VetCAST Susceptibility Test Breakpoints

Peter Damborg, Dipl. ECVM, PhD, Chair of VetCAST, University of Copenhagen

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

What is VetCAST?

- A standing subcommittee of EUCAST since 2015
- Dealing with all aspects of antimicrobial susceptibility testing of bacterial pathogens of animal origin and animal bacteria with zoonotic potential, e.g.
  - To provide advice on the type and quality of the MIC, pharmacokinetic (PK) and clinical data needed for setting clinical breakpoints
  - To define clinical MIC breakpoints for new veterinary antimicrobial agents
  - To revise breakpoints for generic drugs
  - To advice on the bacterial spectrum of veterinary antimicrobial agents

Development of breakpoints is central

Who are we?

Total: 54 members from 14 countries

Steering committee:

Peter Damborg, Chair

Gudrun Overesch, Scientific Secretary

Ronette Gehring, Data Manager (PK)

Ludovic Pelligand, Data Manager (PK)

Kees Veldman, Data manager (PD)

And our "close allies"

Dik Mevius

Pierre-Louis Toutain

Peter Lees

Alain B Melou

Petra Cagnardi

Why VETCAST? Original answer

- **To establish a EMA scientific-based operational body to define/approve veterinary-specific breakpoints**
- **To harmonize veterinary AST in the EU**
- **To initiate and coordinate EU research aimed at filling the current gaps in veterinary AST**
  - **Missing or insufficient breakpoints**
  - **Bacterial species-, animal host- and infection-specific breakpoints**
  - **Optimize methods for AST of animal pathogens**
- **To make veterinary AST protocols and interpretive criteria freely accessible online**

Why VETCAST? My view today

- **(To establish a EMA scientific-based operational body to define/approve veterinary-specific breakpoints)**
- **(To harmonize veterinary AST in the EU)**
- **To initiate and coordinate EU research aimed at filling the current gaps in veterinary AST**
  - **Missing or insufficient breakpoints**
  - **Bacterial species-, animal host- and infection-specific breakpoints**
  - **Optimize methods for AST of animal pathogens**
- **To make veterinary AST protocols and interpretive criteria freely accessible online**
- **To expand the critical mass of expertise by teaching basic and more advanced PK and PD principles and –modelling, and how to create breakpoints**

VetCAST vs CLSI-VAST

- Supplement to CLSI rather than competitor
  - Filling gaps of missing breakpoints
- Risk of diluting the sparse expertise, but mutual openness for collaboration
  - Generic drugs an option

Activities - 1

- Collecting and creating PK and PD data from various sources to create breakpoints
  - Own research projects
  - Contacts to industry and academic partners
  - Literature

Activities are often driven by data availability

- Meetings
  - Monthly Steering Committee meetings
  - Annual open meetings at ECCMID congress
  - Meetings as part of ENOVAT, WG3 (https://enovat.eu)

Activities - 2

- Training schools
  - 2019: determination of clinical breakpoints
  - 2021: Basic PK/PD concepts
  - 2021: PK/PD modelling
  - 2023: Population PK / Monte-Carlo simulation
- Creating guideline for vet diagnostic labs on use of interpretive criteria for AST
- Providing opinions to EMA reflection papers
- Advising on setting up PK and PD studies

Publications

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DOI: 10.1111/jvp.12917

REVIEW ARTICLE

The pharmacokinetic/pharmacod
antimicrobial drugs in veterinary
and critical appraisal

Pierre-Louis Toutain[1,2] | Ludovic Pelligand[2]
Alain Bousquet-Mélou[1] | Aude A. Ferran[1]

[1]INTHERES, INRA, ENVT, Université de Toulouse, Toulouse, France
[2]Royal Veterinary College, University of London, London, UK
[3]School of Biological Sciences, University of Adelaide, Adelaide, SA, Australia

Correspondence
Pierre-Louis Toutain, Intheres INRA, Ecole Nationale Vétérinaire de Toulouse, 23, Chemin des Capelles-BP 87614, 31076 Toulouse Cedex 03, France.
Email: pltoutain@wanadoo.fr

Abstract

Pharmacokinetic/pharma
mechanistic approach for
crobial drugs (AMDs). Nu
and dosing interval on a r
value of PK/PD indices l
Two PK/PD indices are r
under the curve of the f
concentration (MIC) (fAU
ceeds the MIC over the
modelling of AMDs were
reviewed previously and
and provides a critical ap
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reviewed, including (a) the
PK investigations. PK/PD
required to establish clin
particular consideration i
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KEYWORDS
antimicrobials, dosage regim

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Contents lists

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Influence of incubation time on antimic
pathogenic *Vibrio anguillarum* and *Vibrio*

Sandrine Baron[a], Daniela Ceccarelli[b], Inger Dalsgaa
Eva Jansson[f], Lone Madsen[c], Eric Jouy[a], Isabelle K
Joop Testerink[b], Kees Veldman[b], Kári Karbech Mou
Michal Voorbergen-Laarman[e], Eva Säker[f], Eva Blor

[a] ANSES, Ploufragan-Plouzané-Niort Laboratory, Mycoplasmology-Bacteriology and Anti
[b] WBVR, Wageningen Bioveterinary Research, National Reference Laboratory for Antimic
[c] DTU, National Institute of Aquatic Resources, Unit for Fish and Shellfish Diseases, Kgs.
[d] ANSES, Fougères Laboratory, National Reference Laboratory for Antimicrobial Resistan
[e] WBVR, Wageningen Bioveterinary Research, National Reference Laboratory for Fish Di
[f] SVA, National Veterinary Institute, Department of Animal Health and Antimicrobial Str
[g] ANSES, Ploufragan-Plouzané-Niort Laboratory, Unit Viral Fish Diseases, National Refer
[h] Department of Microbiology, School of Natural science, National University of Ireland,

ARTICLE INFO

Keywords:
Vibrio anguillarum
Vibrio vulnificus
CLSI susceptibility testing
MIC
Disc diffusion
Incubation time

ABSTRACT

A multi-laboratory stud
of fish pathogens *Vibri*
anguillarum and 26 *V. v*
Netherlands. Inhibition
Inhibitory Concentratio
tocols for non-fastidiou
made after 48 h incuba
two incubation times.
significant effect on the
the precision of the dat
off values were slight
Vibrio species could be
This study does not
erated by the tests. The
should be adopted for

1. Introduction

Vibrio anguillarum is a serious pathogen of aquatic animals (Haenen et al., 2014) and *Vibrio vulnificus* may cause disease in both aquatic animals and humans (Austin, 2010; Dalsgaard et al., 1999). Therefore, both these species should be included in programmes for monitoring and surveillance of antimicrobial susceptibility of aquatic organisms that are recommend in the OIE Aquatic Animal Health Code (OIE, 2019). The OIE Aquatic Code recommends that susceptibility should be established using internationally-harmonized and standardised testing

appears to be relatively common in the published literature on the susceptibility of human and veterinary pathogens. Schwarz et al. (2010) have commented that these standardised protocols provide strict rules and minor modifications of the testing conditions are not acceptable. Smith and Egan (in press) reported that such modifications of standard protocols were common in published studies of *Vibrio* spp. susceptibility. Therefore, the issue of whether the currently available standardised testing protocols published by CLSI (2006, 2014) without any

* Corresponding author at: Cloonboo, Corrandulla, Galway, H91F3CT, Ireland.
E-mail address: peter.smith@nuigalway.ie (P. Smith).

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REVIEW
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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

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Edited by:
Axel Cloeckaert,
INRA, France

Reviewed by:
Laurent Poirel,
INSERM, France
Pascal Jean Jacques Sanders,
ANSES, France

*Correspondence:
Pierre-Louis Toutain
pltoutain@wanadoo.fr

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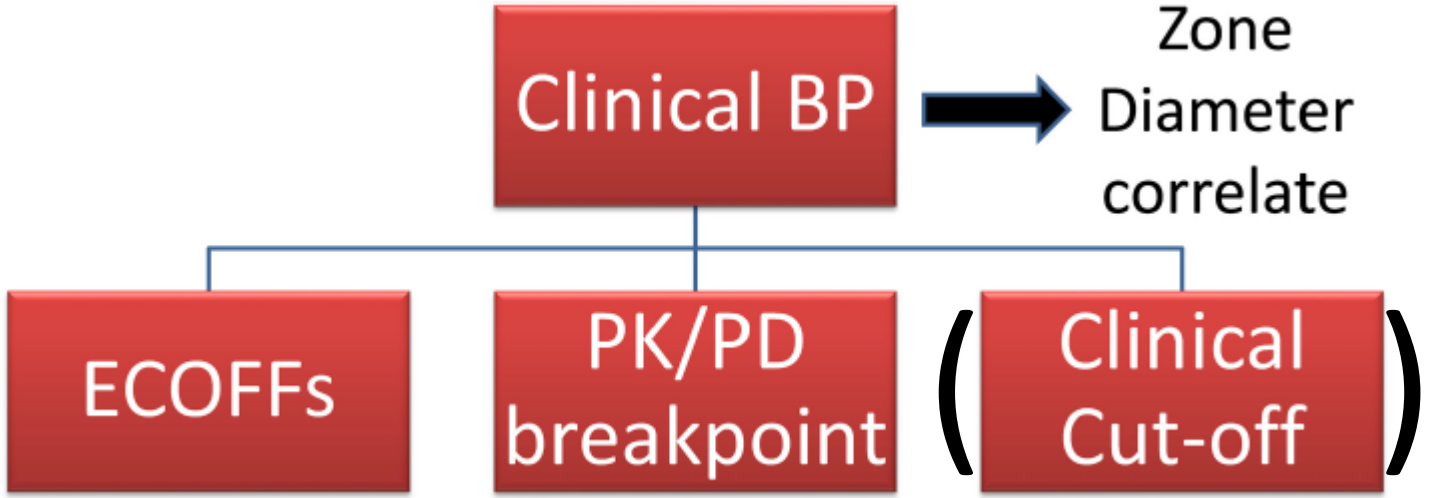
VetCAST is the EUCAST sub-committee for Veterinary Antimicrobial Susceptibility Testing. Its remit is to define clinical breakpoints (CBPs) for antimicrobial drugs (AMDs) used in veterinary medicine in Europe. This position paper outlines the procedures and reviews scientific options to solve challenges for the determination of specific CBPs for animal species, drug substances and disease conditions. VetCAST will adopt EUCAST approaches: the initial step will be data assessment; then procedures for decisions on the CBP; and finally the release of recommendations for CBP implementation. The principal challenges anticipated by VetCAST are those associated with the differing modalities of AMD administration, including mass medication, specific long-acting product formulations or local administration. Specific challenges comprise mastitis treatment in dairy cattle, the range of species and within species breed considerations and several other variable factors not relevant to human medicine. Each CBP will be based on consideration of: (i) an epidemiological cut-off value (ECOFF) – the highest MIC that defines the upper end of the wild-type MIC distribution; (ii) a PK/PD breakpoint obtained from pre-clinical pharmacokinetic data [this PK/PD break-point is the highest possible MIC for which a given percentage of animals in the target population achieves a critical value for the selected PK/PD index (*f*AUC/MIC or *f*T > MIC)] and (iii) when possible, a clinical cut-off, that is the relationship between MIC and clinical cure. For the latter, VetCAST acknowledges the paucity of such data in veterinary medicine. When a CBP cannot be established, VetCAST will recommend use of ECOFF as surrogate. For decision steps, VetCAST will follow EUCAST procedures involving transparency, consensus and independence. VetCAST will ensure freely available dissemination of information, concerning standards, guidelines, ECOFF, PK/PD breakpoints, CBPs and other relevant information for AST implementation. Finally, after establishing a CBP, VetCAST will promulgate expert comments and/or recommendations associated with CBPs to facilitate their sound implementation in a clinical setting.

Keywords: Antimicrobial Susceptibility Testing, VetCAST, breakpoints, veterinary, antimicrobials

To set a CBP, three MIC cutoff values should be determined



Upper limit of the wildtype MIC distribution

The highest MIC value at which 90% of a population reaches the desired PK/PD target at a given dosage

MIC value distinguishing between clinical failure and success

Rationale documents

1. Introduction
2. Dosage
3. MIC distributions and epidemiological cut-off (ECOFF)
4. Breakpoints prior to harmonisation (mg/L) S< / R>
5. Pharmacokinetics
6. Pharmacodynamics
7. Monte Carlo simulations and PK-PD cut-off
8. Clinical data
9. Clinical breakpoints

Rationale Documents from EUCAST

The EUCAST Rationale Documents currently available are listed below. Rationale documents for antifungal agents are listed elsewhere, see
➔ **Antifungal rationale documents**".

The EUCAST rationale documents are explained at
General Information on Rationale Documents

A template for anyone aiming to create a rationale document is available at
Template for producing a Rationale Document (26 June 2014)

Rationale Documents for antibacterial agents:

2019 - 2020: Rationale Documents are currently under review. Many have not been updated with more recent breakpoints. When there are discrepancies between RDs and EUCAST breakpoint Tables or dosing recommendations, always refer to the current version of the breakpoint table. Documents which have been reviewed are dated with the review date.

Amikacin v 2.0 (2020-04-30)
Amoxicillin v 1.0
Bedaquiline v 1.0
Benzylpenicillin v 1.0
Cefotaxime v 1.0
Ceftaroline v 1.0
Ceftazidime v 1.0
Ceftazidime-avibactam v 1.0 (2020-07-30)
Ceftobiprole v 1.0
Ceftolozane-tazobactam v 1.0 (2020-05-15)
Cefuroxime iv v 1.0
Ciprofloxacin v 1.9
Colistin v 1.0
Daptomycin v 1.0
Delamanid v 1.0
Doripenem v 1.0
Doxycycline v 1.0
Ertapenem v 1.3
Florfenicol (from VetCast) v 1.0
Fosfomycin v 1.0

Deciding on a CBP

- Input on rationale document taken into account
- Consensus between VetCAST SC members reached

Pharmaceutical industry may consult in the process but cannot take place in the decision of a CBP and cannot finance VetCAST

Our pipeline

Drug	Host species	ECOFF	Method MIC	PK/PD Cut off	Prot. binding	PK/PD index	CBP/rationale document	Publication link
Florfenicol	Calves	*Mannheimia haemolytica, Pasteurella multocida*	*CLSI*	yes	yes	de novo Time kill curve	Rationale document completed (method issues pending before CBP can be published)	popPK
Cefazolin	Dog	*Staphylococcus pseudintermedius*		yes	yes	literature	in progress	popPK
Tulathromycin	Calves	*Mannheimia haemolytica, Pasteurella multocida*		yes	yes	yes		popPK
Marbofloxacin	Horses	*E. coli, Strep. equi*	*E. coli: CLSI/EUCAST. S. equi: CLSI*	yes	yes	literature	in progress	Accepted
Doxycycline	Pigs (336)	*P. multocida (ECOFF) A. pleuropneumoniae (tECOFF)*		yes	yes	AUC/MIC 24h	in progress	
Amoxicillin/clavulanic acid	Dogs	*Staphylococcus pseudintermedius, Staphylococcus aureus, Escherichia coli*		PK data generated *de novo* : blood, urine and GFR	data generation in clinics		will need UTI and systemic use	
Oxytetracycline	Cattle	*P. multocida M. haemolytica*		PK data modelling (Ronette, Esther)				
Enrofloxacin	Chicken	*E. coli*	*CLSI/EUCAST*	yes	yes	AUC/MIC > 125h		Submitted
Penicillin Procaine	Horses	Pathogens to be defined (e.g. *Streptococcus equi*)		Collecting data (IV data + IM long-acting)				
Sulfa TMP	Mink	*Staphylococcus delphini (tECOFF), Pseudomonas aeruginosa (tECOFF), Streptococcus canis (tECOFF), E. coli*	*S. delphini, P.aeruginosa, E. coli: CLSI/EUCAST. S. canis: CLSI*	Yes (used for dosage determination so far)	yes	yes	*Confirmation of empirical dosage only*	Published

Challenges

- Availability of data for setting breakpoints is scarce
- Adapting EUCAST methods to veterinary pathogens is sometimes complex
- Limited number of people with right expertise and time
- Sustainable funding not achieved, instead:
  - JPIAMR project in 2016
  - 2018: Small grant from French Ministry of Agriculture and Food (DGAL)
  - Projects indirectly funding VetCAST activities
    - IMPART
    - ENOVAT
    - Etc

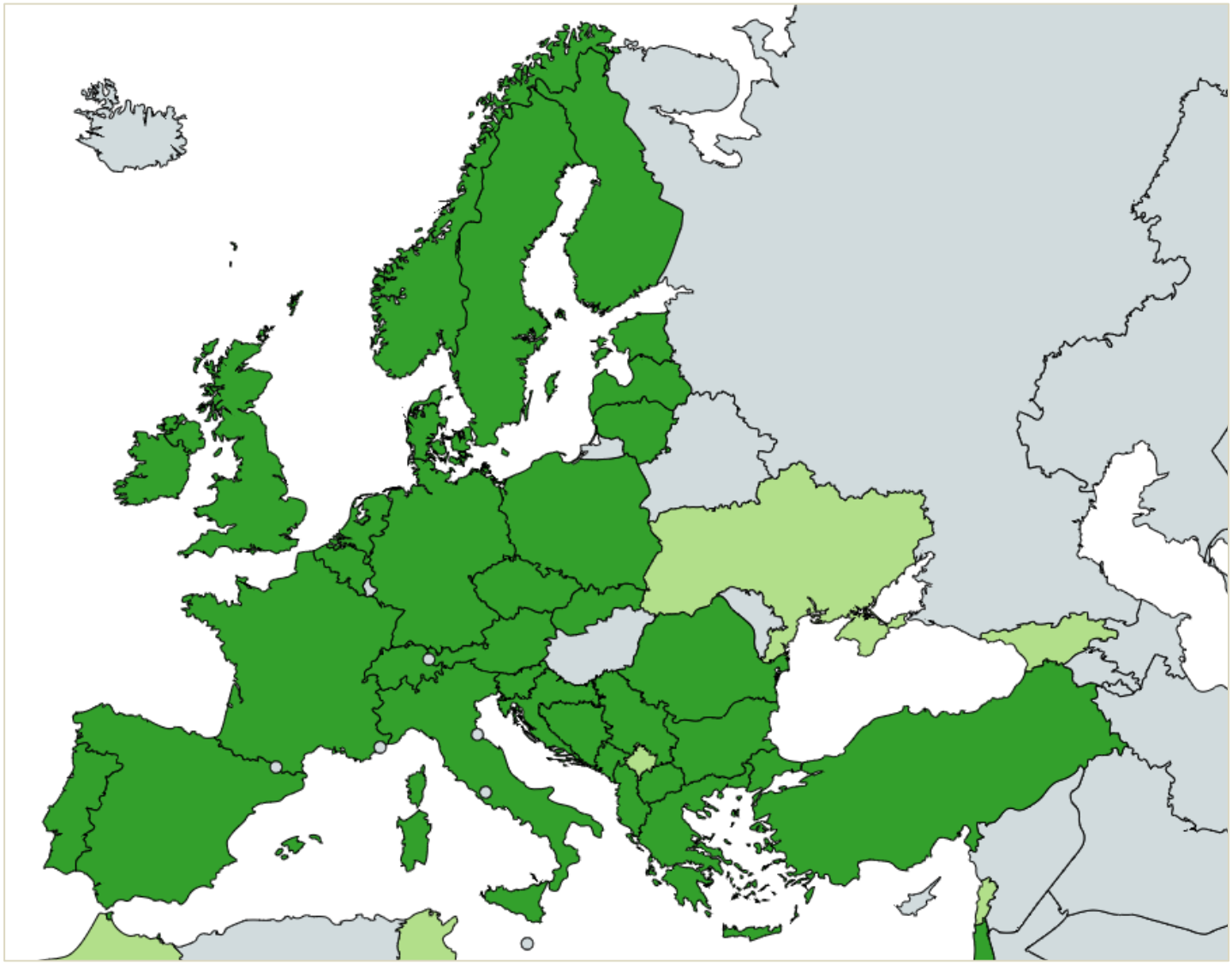
ENOVAT

- European Network for Optimization of Veterinary Antimicrobial Treatment
- https://enovat.eu
- Aim:
  - *"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"*

ENOVAT Working Groups

https://enovat.eu

The ENOVAT consortium



Total: 210 participants from 43 countries

COST Countries

Near Neighbour Countries

International Partner countries:

- Australia
- Canada
- S. Africa

Thanks for your attention ☺