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Population pharmacokinetics and Monte Carlo simulation for setting MIC breakpoints for antimicrobial susceptibility testing. The case of amoxicillin in pigs.

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MIC breakpoints for antimicrobial susceptibility testing (AST)

- The fight against antimicrobial resistance in humans and animals urgently requires promoting the prudent use of antibiotics in food-producing animals

- Antimicrobial therapy is based on antimicrobial susceptibility testing (AST) that categorizes bacteria as **susceptible**, **intermediate** or **resistant** (S/I/R)
  - Breakpoint values of **minimal inhibitory concentrations (MICs)**
  - There is an urgent need of animal species-specific breakpoints to more appropriately categorize veterinary pathogens

- The methodology for setting clinical breakpoints : Turnidge & Paterson, Clinical Microbiological Review, 2007
  - Epidemiological cut-off (ECOFF, CO_{WT}) : MIC distribution of wild-type/non-wild-type bacteria
  - Clinical cut-off (CO_{CL}) : outcomes of clinical trials with MIC recording
  - **PK/PD cut-off ($CO_{PK/PD}$)**

MIC breakpoints for antimicrobial susceptibility testing (AST)

- Objective of the study
  - To set the PK/PD cut-off ($CO_{PK/PD}$) of amoxicillin (AMOX) in pigs

- Methodology
  - Pharmacokinetic-pharmacodynamic (PK/PD) framework
  - Population pharmacokinetics (PopPK)
  - Monte Carlo simulation (MCS)

ORIGINAL ARTICLE BACTERIOLOGY

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

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Materials & Methods

Methodology for setting a PK/PD cut-off : the general case

The setting of a $CO_{PK/PD}$

Step1

Selection of a PK/PD index predictive of clinical efficacy and/or prevention of resistance

Step 2

Determination of the critical value (size) of the selected PK/PD index

Step 3

Computation of the percentage of animals in which the critical value of the selected PK/PD index will be achieved (Probability of Target Attainment, PTA>90%) for **a given animal species**, for **a given dose**, and for **all MICs in a given range**

Materials and methods

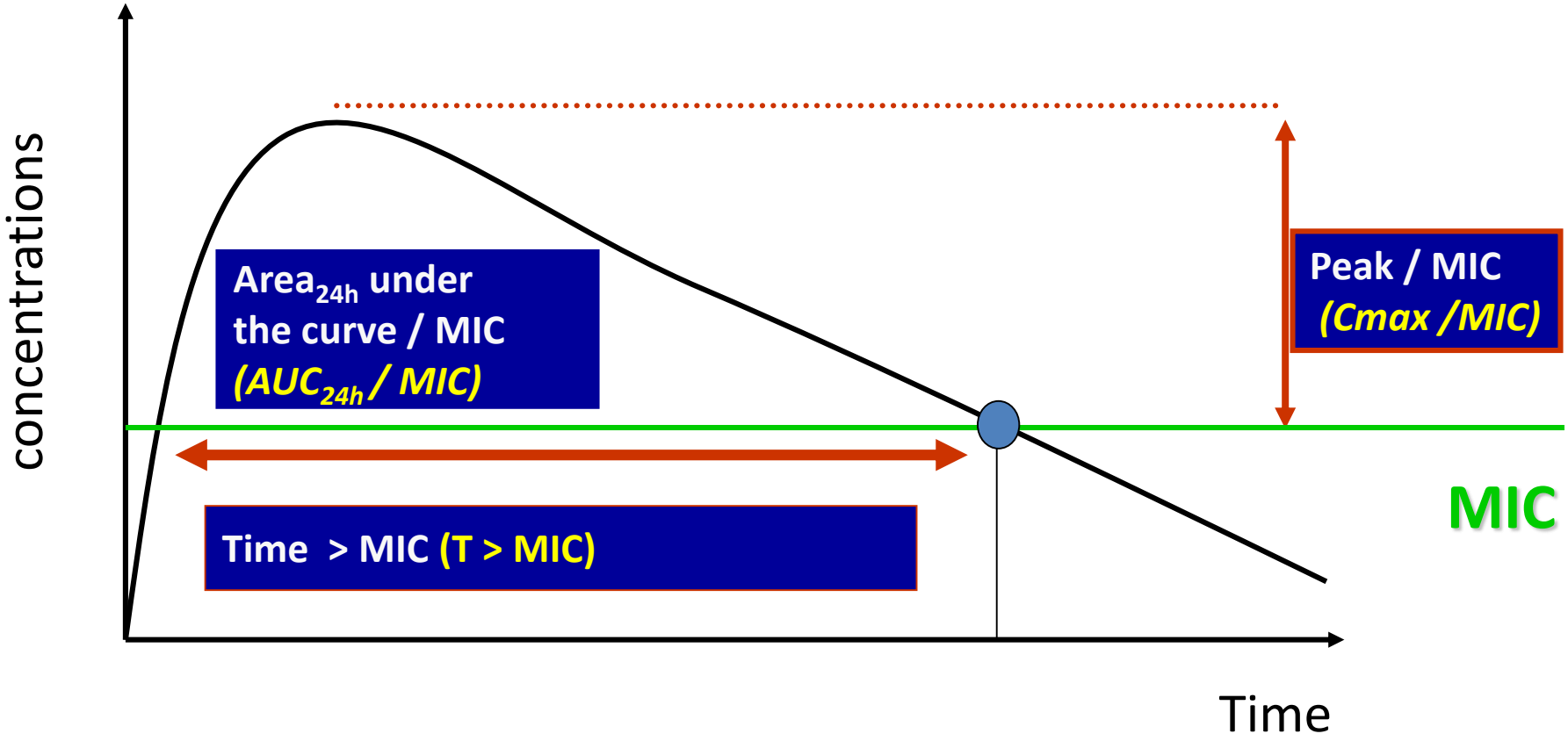
- Amoxicillin raw data (plasma concentrations *versus* time profiles)
  - Raw data from 3 pharmaceutical companies, 1 academic laboratory
  - IV (21), IM (104), PO (66) : 191 individual disposition curves
    2,098 plasma samples
  - Data obtained under GLP, with validated analytical techniques
- Population pharmacokinetic modelling
  - Specialized software : Monolix 4.1.1
  - Population (mean) values of PK parameters and their inter-individual variability
- Monte Carlo simulations (MCS)
  - For each scenario : simulation of 1,000 individual plasma profiles, using the final population pharmacokinetic model
  - Calculation of T>MIC, for MICs ranging from 0.0625 to 4 µg/mL

The Results

Methodology for setting a PK/PD cut-off : the case of AMOXICILLIN

Step 1 and 2 : the critical value of the PK/PD index

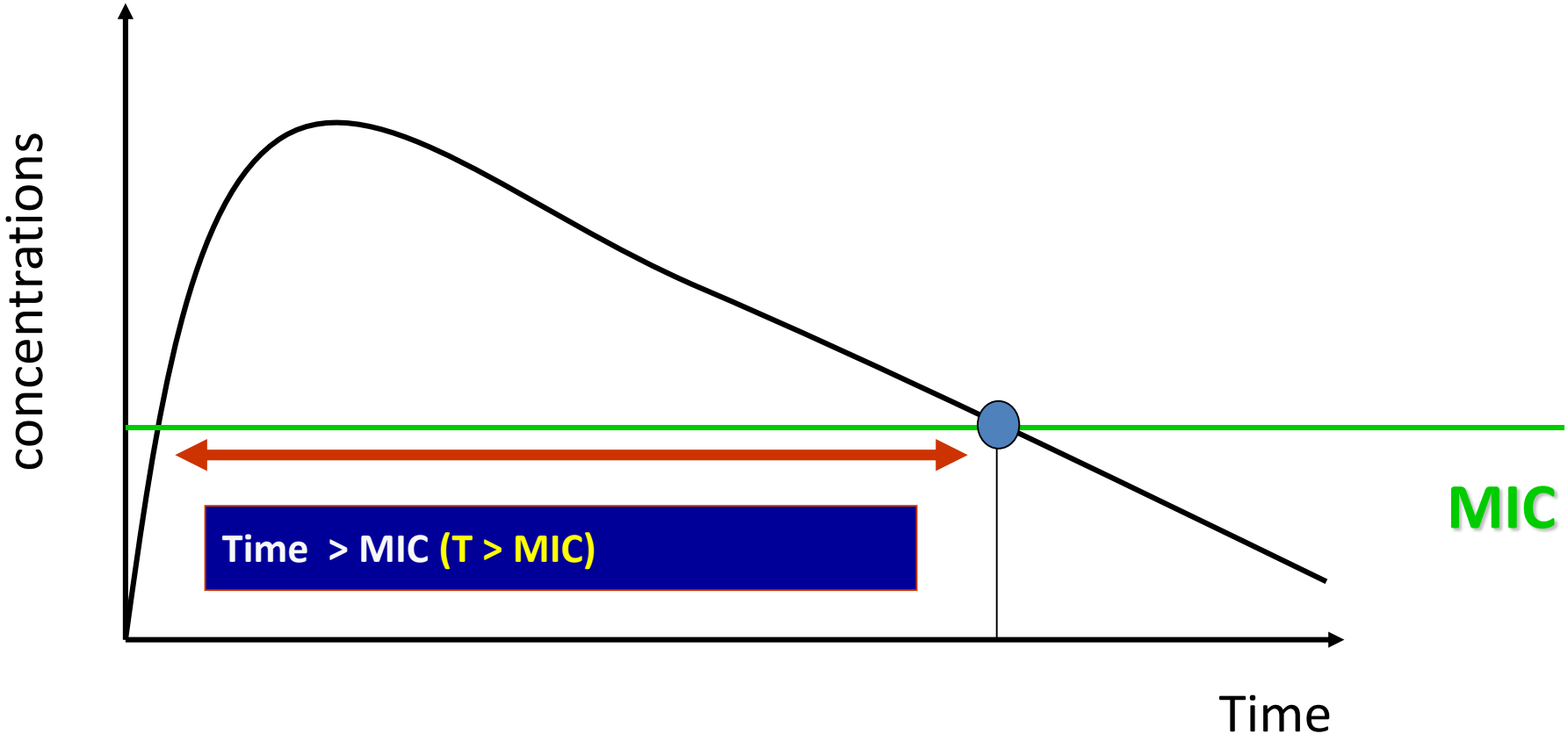
The 3 PK/PD indexes for antibiotics



Methodology for setting a PK/PD cut-off : the case of AMOXICILLIN

Step 1 and 2 : the critical value of the PK/PD index

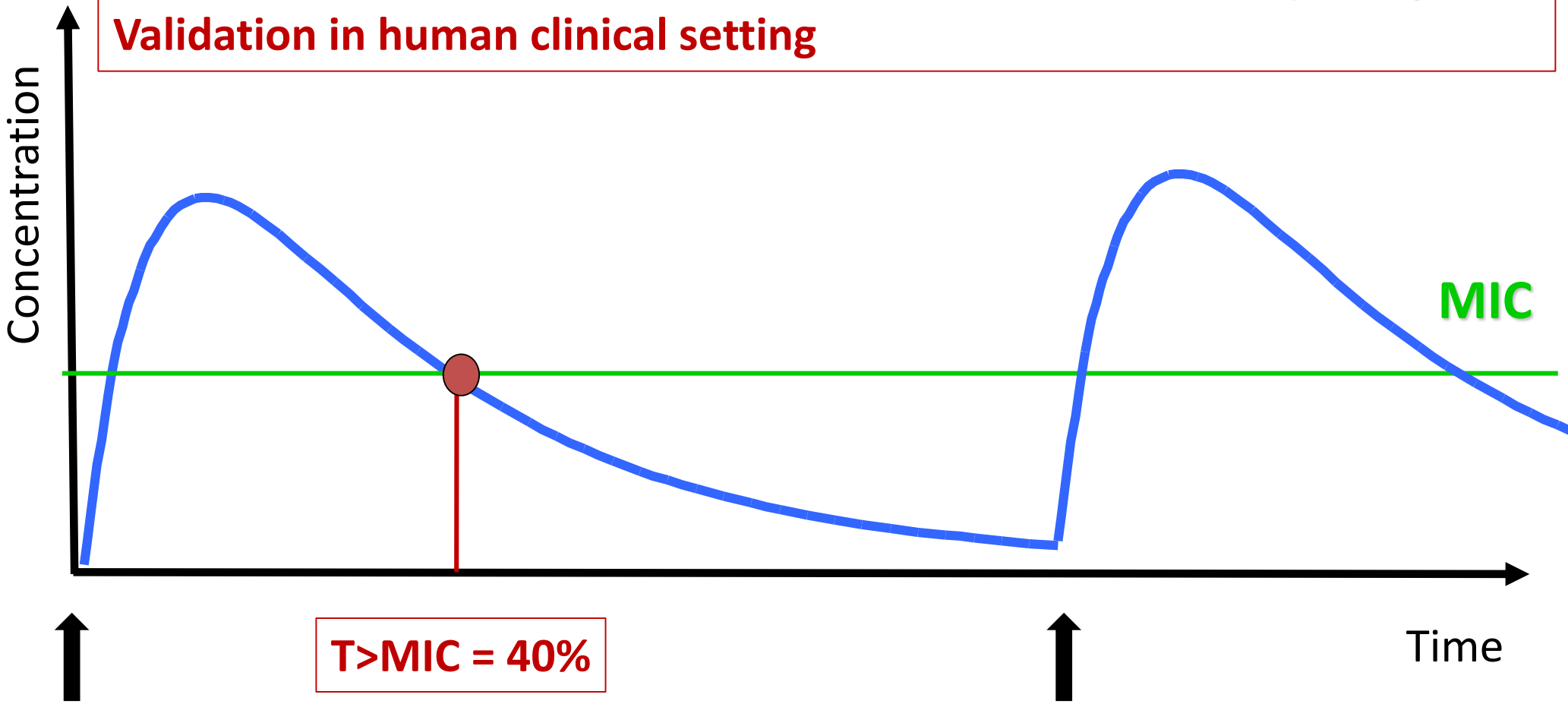
The PK/PD index for beta-lactams



Methodology for setting a PK/PD cut-off : the case of AMOXICILLIN

Step 1 and 2 : the critical value of the PK/PD index

Determination in rodent models of infections with human pathogens
Validation in human clinical setting



Methodology for setting a PK/PD cut-off : the case of AMOXICILLIN

The setting of a $CO_{PK/PD}$

Step1

The PK/PD index predictive of clinical efficacy is **T > MIC**

Step 2

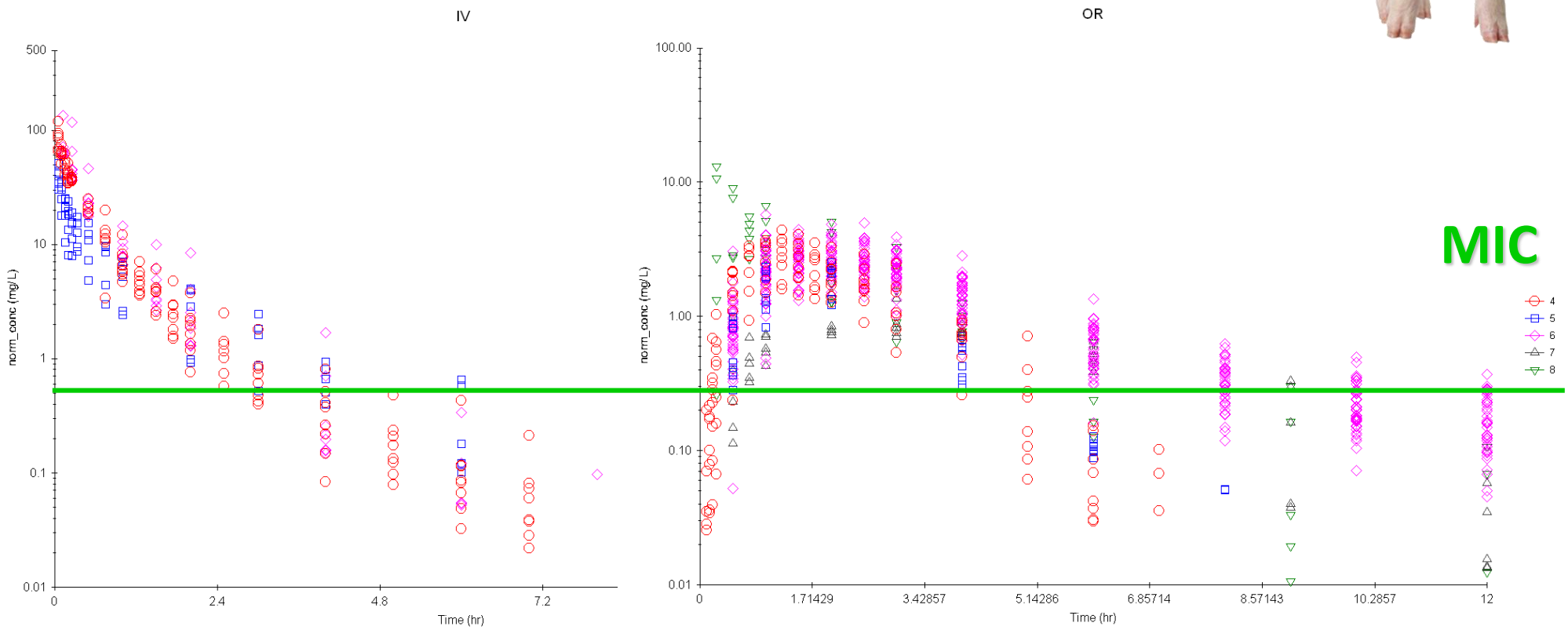
The selected critical value (size) of T > MIC is **40% of dosage interval**

Step 3

Computation of the percentage of animals in which the critical value of the selected PK/PD index will be achieved (Probability of Target Attainment, PTA>90%) for **a given animal species**, for **a given dose**, and for **all MICs in a given range**

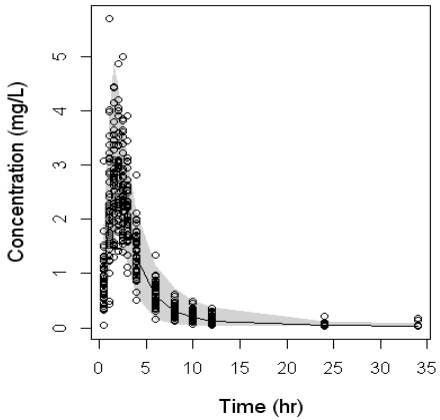
Population pharmacokinetics modelling : raw data

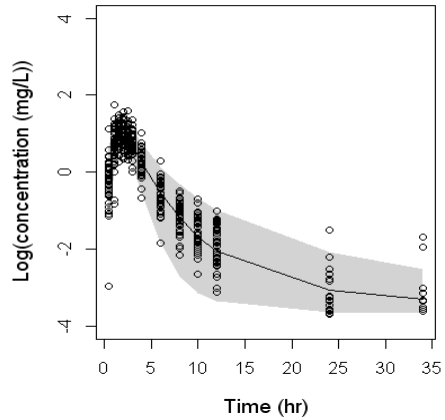
IV **PO**



Population pharmacokinetics modelling : the final model

PO

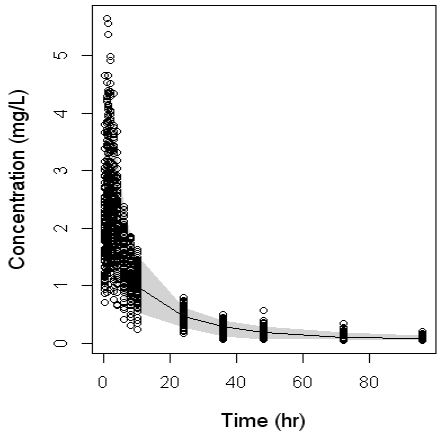


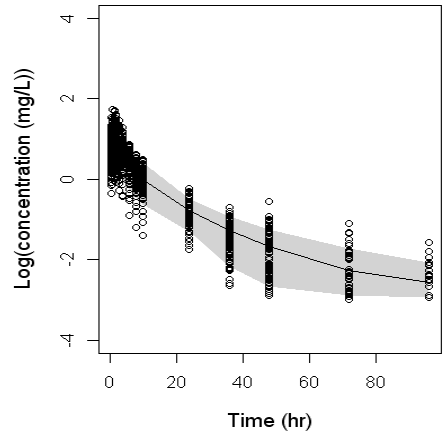


Parameter	Population geometric mean	CV (%)
Lag time (h)	0.094 (4); 0.194 (5,6,7,8)	40.3
Duration of the zero order of absorption (h)	1.73 (4,5,6,8); 6.23 (7)	29.9
CL/F (L/kg/h)	3.1(4,5,7); 1.55 (6,8)	23.4
CL_d/F (L/kg/h)	0.297 (All formulations)	98.1
Vc/F (L/kg)	3.54 (All formulations)	34.6
Vp/F (L/kg)	3.56 (All formulations)	66.4

IM

Grey area = 90% confidence interval





Parameter	Population geometric mean	CV (%)
Ka1 (1/h)	0.343 (9) ; 0.275 (10)	28.8
Ka2 (1/h)	0.041(9); 0.003 (10)	52.5
Fraction of dose absorbed following Ka1 (from 0–1)	0.161 (9) ; 0.403 (10)	52.2
CL/F (L/kg/h)	0.388 (9); 0.279 (10)	14.1
Vc/F (L/kg)	0.252 (9 and 10)	32.1

MCS simulations and Probability of Target Attainment (PTA) : IM route

PTA = Percentage of pigs for which $T_{>MIC}$ is above a given % of the dosing interval for different MICs

for an IM administration of amoxicillin at 15 mg/kg

Time > MIC over 24h	MIC value (mg/L)						
	0.0625	0.125	0.25	0.5	1	2	4
0%	100	100	100	100	100	100	100
10%	100	100	100	99.9	92.95	32.6	0.15
20%	100	99.8	97.8	81.65	30.45	0.1	0
30%	99.15	93.15	73.05	47.1	3.6	0	0
40%	95.1	77	53.8	35.7	0	0	0
50%	89.3	64.45	48.95	16.7	0	0	0
60%	83.5	57.75	43.35	2.35	0	0	0
70%	80.5	55.25	35.6	0.1	0	0	0
80%	78.5	50.9	26.4	0	0	0	0
90%	75.5	46.15	14.85	0	0	0	0
100%	72.55	40.85	7.45	0	0	0	0

AMOX 15 mg/kg IM

Time > MIC over 24h	MIC value (mg/L)						
	0.0625	0.125	0.25	0.5	1	2	4
0%	100	100	100	100	100	100	100
10%	100	100	100	99.9	92.95	32.6	0.15
20%	100	99.8	97.8	81.65	30.45	0.1	0
30%	99.15	93.15	73.05	47.1	3.6	0	0
40%	**95.1**	**77**	**53.8**	**35.7**	**0**	**0**	**0**
50%	89.3	64.45	48.95	16.7	0	0	0
60%	83.5	57.75					
70%	80.5	55.25					
80%	78.5	50.9					
90%	75.5	46.15					
100%	72.55	40.85					

AMOX 30 mg/kg IM

Time >MIC over 24h	MIC value (mg/L)						
	0.0625	0.125	0.25	0.5	1	2	4
0%	100	100	100	100	100	100	100
10%	100	100	100	100	99.95	93.15	30.85
20%	100	100	99.9	98.1	83.05	29.6	0.15
30%	99.95	99.6	94.2	73.35	48.55	3.9	0
40%	**99.8**	**95.55**	**76.55**	**54.45**	**35.95**	**0.1**	**0**
50%	99.4	89.95	64.95	49.9	16.6	0	0
60%	97.85	84.8	59.35	45.95	3.4	0	0
70%	96.9	81.6	56.6	38.25	0.4	0	0
80%	96.1	79.45	53.2	27.75	0.05	0	0
90%	94.95	77	48.85	17.3	0	0	0
100%	94	74.45	43.65	8.4	0	0	0

MCS simulations and Target Attainment Rates (TAR) : PO route

PTA = Percentage of pigs for which $T_{>MIC}$ is above 40% of the dosing interval for different MICs

Dosing regimen	Total daily dose over 24 hours (mg/kg)	MIC value (mg/L)					
		0.0625	0.125	0.25	0.5	1	2
1 administration	10	39.52	18.52	2.44	0	0	0
	15	51.28	31.20	12.04	0.48	0	0
	20	58.08	40.24	19.16	2.78	0.02	0
	40	74.96	58.92	39.42	18.98	2.72	0
2 administrations every 12 hours	10	77.10	55.64	13.22	0.04	0.00	0
	15	85.68	69.22	40.10	2.70	0.00	0
	20	89.90	76.92	56.42	14.08	0.02	0
	40	96.02	89.60	77.40	56.20	13.94	0.02
3 administrations every 5.5 hours	10	94.32	74.36	26.58	0.14	0	0
	15	97.48	89.08	53.04	8.22	0	0
	20	98.64	93.82	73.32	25.48	0.12	0
	40	99.52	98.60	94.32	73.94	25.76	0.12
4 administrations every 3 hours	10	98.64	85.62	33.44	0.24	0	0
	15	99.66	96.72	63.60	12.30	0	0
	20	99.80	98.90	84.52	32.66	0.24	0
	40	99.98	99.82	98.56	85.36	32.58	0.32
15 hours infusion	10	99.26	92.82	40.78	0.82	0	0
	15	99.70	98.46	77.74	18.54	0.02	0
	20	99.88	99.26	92.82	40.78	0.82	0
	40	99.92	99.88	99.26	92.80	40.78	0.82

MCS simulations and Target Attainment Rates (TAR) : Summary

- After IM route, the PTA≥90% could only be achieved for :
  - **MIC ≤ 0.0625 µg/mL** using **15 mg/kg/day**
  - **MIC ≤ 0.125 µg/mL** using **30 mg/kg/day**

- After PO route, the PTA≥90% was (nearly) achieved for :
  - **MIC ≤ 0.0625 µg/mL** using **10 mg/kg each 12 h (20 mg/kg/day)**
  - **MIC ≤ 0.125 µg/mL** using **20 mg/kg each 12 h (40 mg/kg/day)**

- A $CO_{PK/PD}$ of **0.125 µg/mL** could be suggested

- Whatever the route, the PTA≥90% was never achieved with the MIC of 0.5 µg/mL, which is the clinical breakpoint for susceptibility currently recommended (Schwarz et al., Vet Microbiol, 2008)

Discussion & conclusion

Discussion & conclusion

- Assumptions & limits of the study :
  - The value of the PK/PD index, 40% of dosage interval, has not been clinically validated in pigs, with veterinary pathogens
  - The selected PTA, 90% of treated animals, is a classical but arbitrary choice; benefit-risk balance ?
  - PK data were obtained from healthy animals, whereas the disease can influence the body disposition of the antibiotics

- The main factor explaining that we obtained very low $CO_{PK/PD}$ is the magnitude of inter-individual variability of AMOX PK

- The $CO_{PK/PD}$ value is strictly linked to a given dosage regimen

Discussion & conclusion

- In this study we provided a **$CO_{PK/PD}$**, which is one of the 3 CO that should be considered to establish a clinical breakpoint

- Because they allow taking into account **inter-animal variability**, **PopPK** and **MCS** are invaluable tools for setting robust species-specific interpretative criteria for AST

Thank you for your attention