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PK data for supporting PK-PD analyses

Essential PK data

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Outline

- Overview section 4.3 of draft guidelines
  "Clinical pharmacokinetic data to support PK-PD analysis"

- Differences in PK
  - Healthy volunteers vs patients
  - Consequences in terms of PTA

- When is the PK profile important in the PKPD characterization?

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PK Guidelines

- Guideline for **pharmacokinetic studies in man** (EMA/CHMP/EWP/ 3CC3a)
- Guideline on reporting the results of **population pharmacokinetic analyses** (EMEA/CHMP/EWP/185990/2006)
- Guideline on the role of pharmacokinetics in the development of medicinal products in the **paediatric population** (EMEA/CHMP/EWP/147013/2004)
- Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with **impaired hepatic function** (CPMP/EWP/2339/02)
- Note for guidance on the evaluation of the pharmacokinetics of medicinal products in patients with **impaired renal function** (CHMP/EWP/225/02)

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4.3.1. PK data from uninfected subjects

Lines 326-331

- Initial PK data from healthy volunteers
- Intensive PK sampling after single and multiple doses
- Describe plasma /serum profiles and routes of metabolism and elimination
- Effects of renal and/or hepatic impairment may need to be assessed
- Initial POPPK model based on healthy subjects
- Used for preliminary dose assessment

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4.3.2. PK data from infected patients

Lines 334-352

- PK differences in the infected target patient population
  - renal hyperfiltration
  - altered volume of distribution
  - greater inter-individual variability
  - other covariate relationships
- Intensive PK data in a subset and sparse sampling from total population
- Intended target population
  - site of infection
  - severity of infection
- Update POPPK model
- Sparse sampling of all patients in pivotal clinical efficacy studies

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4.3.3. Other relevant data

Lines 354-360

- Degree of binding to plasma proteins for clinically relevant concentrations
- Initially in vitro, spiking human plasma, assess concentration-dependency
- Radiolabelled agent or samples collected during clinical PK studies
- The data collected from infected patients should support a robust estimation of unbound concentrations of the test agent that can be used for PK-PD analyses

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- **Differences in PK**
  - **Healthy volunteers vs patients**
  - **Consequences in terms of PTA**

- When is the PK profile important in the PKPD characterization?

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PK in healthy volunteers vs patients

- PK differences due to pathophysiological alterations
  - Indication
  - Severity of illness
  - Range from “healthy” to critically ill patients
  - Intra-individual changes during course of treatment

- Physicochemical properties of the antibiotic

<u>Reviews: PK in the critically ill:</u>

- *Blot SI, et al. Advanced Drug Delivery Reviews. 2014, 77, 3-11*
- *Robets JA, et al. Lancet Infect Dis 2014 14: 498-509*
- *Felton TW et al. Diag Microbiol Infec Dis 79 (2014) 441–447*
- *De Paepe P et al. Clin Pharmacokinet 2002: 41 (14): 1135-1152*

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PK in healthy volunteers vs patients

Absorption

- Decreased perfusion of muscles, skin and splanchnic organs
- Lower and less reliable absorption from oral, transdermal, subcutaneous and intramuscular routes
- Few examples in literature
- High variability in absorption related parameters

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PK in healthy volunteers vs patients

Distribution

- Vasodilation and increased vascular permeability
- Capillary leak syndrome and fluid shift from intravascular compartment to interstitial space
- Edema and ”third spacing”
- Infusion of fluids to maintain pressure
- Hypoalbuminemia (fu increases)
- Microvascular failure (tissue distribution decreases)

- **Hydrophilic antibiotics**: substantial increase in Vd
  Example aminoglycosides, increase correlated to disease severity
- **Lipophilic antibiotics**: minor influences on Vd
  Example macrolides

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PK in healthy volunteers vs patients

Renal elimination

- Glomerular hyperfiltration, fluid resuscitation, vasopressin use
  - Augmented renal CL (>130 ml/1.73m^2)
  - Young men with trauma, sepsis, burns
- Reduced kidney perfusion and acute kidney injury
  - Decreased renal CL, potential need of renal replacement therapy
  - Potential for compensatory elimination (Example ciprofloxacin)
- High inter-individual variability

Hepatic elimination

- Reduced hepatic blood flow, liver failure, hypoproteinemia cholestasis, hepatocellular injury
- Consequences for PK often unclear

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Consequences in terms of PTA

Example: Flucloxacillin

Healthy volunteers

- 15 healthy volunteers
- Cross-over study, Heracillin®, p.o. 500 mg and 750 mg
- Frequent PK sampling
- 2 compartment disposition, first-order transit absorption model

Parameter	Estimate	IIV
Clearance, CL/F (L/h)	10.5 (7.1)	25.5 (16)
Inter-compartmental clearance, Q/F (L/h)	0.997 (36)	-
Central volume of distribution, Vc/F (L)	1.78 (17)	-
Peripheral volume of distribution, Vp/F (L)	2.68 (18)	12.5 (68)
Absorption rate constant, ka (h^{-1})	0.859 (7.6)	12.3 (27)
Mean transit time, MTT (h)	0.425 (13)	31.4 (21)
Number of transit compartments, N (-)	2.70 (16)	46.3 (28)
Proportional residual error (%)	24.5 (7.7)	-

Nielsen EI. et al. PAGE: 2012; Venice, Italy

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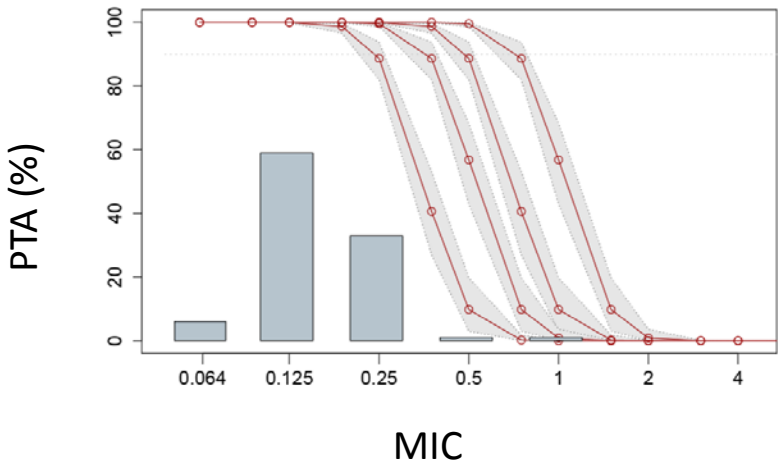
Consequences in terms of PTA

Example: Flucloxacillin

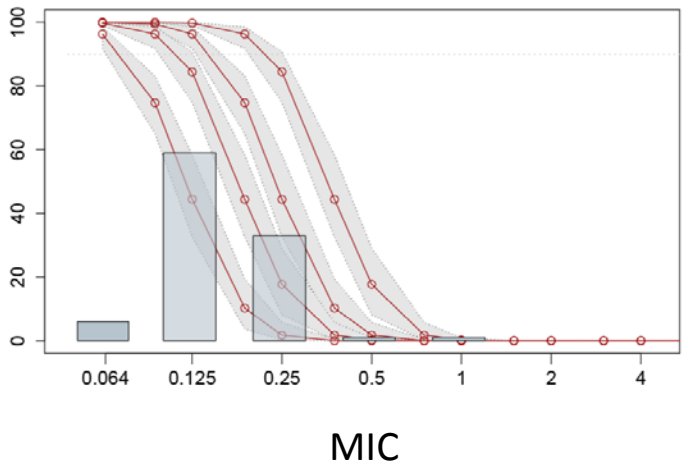
Healthy volunteers

- PTA vs MIC for 500, 750, 1000 and 1500 mg q8h oral flucloxacillin
- Protein binding assumed to be 95% (fu 0.05)
- Parameter uncertainty (non-parametric bootstrap)

PD target: 30% *f*T>MIC



PD target: 50% *f*T>MIC



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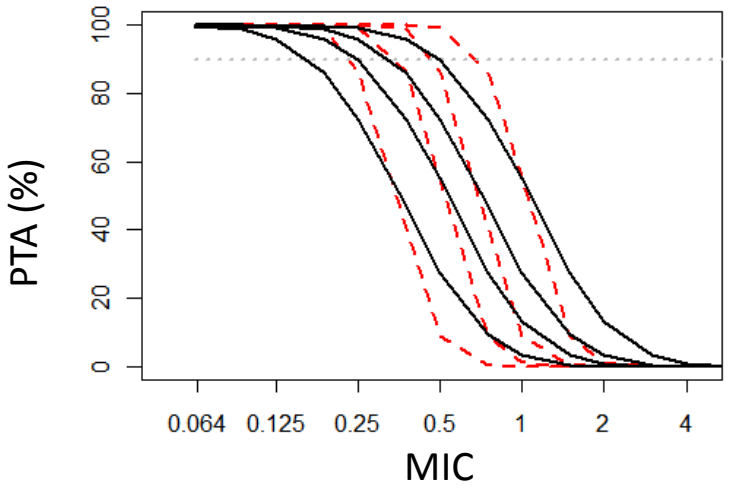
Consequences in terms of PTA

Example: Flucloxacillin

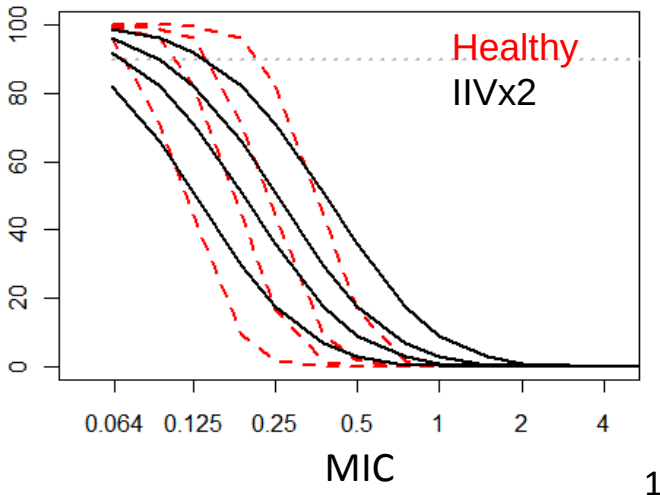
”Healthy” patients

- Increased inter-individual variability in PK parameters (IIVx2)
- Less steep PTA curves
- Lower target attainment in the high, most interesting PTA region

PD target: 30% *f*T>MIC



PD target: 50% *f*T>MIC



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Consequences in terms of PTA

Example: Flucloxacillin

Critically ill patients

- 10 critically ill patients with hypoalbuminemia (≤32 g/L)
- Excluded severe renal dysfunction (Pcrea>170 mmol/L)
- MSSA infections nosocomial pneumonia, bacteremia, epidural abscesses, meningitis and surgical site prophylaxis
- Minor changes in CL, increase in V

Table 2. Pharmacokinetic parameters after a maintenance dose for total flucloxacillin in different patient populations; values are given as median (interquartile range) or mean ± SD

	CL (L/h)	CL (L/kg/h)	*V* (L)	*V* (L/kg)	$t_{1/2}$ (h)
Total flucloxacillin (this study, non-compartmental analysis; $n=10$)	9.01 (8.68–17.55)	0.10 (0.10–0.20)	20.00 (12.45–27.20)	0.22 (0.14–0.30)	2.45 (1.26–2.54)
Total flucloxacillin (healthy volunteers; $n=10$)[20]	8.18 ± 0.20	0.12 ± 0.28	9.97 ± 0.17	0.14 ± 0.24	0.84 ± 0.59
Total flucloxacillin (hospitalized patients; $n=7$)[24]	5.53 ± 0.87	0.08 ± 0.01	12.27 ± 2.27	0.18 ± 0.03	1.54 ± 0.35

Ulldemolins et al. J Antimicrob Chemother 2010; 65: 1771–1778

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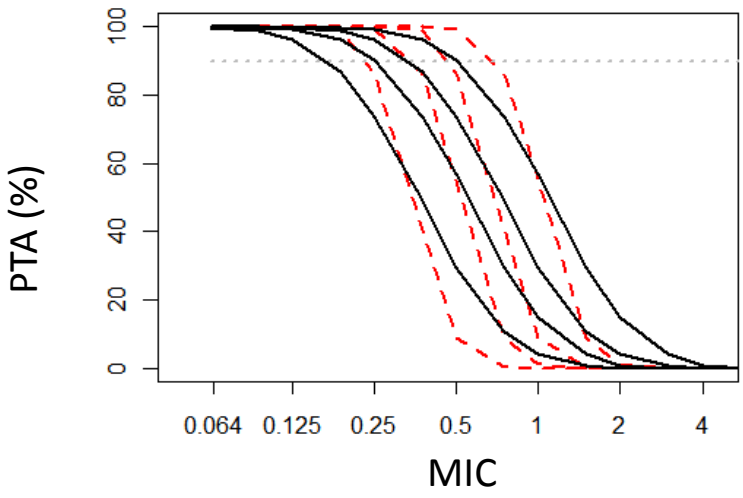
Consequences in terms of PTA

Example: Flucloxacillin

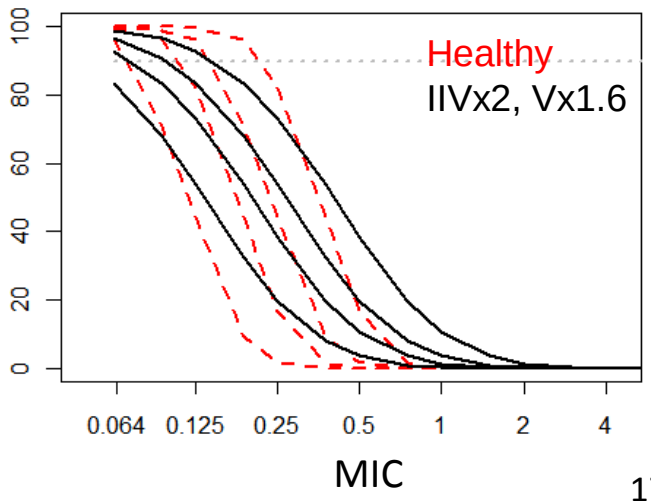
Critically ill patients

- Increased inter-individual variability in PK parameters (IIVx2)
- Increased V (x1.6)
- Increased V -> Only minor alterations in PTA curves

PD target: 30% *f*T>MIC



PD target: 50% *f*T>MIC



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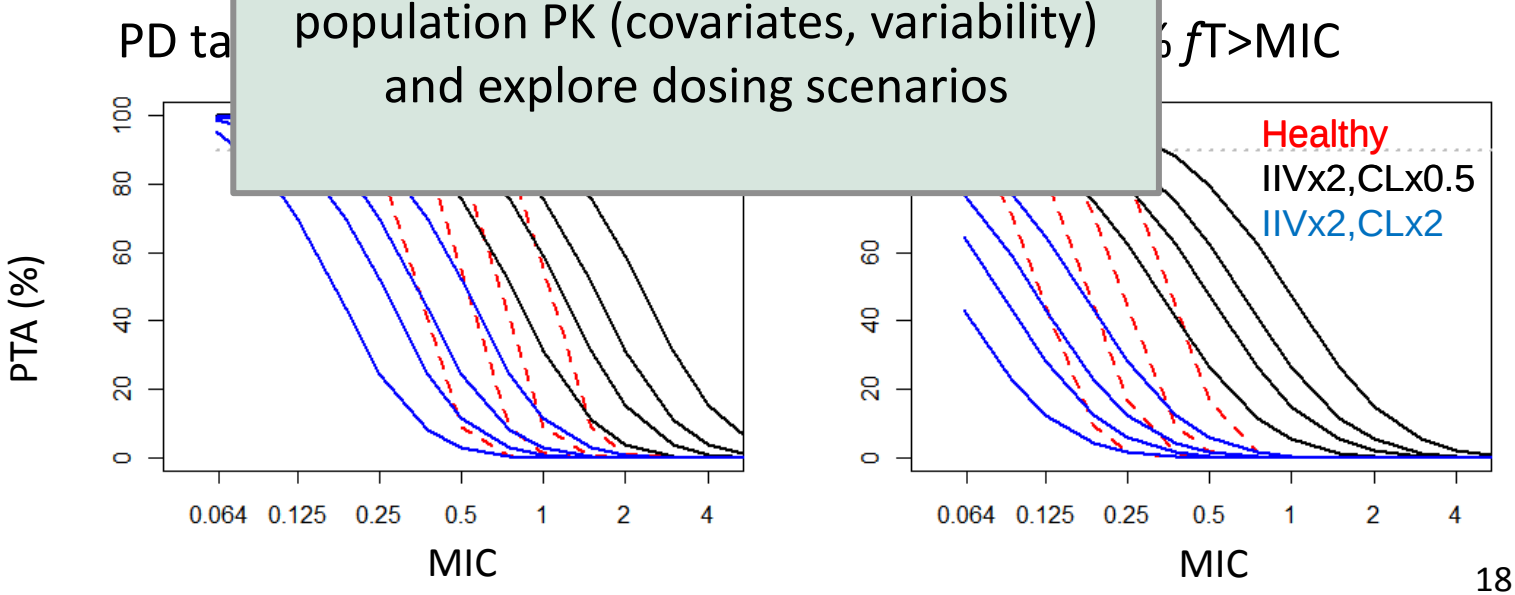
Consequences in terms of PTA

Example: Flucloxacillin

Critically ill patients

- Increased inter-individual variability in PK parameters (IIVx2)
- Augmented or reduced CL (CLx2 and CLx0.5)
- Results in PTA shifts

Modelling and simulation to assess population PK (covariates, variability) and explore dosing scenarios



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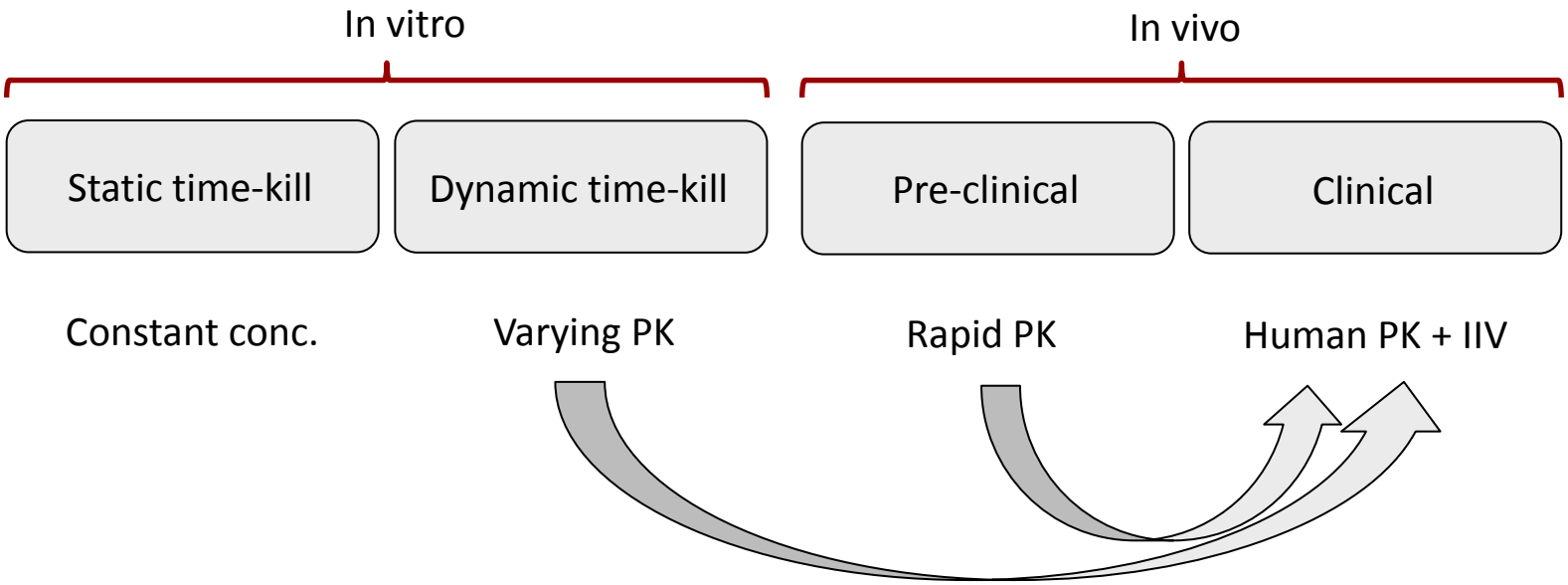
PK importance in PKPD characterization

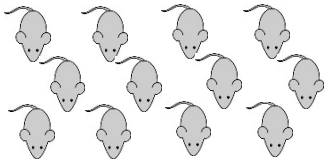


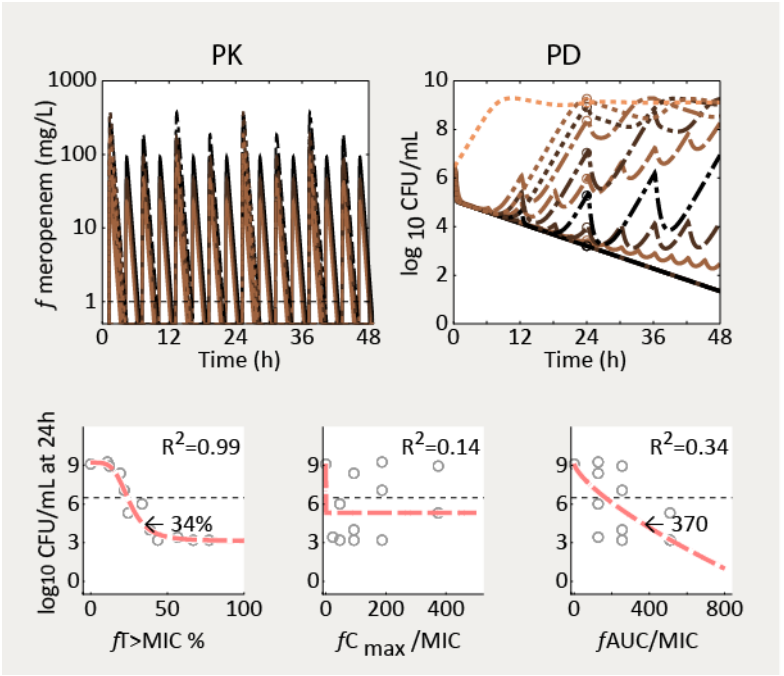
PK/PD indices:
Correlate 24h efficacy to summary exposure

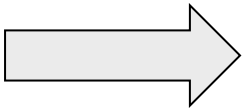
Are the PK/PD indices PK dependent?

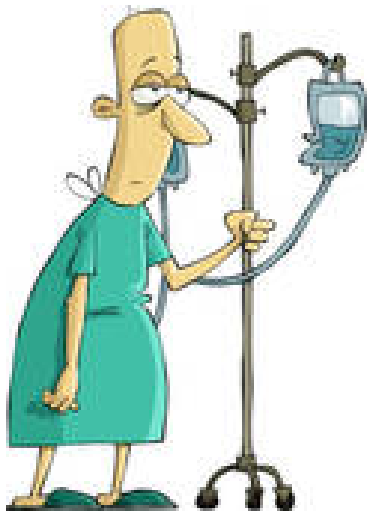
PK importance in PKPD characterization

PK/PD indices









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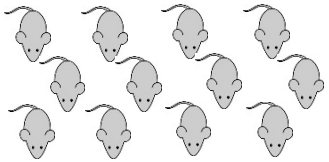
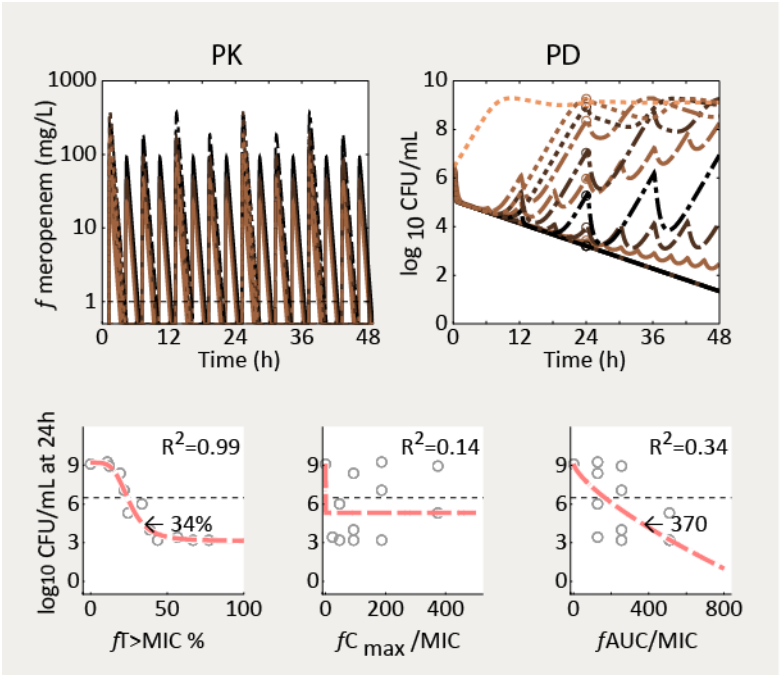
PK importance in PKPD characterization

PK/PD indices





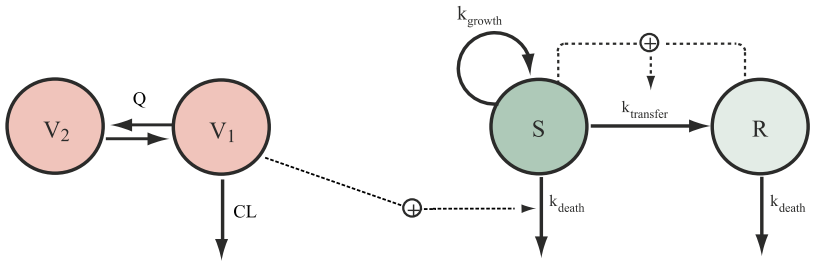
PK importance in PKPD characterization

PK/PD indices

Are the PK/PD indices PK dependent?

PK model

PKPD model



Kristoffersson *et al*, *submitted*

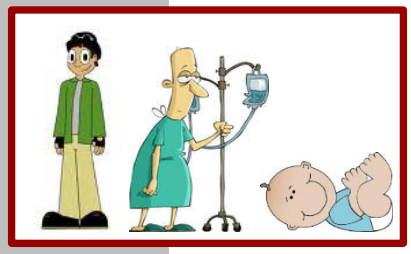
fC_{max}/MIC
fAUC/MIC
fT>MIC

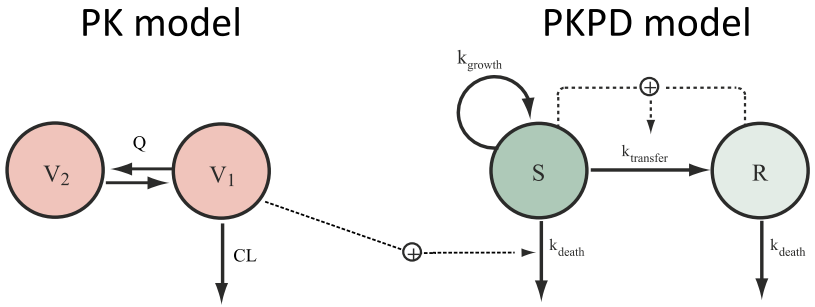
Bacterial count at 24 hrs

PK importance in PKPD characterization

PK/PD indices

Are the PK/PD indices PK dependent?





Kristoffersson *et al*, *submitted*

fC_{max}/MIC
fAUC/MIC
fT>MIC

Bacterial count at 24 hrs

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PK importance in PKPD characterization

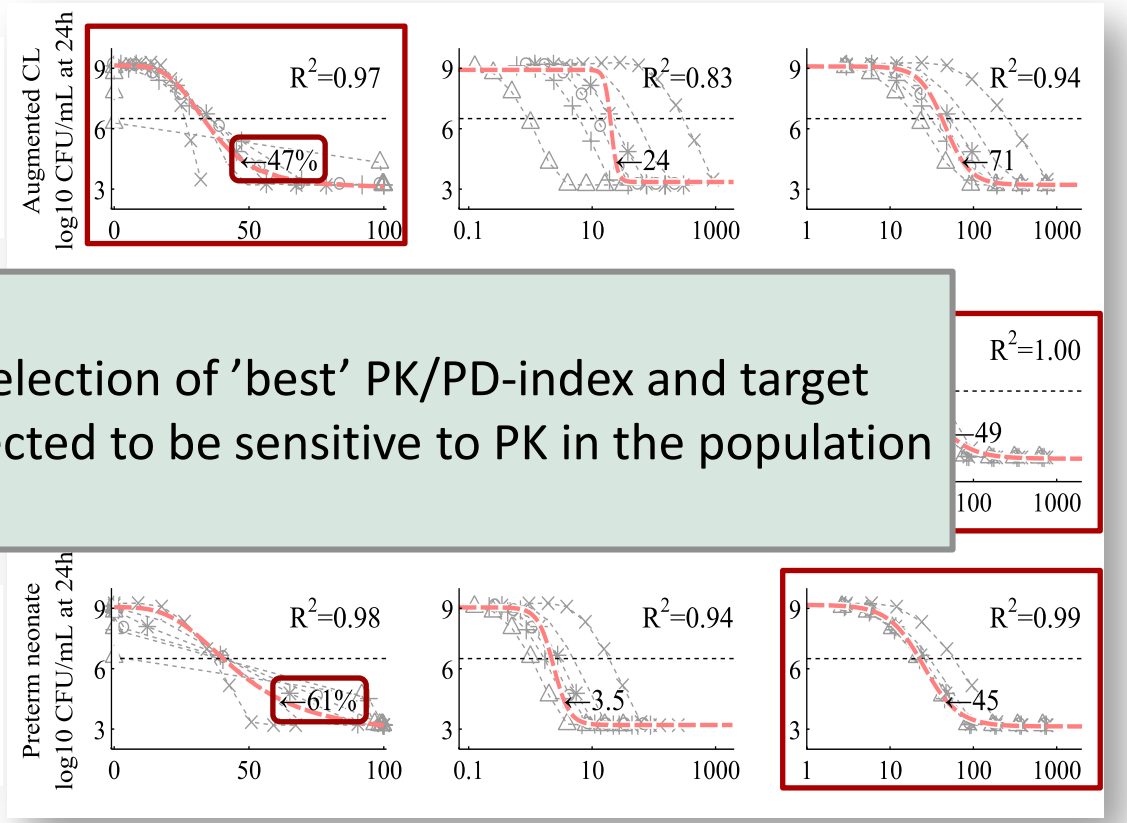
PK/PD indices

Typical:
Adult, CrCL=83 ml/min
2-comp PK, $t_{1/2,\beta}$ ~ **1.4 h**
(Li *et al*, J Clin Pharmacol 2006)

Renal dysfunction:
Adult, CrCL=15 ml/min
2-comp PK, $t_{1/2,\beta}$ ~ **3.5 h**
(Li *et al*, J Clin Pharmacol 200

Preterm neonate:
GA 31w
2-comp PK, $t_{1/2,\beta}$ ~ **2.5 h**
(van den Anker *et al*, AAC 2009)

Selection of 'best' PK/PD-index and target expected to be sensitive to PK in the population



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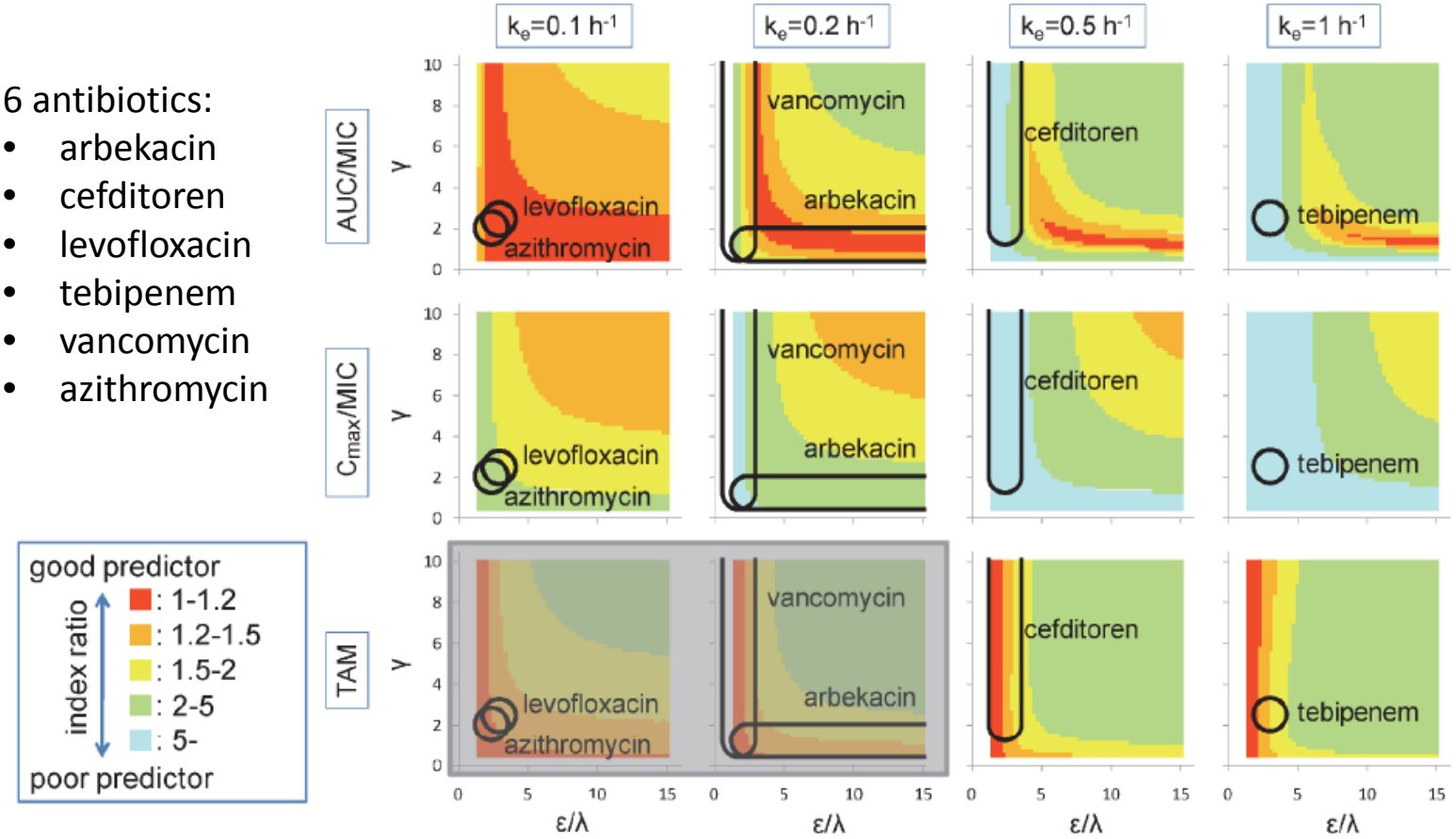
PK importance in PKPD characterization

PK/PD indices

Theoretical mathematical framework

6 antibiotics:

- arbekacin
- cefditoren
- levofloxacin
- tebipenem
- vancomycin
- azithromycin



Kitamura Y, et al. Drug Metab Pharmacokinet. 2014;29(6):455-62.

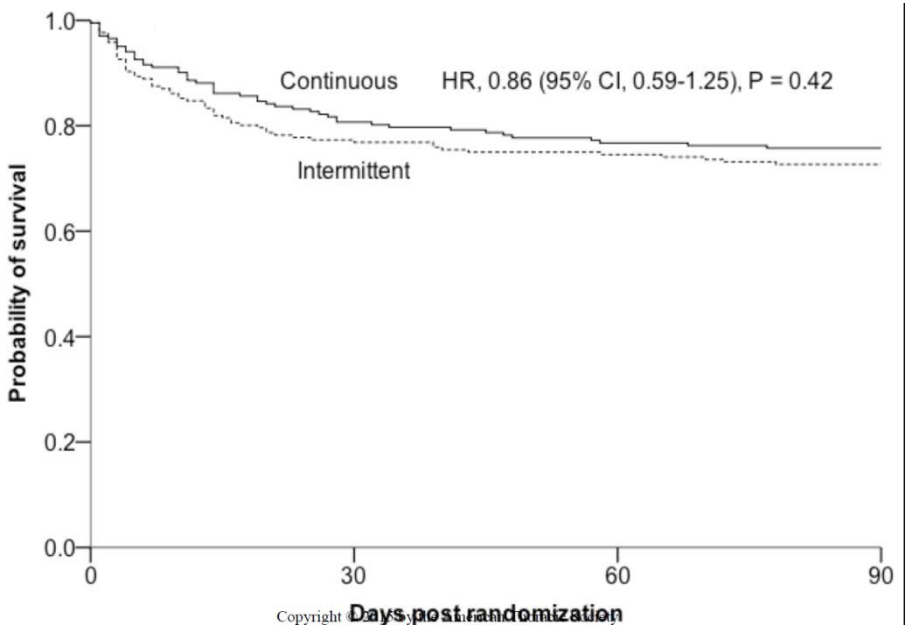
PK importance in PKPD characterization

PK/PD indices

Table 4. List of PK/PD targets for dose adjustment adopted by selected ICUs

	PK/PD targets
For dose increase	100% $fT_{>MIC}$ ($n=5$)
	100% $fT_{2-4\times MIC}$ ($n=1$)
	50% $fT_{>4\times MIC}$ ($n=1$)
	100% $fT_{>4\times MIC}$ ($n=2$)
	40% $fT_{>4\times MIC}$ ($n=1$)
	50% $fT_{>4\times MIC}$ ($n=1$)
	70% $fT_{>4\times MIC}$ ($n=1$)
Threshold of potential toxicity for dose reduction	100% $fT_{10\times MIC}$ ($n=4$)
	100% $fT_{8\times MIC}$ ($n=1$)
	100% $fT_{6\times MIC}$ ($n=1$)
	100% $fT_{4-5\times MIC}$ ($n=1$)
	steady-state concentration exceeding 2 × maximum exposure expected in general population; e.g. piperacillin >100 mg/L (>32 g/24 h in normal patients), meropenem >32 mg/L (>12 g/24 h in normal patients) ($n=1$)

Wong G. et al.
J Antimicrob Chemother 2014; 69: 1416 –1423



Dulhunty JM et al.
Am J Respir Crit Care Med 2015, 22 Jul

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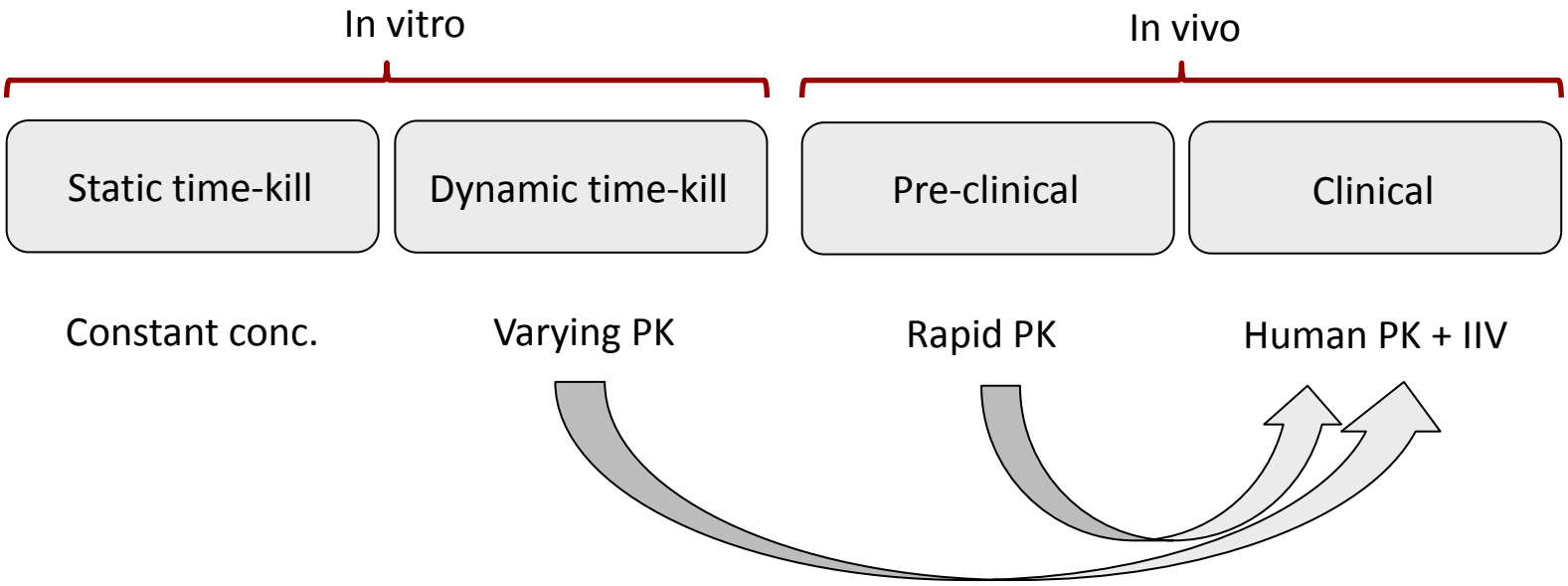
PK importance in PKPD characterization

PK/PD indices vs *Pharmacometric approach*



PK/PD indices:
Correlate 24h efficacy to summary exposure

Pharmacometric approach

Make use of all available data and accumulate knowledge

- *In vitro* (static, dynamic concentration)
- *In vivo* (pre-clinical, clinical)

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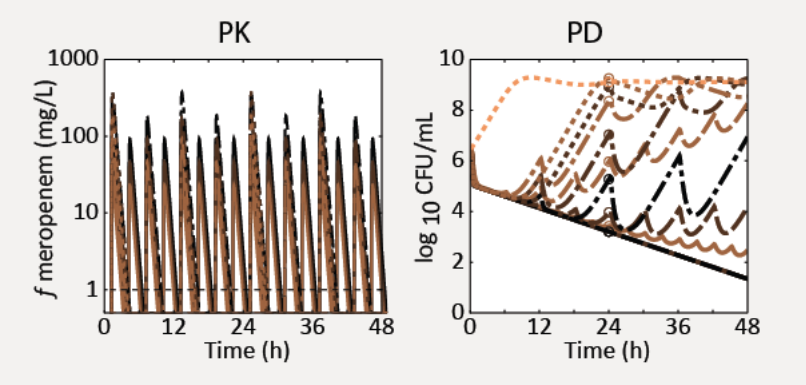
PK importance in PKPD characterization

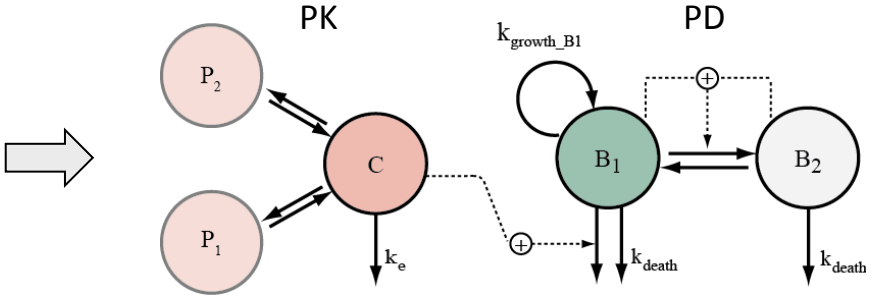
Pharmacometric approach

Translate results from experiments with varying PK profiles

Characterization of full time-course

- PK (one or several drugs)
- Bacterial effect (single and combination treatment)
- Emergence of resistance





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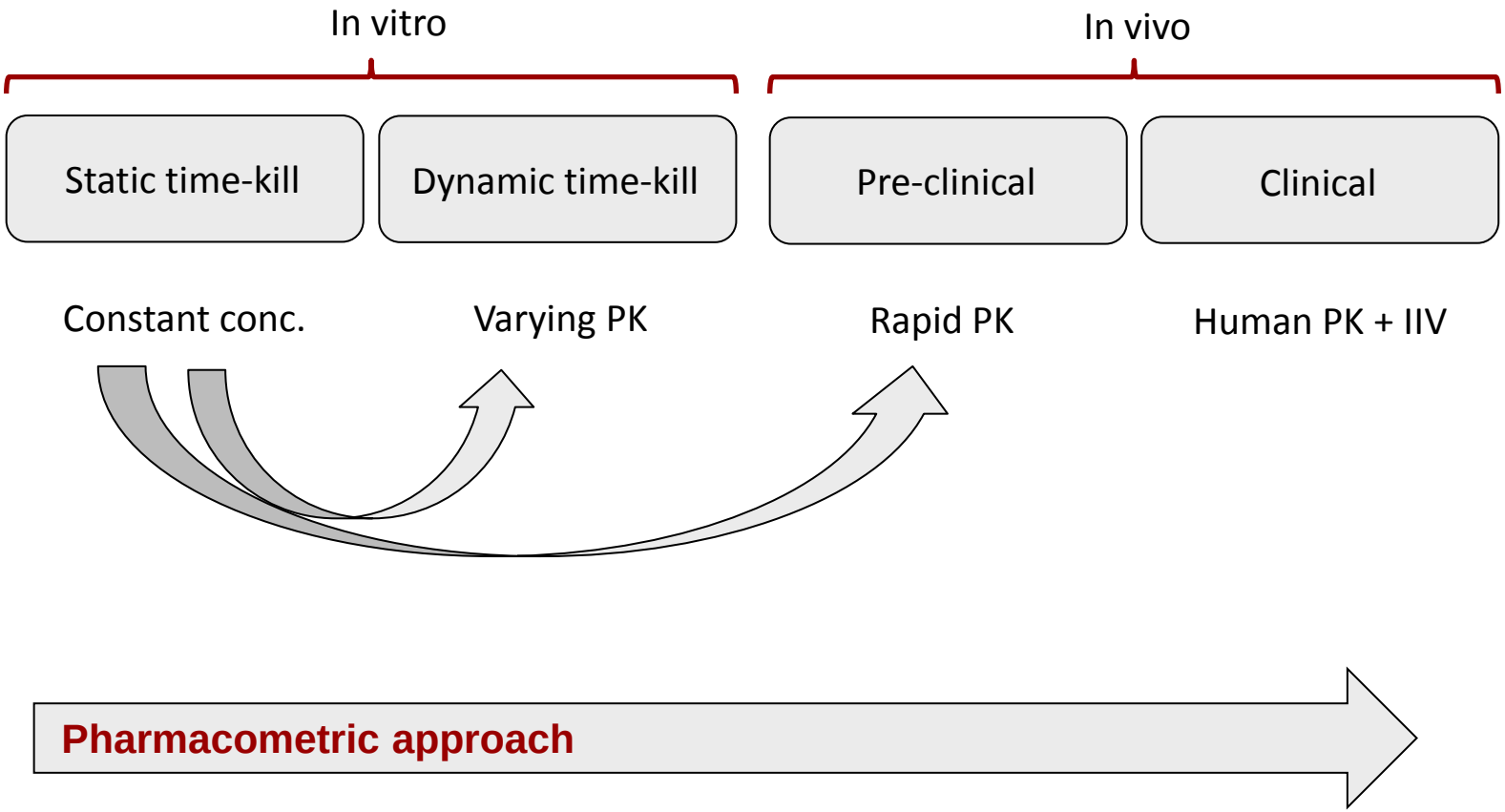
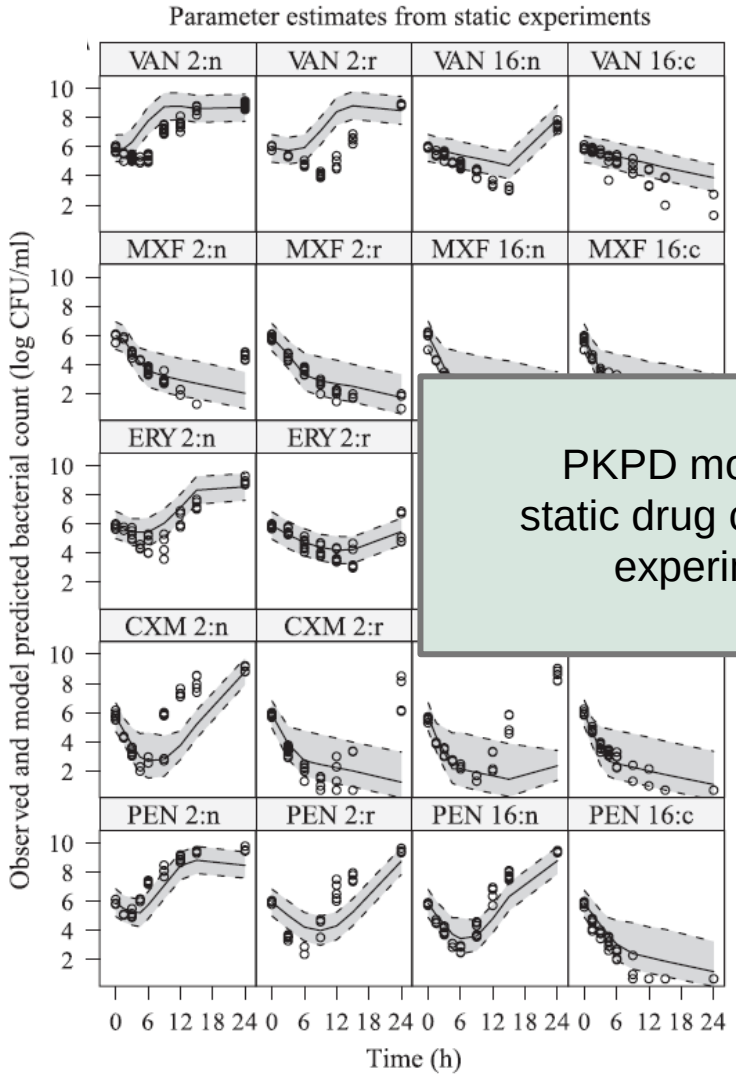
PK importance in PKPD characterization

Pharmacometric approach



PK importance in PKPD characterization

Pharmacometric approach



Are the static time-kill predictive of dynamic time-kill?

- *S. pyogenes,* 5 antibiotics
- PKPD model developed based on static
- luation
- periments

PKPD models based on experiments with static drug concentrations can be predictive of experiments with human PK profiles

2:n	C_0= 2 xMIC, $t_{1/2}$= typical human
2:r	C_0= 2 xMIC, $t_{1/2}$= 1/3 typical human
16:n	C_0=16 xMIC, $t_{1/2}$= typical human
16:c	C_0=16 xMIC, $t_{1/2}$= 0 (constant conc)

Nielsen et al. Antimicrob Agents Chemother, 2011

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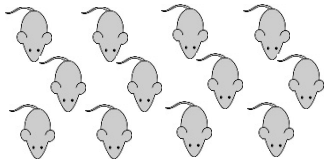
PK importance in PKPD characterization

Pharmacometric approach

Are PKPD models based on in vitro data predictive of in vivo results?



In vivo

Dose fractionation study

Meropenem

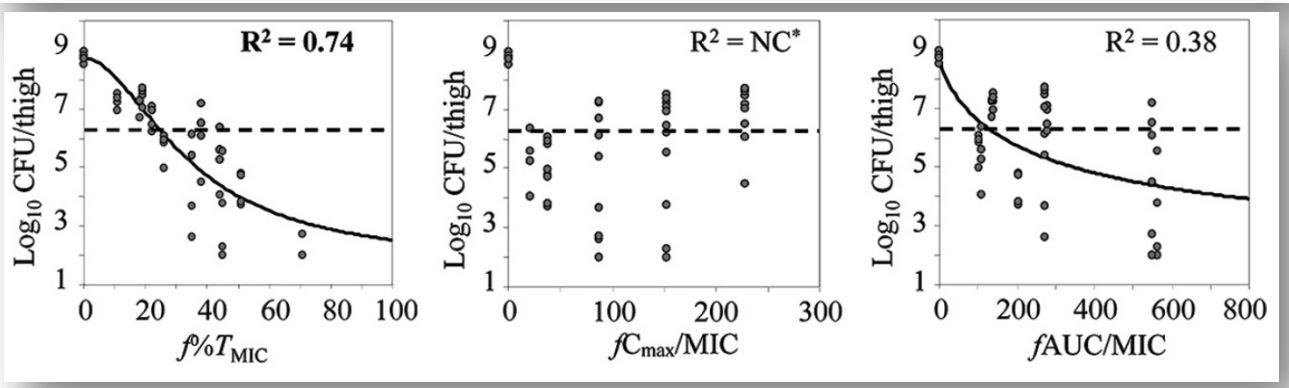
P. aeruginosa 12467

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2010, p. 5298–5302 Vol. 54, No. 12
0066-4804/10/$12.00 doi:10.1128/AAC.00267-10

In Vivo Pharmacodynamic Activity of Tomopenem (formerly CS-023) against *Pseudomonas aeruginosa* and Methicillin-Resistant *Staphylococcus aureus* in a Murine Thigh Infection Model[▽]

Kiyoshi Sugihara,[1]* Chika Sugihara,[1] Yoko Matsushita,[2] Naotoshi Yamamura,[2] Mitsutoshi Uemori,[3] Akane Tokumitsu,[1] Harumi Inoue,[1] Masayo Kakuta,[1] Eiko Namba,[1] Hatsumi Nasu,[1] and Tetsufumi Koga[1]

Biological Research Laboratories IV, Daiichi Sankyo Co., Ltd., Tokyo, Japan[1]; Drug Metabolism and Pharmacokinetics Research Laboratories, Daiichi Sankyo Co., Ltd., Tokyo, Japan[2]; and Clinical Data and Biostatistics Department, Daiichi Sankyo Co., Ltd., Tokyo, Japan[3]



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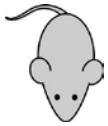
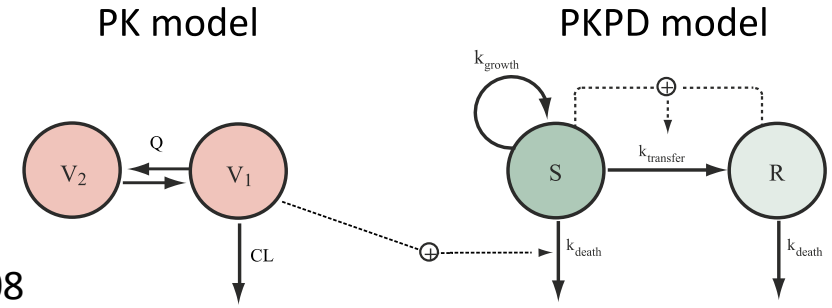
PK importance in PKPD characterization

Pharmacometric approach

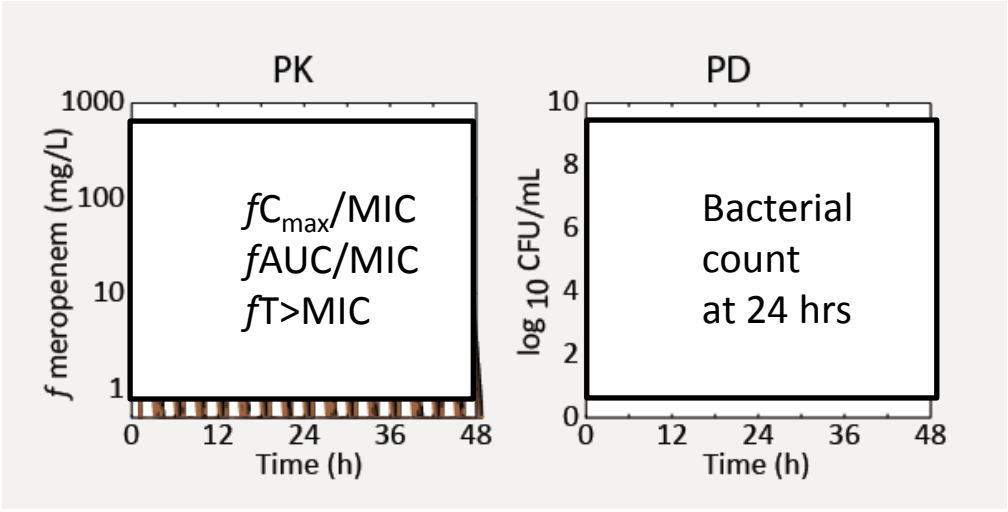
In silico replication of this *in vivo* dose fractionation study



Katsube *et al*,
J Pharm Sci 2008



Kristoffersson *et al*,
Submitted



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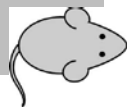


In vivo

P. aeruginosa 12467

Sugihara et al.

In silico

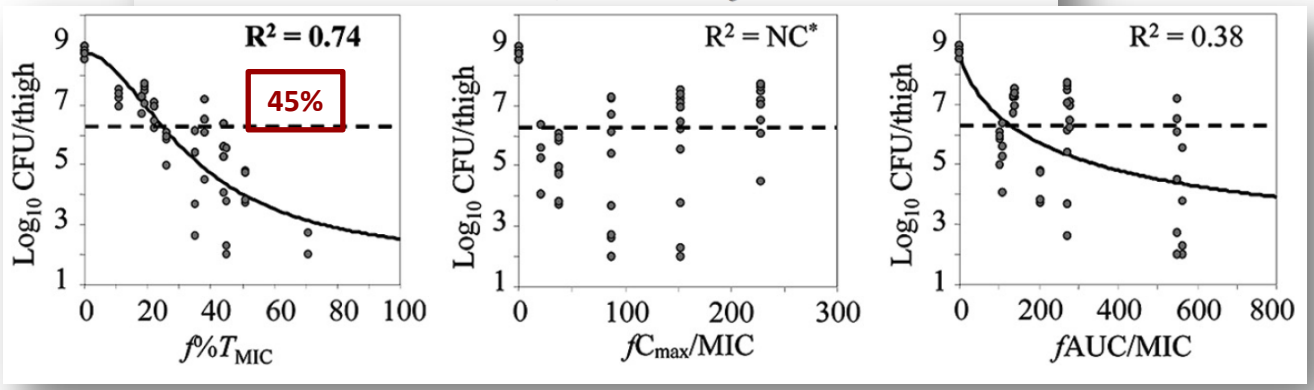
P. aeruginosa ATCC27853

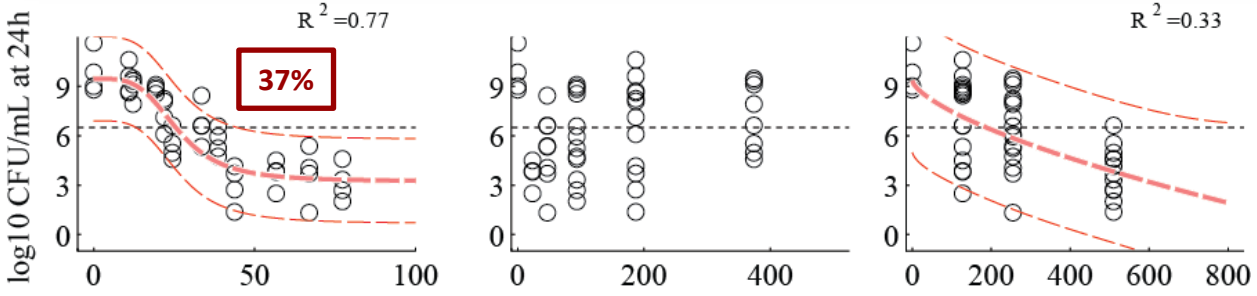
Kristoffersson et al.

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2010, p. 5298–5302 Vol. 54, No. 12
0066-4804/10/$12.00 doi:10.1128/AAC.00267-10

In Vivo Pharmacodynamic Activity of Tomopenem (formerly CS-023) against *Pseudomonas aeruginosa* and Methicillin-Resistant *Staphylococcus aureus* in a Murine Thigh Infection Model[▽]

Kiyoshi Sugihara,[1]* Chika Sugihara,[1] Yoko Matsushita,[2] Naotoshi Yamamura,[2] Mitsutoshi Uemori,[3] Akane Tokumitsu,[1] Harumi Inoue,[1] Masayo Kakuta,[1] Eiko Namba,[1] Hatsumi Nasu,[1] and Tetsufumi Koga[1]





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PK importance in PKPD characterization

Pharmacometric approach

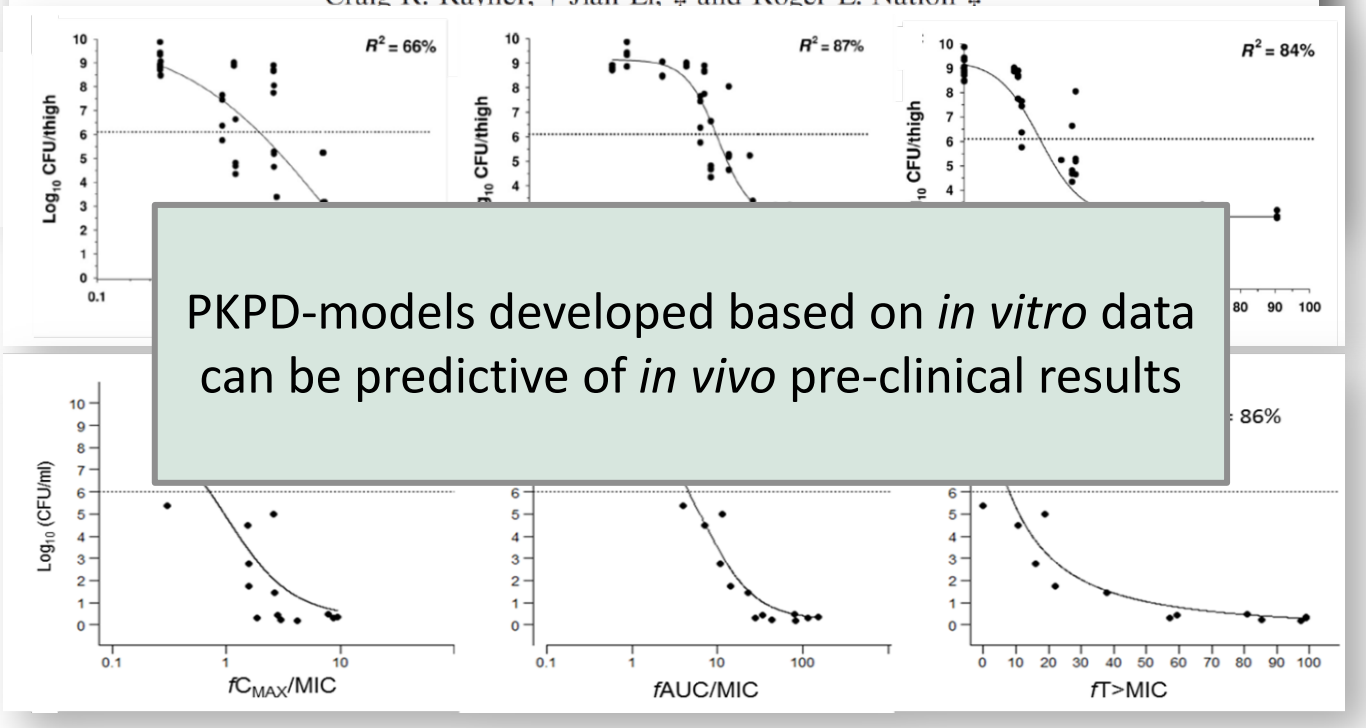
In vivo
Dudhani et al., AAC, 2010

In silico
Mohamed et al., AAC, 2014
Khan et al. *Submitted*

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 2010, p. 1117–1124 Vol. 54, No. 3
0066-4804/10/$12.00 doi:10.1128/AAC.01114-09

Elucidation of the Pharmacokinetic/Pharmacodynamic Determinant of Colistin Activity against *Pseudomonas aeruginosa* in Murine Thigh and Lung Infection Models▽

Rajesh V. Dudhani,[1] John D. Turnidge,[2,3] Kingsley Coulthard,[2,4] Robert W. Milne,[4] Craig R. Rayner,[1]† Jian Li,[1]‡ and Roger L. Nation[1]‡*



PKPD-models developed based on *in vitro* data can be predictive of *in vivo* pre-clinical results

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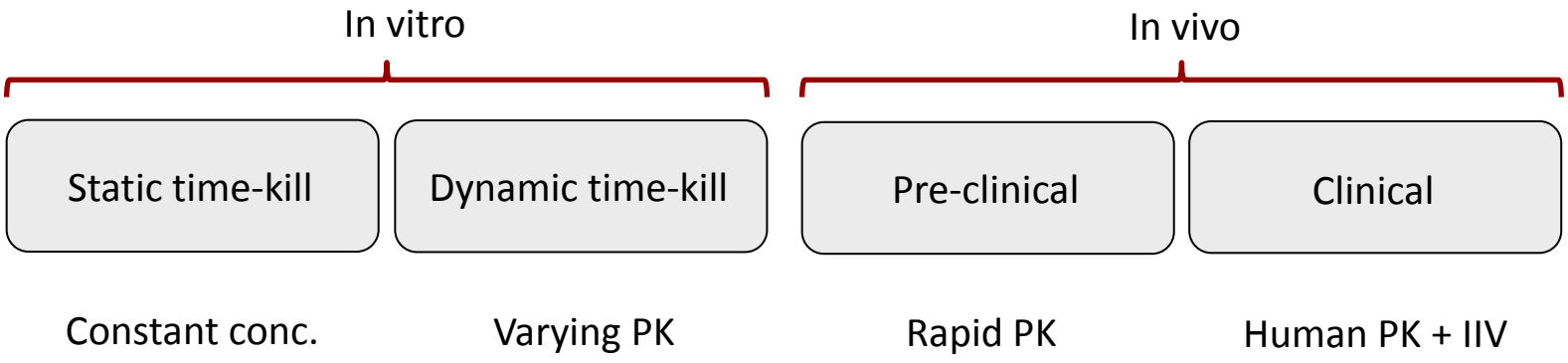
PK importance in PKPD characterization

PK/PD indices or a Pharmacometric approach



PK/PD indices:

- Summary of PK profile:
  Shape of the PK curve of importance, PK dependency might limit the predictive capacity
- Static PD endpoint:
  Relevance of 24h (or other) efficacy assessment?
- No single “true” PK/PD index

Pharmacometric approach:

- Use time-course of PK and PD
- PKPD models based on static time-kill can be predictive of dynamic exposures and vivo pre-clinical results
- Use of all available data
- Combination therapy
- Resistance development

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Acknowledgements

Pharmacometrics group, Uppsala University, Sweden

Roche Pharma Research and Early Development, Innovation Center Basel

Meda AB, Solna, Sweden

Special thanks to:

- Anders Kristoffersson
- Jason Roberts
- Joe Standing