HUVEPHARMA®

Veterinary legislation: the devil is in the details

- Legislation
- Intelligent use of antibiotics

Wouter Depondt

TSPC, 19th March 2025

Political environment EU – use of veterinary (antimicrobials) products in Veterinary Medicine

EU regulation 2019/6

- Data collection on use and antimicrobial resistance
- Promote prudent use (AMEG classification)
- **Veterinarians have a key role in ensuring prudent use of antimicrobials** and consequently they should prescribe the antimicrobial medicinal products based on their knowledge of
  - antimicrobial resistance
  - their epidemiological
  - clinical knowledge and their understanding of
  - the risk factors for the individual animal or group of animals.

➔ Follow strictly SPC

➔ Off-label use

➔ Ensure good application

➔ Plan to harmonize SPC's

➔ Promote availability of veterinary medicines. (Limited market authorisation for minor species / minor use)

Off-label use EU:

- Use of a veterinary product out of the terms of its marketing authorisation,
- To avoid unacceptabel suffering, use
  - a product authorised in the relevant Member State or in another Member State for use in the same **or** in another food-producing terrestrial animal species for the same indication, **or** for another indication;
  - **Also valid if product is not available**

- Withdrawal is minimum 1.5x longest withdrawal time
- If withdrawal time exist for the species, withdrawal time stays

Off-label use GB:

The steps, in descending order of suitability, are:

- Veterinary medicine with a Marketing Authorisation valid in GB or UK wide for indicated species and condition
- Veterinary medicine with a Marketing Authorisation valid in NI for indicated species and condition, in accordance with a Special Import Certificate granted by the VMD
- Veterinary medicine with a Marketing Authorisation valid in GB, NI or UK wide for a different species or condition. For products not authorised in GB or UK wide a Special Import Certificate from the VMD is required

Off-label use GB

- the longest withdrawal period provided in the SPC for meat and offal, multiplied by a factor of 1.5
- 28 days, if the product is not authorised for food-producing animals
- 1 day, if the product has a zeroday withdrawal period

Off-label use: check if MRL exists for the species

Pharmacological active substance shall be used in accordance with **Regulation (EC) No 470/2009 (residues…)**

1. Residues will always be below MRL of the species or in case no MRL exist be absent

2. Always under responsibility of the veterinarian

GB: No need for a MRL for the specific species

MRL list: also valid for GB prior to 31/12/2020

COMMISSION REGULATION (EU) No 37/2010
of 22 December 2009
on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin
(Text with EEA relevance)

Apramycin	Apramycin	Bovine	1 000 µg/kg 1 000 µg/kg 10 000 µg/kg 20 000 µg/kg	Muscle Fat Liver Kidney	Not for use in animals from which milk is produced for human consumption.	Anti-infectious agents/Antibiotics
	NOT APPLICABLE	Ovine, porcine, chicken, rabbit	No MRL required	NOT APPLICABLE	For oral use only. Not for use in animals from which milk or eggs are produced for human consumption.	

Exceptions for off-label EU. NEW!

- Amoxicillin- clavulanic acid:
  - Only after identification and susceptibility testing and no lower AMEG classified.
  - Not in Poultry
- 3rd and 4th generation cephalosporines
  - Only after identification and susceptibility testing and no lower AMEG classified.
  - If used for Salmonella: only individual use for life-threathing infections
- Florfenicol
  - Only after identification and susceptibility testing and no lower AMEG classified.

- Quinolones en fluoroquinoles:
  - Only after identification and susceptibility testing and no lower AMEG classified.
  - If used for Salmonella: only individual use for life-threathing infections

Oral granules/powders. NEW

COMMISSION DELEGATED REGULATION (EU) 2024/1159 of 7 February 2024

supplementing Regulation (EU) 2019/6 of

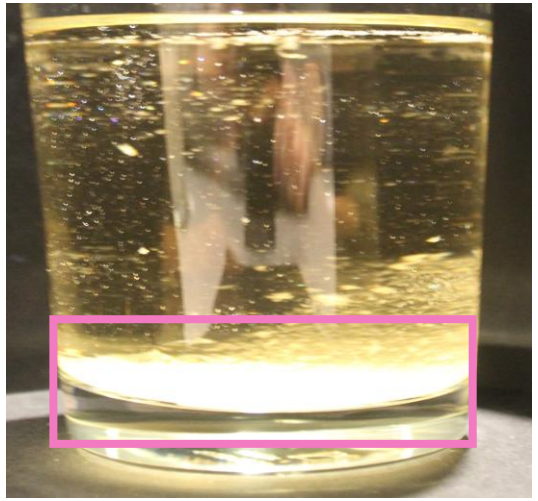
For the effective and safe use of veterinary products for oral application (other than veterinary premixes) and administered by the farmer to food producing animals.

Article 6.2. The veterinarian shall only prescribe antimicrobials and antiparasitics, applied on or through the feed, for the treatment of a small group of animals and if the intake can be ensured/ controlled.

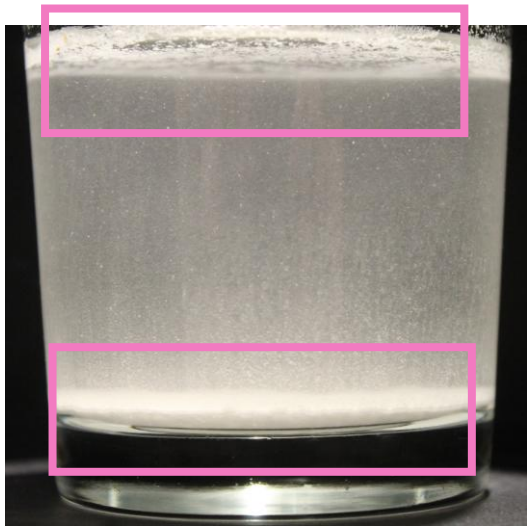
Article 17. The **solubility and stability** of veterinary medicines can be affected by the drinking water. Appropriated measurements might be required. (check compatibility with biocides)

Solubility

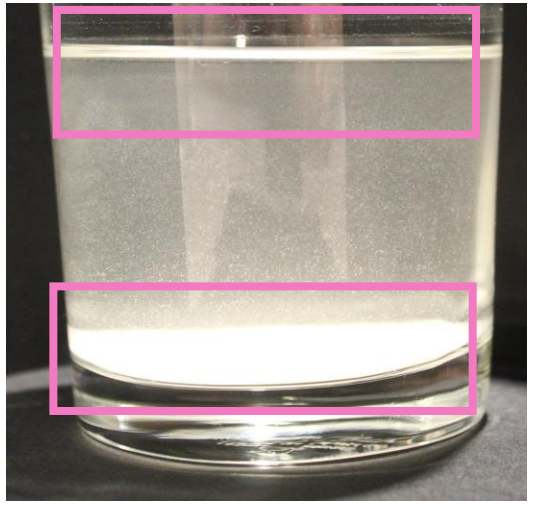
Product A



Product B



Product C



HydroTrim®

NanoTrim®

Trimethoprim

Homogeneity

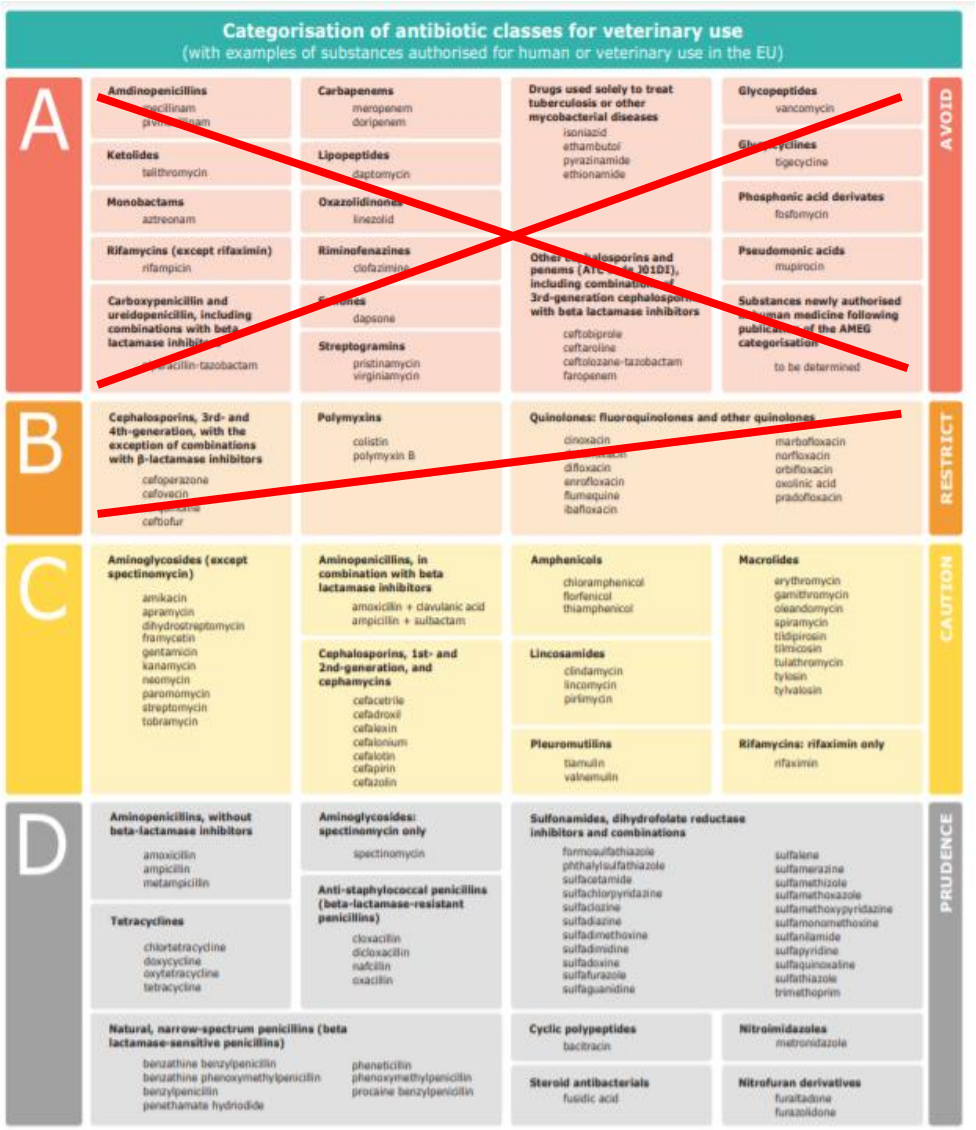
EU categorisation of antibiotics - promotes responsible use to pr public and animal health (EMA/688114/2020). Published 28 Jan 2020; country implementation finished 2023.

Avoid

Restrict

Caution

Prudence



Last line options: **quinolones, cephalosporines, colistin**

2nd line options: **apramycin, paromomycin, tiamulin, lincomycin, tilmicosin, tylosin …**

First line treatment whenever possible: **amoxicillin**, **doxycycline, tetracycline group, sulfa/TMP**

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How to define resistance?

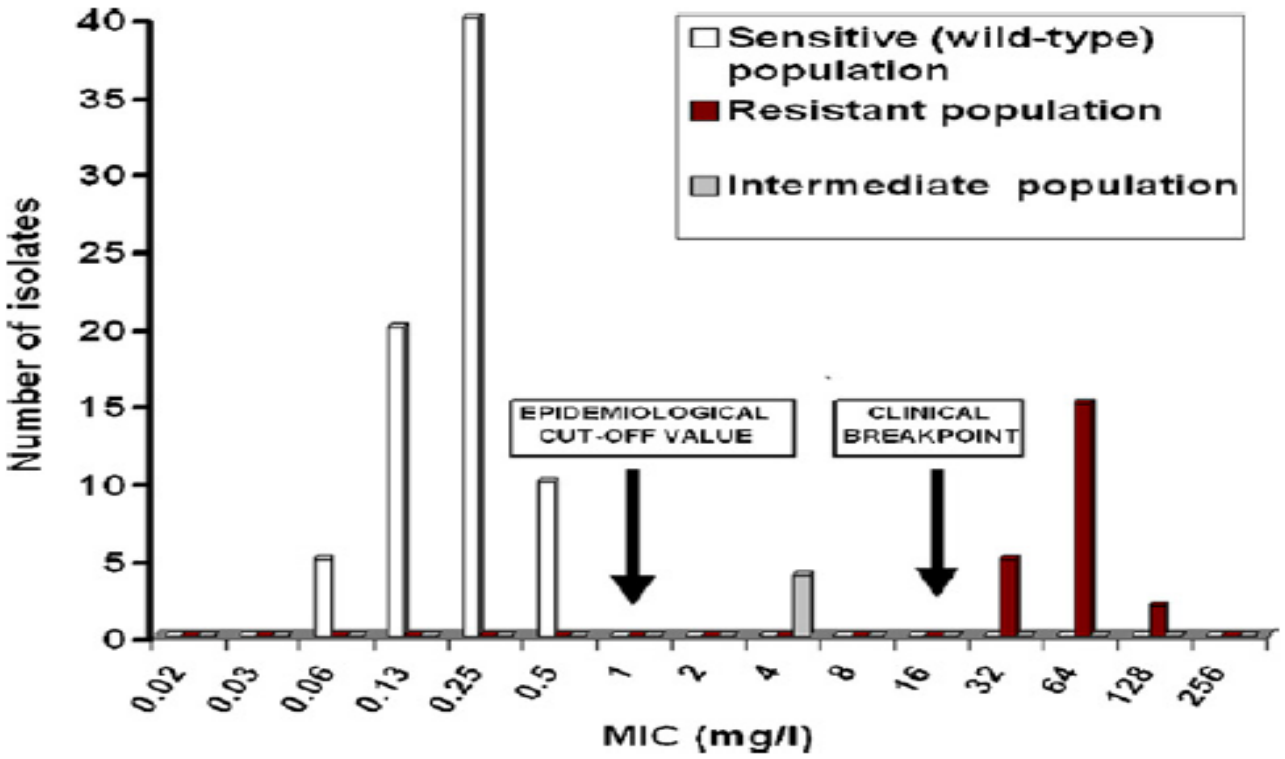


Fig. 1. Illustrative distribution showing wild-type (susceptible), intermediate and resistant bacterial sub-populations.

Bywater, Silley & Simjee (2006)

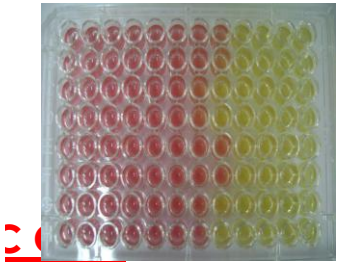
Veterinary Microbiology 118, 158-59

The **ECOFF** is defined as the highest MIC value of isolates that are not known to have resistance and are therefore considered representative of wild type bacterial isolates.

Clinical breakpoint is defined as the highest MIC value that us know to still have clinical effect

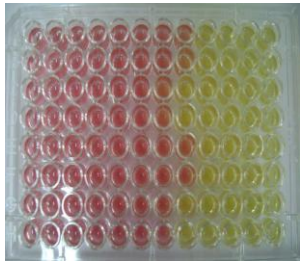
Veterinary-specific breakpoints (CLSI 5th Edition) **respiratory pathogens** from **chickens / turkeys** for

Antimicrobial agent	Pathogen	CLSI breakpoint (µg/ml)		
		S	I	R
Amoxicillin	NA	No breakpoints		
Colistin	NA	No breakpoints		
Doxycycline	NA	**≤4**	**8**	**≥16**
Enrofloxacin	*E. coli*	≤0.25	0.5-1	≥2
Florfenicol	NA	No breakpoints		
Flumequine	NA	No breakpoints		
Lincomycin/spectinomycin (1:2)	NA	No breakpoints		
Spectinomycin	NA	No breakpoints		
Tetracycline	NA	**≤4**	**8**	**≥16**
Tiamulin	NA	No breakpoints		
Tilmicosin	NA	No breakpoints		
Trimethoprim/sulfamethoxazole (1:19)	Enterobacterales	**≤2/38**	**-**	**≥4/76**



Veterinary-specific breakpoints (CLSI 5th Edition) **septicaemia pathogens** from **chickens / turkeys** for **broth dilution (mg/l)**

Antimicrobial agent	Pathogen	CLSI breakpoint (µg/ml)		
		S	I	R
Amoxicillin	NA	No breakpoints		
Cefquinome	NA	No breakpoints		
Ciprofloxacin	NA	No breakpoints		
Colistin	NA	No breakpoints		
Doxycycline	Enterobacterales	**≤4**	**8**	**≥16**
Enrofloxacin	*E. coli* (poultry only)	≤0.25	0.5-1	≥2
Gentamicin	Enterobacterales	**≤4**	**8**	**≥16**
Lincomycin/spectinomycin (1:2)	NA	No breakpoints		
Penicillin/dihydrostreptomycin (1:1)	NA	No breakpoints		
Tetracycline	Enterobacterales	**≤4**	**8**	**≥16**
Trimethoprim/sulfamethoxazole (1:19)	Enterobacterales	**≤2/38**	**-**	**≥4/76**



Comparison PK amoxicillin and doxycycline in broiler chickens

- Amoxicillin dose: 10mg/kg bw / Doxycycline dose: 20mg/kg bw

PK parameter	Amoxicillin	Doxycycline
C_{max} (µg/ml)	**160.40**	54.58
T_{max} (h)	1.0	**0.35**
Absorption/bioavailability (F)	**63%**	41.3%
Decline	Slowly in blood	First fast / than slow
Blood conc.	>15µg/ml (persisted up to 24 hours)	5.29µg/ml (12 hours post dosing)
Elimination half-life t½ß (h)	**9.16**	6.03
Volume of distribution $V_{d(l/kg)}$	0.049	**0.33**
Lung conc. (µg/ml)	- - -	2.54 (12 hours after last oral dose)

Amoxicillin pharmacodynamics – MIC data EU

VetPath IV :

Escherichia coli – septicaemia/respiratory infections. Isolates from broilers, turkeys. Septicaemia/respiratory

- **Country-specific data**

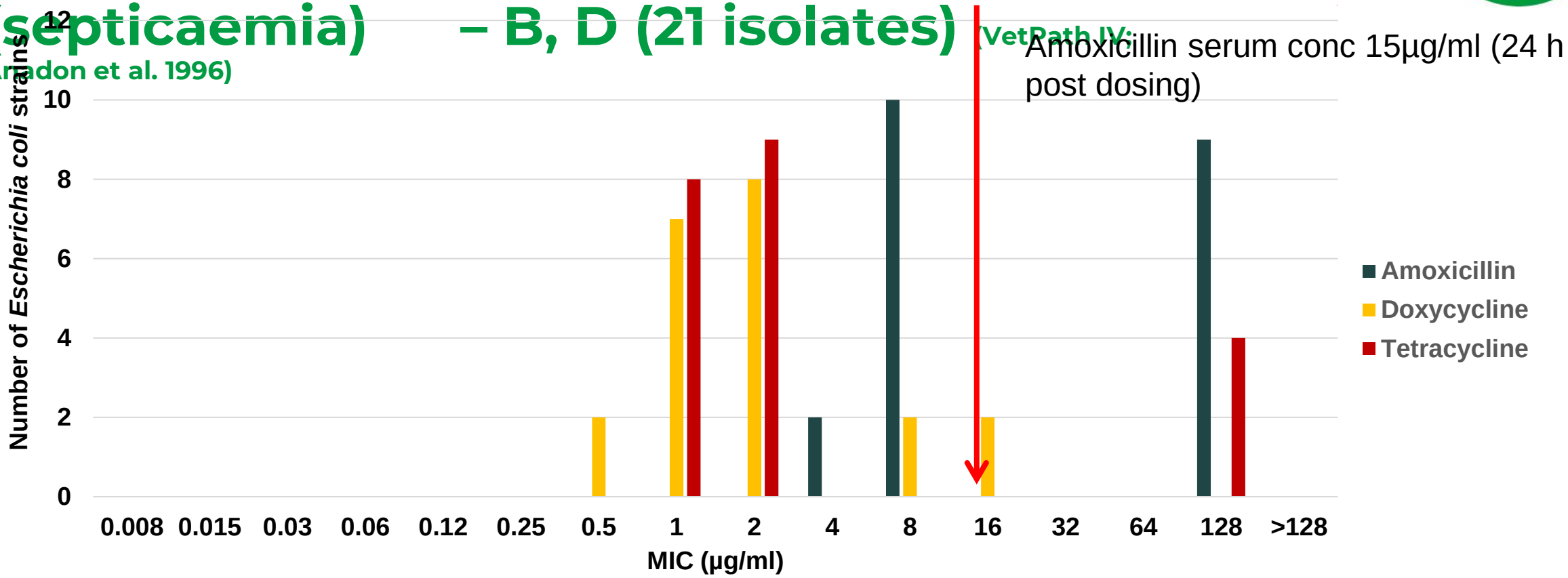
Clostridium perfringens (Necrotic Enteritis). Broiler isolates Belgium.

Ornithobacterium rhinotracheale - turkey & chicken isolates Hungary.

Bordetella avium - turkey & chicken isolates Germany and Hungary.

PK/PD broiler *Escherichia coli* isolates (septicaemia) – B, D (21 isolates)

Amadon et al. 1996)



(VetPath IV:

Amoxicillin serum conc 15µg/ml (24 h post dosing)

Antibiotic	Sensitive	Inter-mediate	Resistant	MIC range	MIC_{50}	MIC_{90}
Amoxicillin	- - -	- - -	- - -	4-128	8	>64
Doxycycline	17 (81%)	2 (9.5%)	2 (9.5%)	0.5-16	2	8
Tetracycline	17 (81%)	0	4 (19%)	1-128	4	>64

58% of *E.coli* strains MIC <15µg/ml

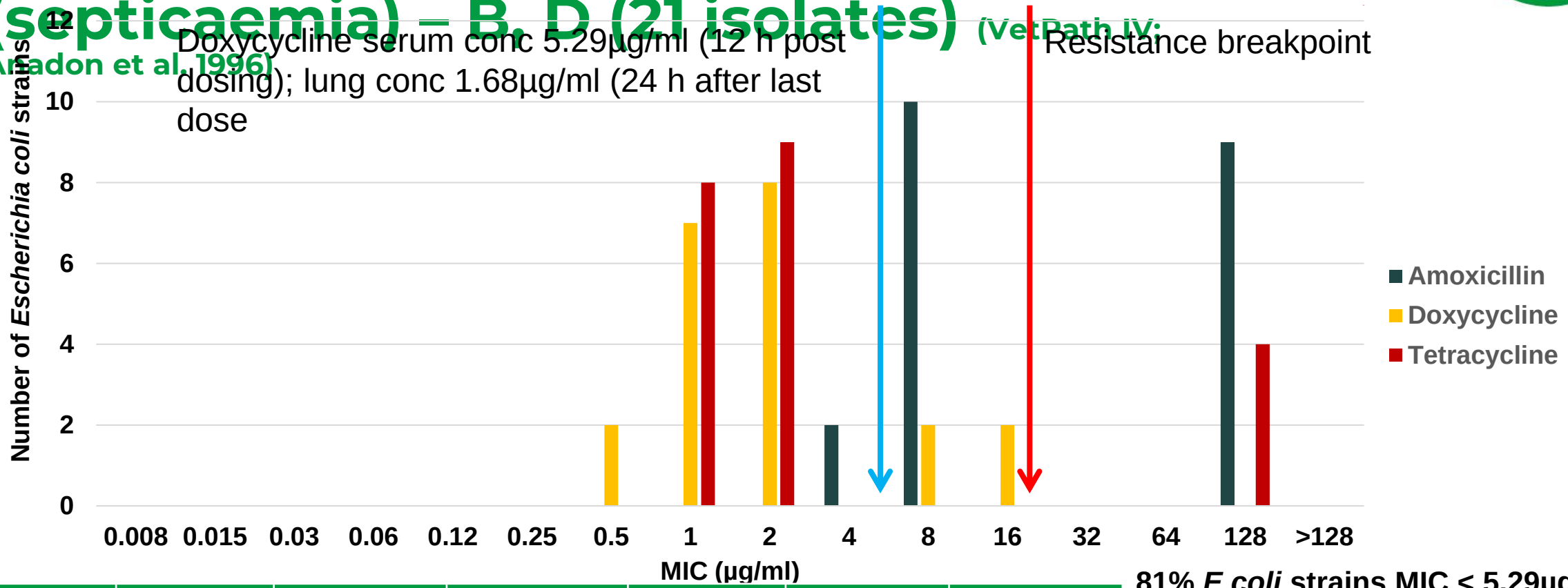
No amoxicillin CLSI breakpoints available

PK/PD broiler *Escherichia coli* isolates (septicaemia) – B, D (21 isolates)

Amadon et al, 1996)

Doxycycline serum conc 5.29µg/ml (12 h post dosing); lung conc 1.68µg/ml (24 h after last dose

(VetPath iV: Resistance breakpoint



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Amoxicillin	- - -	- - -	- - -	4-128	8	>64
Doxycycline	17 (81%)	2 (9.5%)	2 (9.5%)	0.5-16	2	8
Tetracycline	17 (81%)	0	4 (19%)	1-128	4	>64

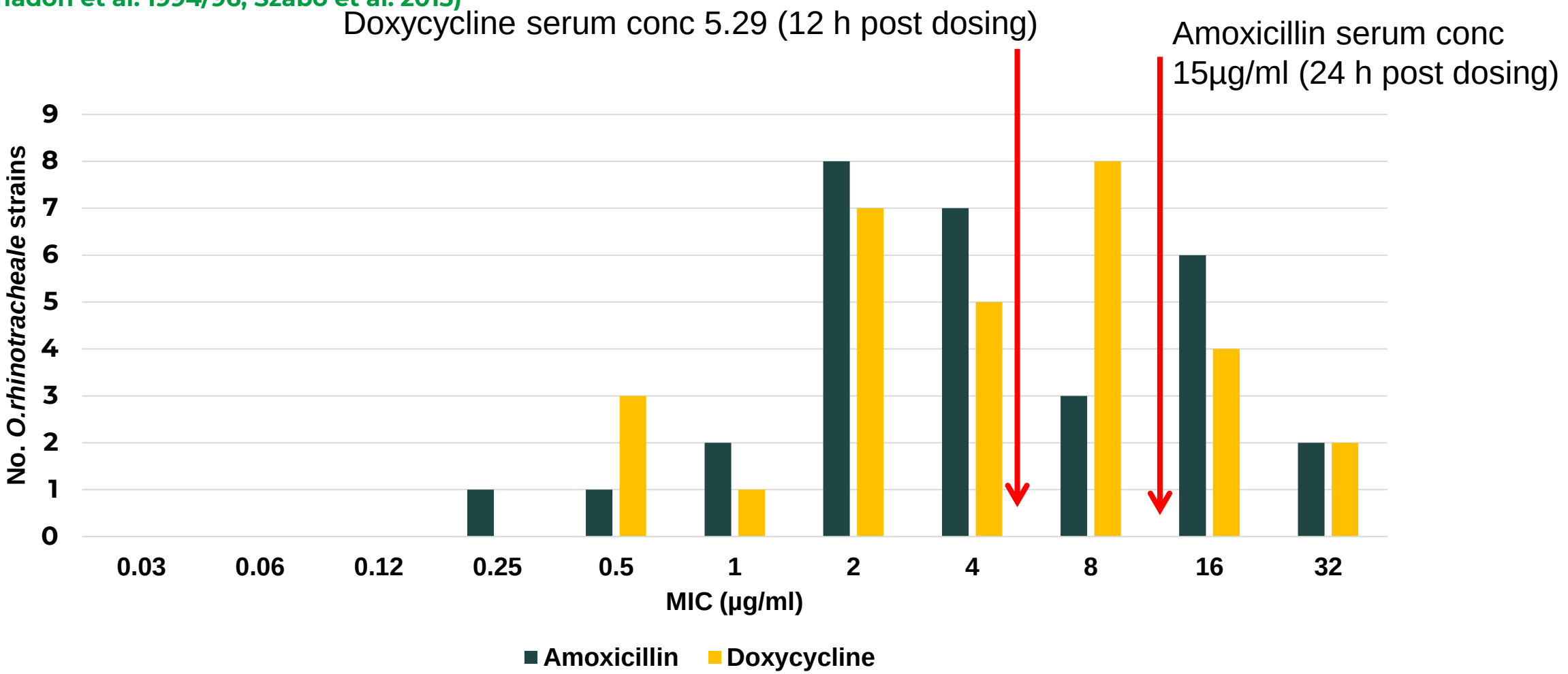
81% *E.coli* strains MIC < 5.29µg/ml

Tetracycline CLSI breakpoints:

Sensitive	Inter-mediate	Resistent
≤4	8	≥16

PK/PD turkey/chicken *Ornithobacterium rhino-tracheale* isolates – H (30 isolates)

(Anadon et al. 1994/96, Szabo et al. 2015)



Similar sensitivity patterns and variations

Sensitivity patterns *Mycoplasma synoviae* isolates (EU MycoPath II project, strain isolation 2014-2016) –

Antibiotic *	MIC range	MIC_{50}	MIC_{90}
Doxycycline (chicken isolates)	**0.062-2**	**0.5**	**1.0**
Doxycycline (turkey isolates)	**0.062-1**	**0.25**	**1.0**
Oxytetracycline (chicken)	0.031-32	0.5	1.0
Oxytetracycline (turkey)	0.031-4	0.25	1.0
Tylosin (chicken)	**0.008-64**	**0.25**	**32**
Tylosin (turkey)	**0.008-16**	**0.062**	**0.12**
Tilmicosin (chicken)	**0.004-8**	**0.062**	**2**
Tilmicosin (turkey)	**0.008-2**	**0.062**	**0.12**
Tiamulin (chicken)	**0.004-2**	**0.25**	**0.5**
Tiamulin (turkey)	**0.016-1**	**0.12**	**0.5**

* Amoxicillin not tested

Chicken vs. turkey MS isolates: differences susceptibility patterns against tylosin, tilmicosin

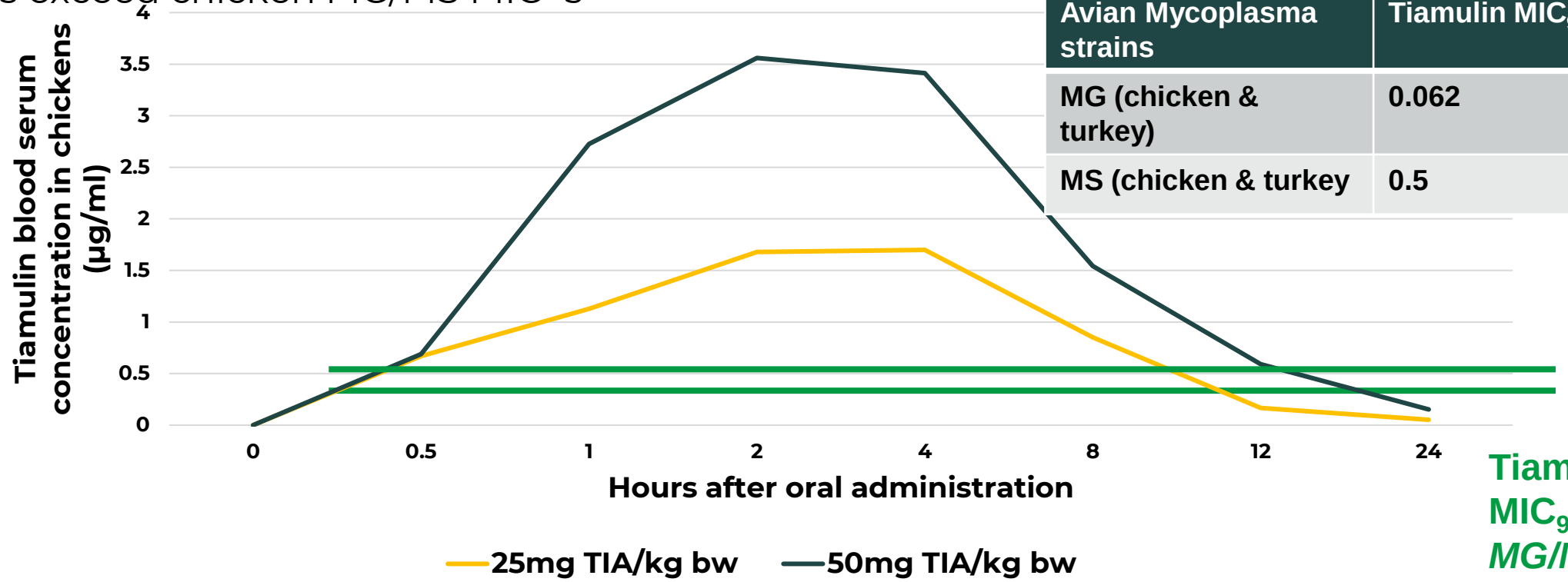
PK tiamulin in plasma of chickens – oral administration (Laber and Schütze 1977)

Tiamulin plasma concentrations measurable over period of 12 hours. After 24 hours no detection of tiamulin conc valuable for calculation.

Blood levels exceed chicken MG/MS MIC`s

<u>Dose 25mg/kg bw</u>
C_{max}: 1.7 µg/ml
T_{max} (h): 4.00

<u>Dose 50mg/kg bw</u>
Cmax: 3.56 µg/ml
Tmax (h): 2.00



Avian Mycoplasma strains	Tiamulin MIC_{90}
MG (chicken & turkey)	0.062
MS (chicken & turkey	0.5

Tiamulin MIC_{90} *MG/MS*

PK tiamulin in plasma of turkeys – oral administration (Laber and Schütze 1977)

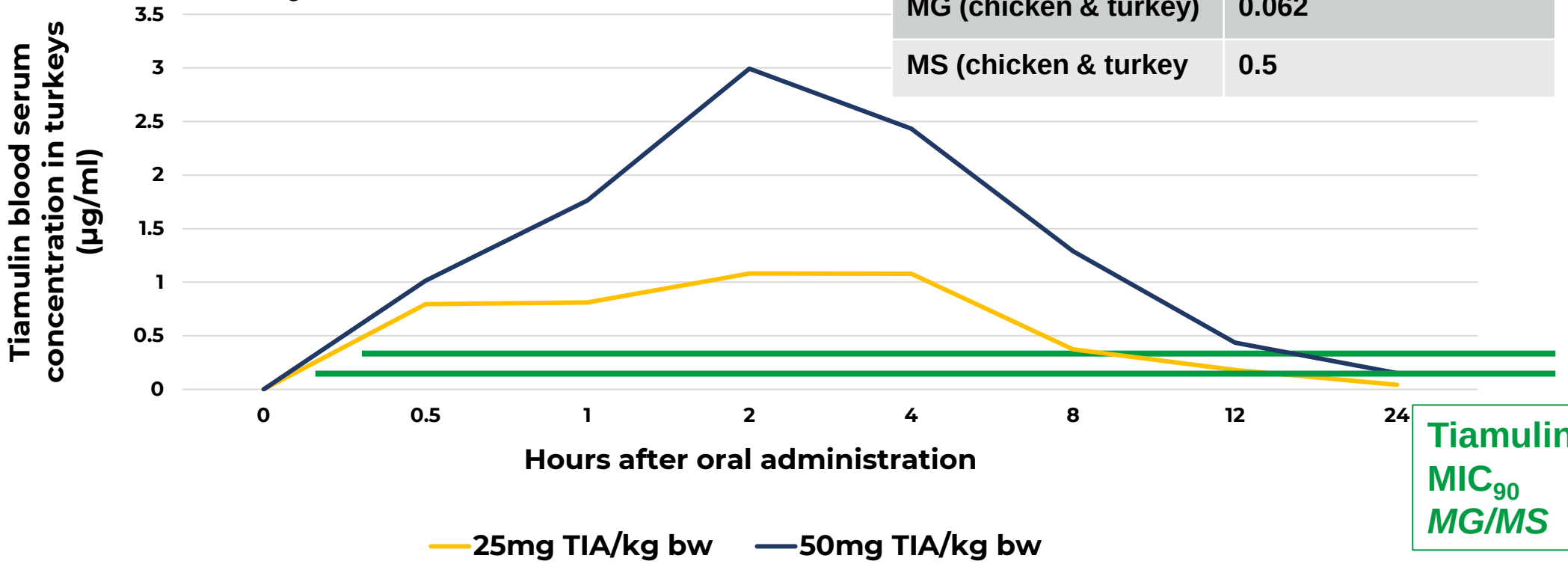
Tiamulin plasma concentrations measurable over period of 12 hours. After 24 hours no detection of tiamulin conc valuable for calculation.

Blood levels exceed turkey MG/MS MIC`s

Avian Mycoplasma strains	Tiamulin MIC_{90}
MG (chicken & turkey)	0.062
MS (chicken & turkey	0.5

Dose 25mg/kg bw
C_{max}: 1.081µg/ml
T_{max} (h): 2.00

Dose 50mg/kg bw
Cmax: 2.993µg/ml
Tmax (h): 2.00



Tiamulin MIC_{90} *MG/MS*

PK/PD tiamulin – oral administration in chickens/turkeys conclusions (Laber & Schütze 1977; MycoPath I and II)

- Rapid absorption and plasma peak conc. after 2 hours (50mg/kg bw) and 4 hours (25mg/kg bw)

- Tiamulin plasma concentration in chickens and turkeys above MICs 12 to 18 hours after administration stop

Vetmulin® **tiamulin** PK/PD data – excellent clinical efficacy predicted for *Mycoplasma gallisepticum* & *Mycoplasma synoviae* treatment

Vetmulin® **tiamulin** chicken/turkey treatment dose: 10/25mg/kg bw

(3-)5 consecutive days.

Conclusions

- Off-label use, yes but be careful/ intelligent
- Solubility and stability of used products
- Intelligent use of antibiotics: Pk/ Pd knowledge

Wouter.Depondt@huvepharma.com

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