Pharmacology of amoxicillin and doxycycline by oral route in pigs

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Pharmacological approach to optimize dosage regimen

- Pharmacodynamics (PD) : *in vitro* determination of antimicrobial activity
- Pharmacokinetics (PK) : *in vivo* antimicrobial concentrations as a function of time after drug administration
- Correlation PK/PD: definition of dosage regimen adapted to antimicrobial mode of action for control of infection and limitation of resistance

Pharmacodynamics: *In vitro* determination of antimicrobial activity

- Routine susceptibility tests
- Minimum inhibitory concentrations determinations
- Time kill curves studies

Pharmacodynamics: routine susceptibility tests

- Agar disk diffusion test

- Reading: inhibition diameter of bacterial growth following a 18-24 h incubation period

- Classification (according to breakpoints): susceptible, intermediate, resistant

Susceptibility rates of pig pathogens to amoxicillin

Country	Species	Number of isolates	Susceptibility rate	Source
France	*Str. suis*	204	100 %	Resapath 2010
	P. multocida	124	98 %	
	Actinobacillus pleuropneumoniae	148	96 %	
Italy	*Str. suis*	379	86 %	Barigazzi et al 2007
Poland	*Str. suis*	393	99 %	Pejsak et al 2005
	P. multocida	158	99 %	
	Actinobacillus pleuropneumoniae	85	96 %	
	H. parasuis	40	98 %	

- No emergence of resistance over time

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Susceptibility rates of pig pathogens to doxycycline

Country	Species	Number of isolates	Susceptibility rate	Source
France	*Actinobacillus pleuropneumoniae*	109	92 %	Resapath 2010
	P. multocida	124	89 %	
Poland	*Haemophilus parasuis*	40	98 %	Pejsak et al 2005
	P. multocida	158	97 %	
	Actinobacillus pleuropneumoniae	85	92 %	

- No emergence of resistance over time

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Routine susceptibility tests: conclusions

- Interests:
  - Clinical tool to detect resistant isolates
  - Epidemiological tool to follow - up susceptibility over time
- Limits:
  - Classification (S, I, R) based on definition of breakpoints

Pharmacodynamics: minimum inhibitory concentrations (MICs)

- Agar or broth dilution method

- MIC: minimum antibiotic concentration inhibiting visible bacterial growth after a 18 to 24 h incubation period

MICs of amoxicillin against pig pathogens (I)

Bacteria	Country	Number of isolates	MIC_{90} (µg/ml)	Source
Streptococcus suis	Spain	151	< 0.25	Vela et al 2005
	Germany	77	0.03	Schwarz et al 2007
	Europe	110	0.03	Vetpath 2008
H. parasuis	France	20	0.125	Allix et al 2003

- MIC_{90} : concentration inhibiting 90% of isolates

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MICs of amoxicillin against pig pathogens (II)

Bacteria	Country	Number of isolates	MIC_{90} (µg/ml)	Source
Pasteurella multocida	Spain	132	< 0.25	Lizarazo et al 2006
	Europe	129	0.25	Vetpath 2008
Actinobacillus pleuropneumoniae	Germany	124	0.25	Schwarz et al 2008
	Europe	129	0.5	Vetpath 2008
	Sweden	24	0.25	Svarm 2009

- MIC_{90} : concentration inhibiting 90% of isolates

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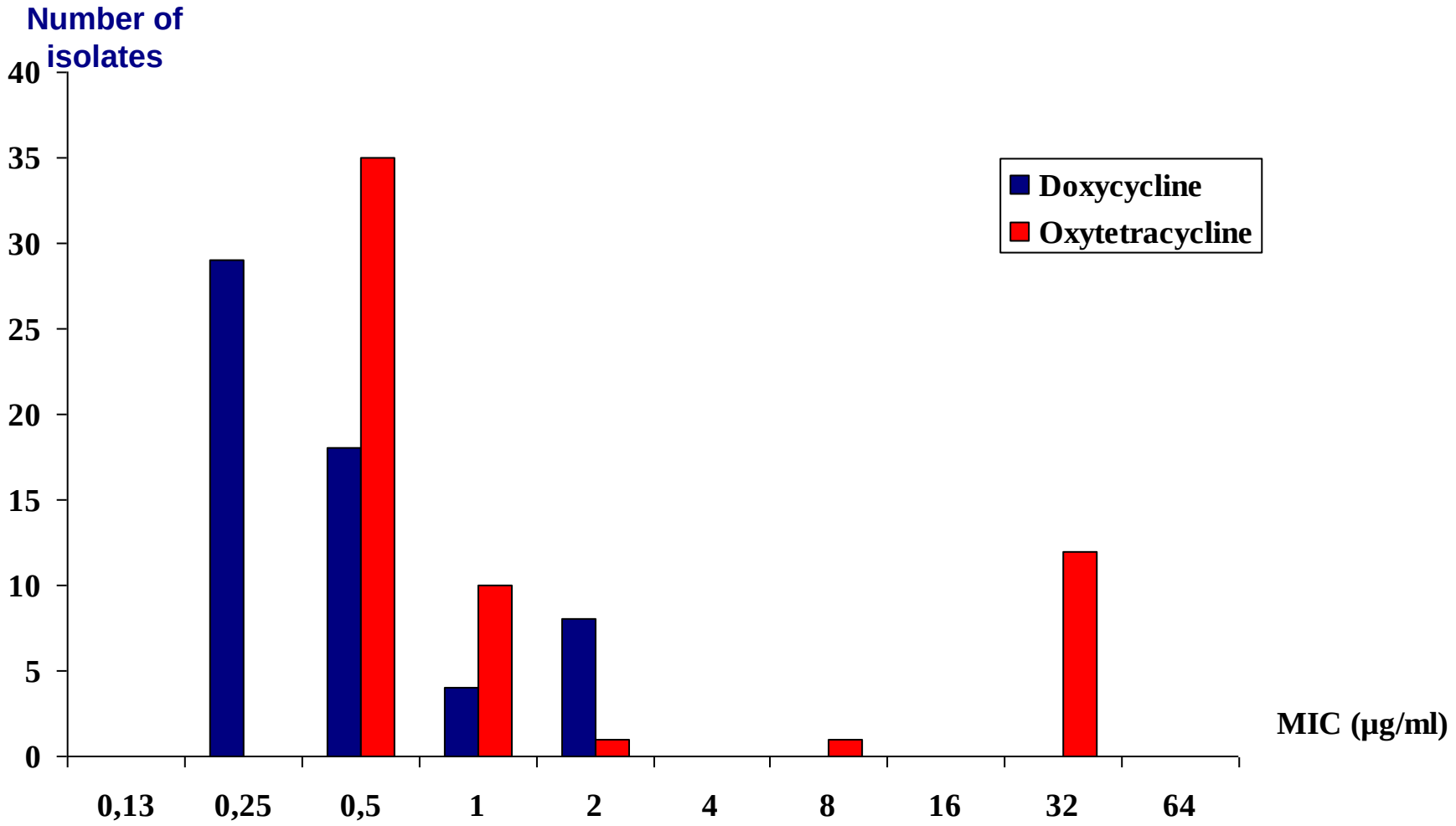
MICs of doxycycline against pig pathogens

Species	Country	Number of isolates	MIC_{90} (µg/ml)	Source
P. multocida	France	131	1	Bousquet et al 1997
	Hungary	10	0.25	Fodor et al 2004
	Germany	25	0.75	Allix et al 2004
	Spain	21	0.5	Prats et al 2005
A. pleuropneumoniæ	France	68	1	Bousquet et al 1997 Gicquel et al 1998
	Hungary	10	1	Fodor et al 2004
H. parasuis	France	34	0.5	Gardey et al 2002

Comparative MICs of doxycycline and oxytetracycline against *Actinobacillus pleuropneumoniae* (59 French isolates)



Higher liposolubility of doxycycline compared to first generation tetracyclines : enhanced bacterial penetration (Bousquet et al 1997)

MICs of tetracyclines against *Mycoplasma hyopneumoniae (I)*

Country	Antibiotic	N° of isolates	MIC_{90} (µg/ml)	Source
Netherlands	DC	10	0.03	Ter Laak et al 1991
	CTC	10	1	
France	DC	3	0.03	Kobisch 1993
UK	DC	26	1	Bousquet et al 1997
	OTC	26	2	

DC: Doxycycline
CTC: Chlortetracycline
OTC: Oxytetracycline

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MICs of tetracyclines against *Mycoplasma hyopneumoniae (II)*

Country	Number of isolates	MIC_{90} (µg/ml)	Source
Belgique	21	Doxy : 0.5 OTC : 1	Vicca et al 2004
Espagne	19	Doxy : 0.2	Prats et al 2005

Minimum inhibitory concentrations : conclusions

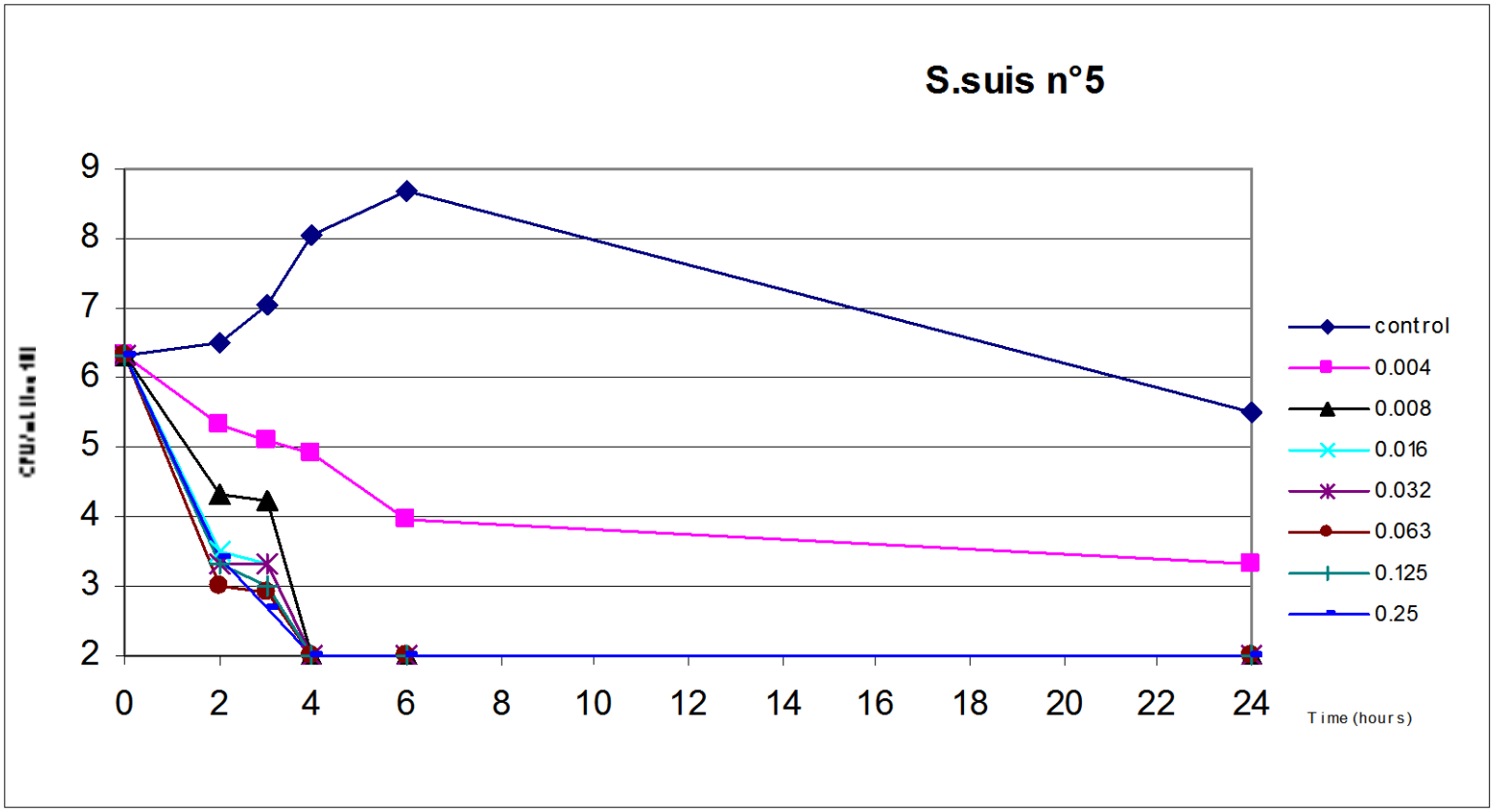
- Standardized quantitative method but no information on bacterial killing and static method (fixed endpoint reading)
- Amoxicillin MICs : from 0.03 – 0.125 µg/ml (*Streptococcus suis and Haemophilus parasuis)* to 0.25 – 0.5 µg/ml (*Pasteurella multocida and Actinobacillus pleuropneumoniae)*
- Doxycycline MICs (lower than first generation tetracyclines) : 1 µg/ml (*Pasteurella multocida, Actinobacillus pleuropneumoniae, Haemophilus parasuis, Mycoplasma hyopneumoniae)*

Pharmacodynamics: time kill curves studies

- Dynamic method: evolution of bacterial population following exposure to antibiotic

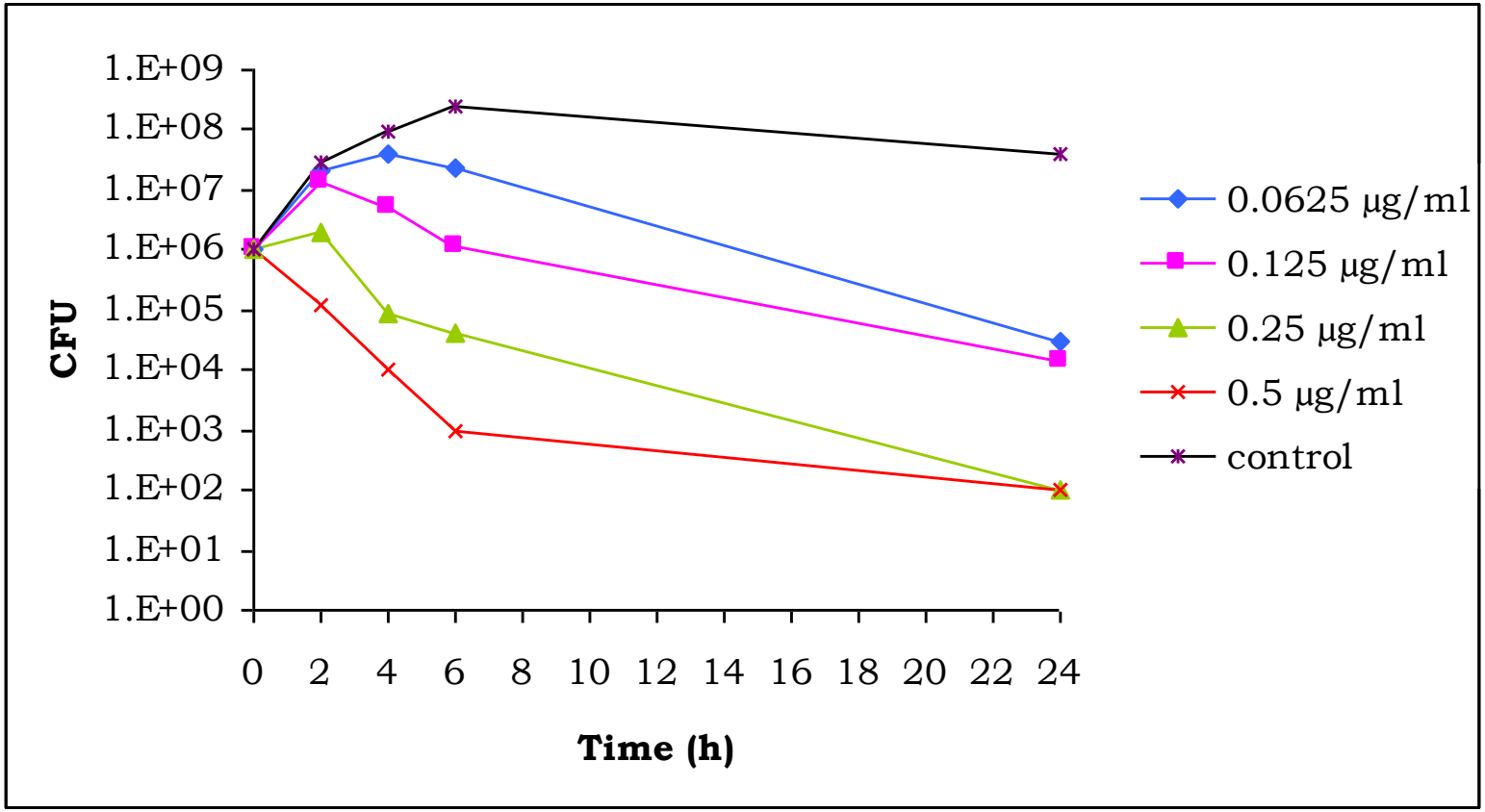
- Classification of antibiotics: bacteriostatic or bactericidal (time/concentration dependent)

Time-kill curve of amoxicillin against *Streptococcus suis*



From Ricouleau et al 2006

Time kill curve of amoxicillin against *H. parasuis*



From Allix et al 2003

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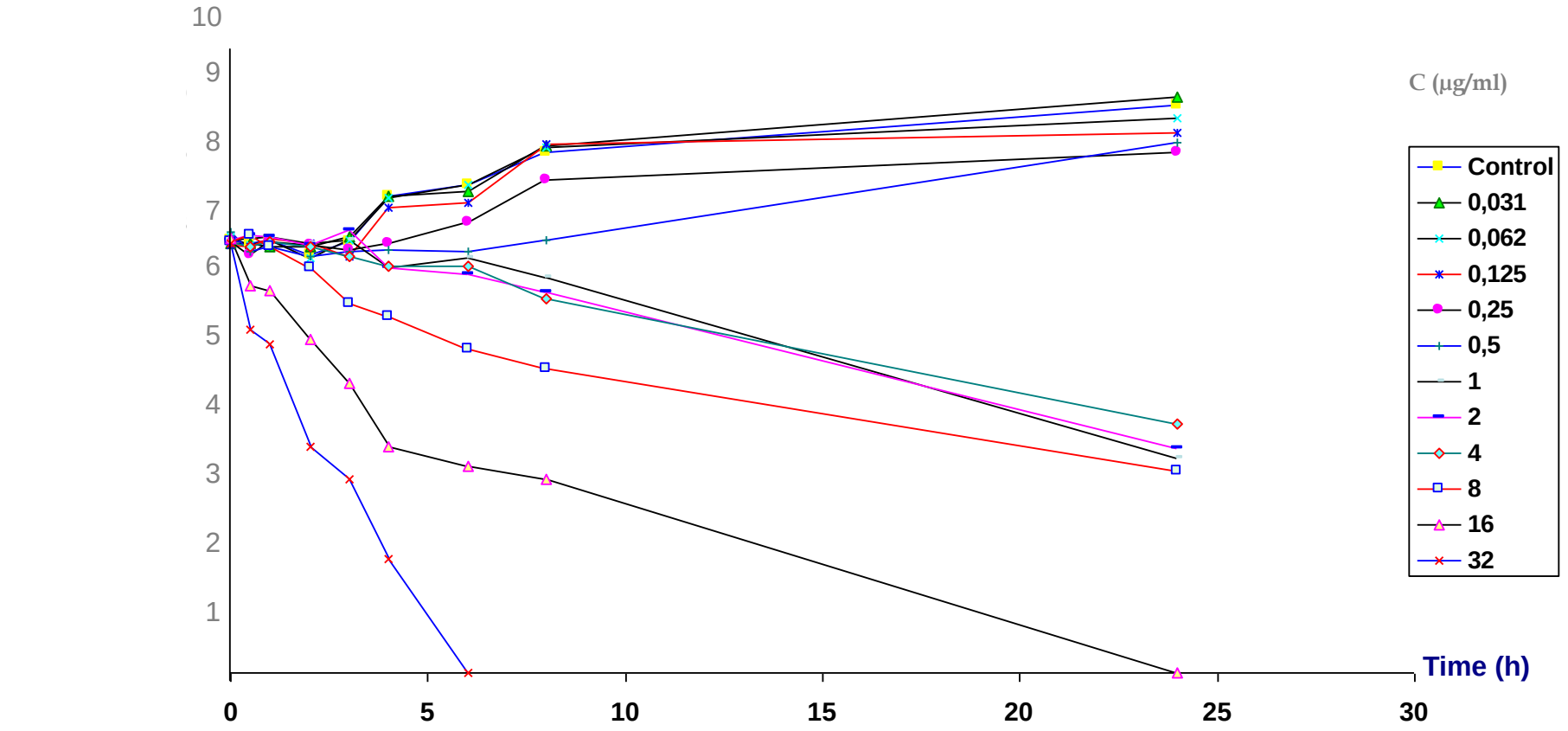
Time kill curve of doxycycline against *Actinobacillus pleuropneumoniae*



Gicquel et al 1999

Time kill curves studies : conclusions

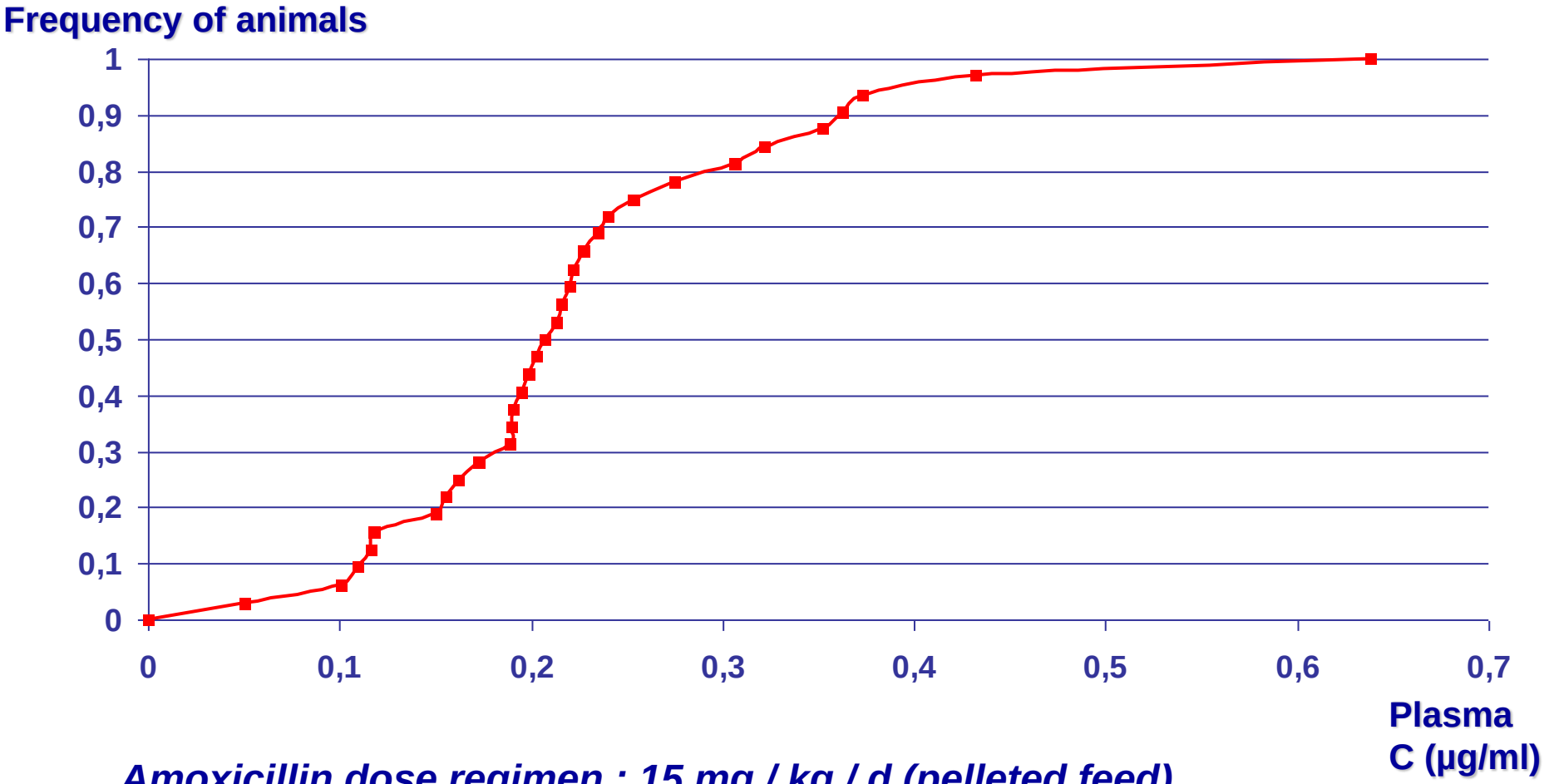
- Tool to optimize dose regimens (daily continuous or pulse medication)
- Amoxicillin : bactericidal action which may be concentration dependent
- Doxycycline : bactericidal time dependent action

Pharmacokinetics of amoxicillin and doxycycline in pigs by oral route (feed and water)

- PK of amoxicillin

- PK of doxycycline compared to first generation tetracyclines

Population PK of amoxicillin in pigs via feed (I)



Amoxicillin dose regimen : 15 mg / kg / d (pelleted feed)
sampling time : 6 a.m.
From Colin, 2000

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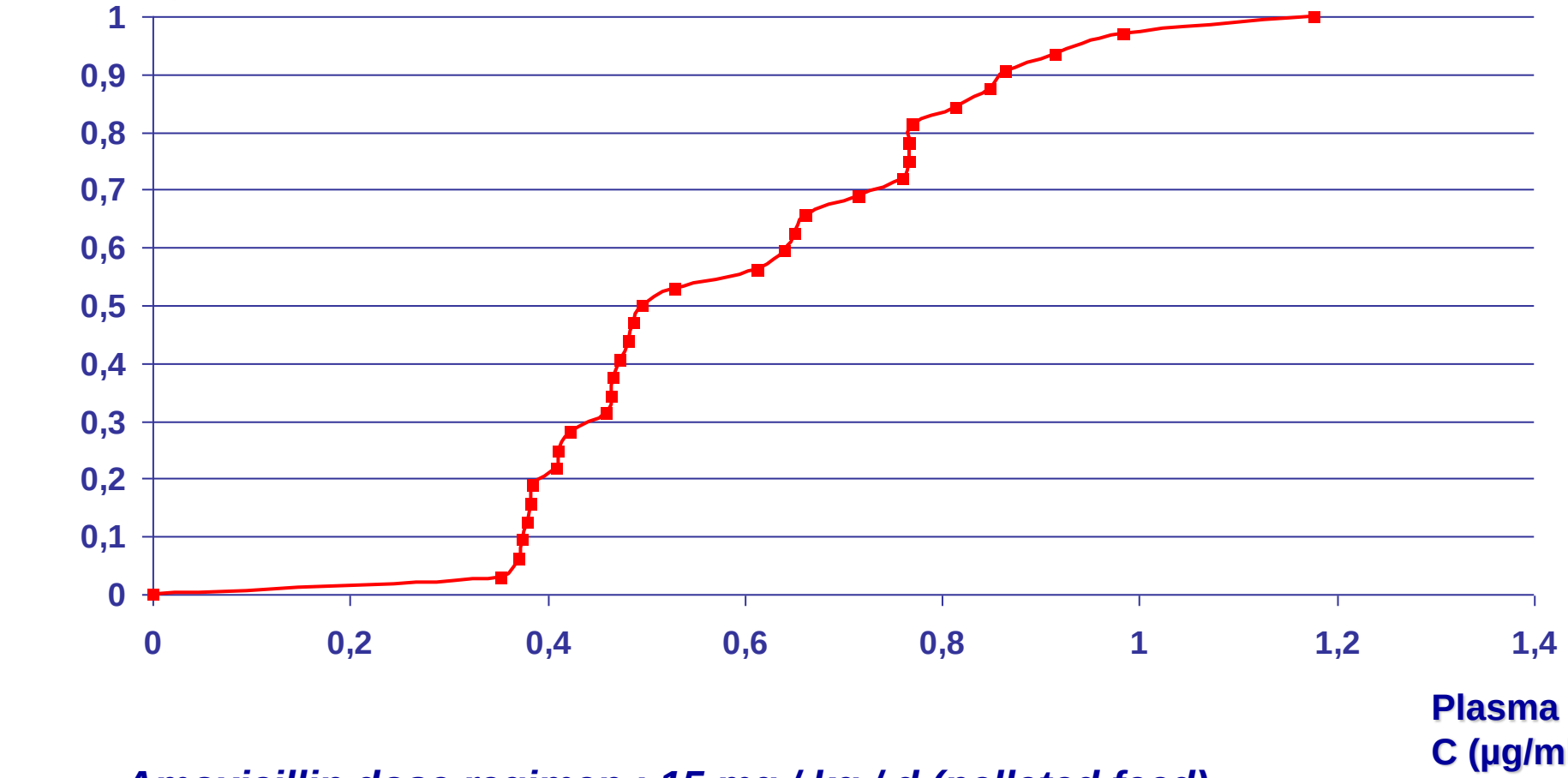
Population PK of amoxicillin in pigs via feed (II)



Amoxicillin dose regimen : 15 mg / kg / d (pelleted feed)
sampling time : 8.45 p.m.
From Colin, 2000

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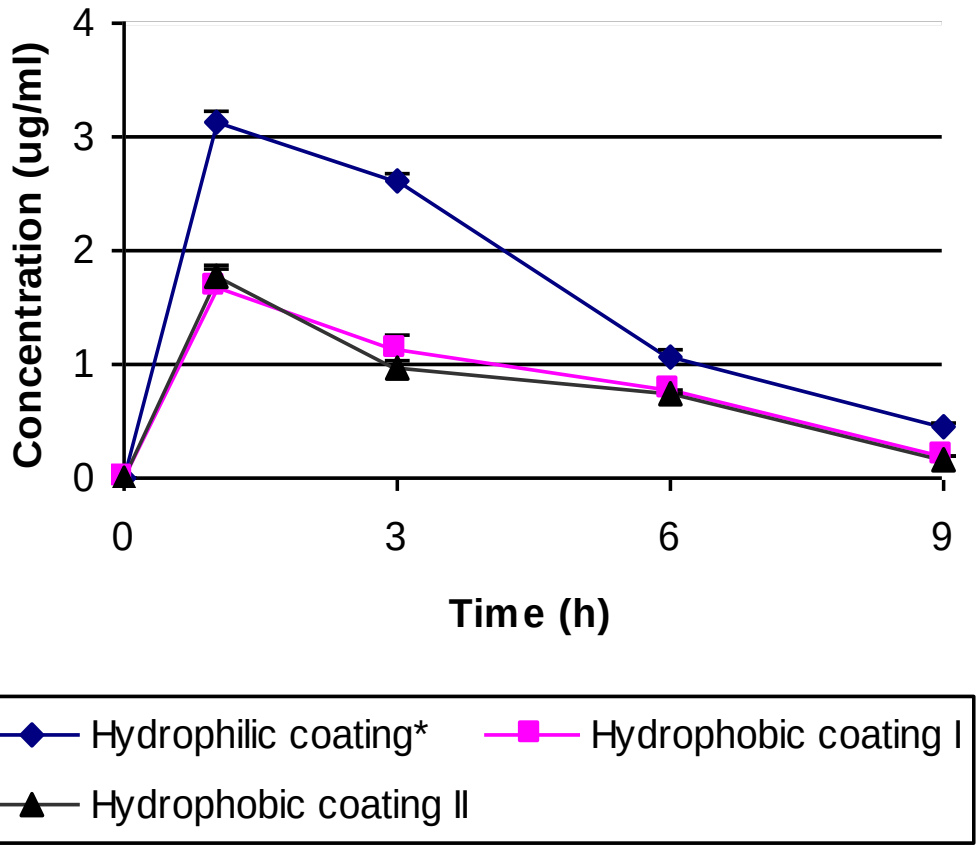
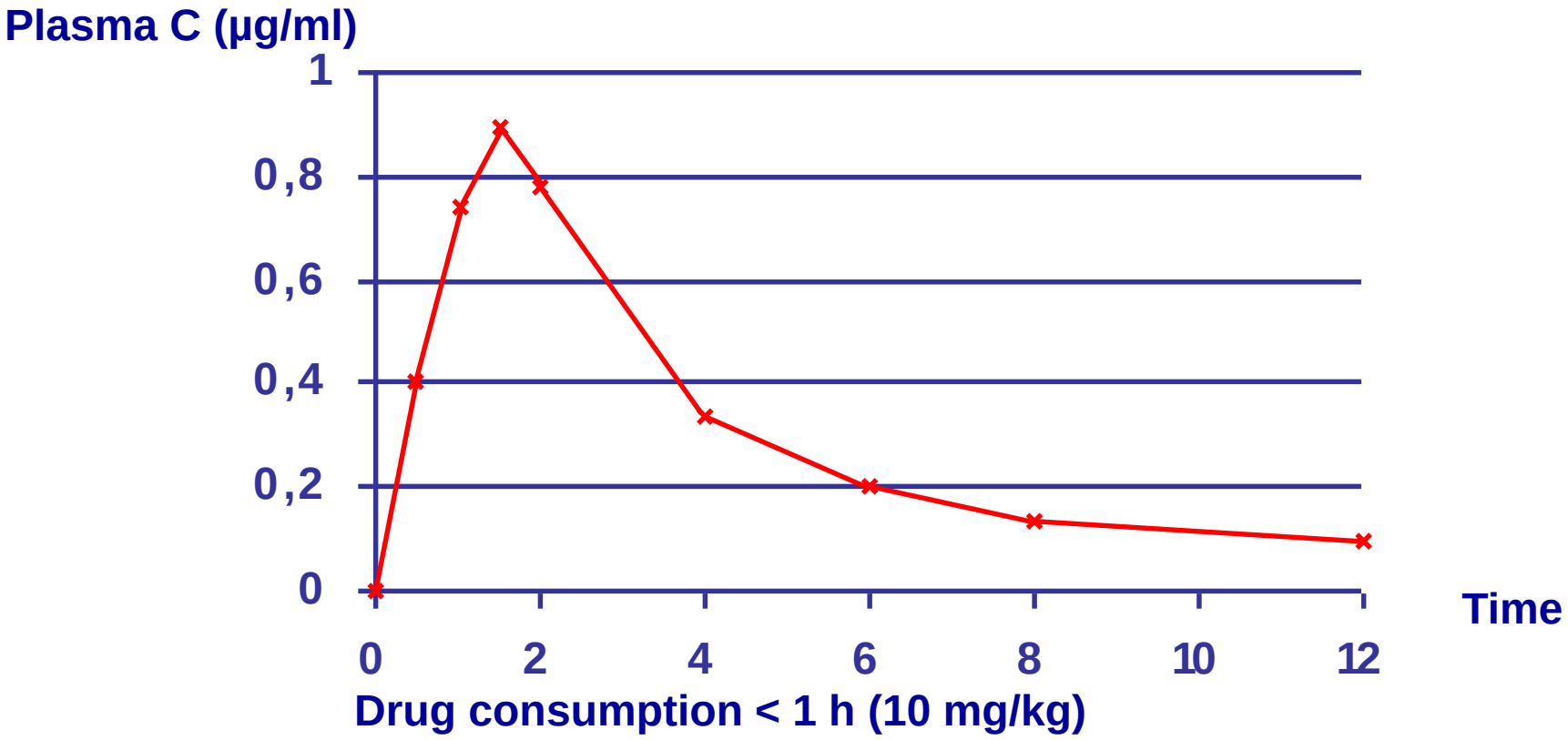
Mean amoxicillin serum concentrations in pigs following oral bolus gavage of 3 premixes mixed with feed (posology: 20 mg/kg, from Sumano 2004)



Possible influence of drug formulation on bioavailability

PK of amoxicillin in pigs via drinking water



Data in file

PK of amoxicillin in pigs : conclusions

- Daily dose regimen : 15-20 mg/kg/d
- Control of *Str. suis or H. parasuis* infections : treatment via feed or water (continuous or pulse)
- *P. multocida or A. pleuropneumoniae* : treatment via water or liquid feed (pulse)

PK of doxycycline in pigs

- Pharmacokinetic characteristics

- Plasma and tissular concentrations after administration in feed or drinking water

Absolute bioavailability of tetracyclines via feed in pigs

	F (%)	Source
Oxytetracycline	3 ± 1	Nielsen et al 1996
Chlortetracycline	6 ± 2	Nielsen et al 1996
Doxycycline	50.3 ± 8.5	Sanders et al 1996

Higher bioavailability of doxycycline due to higher liposolubility

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Pharmacokinetic parameters of tetracyclines in pigs

	Chlortetracycline	Doxycycline
Vss (l/kg)	0.7 ± 0.2	1.3 ± 0.1
MRT (h)	3.6 ± 0.7	8.1 ± 0.7
$t_{1/2}$ (h)	4.8	7.1 ± 0.6
Source	Nielsen et al 1996	Anadon et al 1996

$t_{1/2}$: elimination half life
MRT: mean residence time
Vss: steady-state volume of distribution

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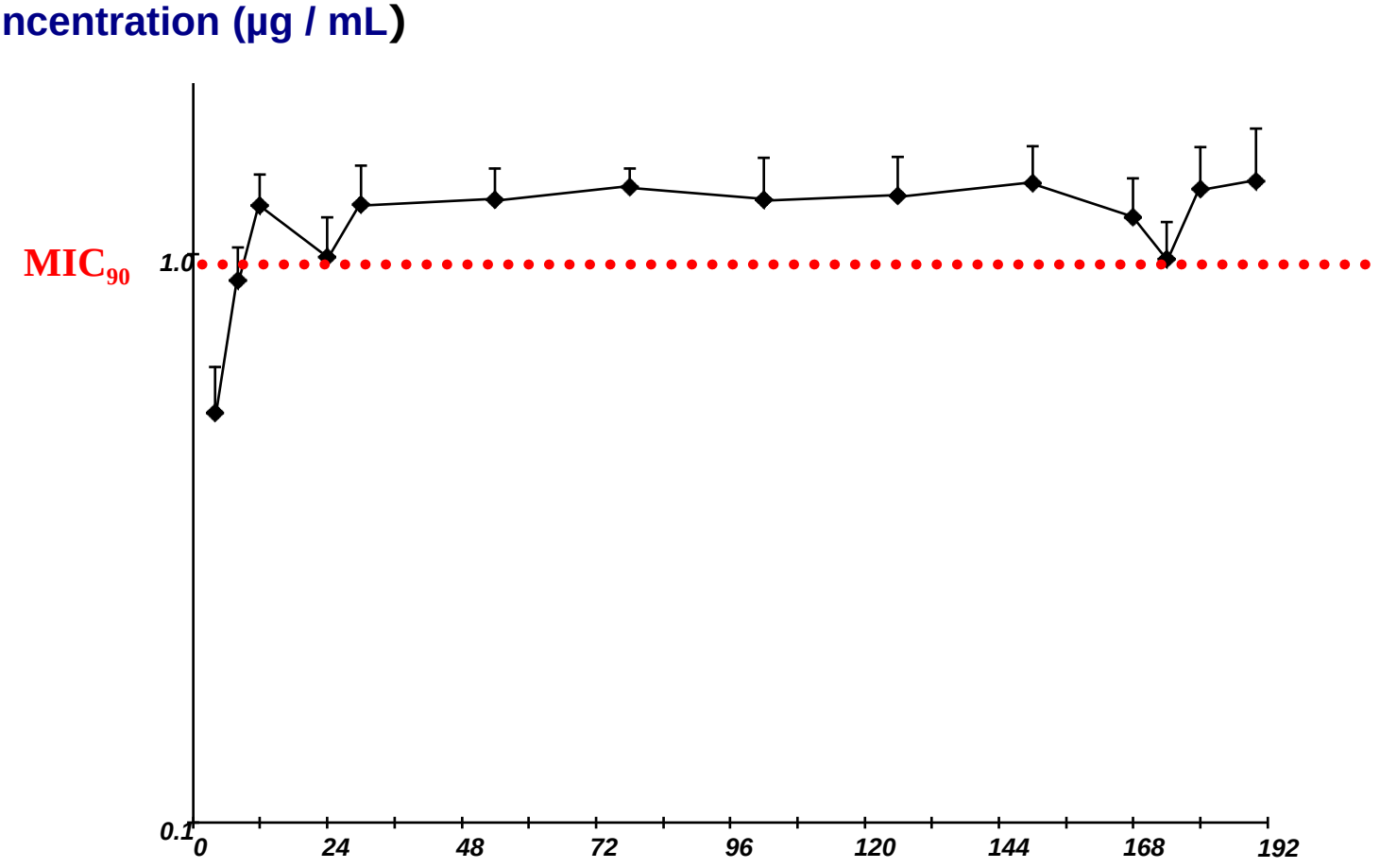
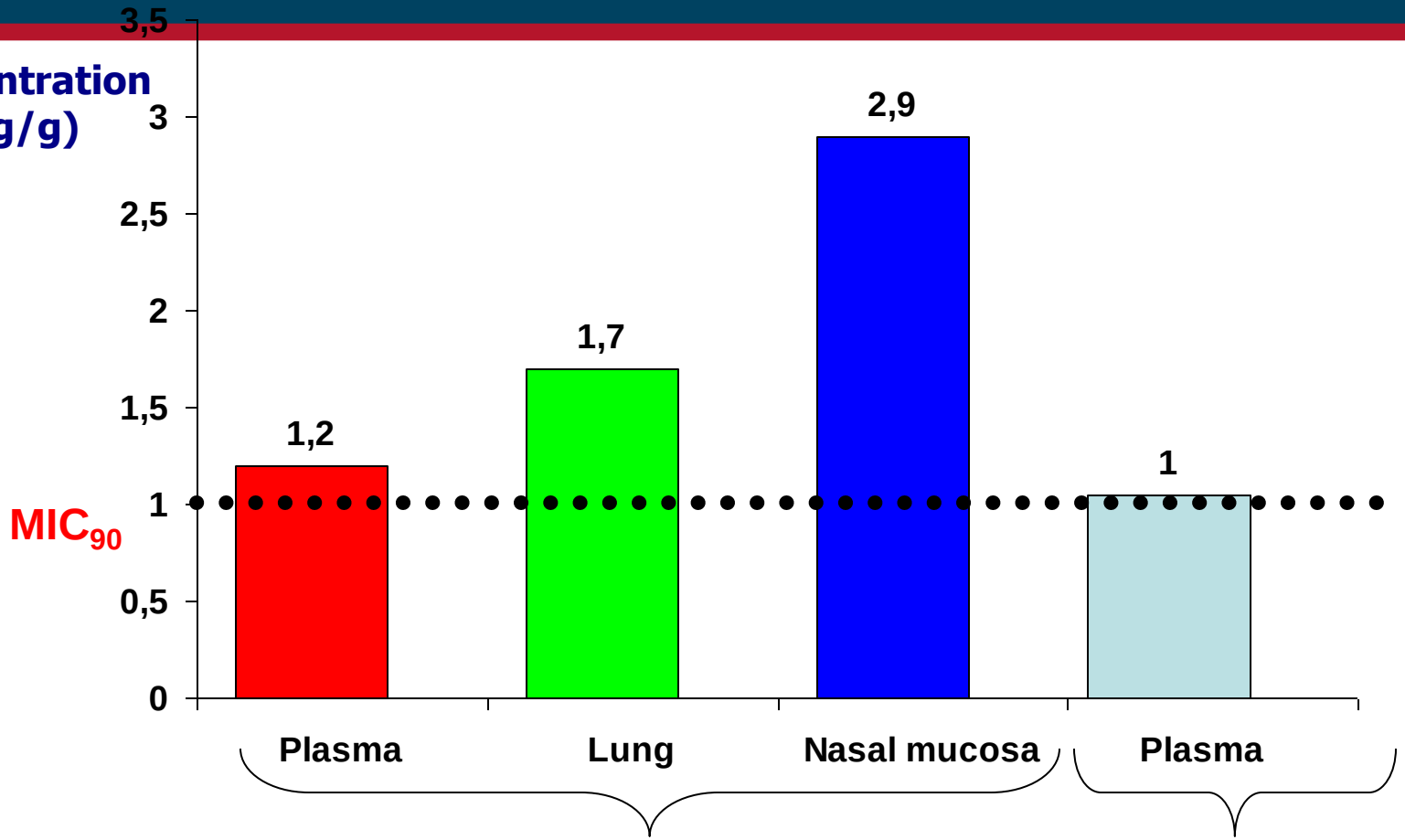
Doxycycline plasma concentrations in pigs during *ad libitum* administration in feed (13 mg/kg/d)



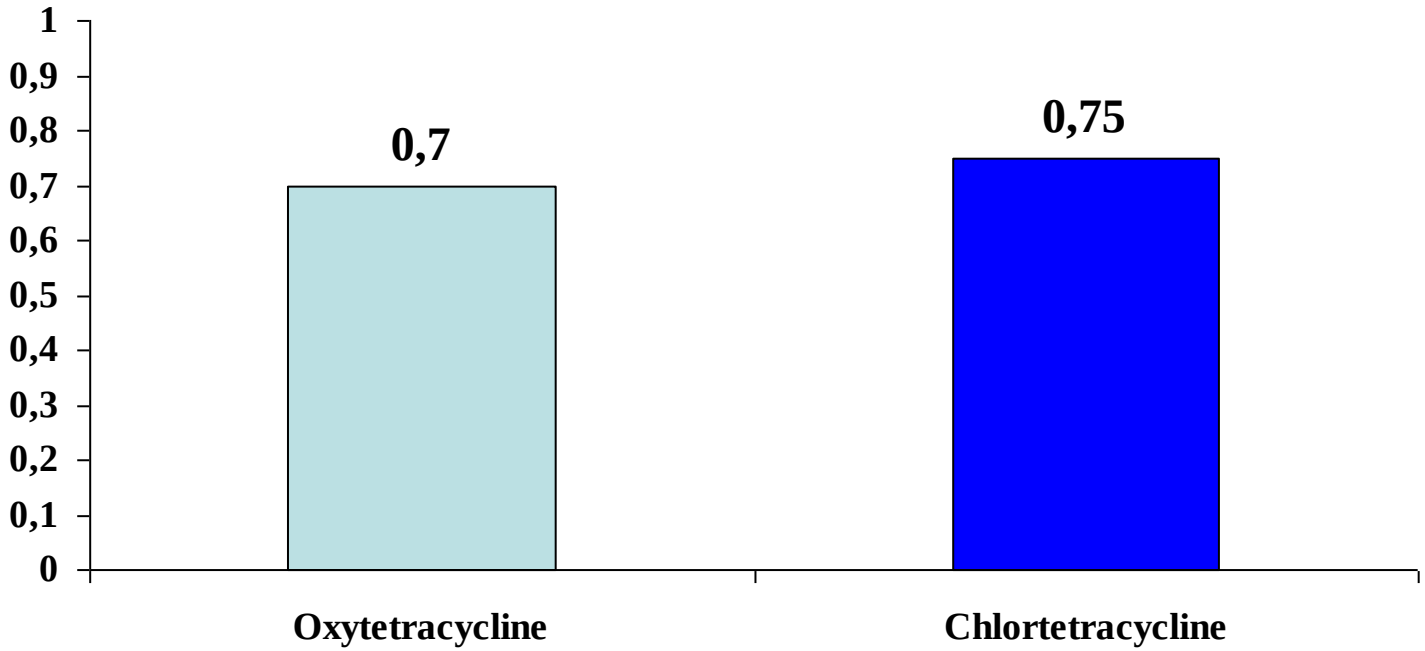
Bousquet et al 1998

Mean steady-state doxycycline concentrations after oral administration to pigs



First generation tetracyclines steady-state plasma concentrations in pigs after administration in feed

Concentration (µg/ml)



OTC : 62 mg/kg/d **(Pijpers, 1990)**

CTC : 1000 ppm **(Kilroy et al, 1990)**

PK of doxycycline in pigs : conclusions

- Dose regimen : 10 – 13 mg/kg/d

- Control of respiratory infections due to *Mycoplasma hyopneumoniae, Actinobacillus pleuropneumoniae, Pasteurella multocida, Haemophilus parasuis :* continuous administration in feed or drinking water

Conclusions

- Pharmacological approach (PK/PD) : useful to optimize dose regimens

- Controlled field trials : necessary to confirm efficacy