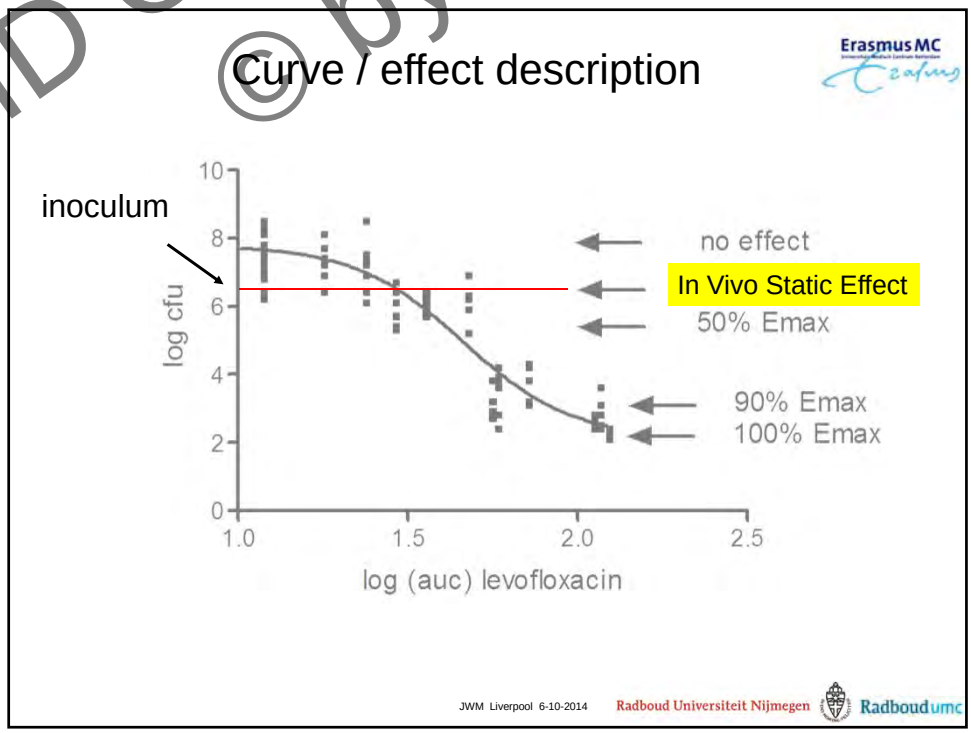


Might be a human, though…

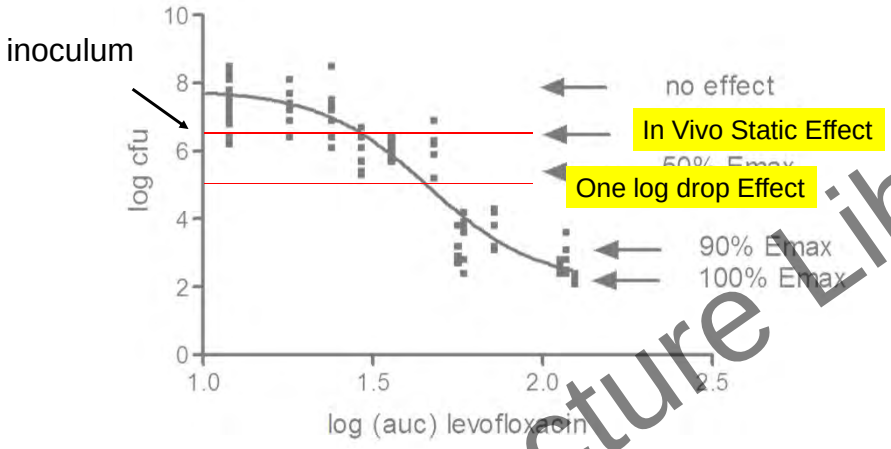


THE TARGET IS THE MICRO-ORGANISM



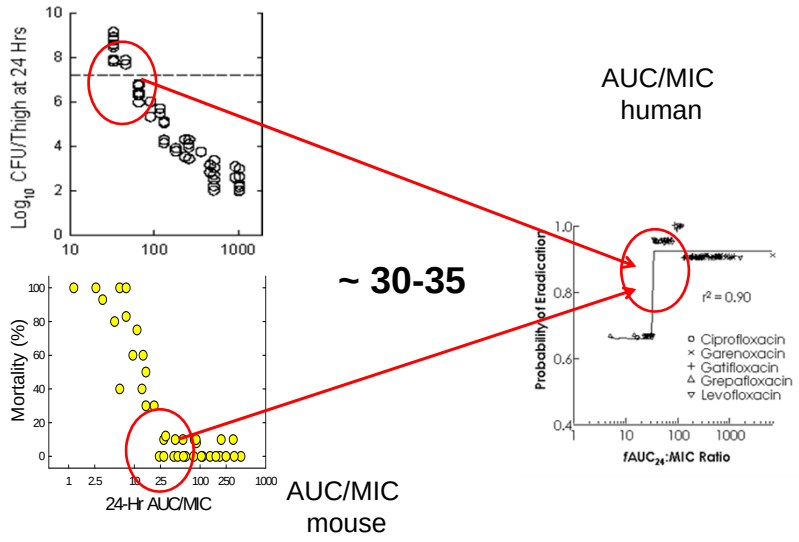


Curve / effect description



Pharmacodynamic target

exposure in mice and men



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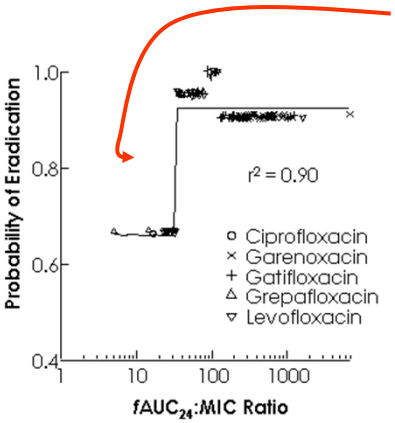
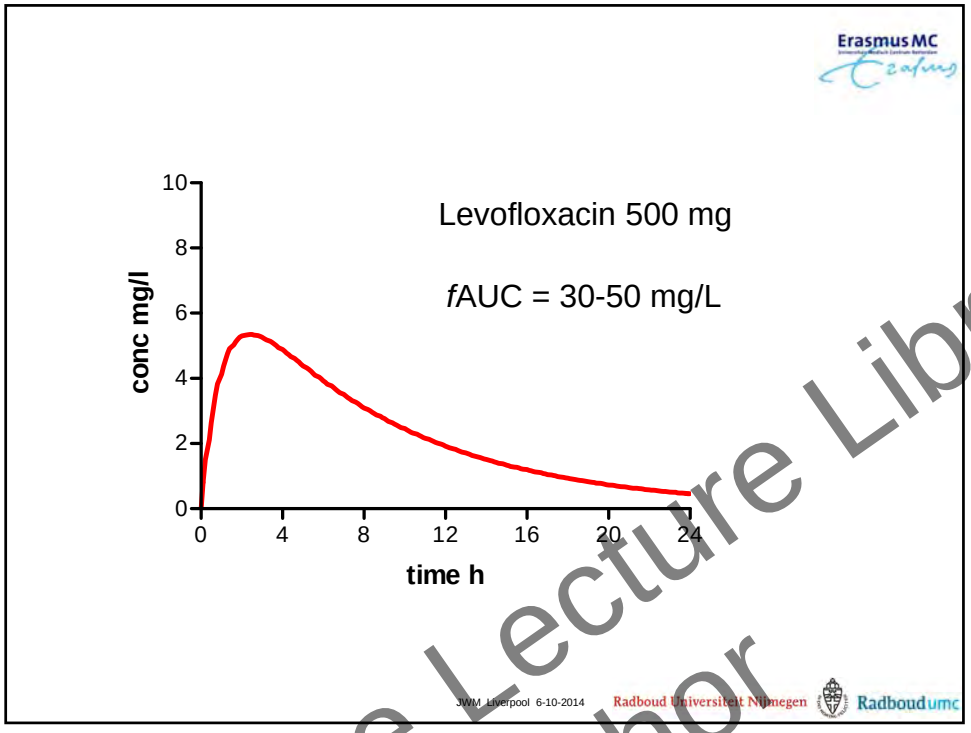
GOOD Clinical Practice

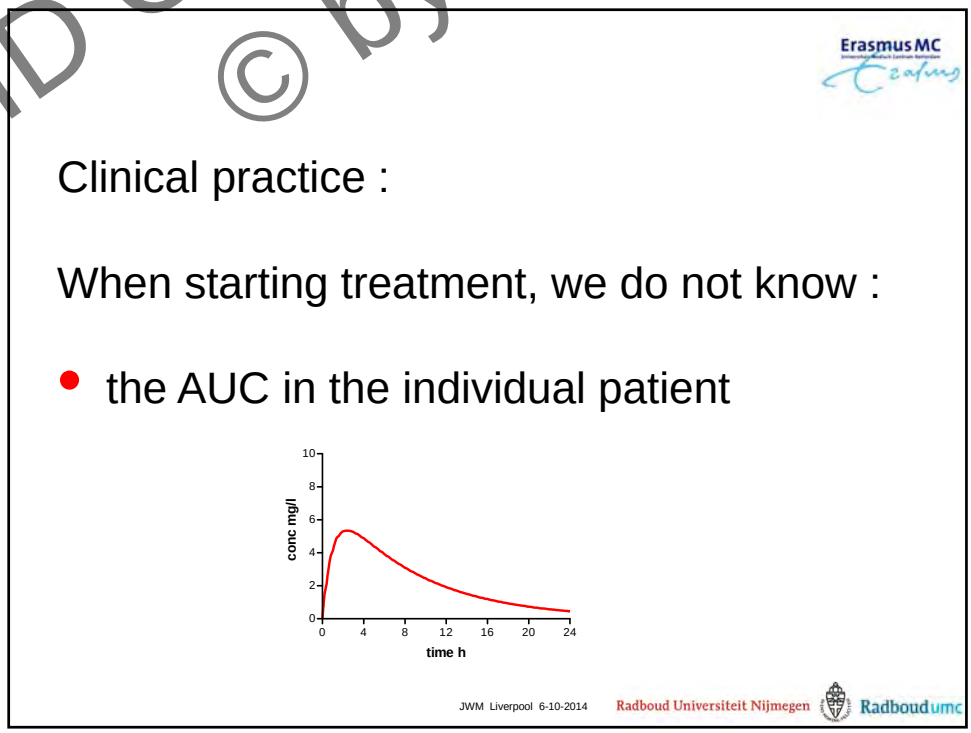


Be sure that the *f*AUC/MIC ratio is at least appr. 34 in every patient

AUC

MIC

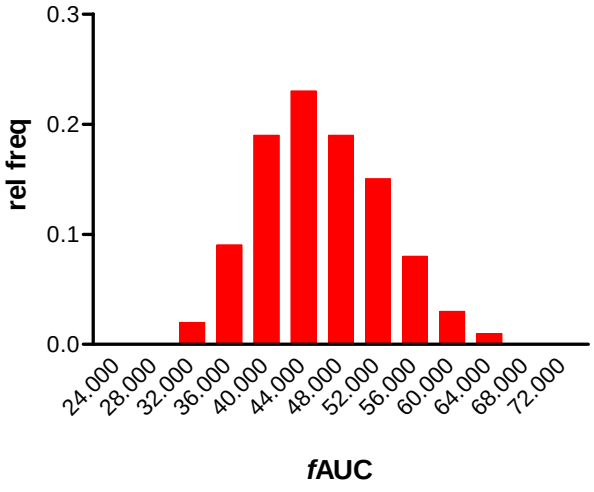




Pharmacokinetics

Some people are more equal than others…

fAUC distribution levofloxacin
(monte carlo simulation)



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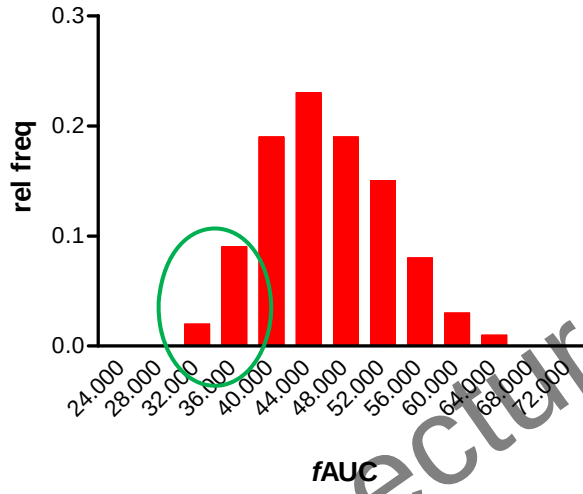

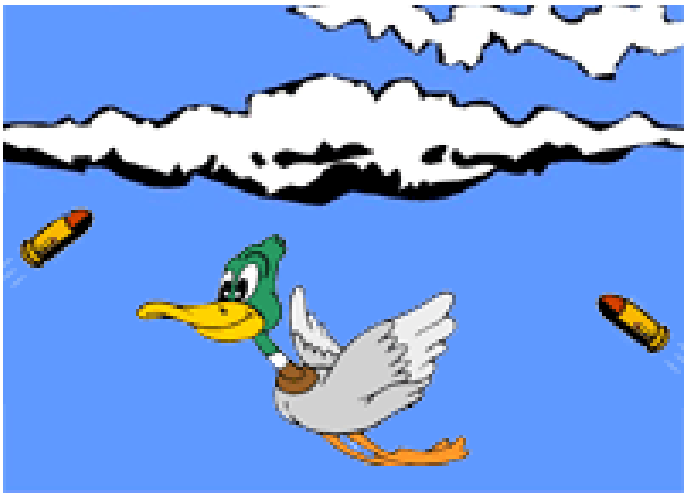

On the average, this duck is dead

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

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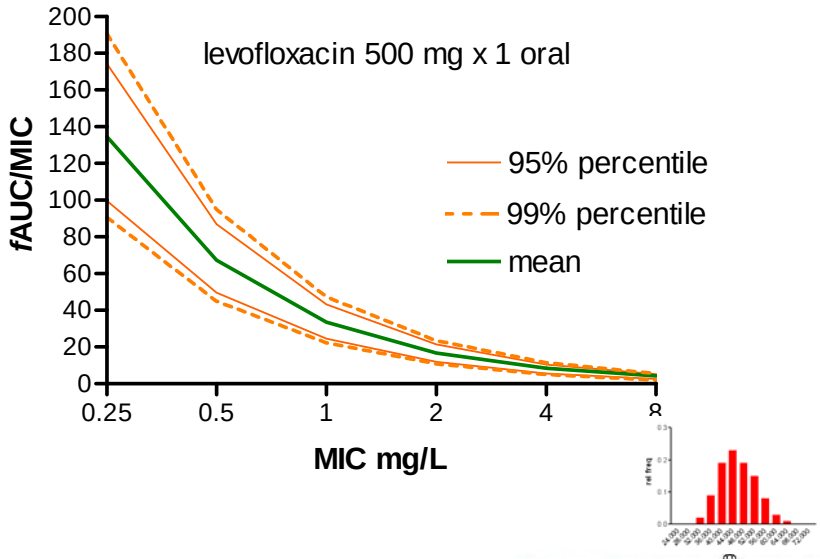
CALCULATE PK/PD BREAKPOINT from *PK/PD target = PK/PD Index*

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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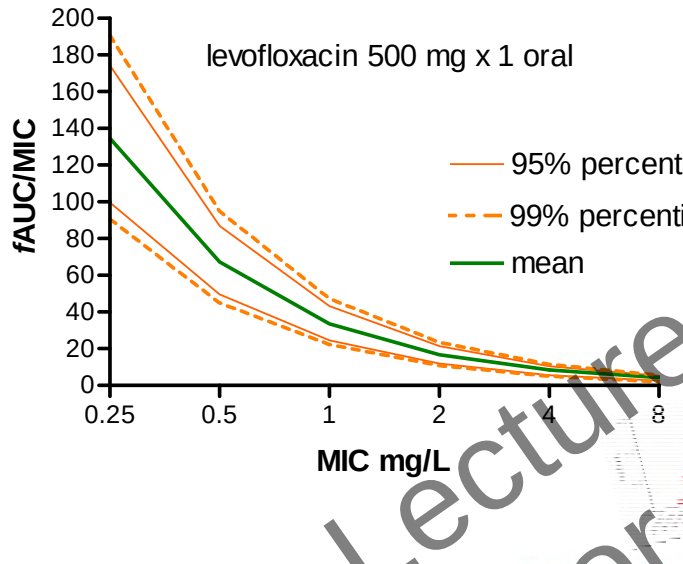

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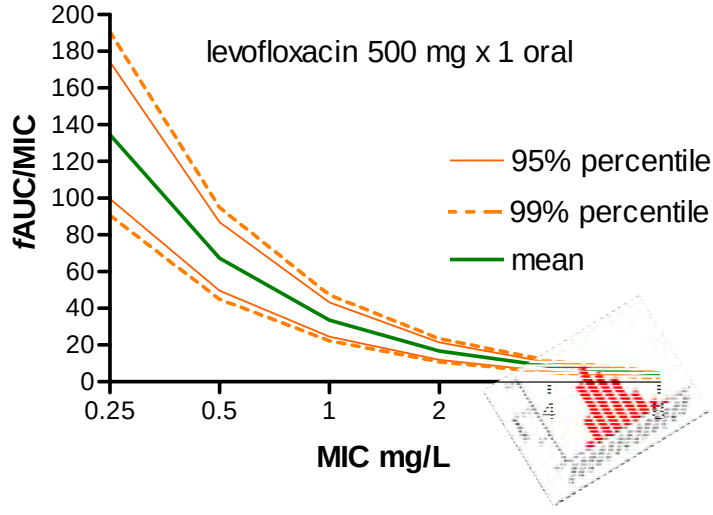

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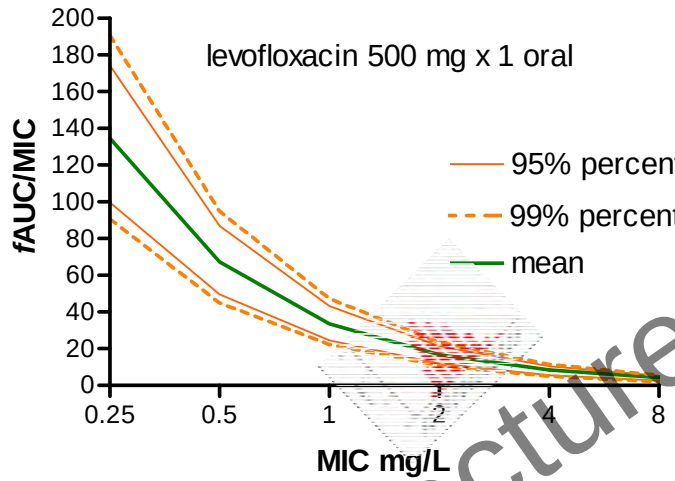

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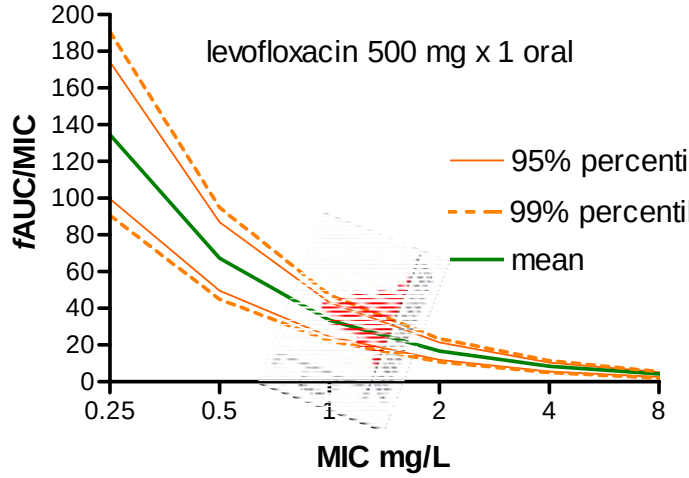

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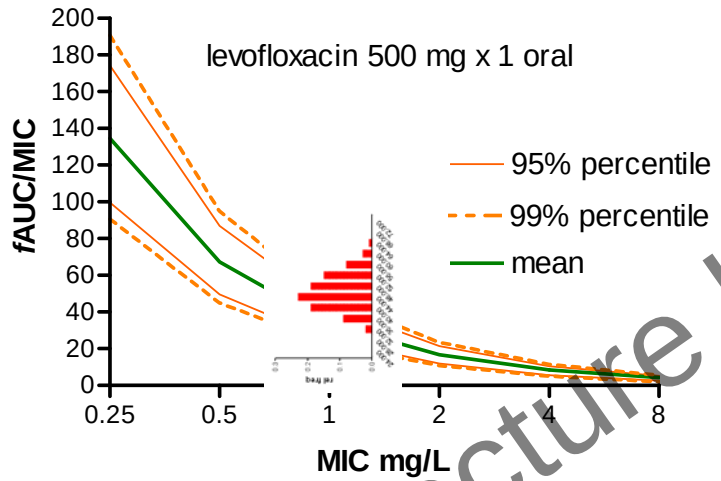

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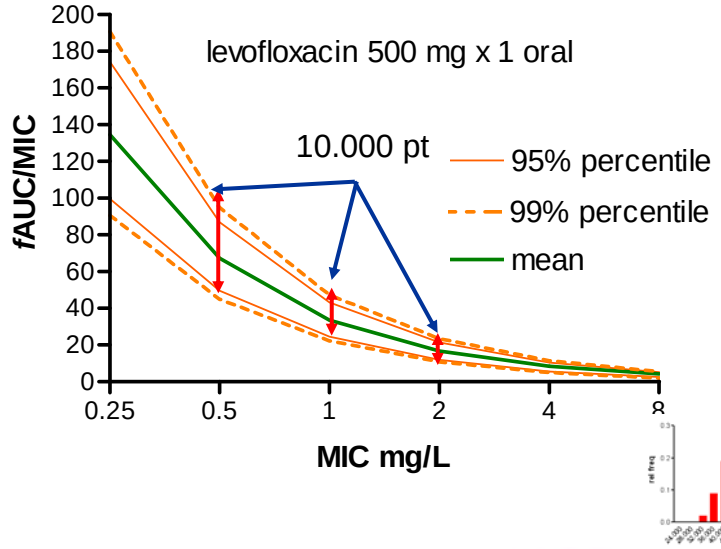

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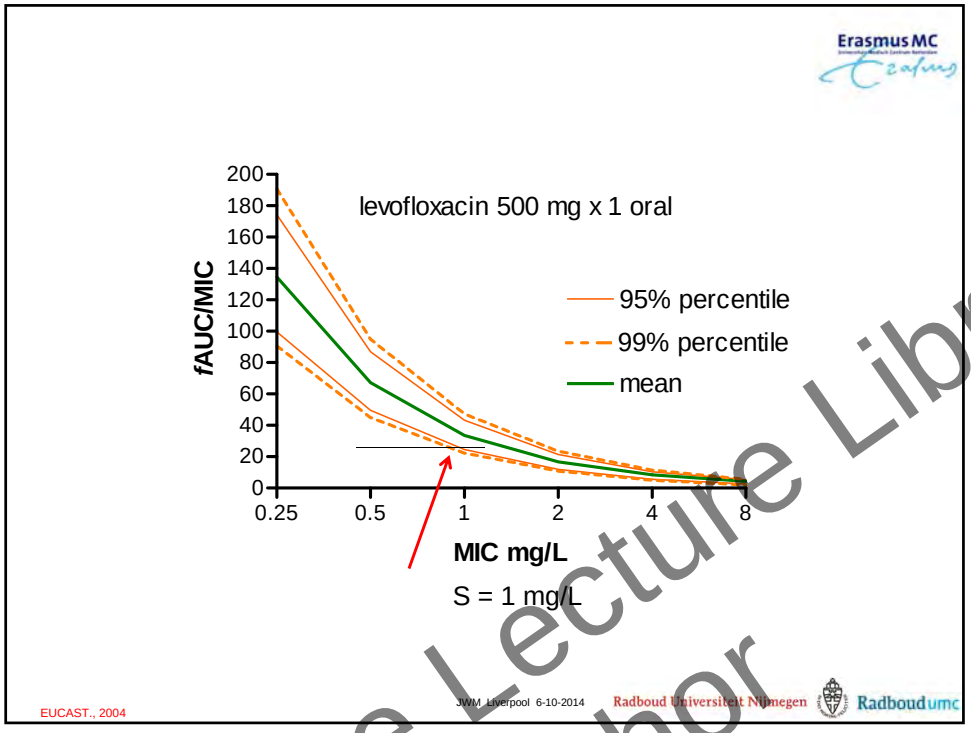

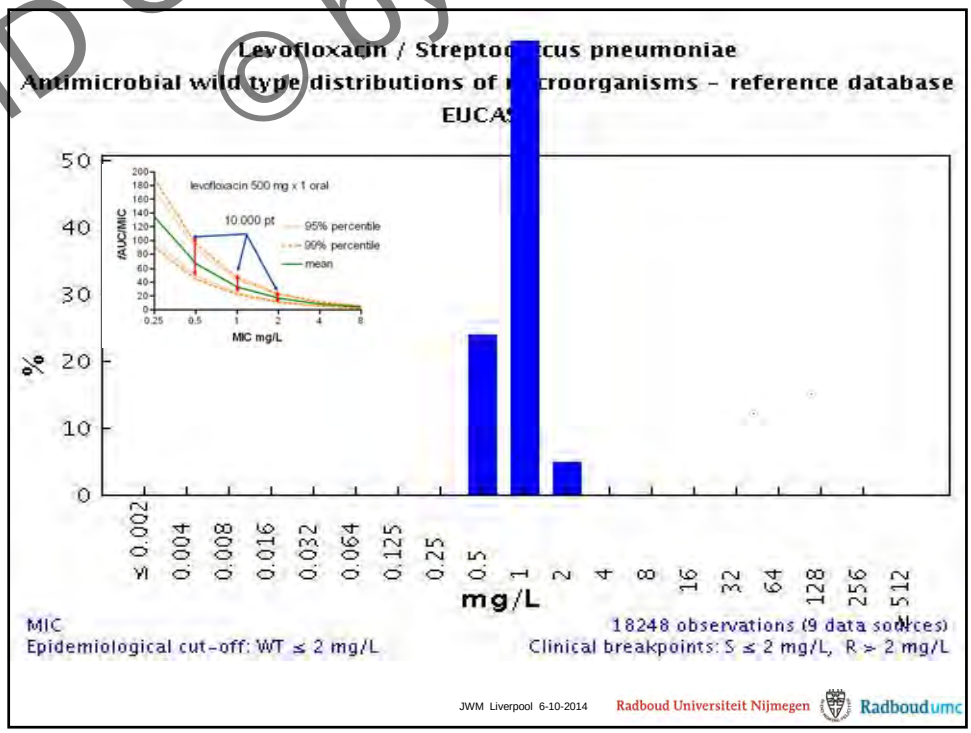

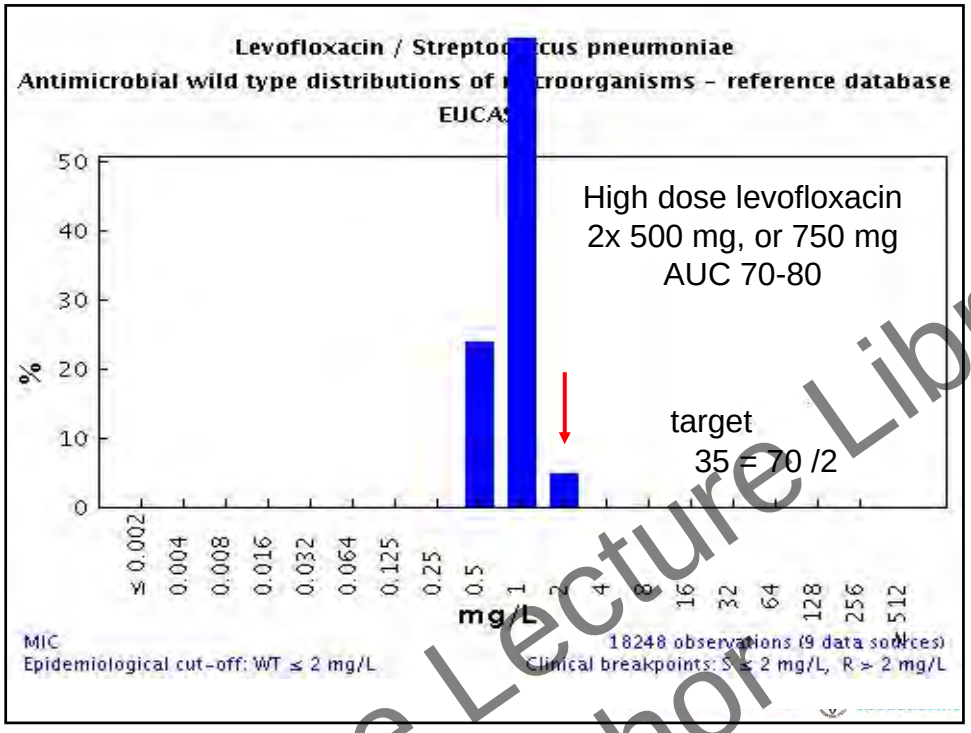

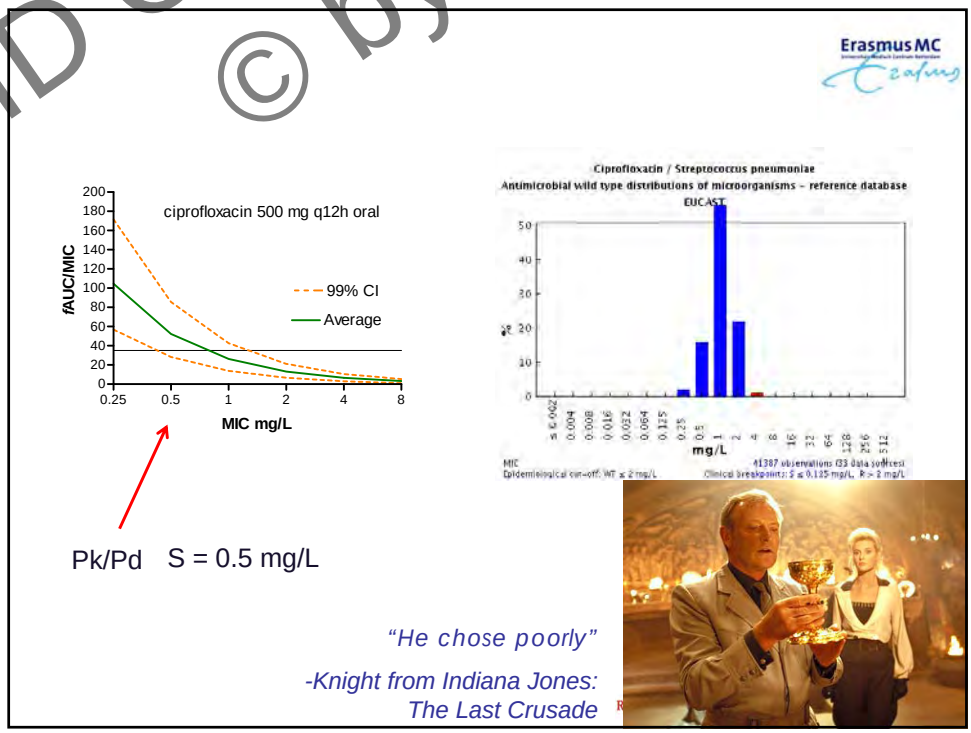

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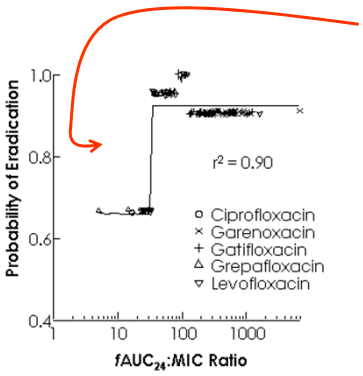


Be sure that the *f*AUC/MIC ratio is at least appr. 34 in every patient

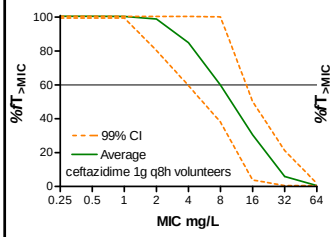
This includes patients with a high clearance

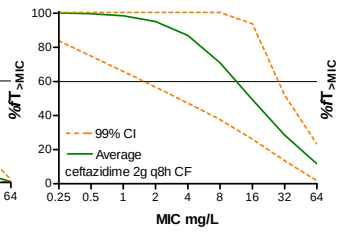
Bugs with MICs that can be expected

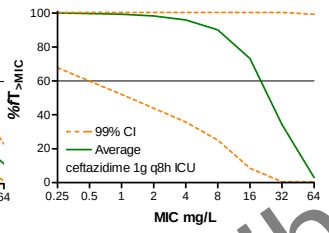
Population Models and MCS

Monte Carlo Simulations are as good as the Model is
- Input (which patients?)
- Output (which model?)

Different Models.....







MIC	% Time > MIC			
(mg/L)	30	40	50	60
0.5	100	100	100	100
1	100	100	100	100
2	100	100	100	100
4	100	100	100	100
8	100	99	84	42
16	54	10	1	0
32	0	0	0	0
100% PTA	8	4	4	4

% Time > MIC			
30	40	50	60
100	100	100	100
100	100	100	100
100	100	100	99
100	100	99	95
100	99	92	72
98	78	42	17
37	6	1	0
8	4	2	1

% Time > MIC			
30	40	50	60
100	100	100	100
100	100	100	99
100	100	99	98
100	99	98	96
99	96	93	88
89	80	72	65
39	32	27	23
4	2	1	0.5

Mouton et al, Clin Ther 2005 27:762

Translation

DOSE FINDING: 7 MAJOR STEPS

STEP	ACTION
1	Establish PK/PD index that is correlated with effect of DRUG
2	Establish the pharmacodynamic target of DRUG
3	Determine is protein binding in mice and in humans of DRUG
4	Determine the wild type (WT) distribution of micro-organisms to be covered
5	Set the highest MIC that proposed dosing regimens are required to cover (usually the highest ECOFF of target micro-organisms)
6	Establish the dose – exposure relationship of the drug
7	Determine dosing regimens that cover target micro-organisms

Mouton In: PKPD handbook

DOSE FINDING: 7 MAJOR STEPS

STEP	ACTION	METHODS
1	Establish PK/PD index that is correlated with effect of DRUG	Time-kill studies; Preclinical studies in animals and IVPM; PD modeling
2	Establish the pharmacodynamic target of DRUG	Interpretation of models in step 1 (neutropenic vs non-neutropenic animals; static effects; 1 or 2 log kill effects)
3	Determine is protein binding in mice and in humans of DRUG	Protein binding in mice and men over full concentration range expected
4	Determine the wild type (WT) distribution of micro-organisms to be covered	Epidemiological studies of target-micro-organisms (surveys)
5	Set the highest MIC that proposed dosing regimens are required to cover (usually the highest ECOFF of target micro-organisms)	Review and interpret survey results
6	Establish the dose – exposure relationship of the drug	Phase 1 studies – single and multiple dose; dose escalation
7	Determine dosing regimens that cover target micro-organisms	Population pharmacokinetic analysis; Monte Carlo simulations

DOSE FINDING: 7 MAJOR STEPS

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