

Why Have Susceptibility Testing Breakpoints Changed for Veterinary Antibiotics?

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Affiliations, Conflicts of Interests, and Disclosures:

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Disclosures related to my presentation:

- Employee: North Carolina State University, College of Veterinary Medicine
- Active grants/Research contracts: Merck Animal Health.
- Consulting contracts: Elanco, Zoetis, Merck, Dechra, Verté Therapeutics
- Unpaid volunteer: CLSI-VAST Subcommittee, AVMA Committee on Antibiotics, USP Expert Committee on Antibiotics (BIO4) Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB)
- Books / Royalties: Author of books relating to drug therapy published by Elsevier and Wiley-Blackwell
- I will discuss drugs/dosages that are currently NOT approved for use in animals

Part 2

CLSI – VAST

Revision of Breakpoints

CLSI-VAST

Breakpoints for Susceptibility Testing Bacteria from Animals:

- Since 1999, CLSI-VAST has developed breakpoints for approximately 280 drug-bug combinations, included in 7th Edition of Vet01
- 12 new breakpoints were added in 7th Edition, including revision of fluoroquinolone breakpoints
- 8th Edition is in progress
With several new breakpoints (maybe 13)

Antimicrobial Guidelines and Consensus Statements

ISCAID Consensus Statement Guidelines (www.ISCAID.org)



The screenshot shows the homepage of the International Society for Companion Animal Infectious Diseases (ISCAID). The page features a yellow header with the ISCAID logo on the left, which includes a globe and silhouettes of a dog and a cat. To the right of the logo is the text "ISCAID" in a large, purple, serif font, with "International Society for Companion Animal Infectious Diseases" in a smaller, purple, sans-serif font below it. Further right is the tagline "Dedicated to the Animals That Improve Our Quality of Life." in a purple, italicized, serif font. Below the header is a yellow navigation bar with links for "Donate", "Join", "Contact", and "Home", a search box, and a "Search" button. The main content area is a collage of four images: a woman holding a kitten, a man petting a horse, a woman holding a parrot, and a man petting a dog on a beach. Below the collage is a white navigation bar with links for "About Us", "Pet Owners", "Health Scientists", "Links", "Sponsors", "Meeting Info", and "Members". At the bottom is a purple footer with the text "International Society for Companion Animal Infectious Diseases (ISCAID)" in orange and a "Member Sign In" box with a text input field labeled "Username or Email Address".

ISCAID
International Society for Companion
Animal Infectious Diseases

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**International Society for Companion
Animal Infectious Diseases (ISCAID)**

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Guidelines for the diagnosis and antimicrobial therapy of canine superficial bacterial folliculitis (Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Diseases)

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Old version.

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GUIDELINES

Veterinary Dermatology



Antimicrobial use guidelines for canine pyoderma by the International Society for Companion Animal Infectious Diseases (ISCAID)

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Abstract

Background: Canine pyoderma is one of the most common presentations in small animal practice, frequently leading to antimicrobial prescribing.

Objectives: To provide clinicians with antimicrobial treatment guidelines for staphylococcal pyoderma, including those involving methicillin-resistant staphylococci. Guidance on diagnosing surface, superficial and deep pyoderma and their underlying primary causes, is included. Recommendations aim to optimise treatment outcomes while promoting responsible antimicrobial use.

Materials and Methods: Evidence was gathered from a systematic literature review of English-language treatment studies for canine pyoderma up to 23 December 2023. Quality was assessed using SORT criteria and combined with authors' consensus evaluation. Recommendations were voted on in an iterative process, followed by a Delphi-style feedback process before final agreement by the authors.

Results: Cytology should be performed in all cases before antimicrobials are used. Topical antimicrobial therapy alone is the treatment-of-choice for surface and superficial pyodermas. Systemic antimicrobials should be reserved for deep pyoderma and for superficial pyoderma when topical therapy is not effective. Systemic therapy, with adjunctive topical treatment, is initially provided for 2 weeks in superficial and 3 weeks in deep pyoderma, followed by re-examination to assess progress and manage primary causes. First-choice drugs have expected efficacy against the majority of methicillin-susceptible *Staphylococcus pseudintermedius*; for all other drugs, laboratory testing should confirm susceptibility and exclude suitability of safer alternatives. As culture and susceptibility testing are essential for rationalising systemic therapy, laboratories and practices should price them reasonably to encourage use. Proactive topical therapy using antiseptics may help prevent recurrences.

Conclusions and Clinical Relevance: The accessibility of the skin offers excellent, achievable opportunities for antimicrobial stewardship.

Why is it important to update and revise antimicrobial susceptibility testing breakpoints?

Old In Vitro Antimicrobial Breakpoints Are Misleading Stewardship Efforts, Delaying Adoption of Innovative Therapies, and Harming Patients

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The current antimicrobial market and old (pre-2000) in vitro antimicrobial susceptibility test interpretative criteria (STIC) are not working properly. Malfunctioning susceptibility breakpoints and antimicrobial markets have serious implications for both patients (ie, from a safety and efficacy perspective) and antibiotic-focused pharmaceutical and biotechnology company economic viability. Poorly functioning STIC fail both patients and clinicians since they do not discriminate between likely effective and ineffective antimicrobial regimens. Poor economic viability fails patients and clinicians as it decreases the industry's ability to develop antimicrobial agents that clinicians and patients urgently require now and in the future. Herein, we review how STIC for older antimicrobial agents were determined and how their correction can impact the perceived utility of old relative to new antimicrobial agents. Moreover, we describe the data and analysis needs to systematically reevaluate older STIC values. We call for professional infectious diseases societies, government agencies, and other consensus bodies interested in the appropriate use of antimicrobial agents to join an effort to systematically evaluate and, where warranted, correct STIC for all relevant antimicrobial agents. This effort will amplify the effects of other measures designed to increase appropriate antimicrobial use (ie, good antimicrobial stewardship), development, and regulation.

Table 1. Clinical Breakpoints Evaluated by the College of American Pathologists Survey to Laboratories Participating in Bacteriology Proficiency Testing Program

Organism	Antimicrobial	Year BP Updated by CLSI ^a	Rationale for BP Update [4]	Obsolete Susceptible BP	Current Susceptible BP
Enterobacterales	Ceftazidime	2010	A public health need was identified due to the spread of AMR (ie, ESBL producers) Revised BPs simplified testing and eliminated the need for additional tests to detect AMR	≤8 µg/mL	≤4 µg/mL
Enterobacterales	Ceftriaxone	2010		≤8 µg/mL	≤1 µg/mL
Enterobacterales	Ciprofloxacin	2019	New PK/PD data indicated the previous breakpoints were set too high	≤1 µg/mL	≤0.25 µg/mL
Enterobacterales	Levofloxacin	2019	Revised BPs allowed harmonization across SDOs	≤2 µg/mL	≤0.5 µg/mL
Enterobacterales	Meropenem	2010	A public health need was identified related to recognition of a new AMR mechanism (ie, carbapenemase genes) Revised BPs simplified testing and eliminated the need for additional tests to detect AMR	≤4 µg/mL	≤1 µg/mL
<i>Pseudomonas aeruginosa</i>	Piperacillin-tazobactam	2012	New data demonstrated poor prediction of clinical response using existing breakpoints	≤64/4 µg/mL	≤16/4 µg/mL
<i>Acinetobacter baumannii</i>	Imipenem	2014	New data demonstrated poor prediction of clinical response using existing breakpoints	≤4 µg/mL	≤2 µg/mL

Abbreviations: AMR, antimicrobial resistance; BP, breakpoint; CLSI, Clinical and Laboratory Standards Institute; ESBL, extended-spectrum β-lactamase; PK/PD, pharmacokinetic/pharmacodynamic; SDO, standards development organization.



CLINICAL AND
LABORATORY
STANDARDS
INSTITUTE®

How Does CLSI Create Standards?

Guidelines for Setting Breakpoints in the Interpretive Categories

1. Pharmacokinetic/Pharmacodynamic data (PK-PD)
2. MIC data from bacteria collected in the field (population distribution)
3. Clinical efficacy data at approved dose

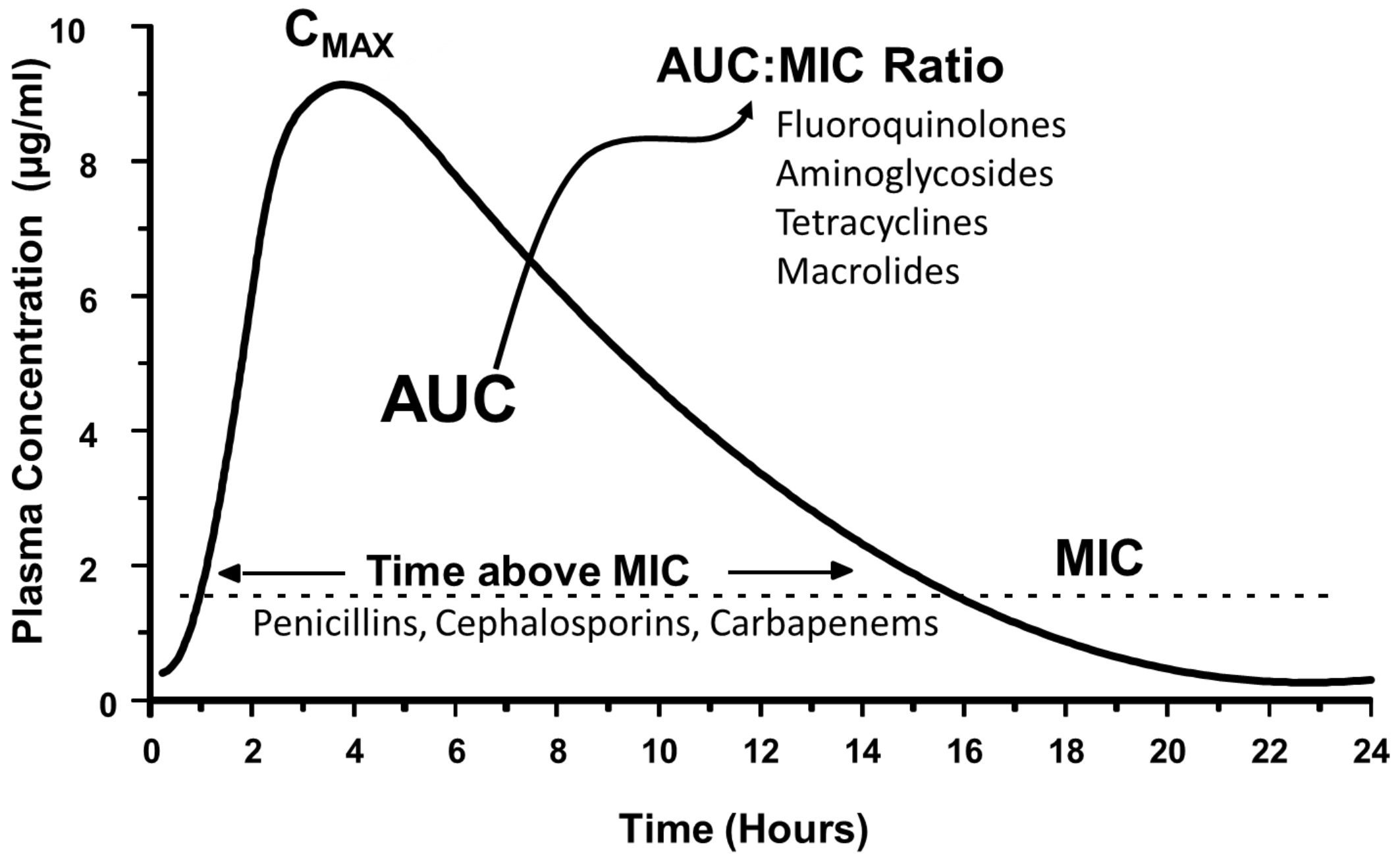
Pharmacokinetic-Pharmacodynamic (PK-PD) Principles to Optimize Therapy

Pharmacokinetics (PK):

- Describes the disposition of drugs in the body.

Pharmacodynamics (PD):

- Describes the action of drug on the organism.



Veterinary-Specific Interpretation: Companion Animals

- Fluoroquinolones
 - Enrofloxacin, Marbofloxacin, Orbifloxacin, Pradofloxacin (dogs & cats)
 - Levofloxacin, Difloxacin (dogs only); Enrofloxacin (horses)
- Gentamicin (dogs, horses)
- Amikacin (dogs, horses, foals)
- Clindamycin (dogs)
- Cephalosporins 3rd generation: Cefpodoxime & Ceftazidime (dogs); Cefovecin (dogs & cats)
- Cephalosporins 1st Generation: Cefazolin (dogs, horses), Cephalexin (dogs)
- Chloramphenicol (dogs)
- Ampicillin/Amoxicillin (dogs, cats, horses)
- Amoxicillin-Clavulanate (dogs, cats)
- Piperacillin-tazobactam (dogs)
- Tetracyclines
 - Doxycycline, Tetracycline (dogs, horses), Minocycline (dogs, horses)



Veterinary Antimicrobial Susceptibility Testing (VAST)

Generic Drug Working Group:

- Develop breakpoints for older drugs that do not have veterinary sponsors
- Rely on PK-PD criteria, MIC distributions, and evidence of use in the published literature
- Dosages and efficacy based on clinical consensus

CLSI-VAST (VET01, 2023)

New breakpoints for susceptibility testing:

- Cephalosporins (1st gen): $\leq 8 \mu\text{g/mL} \rightarrow \leq 2 \mu\text{g/mL}$
- Changed Cephalothin to Cephalexin for testing
- Amoxicillin-Clav: $\leq 8 \mu\text{g/mL} \rightarrow \leq 0.25 \mu\text{g/mL}$
- Ampicillin: $\leq 8 \mu\text{g/mL} \rightarrow \leq 0.25 \mu\text{g/mL}$
- Gentamicin: $\leq 4 \mu\text{g/mL} \rightarrow \leq 2 \mu\text{g/mL}$
- Chloramphenicol: $\leq 8 \mu\text{g/mL} \rightarrow \leq 2 \mu\text{g/mL}$
- Oxacillin (Resistant *Staph pseudintermedius*): $\geq 4 \mu\text{g/mL} \rightarrow \geq 0.5 \mu\text{g/mL}$

CLSI-VAST (VET08, 2023)

New breakpoints for susceptibility testing:

- Doxycycline: $\leq 4 \mu\text{g/mL}$ \rightarrow Dogs, Horses $\leq 0.125 \mu\text{g/mL}$
- Minocycline: $\leq 4 \mu\text{g/mL}$ \rightarrow Dogs $\leq 0.5 \mu\text{g/mL}$,
Horses $\leq 0.125 \mu\text{g/mL}$
- Amikacin: $\leq 16 \mu\text{g/mL}$ \rightarrow Dogs $\leq 4 \mu\text{g/mL}$,
Horses $\leq 4 \mu\text{g/mL}$, Foals $\leq 2 \mu\text{g/mL}$
- Enrofloxacin: $\leq 0.5 \mu\text{g/mL}$ $\rightarrow \leq 0.06 \mu\text{g/mL}$ (+ SDD)
- Marbofloxacin: $\leq 1 \mu\text{g/mL}$ $\rightarrow \leq 0.12 \mu\text{g/mL}$ (+SDD)

CLSI-VAST (VET01)

Breakpoints for susceptibility testing:

- Piperacillin-Tazobactam (dogs): Dogs $\leq 8 \mu\text{g/mL}$
 - Ceftazidime (dogs): same as human breakpoint
 - ♦ $\leq 4 \mu\text{g/mL}$, *E. coli* ; $\leq 8 \mu\text{g/mL}$ *Pseudomonas aeruginosa*
 - Levofloxacin (dogs): same as human breakpoint
 - $\leq 0.5 \mu\text{g/mL}$ Enterobacteriaceae; $\leq 1 \mu\text{g/mL}$ *Pseud. aeruginosa*
 - Meropenem (dogs): same as human breakpoint
 - ♦ $\leq 1 \mu\text{g/mL}$ Enterobacteriaceae; $\leq 2 \mu\text{g/mL}$ *Pseud. aeruginosa*
 - ♦ *Not yet approved.*
- Human-label antibiotics

Some Examples

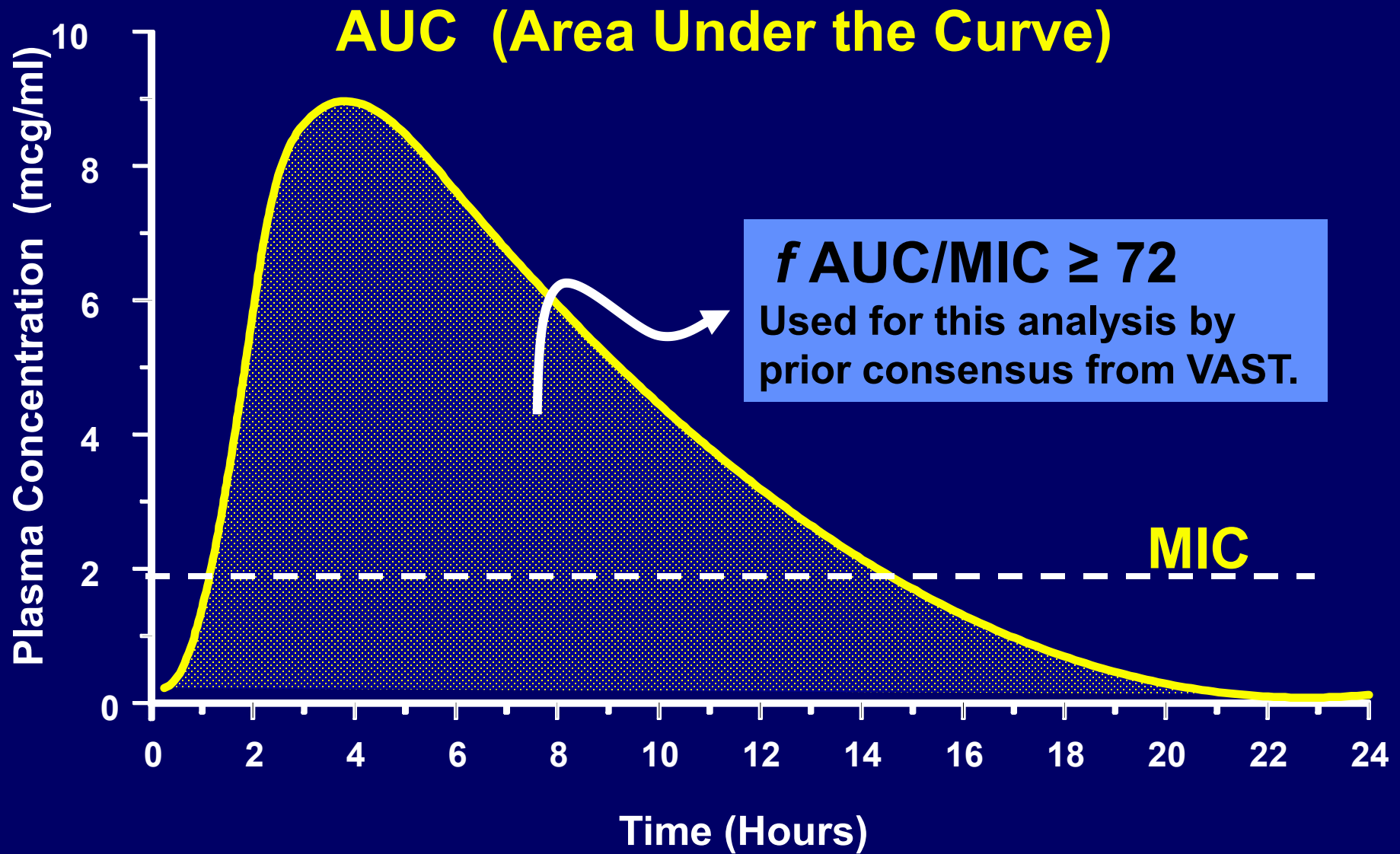
CLSI – VAST
Revision of Fluoroquinolone Breakpoints
for Dogs

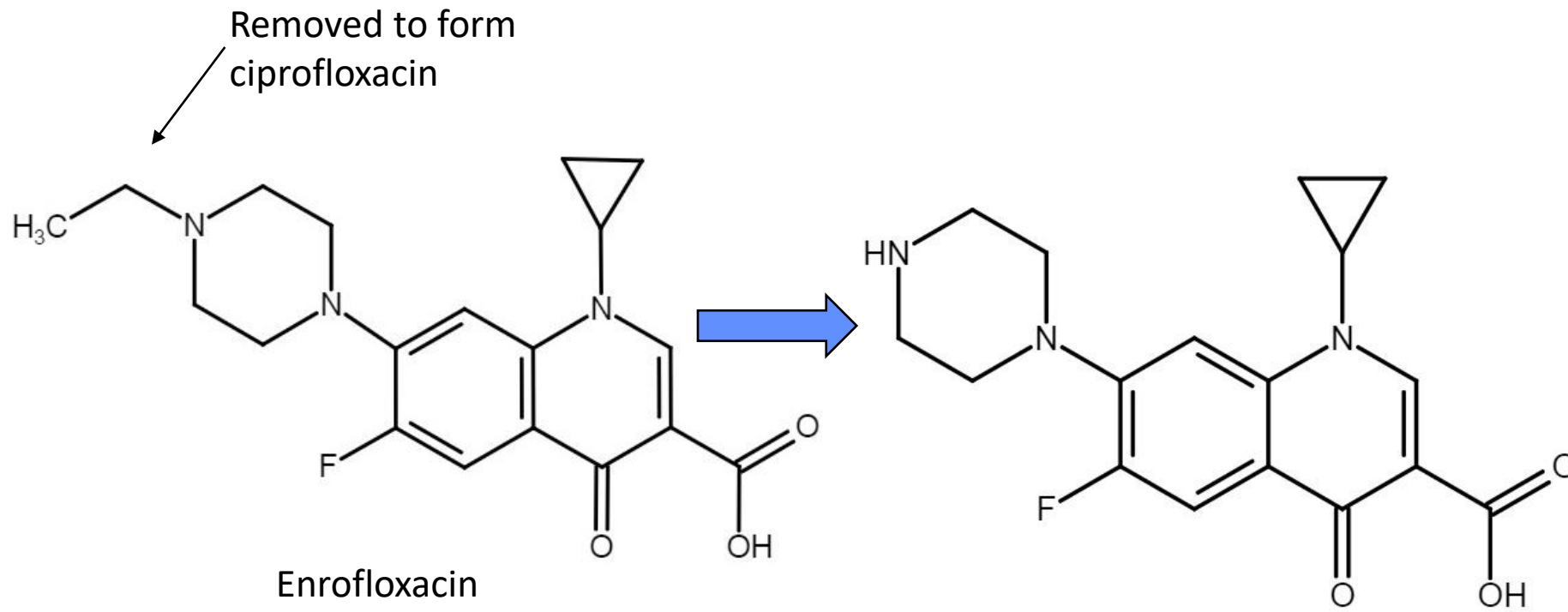
CLSI - VAST

Introduction of a new SDD* category
for susceptibility testing.

* Susceptible Dose-Dependent

PK-PD for Fluoroquinolones





Ciprofloxacin:

- Less lipophilic
- More active against gram-negative bacteria
- Lower oral absorption

Monte Carlo Simulations

AUC/MIC =

$$\text{AUC}_{\text{Enrofloxacin}} = fu \times \text{Enrofloxacin AUC}$$

+

$$\text{AUC}_{\text{Ciprofloxacin}} = fu \times \text{Ciprofloxacin AUC}$$

Addition of
Ciprofloxacin
to total AUC

Correction
for protein
binding

Determination of AUC / MIC

$$\text{Dose} = \frac{\text{CL} \cdot \text{AUC/MIC} \cdot \text{MIC}}{f_u \cdot F \cdot 24 \text{ hr}}$$

$$\text{AUC/MIC} = \frac{f_u \cdot F \cdot 24 \text{ hr} \cdot \text{Dose}}{\text{CL} \cdot \text{MIC}}$$

Revision of fluoroquinolone breakpoints used for interpretation of antimicrobial susceptibility testing of canine bacterial isolates

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ABSTRACT

The fluoroquinolone antimicrobial agents, enrofloxacin and marbofloxacin, were US Food and Drug Administration (FDA) approved in the United States for use in dogs in 1988 and 1999, respectively. There have been many advances since then concerning the pharmacokinetic-pharmacodynamic (PK-PD) evaluation of fluoroquinolones, and there are data available on the susceptibility of targeted pathogens since the original approval. Using this information, the Clinical and Laboratory Standards Institute (CLSI) Veterinary Antimicrobial Susceptibility Testing Subcommittee (VAST) revised its antimicrobial susceptibility testing breakpoints. The previous breakpoints (used in older editions of CLSI standards) for enrofloxacin in dogs were susceptible (S), ≤ 0.5 $\mu\text{g/mL}$, intermediate (I) 1–2 $\mu\text{g/mL}$, and resistant (R) ≥ 4 $\mu\text{g/mL}$. The new breakpoints are S ≤ 0.06 $\mu\text{g/mL}$ for a dose of 5 mg/kg, 0.12 $\mu\text{g/mL}$ for a dose of 10 mg/kg, 0.25 $\mu\text{g/mL}$ for a high dose of 20 mg/kg, and R ≥ 0.5 $\mu\text{g/mL}$. The breakpoints of 0.12 and 0.25 $\mu\text{g/mL}$ represent a new susceptible-dose dependent (SDD) category. For marbofloxacin, previous breakpoints were S, ≤ 1 $\mu\text{g/mL}$, I 2 $\mu\text{g/mL}$, and R ≥ 4 $\mu\text{g/mL}$. The new breakpoints are S ≤ 0.12 $\mu\text{g/mL}$ for a dose of 2.8 mg/kg, 0.25 $\mu\text{g/mL}$ for a dose of 5.5 mg/kg (SDD), and R ≥ 0.5 $\mu\text{g/mL}$. The new breakpoints will be published in the next edition of CLSI-Vet01(S) and deviate considerably from the prior breakpoints. Laboratories are encouraged to revise their testing standards. These changes will likely reduce the unnecessary use of these fluoroquinolones in dogs.

Monte Carlo Simulations

- $fAUC_{24} / MIC$ calculated
- Crystal Ball software (Oracle)
- 10,000 random trials simulated
- Input
 - ◆ MIC: 0.03 → 8 $\mu\text{g}/\text{mL}$
 - ◆ Four oral doses: 5-, 7.5-, 10-, and 20 mg/kg
 - ◆ Dose interval: 24 hours
 - ◆ CL/F (mean & variance)
 - ◆ Protein binding (*for both enrofloxacin and ciprofloxacin*)

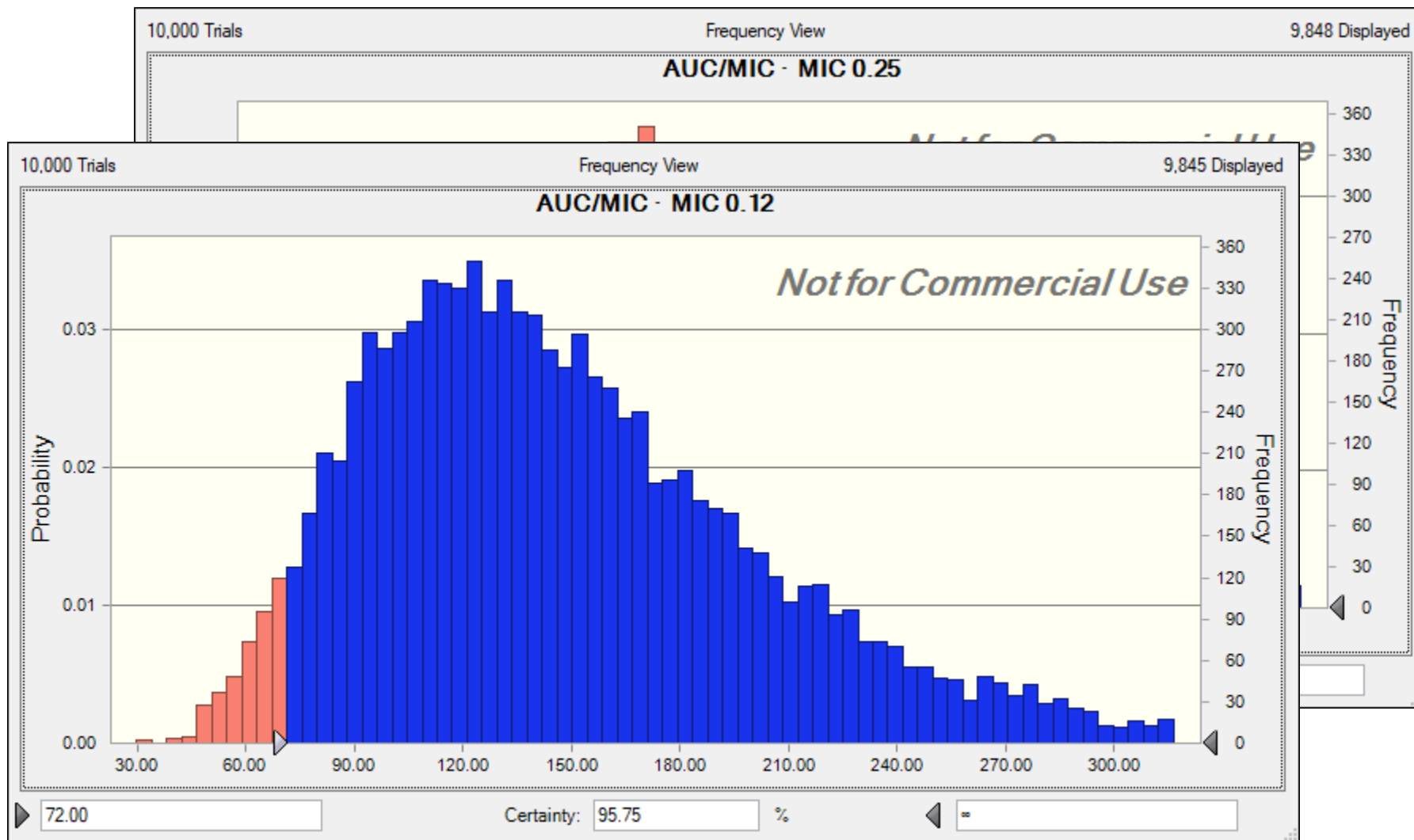
Label Indications and Dose

Approved Label for Dogs

- For management of diseases associated with bacteria susceptible to enrofloxacin.
- 5 to 20 milligrams per kilogram (2.27 to 9.07 milligrams per pound) of body weight.

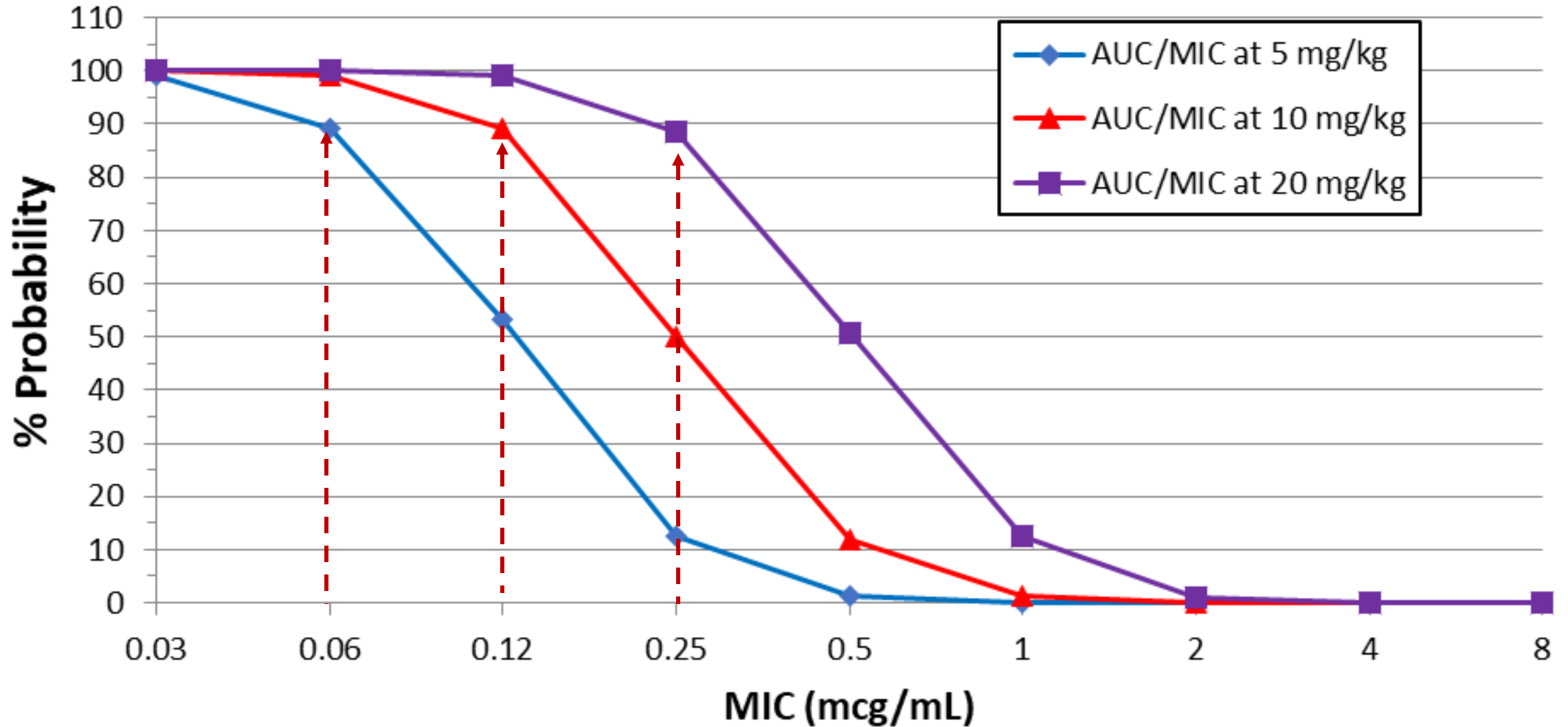


Results

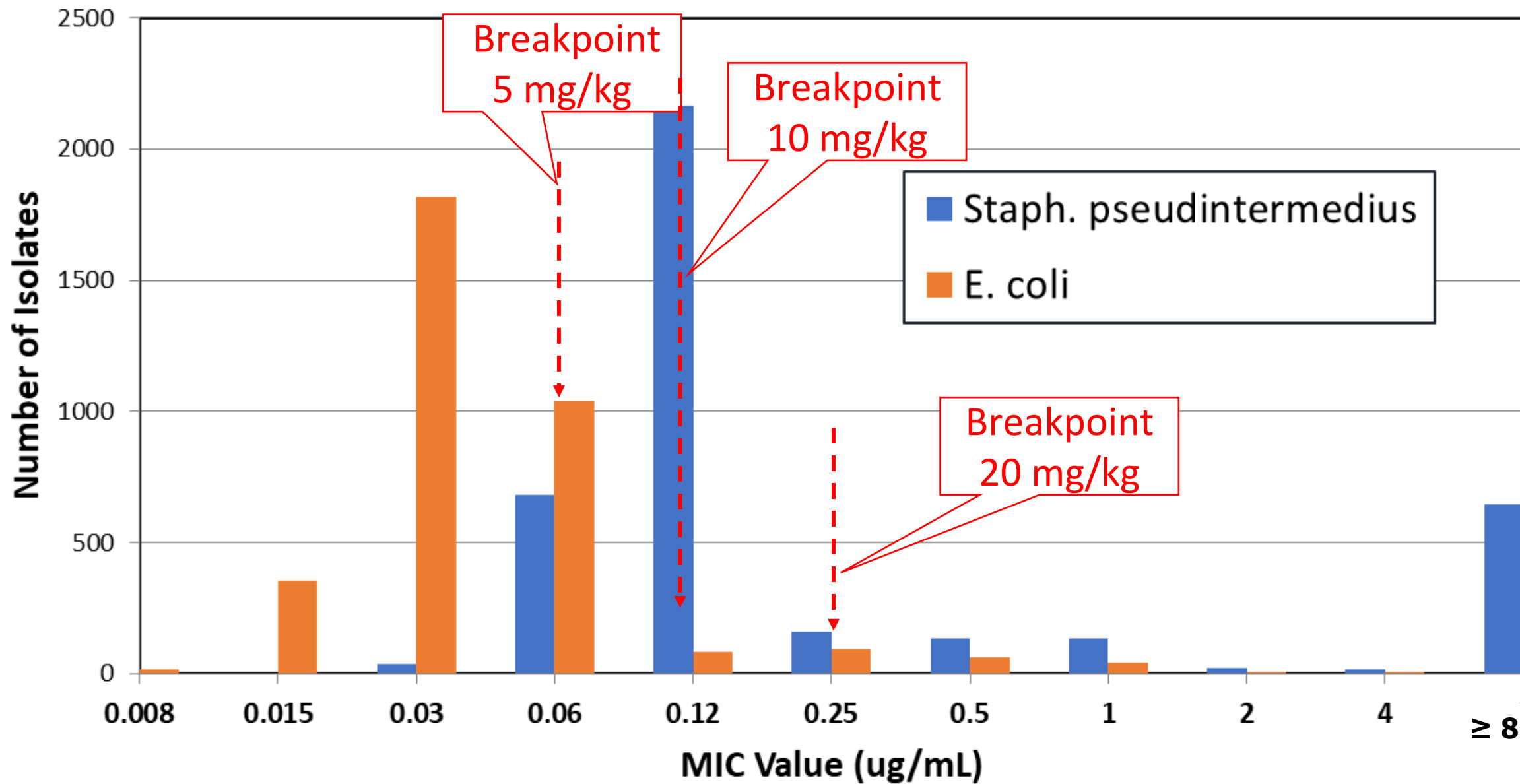


Probability of Target Attainment (PTA) for Enrofloxacin Administered to Dogs

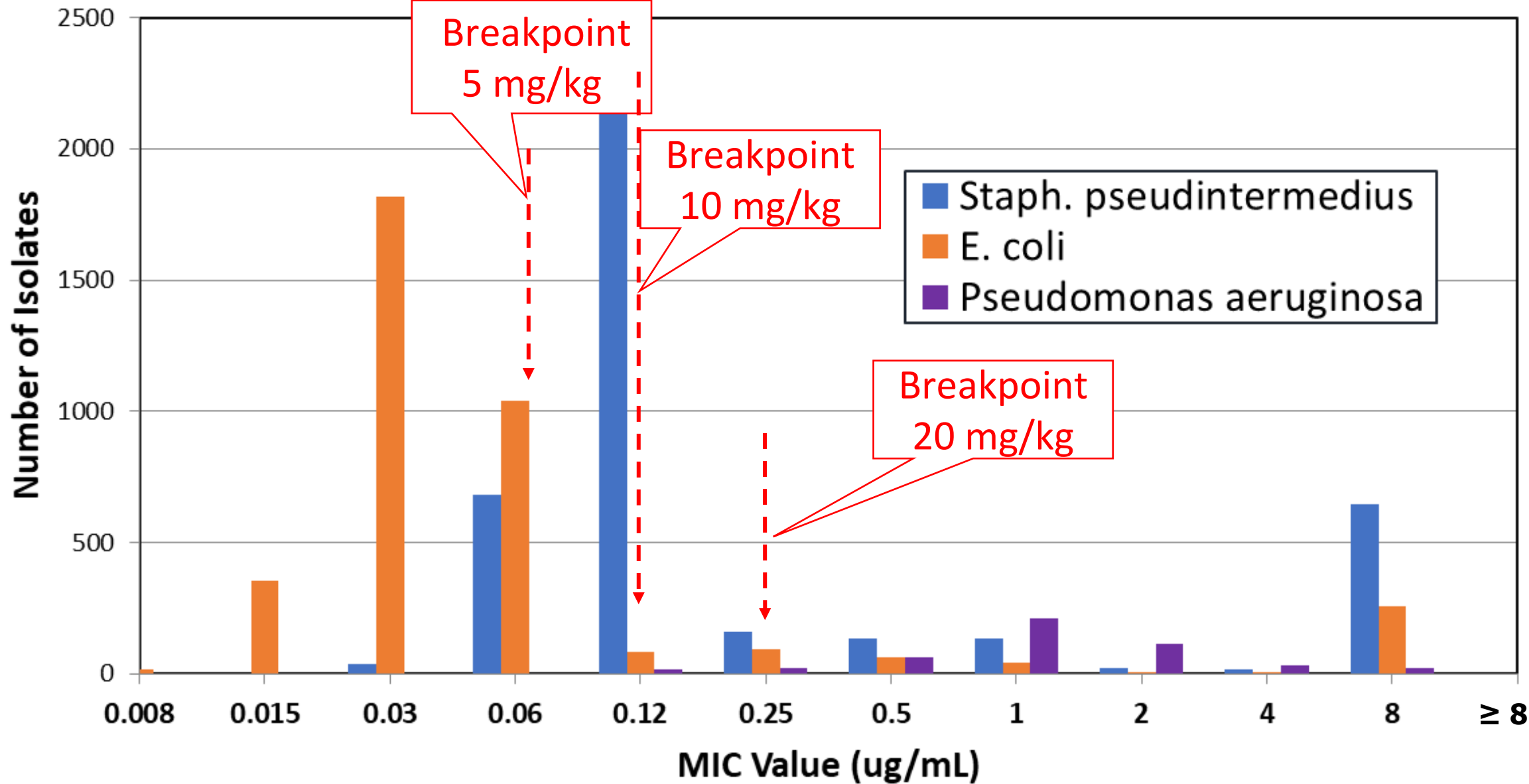
Probability of $fAUC/MIC > 72$ at 3 Doses



Enrofloxacin MIC Distribution (Zoetis/ComPathData)

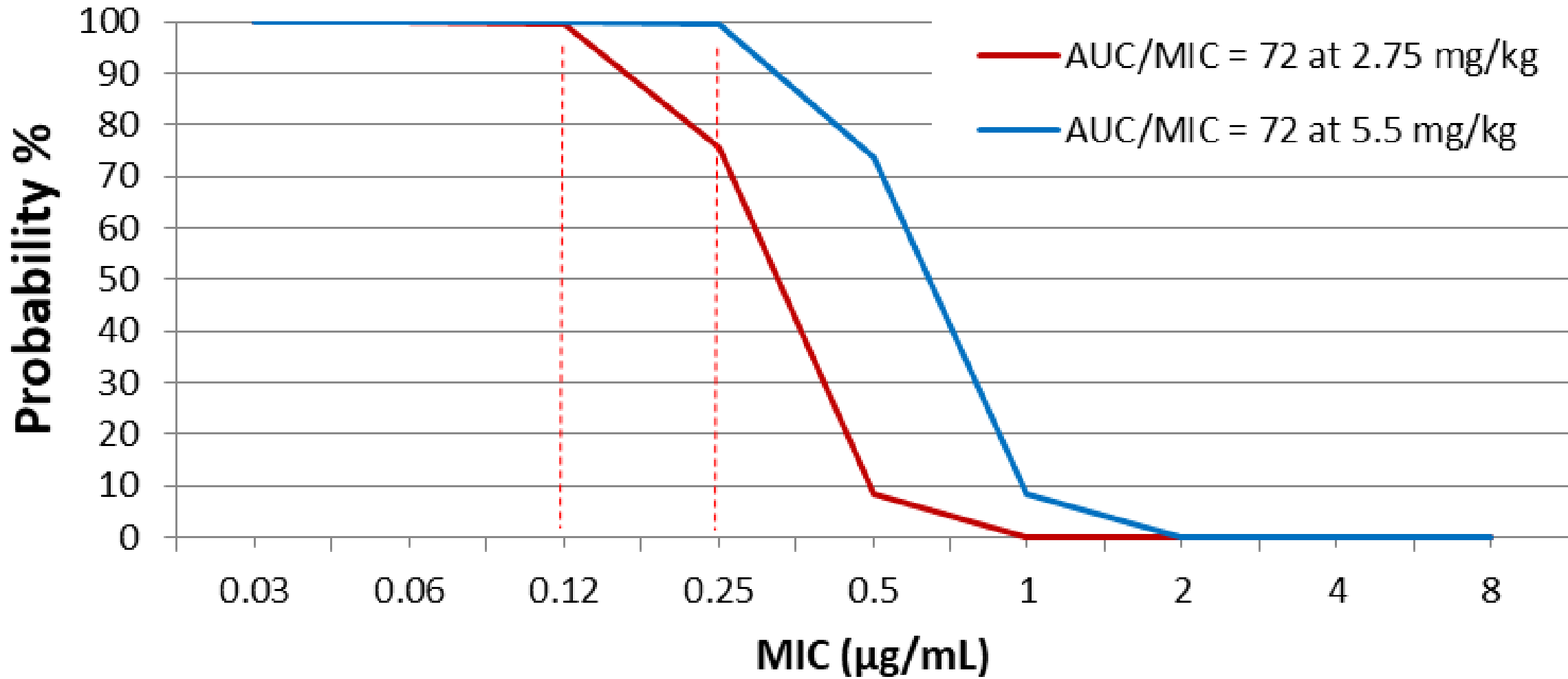


Enrofloxacin MIC Distribution (Zoetis/ComPathData)

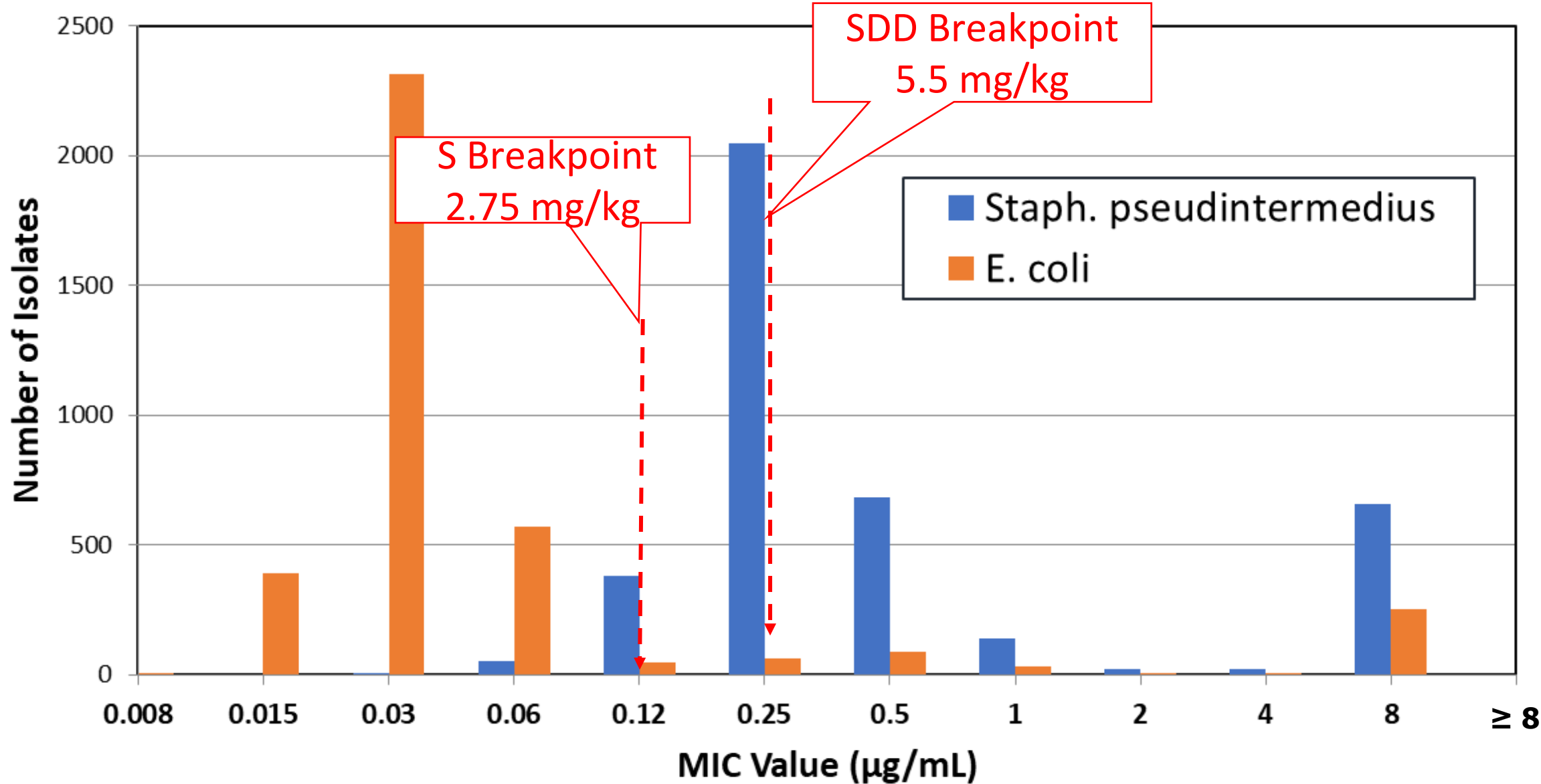


Monte Carlo Simulations

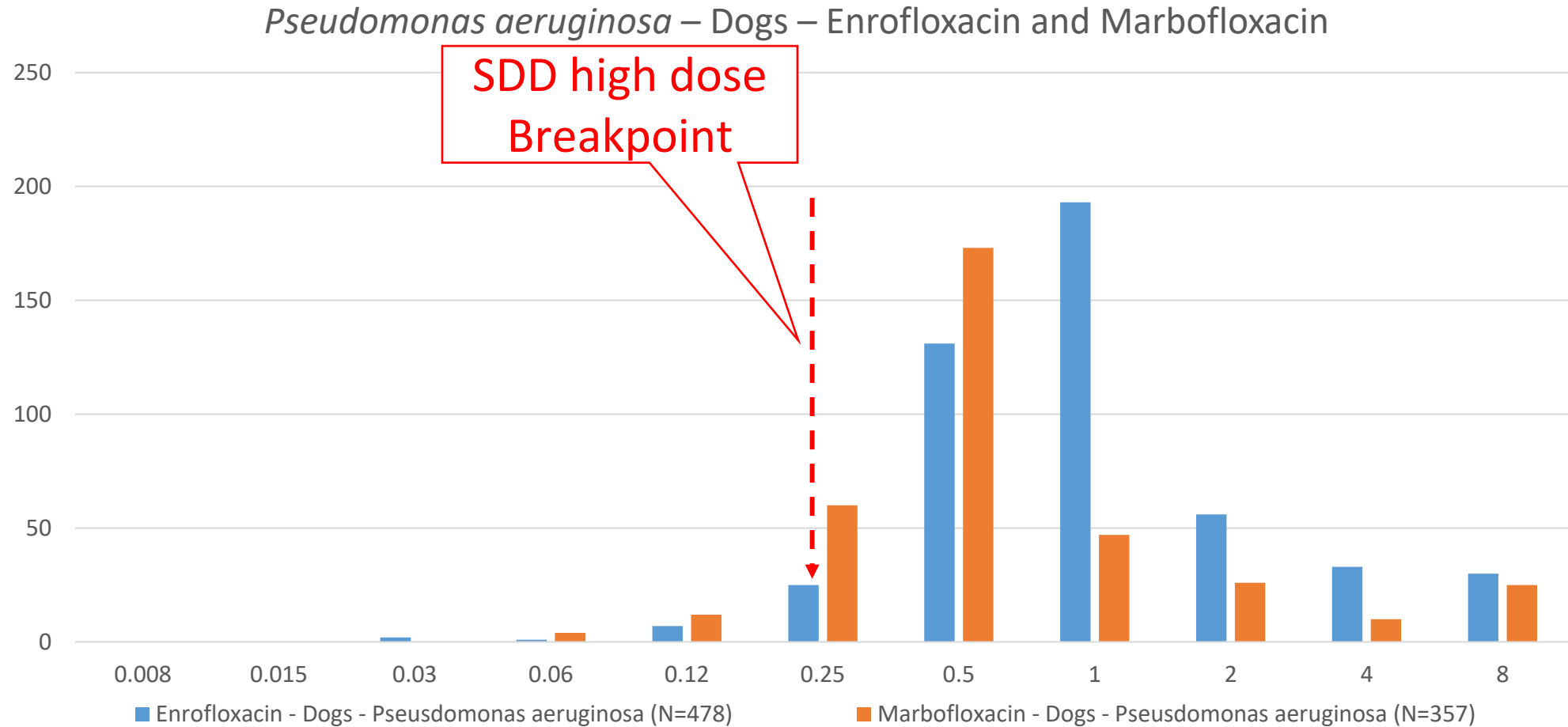
Marbofloxacin *f*AUC/MIC 2.75 vs 5.5 mg/kg



Marbofloxacin MIC Distribution (Zoetis/ComPathData)



MIC Distribution – *Pseudomonas aeruginosa* - Enrofloxacin and Marbofloxacin- dog isolates



Marbofloxacin and Enrofloxacin Breakpoint

Body Site	Antimicrobial Agent	Antimicrobial Agent Class	Interpretive Categories and MIC Breakpoints, µg/mL			
			S	I	SDD	R
Dogs (Continued)						
Resp, SST, U	Enrofloxacin (OLD)	Fluoroquinolones	≤ 0.5	1–2		≥ 4
Resp, SST, U	Enrofloxacin (NEW)	Fluoroquinolones	≤ 0.06		0.12–0.25	≥ 0.5
SST			≤ 0.5	1		≥ 2
SST			≤ 1	2		≥ 4
SST, Ur	Marbofloxacin (NEW)	Fluoroquinolones	≤ 0.12		0.25	≥ 0.5
SST, Ur	Orbifloxacin	Fluoroquinolones	≤ 1	2–4		≥ 8
Skin, Ur	Pradofloxacin	Fluoroquinolones	≤ 0.25	0.5–1		≥ 2

“S” = 5 mg/kg/day
“SDD” = 10-20 mg/kg, once daily

Marbofloxacin and Enrofloxacin Breakpoint

Body Site	Antimicrobial Agent	Antimicrobial Agent Class	Interpretive Categories and MIC Breakpoints, µg/mL			
			S	I	SDD	R
Dogs (Continued)						
Resp, SST, U	Enrofloxacin (OLD)	Fluoroquinolones	≤ 0.5	1–2		≥ 4
Resp, SST, U	Enrofloxacin (NEW)	Fluoroquinolones	≤ 0.06		0.12–0.25	≥ 0.5
SST	Levofloxacin	Fluoroquinolones	≤ 0.5	1		≥ 2
SST, Ur	Marbofloxacin (OLD)	Fluoroquinolones	≤ 1	2		≥ 4
SST, Ur	Marbofloxacin (NEW)	Fluoroquinolones	≤ 0.12		0.25	≥ 0.5
			≤ 1	2–4		≥ 8
			≤ 0.25	0.5–1		≥ 2

“S” = 2.75 mg/kg/day
“SDD” = 5.5 mg/kg, once daily

CLSI – VAST
Revision of Chloramphenicol
Breakpoint

Revision of Chloramphenicol Breakpoint for Dogs

- Dose:

- ◆ Approved dose: 55.5 mg/kg (25 mg/pound), q6h, PO.
- ◆ Off-label (consensus in publications): 50 mg/kg q8h, PO.

- Indications:

- ◆ Approved label: Treatment of “bacterial pulmonary infections, bacterial infections of the urinary tract, bacterial enteritis, and bacterial infections associated with canine distemper caused by susceptible organisms”.
- ◆ Off-Label: Skin, soft tissue infections. (primarily staphylococci).

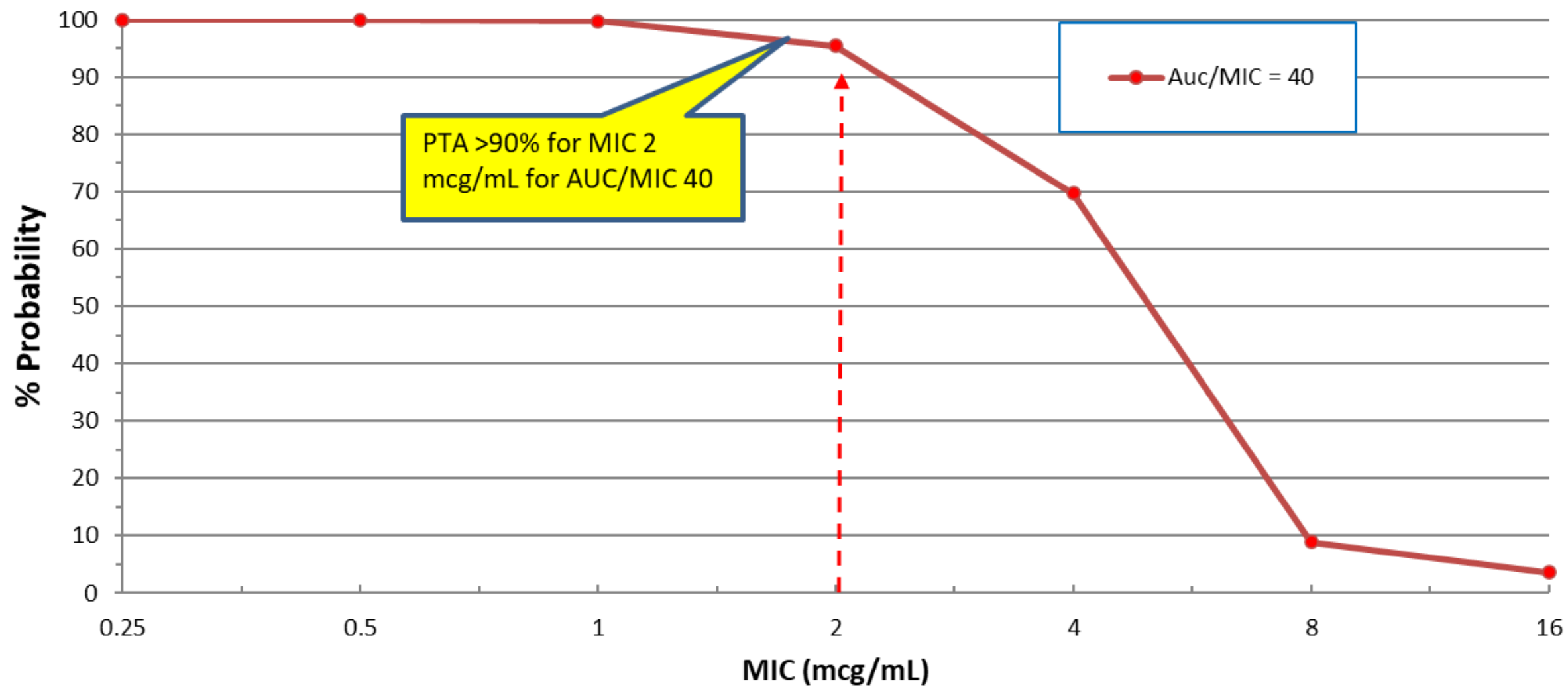
Current Breakpoint (M100) Table 2A, 2C, 2D, 2H
 (Enterobacterales, *Staphylococcus* spp. *Enterococcus* spp.
Pasteurella multocida)

Antimicrobial Agent	Organism	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	
Humans (Continued)									
Chloramphenicol	Enterobacterales	30 µg	≥ 18	13–17	≤ 12	≤ 8	16	≥ 32	(19) MIC distribution data from canine isolates support these breakpoints for use in canine skin and soft tissue infection; however, efficacy data and PK/PD targets were unavailable. ^f (21) Not routinely reported on isolates from the urinary tract. ^e

Most Labs still use the human breakpoint.

Chloramphenicol in Dogs

Probability of AUC/MIC Target Attainment

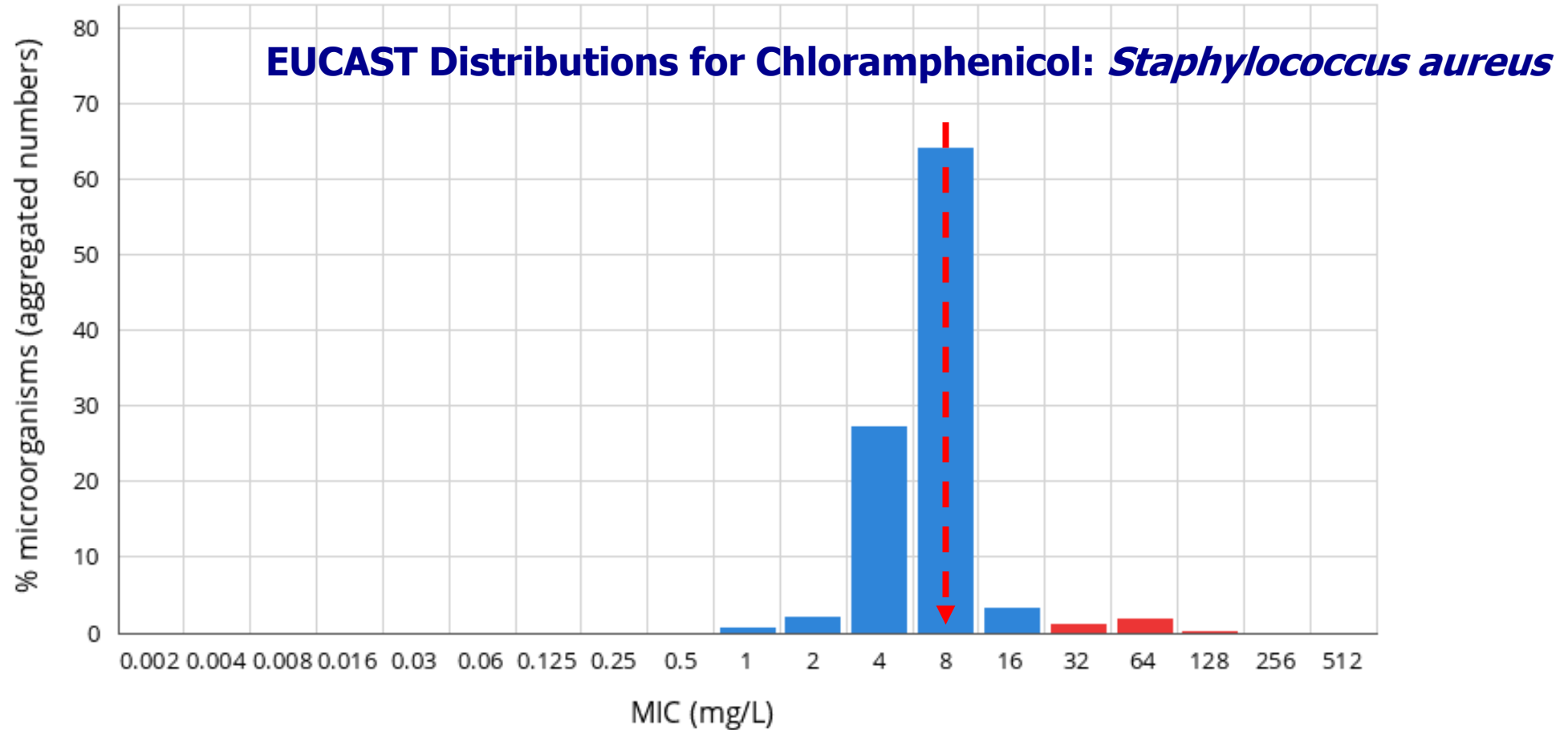


Proposed Breakpoint: Table 2A, 2C, 2D, 2E, 2H
 (Enterobacterales, *Staphylococcus* spp., *Enterococcus* spp.,
Pasteurella multocida, *Streptococcus* spp.)

Antimicrobial Agent	Organism	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm			Interpretive Categories and MIC Breakpoints, µg/mL			Comments
		S	I	R	S	I	R	
Dogs								
Chloramphenicol	Enterobacterales <i>Staphylococcus</i> spp., <i>Enterococcus</i> spp., <i>Pasteurella multocida</i> , <i>Streptococcus</i> spp.	≥18	13–17	≤12	≤2	4	≥8	Breakpoints determined from PK-PD analysis and a dose of 50 mg/kg, administered oral to dogs three times daily.

Chloramphenicol / *Staphylococcus aureus*
International MIC distribution - Reference database 2022-12-02
Based on aggregated distributions

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance

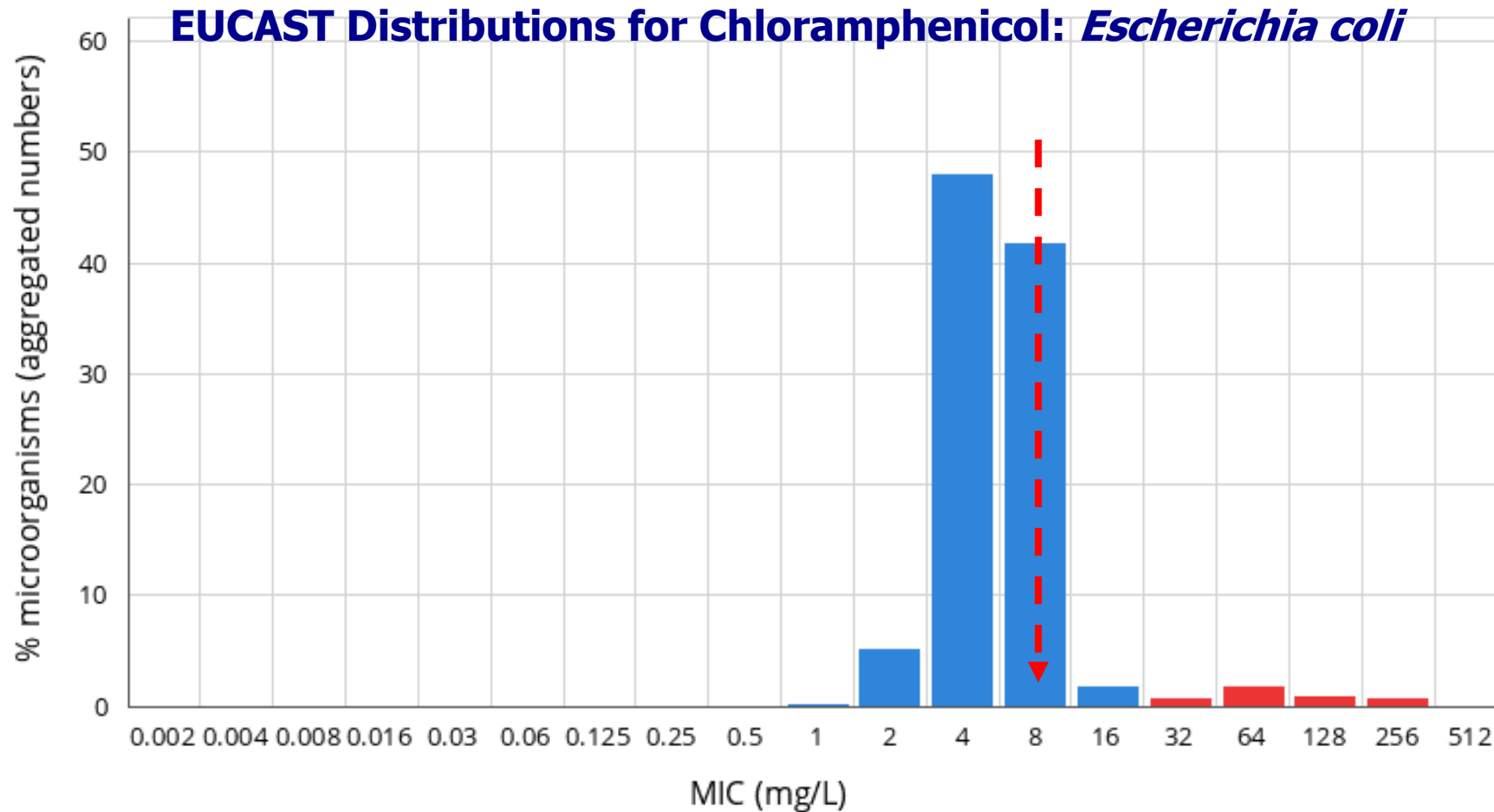


MIC
Epidemiological cut-off (ECOFF): 16 mg/L
Wildtype (WT) organisms: ≤ 16 mg/L

Confidence interval: 8 - 16
1898 observations (6 data sources)

Chloramphenicol / Escherichia coli
International MIC distribution - Reference database 2022-12-02
Based on aggregated distributions

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance

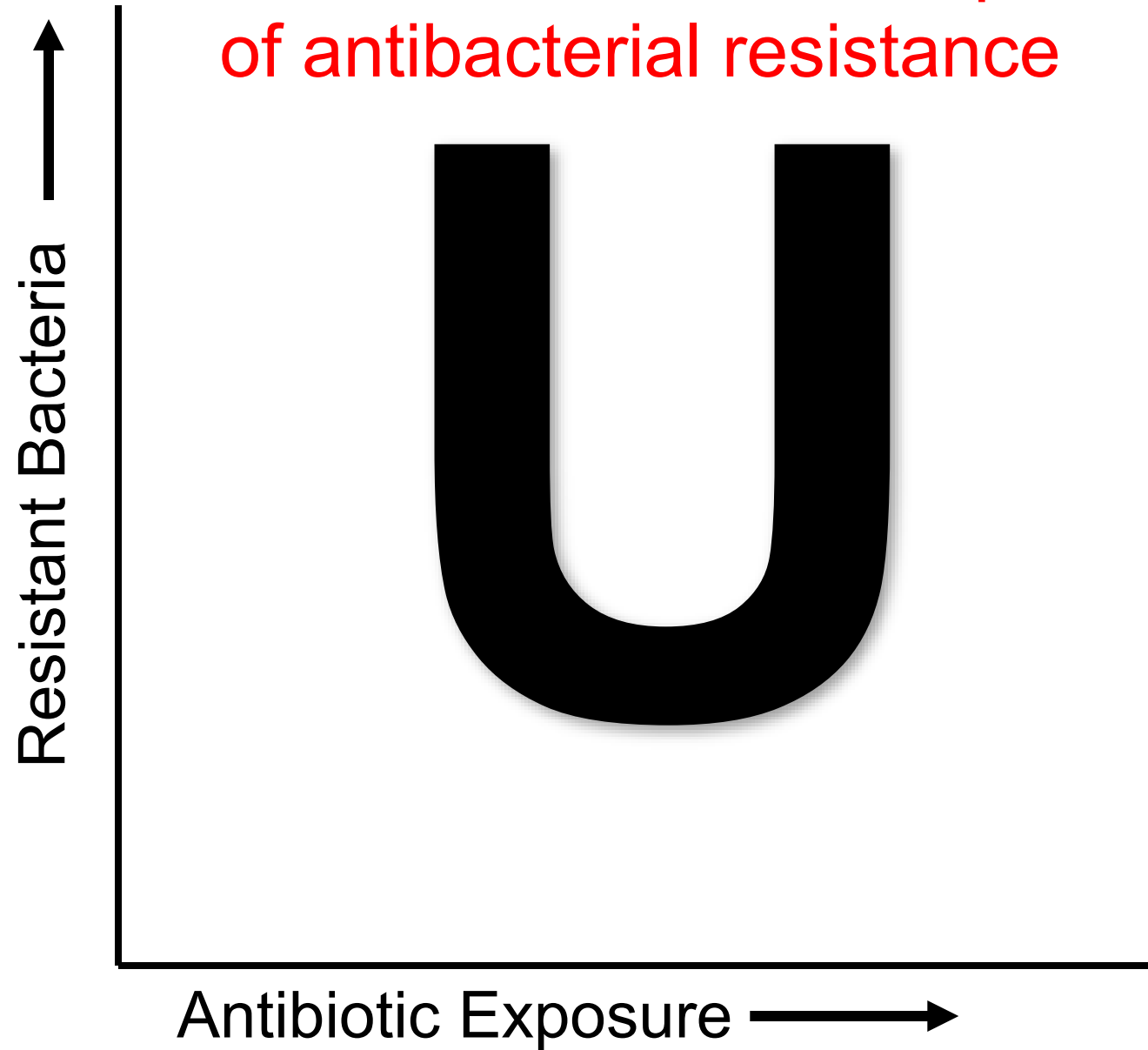


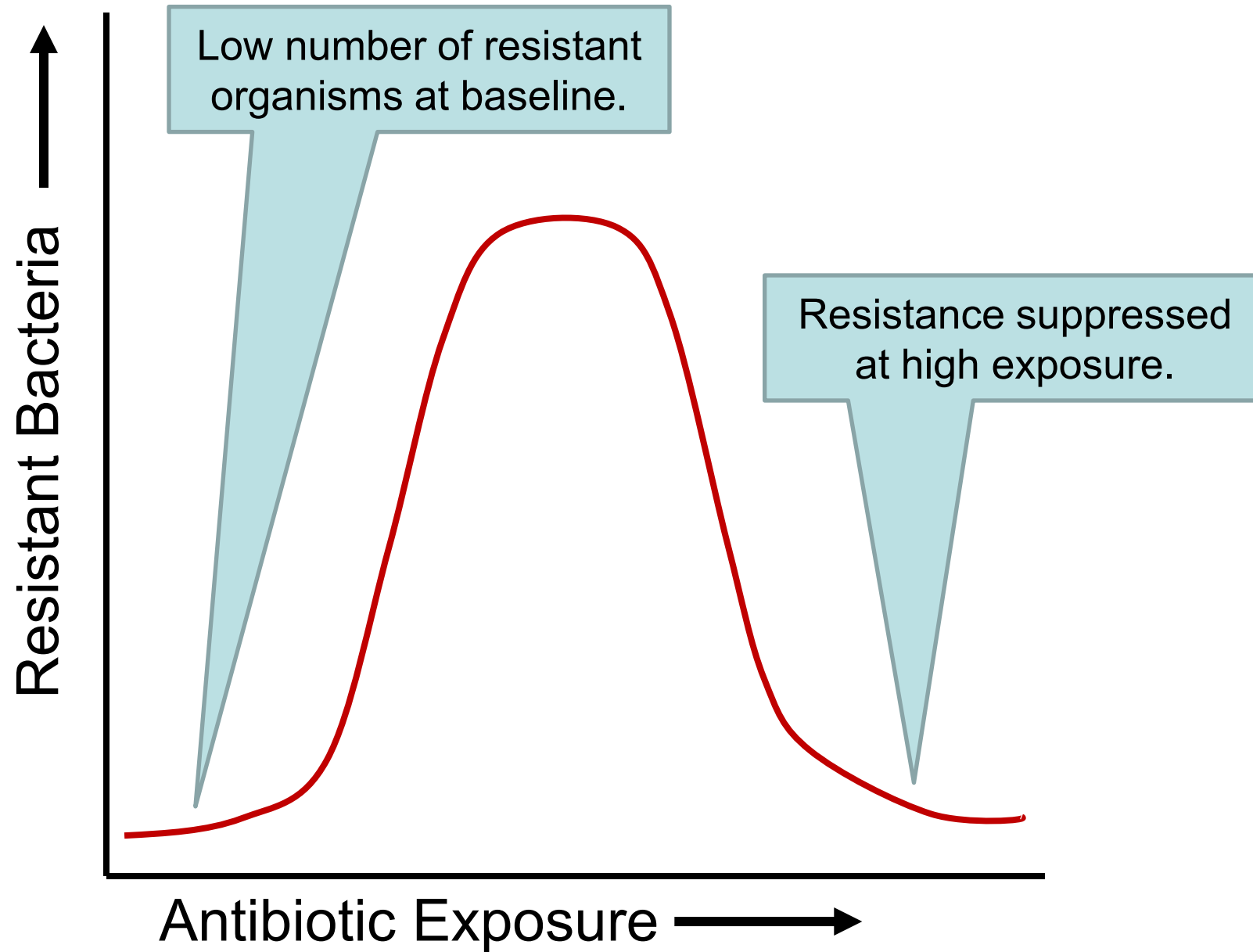
MIC
Epidemiological cut-off (ECOFF): 16 mg/L
Wildtype (WT) organisms: ≤ 16 mg/L

Confidence interval: 8 - 16
45852 observations (40 data sources)

What's the risk of not meeting PK-PD targets?

The “inverted U” concept
of antibacterial resistance





Thank you for your attention.

Any questions?

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