What do you do when the susceptilbity breakpoints are broken?
(How antibiotic breakpoints get updated)

Alexandra Bryson, Ph.D., D(ABMM)
VCU Health
9/24/24

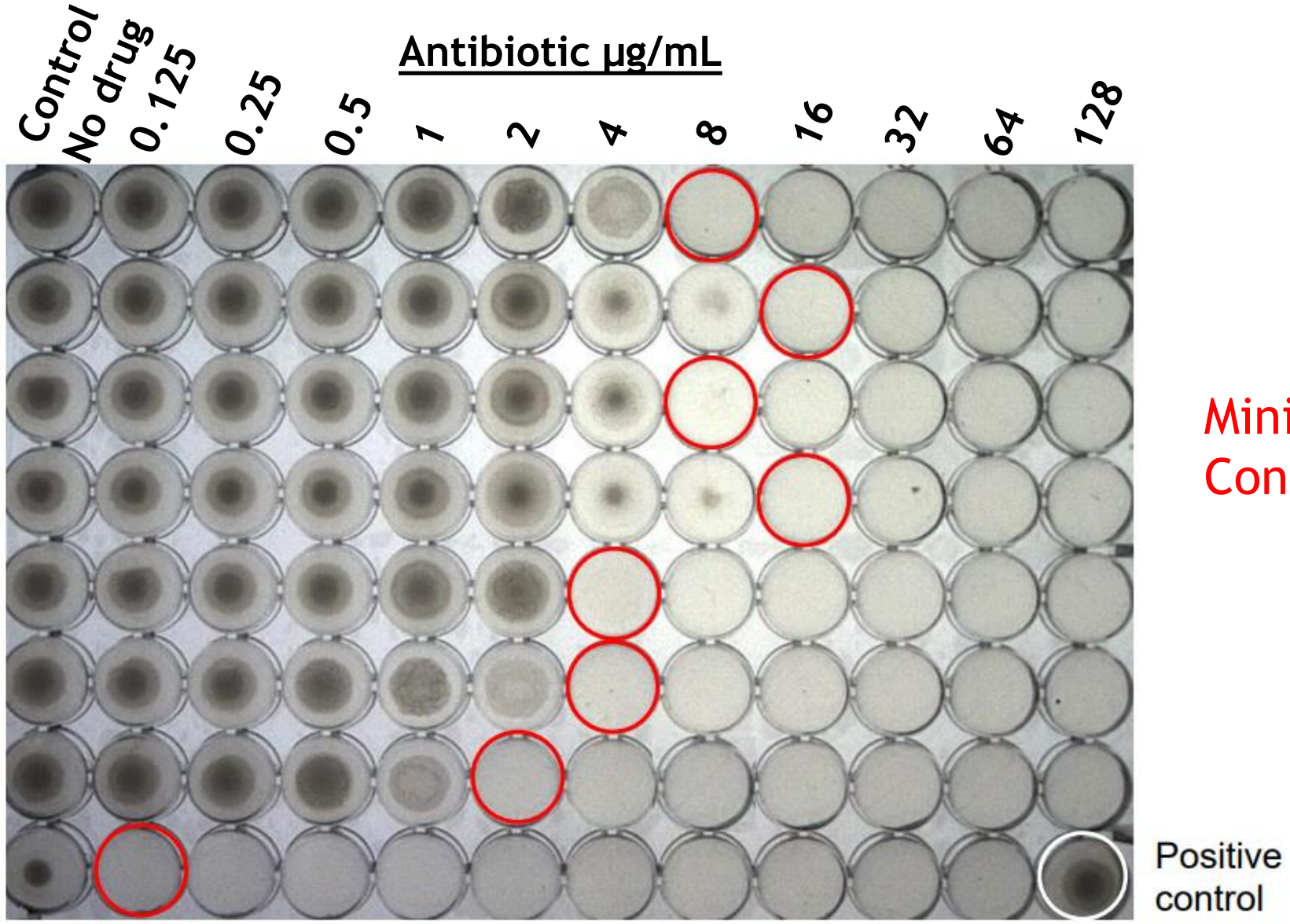
Learning Objectives

- 1. Identify the breakpoint setting organizations:
  - FDA, CLSI, and EUCAST
- 2. Learn why breakpoints may need to be updated over time
- 3. Understand how CLSI changes/updates antibiotic breakpoints

Today's examples:
Stenotrophomonas maltophilia

March 2024 CLSI Breakpoint Updates
- Ceftazidime
- Minocycline

Background Methods: Broth Microdilution



Minimum Inhibitory Concentration (MIC)

Shams et al., 2021

Breakpoint Setting Organizations

FDA
(U.S. Food and Drug Administration)

- Initial breakpoint set when the drug receives FDA approval
- Can choose to accept updated CLSI breakpoints or not

CLSI
(Clinical and Laboratory Standards Institute)

- Updates existing breakpoints

EUCAST
(European Committee on Antimicrobial Susceptibility Testing)

- European equivalent to CLSI

FDA Breakpoints are Online

https://www.fda.gov/drugs/development-resources/antibacterial-susceptibility-test-interpretive-criteria

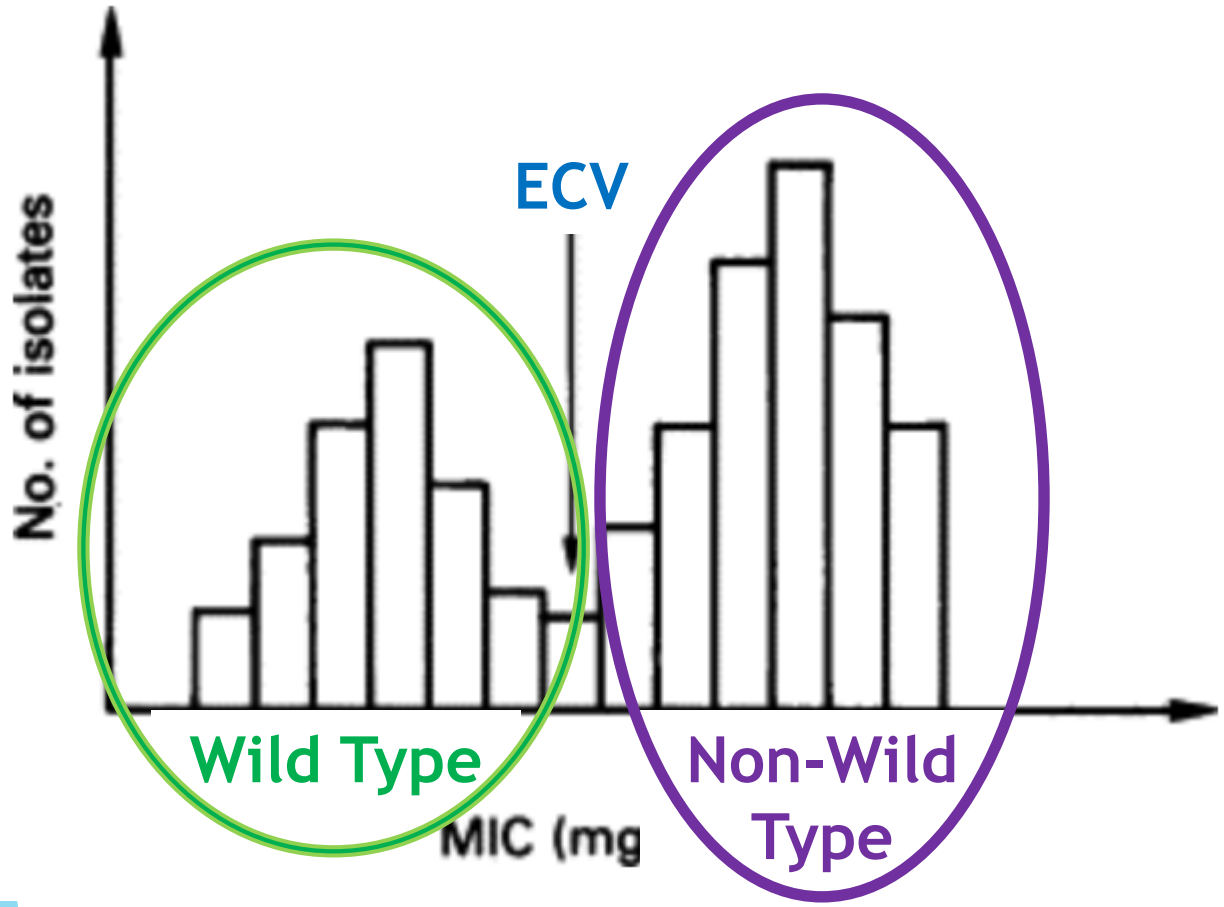
What data do you need to set a breakpoint?

CLSI M23: Development of *In Vitro* Susceptibility Testing Criteria and Quality Control Parameters

ECV •Epidemiological Cutoff Value	

Breakpoints and Epidemiological Cutoff Value (ECV)

- ECV: MIC separating wild-type bacterial population from acquired or mutational resistance mechanisms based on phenotypes



ECV

- Before we study how the antibiotic works in human infections
- Does not officially classify bacteria into resistant and susceptible

Breakpoint

- After we study how the antibiotic works in human infections
- Does officially classify bacteria into resistant and susceptible

Gillespie, Medical Microbiology Illustrated- Antimicrobial Susceptibility 1994

ECV Calculator
EUCAST calls them ECOFF (Epidemiology Cut-off)

CLSI

Shop Membership Participate Standards Global Training About

ECOFFinder

ECOFFinder is a Microsoft Excel spreadsheet calculator that is freely available to the public. It is designed to estimate epidemiological cutoff values (ECVs, ECOFFs) for the minimal inhibitory concentrations or minimal effective concentrations of wild-type bacterial or fungal populations. It follows the methodology described in "Turnidge J, Kalhmeter G, Kronvall G. Statistical characterization of bacterial wild-type MIC value distributions and the determination of epidemiological cut-off values. Clin Microbiol Infect. 2006;12:418-425." Instructions for use are provided on the Instructions sheet.

This version is an update to the previously released version. It overcomes the problem of requiring separate versions for PC and Mac. Includes a number of enhancements, including a "Results summaries" tab where some of the main results can be stored. Also included is "IMPORTANT ADVICE FOR USERS" which provides important caveats about the use of the product and the interpretation of results.

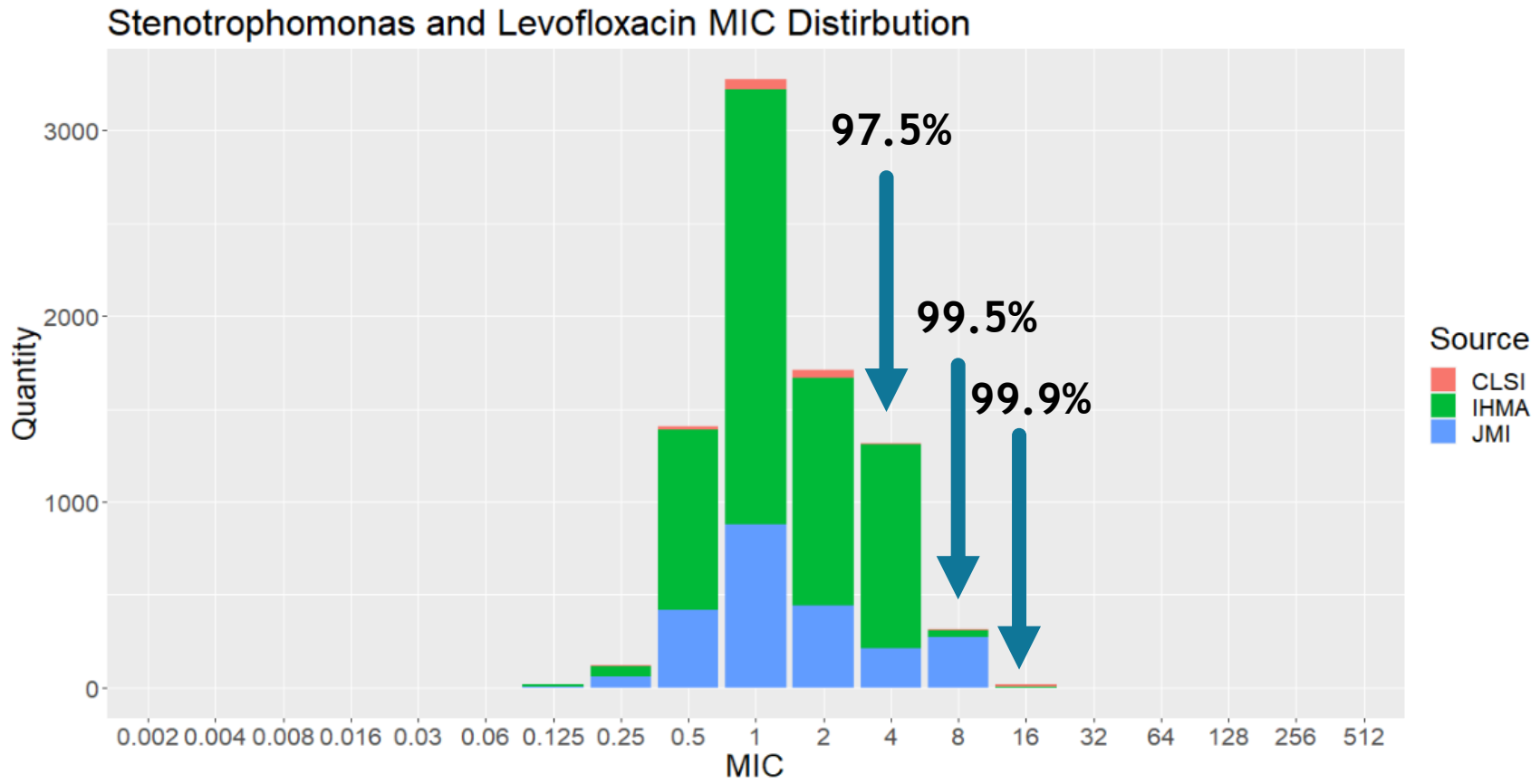
ECOFFinder XL 2010 v2.1

ECOFFinder for Excel Prior to 2010 (v1 for PC)

You will need to enable the Add-in "Solver." Also, if you have enabled Solver and you get a runtime error the first time you use it, close and then re-open Excel to see if that fixes the problem.

For any issues or questions, contact John Turnidge (author): jturnidge@gmail.com.

ECV Example Stenotrophomonas Levofloxacin MIC Distribution



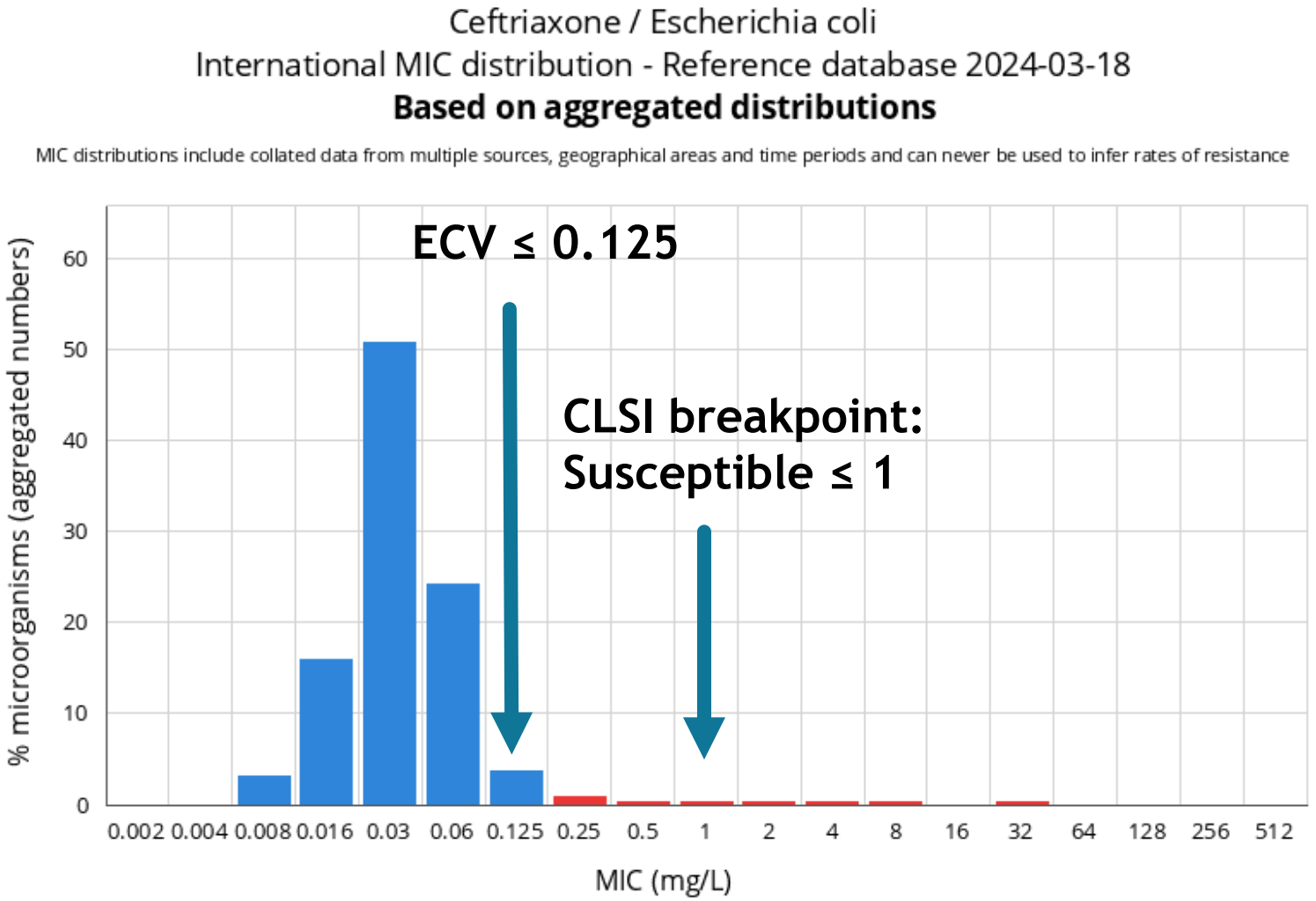
Note: Due to the scale of the y-axis, low frequency MIC counts are not visible on this figure

What would you pick as the ECV?

ECOFF Finder
97.5%: MIC 4
99.0% and 99.5%: MIC 8
99.9%: MIC 16

Example of ECV/ ECOFF from EUCAST

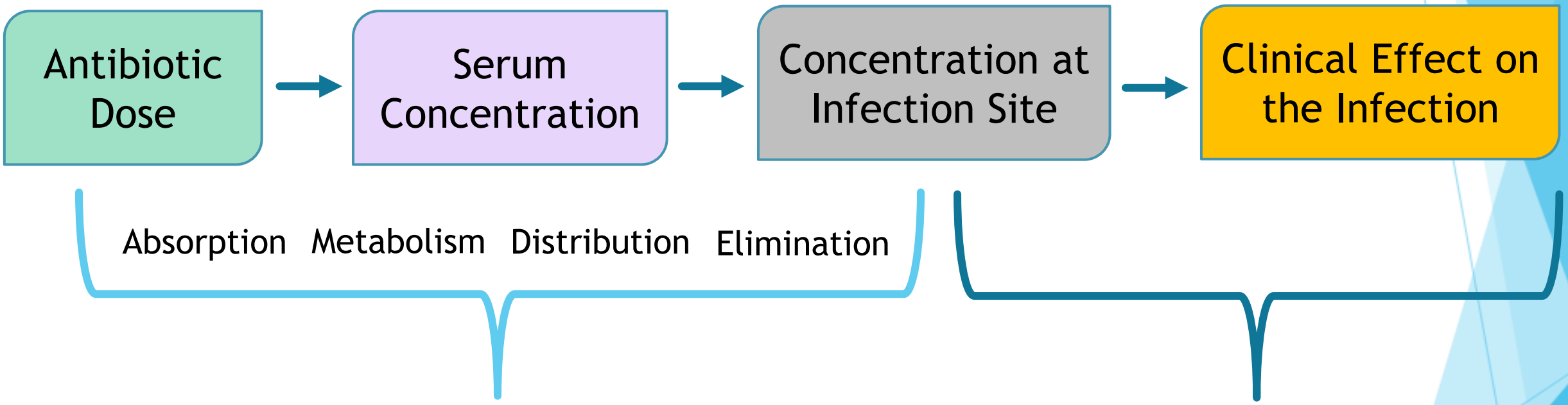
What would you pick as the ECV?



CLSI M23: Development of *In Vitro* Susceptibility Testing Criteria and Quality Control Parameters

ECV •Epidemiological Cutoff Value	PK/PD • Nonclinical Pharmacokinetic - Pharmacodynamics (PK/PD) Cutoff

Nonclinical Pharmacokinetics - Pharmacodynamics (PK/PD) Cutoff



Pharmacokinetics (PK)

The effect the body has on the drug

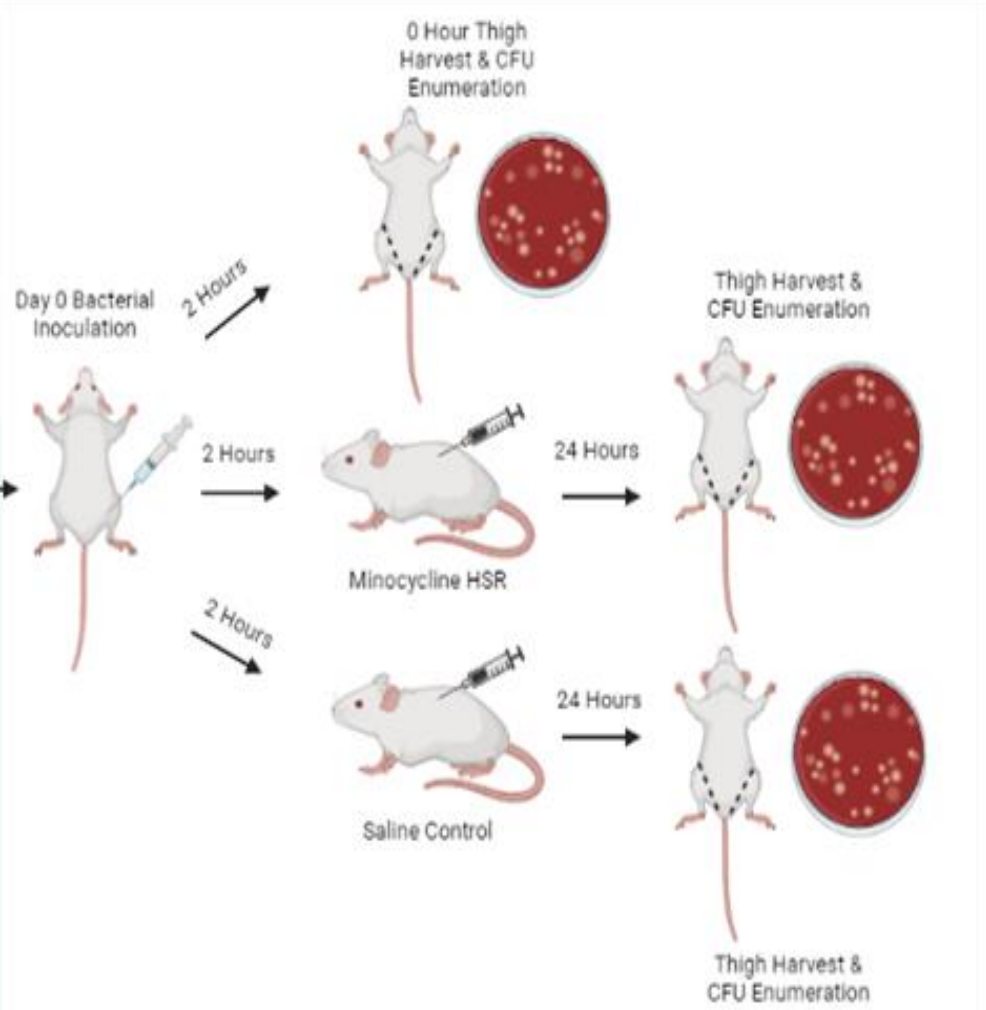
Pharmacodynamics (PD)

The effect of the drug on the body/ pathogen

Pharmacokinetics - Pharmacodynamics (PK/PD) Cutoff

Goal: Predict the highest MIC where treatment is effective

Time-kill studies



Monte Carol simulation

- probability of attaining the target drug exposure
- Statistical technique to account for the PK variations in human populations

CLSI M23: Development of *In Vitro* Susceptibility Testing Criteria and Quality Control Parameters

ECV •Epidemiological Cutoff Value	PK/PD • Nonclinical Pharmacokinetic - Pharmacodynamics (PK/PD) Cutoff
Clinical: • Clinical Exposure-response (CER) Cutoff • Clinical Cutoff	

Clinical Exposure-response (CER) Cutoff

- CER: Highest MIC where the target efficacy is achieved in 90% of the patient population using the standard dose
- Clinical trial in an infected patient population
  - PK/PD
  - Clinical outcome
  - MICs

Clinical Cutoff

- Treatment success or failure by MIC

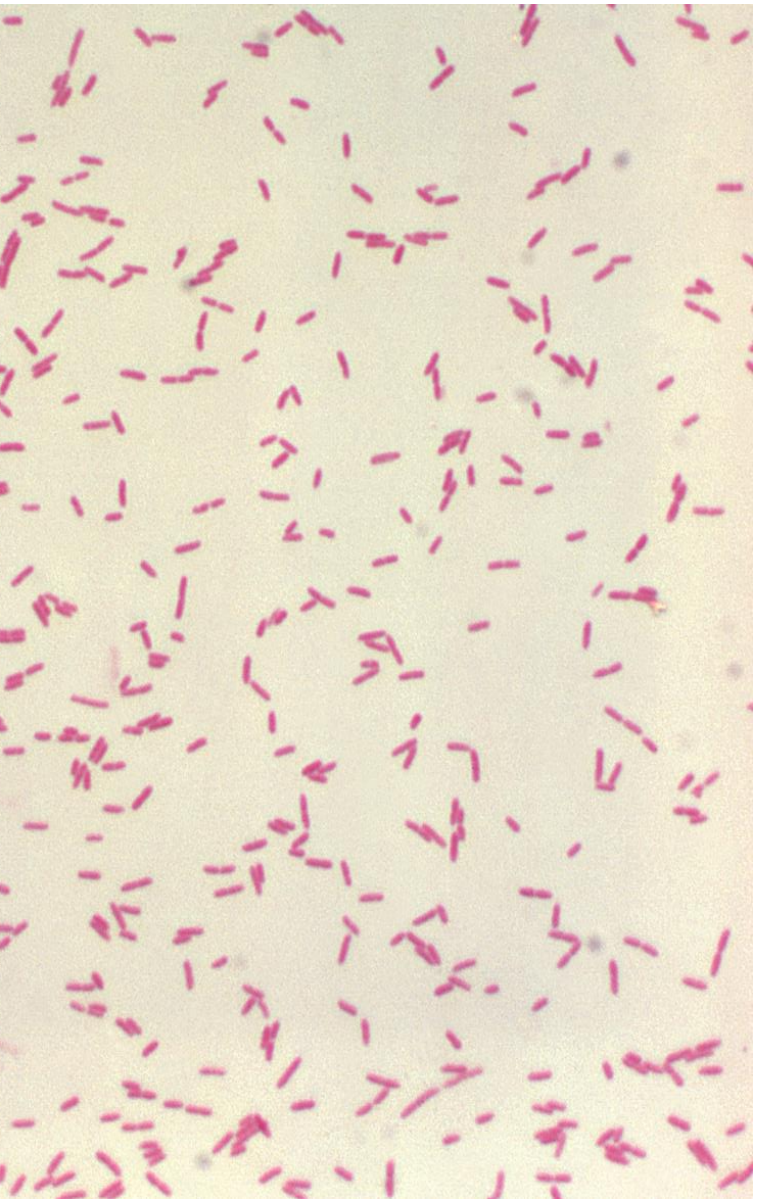
CLSI M23: Development of *In Vitro* Susceptibility Testing Criteria and Quality Control Parameters

ECV •Epidemiological Cutoff Value	PK/PD • Nonclinical Pharmacokinetic - Pharmacodynamics (PK/PD) Cutoff
Clinical: • Clinical Exposure-response (CER) Cutoff • Clinical Cutoff	Final Breakpoint Decision!

Why would breakpoints need to be updated?

- New resistance mechanism
- Increased prevalence of an existing resistance mechanism
- New data available
  - Clinical outcomes
  - PK/PD
  - Test method improvement
  - Test method problems

Stenotrophomonas maltophilia: Update Breakpoints



- Environmental organism
- Non-fermenting, Gram-negative bacillus
- Opportunistic infections:
  - Critically ill
  - Immunocompromised
- CLSI M100 just published in March 2024!

https://phil.cdc.gov/Details.aspx?pid=15905

Why reevaluate *S. maltophilia* breakpoints?

1) Poor outcomes in patients with *S. maltophilia*

2) Breakpoints were set in the early 2000's without much PK/PD data

3) New data available
    1) PK/PD studies
    2) AST reproducibility issues for some drugs

https://theprologues.tumblr.com/post/637455987556679680

Poor Clinical Outcomes

Time to Demise from Positive Culture

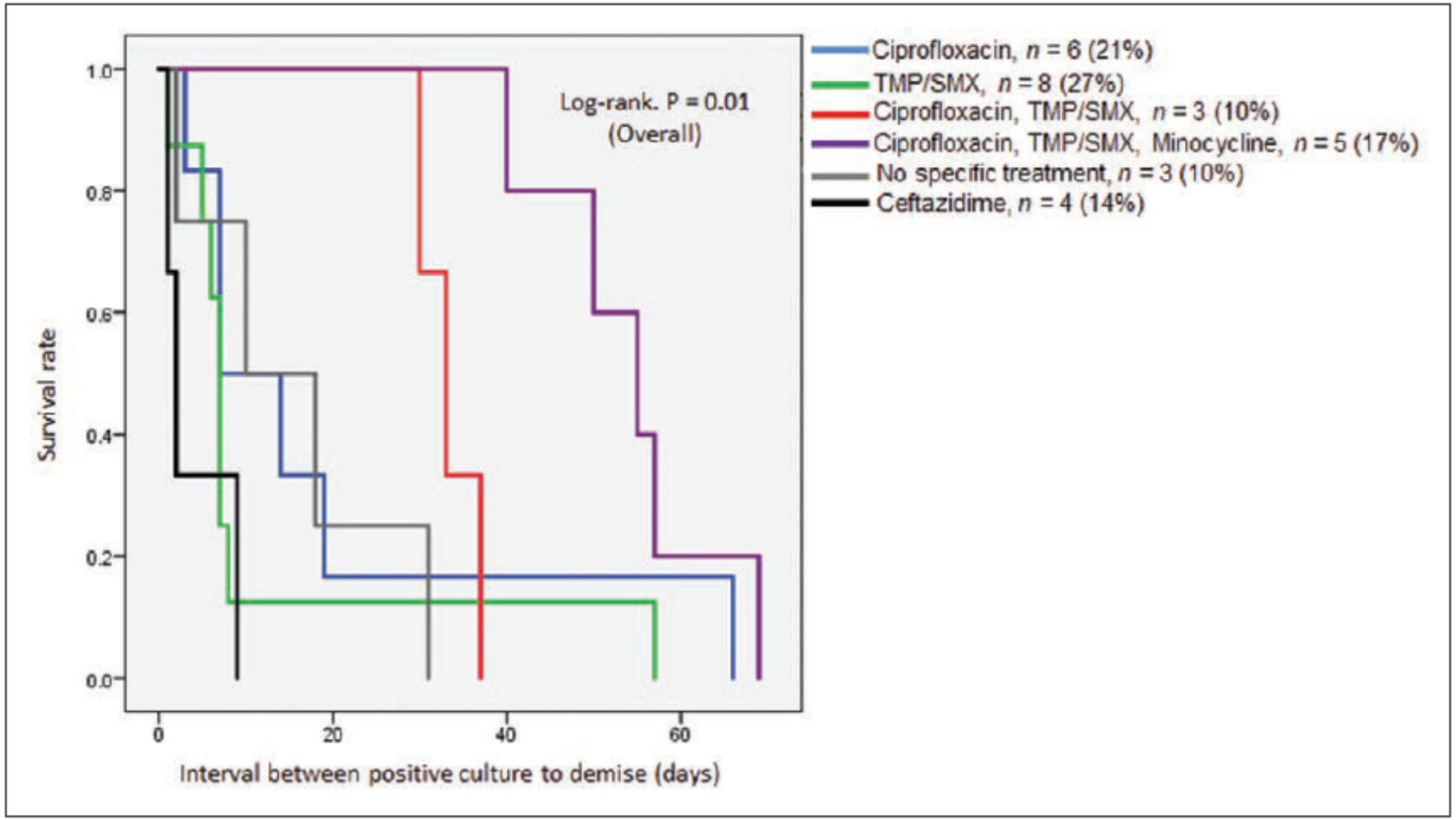
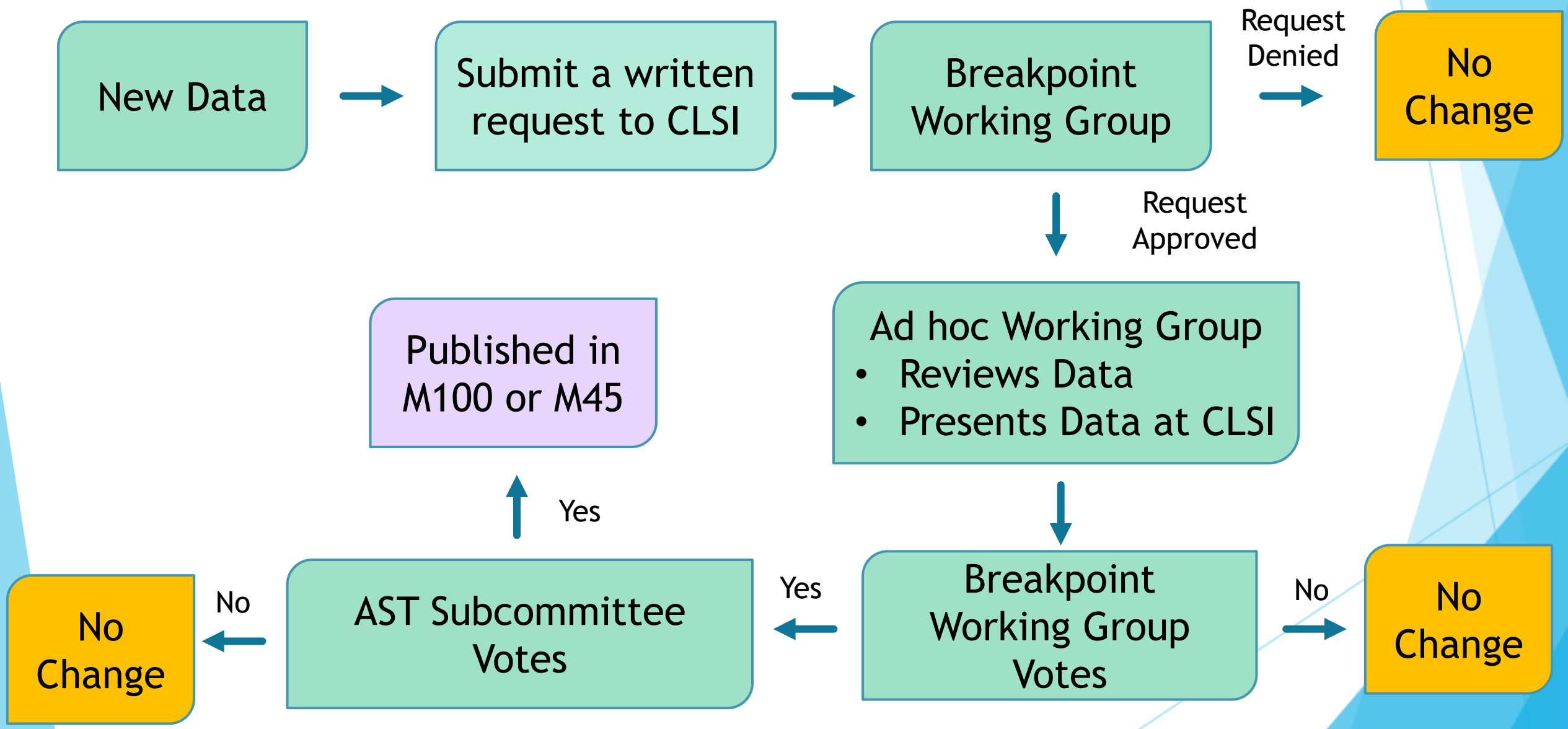


Figure 2. A Kaplan-Meier plot depicting the interval (d), between the positive cultures of *Stenotrophomonas maltophilia* to demise. TMP/SMX = trimethoprim-sulfamethoxazole.

- Retrospective study
- 68 Bacteremia cases
- Indicated combination therapy may be necessary

Tokatly Latzer, 2019
PMID: 31058792

How do you update the breakpoints?



S. maltophilia AHWG 2021 - 2023

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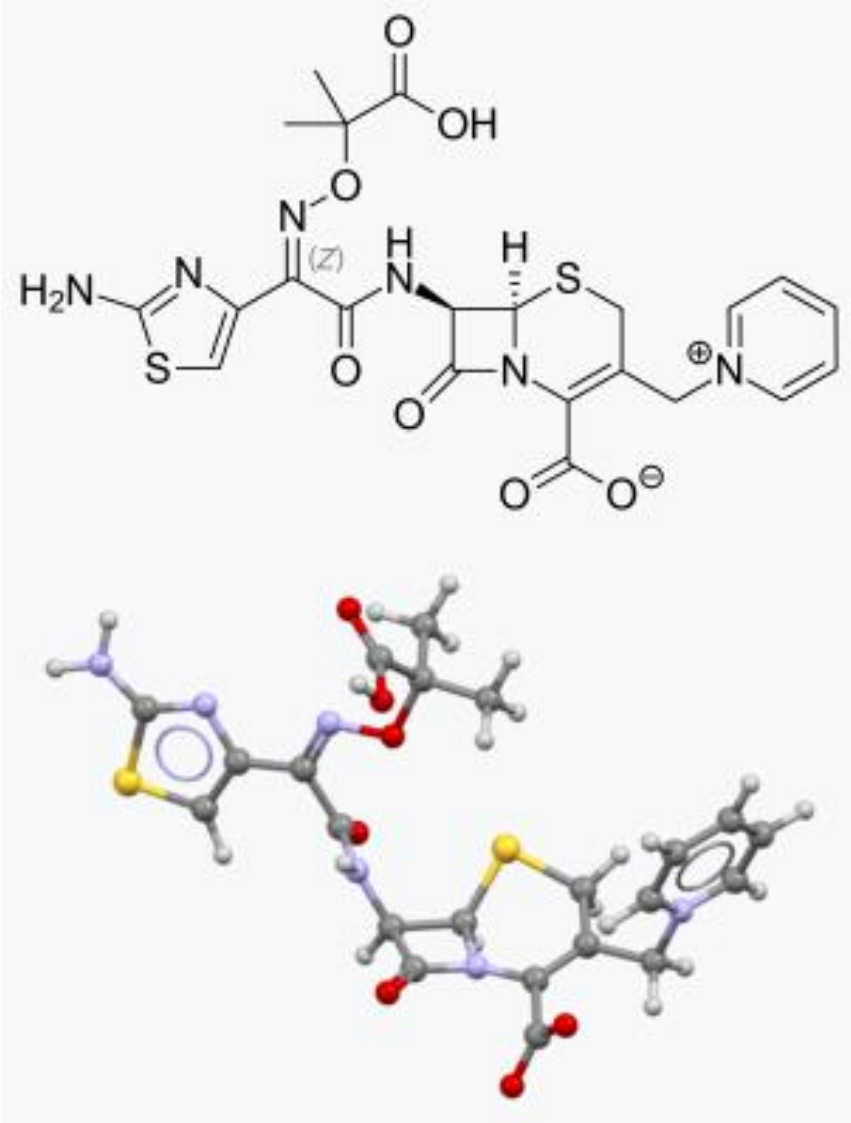
Ceftazidime and *S. maltophilia*



https://en.wikipedia.org/wiki/Ceftazidime

PK/PD: Studies

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 1996, p. 2859–2864
0066-4804/96/$04.00+0

Vol. 40, No. 12

Stenotrophomonas maltophilia: Emergence of Multidrug-Resistant Strains during Therapy and in an In Vitro Pharmacodynamic Chamber Model

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www.elsevier.com/locate/diagmicrobio

Antibiotic combinations significantly more active than monotherapy in an in vitro infection model of *Stenotrophomonas maltophilia*

Sheryl A. Zelenitsky[a,b,c,*], Harris Iacovides[a], Robert E. Ariano[a,b,c], Godfrey K.M. Harding[b,d,e]

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PHARMACOLOGY

Check for updates

Comparative *In Vivo* Antibacterial Activity of Human-Simulated Exposures of Cefiderocol and Ceftazidime against *Stenotrophomonas maltophilia* in the Murine Thigh Model

Iris H. Chen,[a] James M. Kidd,[a] Kamilia Abdelraouf,[a] David P. Nicolau[a]

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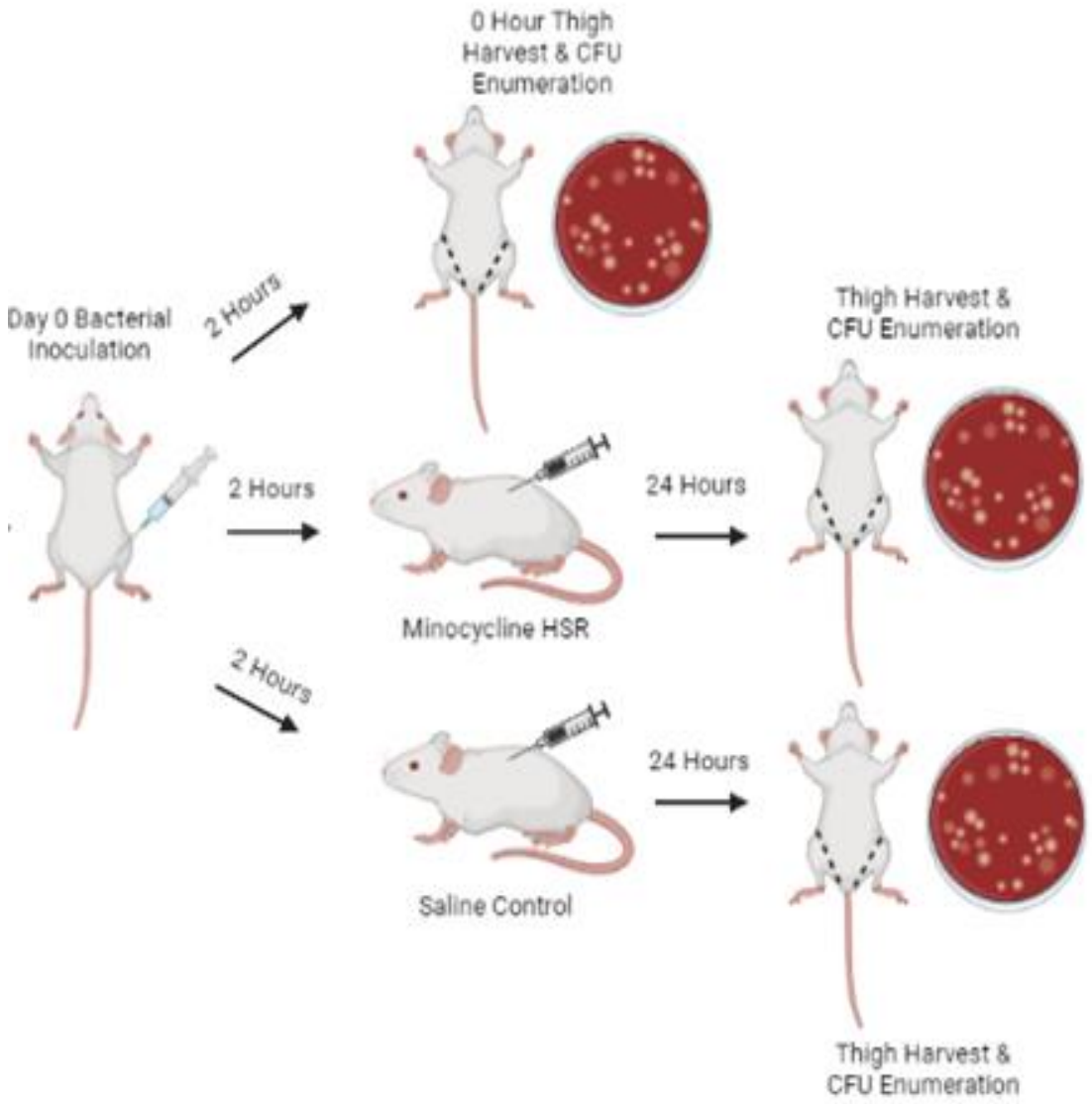
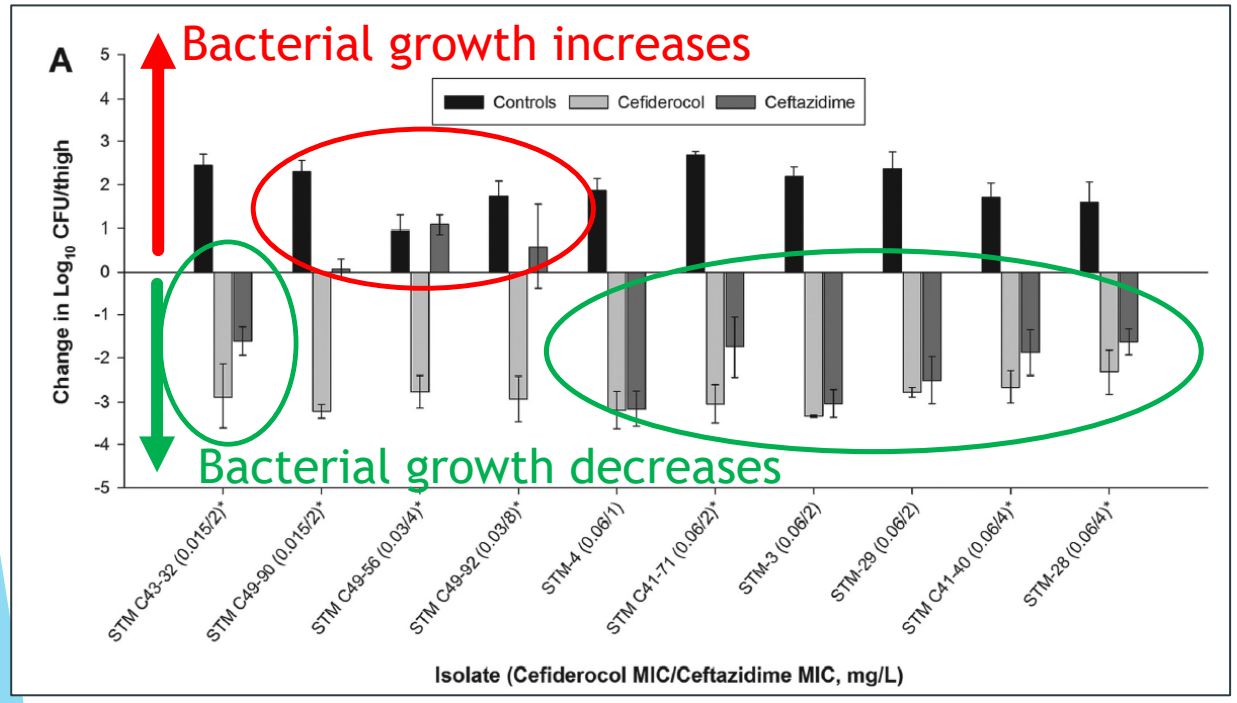
PK/PD: Murine thigh model

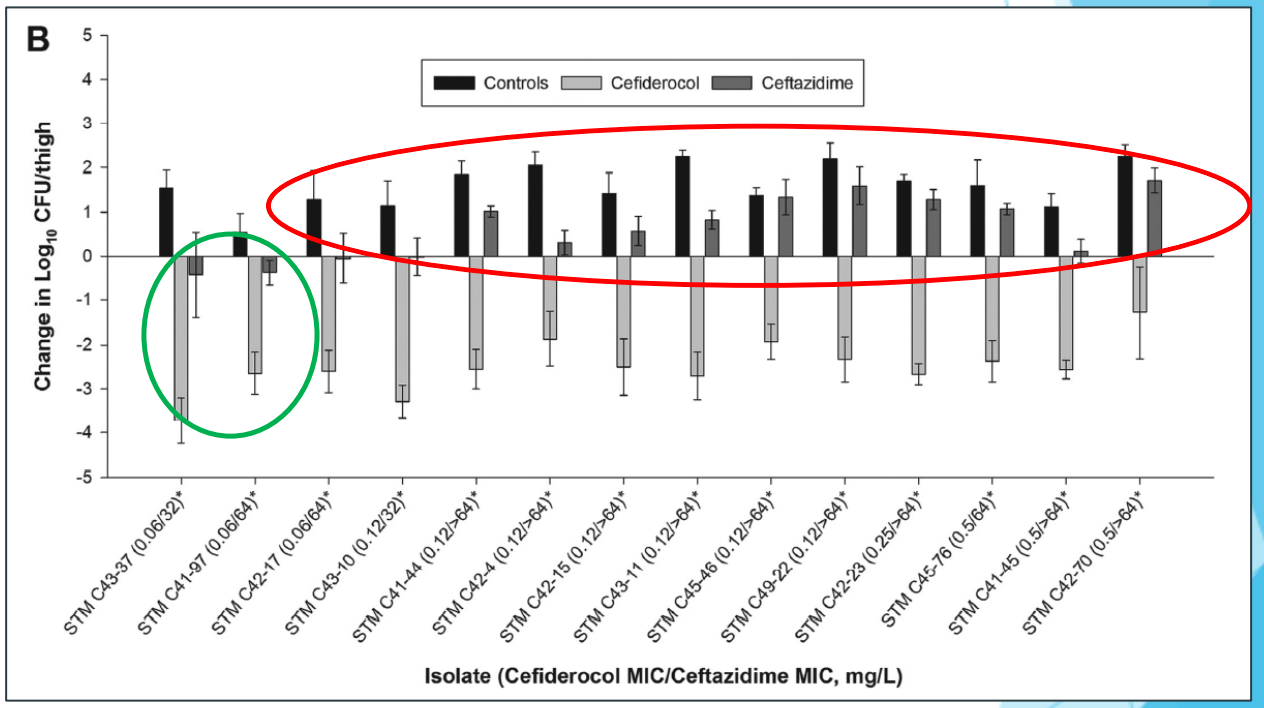


PK/PD: Murine thigh model

- Ceftazidime MIC ≤ 8

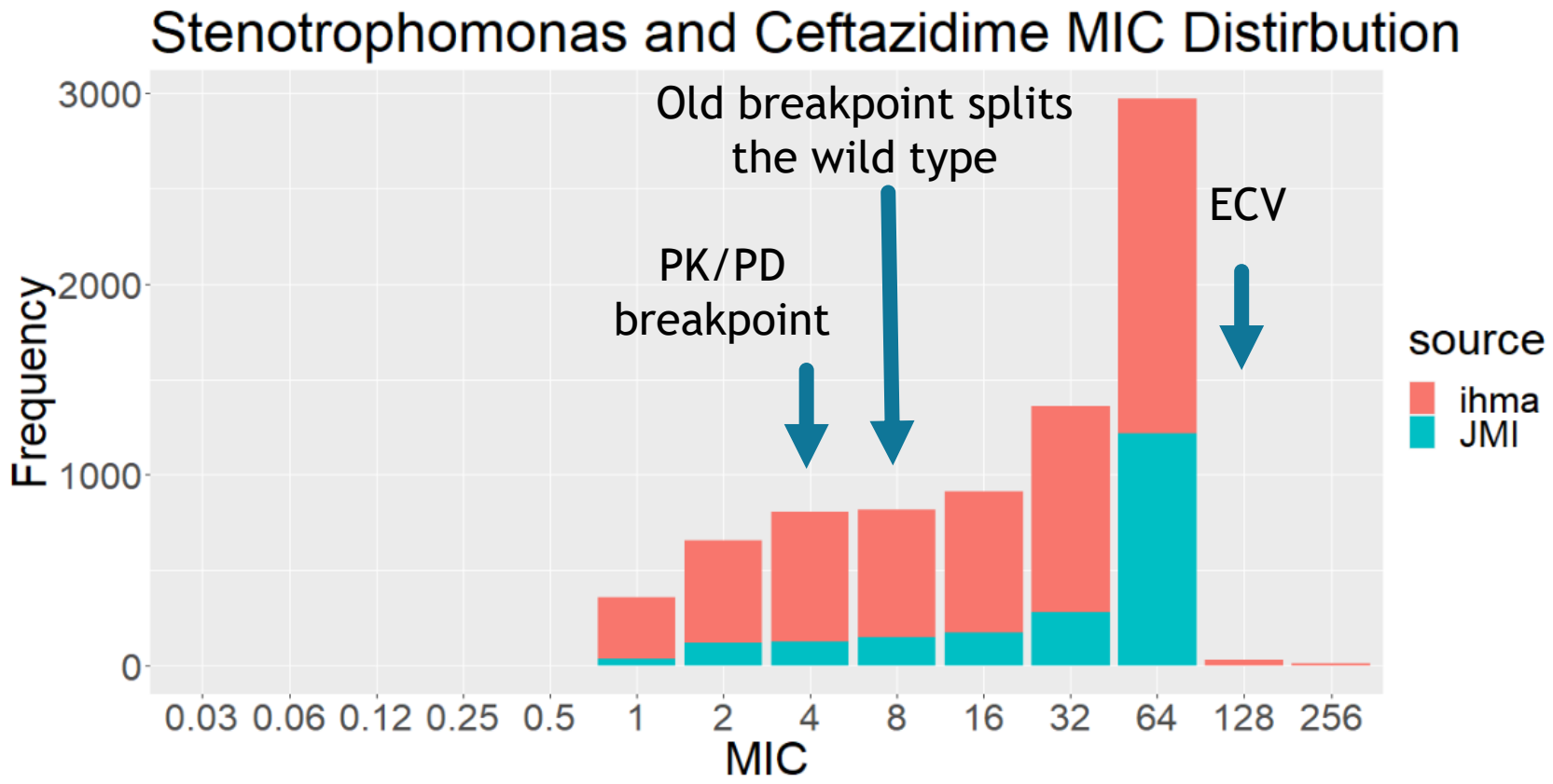


- Ceftazidime MIC ≥ 32



Chen I et al. AAC. 2019.

S.maltophilia Ceftazidime MIC Distribution



2017 – 2021 Worldwide Isolates:

- Ihma: 5,826
- JMI: 2,107

Old CLSI breakpoints:
≤8 S
16 I
≥32 R

Ceftazidime: Low AST Reproducibility

Replicate Agreement	Lab 1 (n = 48) BMD	Lab 2 (n = 119) AD	Lab 3(n =20)* BMD
Absolute	54%	40%	25%
1 Dilution	29%	42%	55%
2 Dilutions	8%	16%	20%
3 or more Dilutions	8%	2%	0%
Absolute + 1 Dilution	**83%**	**82%**	**80%**

*BMD performed in triplicate –recorded the mode

- Some were retested due to discrepancies or QC failures – mode recorded
- May be biased towards more difficult isolates

AD: Agar Dilution
BMD: Broth microdilution

Ceftazidime: Low disk diffusion reproducibility in 2003 CLSI data

- Raw disk diffusion data is in the CLSI 2003 minutes, but we could not find discussion of the data
- No disk diffusion breakpoints

	Zone Size (mm) - Ceftazidime																	
	BBL MHA - Remel Disks						Hardy MHA - Remel Disks						Remel MHA - Remel Disks					
Organism	Log Phase			Direct			Log Phase			Direct			Log Phase			Direct		
	D1	D2	D3	D1	D2	D3	D1	D2	D3	D1	D2	D3	D1	D2	D3	D1	D2	D3
Sm 11-313C	28	29	25	30	25	25	29	29	25	30	25	25	30	29	26	30	27	27
Sm 17-9715A	6	15	6	6	12	12	6	6	6	6	6	6	6	12	6	6	12	6
Sm 22-151C	19	18	16	17	17	14	6	6	6	6	6	6	22	21	20	21	20	20
Sm 31-2000C	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Sm 32-105C	21	17	21	20	17	21	6	6	6	10	6	13	26	23	23	25	21	26
Sm 43-9189A	23	21	20	20	18	17	20	18	15	17	16	13	27	25	25	23	20	23
Sm 50-397C	28	32	29	30	30	29	24	32	29	24	23	23	30	36	29	32	31	30
Sm70-12362A	25	24	25	25	24	24	17	16	17	17	16	17	28	27	29	27	27	27
Sm 82-4300C	10	14	6	10	11	6	6	6	6	6	6	6	18	18	17	17	16	17
Sm 84-2597C	13	12	6	11	10		6	6	6	6	6	6	20	19	17	20	16	16

Comparison of commercial methods to BMD Ceftazidime

Breakpoint	S	I	R
Current CLSI	≤ 8	16	≥32
PK/PD	≤4	8	>8

Current CLSI breakpoint

Method	EA (%)	CA (%)	# VME (%)	# ME (%)	# mE (%)
Vitek 2	55/108 (50.9%)	73/108 (67.6%)	19/43 (44.2%)	0/54 (0%)	16/108 (14.8%)
MicroScan	83/108 (76.9%)	75/108 (69.4%)	4/43 (9.3%)	7/54 (13%)	22/108 (20.4%)
Phoenix	72/107 (67.3%)	76/107 (71%)	7/43 (16.3%)	11/53 (20.8%)	13/107 (12.1%)

PK/PD breakpoint

Method	EA (%)	CA (%)	# VME (%)	# ME (%)	# mE (%)
Vitek 2	ND	79/109 (72.5%)	23/55 (41.8%)	0/40 (0%)	21/109 (19.3%)
MicroScan	ND	78/108 (72.2%)	6/54 (11.1%)	8/40 (20%)	16/108 (14.8%)
Phoenix	ND	67/107 (62.6%)	9/54 (16.7%)	8/39 (20.5%)	23/107 (21.5%)

Khan A, Arias CA, Abbott A, Dien Bard J, Bhatti MM, Humphries RM. Evaluation of the Vitek 2, Phoenix, and MicroScan for Antimicrobial Susceptibility Testing of Stenotrophomonas maltophilia. J Clin Microbiol. 2021 Aug 18;59(9):e0065421. doi: 10.1128/JCM.00654-21. Epub 2021 Aug 18. PMID: 34011524; PMCID: PMC8373028.

ß-lactamase Production

- L:1 class B3 metallo-ß-lactamase: hydrolyzes carbapenems and other b-lactams, but not aztreonam
  - L1 is resistant to ß-lactamase inhibitors
- L2: class A cephalosporinase -> resistance to broad-spectrum cephalosporins and aztreonam, but is inhibited by serine- ß-lactamase inhibitors such as tazobactam and avibactam
- Ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, imipenem-relebactam inhibit Class A carbapenemases, but don’t work against L1
- PhoPQ plays a role in L1/L2 regulation
  - Deletion/Mutation of PhoPQ and its system results in lower MICs to beta lactams

β-lactamase Production

Dr. Maria Mojica and Dr. Robert Bonomo (2019, PMID: 31266860)

- *Bla* L1: detected in 100/130 isolates (77%)
- *Bla* L2: detected in 116/130 isolates (89%)
- In discussion with the authors:
  - Diversity in L1 makes it hard to design primers to the detect L1
- JMI has sequenced ~80 isolates, mostly resistant, and all have L1 and/or L2

Clinical Outcomes: Ceftazidime

- Endocarditis/pericarditis
  - n = 4 papers (case series/reports)
- Catheter-related bacteremia
  - n = 4 papers (case series/reports)
- Pneumonia
  - n = 4 papers (case reports)
- Peritonitis
  - n = 5 papers (case series/reports)
- Skin/soft tissue infections (bacteremic)
  - n = 2 papers (case series/reports)
- Meningitis
  - n = 6 (case series/reports)
- Endophthalmitis
  - n = 8 (case series/reports)

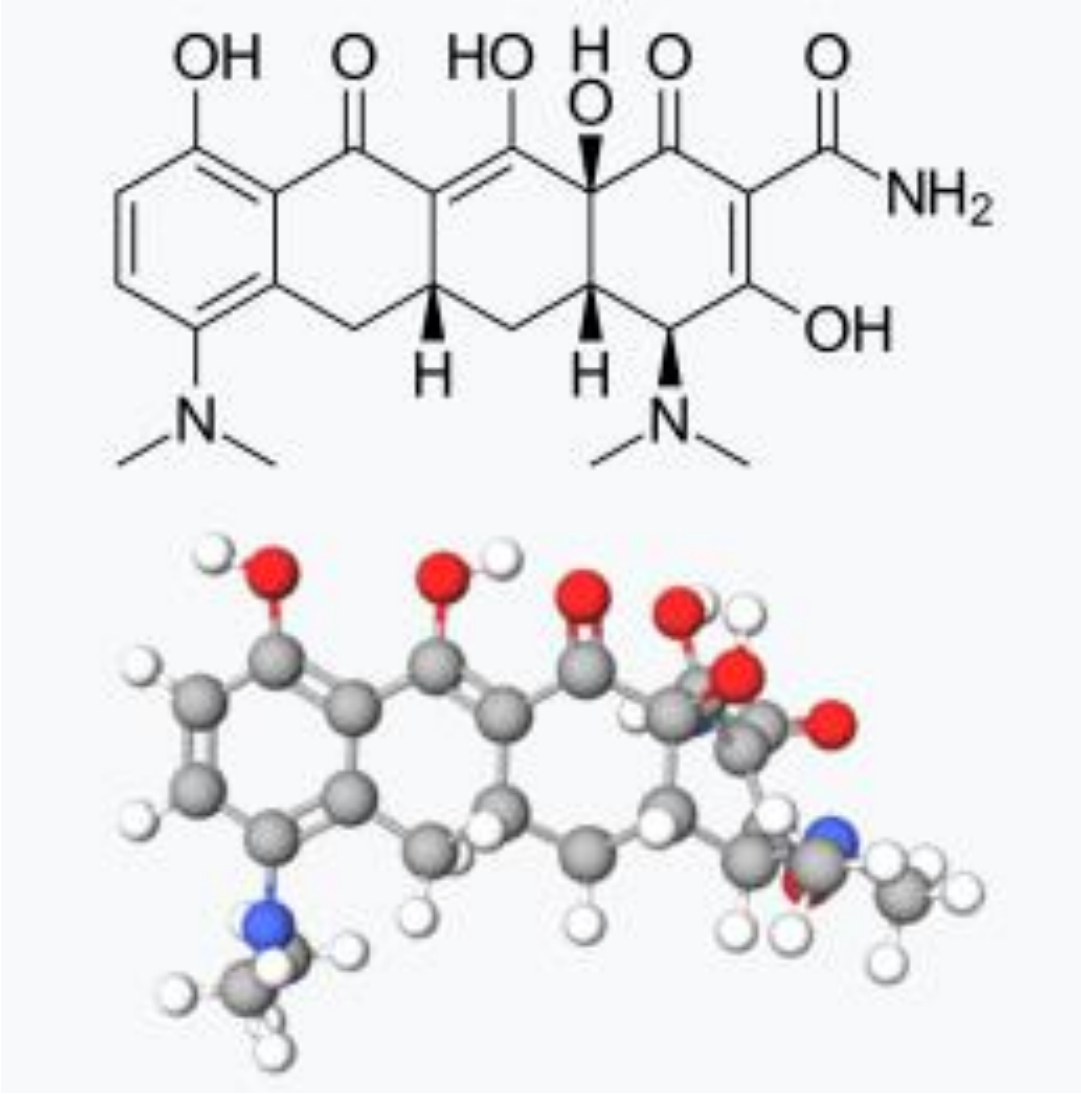
Clinical Outcomes: Ceftazidime

- No high-quality comparative studies of ceftazidime vs other antimicrobials for *Stenotrophomonas maltophilia*
- Sparse data published for clinical outcome by MIC
- Limited examples of successful treatment with ceftazidime monotherapy without removable foci of infection/surgical intervention
- Development of resistance during treatment reported
- Outcome not always correlated with susceptibility interpretation

Ceftazidime and *S. maltophilia*

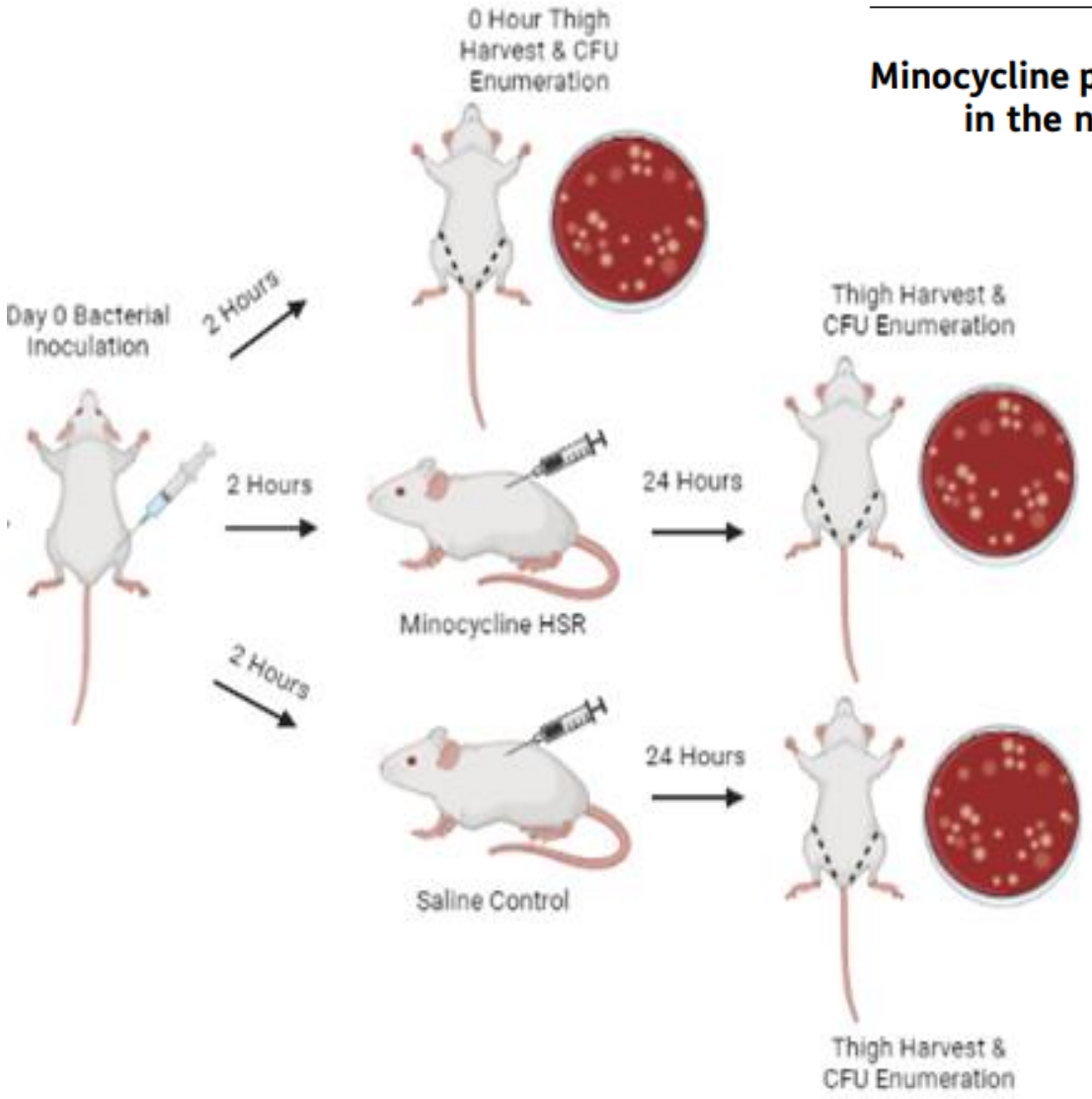
ECV • > 64µg/mL • AST is not reproducible • Most have: *Bla* L1 and *Bla* L2	PK/PD • 4µg/mL • Would split the wild type population
Clinical: • Not enough data to establish a clinical breakpoint • Not FDA approved	Final Breakpoint Decision! Remove the Breakpoint

Minocycline and *S. maltophilia*



https://en.wikipedia.org/wiki/Minocycline

PK/PD: Murine thigh model



J Antimicrob Chemother 2022; **77**: 1052–1060
https://doi.org/10.1093/jac/dkac018 Advance Access publication 2 February 2022

Journal of Antimicrobial Chemotherapy

Minocycline pharmacodynamics against *Stenotrophomonas maltophilia* in the neutropenic murine infection model: implications for susceptibility breakpoints

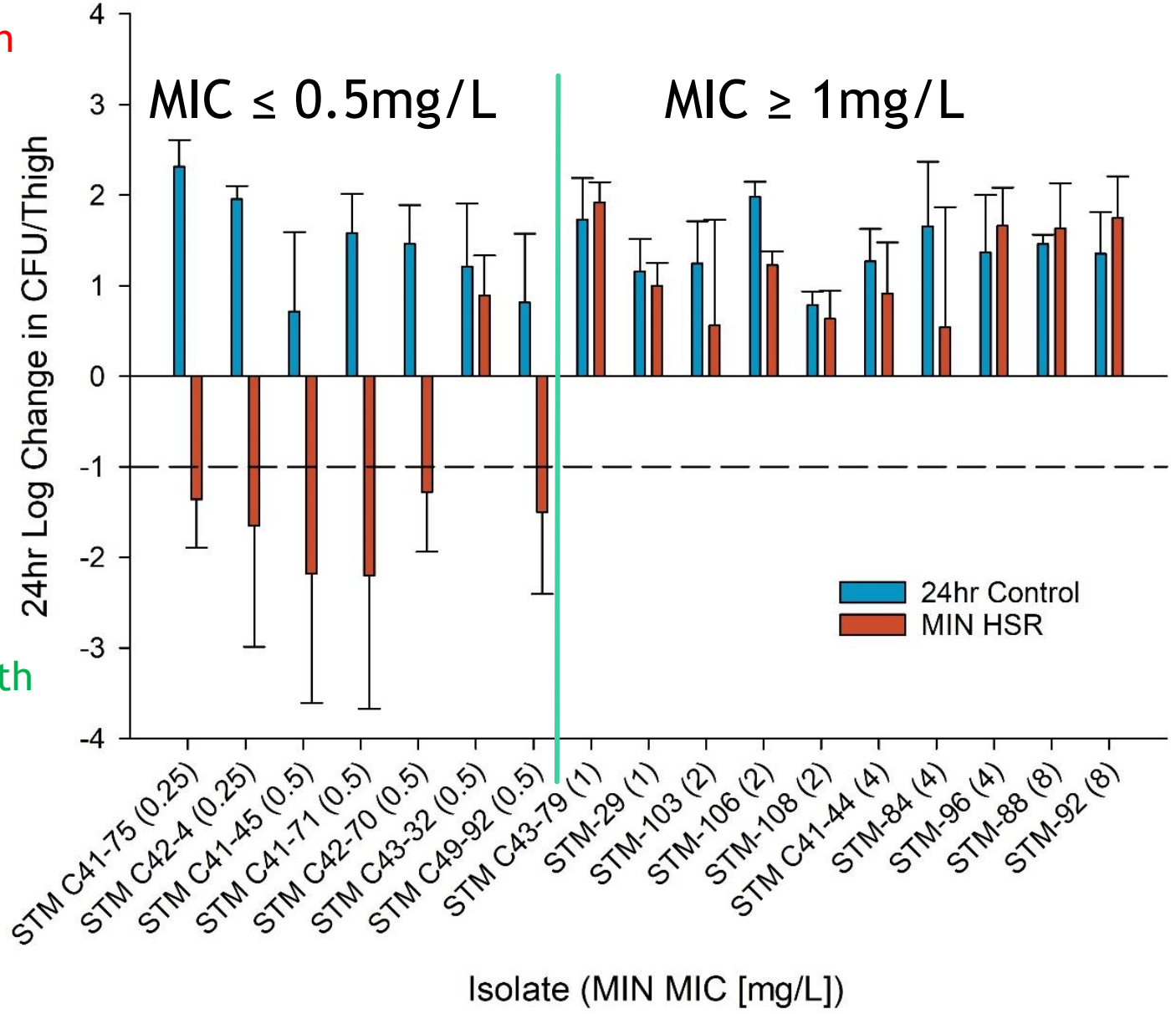
Andrew J. Fratoni, David P. Nicolau and Joseph L. Kuti*

Fratoni *et al*. 2022
PMID: 35134195

PK/PD: Murine thigh model for Minocycline

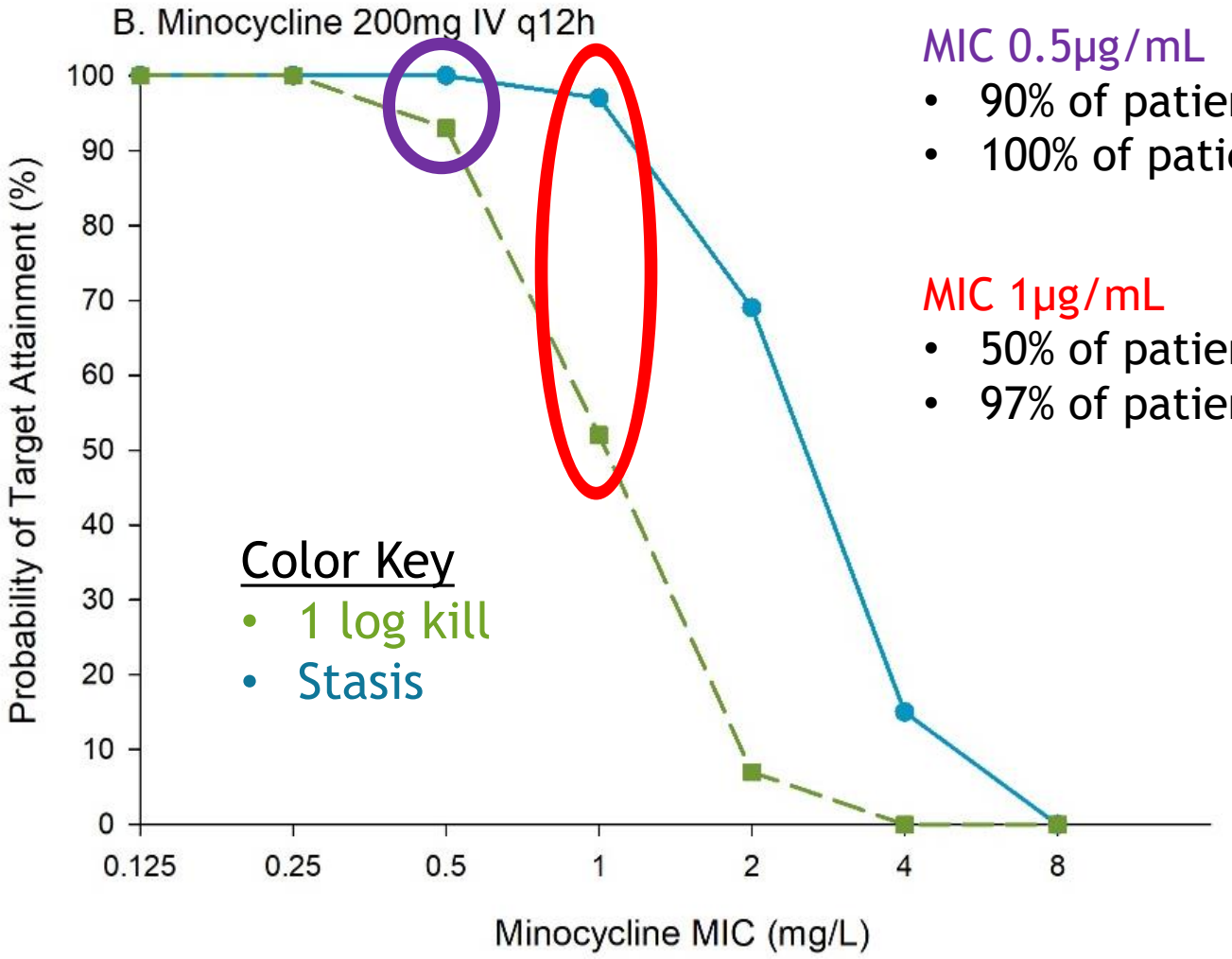
Bacterial growth increases

Bacterial growth decreases



Fratoni *et al*. 2022
PMID: 35134195

Monte Carlo Simulation
Probability of Target Attainment for Minocycline

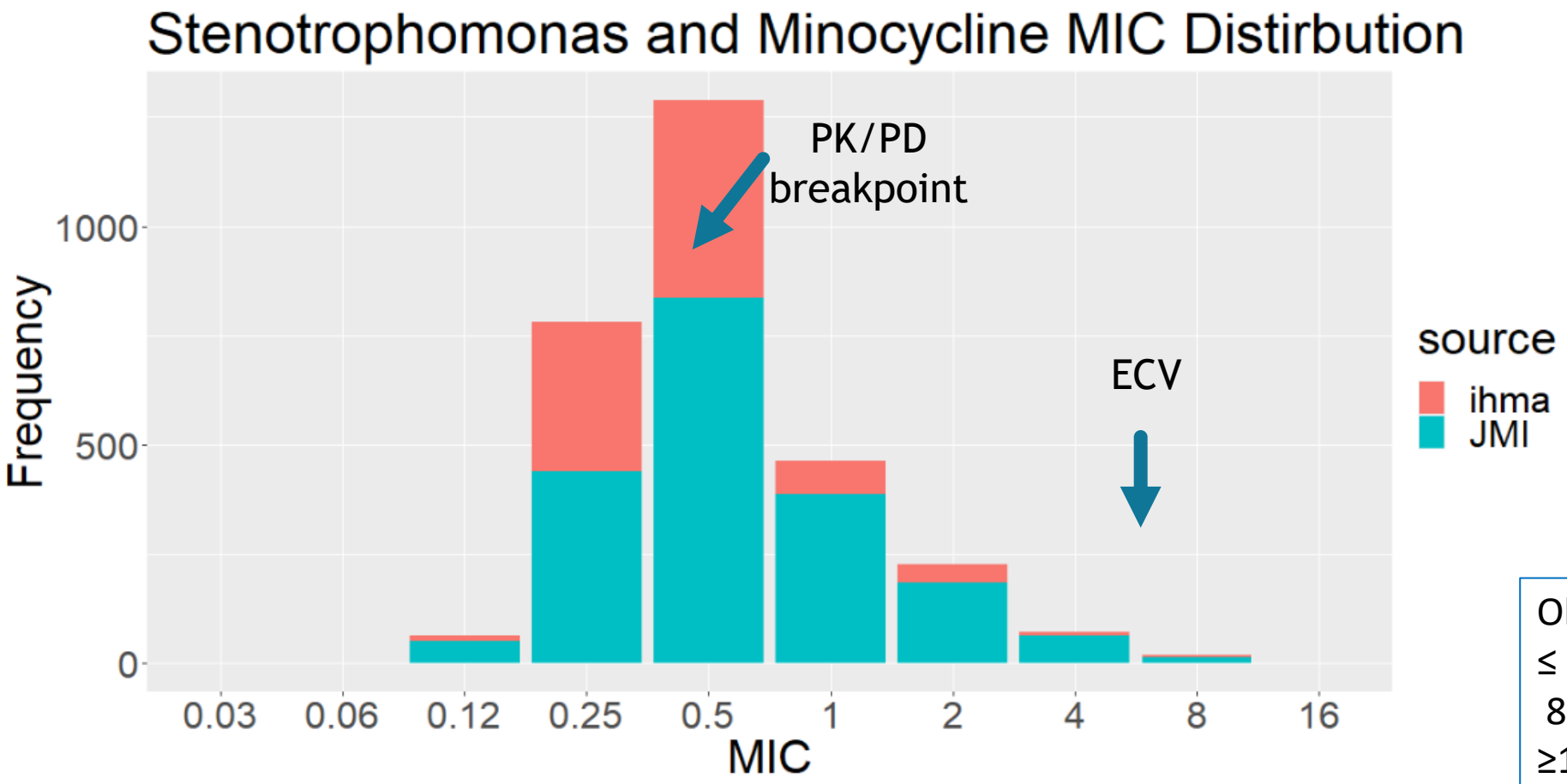


MIC 0.5µg/mL
- 90% of patients see decrease in bacteria
- 100% of patients see stasis

MIC 1µg/mL
- 50% of patients see decrease in bacteria
- 97% of patients see stasis

Fratoni *et al*. 2022
PMID: 35134195

Stenotrophomonas maltophilia Minocycline MIC Distribution



Old CLSI breakpoints:
≤ 4 S
8 I
≥16 R

Note: ECOFF/ECV finder notes that at least two dilutions below the mode need to be tested to ensure accurate estimates; however may isolates here are classified as ≤ 0.5 or ≤ 0.25 and could actually be lower, so an ECV was not calculated

Minocycline: AST Reproducibility

Minocycline

Replicate Agreement	**Lab 1 (n = 67) BMD**	**Lab 2 (n = 119) AD**	**Lab 3(n =21)* BMD**
Absolute	45%	93%	48%
1 Dilution	40%	5%	42%
2 Dilutions	9%	0%	10%
3 or more Dilutions	6%	2%	0%
Absolute + 1 Dilution	**85%**	**98%**	**90%**

*BMD performed in triplicate –recorded the mode

- Some were retested due to discrepancies or QC failures – mode recorded
- May be biased towards more difficult isolates

Minocycline Clinical Data

- 4 retrospective observational studies
  - **Jacobson Junco** 2021 (PMID 34058337)
  - **Tokatly Latzer** 2019 (PMID 31058792)
  - **Hand** 2016 (PMID 26801080)
  - **Jacobson** 2016 (PMID 27516472)

Minocycline Clinical Data

- Retrospective observational data
- Majority of isolates from a respiratory source, many polymicrobial
- Within these limitations, rates of failure with minocycline and TMP/SMX in these studies appear to be similar
- One study that looked at minocycline MICs in relation to therapy found MICs of 4 mg/L were more frequent in patients with clinical failure
  - **Jacobson** 2016 PMID 27516472

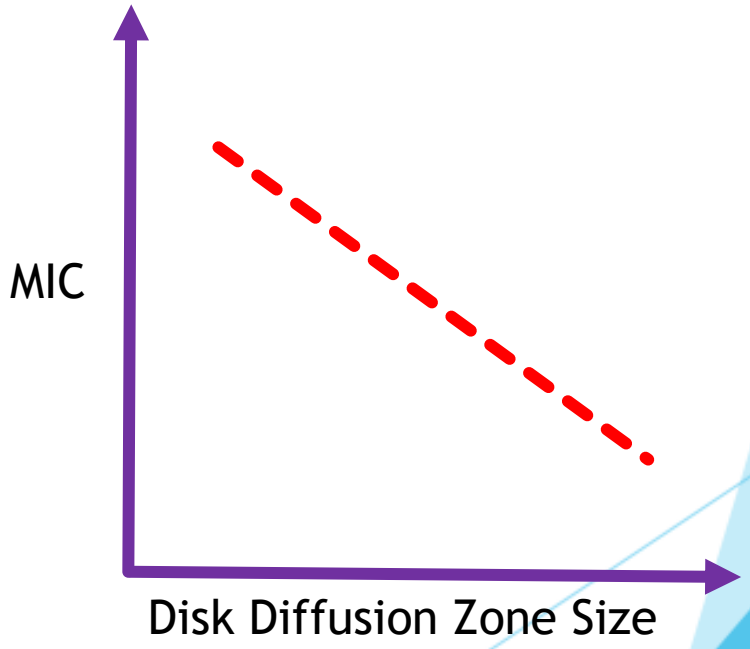
Minocycline and *S. maltophilia*

ECV • ≥4µg/mL • AST is reproducible	PK/PD • 0.5 µg/mL, 200 mg Q12H, PTA 1-log kill >90% • 1 µg/mL, 200 mg Q12H, PTA stasis >90%
Clinical: • Limited data • Outcomes similar to SXT • MIC 4µg/mL → higher failure rate	

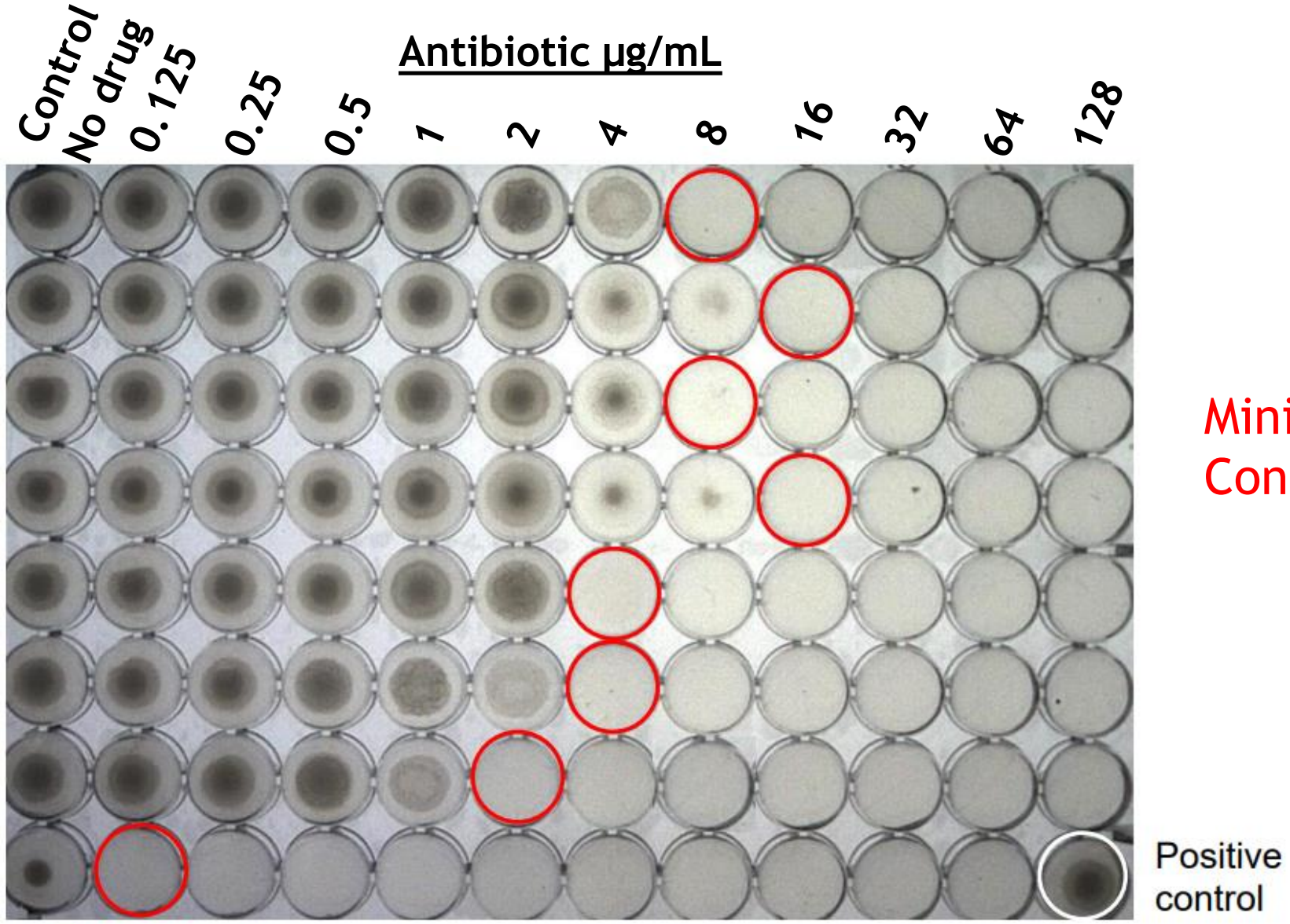
Minocycline and *S. maltophilia*

- The MIC breakpoint changed
- How do we update the corresponding disk diffusion breakpoint?

Compare Broth Microdilution to Disk Diffusion!



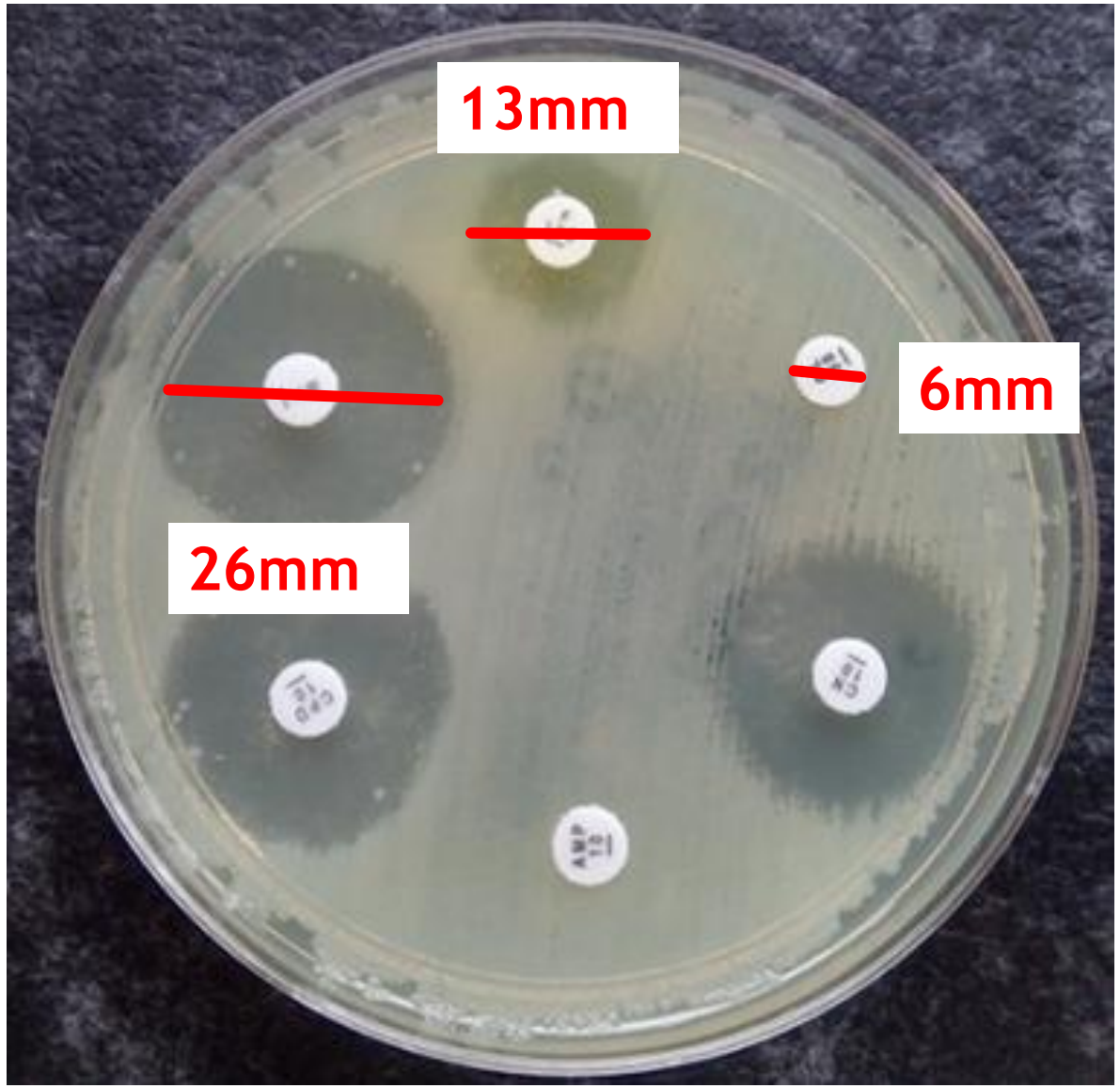
Background Methods: Broth Microdilution



Minimum Inhibitory Concentration (MIC)

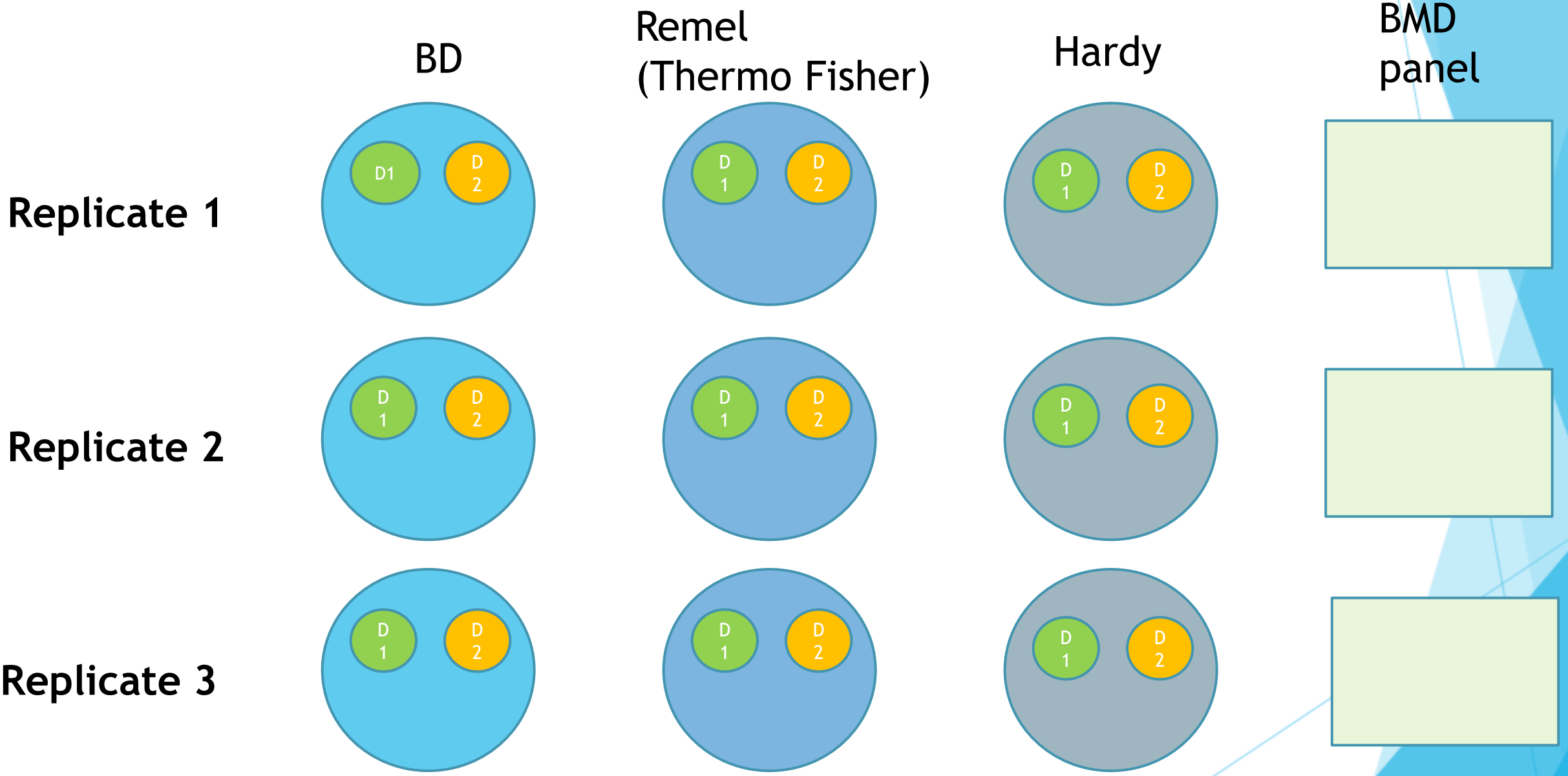
Shams et al., 2021

Background Methods: Disk Diffusion



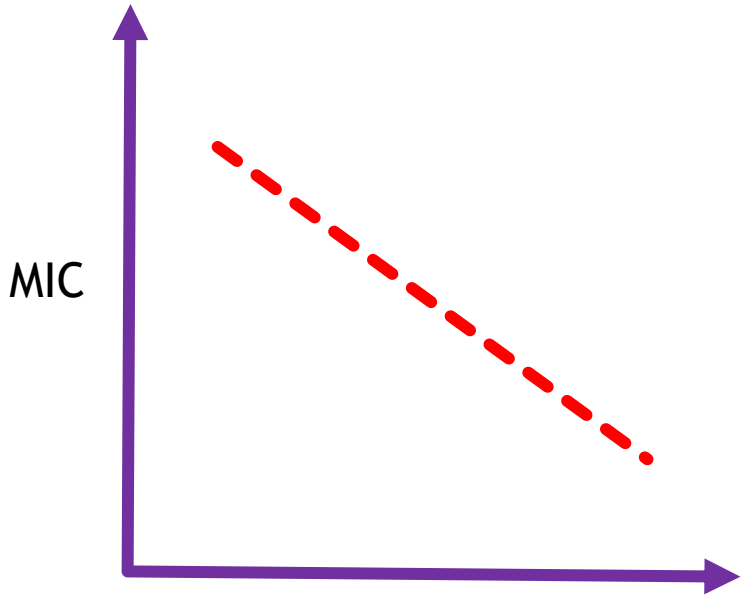
Measure the zone diameter

For each isolate: 3 media and 2 disks will be tested



QC set up each time an experiment is run

Minocycline Disk Diffusion Breakpoint

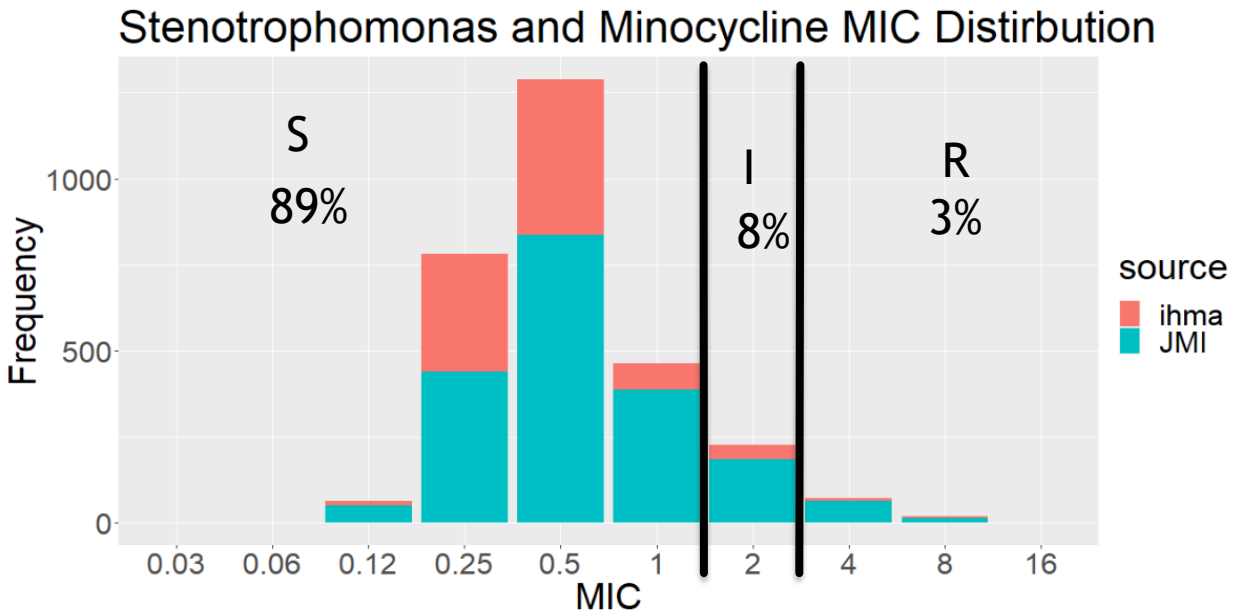


MIC

	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
8				1	5																				
4	8	1	9	7	3	16	6	13	22	14	13	1	7	1	1										
2			1	11		18	6	7	18	22	15	9	16	6	9	2	2	5	1	6	1	4			
1						4	2	5	12	28	50	44	37	32	36	26	13	11	4	4					
0.5							2	8	6	9	17	28	29	38	53	38	40	34	28	22	6	4	5	4	
0.25											2	8	7	22	16	22	17	40	30	20	6	8	6		2
≤0.125													1	4	7	9	8	16	13	9	2	5	2	2	

Disk Diffusion Zone Size

Error-Rate Bounded Method



Because we split the wild type population

- we tolerate a higher error rate with susceptibility testing
- Use M23 Error-Rate Bounded Method

CLSI M23 Document

6.3 Error-Rate Bounded Method for Selecting Disk Diffusion Breakpoints Based on Comparison With Dilution Test Results

6.3.1 * Breakpoints and Discrepancy Rates

Minocycline Disk Diffusion Breakpoint

8				1	5																				
4	8	1	9	7	3	16	6	13	22	14	13	1	7	1	1										
2			1	11		18	6	7	18	22	15	9	16	6	9	2	2	5	1	6	1	4			
1						4	2	5	12	28	50	44	37	32	36	26	13	11	4	4					
0.5							2	8	6	9	17	28	29	38	53	38	40	34	28	22	6	4	5	4	
0.25											2	8	7	22	16	22	17	40	30	20	6	8	6		2
≤0.125													1	4	7	9	8	16	13	9	2	5	2	2	
	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40

Breakpoint
≤ 20 is Resistant
21-25 is Intermediate
≥ 26 is Susceptible

Analysis – meets CLSI requirements (6.3.1)

- 47% (589/1250) are within one dilution of the intermediate range

MIC Range 1-dilution intermediate	Number in MIC Range	VME	ME	MI
≥I high +2	6	0/6 (0%)	N/A	0/6 (0%)
I high +1 to I low -1	589	23/589 (3.4%)	0/589 (0%)	210/589 (35.6%)
≤I low -2	655	N/A	0/655 (0%)	25/655 (3.8%)
Total	1250	23/1250 (1.8%)	0/1250 (0%)	235/1250 (18.8%)

Table 7. Guideline for Acceptable Discrepancy Rates (With Intermediate Ranges)*

MIC Range		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	< 2%	< 5%

Note: 70% of VMEs are from one media type

Antimicrobial Agent	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	
β-LACTAM COMBINATION AGENTS								
Ticarcillin-clavulanate*	–	–	–	–	≤ 16/2	32/2–64/2	≥ 128/2	
CEPHEMS (PARENTERAL) (Including cephalosporins I, II, III, and IV. Please refer to Glossary I.)								
Cefiderocol	30 µg	≥ 15	–	–	≤ 1	–	–	**(3)** Breakpoints are based on PK/PD properties, MIC distributions, and limited clinical data. **(4)** The accuracy and reproducibility of cefiderocol testing results by disk diffusion and broth microdilution are markedly affected by iron concentration and inoculum preparation and may vary by disk and media manufacturer. Depending on the type of variance observed, false-resistant or false-susceptible results may occur. Testing subsequent isolates is encouraged. Discussion with prescribers and antimicrobial stewardship members regarding the potential for inaccuracies is recommended.
TETRACYCLINES								
Minocycline	30 µg	**≥ 26**	**21–25**	**≤ 20**	**≤ 1**	**2**	**≥ 4**	
FLUOROQUINOLONES								
Levofloxacin	5 µg	≥ 17	14–16	≤ 13	≤ 2	4	≥ 8	**(5)** ***Rx:*** Levofloxacin should not be used alone for antimicrobial therapy.
FOLATE PATHWAY ANTAGONISTS								
Trimethoprim-sulfamethoxazole	1.25/23.75 µg	≥ 16	11–15	≤ 10	≤ 2/38	–	≥ 4/76	**(6)** ***Rx:*** **Trimethoprim-sulfamethoxazole should not be used alone for antimicrobial therapy.**
PHENICOLS								
Chloramphenicol*	–	–	–	–	≤ 8	16	≥ 32	**(7)** Not routinely reported on organisms isolated from the urinary tract.

New CLSI Breakpoints

- Removed Ceftazidime
- Updated Minocycline
- Comment for Levofloxacin and Trimethoprim-sulfamethoxazole
  - Should not be used alone for antimicrobial therapy
  - Matches IDSA 2023 treatment guidelines

If you want to read more!

Current Infectious Disease Reports (2024) 26:47–55
https://doi.org/10.1007/s11908-024-00830-2

ANTIMICROBIAL DEVELOPMENT AND DRUG RESISTANCE (KC CLAEYS AND J SMITH, SECTION EDITORS)

Check for updates

Long Story Short: Establishing Breakpoints for Antimicrobials and 2023 Updates

Morgan L. Bixby[1] · Dina Zheng[1] · Elizabeth B. Hirsch[1]

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Questions?

Minocycline Disk Diffusion Thank You!

- Darcie Carpenter, Ph.D. Director at ihma
- Dana Dressel, Associate Lab Director at ihma
  - MIC distribution data
  - Stenotrophomonas isolates
- Karen Fischbein, Senior Scientist BD Life Sciences
- Andrea Ferrell, Senior R&D Manager BD Life Sciences
  - Minocycline disk diffusion reagents
  - BMD reagents
- Andre Hsiung, M(ASCP), MBA, CSO at Hardy Diagnostics
  - Minocycline disk diffusion reagents
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