Current Tools and Approaches for setting (clinical) Breakpoints

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European Society of Clinical Microbiology and Infectious Diseases

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

Radboud Universiteit Nijmegen Radboudumc

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)
colimoxazole	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)

Clinical Breakpoints

- ***Distinguish, based on in vitro test results, patients with high likelihood of cure from those with a low(er) likelihood.***
- ***We use the terms susceptible and resistant as class markers***
- ***Thereby help the clinician in informed decision making***
- ***Are not absolute, but provide a means to the former***
  - ***Is therefore dependent on risk versus benefit***
- ***Are dependent on dose / exposure***

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2016
EMA/CHMP/594085/2015
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the use of pharmacokinetics and pharmacodynamics in the development of antimicrobial medicinal products

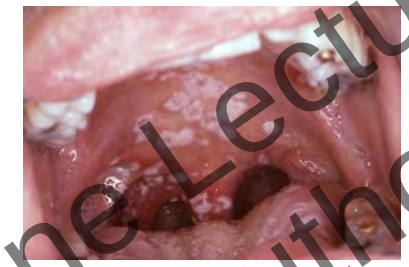
SETTING A BREAKPOINT (the easy approach)

DETERMINE DOSE-RESPONSE RELATIONSHIP

DETERMINE BREAKPOINT (dosedependent)

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

Treatment with fluconazol
Doses 50 – 800 mg



Culture-results with
MIC-values

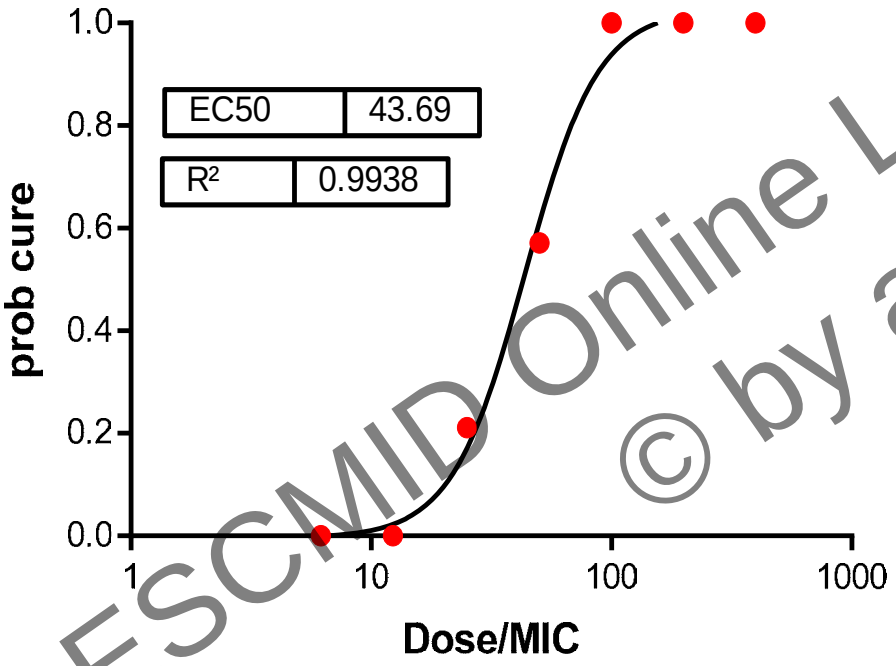
Individual Dose

MIC-values per individual

Determine Dose/MIC for each patient

Microbiological outcome (candida cured)
Clinical outcome

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



- Prob cure correlates with Dose/MIC
- POSITIVE correlation with Dose
- INVERSE correlation with MIC

Each data point represents the proportion of patients cured within a group representing a certain Dose/MIC value

Rodriguez- Tudela et al, AAC 2007

Usually however, it is slightly more complicated than just dose.....

Dose is just a **means** to reach adequate (effective) concentrations / concentration profiles

Usually however, it is slightly more complicated than just dose.....

……because in development we usually do not have Dose – response relationships

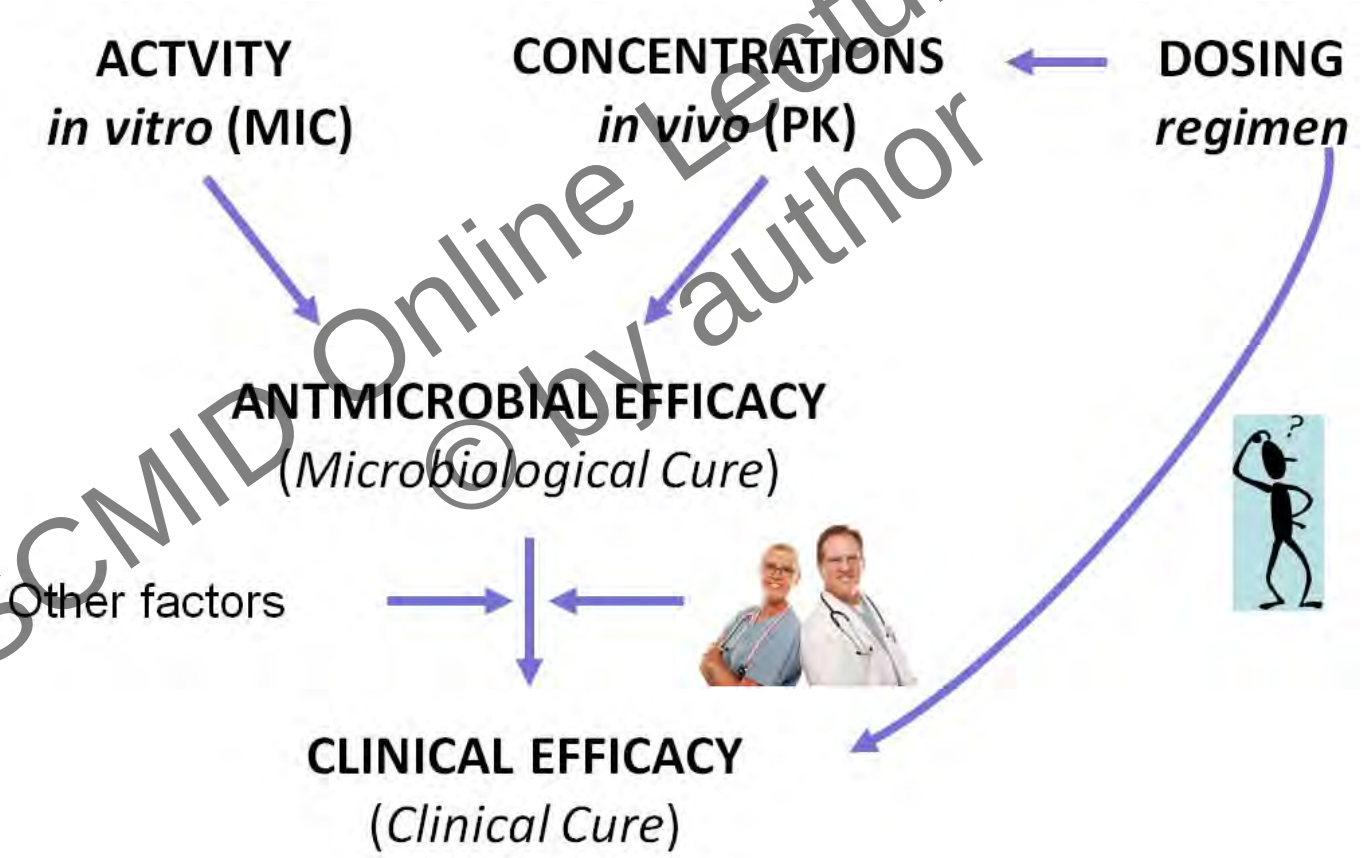
…..we need to know how to dose adjust, if required, based on patient-specific characteristics

Usually however, it is slightly more complicated than just dose.....

Dose is just a **means** to reach adequate (effective) concentrations / concentration profiles

Establish Exposure-Response Relationships

Unravelling the relationship between dose and response



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Establish Exposure-Response Relationships

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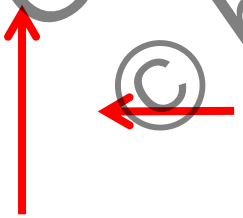


Optimal exposure

Pharmacodynamic target

Establish Exposure-Response Relationships

Pharmacodynamic Target

The exposure required for the desired effect

SETTING A BREAKPOINT

DETERMINE DOSE-RESPONSE RELATIONSHIP

↓

DETERMINE BREAKPOINT (dosedependent)

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

↓

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

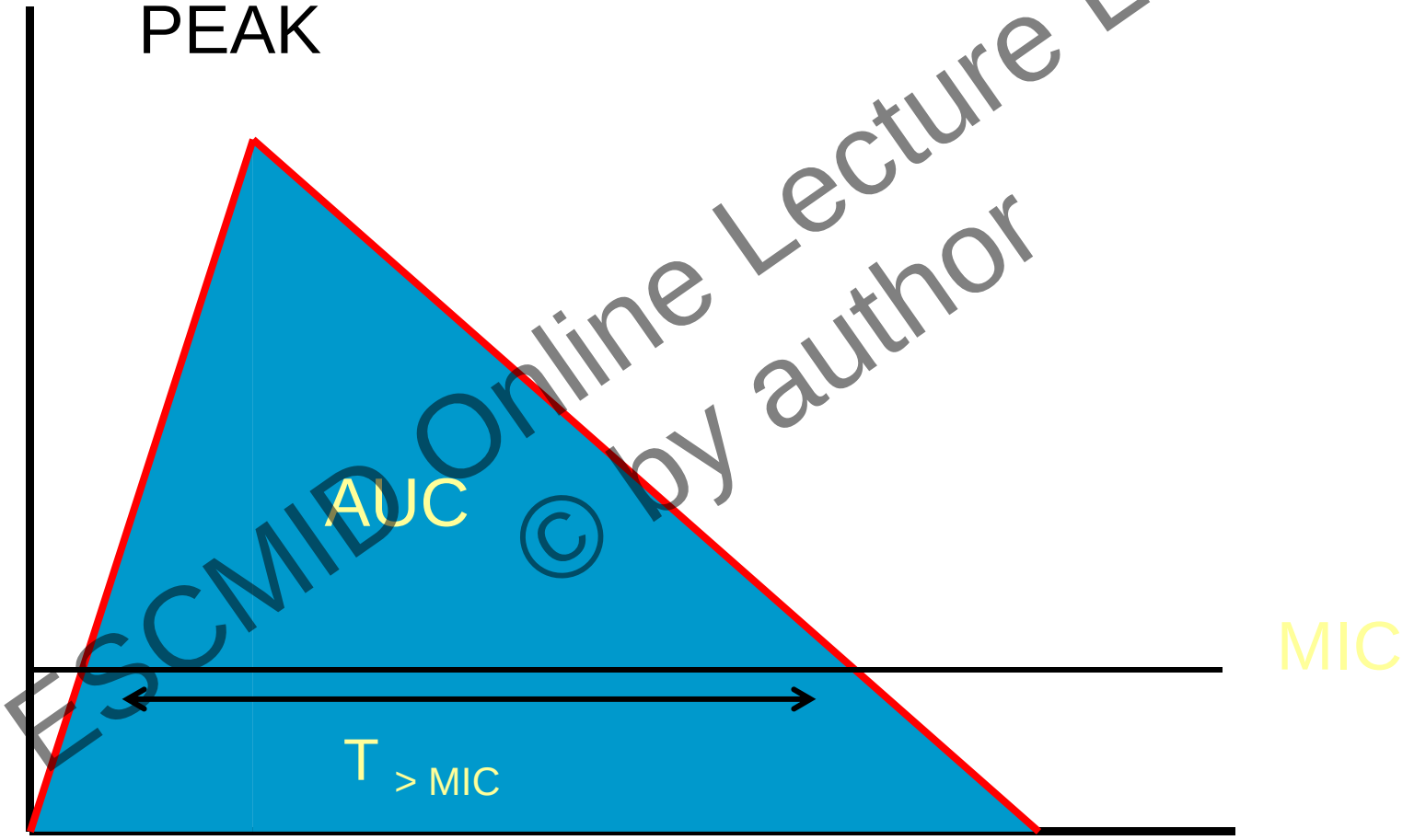
SETTING A BREAKPOINT

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

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

Pharmacokinetic parameters : Measures of Exposure



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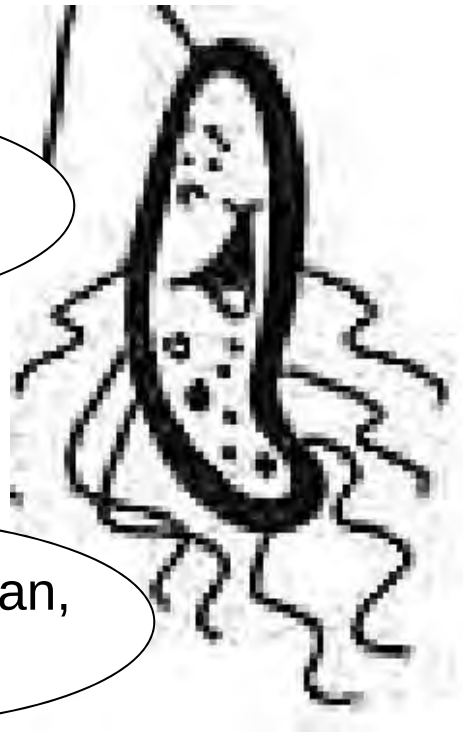
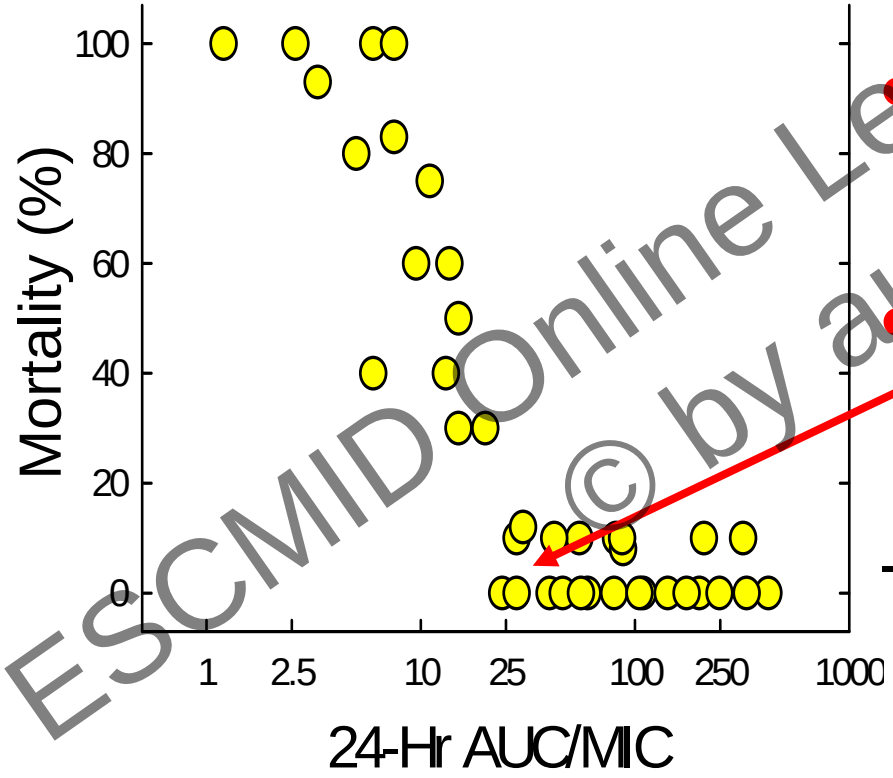
Any idea where we are today?

No idea…
may be a mouse?



Might be a human,
though…

Relationships Between 24-Hr *f*AUC/MIC and Efficacy against Pneumococci for Fluoroquinolones in Animals

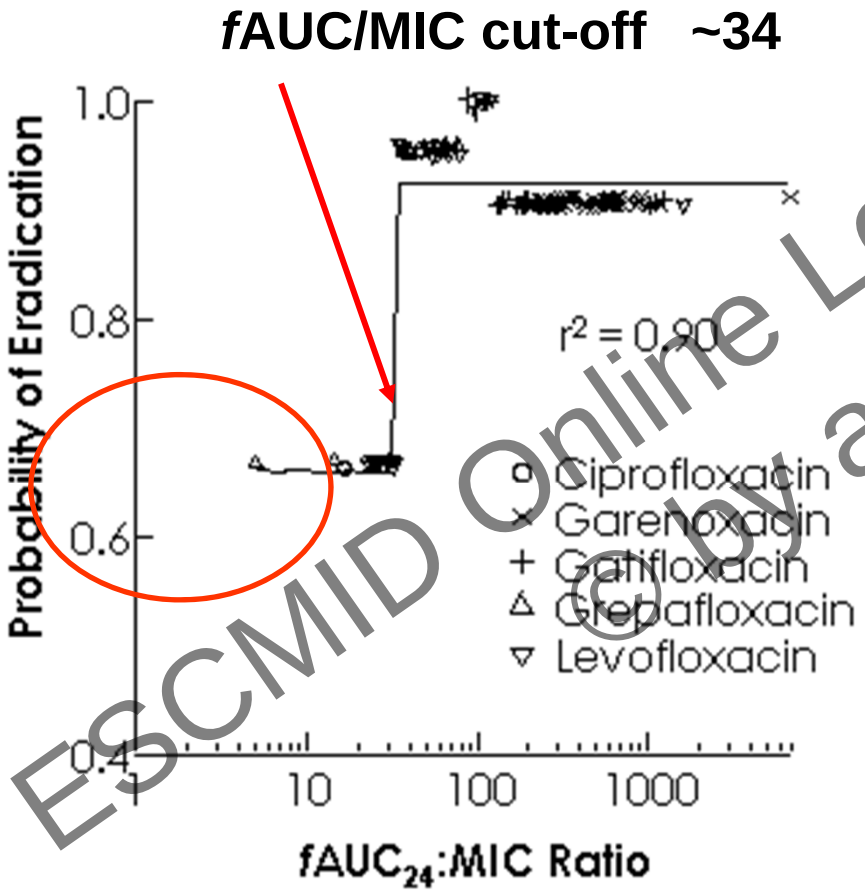


- A clear relationship exists between exposure and effect
- A maximum effect is reached at ratio's of 25-35 (mortality)
- The pharmacodynamic target

Each data point represents the proportion of mice cured within a group representing a certain AUC/MIC value

Andes & Craig, Int J of Antimicrob Agents 19:259, 2002

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.

Pharmacodynamic targets

- ***Animal models***
- ***In vitro models (Hollow fiber)***
- ***Time kill curves and modelling***

The Target should Reflect the Indication

SETTING A BREAKPOINT

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

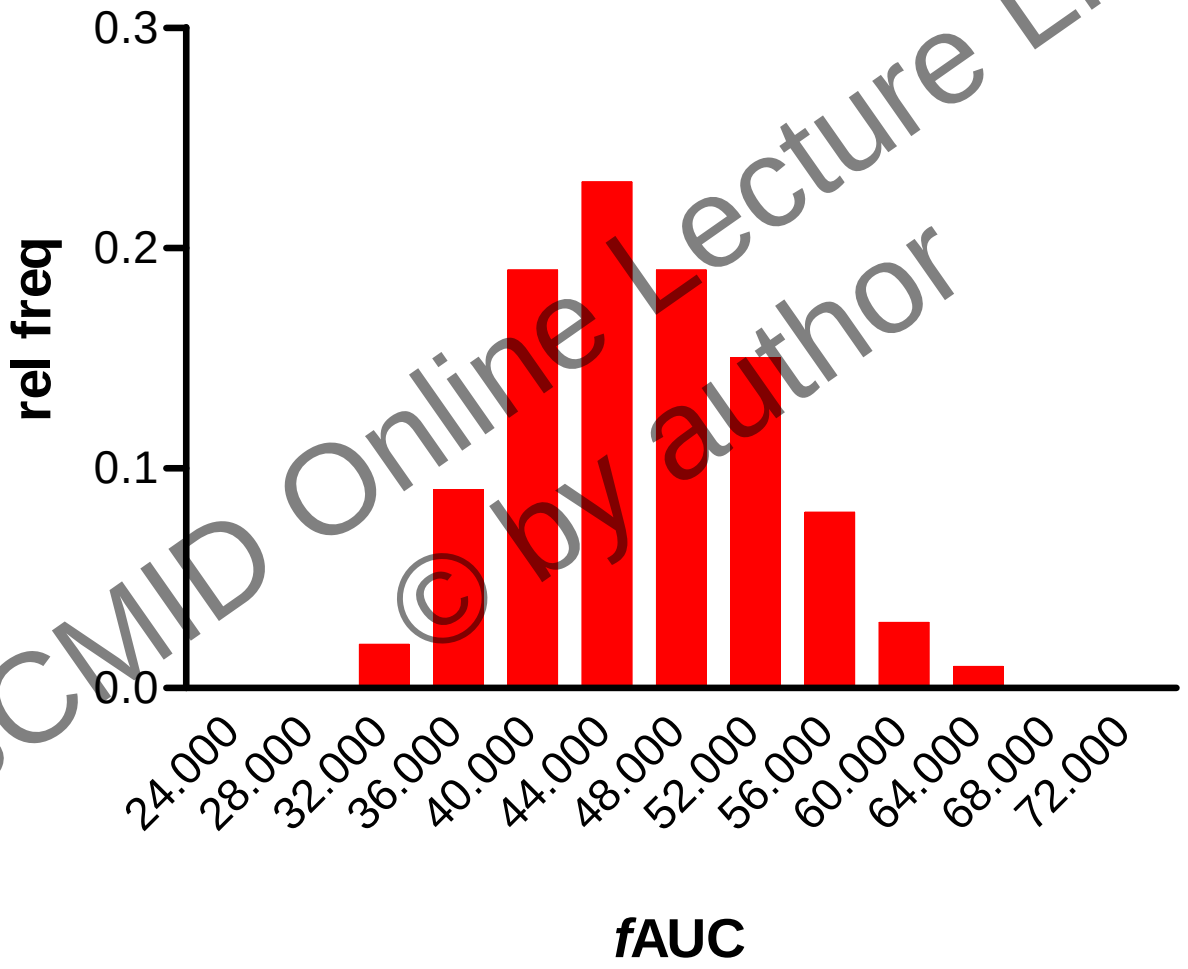
DETERMINE PK/PD BREAKPOINT from *PK/PD target = PK/PD Index*

Pharmacokinetics

Some people are more equal than others…

fAUC distribution levofloxacin

(monte carlo simulation)



fAUC distribution levofloxacin

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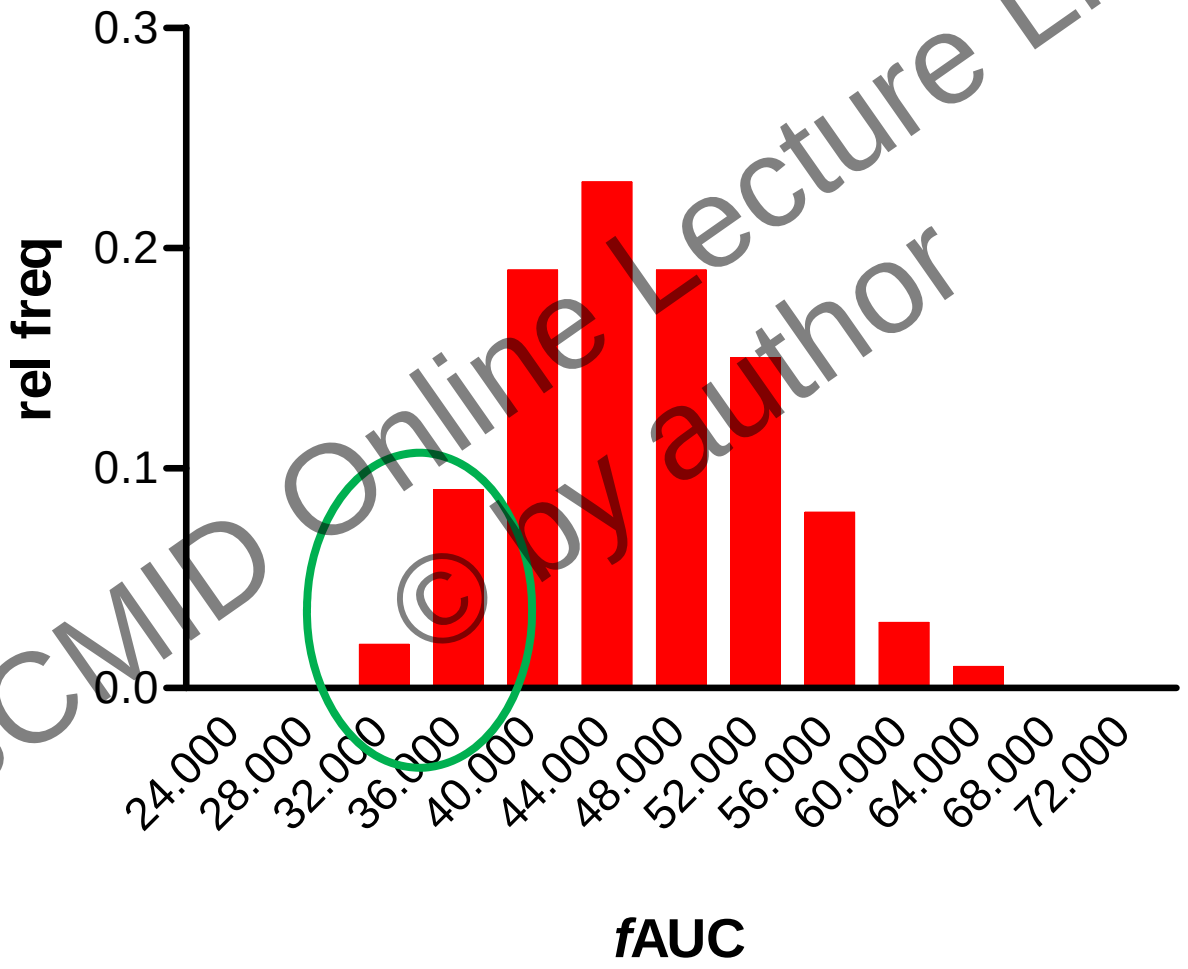

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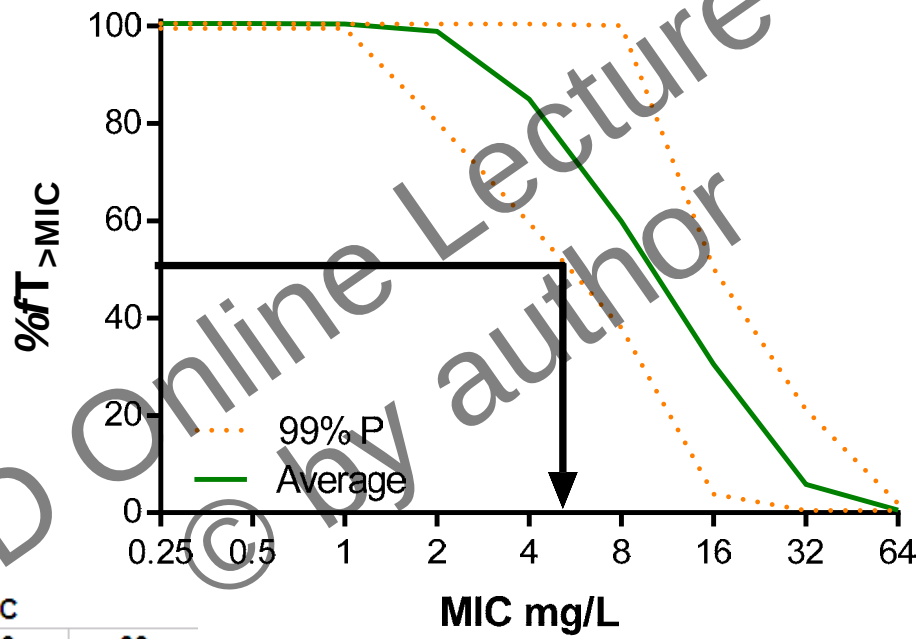
PTA of ceftazidime, volunteers 1000 mg q8h



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

Mouton et al, Clin Ther 2005 27:762; EUCAST rationale document

Population modelling and Monte Carlo simulations

- ***Purpose of population modelling***
  - Try to capture all variation as much as possible in a set of pharmacokinetic parameters
  - Explain and predict concentrations in individual patients
    - Sparse sampling
    - Co-variates

- ***Purpose of MCS (using a population model) in breakpoint setting***
  - try to predict the future using parameter estimates and its variation to capture the variation in the population to be treated – and derive the clinical breakpoint

Purpose of population modelling and monte carlo simulations

- ***Purpose of population modelling***
  - Try to capture all variation as much as possible in a set of parameters
  - Predict concentrations in individual patients
    - Sparse sampling
    - Co-variates

- ***Purpose of MCS in breakpoint setting***
  - try to predict the future using poppk parameter estimates and its variation to capture the variation in the population to be treated

Problem : MCS is used using POPPK developed for another purpose
And therefore 'true' variation may be underestimated

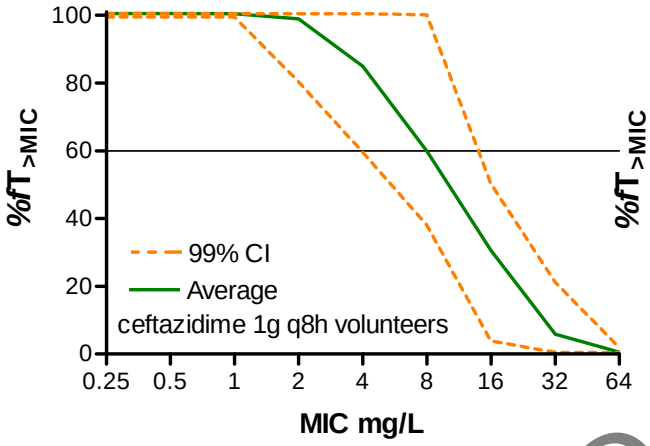
Specific issues

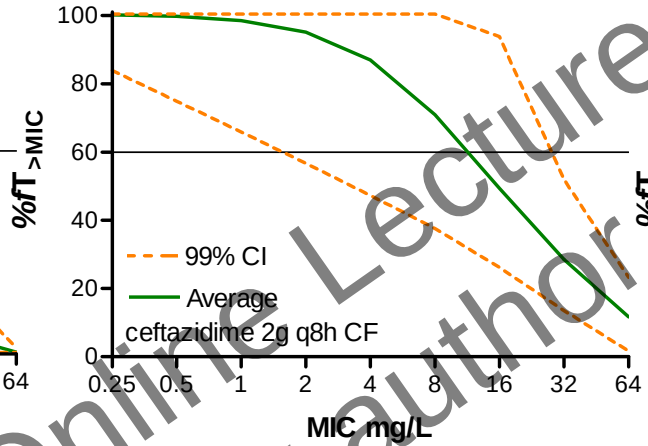
1

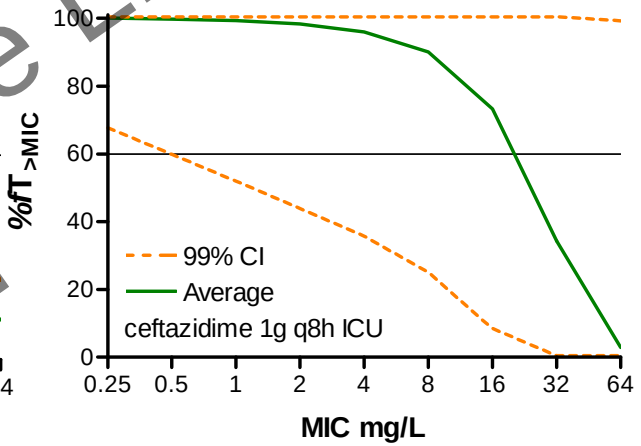
- Different populations will yield different models
  - Parameter estimates
  - Variation

- Different simulations

Different Models.....different simulations
ceftazidime







Volunteers

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

CF patients

% 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

ICU patients

% 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

Specific issues

- The variation present in the population will determine the outcome of the MCS

- More variation : wider confidence interval

- Which range of covavariates to include to build the model? Or sims with different covariate values?
  - 50-150 crcl? Or 20-200? Or 80 -120?
  - 50-100 kg? Or 120?
  - Older patients? Younger patients?

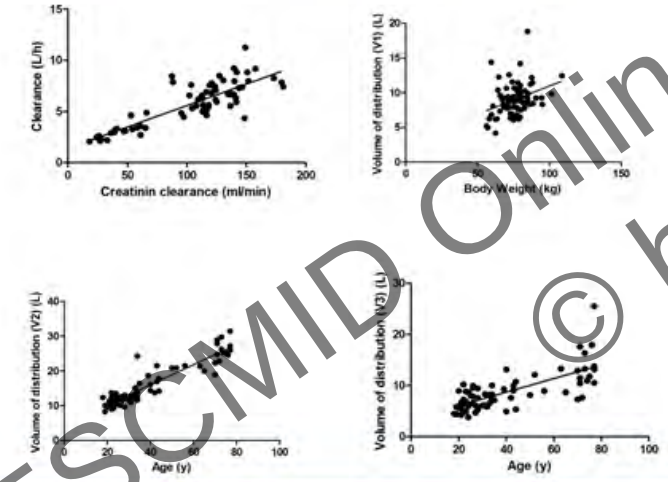
Should represent the population to be treated

2

POPPK model of POL7080 including covariates

	Mean	Range
Age (y)	39.4	18-77
Weight (kg)	76.1	56.4-108.8
BMI (kg/m2)	25.0	19.6-34.9
Creatinine clearance (ml/min)	103.2	18-181.0
Sex (male/female)	62/11	

Table 1. Characteristics of the study-population of 52 volunteers and 21 patients with renal impairment



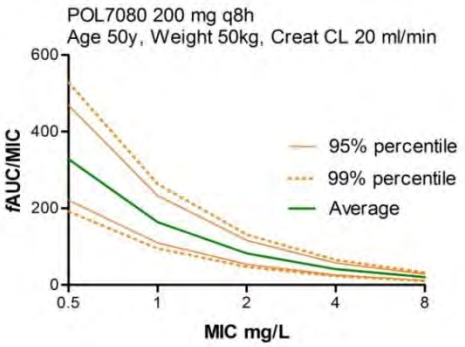
Parameter estimate	Formula
CL	CL=1.377+(0.04197 x Creatinine clearance)
V1	V1= 2.842 + (0.08112 x Body Weight)
V2	V2= 4.467 + (0.2892 x Age)
V3	V3= 3.399 + (0.1329 x Age)

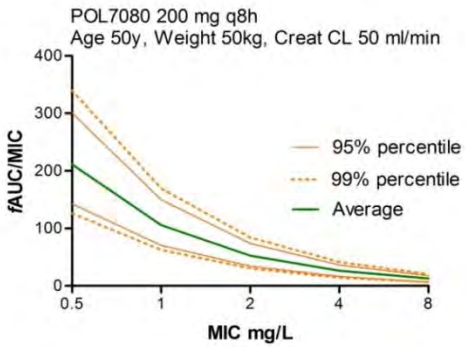
Figure 1. Relationship between covariate and parameter estimate in the model as well as the equations.

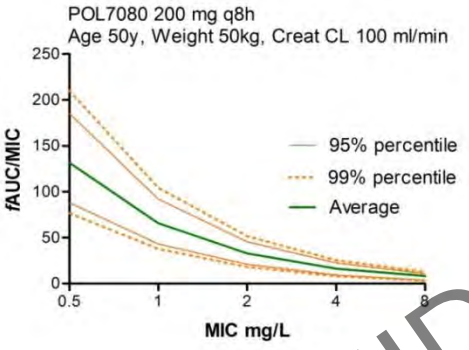
	Value		
Parameter	Mean	SE	Relative SE (%SE)
Θ1: Clearance (liters/h)[a]	5.62	0.139	2.47
Θ2: Volume of distribution 1 (liters)[a]	8.82	0.487	5.52
Θ3: Volume of distribution 2 (liters)	15.8	0.858	5.43
Θ4: Volume of distribution 3 (liters)	8.31	0.518	6.23
Θ5: Intercompartmental clearance V1 and V2 (liters/h)	2.06	0.184	8.93
Θ6: Intercompartmental clearance V1 and V3 (liters/h)	7.86	0.981	12.5
Θ7: Covariate creatinine clearance on clearance	0.00758	2.38×10^{-4}	3.14
Θ8: Covariate weight on V1	0.0106	0.00369	34.8
Θ9: Covariate age on V2	0.0183	0.00149	8.14
Θ10: Covariate age on V3	0.0145	0.00245	16.9
η1: Variability on clearance	0.0357	0.00798	22.4
η2: Variability on V1	0.0762	0.0246	32.3
η3: Variability on V2	0.032	0.0101	31.6
η4: Variability on V3	0.0998	0.0253	25.4
σ: Residual error, proportional	0.0234	0.00681	29.1

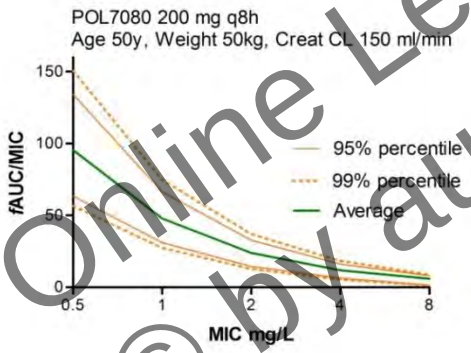
[a] A correlation between clearance and V1 was included in the final model.

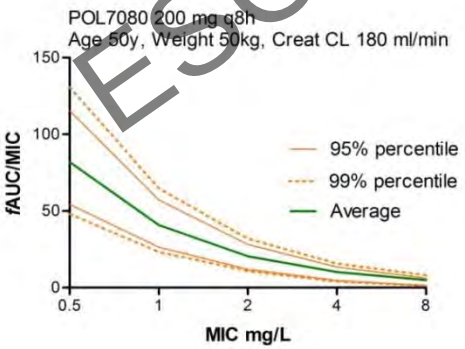
Table 2. Estimates of the final population PK model. The final model consisted of 3 compartments, variability on CL, V1, V2 and V3 and 4 covariates: creatinine clearance on the clearance of POL7080, weight on V1, and age on V2 as well as on V3.









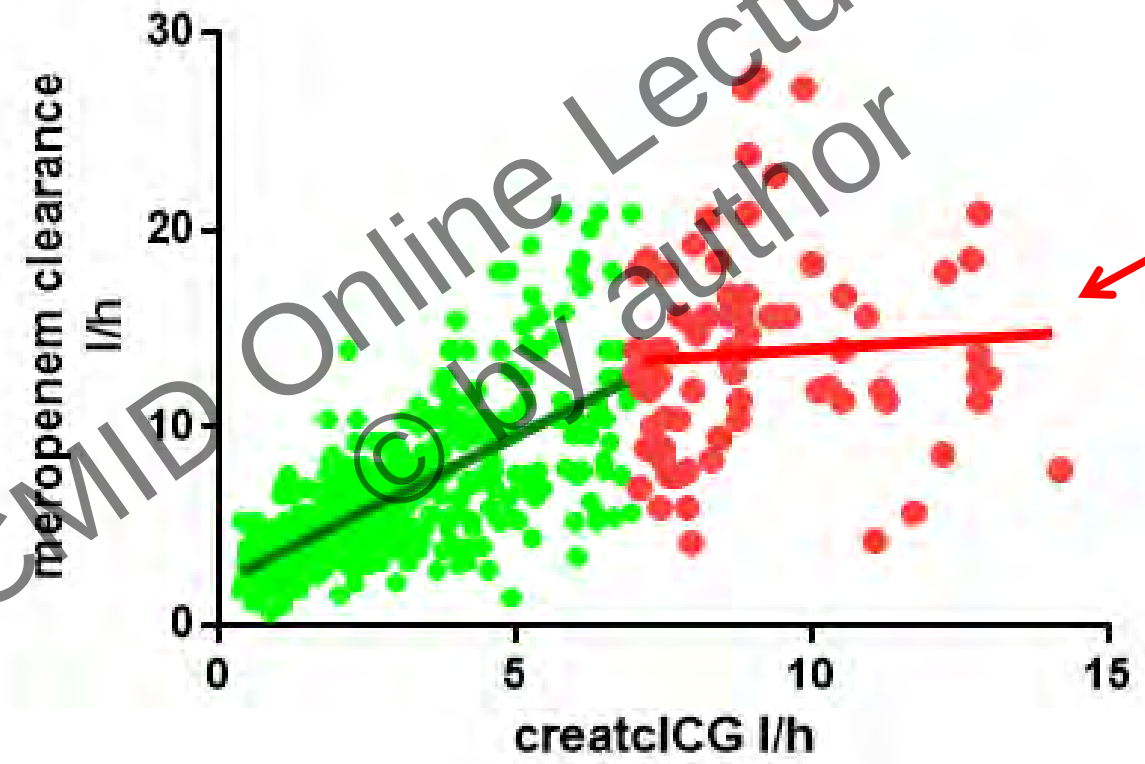


PTA for different creatinin clearances

Model with covariates

Muller et al, ECCMID 2014

Relation between Creatinin Clearance and Meropenem Clearance In 238 Criticall Ill Patients on 557 occacions during Continuous Infusion



Regression=
Not significant

No model assumptions

Rohr et al., ECCMID 2015

Specific issues

- Should covariates be build in the model when simulating?
  - Purpose of MCS is *not* knowing the covariate values!!

- More variation : wider confidence interval

3

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- ***Purpose of population modelling***
  - Try to capture all variation as much as possible in a set of parameters
  - Predict concentrations in individual patients
    - Sparse sampling
    - Co-variates

- ***Purpose of MCS in breakpoint setting***
  - try to predict the future using parameter estimates and its variation to capture the variation in the population to be treated

- ***What is acceptable without over- or underestimating***?

What do we need after modelling?

Judgement, informed decision making

What do we need after modelling?

- ***Judgement is a human task taking into account all the information available and weighing the risks and benefits***
  - Dosing regimens : efficacy, toxicity
  - How much predicted failure is accepted? 1, 5, 10%?
  - How can risks be minimized by finetuning methods and assumptions?
  - How can variation in the population be captured in the PTA

- ***Every simulation is just a part of a chain – decision making is an iterative process. If new information becomes available, it should be used.***

What do we need during development ?

- ***Based on pkpd, determine optimal dosing based on the clinical indication and micro-organisms expected using the iterative process***
- ***Determine the risks and benefits of specific circumstances and patients***
- ***Optimal dosing will provide the clinical breakpoint***
- ***In the end during and after, determine the factors that allow individualized (personalized) treatment***

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

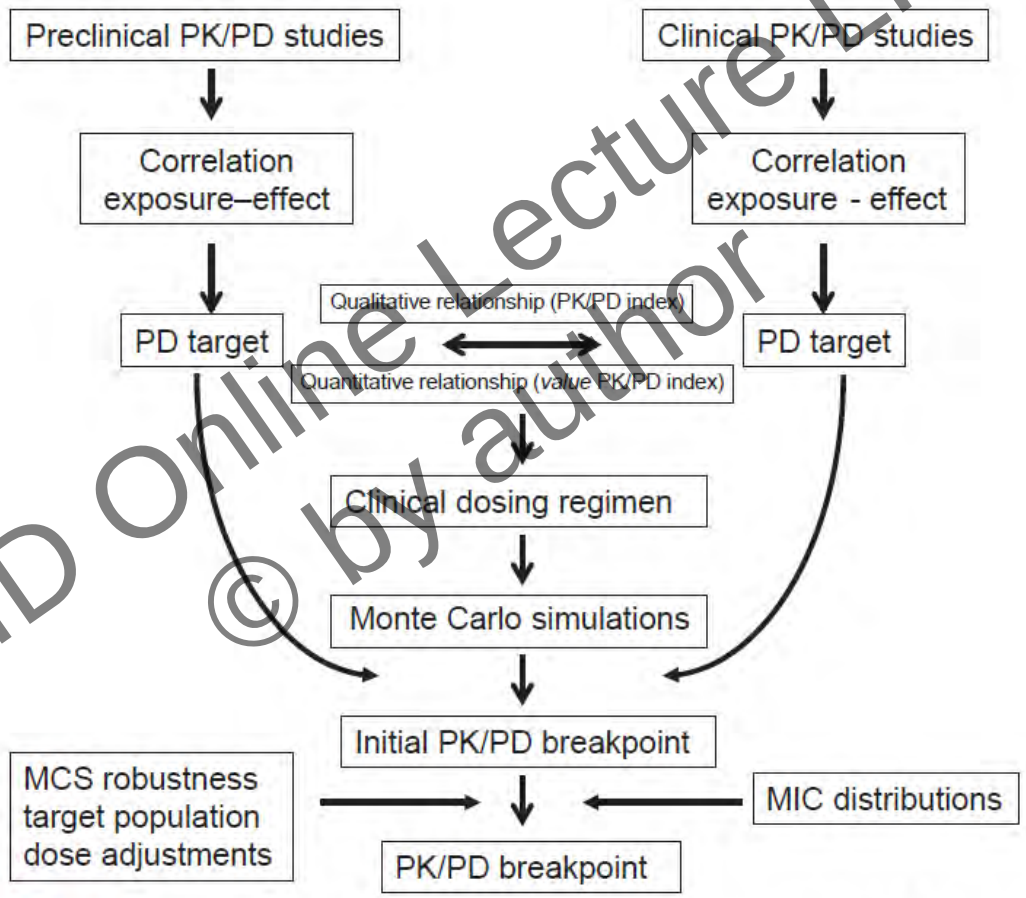

FIG. 7. Summary of the process of setting pharmacokinetic/pharmacodynamic (PK/PD) breakpoints by EUCAST.

Mouton et al, CMI 2012

Conclusions

- PKPD is useful to define clinical breakpoints but consider:
  - The variation in pharmacodynamic targets
  - The population of interest should reflect the population modelled
  - The inclusion of covariates should be considered carefully

- It would be more useful to determine the PTA for different values and combinations of covariates (in particular renal clearance) to draw overall conclusions instead of just one model

- Acceptable PTA ‘s are relative

- Clinical breakpoints do not cover all eventualities but provide general recommendations. Dose adjustment is always required by the clinician in specific circumstances to compensate for exceptional circumastances (covariate values).