Estimating Probability of Target Attainment

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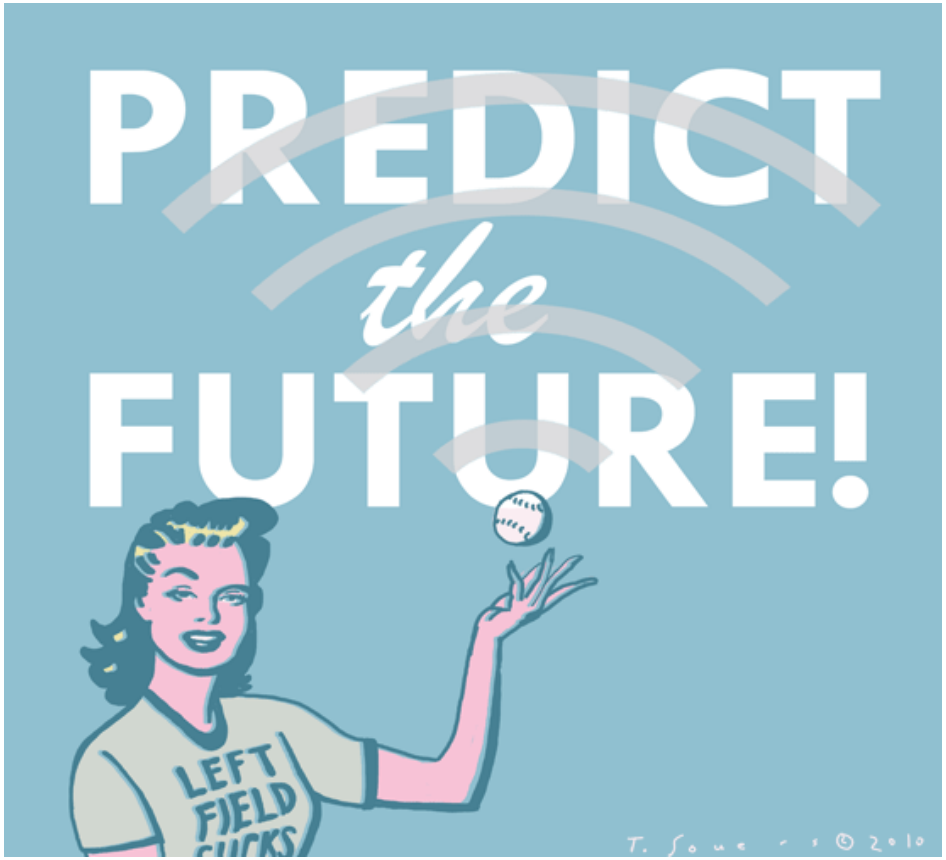
Estimating Probability of Target Attainment



Purpose of estimating PTA

- ***Helps in informed decision making***
  - On a population level:
    - optimized dosing regimens for registration
    - clinical breakpoints
  - On a patient level
    - optimizing individual dosing regimens

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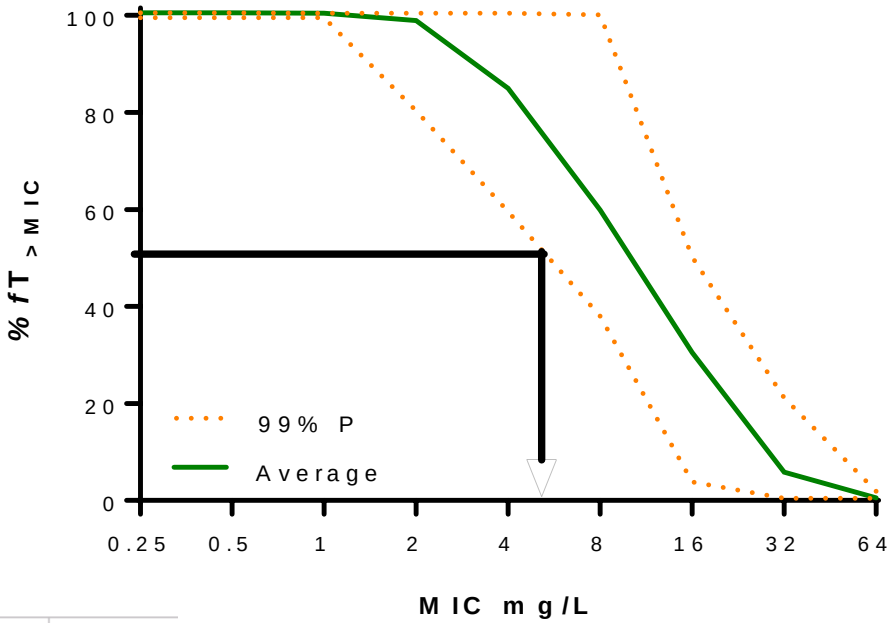
  - On a patient level
    - optimizing individual dosing regimens (**the real future**)

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

What do we need before PTA?

- ***A Pharmacodynamic Target (PT)***
  - Obtained from in vitro and in vivo studies
  - A point estimate of the target (e.g. 50% *f*T>MIC)
    - The target may depend on the disease/infection
    - The target may depend on the species
  - Validation in a patient trial (another presentation….)

- ***A (population pk) model that represents the population to be treated (to use in monte carlo sims, MCS)***
  - Populations may vary ……
  - Population models may vary…..

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 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

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

General procedure poppk

Explore different basic models
(1C, 2C, 3C etc.)

↓

Explore whether and which parameters have variation that can improve the model (e.g. eta's in nonmem)

↓

Explore whether and wich covariates can improve the (predictive performance of) the model (creatinin, weight, age)

↓

Validate model (e.g. bootstraps, NPDE, VPC)

↓

Final model that best describes the data

Population and individual predictions ceftobiprole

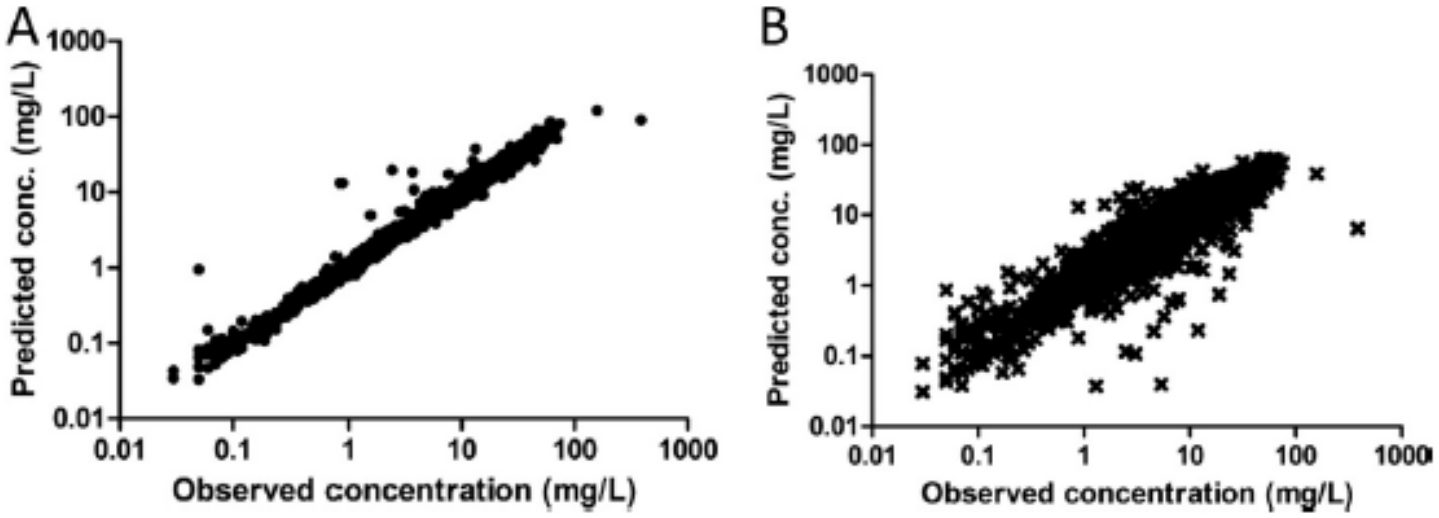

FIG 1 Individual (A) and population (B) predicted versus observed concentrations (conc.) of ceftobiprole in 171 patients.

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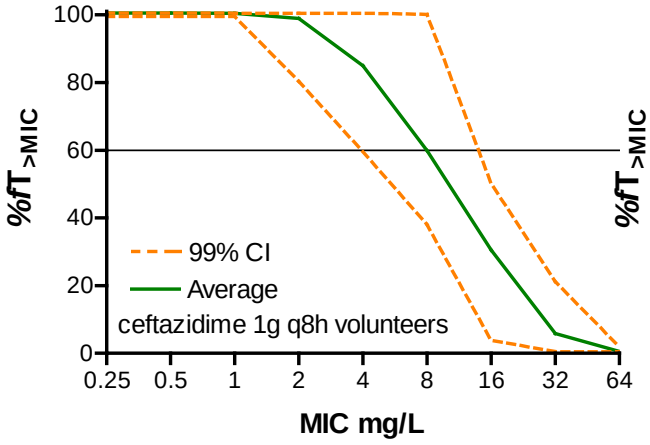
Three issues

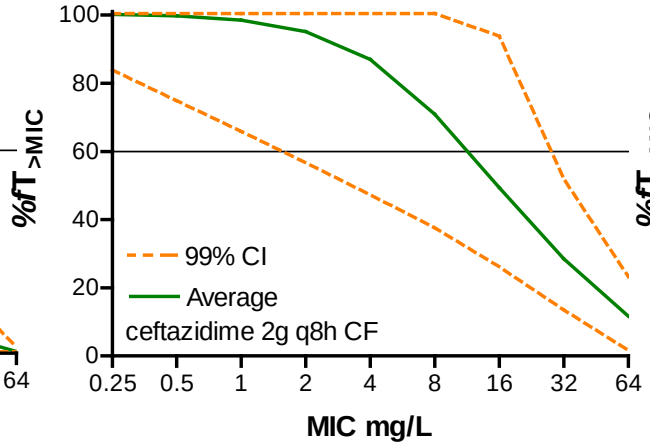
1

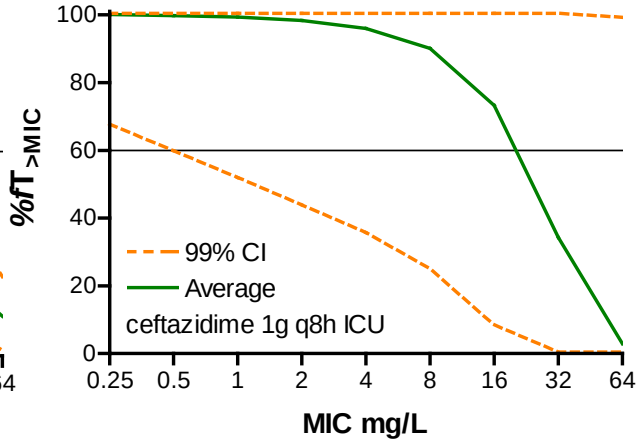
- Different populations will yield different models
  - Parameter estimates
  - Variation

- Different simulations

Different Models.....different simulations
ceftazidime







Volunteers

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(mg/L)	30	40	50	60
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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

Three issues

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

↓

- More variation : wider confidence interval

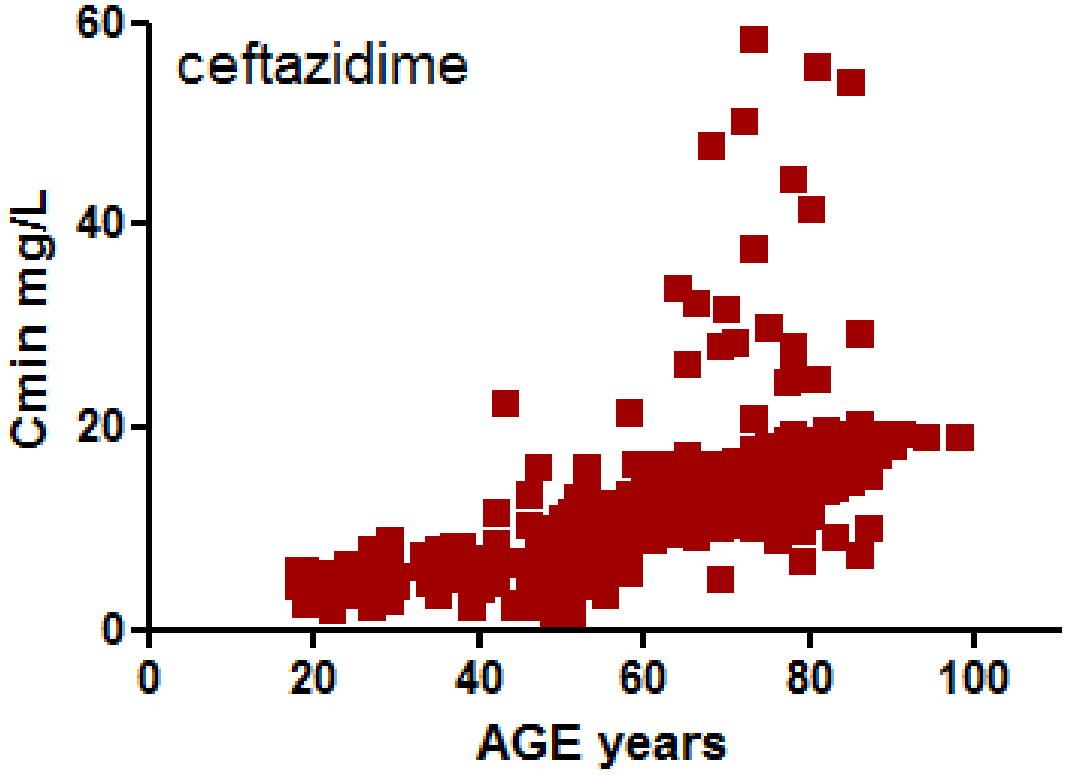
↓

- 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

Ceftazidime Cmins, 3x2 gr

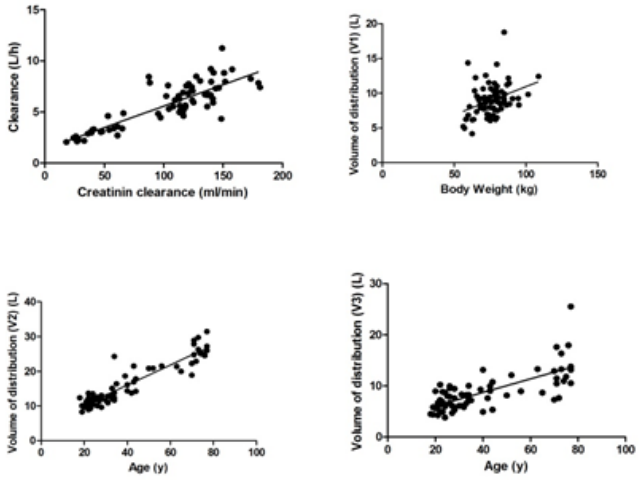


Mouton & Muller Unpublished data

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



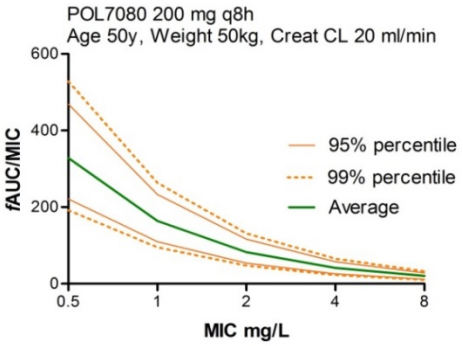
Parameter estimate	Formula
CL	CL=1.377+(0.04197 x Creatinine clearance)
V1	V1= 2.842 + (0.08112 x Body Weight)
V2	V2= 4.467 + (0.2892 x Age)
V3	V3= 3.399 + (0.1329 x Age)

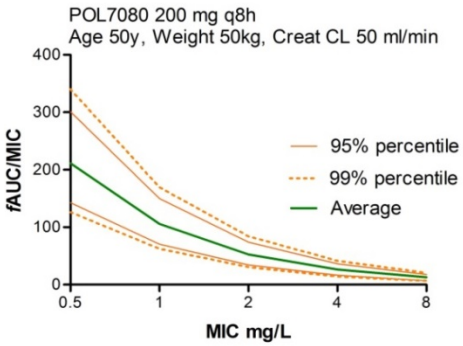
Figure 1. Relationship between covariate and parameter estimate in the model as well as the equations.

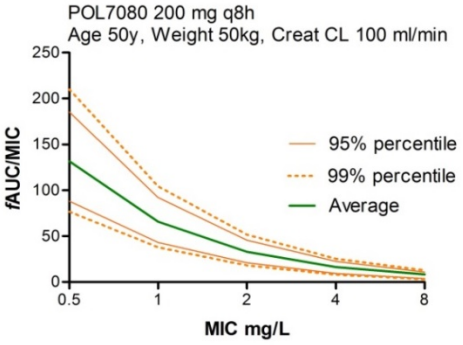
	Value		
Parameter	Mean	SE	Relative SE (%SE)
Θ1: Clearance (liters/h)[a]	5.62	0.139	2.47
Θ2: Volume of distribution 1 (liters)[a]	8.82	0.487	5.52
Θ3: Volume of distribution 2 (liters)	15.8	0.858	5.43
Θ4: Volume of distribution 3 (liters)	8.31	0.518	6.23
Θ5: Intercompartmental clearance V1 and V2 (liters/h)	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: Variabillity on clearance	0.0357	0.00798	22.4
η2: Variabillity on V1	0.0762	0.0246	32.3
η3: Variabillity on V2	0.032	0.0101	31.6
η4: Variabillity on V3	0.0998	0.0253	25.4
σ: Residual error, proportional	0.0234	0.00681	29.1

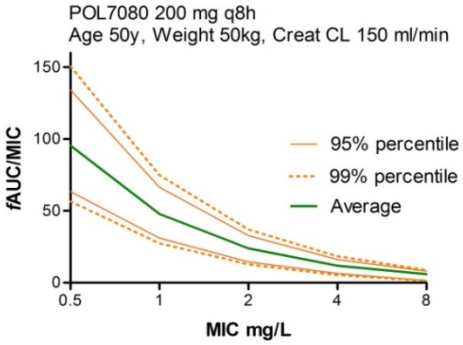
[a] A correlation between clearance and V1 was included in the final model.

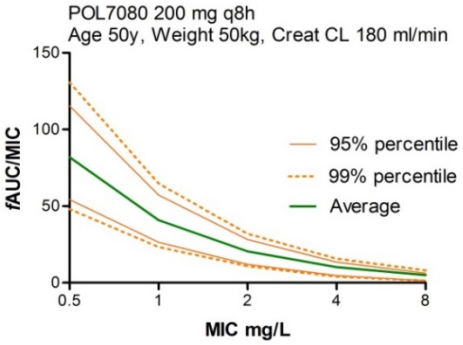
Table 2. Estimates of the final population PK model. The final model consisted of 3 compartments, variability on CL, V1, V2 and V3 and 4 covariates: creatinine clearance on the clearance of POL7080, weight on V1, and age on V2 as well as on V3.











PTA for different creatinin clearances

Model with covariates

Muller et al, ECCMID 2014

Three issues

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

3

- More variation : wider confidence interval

POPPK of Ceftobiprole

Parameter	Value [mean (range)][a]
	Patients included in PK model
No. of patients	171
Age (yr)	51.5 (17–92)
Sex (no. male/female)	121/50
Wt (kg)	73.6 (40–115); $n = 170$
Body mass index	25.0 (15.6–41.4); $n = 169$
Creatinine clearance	110.4 (11.8–612.1)
SIRS[b] (no. yes/no)	49/122
VAP (no. yes/no)	67/104
APACHE II score (range)	14.5 (8–24); $n = 79$)

Muller et al, 2013 AAC, 57(5):2047

TABLE 3 Final results of the PK model in patients

Parameter	Value		
	Mean	SE	Relative SE (SE%)
Clearance (liters/h)[a]	4.74	0.24	5.06
Vol of distribution 1 (liters)[a]	15.5	1.26	8.13
Vol of distribution 2 (liters)	1.93	0.34	17.6
Vol of distribution 3 (liters)	3.76	1.18	31.4
V_{ss} (liters)[b]	21.2		
Intercompartmental clearance V_1 and V_2 (liter/h)	0.372	0.108	29
Intercompartmental clearance V_1 and V_3 (liters/h)	3.05	1.83	60
Covariate creatinine clearance on clearance	0.00518	0.0011	21.2
Covariate age on vol of distribution 1	0.0117	0.00153	31.1
Variability on clearance	0.423	0.233	55.1
Variability on vol of distribution 1	0.478	0.179	37.4
Residual error, proportional	0.0288	0.00599	20.8
Residual error, additive (mg/liter)	2.31×10^{-4}	4.09×10^{-4}	177

[a] A correlation between clearance and volume of distribution 1 was included in the final model.
[b] The volume of distribution at steady state (V_{ss}) was calculated.

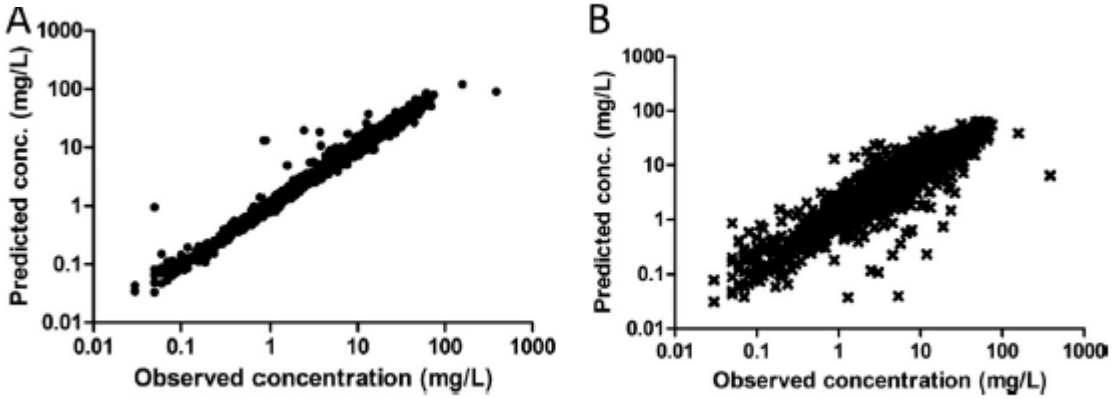
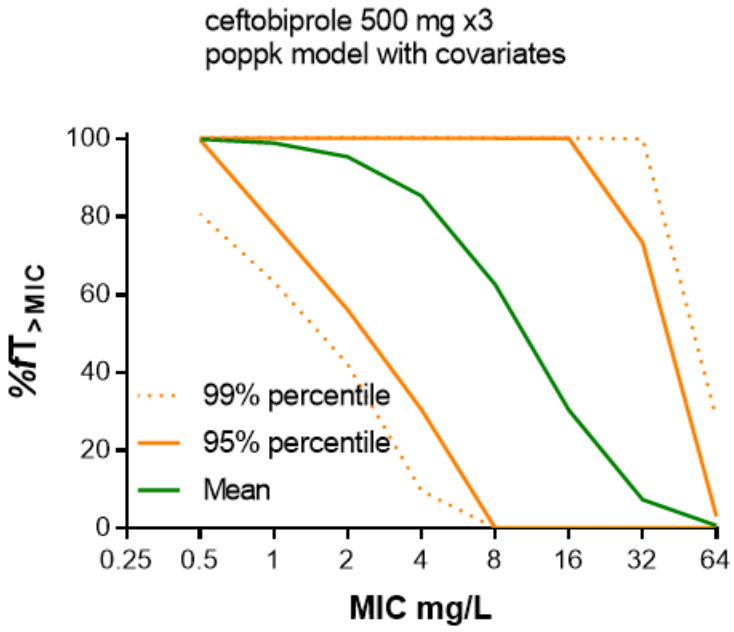
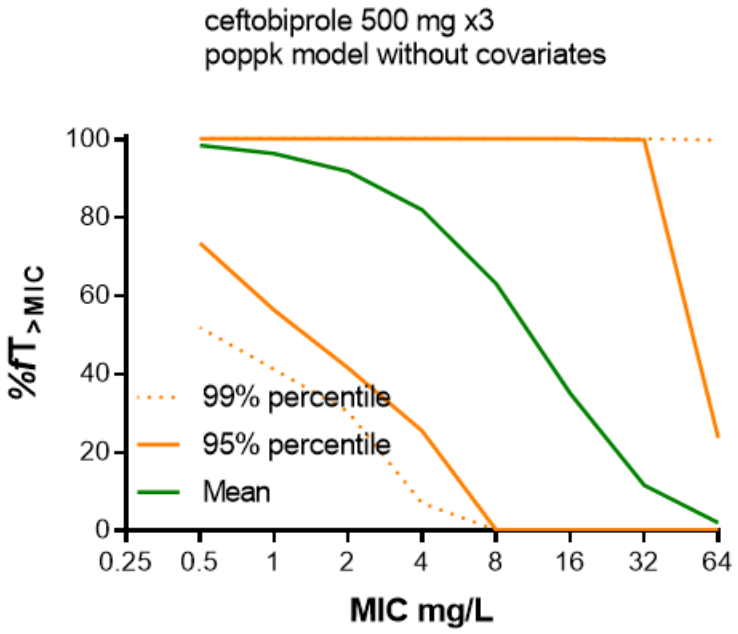


FIG 1 Individual (A) and population (B) predicted versus observed concentrations (conc.) of ceftobiprole in 171 patients.

MCS using same population with and without covariates





Note : variation large because of large differences in individual patients
Note : typical example of model developed to predict individual exposures possibly overestimating variation

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

What do we need after PTA?

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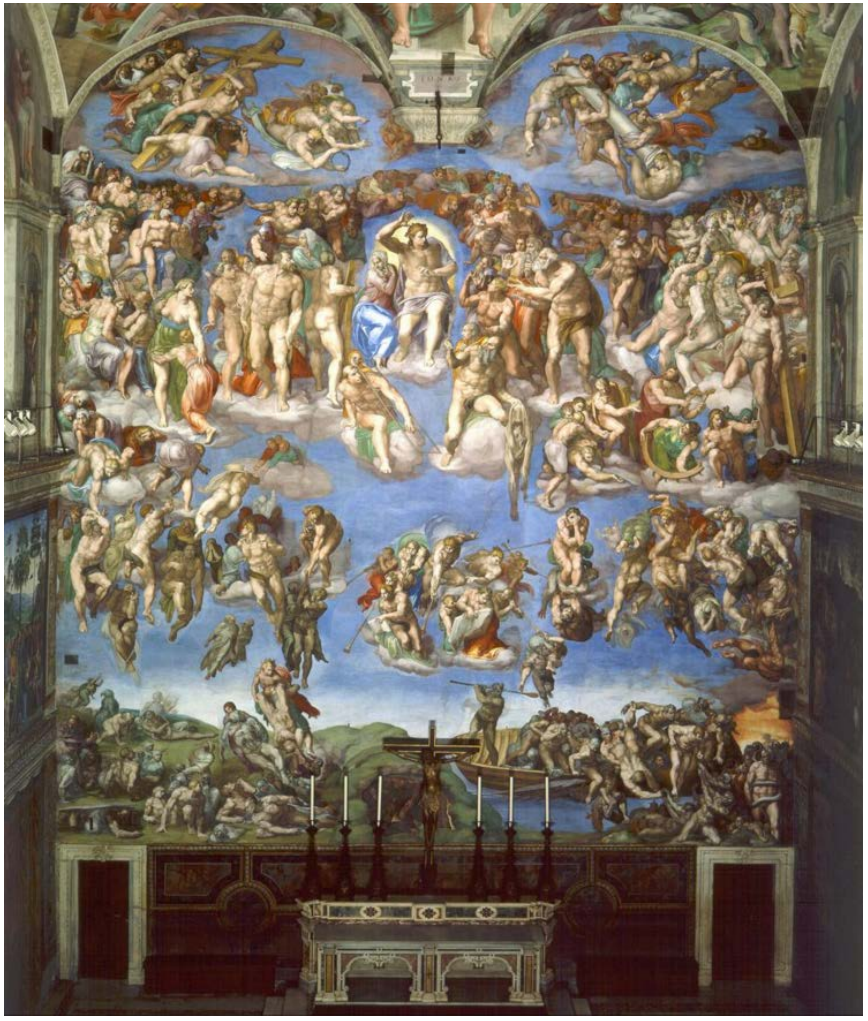

Judgement, informed decision making

What do we need after PTA?

- ***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 PTA 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 PTA, 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***
- ***In the end during and after, determine the factors that allow individualized (personalized) treatment***

Conclusions and recommendations

- PTA is useful to define clinical breakpoints but:
  - 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 should be defined (90? 95? 99%?)

- 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).

- Ideally data will (using Bayesian feedback) provide the framework for personalized dosing

7 major steps For Dosefinding

STEP	ACTION
1	Establish PK/PD index that is correlated with effect of DRUG
2	Establish the pharmacodynamic target of DRUG in animals (mice)
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 handbook pkpd 2014