Exposure - Response

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ACTVITY
***in vitro* (MIC)**

CONCENTRATIONS
***in vivo* (PK)**

DOSING
regimen

ANTMICROBIAL EFFICACY
(*Microbiological Cure*)

Other factors

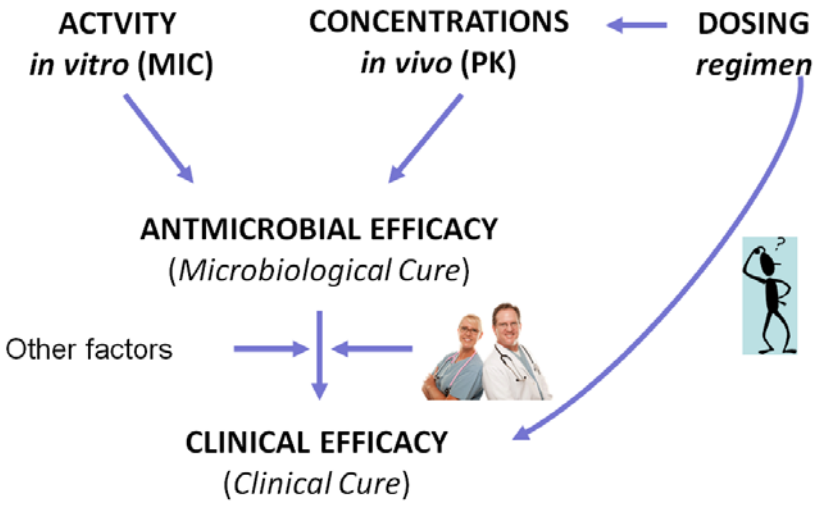
CLINICAL EFFICACY
(*Clinical Cure*)

Mouton et al., *Drug Resistance Updates 2011*

Unravelling the relationship between Dose / exposure and response

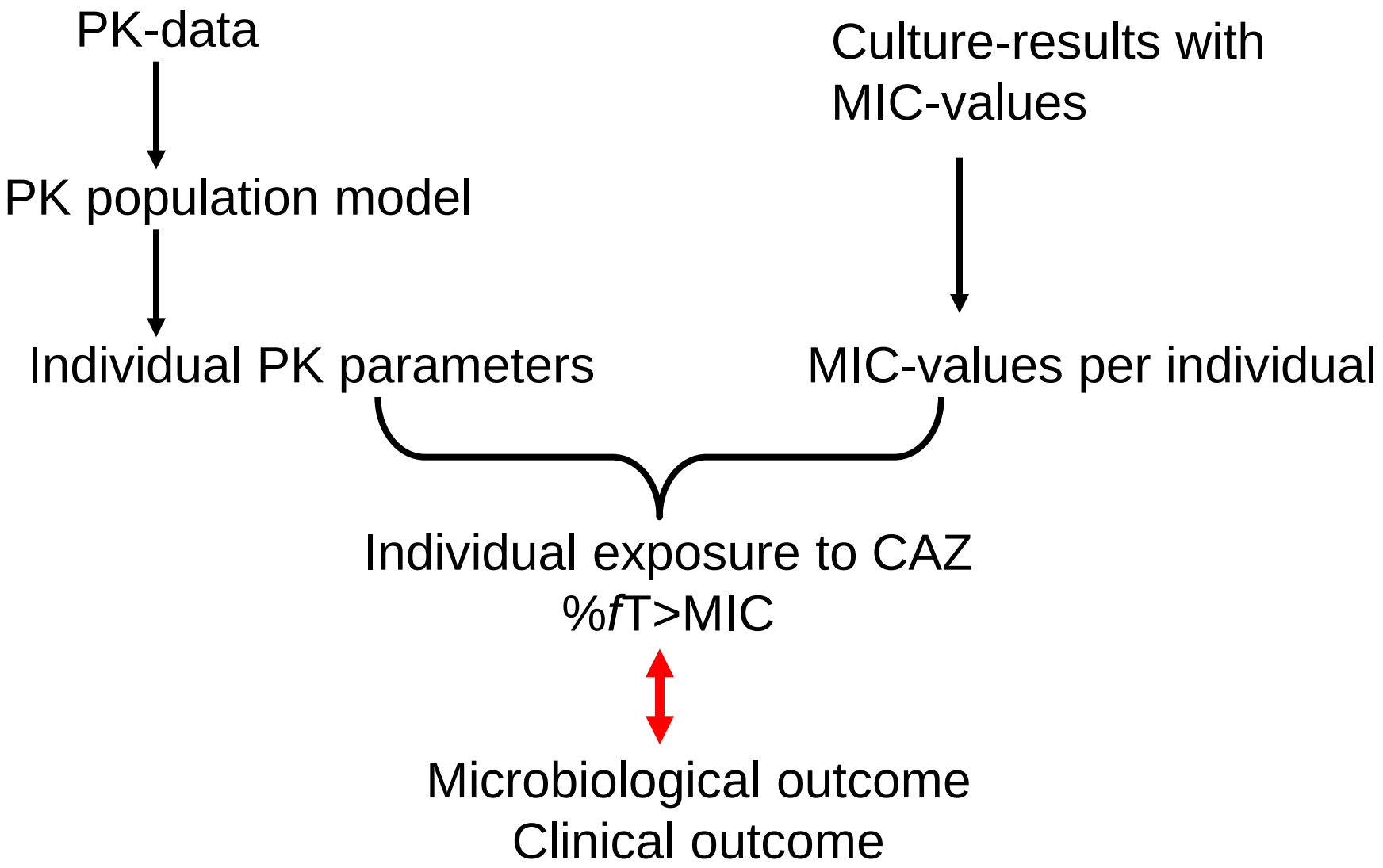
- The challenge is to power the CER study in such a way that the a meaningful answer is derived
- Until recently, individual factors that determined CER were not described adequatedly
- Wrong conclusions were therefore drawn : pk/pd does not matter (!)

Unravelling the relationship between dose and response



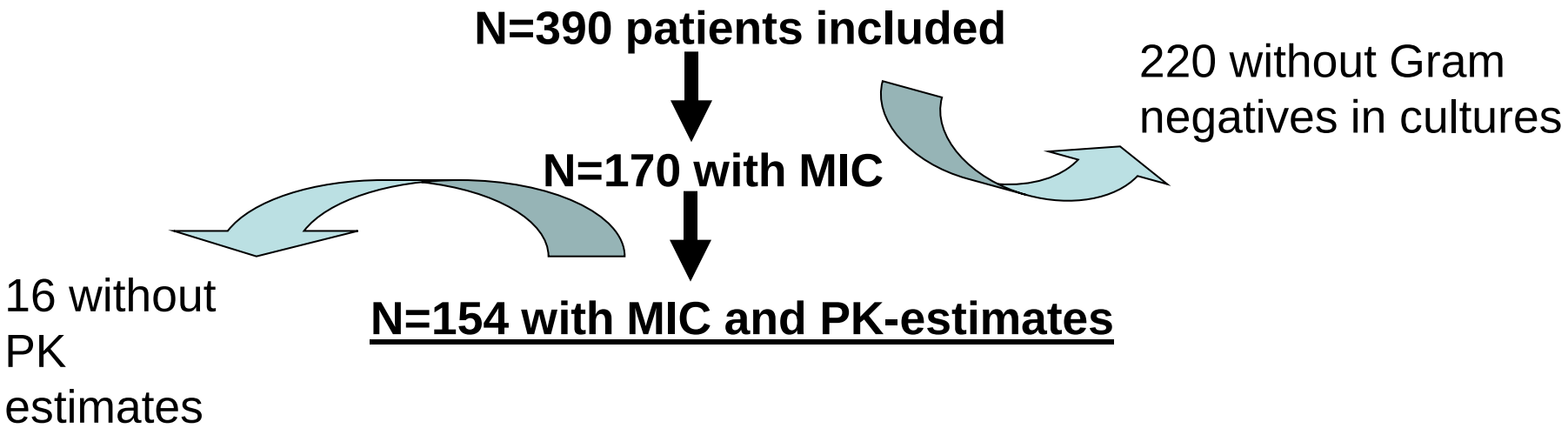
- Measures of exposure
  - Susceptibility, culture, pcr
  - PK in individual patients
- Measures of response
  - Microbiological
  - Clinical
- Covariates

Clinical phase 3 study



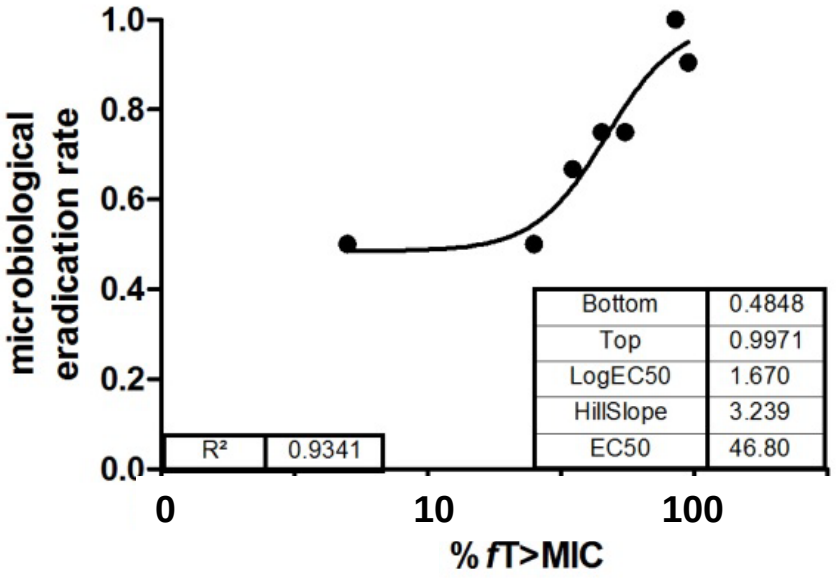
Ceftazidime in patients with nosocomial pneumonia

- 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

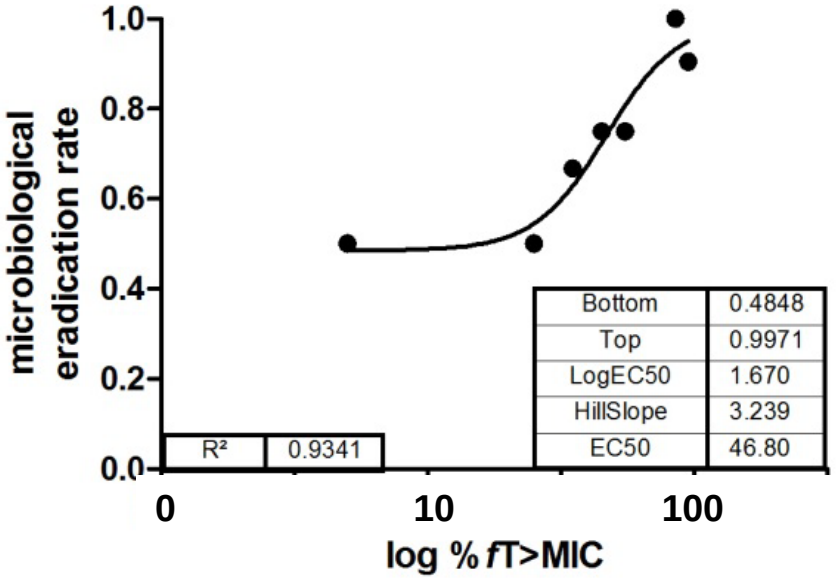
Exposure-response Emax model
microbiological eradication



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

Exposure-response Emax model

microbiological eradication



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CART

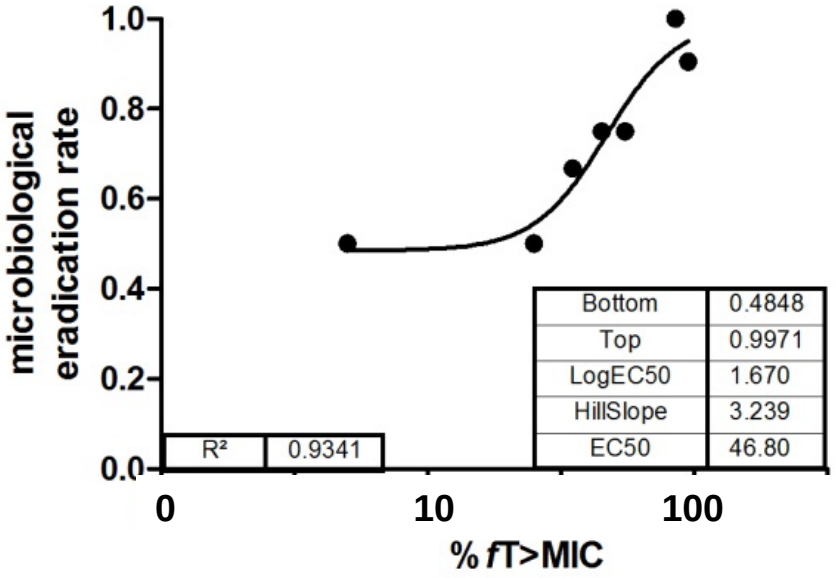
%*f*T>MIC breakpoint = 44.9 %

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

Exposure-response Emax model
microbiological eradication



- Baseline : 50%
- Max response : 99.7%
- Attributed cure : 50%
- ***Probability of cure further increases above the %fT>MIC breakpoint***

CART

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≥44.9	83 (90.2%)	9 (9.8%)
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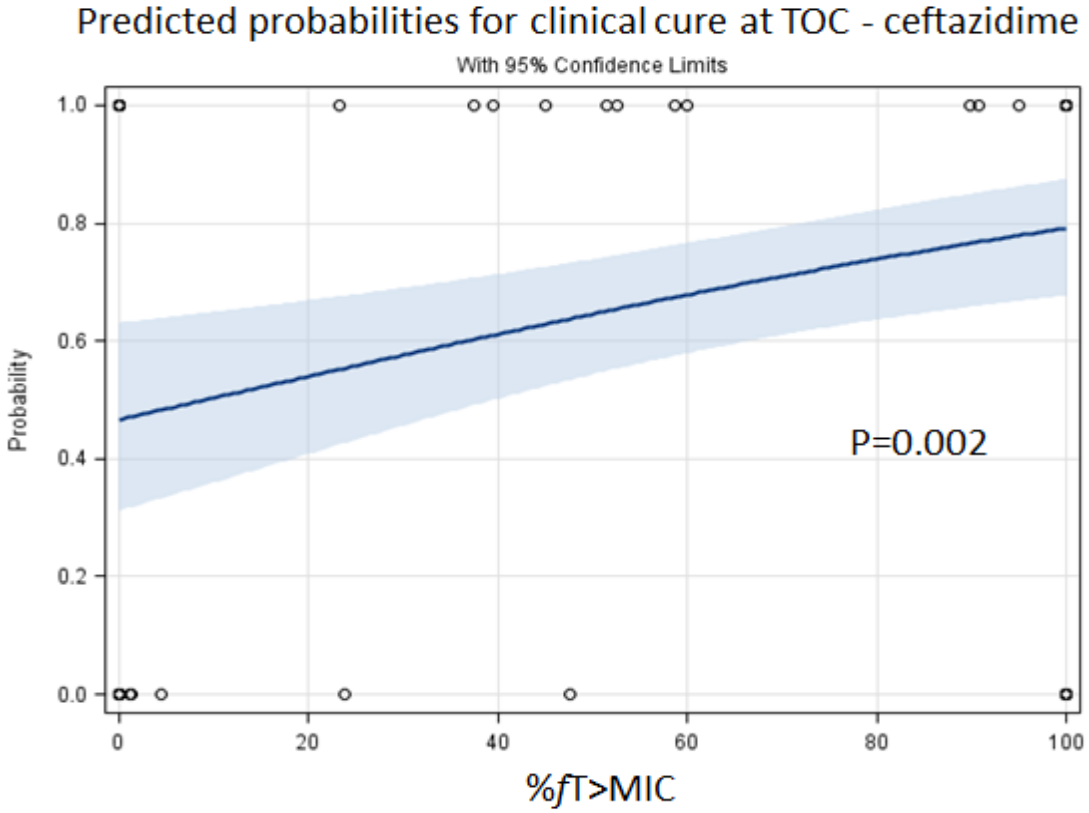
When to measure microbiological eradication?

NOT at TOC – often three/four weeks after stopping therapy!!

EOT?

Probability plot of the logistic regression analysis for ceftazidime showing the relationship between %*f*T>MIC (Gram-negatives at baseline/EOT) and probability of cure at TOC



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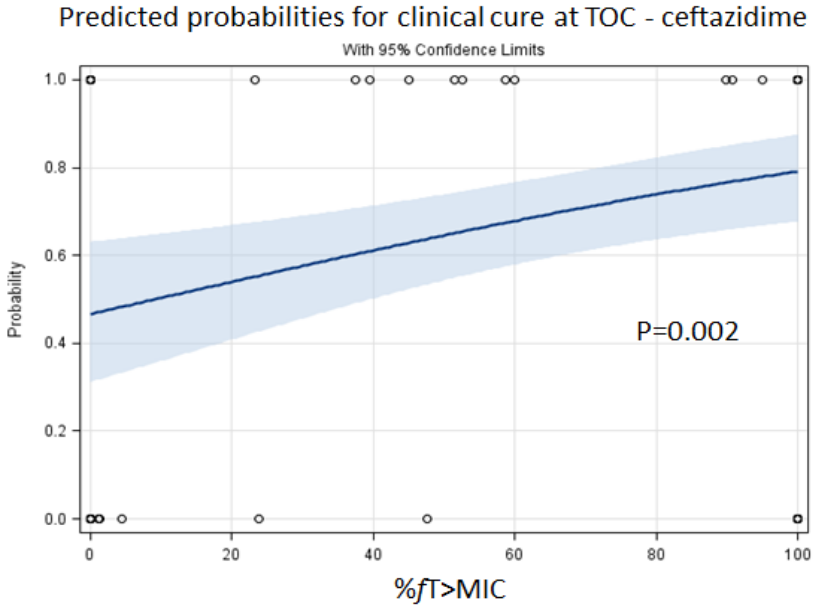


- ***Probability of cure further increases above the %fT>MIC breakpoint***

CART

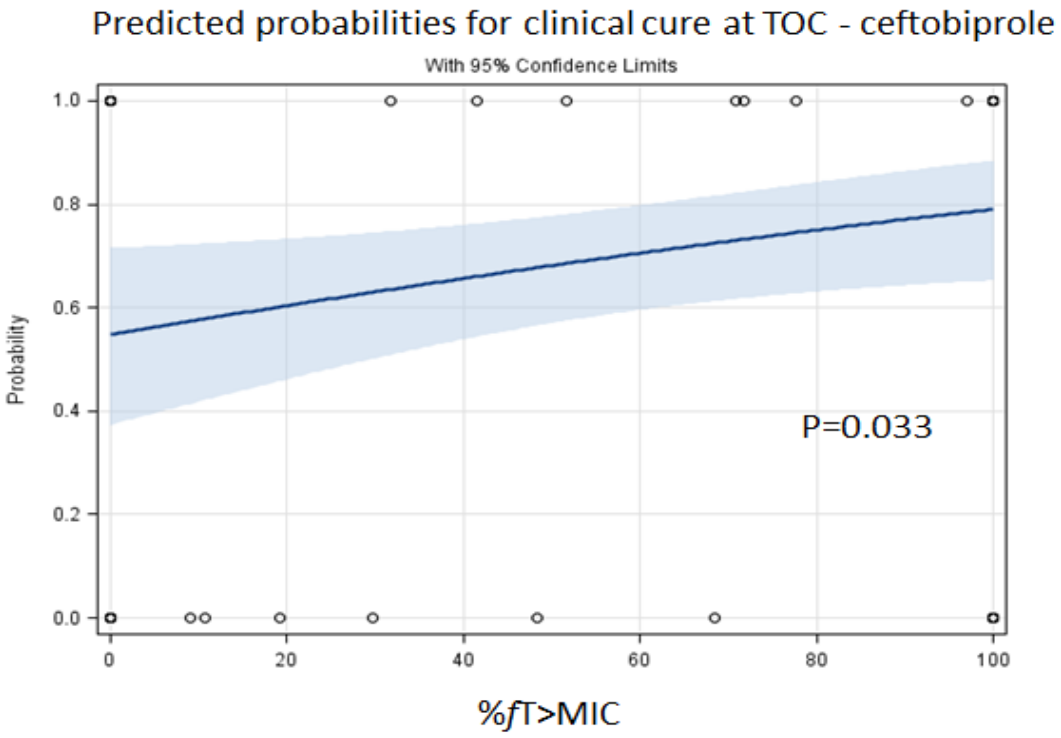
%*f*T>MIC breakpoint = 37.4 %

P = 0.0007

%*f*T>MIC	Success	Failure
≥37.4	56 (78.9%)	15 (21.1%)
<37.4	15 (44.1%)	19 (55.9%)

Muller et al, JAC 2013 68:900-906

Probability plot of the logistic regression analysis for ceftobiprole showing the relationship between %*f*T>MIC (Gram-negatives at baseline/EOT) and probability of cure at TOC (nosocomial pneumonia [excluding VAP] PK/PD CE subjects with positive cultures, n=82)



Muller et al, AAC 2014

How can the power of a study be improved further?

- Quantify outcome parameters instead of dichotomous outcomes

- Microbiology
  - Quantify cfu (we do it in animal studies……)
  - Time to negative

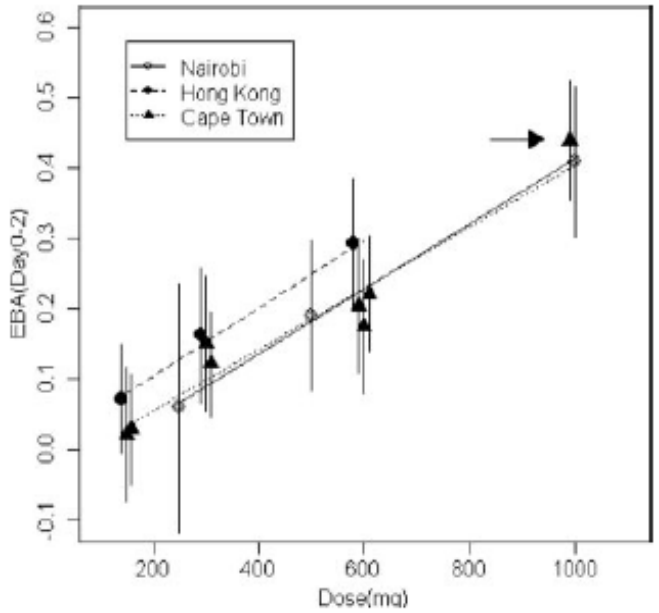
- Clinical
  - Quantitative parameter
  - Time to response

PanACEA
Pan African Consortium for the Evaluation of Antituberculosis Antibiotics

Bactericidal and Sterilizing Activities of Antituberculosis Drugs during the First 14 Days

Amina Jindani, Caroline J. Doré, and Denis A. Mitchison

Group	Treatment	*n*	EBA0–2 Mean	EBA0–2 SD	b2–14 Mean	b2–14 SD
3 (all with RMP)	RMP20	8	0.383	0.326	0.154	0.086
	RMP10	8	0.174	0.228	0.096	0.051
	RMP5	3	0.062	0.175	0.072	0.052
	RM	4	0.564	0.176	0.125	0.022
	SR	4	0.332	0.156	0.211	0.138
Total	p = 0.0039*	27	0.305	0.275	0.132	0.084



Early Bactericidal Activity of High-Dose Rifampin in Patients with Pulmonary Tuberculosis Evidenced by Positive Sputum Smears[▽]

A. H. Diacon,[1]* R. F. Patientia,[2] A. Venter,[3] P. D. van Helden,[3] P. J. Smith,[4] H. McIlleron,[4] J. S. Maritz,[5] and P. R. Donald[6]

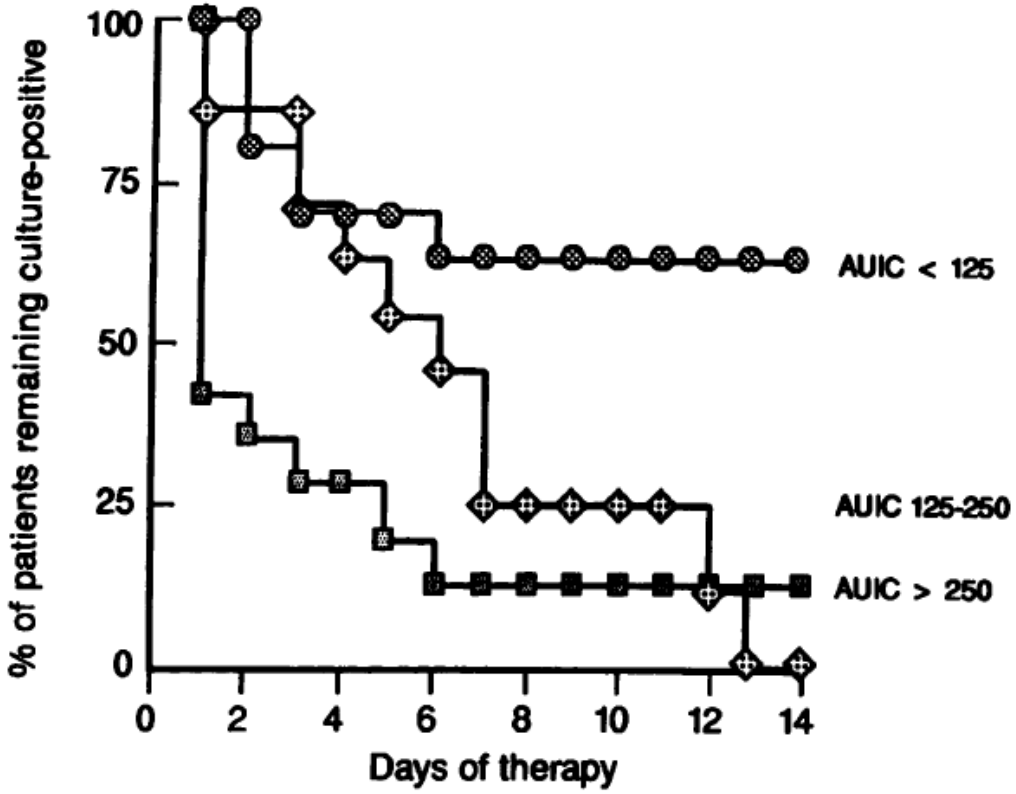
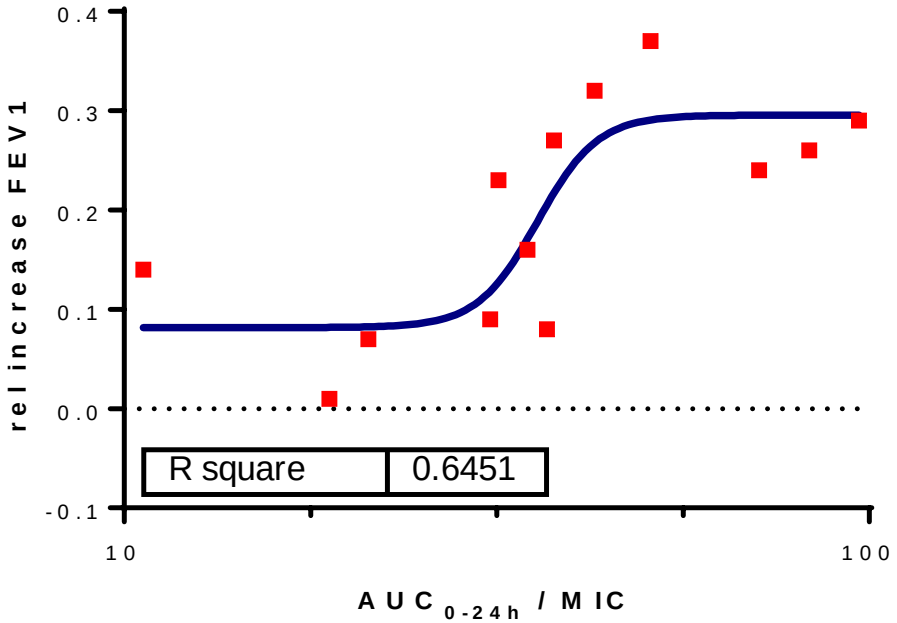


FIG. 5. Time (days of therapy) to bacterial eradication versus AUIC illustrated by a time-to-event (survival) plot. Shown is the day of therapy versus the percent patients remaining culture positive on that day. The three AUIC groups differed significantly ($P < 0.005$).

Forrest et al AAC 1993 37:1073

Relationship between AUC/MIC and Effect in CF patients Tobramycin



- Individual exposures to tob
- Cohort, 13 patients
- MIC tob before
- FEV1 before and after

CART

AUC/MIC breakpoint = 35.8

P = 0.0003

AUC/MIC	RI FEV1	SD
≥35.8	0.292	0.047
<35.8	0.111	0.072

Mouton et al 2005 Diagn Microbiol Infect Dis 52:123-127

Conclusions

- In DD, CER ***should*** be part of the development plan
- Even ***without*** differences with the comparator, it will show its merit (or not…).
- (semi) Quantitative parameters used preferably and more precise measurements – (we could show efficacy in 13 patients!)
- Estimate the number of patients in each arm based on prior information on variability and predicted responses. A power analysis should be performed

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

Treatment with fluconazol
Doses 50 – 800 mg

Culture-results with
MIC-values

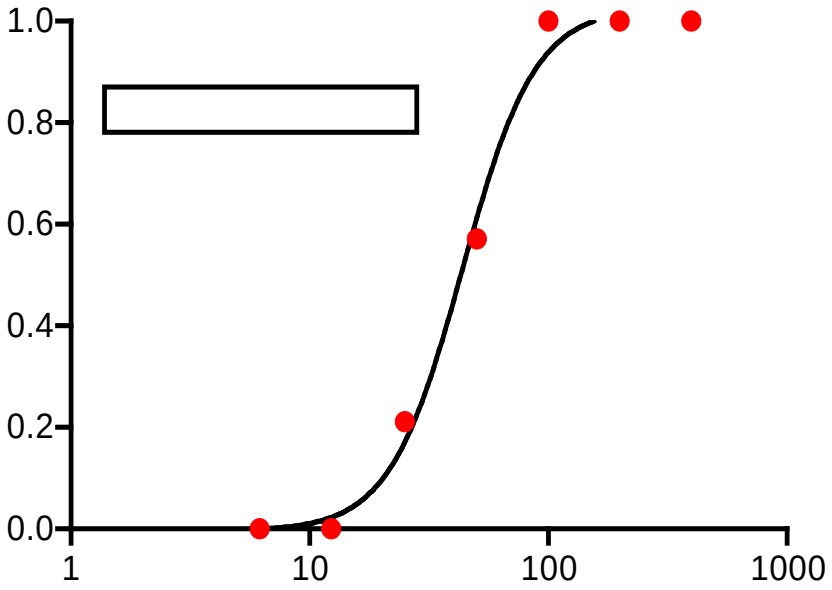
Individual Dose

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



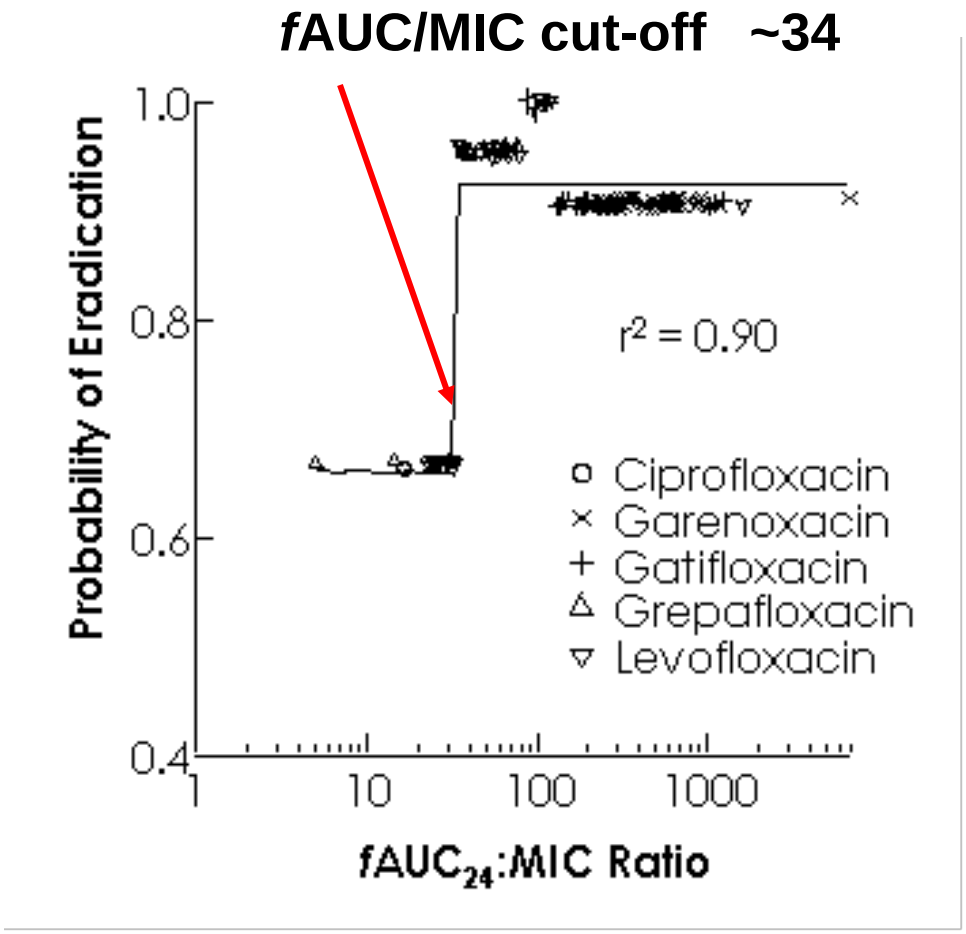
- Prob cure correlates with Dose/MIC
- POSITIVE correlation with dose
- INVERSE correlation with MIC

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

Rodriguez- Tudela et al, AAC 2007

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.