AAVLD – AST Mini-symposium

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Speaker Disclosure – Brian Lubbers

FINANCIAL DISCLOSURE:
- Employee – Kansas State Veterinary Diagnostic Laboratory
- Speaker / Consulting Engagement – Merck Animal Health; Boehringer Ingelheim Vetmedica
- Research Support – Merck Animal Health; Zoetis

UNLABELED/ UNAPPROVED USES DISCLOSURE:
- NONE

**** THERAPEUTIC USES DISCLOSURE:**
- ANY reference to a therapeutic is for illustrative purposes and is NOT an endorsement of a specific product

Other Disclosure

*Much of this presentation is **MY PERSPECTIVE**, based on my training and experiences.*

I do not presume to tell other laboratories how to operate. In fact, I would not encourage you to adopt / do anything that is outside your "comfort zone".

*However, I encourage **OPEN DISCUSSION** about how we can all get better…….*

MY PERSPECTIVE

- Clinical Veterinarian
- Clinical Pharmacologist
- Microbiology Laboratory Section Head
- CLSI – VAST volunteer

From: OpenTip.com

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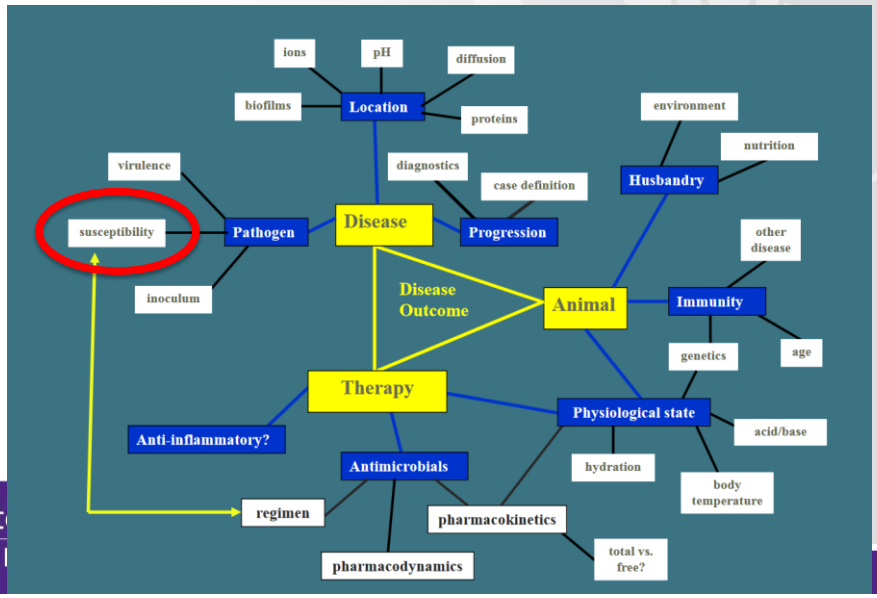
What I want you to know from today

- The given factors that a veterinarian will consider when selecting an antimicrobial are NUMEROUS
  - There are opportunities for diagnostic labs to assist



What I want you to know from today

- CLSI is NOT a secretive organization conspiring against microbiology lab personnel
  - There are opportunities for diagnostic labs to assist

https://thoughtcatalog.com/jacob-geers/2016/04/creepy-stories-of-the-real-men-in-black/

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What do *you* want to get from today?

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Antibiotic Stuff

Antibiotic Stewardship and Diagnostic Testing???

NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

Clinical Infectious Diseases

IDSA GUIDELINE

Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America

Tamar F. Barlam,[1,a] Sara E. Cosgrove,[2,a] Lilian M. Abbo,[3] Conan MacDougall,[4] Audrey N. Schuetz,[5] Edward J. Septimus,[6] Arjun Srinivasan,[7] Timothy H. Dellit,[8] Yngve T. Falck-Ytter,[9] Neil O. Fishman,[10] Cindy W. Hamilton,[11] Timothy C. Jenkins,[12] Pamela A. Lipsett,[13] Preeti N. Malani,[14] Larissa S. May,[15] Gregory J. Moran,[16] Melinda M. Neuhauser,[17] Jason G. Newland,[18] Christopher A. Ohl,[19] Matthew H. Samore,[20] Susan K. Seo,[21] and Kavita K. Trivedi[22]

CDC

The Core Elements of **Outpatient Antibiotic Stewardship**

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Antibiotic Stewardship in Veterinary Medicine

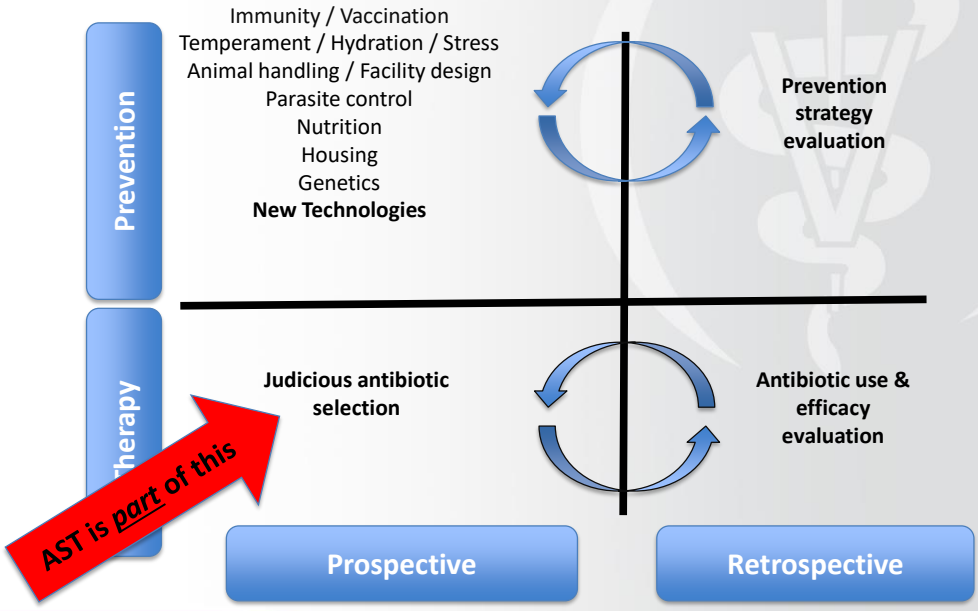
- Actions veterinarians take individually and as a profession to preserve the effectiveness and availability of antimicrobial drugs through conscientious oversight and responsible medical decision-making while safeguarding animal, public and environmental health.

- Core principles
  - Commit to stewardship
  - Advocate for a system of care to prevent common diseases
  - Select and use antimicrobials judiciously
  - Evaluate antimicrobial use practices
  - Educate and build expertise

STEWARDSHIP FALLS ON THE VETERINARIAN!!

https://www.avma.org/KB/Policies/Pages/Antimicrobial-Stewardship-Definition-and-Core-Principles.aspx

Antibiotic Stewardship in Veterinary Medicine



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How veterinarians select antibiotics……

- Is an antibiotic even necessary for this patient?

How veterinarians select antibiotics……
& how the micro lab can help!

- Is an antibiotic even necessary for this patient?

Specimen Desc:	URINE
Organism Id:	ESCHERICHIA COLI (NON-HEMOLYTIC)
Comments:	-->10,000 cfu/ml
Received Date:	February 20, 2018
Test Finalized:	February 22, 2018
Update 1:	2/21/2018, No growth at this time.
Update 2:	2/22/2018, No growth.

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How veterinarians select antibiotics……

- Is an antibiotic even necessary for this patient?

YES

- How do veterinarians select the most appropriate antibiotic?

The “best” antimicrobial……

- is ***Legal*** to use in that patient,
- has a reasonable expectation of ***Efficacy*** and
- is reasonably ***Safe*** for the patient, the owner (or whoever is administering) and the end consumer (if the patient is a food animal).

The ideal antimicrobial is also ***available*** for prescribing, can be ***readily administered*** to the patient, is within the ***financial constraints*** of the owner and is ***familiar*** to the clinician.

1) Antimicrobial selection is NOT “cookie cutter”
2) It is a fluid process and requires consideration of the above in each and every case

Legal Use of Antimicrobials in Veterinary Medicine

- For food animals
  - Animal Medicinal Drug Use Clarification Act of 1994 [AMDUCA]
  - Animal Drug Availability Act of 1996
  - Veterinary Feed Directive

  - FDA Guidance 209
  - FDA Guidance 213
  - Compliance Policy Guide Sec 615.115

Legal Use of Antimicrobials in Veterinary Medicine & how the micro lab can help!

- Animal Medicinal Drug Use Clarification Act
  - 21 CFR Part 530.41
  - The following drugs, families of drugs, and substances are prohibited for extralabel animal and human drug uses in food-producing animals:
    (BVL note -- only antibiotics listed here)

1. Chloramphenicol
2. Dimetridazole
3. Ipronidazole
4. Other nitroimadazoles
5. Furazolidone
6. Nitrofurazone
7. Glycopeptides

} NEVER report for Food Animals

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Legal Use of Antimicrobials in Veterinary Medicine & how the micro lab can help!

- Animal Medicinal Drug Use Clarification Act
  - 21 CFR Part 530.41
  - The following drugs, families of drugs, and substances are prohibited for extralabel animal and human drug uses in food-producing animals:

1. Sulfonamide drugs in lactating dairy cattle
   - (except approved uses of sulfadimethoxine)
2. Cephalosporins***
   - For disease prevention
   - Unapproved doses, routes, durations, frequencies
   - Not approved for that species / production class
3. Fluoroquinolones

Conditionally report in Food Animals??

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What about reporting aminoglycosides?

Aminoglycoside Use in Cattle and Small Ruminants

Due to food safety concerns from extended withdrawal times and associated drug residue risks, the AVMA does not support the use of aminoglycosides in cattle or small ruminants except those products specifically approved by FDA for use in cattle or small ruminants.

Formerly titled "Aminoglycosides"

https://www.avma.org/KB/Policies/Pages/Aminoglycoside%20Use%20in%20Cattle%20and%20Small%20Ruminants.aspx

Legal Use of Antimicrobials in Veterinary Medicine

- What is a Food Animal?
  - Cattle, Swine, Chickens, Turkeys ☆
  - Bear in zoo ⊘
  - Cervids ☆
  - Game birds (pheasant, chukar, quail) ☆
  - Llama & alpaca ⊘
  - Pot-bellied pigs ☆
  - Pygmy goats ☆
  - Rabbits ☆
  - Sheep & Goats ☆
  - Wild bear ☆

Extracted from FDA Draft Guidance 210

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Legal Use of Antimicrobials in Veterinary Medicine & how the micro lab can help!

- For companion animals
  - Animal Medicinal Drug Use Clarification Act of 1994
  - Veterinarian has virtually unlimited discretion – currently, however……
  - Should we be reporting????
    - Carbepenems
    - Linezolid
    - Vancomycin

The “best” antimicrobial……

- is ***Legal*** to use in that patient,
- has a reasonable expectation of ***Efficacy*** and
- is reasonably ***Safe*** for the patient, the owner (or whoever is administering) and the end consumer (if the patient is a food animal).

The ideal antimicrobial is also ***available*** for prescribing, can be ***readily administered*** to the patient, is within the ***financial constraints*** of the owner and is ***familiar*** to the clinician.

1) Antimicrobial selection is NOT “cookie cutter”
2) It is a fluid process and requires consideration of the above in each and every case

What factors would a veterinarian use to support efficacy, or lack of & how the micro lab can help!

- Empiric therapy – Before you have a pathogen identified
  - Antimicrobial spectrum
  - Site of infection
  - Cumulative antimicrobial susceptibility data
  - Non-response to prior therapy

- Definitive therapy – You have a “target” pathogen
  - Intrinsic resistance
  - Antimicrobial label
  - Clinical trials
  - Individual antimicrobial susceptibility report
  - Non-response to prior therapy

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Intrinsic Resistance / Clinical Inefficacy

- Inherent or innate -- not acquired -- resistance to an antimicrobial or antimicrobial class. Susceptibility testing is unnecessary in cases of intrinsic resistance [or result reporting should be reflective].
- Common veterinary intrinsic / clinical resistances
  - *Proteus mirabilis*: tetracycline, tigecycline, nitrofurantoin, polymixin B
  - *Pseudomonas aeruginosa*: amp/amoxicillin, amp-sulbactam, amoxi-clavulanate, cefotaxime, ceftriaxone, ertapenem, tetra/tigecycline, trimethoprim, TMS-SMZ, chloramphenicol
  - *Enterococcus* spp.: cephalosporins, aminoglycosides, clindamycin, trimethoprim, TMS-SMZ, fusidic acid
  - *Salmonella* spp.: aminoglycosides, 1st/2nd generation cephalosporins (cefazolin, cephalexin), cephamycins
  - Anaerobes: aminoglycosides
- Appendix B in M100 / Appendix B in VET08

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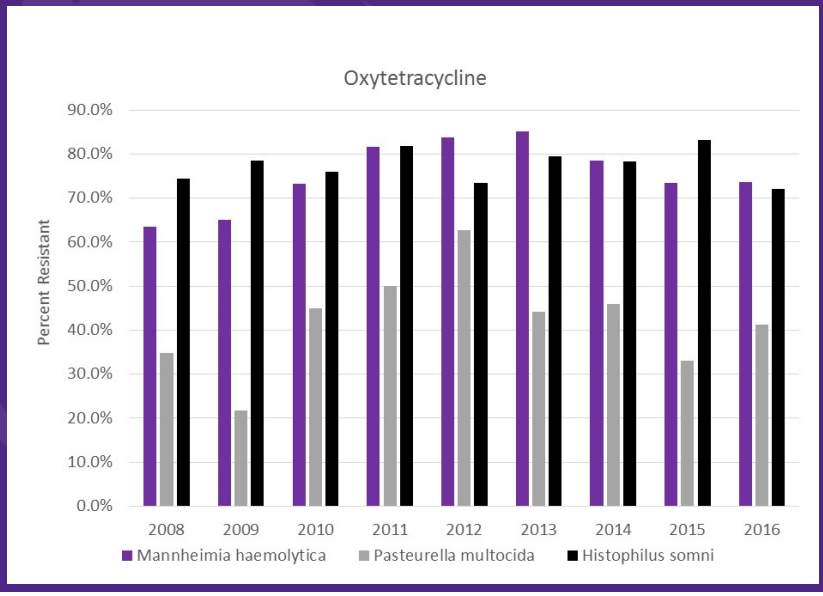
Using Cumulative AST data to support efficacy



Standards for presenting cumulative AST data

- M39: Analysis and Presentation of Cumulative Antimicrobial Susceptibility Test Data
- M39QG: Antibiograms: Developing Cumulative Reports for Your Clinicians

Analysis and Presentation of Cumulative Antibiograms: A New Consensus Guideline from the Clinical and Laboratory Standards Institute

Janet F. Hindler[1] and John Stelling[2]
[1]University of California Los Angeles Medical Center, Los Angeles; and [2]Brigham and Women's Hospital, Boston, Massachusetts

Clinical Infectious Diseases. 2007. 44: 867-873.

- Cumulative AST data are often used in human healthcare (and veterinary medicine) to prescribe empirical antimicrobial therapy

Intermountain Healthcare Southern Region Rural Hospitals 2014 ANTIBIOGRAM

Gram Negative Bacilli % Susceptible

# Tests	Species/Organism	Amikacin	Amoxicillin/Clavulanic Acid	Ampicillin	Ampicillin/Sulbactam	Aztreonam	Cefazolin	Cefepime	Cefotaxime	Cefoxitin	Ceftazidime	Ceftriaxone	Cefuroxime	Ciprofloxacin	Ertapenem	Gentamicin	Imipenem	Levofloxacin	Meropenem	Nitrofurantoin %%	Piperacillin/Tazobactam	Tetracycline	Tobramycin	Trimethoprim/Sulfamethoxazole
35	Citrobacter species	97	0	0	0	89	0	97	89	0	86	89	0	91	100	91	100	97	100	75	97	80	94	77
38	Enterobacter cloacae	100	0	0	0	89	0	97	95	0	89	89	0	100	100	97	100	100	100	11	89	87	97	89
787	Escherchia coli	99	83	58	62	97	88	98	98	93	98	98	94	85	100	94	100	85	100	98	97	79	95	78
45	Klebsiella oxytoca	100	98	0	74	93	44	100	100	91	100	100	93	93	100	100	100	96	100	76	100	87	100	87
131	Klebsiella pneumoniae	100	93	0	80	98	95	100	100	94	100	100	97	98	100	100	100	98	100	33	94	88	100	87
42	Proteus mirabilis	98	90	67	78	93	83	98	95	90	95	98	90	83	100	86	100	83	100	0	98	0	86	74
67	Pseudomonas aeruginosa	94				82		94	0		94	0		91		84	96	93	99		97		99	

https://intermountainphysician.org/gw/Antibiograms2/Rural%202014.pdf

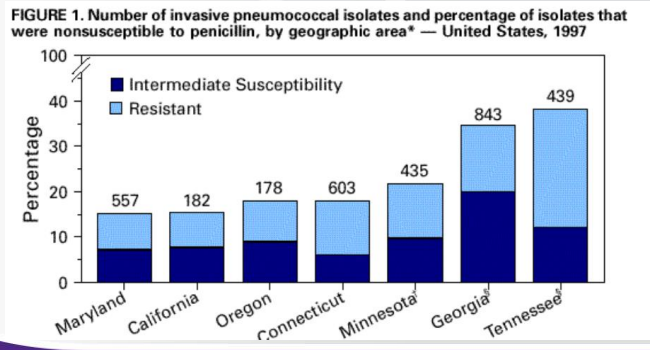
- **Caution**: extrapolation to an individual is only as good as the underlying patient population from which the cumulative data is drawn

Comparison of hospital-wide and age and location - stratified antibiograms of *S. aureus, E. coli,* and *S. pneumoniae*: age- and location-stratified antibiograms

Sanjeev K Swami[1] and Ritu Banerjee[2*]

Conclusions: Stratified antibiograms reveal age - associated differences in susceptibility of *E. coli, S. aureus*, and *S. pneumoniae* that are obscured by hospital-wide antibiograms. Age-stratified antibiograms have potential to influence antibiotic selection.

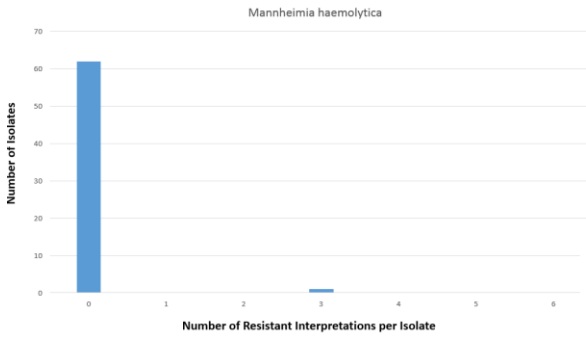
Swami SK. 2013. Springerplus. 2; 63-67.



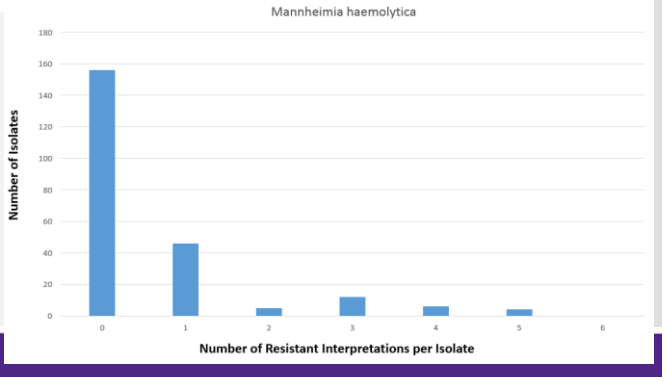
CDC. 1999. MMWR. 48; 656-661.

- **Caution**: extrapolation to an individual is only as good as the underlying patient population from which the cumulative data is drawn

Cow-Calf (n=63 isolates)



Feedlot (n=229 isolates)



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Cumulative AST summaries

- Summaries from KSVDL diagnostic submissions
  - *Mannheimia haemolytica*
  - *Pasteurella multocida*
  - *Histophilus somni*

  - Isolates recovered from bovine lung
    - Animal died of BRD
    - Likely received antimicrobial(s) ante-mortem

  - Antimicrobials
    - Ceftiofur, Enrofloxacin, Florfenicol, Oxytetracycline, Penicillin, Spectinomycin Tilmicosin

WHY ONLY THESE?

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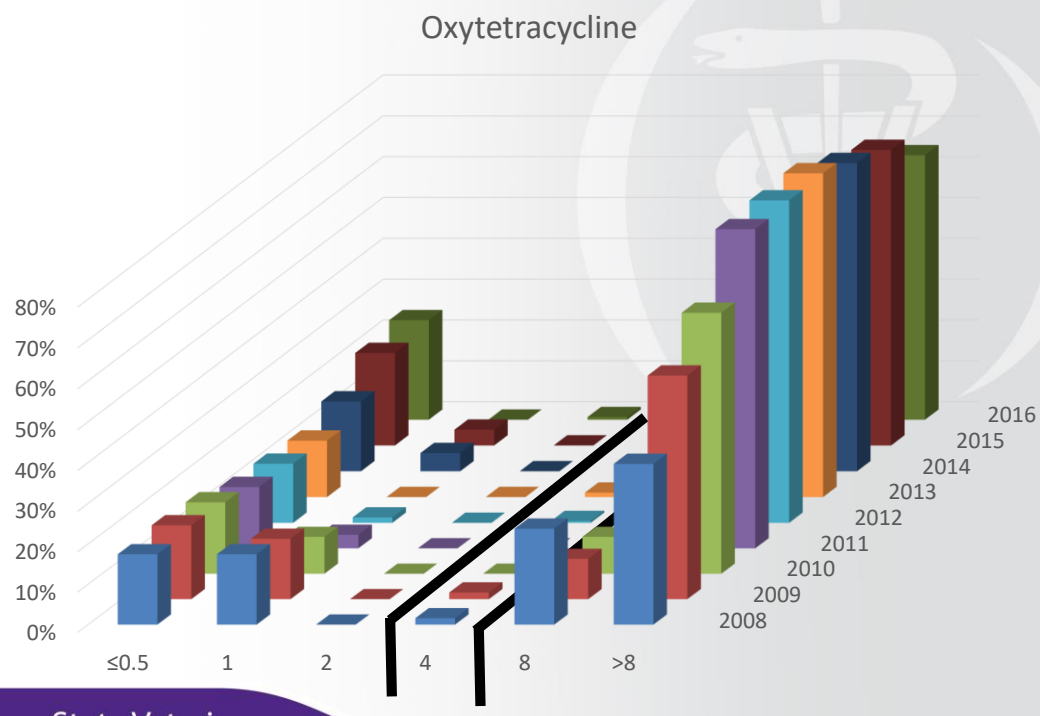
Mannheimia haemolytica



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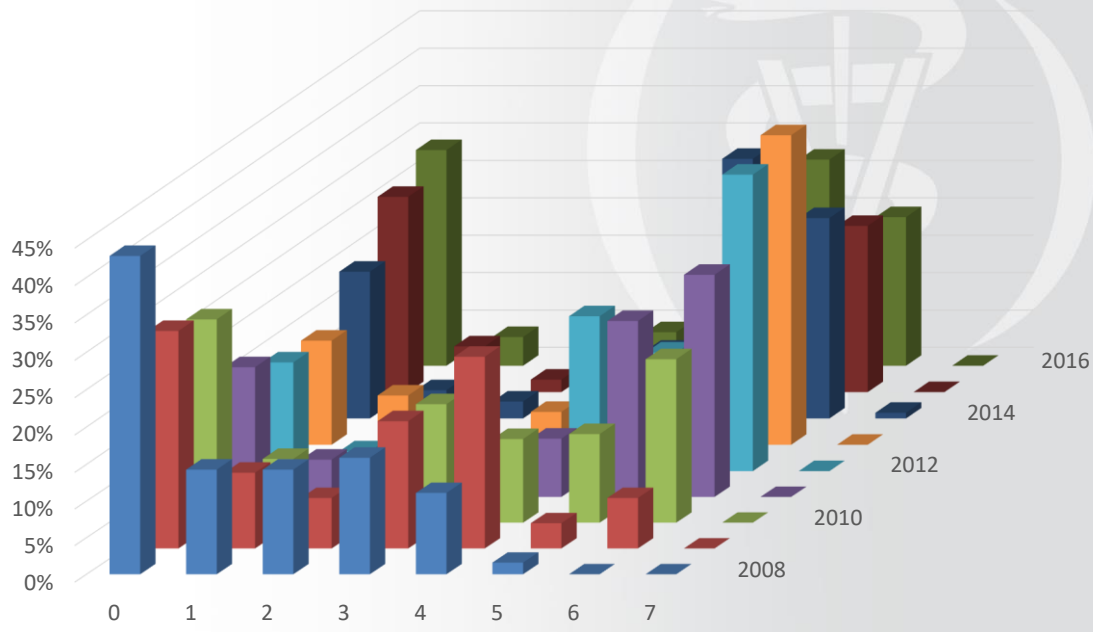
Cumulative AST summaries

- Other uses….
  - Co-resistance / MDR
  - Cross-resistance

Mannheimia haemolytica Multi-drug resistance



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Mannheimia haemolytica (n=1550 isolates)

tilmicosin \ tulathromycin	≤1	2	4	8	16	32	64	>64
>64			1		27	94	15	693
64				5	8	3	6	99
32			8	4	1	3	4	53
16			46	44	5	1	1	16
8		2	62	34	1	1	2	
≤4	8	71	204	26		2		

83% - S/S or I/I or R/R
3.6% - S/R mismatch

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The “best” antimicrobial……

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2) It is a fluid process and requires consideration of the above in each and every case

Patient safety…….
and how the micro lab can help??

- Overt toxicities??
  - Where do you draw the line????
    - Lincosamides in horses & rabbits
    - Tilmicosin (injectable) in pigs & goats
    - Sulfonamides in dogs

- AST results in alphabetical order????

	Interpretation	MIC	Test Range
AMIKACIN	S	<=4.0000	4 - 32
AMOXI/CLAV	S	<=0.1200	0.12 - 1

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For discussion….
A or B?

A or B?

History: Neonatal pot-bellied pig with diarrhea. *E. coli* isolated on culture.

	Interpretation	MIC	Test Range
AMPICILLIN	S	2.0000	0.25 - 16
CEFTIOFUR	NI	0.5000	0.25 - 8
CHLORTETRACYCLINE	NI	>8.0000	0.5 - 8
CLINDAMYCIN	NI	>16.0000	0.25 - 16
ENROFLOXACIN	NI	<=0.1200	0.12-2
FLORFENICOL	NI	2.0000	0.25-8
GENTAMICIN	S	<=1.0000	1-16
NEOMYCIN	NI	<=4.0000	4-32
OXYTETRACYCLINE	NI	>8.0000	0.5-8
PENICILLIN	NI	>8.0000	0.12-8
SPECTINOMYCIN	NI	16.0000	8-64
SULFADIMETHOXINE	NI	<=256.0000	256
TIAMULIN	NI	>32.0000	0.5-32
TILMICOSIN	NI	64.0000	4-64
TRIMETH/SULFA	S	<=2.0000	2/38
TULATHROMYCIN	NI	8.0000	1-64
TYLOSIN TARTRATE	NI	>32.0000	0.5-32

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	Interpretation	MIC	Test Range
AMIKACIN	S	<=4.0000	4 - 32
AMOXI/CLAV	S	<=0.1200	0.12 - 1
AMPICILLIN	NI		0.12 - 1
CEFAZOLIN	S	<=1.0000	1 - 8
CEFOVECIN	NI	<=0.2500	0.25 - 4
CEFOXITIN	S	<=2.0000	2 - 16
CEFPODOXIME	S	<=2.0000	2 - 16
CEFTIOFUR	S	<=0.2500	0.25 - 4
CEPHALOTHIN	S	<=2.0000	2 - 8
CHLORAMPHENICOL	S	<=4.0000	4 - 16
CLINDAMYCIN	S	<=0.5000	0.5 - 4
DOXYCYCLINE	S	<=2.0000	2 - 8
ENROFLOXACIN	S	<=0.2500	0.25 - 2
ERYTHROMYCIN	S	<=0.5000	0.5 - 4
GENTAMICIN	S	<=1.0000	1 - 8
IMIPENEM	S	2.0000	1 - 8
MARBOFLOXACIN	S	<=0.2500	0.25 - 2
OXACILLIN + 2% NACL	S	<=0.2500	0.25 - 4
PENICILLIN	NI		0.06 - 8
RIFAMPIN	NI	<=1.0000	1 - 2
TICAR/CLAV ACID	S	<=8.0000	8/2 - 64/2
TICARCILLIN	NI		8 - 64
TRIMETH/SULFA	S	<=0.5000	0.5/9.5 - 2/38

A: Pot bellied pigs are considered food animals – avoid reporting prohibited drugs

	Interpretation	MIC	Test Range
AMPICILLIN	S	2.0000	0.25 - 16
CEFTIOFUR	NI	0.5000	0.25 - 8
CHLORTETRACYCLINE	NI	>8.0000	0.5 - 8
CLINDAMYCIN	NI	>16.0000	0.25 - 16
ENROFLOXACIN	NI	<=0 [illegible] 0	0.12-2
FLORFENICOL	NI	[illegible]000	0.25-8
GENTAMICIN	S	[illegible]=1.0000	1-16
NEOMYCIN		<=4.0000	4-32
OXYTETRACYCLINE		>8.0000	0.5-8
PENICILLIN	NI	>8.0000	0.12-8
SPECTINOMYCIN	NI	16.0000	8-64
SULFADIMETHOXINE	NI	<=256.0000	256
TIAMULIN	NI	>32.0000	0.5-32
TILMICOSIN	NI	64.0000	4-64
TRIMETH/SULFA	S	<=2.0000	2/38
TULATHROMYCIN	NI	8.0000	1-64
TYLOSIN TARTRATE	NI	>32.0000	0.5-32

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	Interpretation	MIC	Test Range
AMIKACIN	S	<=4.0000	4 - 32
AMOXI/CLAV	S	<=0.1200	0.12 - 1
AMPICILLIN	NI		0.12 - 1
CEFAZOLIN	S	<=1.0000	1 - 8
CEFOVECIN	NI	<=0.2500	0.25 - 4
CEFOXITIN	S	<=2.0000	2 - 16
CEFPODOXIME	S	<=2.0000	2 - 16
CEFTIOFUR	S	<=0.2500	0.25 - 4
CEPHALOTHIN	S	<=2.0000	2 - 8
CHLORAMPHENICOL	S	<=4.0000	4 - 16
CLINDAMYCIN	S	<=0.5000	0.5 - 4
DOXYCYCLINE	S	<=2.0000	2 - 8
ENROFLOXACIN	S	<=0.2500	0.25 - 2
ERYTHROMYCIN	S	<=0.5000	0.5 - 4
GENTAMICIN	S	<=1.0000	1 - 8
IMIPENEM	S	2.0000	1 - 8
MARBOFLOXACIN	S	<=0.2500	0.25 - 2
OXACILLIN + 2% NACL	S	<=0.2500	0.25 - 4
PENICILLIN	NI		0.06 - 8
RIFAMPIN	NI	<=1.0000	1 - 2
TICAR/CLAV ACID	S	<=8.0000	8/2 - 64/2
TICARCILLIN	NI		8 - 64
TRIMETH/SULFA	S	<=0.5000	0.5/9.5 - 2/38

A or B?

History: 9 yr old DLH with clinical signs of UTI. *Enterococcus faecalis* isolated on culture.

	Interpretation	MIC	Test Range
AMIKACIN	R		16-32
AMOXI/CLAV	S	0.5000	0.25/0.12-8/4
AMPICILLIN	S	1.0000	0.25-8
CHLORAMPHENICOL	S	<=8.0000	8-32
DOXYCYCLINE	S	<=0.1200	0.12-0.5
ENROFLOXACIN	I	1.0000	0.25-4
ERYTHROMYCIN	I	1.0000	0.25-4
GENTAMICIN	R		4-16
IMIPENEM	S	<=1.0000	1-4
MARBOFLOXACIN	I	2.0000	1-4
MINOCYCLINE	S	<=0.5000	0.5-2
NITROFURATOIN	S	<=16.0000	16-64
OXACILLIN + 2% NACL	NI	>2.0000	0.25-2
PENICILLIN	S	2.0000	0.06-8
PRADOFLOXACIN	NI	<=0.2500	0.25-2
RIFAMPIN	S	<=1.0000	1-2
TETRACYCLINE	S	<=0.2500	0.25-1
VANCOMYCIN	S	2.0000	1-16

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	Interpretation	MIC	Test Range
AMIKACIN	R		16-32
AMOXI/CLAV	S	0.5000	0.25/0.12-8/4
AMPICILLIN	S	1.0000	0.25-8
CEFAZOLIN	R	>4.0000	2-4
CEFOVECIN	NI	>8.0000	0.06-8
CEFPODOXIME	NI	4.0000	2-8
CEPHALOTHIN	NI	>4.0000	2-4
CHLORAMPHENICOL	S	<=8.0000	8-32
CLINDAMYCIN	NI	>4.0000	0.5-4
DOXYCYCLINE	S	<=0.1200	0.12-0.5
ENROFLOXACIN	I	1.0000	0.25-4
ERYTHROMYCIN	I	1.0000	0.25-4
GENTAMICIN	R		4-16
IMIPENEM	S	<=1.0000	1-4
MARBOFLOXACIN	I	2.0000	1-4
MINOCYCLINE	S	<=0.5000	0.5-2
NITROFURATOIN	S	<=16.0000	16-64
OXACILLIN + 2% NACL	NI	>2.0000	0.25-2
PENICILLIN	S	2.0000	0.06-8
PRADOFLOXACIN	NI	<=0.2500	0.25-2
RIFAMPIN	S	<=1.0000	1-2
TETRACYCLINE	S	<=0.2500	0.25-1
TRIMETH/SULFA	NI	<=2.0000	2/38-4/76
VANCOMYCIN	S	2.0000	1-16

A: Enterococci are intrinsically resistant to aminoglycosides, cephalosporins, clindamycin, TMS

	Interpretation	MIC	Test Range
AMIKACIN	R		16-32
AMOXI/CLAV	S	0.5000	0.25/0.12-8/4
AMPICILLIN	S	1.0000	0.25-8
CHLORAMPHENICOL	S	<=8.0000	8-32
DOXYCYCLINE	S	<=0.1200	0.12-0.5
ENROFLOXACIN	I	1.0000	0.25-4
ERYTHROMYCIN	I	1.0000	0.25-4
GENTAMICIN	R		4-16
IMIPENEM	S	<=1.0000	1-4
MARBOFLOXACIN	I	2.0000	1-4
MINOCYCLINE	S	<=0.5000	0.5-2
NITROFURATOIN	S	<=16.0000	16-64
OXACILLIN + 2% NACL	NI	>2.0000	0.25-2
PENICILLIN	S	2.0000	0.06-8
PRADOFLOXACIN	NI	<=0.2500	0.25-2
RIFAMPIN	S	<=1.0000	1-2
TETRACYCLINE	S	<=0.2500	0.25-1
VANCOMYCIN	S	2.0000	1-16

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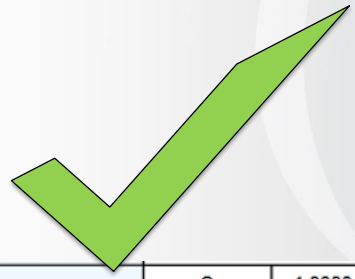
	Interpretation	MIC	Test Range
AMIKACIN	R		16-32
AMOXI/CLAV	S	0.5000	0.25/0.12-8/4
AMPICILLIN	S	1.0000	0.25-8
CEFAZOLIN	R	>4.0000	2-4
CEFOVECIN	NI	>8.0000	0.06-8
CEFPODOXIME	NI	4.0000	2-8
CEPHALOTHIN	NI	>4.0000	2-4
CHLORAMPHENICOL	S	<=8.0000	8-32
CLINDAMYCIN	NI	>4.0000	0.5-4
DOXYCYCLINE	S	<=0.1200	0.12-0.5
ENROFLOXACIN	I	1.0000	0.25-4
ERYTHROMYCIN	I	1.0000	0.25-4
GENTAMICIN	R		4-16
IMIPENEM	S	<=1.0000	1-4
MARBOFLOXACIN	I	2.0000	1-4
MINOCYCLINE	S	<=0.5000	0.5-2
NITROFURATOIN	S	<=16.0000	16-64
OXACILLIN + 2% NACL	NI	>2.0000	0.25-2
PENICILLIN	S	2.0000	0.06-8
PRADOFLOXACIN	NI	<=0.2500	0.25-2
RIFAMPIN	S	<=1.0000	1-2
TETRACYCLINE	S	<=0.2500	0.25-1
TRIMETH/SULFA	NI	<=2.0000	2/38-4/76
VANCOMYCIN	S	2.0000	1-16

C: Amoxicillin is the preferred therapy for Enterococcal infections



AMPICILLIN	S	1.0000	0.25-8

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A or B?

History: Respiratory disease in an alpaca. *Pasteurella multocida* isolated on culture.

	Interpretation	MIC	Test Range
AMPICILLIN	R	8.0000	0.25 - 16
CEFTIOFUR	NI	>8.0000	0.25 - 8
CHLORTETRACYCLINE	NI	<=0.5000	0.5 - 8
CLINDAMYCIN	NI	>16.0000	0.25 - 16
DANOFLOXACIN	NI	0.2500	0.12 - 1
ENROFLOXACIN	NI	<=0.1200	0.12 - 2
FLORFENICOL	S	1.0000	0.25 - 8
GENTAMICIN	S	<=1.0000	1 - 16
NEOMYCIN	NI	<=4.0000	4 - 32
OXYTETRACYCLINE	NI	<=0.5000	0.5 - 8
PENICILLIN	NI	>8.0000	0.12 - 8
SPECTINOMYCIN	NI	>64.0000	8 - 64
SULFADIMETHOXINE	NI	>256.0000	256
TIAMULIN	NI	>32.0000	0.5 - 32
TILMICOSIN	NI	16.0000	4 - 64
TRIMETH/SULFA	S	<=2.0000	2/38
TULATHROMYCIN	S	2.0000	1 - 64
TYLOSIN TARTRATE	NI	>32.0000	0.5 - 32

	Interpretation	MIC	Test Range
AMPICILLIN	R	8.0000	0.25 - 16
CEFTIOFUR	NI	>8.0000	0.25 - 8
CHLORTETRACYCLINE	NI	<=0.5000	0.5 - 8
CLINDAMYCIN	NI	>16.0000	0.25 - 16
DANOFLOXACIN	NI	0.2500	0.12 - 1
ENROFLOXACIN	NI	<=0.1200	0.12 - 2
FLORFENICOL	S	1.0000	0.25 - 8
GENTAMICIN	S	<=1.0000	1 - 16
NEOMYCIN	NI	<=4.0000	4 - 32
OXYTETRACYCLINE	NI	<=0.5000	0.5 - 8
PENICILLIN	NI	>8.0000	0.12 - 8
SPECTINOMYCIN	NI	>64.0000	8 - 64
SULFADIMETHOXINE	NI	>256.0000	256
TIAMULIN	NI	>32.0000	0.5 - 32
TRIMETH/SULFA	S	<=2.0000	2/38
TULATHROMYCIN	S	2.0000	1 - 64
TYLOSIN TARTRATE	NI	>32.0000	0.5 - 32

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B: Tilmicosin is potentially fatal in alpacas

	Interpretation	MIC	Test Range
AMPICILLIN	R	8.0000	0.25 - 16
CEFTIOFUR	NI	>8.0000	0.25 - 8
CHLORTETRACYCLINE	NI	<=0.5000	0.5 - 8
CLINDAMYCIN	NI	>16.0000	0.25 - 16
DANOFLOXACIN	NI	0.2500	0.12 - 1
ENROFLOXACIN	NI	<=0.1200	0.12 - 2
FLORFENICOL	S	1.0000	0.25 - 8
GENTAMICIN	S	<=1.0000	1 - 16
NEOMYCIN	NI	<=4.0000	4 - 32
OXYTETRACYCLINE	NI	<=0.5000	0.5 - 8
PENICILLIN	NI	>8.0000	0.12 - 8
SPECTINOMYCIN	NI	>64.0000	8 - 64
SULFADIMETHOXINE	NI	>256.0000	256
TIAMULIN	NI	>32.0000	0.5 - 32
TILMICOSIN	NI	16.0000	4 - 64
TRIMETH/SULFA	S	<=2.0000	2/38
TULATHROMYCIN	S	2.0000	1 - 64
TYLOSIN TARTRATE	NI	>32.0000	0.5 - 32

	Interpretation	MIC	Test Range
AMPICILLIN	R	8.0000	0.25 - 16
CEFTIOFUR	NI	>8.0000	0.25 - 8
CHLORTETRACYCLINE	NI	<=0.5000	0.5 - 8
CLINDAMYCIN	NI	>16.0000	.25 - 16
DANOFLOXACIN	NI	0.	0.12 - 1
ENROFLOXACIN	NI		200 0.12 - 2
FLORFENICOL	S		.0000 0.25 - 8
GENTAMICIN		<=1.0000	1 - 16
NEOMYCIN		<=4.0000	4 - 32
OXYTETRACYCLINE		<=0.5000	0.5 - 8
PENICILLIN	NI	>8.0000	0.12 - 8
SPECTINOMYCIN	NI	>64.0000	8 - 64
SULFADIMETHOXINE	NI	>256.0000	256
TIAMULIN	NI	>32.0000	0.5 - 32
TRIMETH/SULFA	S	<=2.0000	2/38
TULATHROMYCIN	S	2.0000	1 - 64
TYLOSIN TARTRATE	NI	>32.0000	0.5 - 32

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Questions?
Discussion?

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CLSI stuff

Developing Breakpoints

- *Breakpoint / Interpretive criteria*
  - Minimal inhibitory concentration (MIC) used to indicate susceptible “S”, intermediate “I” or resistant “R”.

  - ***Susceptible***
  - Category implies an infection that may be appropriately treated with the **dosage regimen** of an **antimicrobial agent** recommended for that **type of infection** and **infecting [bacterial] species** [in **that host animal species**]

  - ***Intermediate***
  - Category implies an infection that may be appropriately treated in body sites where the drugs are physiologically concentrated, or when a high dosage of drug can be used

  - ***Resistant***
  - Strains [in this category] are not inhibited by the usually achievable concentrations of the agent with normal dosage schedules and/or fall in the range [of MICs] where specific microbial resistance mechanisms are likely and clinical outcome has not been predictable in effectiveness studies

Developing Breakpoints

1. Reproducible method and QC

2. Data needed to set a *veterinary specific* MIC breakpoint
   a) Wild-type cut-off
   b) PK/PD cut-off
   c) Clinical cut-off

3. MIC – zone diameter correlation to set disk diffusion breakpoint

Does the Breakpoint still apply if……

- Test conditions change….
  - Increase / decrease inoculum density
  - Incubate in CO_2
  - Use a different strength disk
  - Supplement testing media with serum

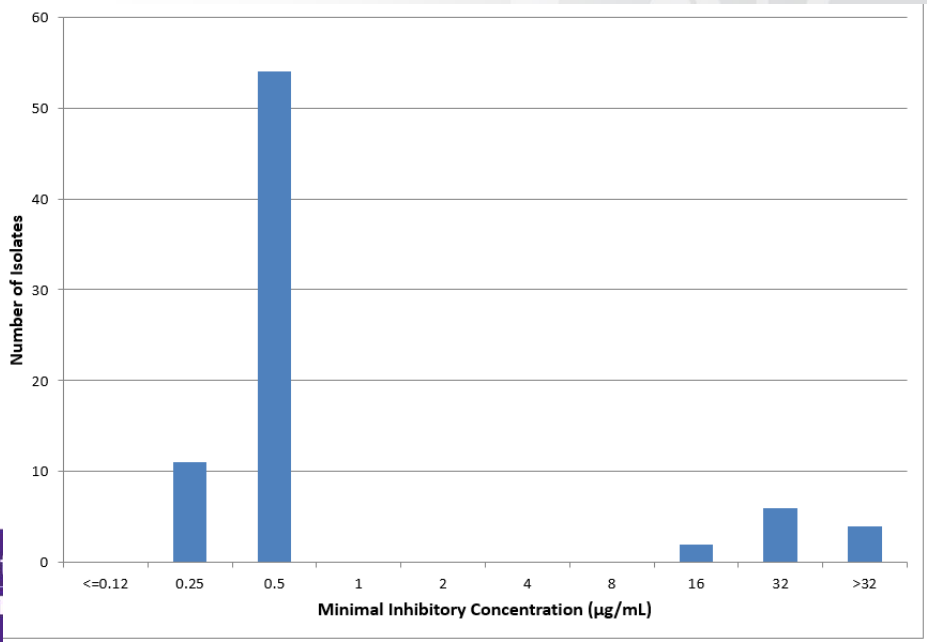
  - Someone stores dry ice (for a 4th of July party) in the -80 freezer that holds your custom frozen AST panels

Results for plate L1FBRP, organism S.aur 29213

Drug Descri...	MIC	Interpretation
Positive Gro...	-	Valid Growth Control
Tulathrom...	**128**	**Out of Range High**
Tildipirosin	**64**	**Out of Range High**
Spectinom...	**512**	**Out of Range High**
Ceftiofur	0.25	In Range
Florfenicol	4	In Range
Tilmicosin	4	In Range
Oxytetracycl...	<=0.12	In Range
Enrofloxacin	0.12	In Range

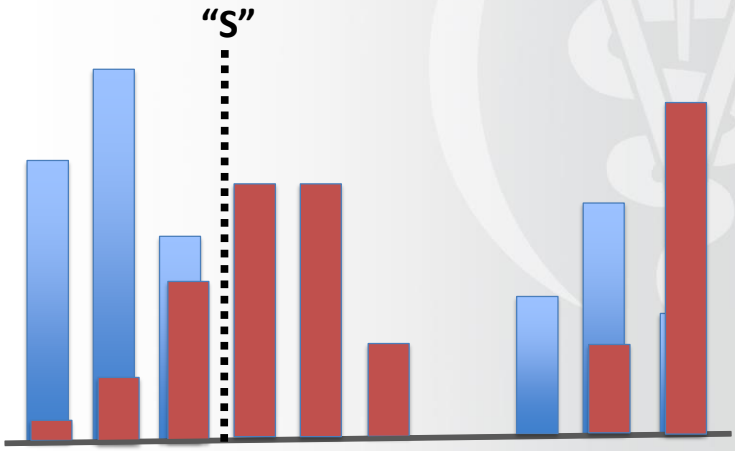
Developing Breakpoints

- Wild-type cut-off



Does the Breakpoint still apply if……

- I change the organism or antibiotic?



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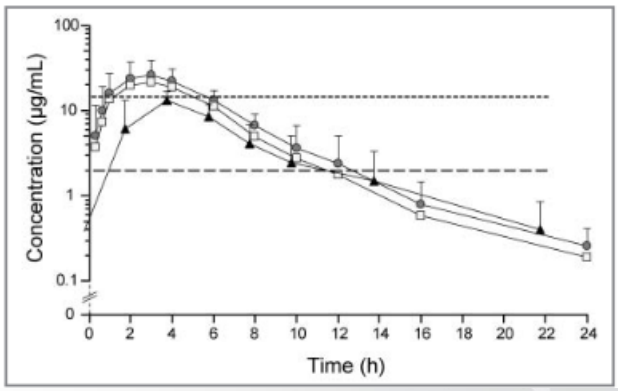
Developing Breakpoints

- PK/PD cut-off



Papich. 2010. AJVR. 71; 1484-1491.

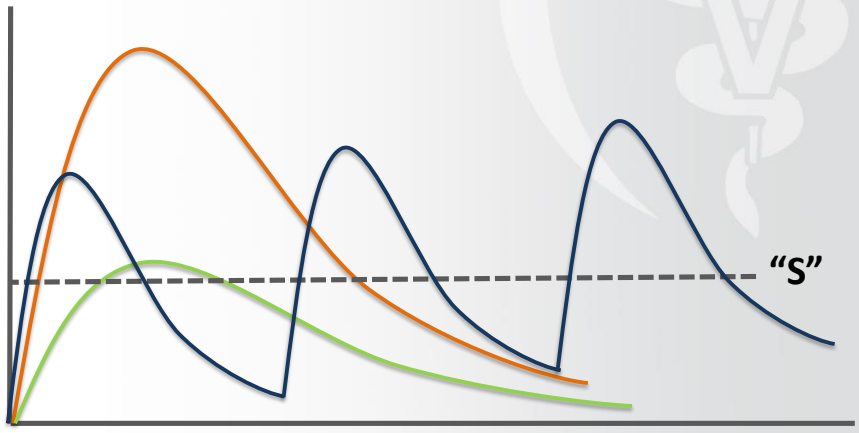
Table 4. Probability of target attainment (PTA) for administration of cephalexin oral to dogs using Monte Carlo simulations.

	PTA from Monte Carlo simulation for the indicated MIC values								
Drug and dose regimen	0.25	0.5	1	2	4	8	16	32	64
Cephalexin in dogs (25 mg/kg oral) every 12 h	98.7%	97.93%	94.8%	89.6%	72.9%	47.05%	14.03%	1.74%	0%

Papich. 2018. JVDI. 30; 113-120.

Does the Breakpoint still apply if……

- I change the antibiotic or the host species?
- I change the dosing regimen?



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Does the Breakpoint still apply if……

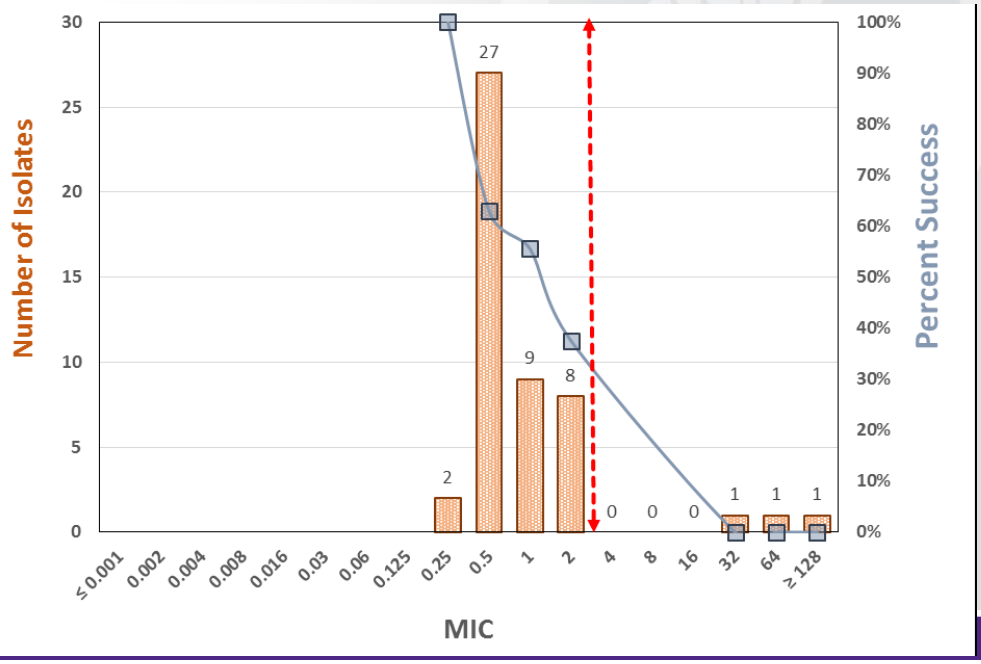
- I change to a different class of animal

Table 2A. *Enterobacteriaceae* (Continued)

Test/ Report Group	Body Site	Antimicrobial Agent	Organism	Disk Content	Zone Diameter Interpretive Criteria (nearest whole mm)			MIC Interpretive Criteria (µg/mL)			Comments
					S	I	R	S	I	R	
Aminoglycosides/Aminocyclitols											
Dogs											
A		**Amikacin**	***E. coli***	**–**	–	–	–	**≤4**	**8**	**≥16**	**(5) Breakpoints derived from microbiological, PK (using accepted clinical doses), and PD data. For dogs, the dose of amikacin modeled was 15 mg/kg, every 24 hours IM, IV, or SC.**
A		Gentamicin	*Enterobacteriaceae*	10 µg	≥16	13–15	≤12	≤2	4	≥8	(6) Breakpoints derived from microbiological, PK (using accepted clinical doses), and PD data. For dogs, the dose of gentamicin modeled was 10 mg/kg every 24 hours IM.
Horses (Foals)											
A		**Amikacin**	***E. coli***	**–**	–	–	–	**≤2**	**4**	**≥8**	**(7) Breakpoints derived from microbiological, PK (using accepted clinical doses), and PD data. For foals < 11 days of age, the dose of amikacin modeled was 20 mg/kg, every 24 hours IV.**
Horses (Adults)											
A		**Amikacin**	***E. coli***	**–**	–	–	–	**≤4**	**8**	**≥16**	**(8) Breakpoints derived from microbiological, PK (using accepted clinical doses), and PD data. For adult horses, the dose of amikacin modeled was 10 mg/kg, every 24 hours, IM or IV.**

Developing Breakpoints

- Clinical cut-off



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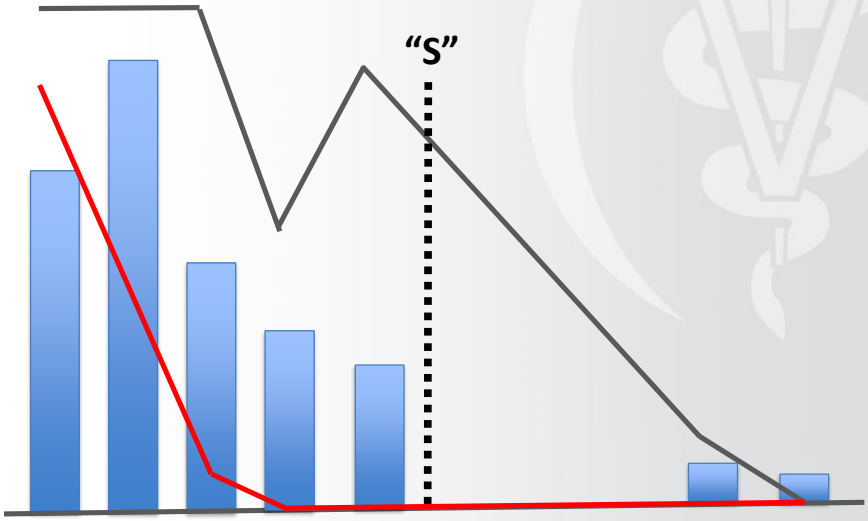
Does the Breakpoint still apply if……

- I change the clinical disease process?



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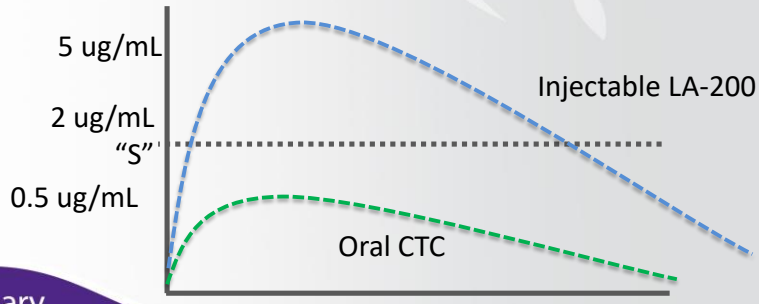
What do you think???

Most Dx labs report susceptibility summaries yearly. For example, Lab XYZ reported P. mult to be 85% susceptible to CTC. **As I understand CLSI has not established an S-I-R for CTC, only for parentally administered tetracyclines. If this is correct, Dx labs shouldn't report a CTC S-I-R for P. mult.** For parentally admin tetracyclines, the CLSI list 2 ug/ml as the MIC. If Dx labs are using 2.0 ug/ml at the MIC this is problematic in light of a 2009 Reinbold, et-al paper. [A 2009 study (REINBOLD, et-al. Plasma pharmacokinetics of oral chlortetracycline in group fed, ruminating, Holstein steers in a feedlot setting. J. vet. Pharmacol. Therap. 33, 76–83) demonstrated the C-Max for CTC was 0.5 ug/ml.]

This makes me wonder if there is a disconnect between the CTC S-I-R Dx labs report for P mult and the pharmacokinetics of CTC in cattle.

Host species
Bacterial species
Dosing regimen
Disease process
Antibacterial



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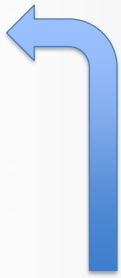
"Generic" BPs

…and how the micro lab can help!

- Older antimicrobials unlikely that a single sponsor will bring forth data to support a veterinary specific BP
- Use available literature to support BP development
  - Wild-type cutoff
  - PK-PD cutoff
  - Clinical cutoff



This is often needed by the CLSI "generic" working group.
Can diagnostic labs help with future BP development???

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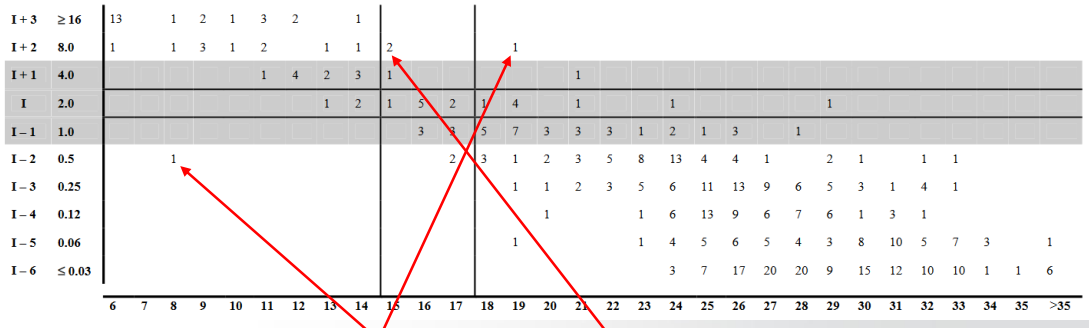
Why don't we have disk diffusion BPs?

- Disk diffusion BPs are developed by correlating the MIC to zone diameter using a process called "error rate bounding"
  - CLSI VET02
- MIC – zone diameter correlation not available for most (any?) "generic" BPs

Developing (disk diffusion) Breakpoints

Table 1. Guideline for Acceptable Discrepancy Rates (With Intermediate Ranges) (see Note)

		Discrepancy Rates		
1-dilution Intermediate Range	**2-dilution Intermediate Range**	**Very Major**	**Major**	**Minor**
≥ I+2	≥ I_{High}+2	< 2%	N/A	< 5%
I+1 to I-1	I_{High}+1 to I_{Low} -1	<10%	<10%	< 40%
≤ I-2	≤ I_{Low}-2	N/A	<40%	< 5%



	Number of Discrepancies (Discrepancy Rate)			
MIC Range	Number	Very Major (%)	Major (%)	Minor (%)
≥ I + 2	36	1 (2.8)[†]	NA	2 (5.6)
I + 1 to I – 1	66	1 (1.5)	0	18 (27.3)
≤ I – 2	393	NA	1 (0.3)	2 (0.5)
Total	495	2 (0.4)	1 (0.2)	22 (4.4)

From CLSI M37 (now VET02)

What if there is NO BREAKPOINT???

I do not presume to tell other laboratories how to operate. In fact, I would not encourage you to adopt / do anything that is outside your "comfort zone".

I do NOT put any of the following on a report or create system rules that would make my suggestions seem like real breakpoints. I will use any / all of the following, but it is done on a one-on-one basis with the individual clinician.

Most of these strategies are aimed at identifying "unreasonable" drug choices…

Rule-out drugs that won't work

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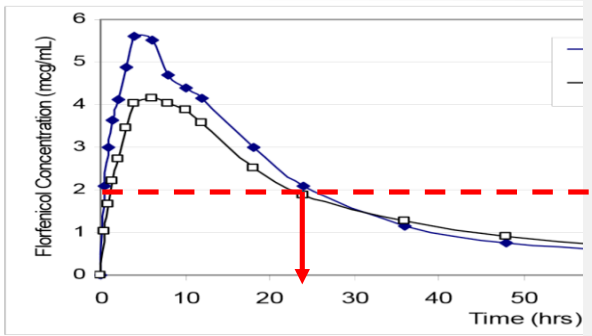
What if there is NO BREAKPOINT???

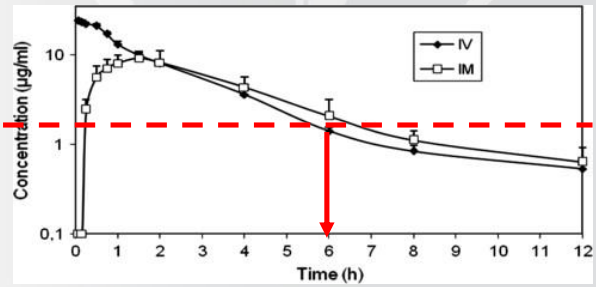
1. Extrapolate a breakpoint from another animal species for that antimicrobial – pathogen combination
   - Historically, most common approach – use of human breakpoints
   - Concern with differences in pharmacokinetics

Florfenicol - Cattle



NADA 141-265: Nuflor Gold FOI

Florfenicol - Rabbits



Koc *et al.* (2009) Res Vet Sci, Vol 87(1); 102 - 105

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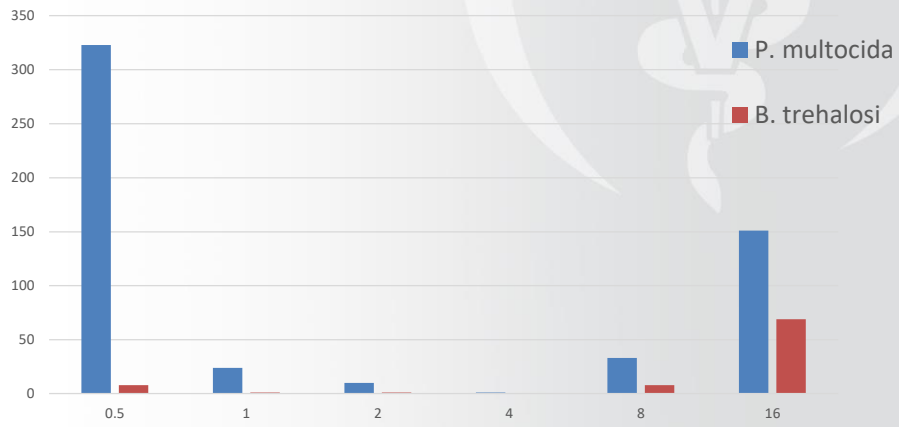
What if there is NO BREAKPOINT???

2. Extrapolate a breakpoint from that host species and antimicrobial for another pathogen
   - Concern with MIC distribution match for the 2 bacterial species



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What if there is NO BREAKPOINT???

3. Use an Epidemiological Cut-Off (ECV / ECOFF)
   - Not a clinical breakpoint, but may suggest if a resistance element is present

Antimicrobial wild type distributions of microorganisms

Search

Method: MIC Disk diffusion

Antimicrobial: Antimicrobial... Species: Pasteurella multocida Disk content: Disk content...

Species: **Pasteurella multocida** (Method: **MIC**)

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

	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF	Distributions	Observations
Amoxicillin	0	0	0	0	0	11	36	104	90	2	1	2	1	1	0	3	0	0	0	1.0	6	251
Ampicillin	0	0	0	0	0	4	40	120	53	2	1	0	2	1	0	0	0	0	1	1.0	6	226
Benzylpenicillin	0	0	0	0	14	60	124	79	1	2	7	1	1	4	0	0	0	0	0	0.5	6	293
Cefotaxime	1	15	103	35	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.032	4	157
Chloramphenicol	0	0	0	0	0	0	14	107	139	45	10	9	44	18	6	1	0	0	0	2.0	5	393
Ciprofloxacin	0	9	61	135	17	3	2	0	0	0	0	0	0	0	0	0	0	0	0	0.064	6	227
Doxycycline	0	0	0	0	0	2	51	218	40	12	12	2	1	0	0	0	0	0	0	1.0	5	338
Enrofloxacin	0	8	33	14	6	1	1	0	26	20	6	0	0	0	0	2	0	0	0	ND	3	117
Florfenicol	0	0	0	0	0	8	50	202	378	58	3	6	0	0	0	0	0	0	0	1.0	6	705
Flumequine	0	0	0	0	1	73	56	80	14	6	5	4	0	68	4	46	0	0	0	ND	5	357
Gentamicin	0	0	0	0	0	2	4	5	27	118	225	90	46	29	67	45	4	0	0	8.0	7	659
Kanamycin	0	0	0	0	0	0	0	2	2	26	44	83	108	61	10	20	10	7	0	ND	2	373
Neomycin	0	0	0	0	0	0	0	4	4	32	66	169	84	93	64	54	19	0	0	ND	6	589
Oxytetracycline	0	0	0	0	0	0	10	15	35	28	37	5	1	2	6	0	0	0	0	ND	1	139
Spectinomycin	0	0	0	0	0	0	0	0	0	0	0	8	28	88	29	0	1	6	0	ND	4	160
	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF	Distributions	Observations
Tetracycline	0	0	0	0	0	3	37	411	853	259	150	31	51	76	67	26	2	0	1	2.0	19	1967
Thiamphenicol	0	0	0	0	0	0	0	3	24	101	0	0	0	0	0	6	3	3	0	ND	1	140
Tilmicosin	0	0	0	0	0	0	4	22	28	53	135	120	77	25	24	17	15	9	4	ND	6	533

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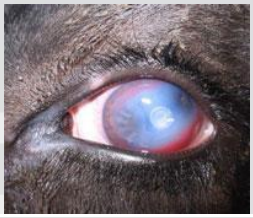
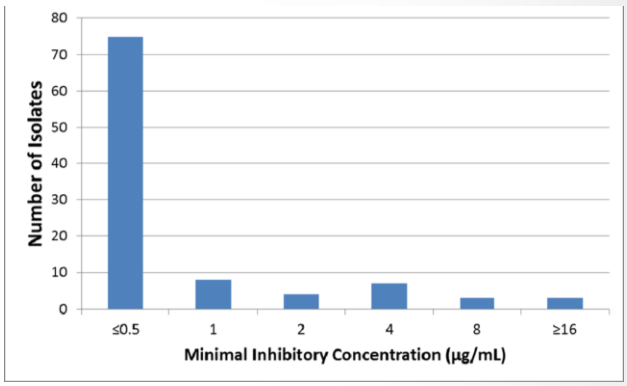
What if there is NO BREAKPOINT???



4. Use in-house data to create an ECV

Moraxella – Oxytetracycline MIC distribution



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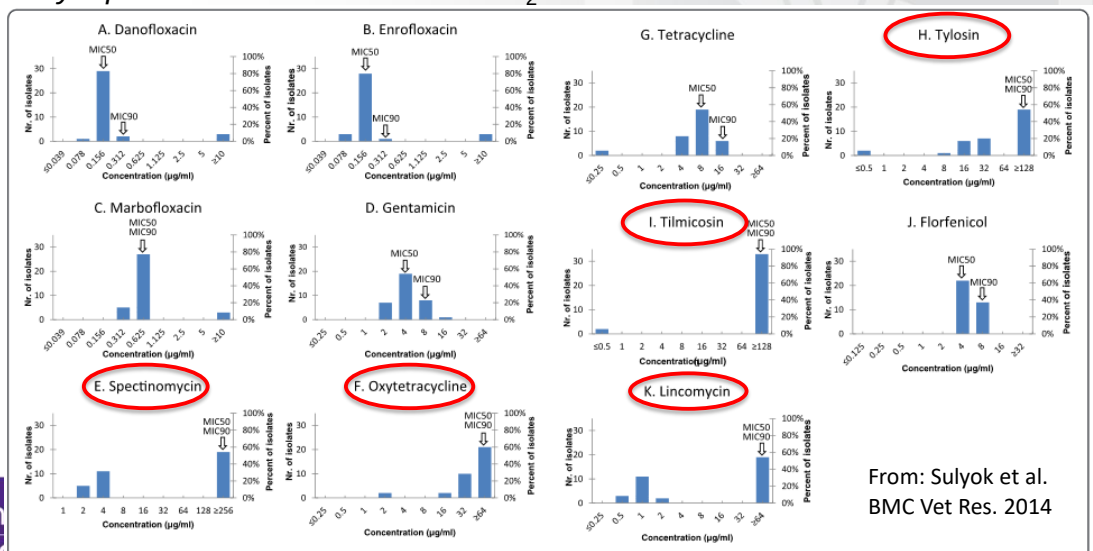
	MORAXELLA SP. - 1
AMPICILLIN	NI <=0.2500(0.25 - 16)
CEFTIOFUR	NI <=0.2500(0.25 - 8)
CHLORTETRACYCLINE	NI <=0.5000(0.5 - 8)
CLINDAMYCIN	NI 2.0000(0.25 - 16)
FLORFENICOL	NI 0.5000(0.25-8)
GENTAMICIN	S <=1.0000(1-16)
NEOMYCIN	NI <=4.0000(4-32)
OXYTETRACYCLINE	NI <=0.5000(0.5-8)
PENICILLIN	NI <=0.1200(0.12-8)
SPECTINOMYCIN	NI <=8.0000(8-64)
SULPHADIMETHOXINE	NI <=256.0000(256)
TIAMULIN	NI <=0.5000(0.5-32)
TILMICOSIN	NI <=4.0000(4-64)
TRIMETH/SULFA	S <=2.0000(2/38)
TULATHROMYCIN	NI <=1.0000(1-64)
TYLOSIN TARTRATE	NI 4.0000(0.5-32)

What if there is NO BREAKPOINT???

- (Cautiously) Use published MIC distribution data
  - Attention to methodology

Mycoplasma MIC distributions – CO_2 incubation???



From: Sulyok et al. BMC Vet Res. 2014

Figure 2 MIC distribution of the Hungarian isolates for each antibiotic tested in this study. Arrows indicate the MIC50 and MIC90 values.

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Other CLSI stuff

- VAST is always looking for MIC distribution data

- Next meeting – Jan 24-29, 2019 – St. Augustine, FL

- New revision of VET01
- New revision of VET08

- VET09

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Other Questions? Discussion?

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