Optimizing veterinary antibiotic use through development of treatment guidelines and clinical breakpoints

Peter Damborg, DVM, PhD, Dipl ECVM,
Associate Professor at the University of Copenhagen

UNIVERSITY OF COPENHAGEN

Outline

- Brief intro to ENOVAT
- Antimicrobial treatment guidelines
- Clinical breakpoints
- Question time ☺

ENOVAT = European Network for Optimization of Veterinary Antimicrobial Treatment

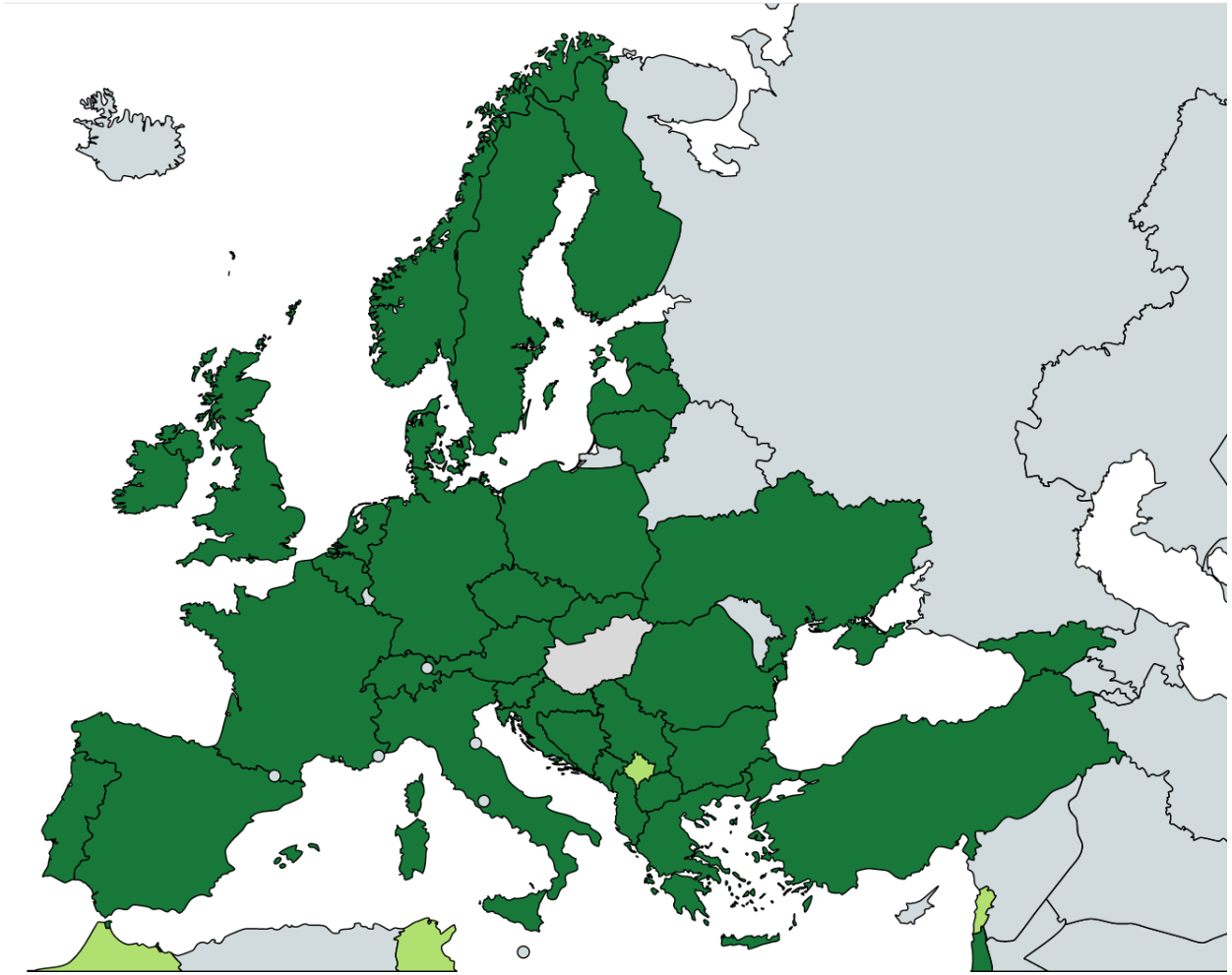
- A COST Action network funded by COST = European Cooperation in Science and Technology

- Networking activities are funded
  - Meetings
  - Workshops and training schools
  - Short-Term Scientific Missions
  - Dissemination activities

ENOVAT
European Network for Optimization of Veterinary Antimicrobial Treatment

- Currently >260 persons from 45 countries

The ENOVAT consortium



COST Countries

Near Neighbour Countries

<u>International Partner countries:</u>

- Australia
- Canada
- S. Africa
- St Kitts & Nevis
- USA

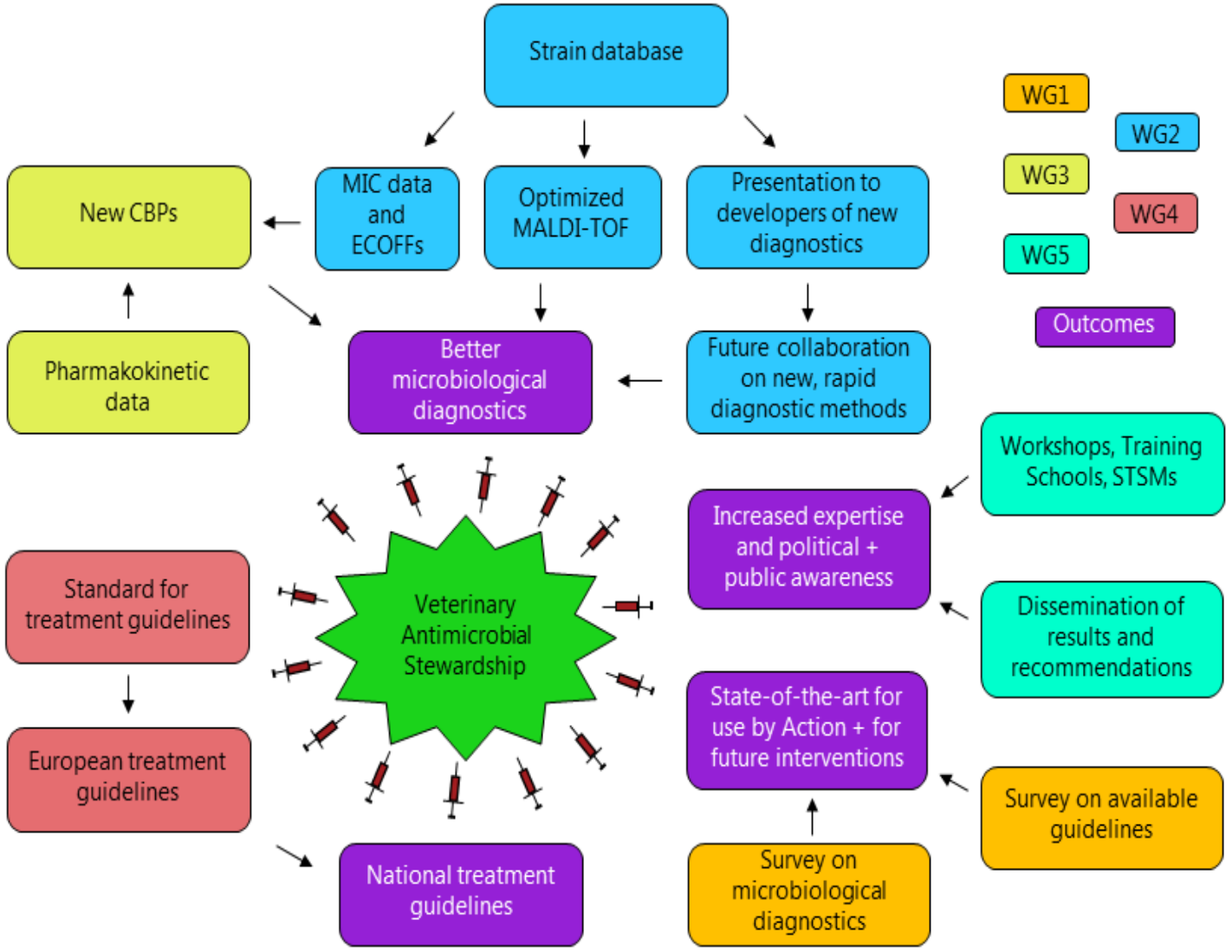
The network is growing over time – possible to join still (enovat.eu)

Microbiologists, pharmacologists, veterinary practitioners, epidemiologists, communication experts, etc.

Overall aim of ENOVAT

- To optimise veterinary antimicrobial use with special emphasis on the development of animal- and disease-specific treatment guidelines and refinement of microbiological diagnostic procedures. Combined with diverse educational activities, the Action will contribute to build a larger critical mass of experts in veterinary antimicrobial stewardship throughout Europe

Five Working Groups – one common goal



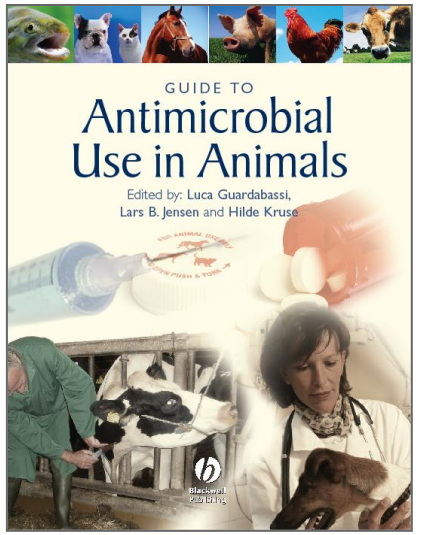
Antimicrobial treatment guidelines

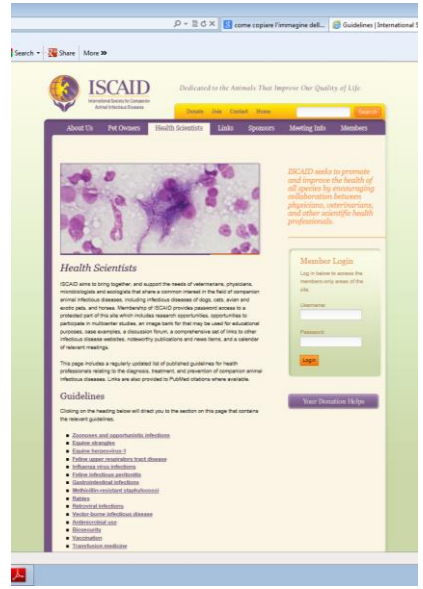
International treatment guideline for antimicrobial use

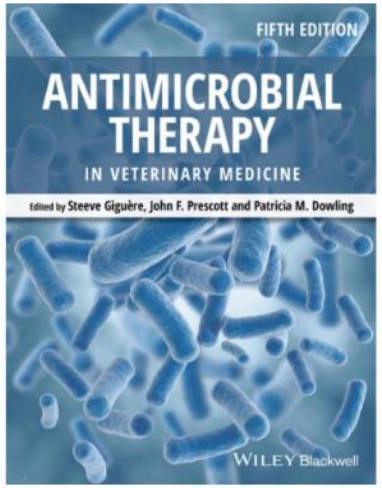
- Pros
  - Broadly available
  - Often made by leading experts
  - May establish consensus among vets

- Cons
  - Don't take into account local factors
    - resistance patterns
    - availability of antibiotics + diagnostics
    - legislation
    - traditions and culture

National guidelines are preferable!







Danish guide for antibiotic treatment of companion animals

2012

2017

Survey on impact according to end users (practitioners)

2018*

* Available online (also in Danish (☺), Polish, Slovene and English): https://www.ddd.dk/faggrupper/faggruppe-familiedyr/vejledninger-og-guidelines/antibiotikavejledning-til-familiedyr/

National guidelines for small animal practices in Europe were recently evaluated by ENOVAT members

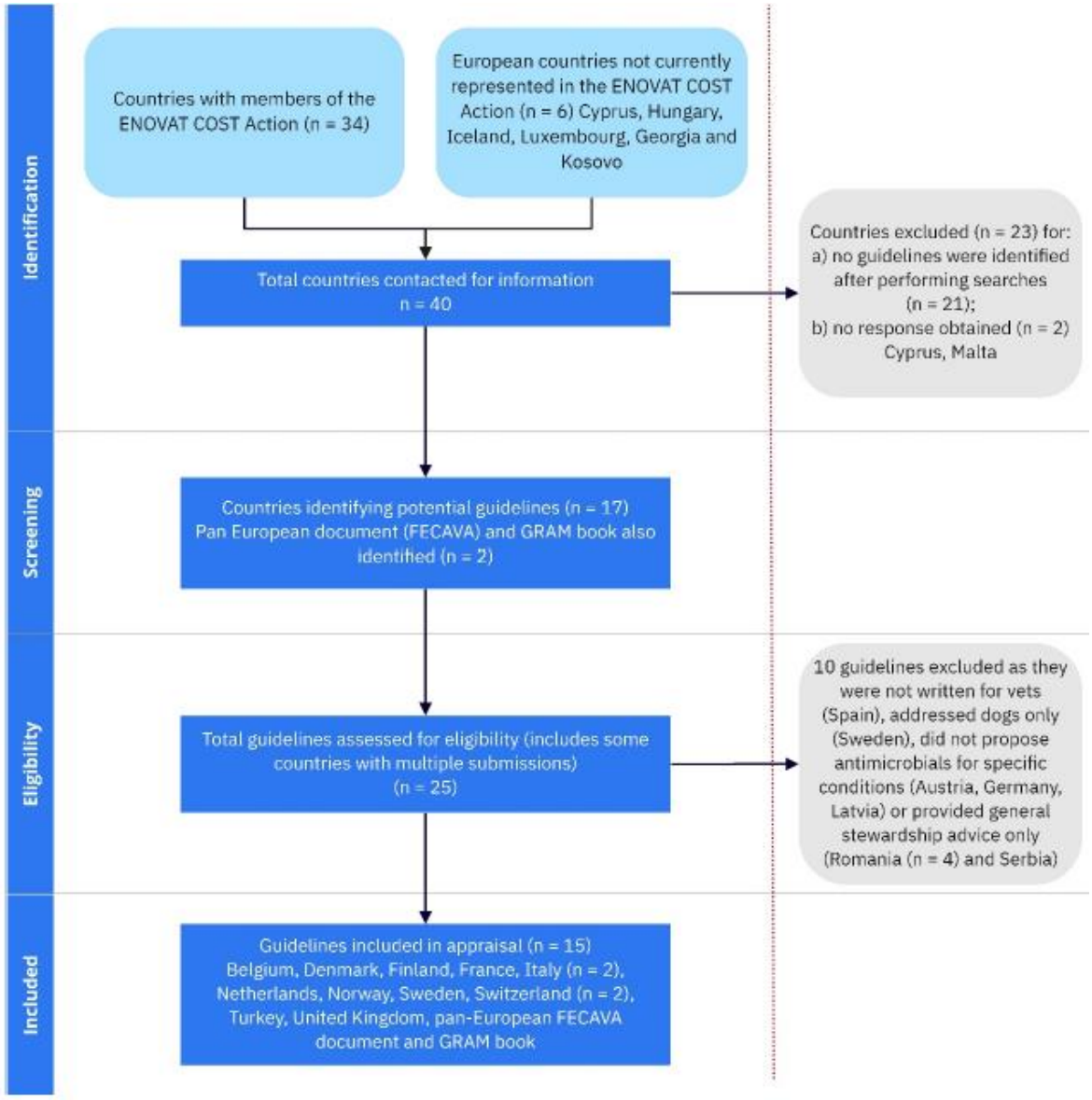
antibiotics MDPI

Article

Overview and Evaluation of Existing Guidelines for Rational Antimicrobial Use in Small-Animal Veterinary Practice in Europe

Fergus Allerton [1,*], Cameron Prior [2], Arzu Funda Bagcigil [3], Els Broens [4], Bénédicte Callens [5], Peter Damborg [6], Jeroen Dewulf [7], Maria-Eleni Filippitzi [8], Luís Pedro Carmo [9], Jonathan Gómez-Raja [10], Erez Harpaz [11], Ana Mateus [12], Mirja Nolff [13], Clare J. Phythian [11], Dorina Timofte [14], Flavia Zendri [14] and Lisbeth Rem Jessen [15]

Antibiotics 2021, 10, 409. https://doi.org/10.3390/antibiotics10040409



Objective and subjective evaluation of the guidelines were performed

- Specificities relating to AMU recommendations:
  - Suggested doses: 11/15 guides
  - Treatment durations: 14/15 guides
  - Potential adverse effects: 11/15 guides
  - When not to prescribe antimicrobials: 15/15 guides

Selected results

Table 2. Frequency of recommendations in ASGs.

Recommendation	Number of ASGs (n = 15)	Percentage of ASGs (%)
Antimicrobials are not indicated for management of:		
Acute diarrhea	15	100
Clean/elective surgical procedures	13	87
Feline lower urinary tract disease	11	73
subclinical bacteriuria	8	53
Non-antimicrobial therapeutic options described	14	93
Use topical medication instead of systemic medication where appropriate	15	100
Select narrow over broad-spectrum antimicrobials or encourage de-escalation to a narrower spectrum	13	87
Avoid certain antimicrobials reserved for human use only, e.g., vancomycin or carbapenems	12	80
Mention highest priority critically important antimicrobials (HPCIAs)	10	66
Tier antimicrobial suggestions (first line, second line)	13	87
Promote use of diagnostic techniques (cytology/culture) to identify putative bacteria	15	100
List common pathogens found in specific conditions	14	93
Monitor local antimicrobial resistance patterns	5	33
Audit/monitor individual/practice AMU	8	53

Some concerns by the authors

- Few countries in Europe had national guidelines
- None of them were initiated by governmental initiatives
- Large differences in structure and recommendations
- Failure to declare the evidence base and conflicts of interest
- Too little follow-up on implementation and effect on AMU

"This study provides a framework highlighting some of the fundamental stewardship principles that should be integral to future ASG"

"A greater awareness of the need to use a structured approach to guideline development could improve the quality of ASGs in the future."

Objectives of the ENOVAT guidelines initiative (WG4)

- To draft a standard for veterinary practice guidelines
  - Available here: https://sid.erda.dk/share_redirect/AMVBLfczST

- To write high-quality, species- and disease-specific, veterinary practice guidelines in a structured and transparent process

- To promote the transformation of ENOVAT guidelines into national/local guidelines

ESGVM ESCMID STUDY GROUP FOR VETERINARY MICROBIOLOGY
European Society of Clinical Microbiology and Infectious Diseases

WSAVA Global Veterinary Community

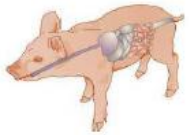
ISCAID International Society for Companion Animal Infectious Diseases

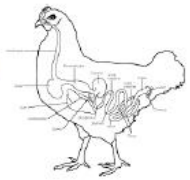
Organization

WG 4 chairs
Lisbeth Rem Jessen &
Jeroen Dewulf &
Luis Carmo

Methodology taskforce
Luis Carmo (Chair)
Marnie Brennan &
Helena Ferreira

Persons involved:
- Complementing expertise
- Fill out transparency declarations
- Animal owners



TOPICs	PWD	BM	BRD	PCB	SPH	CAD	CPYO
DG leaders	Ken Ana	Volker Aude	Luca Lutz	Alessandra Jeroen	Fergus Scott	Lisbeth David	ISCAID Anette/Emi

cost EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

ENOVAT European Network for Optimization of Veterinary Antimicrobial Treatment

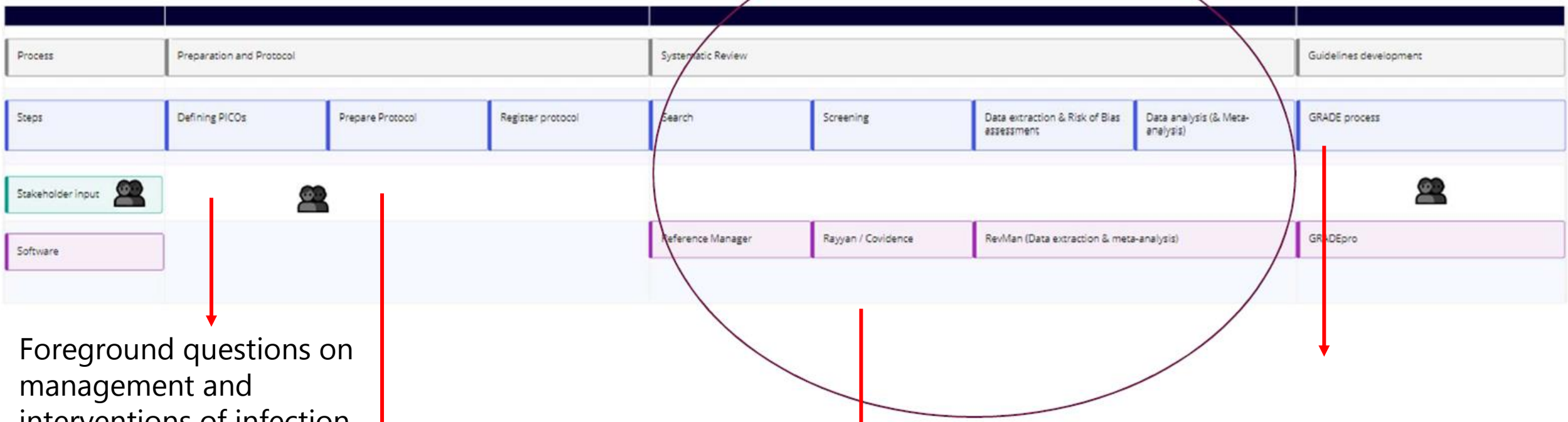
ESGVM ESCMID STUDY GROUP FOR VETERINARY MICROBIOLOGY
European Society of Clinical Microbiology and Infectious Diseases

5

Topics selected based on a) the amount and critical importance of antimicrobials used for treatment of the disease condition, b) the potential to impact animal and public health derived from such antimicrobial use, and c) lack of similar European guidelines.

ENOVAT
European Network for Optimization of Veterinary Antimicrobial Treatment

II objective - European vet practice guidelines



Foreground questions on management and interventions of infection

How to review the questions systematically

Ongoing reviews of evidence pertaining to questions

GRADE* approach:

- Evidence: good/moderate/low
- Direction: for/against
- Strength of recommendation: strong/weak

cost
EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

*GRADE: Grading of Recommendations Assessment, Development and Evaluation

What is next?

- Systematic reviews of evidence pertaining to specific questions on treatment to be published in 2022-2023
- Guidelines will follow afterwards

the Veterinary Journal

- Dialogue with national stakeholders wishing to implement the ENOVAT guidelines

Both guidelines and the approach to make them can go beyond Europe!

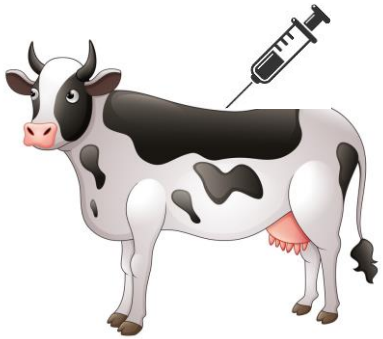
Clinical breakpoints

What is a clinical breakpoint?

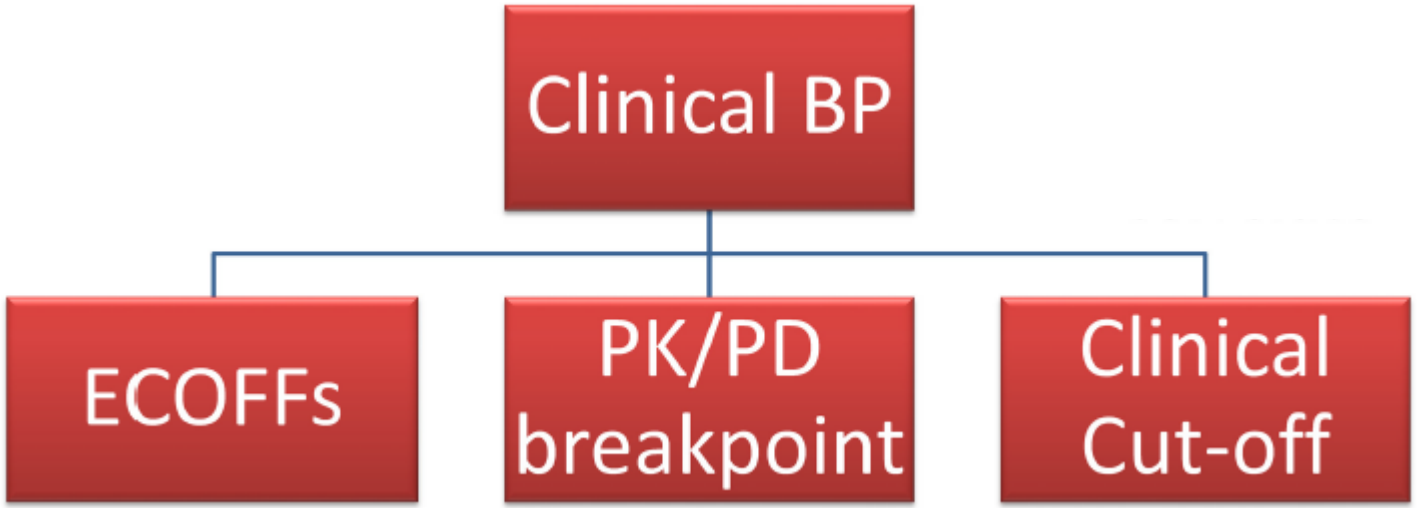
- Clinical breakpoints (CBPs) are MIC values (expressed in mg/L), or their surrogates such as zone diameters (in mm) used by diagnostic laboratories to categorize results of AST as Susceptible (S), Intermediate (I), or Resistant (R).

- Ideally, CBPs should be specific for
  - Animal species
  - Infection site
  - Bacterial species
  - Dosage

Example: *Pasteurella multocida* from respiratory infections in cattle are susceptible to florfenicol at a single dosage of 40 mg/kg SC at a MIC ≤ 1 mg/L



How CBPs are defined – the VetCAST* approach




frontiers in Microbiology

REVIEW
published: 15 December 2017
doi: 10.3389/fmicb.2017.02344

En Route towards European Clinical Breakpoints for Veterinary Antimicrobial Susceptibility Testing: A Position Paper Explaining the VetCAST Approach

Pierre-Louis Toutain[1,2], Alain Bousquet-Mélou[1], Peter Damborg[3], Aude A. Ferran[1], Dik Mevius[4], Ludovic Pelligand[2], Kees T. Veldman[5] and Peter Lees[2]*

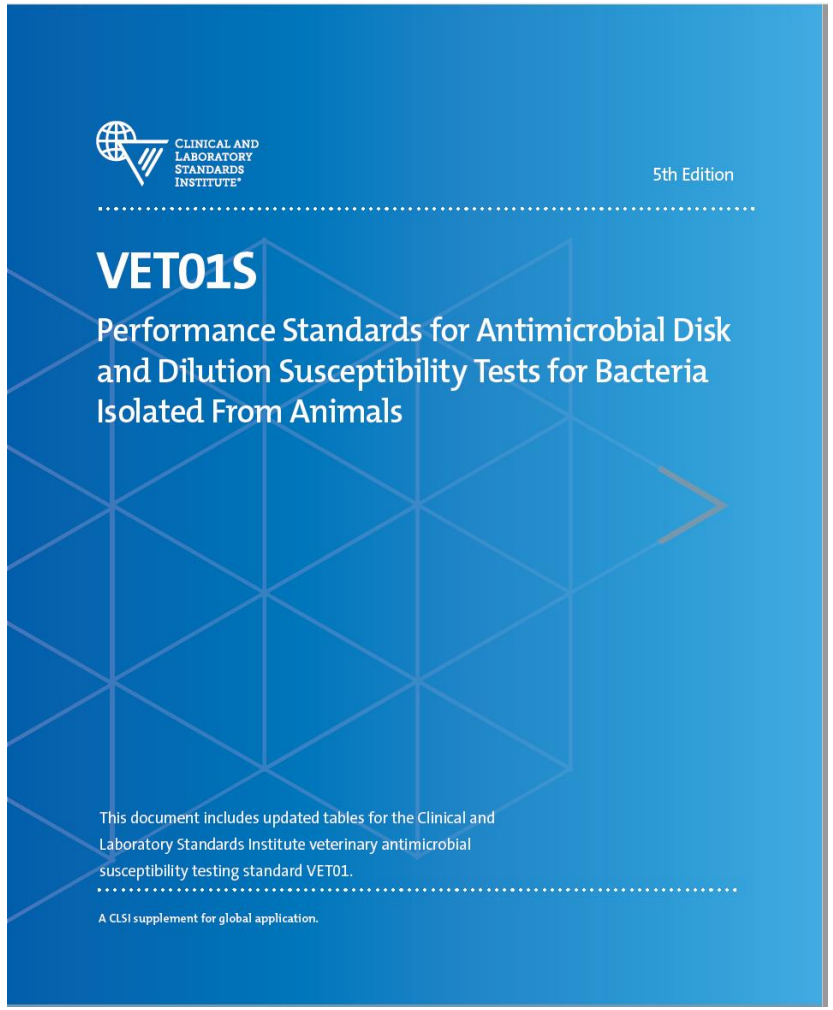
[1] UMR 1331 Toxalim, INRA, ENVT, Toulouse, France, [2] The Royal Veterinary College, University of London, London, United Kingdom, [3] Department of Veterinary and Animal Sciences, University of Copenhagen, Frederiksberg, Denmark, [4] Wageningen Bioveterinary Research, Lelystad, Netherlands, [5] National Reference Laboratory on Antimicrobial Resistance in Animals, Lelystad, Netherlands

→ Based on cutoff's: consensus-based decision on CBP

*VetCAST: EUCAST Veterinary subcommittee for antimicrobial susceptibility testing

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

Which internationally-recognized veterinary CBPs exist?



+ other VET documents, including VET06 on fastidious bacteria and VET03 and VET04 on aquatic animals etc

VetCAST: working on it – currently for florfenicol

Table shows the existing veterinary CLSI CBPs

For many drug/bug combinations, there are no specific CBPs, especially for food animal infections

What to do when a specific CBP is missing - can we just use another breakpoint?

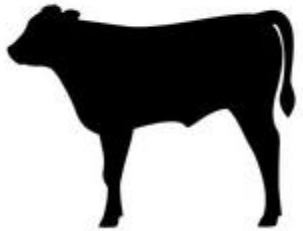
Ref: draft v6 of Antimicrobial Therapy in Veterinary Medicine

Table 2.1. Drugs with veterinary-specific CLSI resistance breakpoints according to the VET01S5-Ed5 document (CLSI, 2020).

Drug	Animal Species[a]				
	Dog	Cat	Cattle	Horse	Pig
Amikacin	EC, PA, *Staph* spp.			EC, PA, SA, *S. equi*	
Amoxicillin-clavulanate	EC, *Staph* spp. (SST, UTI)	EC, *Staph* spp., *Strep* spp., PM (SST, UTI)			
Ampicillin	EC (SST, UTI), SP, *Strep* spp. (SST)	EC (SST), *Staph* spp., *Strep* spp., PM (SST, UTI)	EC (metritis), HS/MH/PM (resp)	SA (resp, SST), *S. equi* (resp), Ent	APP, BB, *S. suis*, PM (resp)
Cefazolin	EC, *K. pneumonia, P. mirabilis* (SST, UTI), SA, SP (resp, SST, UTI), β-hem *Strep* spp. (resp, SST, ur/gen), PM (resp, SST)			EC, β-hem *Strep* spp. (gen, resp)	
Cefoperazone			EC, *Staph* spp., *S. agalactiae, S. dysgalactiae, S. uberis* (mastitis)		
Cefovecin	EC, *P. mirabilis* (UTI), SP, β-hem *Strep* spp. (SST)	EC (UTI), PM (SST)			
Cefpodoxime	EC, *P. mirabilis* (UTI, wound/abscess), SA, SP, *S. canis*, PM (wound/abscess)				
Ceftazidime	Ent, PA (SST)				
Ceftiofur			EC, SA, *S. agalactiae, S. dysgalactiae, S. uberis* (mastitis), HS/MH/PM (resp)	*S. equi* subsp *zooepidemicus* (resp)	APP, *S.* Choleraesuis, *S. suis*, PM (resp)
Cephalexin	EC, *K. pneumoniae, P. mirabilis* (UTI), SA, SP, β-hem *Strep* spp. (SST)				
Cephalothin	SA, SP, β-hem *Strep* spp. (SST)				
Clindamycin	*Staph* spp., β-hem *Strep* spp. (SST)				
Danofloxacin			MH, PM (resp)		
Difloxacin	Ent, *Staph* spp., β-hem *Strep* spp. (SST, UTI)				
Doxycycline	SP (SST)			EC, SA, *S. equi*	
Enrofloxacin	Ent, *Staph* spp., β-hem *Strep* spp. (resp, SST, UTI)	Ent, PA, *Staph* spp., *Strep* spp. (SST)	HS/MH/PM (resp)	EC, PA, SA, *S. equi* (resp, SST)	APP, *S. suis*, PM (resp)
Florfenicol			HS/MH/PM (resp)		APP, BB, *S.* Choleraesuis, *S. suis*, PM (resp)
Gamithromycin			HS/MH/PM (resp)		
Gentamicin	Ent, PA			Ent, PA, *Actinobacillus* spp.	
Levofloxacin	Ent, PA (SST)				
Marbofloxacin	Ent, *Staph* spp., β-hem *Strep* spp. (SST, UTI)	Ent, *Staph* spp., *Strep* spp. (SST)			
Minocycline	SP (SST)			EC, SA, *Strep* spp. (resp, SST)	
Orbifloxacin	Ent, *Staph* spp., β-hem *Strep* spp. (SST, UTI)	Ent, *Staph* spp., *Strep* spp. (SST)			
Penicillin G			HS/MH/PM (resp)	*Staph* spp., *Strep* spp. (resp, soft tissue)	*S. suis*, PM (resp)
Penicillin-novobiocin			SA, *S. agalactiae, S. dysgalactiae, S. uberis* (mastitis)		
Pirlimycin			SA, *S. agalactiae, S. dysgalactiae, S. uberis* (mastitis)		
Piperacillin-tazobactam	Ent, PA, *Staph* spp. (SST, UTI)				
Pradofloxacin	EC, SP (skin, UTI)	EC, SA, SP, *S. felis, S. canis*, PM (resp, skin)			
Spectinomycin			HS/MH/PM (resp)		
Tetracycline	*Staph* spp. (SST)		HS/MH/PM (resp)		APP, *S. suis*, PM (resp)
Tiamulin					APP (resp)
Tildipirosin			HS/MH/PM (resp)		APP, BB, PM (resp)
Tilmicosin			MH (resp)		APP, PM (resp)
Tulathromycin			HS/MH/PM (resp)		APP, BB, PM (resp)

[a] SST, skin and soft tissue; resp, respiratory; UTI, urinary tract infection; ur/gen, urinary and/or genital; EC, *E. coli*; SP, *Staphylococcus pseudintermedius*; SA, *S. aureus*; Ent, Enterobacterales; PA, *Pseudomonas aeruginosa*; APP, *Actinobacillus pleuropneumoniae*; HS, *H. somni*; MH, *M. haemolytica*; PM, *P. multocida*; BB, *Bordetella bronchiseptica*. Note: a single avian breakpoint for enrofloxacin for *E. coli* has not been included in this table.

Source: Vet01S5 ED5, CLSI



Example of breakpoint difference between animal species

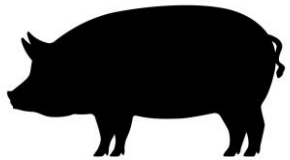


Table 2H. *Pasteurella multocida* (Continued)

Test/ Report Group	Body Site	Antimicrobial Agent	Antimicrobial Agent Class or Subclass	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm			Interpretive Categories and MIC Breakpoints, µg/mL			Comments
					S	I	R	S	I	R	
Cattle											
A	Resp	Ampicillin	Penicillinase-labile penicillins	-	-	-	-	≤0.03	0.06-0.12	≥0.25	**(7)** Breakpoints were derived from microbiological and PK/PD data. The dose of ampicillin trihydrate used to derive this breakpoint was 11 mg/kg every 24 hours IM.
A	Resp	Ceftiofur	Cephalosporin III	30 µg	≥21	18-20	≤17	≤2	4	≥8	
A	Resp	Danofloxacin	Fluoroquinolones[c]	5 µg	≥22	18-21	≤17	≤0.25	0.5	≥1	**(8)** The breakpoints and interpretive categories apply to approved doses of 6 mg/kg (twice) and 8 mg/kg (once), but they do not apply to a 1.25 mg/kg dose, because it is not assured to meet currently accepted PK/PD targets.
A	Resp	Enrofloxacin	Fluoroquinolones[c]	5 µg	≥21	17-20	≤16	≤0.25	0.5-1	≥2	
A	Resp	Florfenicol	Phenicols	30 µg	≥19	15-18	≤14	≤2	4	≥8	
A	Resp	Gamithromycin	Macrolides	15 µg	≥15	12-14	≤11	≤4	8	≥16	
A	Resp	Penicillin G	Penicillinase-labile penicillins	-	-	-	-	≤0.25	0.5	≥1	**(9)** Breakpoints were derived from microbiological, PK data (using accepted clinical but extralabel doses), and PD data. The dose of procaine penicillin G modeled was 22 000 U/kg every 24 hours IM.
A	Resp	Spectinomycin	Aminocyclitols	100 µg	≥14	11-13	≤10	≤32	64	≥128	
A	Resp	Tetracycline	Tetracyclines	-	-	-	-	≤2	4	≥8	**(10)** Breakpoints were derived from PK data of oxytetracycline at 20 mg/kg IM, once, and PD data. **(11)** These breakpoints are applicable only for the injectable formulations. Tetracycline is the class representative.
A	Resp	Tildipirosin	Macrolides	60 µg	≥21	18-20	≤17	≤8	16	≥32	
A	Resp	Tulathromycin	Macrolides	30 µg	≥18	15-17	≤14	≤16	32	≥64	

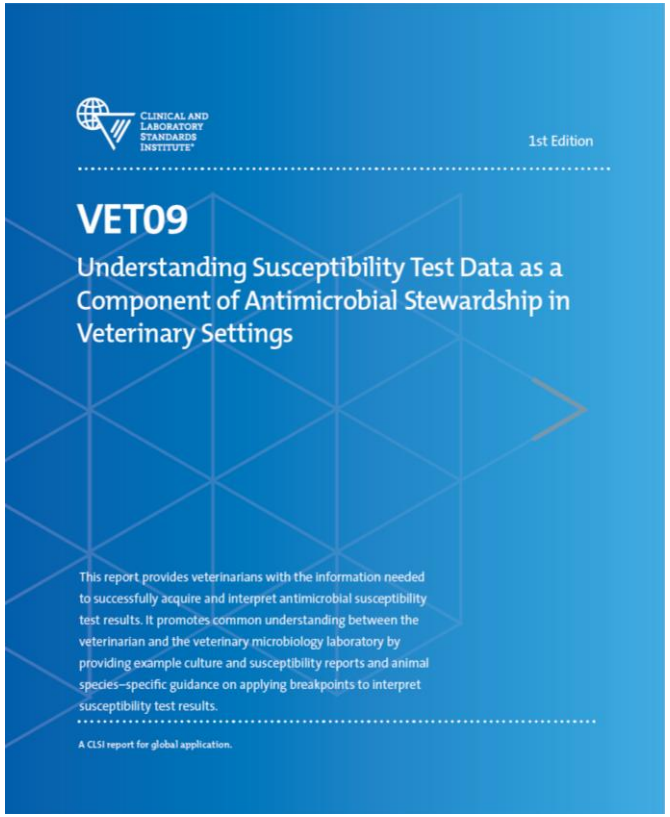
Table 2I. *Actinobacillus pleuropneumoniae* (Continued)

Test/ Report Group	Body Site	Antimicrobial Agent	Antimicrobial Agent Class or Subclass	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm			Interpretive Categories and MIC Breakpoints, µg/mL			Comments
					S	I	R	S	I	R	
Swine (Continued)											
A	Resp	Tilmicosin	Macrolides	15 µg	≥11	-	≤10	≤16	-	≥32	
A	Resp	Tulathromycin	Macrolides	30 µg	≥10	-	-	≤64	-	-	**(9)** Hazy growth or double zones should be ignored. The outer, discrete zone of inhibition should be read. To detect isolates nonsusceptible to tulathromycin, broth microdilution testing is required.

A zone diameter of 12 mm is resistant for *P. multocida* in cattle, but susceptible for *A. pleuropneumoniae* in pigs

What alternatives exist when a specific breakpoint is lacking?

- CBP for another bacterial species
- CBP for another infection site
- CBP for another dosage
- CBP for another animal species
- CBP for humans
- ECOFF
- Report "No interpretation"



Vet09: General suggestions, but **no solutions are ideal** when specific CBPs are missing

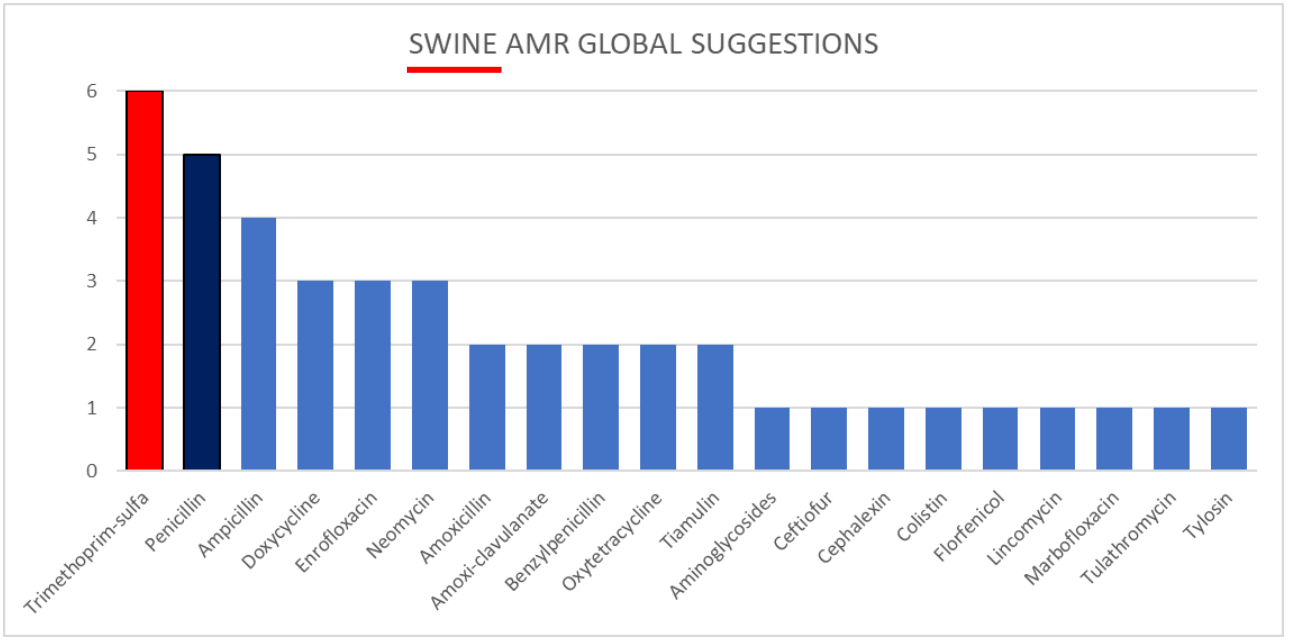
VetCAST is working towards new veterinary CBPs

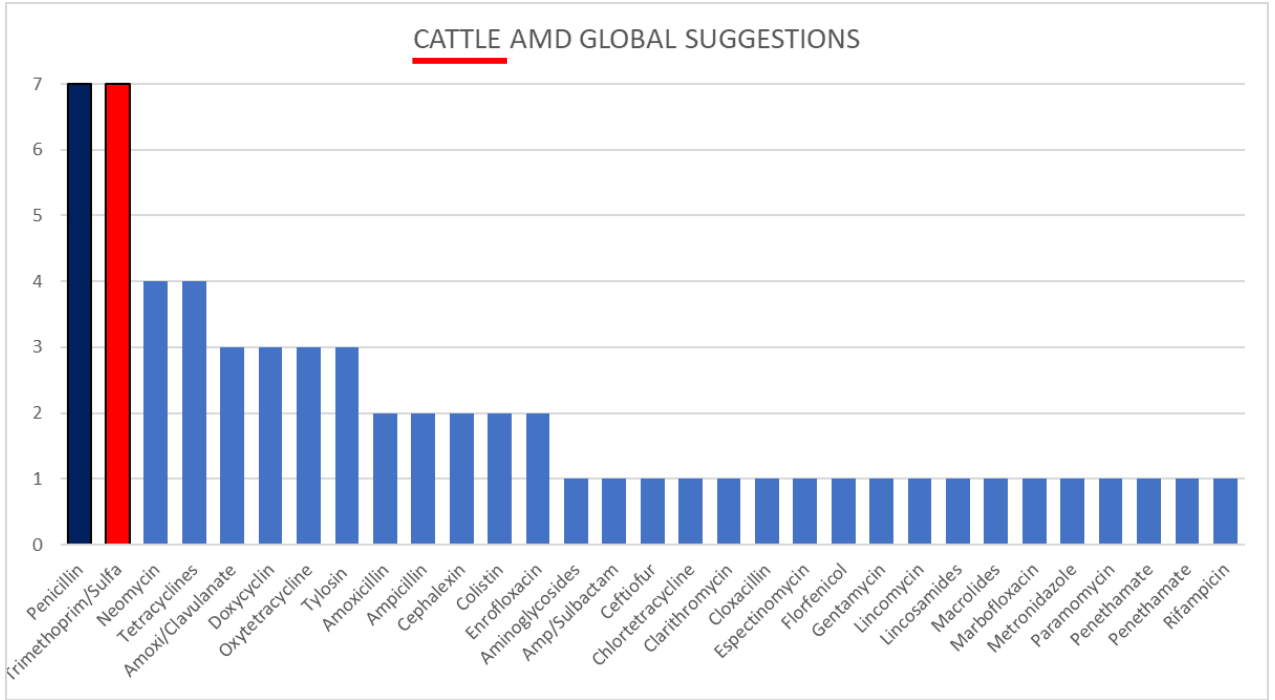
- Prioritizing CBPs
  - Data gaps / which are highly needed?
  - For which do we have data or funding?
  - For which do we have expertise?
- Production/collection of data
  - PK data from animal trials
  - MIC data
- Modelling of data
- Collaboration with ENOVAT WG3
  - Training schools
  - Survey: which breakpoints to prioritize acc. to end users?

For more details, contact me (pedam@sund.ku.dk)

ENOVAT survey - wishes for new CBPs

- Cattle
  - Respiratory tract infections
  - Mastitis
- Pigs
  - Gastrointestinal infections
  - Respiratory infections





Is VetCAST of relevance outside Europe?

- Anyone can contribute to the work of VetCAST
  - Data provision
  - Data modelling
  - Expert input or questions/queries
  - Teaching

- When available, VetCAST CBPs can be used anywhere
  - Just follow the VetCAST (EUCAST) protocol

Thanks for your attention!

Questions welcome ☺