Using Clinical Breakpoints to Improve Antimicrobial Resistance Detection

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Disclosures

- Speakers Bureau:
  - BD Integrated Diagnostic Solutions
- Research Contracts:
  - BD Integrated Diagnostic Solutions, Accelerate Diagnostics, OpGen Inc., Affinity Biosensors, Qiagen
- Speaker's Bureau
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- Research Collaborators:
  - Ares-Genetics, CosmosID, IDbyDNA, Illumina
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- CLSI AST Subcommittee voting member & member of the CAP Microbiology committee

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Objectives

1. Define the ongoing pandemic of antimicrobial resistance

2. Discuss how we can address the ongoing pandemic in the Clinical Microbiology Laboratory

3. Demonstrate the need to apply updated clinical breakpoints to interpret antimicrobial susceptibility testing results

Let's Rewind to March, 1942

Source: National Museum of American History

- Mrs. Anne Miller of New Haven, Connecticut was near death due to a bloodstream infection
  - Administered an experimental drug: penicillin
  - A drug that was discovered by Alexander Flemming in 1928
- 1st person to be saved by antibiotics
- Widely used in World Word II for surgical and wound infections

www.nytimes.com/1999/06/09/us/anne-miller-90-first-patient-who-was-saved-by-penicillin.html

1960's: "[It] is time to close the book on infectious diseases and declare the war against pestilence won"
– William H Stewart (US Surgeon General)

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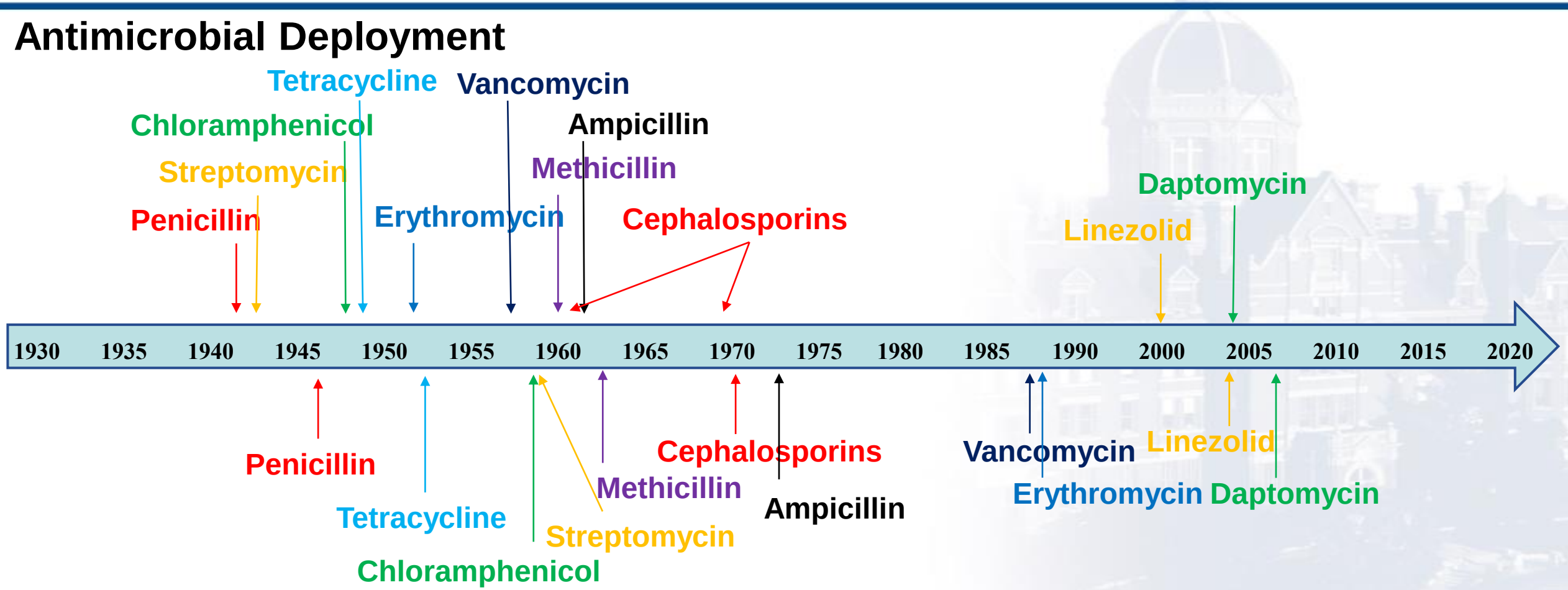
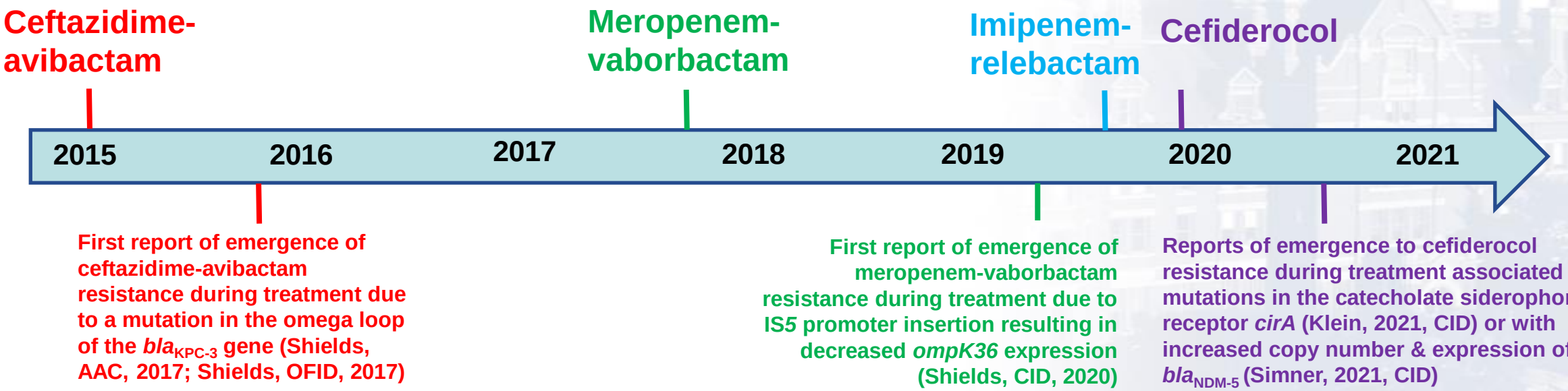
The Bugs are Always Smarter Than the Drugs



The Bugs are Always Smarter Than the Drugs

Antimicrobial Deployment



Antimicrobial Resistance Detected

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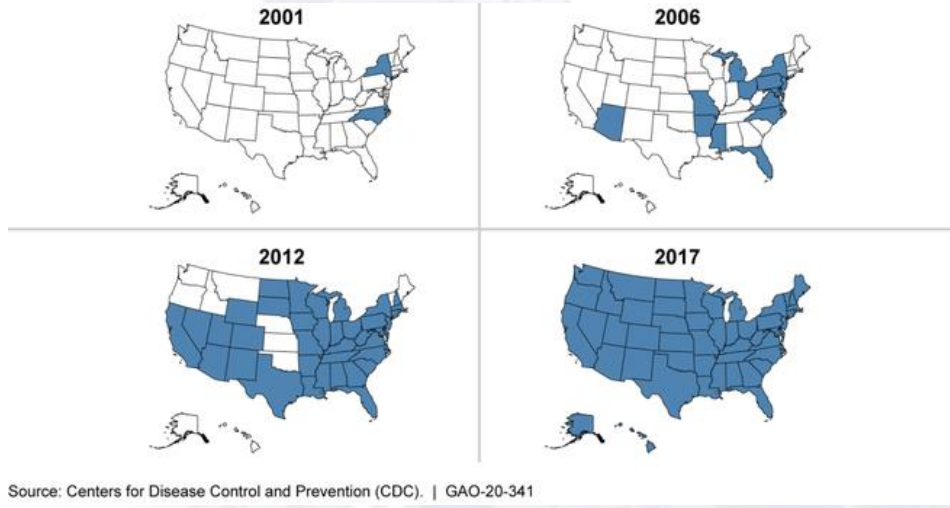
The Threat of Antimicrobial Resistance

- One of the biggest global public health threats
  - Recognized by many international bodies
- Leading cause of death
  - Highest burden in resource limited settings
- Precise magnitude is not well understood
  - 2019: 4.95 million deaths associated with AMR, including 1.27 million deaths attributed to bacterial AMR
- Global collective action is required
  - Improve Global Surveillance for Antimicrobial Resistance
  - Promote New, Rapid Diagnostics to Reduce Unnecessary Use of Antimicrobials



Tracking the spread of *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Enterobacterales* a type of carbapenem-resistant *Enterobacterales* (CRE) by the CDC.

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Antimicrobial Resistance Collaborators, Lancet, 2022. O'Neil, The Review on Antimicrobial Resistance, 2016; Burnham et al, ICHE, 2019; https://www.gao.gov/products/GAO-20-341.

The Post-Antibiotic Era

- “Stop referring to a coming post-antibiotic era – it’s already here”
  – Robert Redfield, M.D.

www.cdc.gov/DrugResistance/Biggest-Threats.html

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We Are Facing It in the Microbiology Laboratory

Susceptibility

	Klebsiella pneumoniae	
	MIC	BP
Amikacin		>128 ug/mL
Ampicillin	>16 ug/mL R	
Ampicillin + Sulbactam	>16/8 ug/mL R	
Aztreonam	>16 ug/mL R	
Cefazolin	>16 ug/mL R	
Cefepime		>16 ug/mL
Cefoxitin	>16 ug/mL R	
Ceftazidime		
Ceftriaxone		
Ciprofloxacin		
Ertapenem		
Gentamicin		
Meropenem		
Piperacillin + Tazobactam		
Tetracycline		
Tigecycline		
Tobramycin		
Trimethoprim + Sulfamethoxazole		

Susceptibility

Amikacin		
Amoxicillin-Clavulanate		
Ampicillin		
Ampicillin-Sulbactam		
Aztreonam		
Cefazolin		
Cefepime		
Cefiderocol		
Ceftazidime		
Ceftazidime-Avibactam		
Ceftriaxone		
Cefuroxime	>16 ug/mL R	
Ciprofloxacin	>2 ug/mL R	
Ertapenem	>2 ug/mL R	
Fosfomycin		S
Gentamicin	<=2 ug/mL S	
Meropenem	>8 ug/mL R	
Meropenem-Vaborbactam	>16/8 ug/mL R	
Nitrofurantoin	32 ug/mL S	
Piperacillin-Tazobactam	>64/4 ug/mL R	
Tetracycline	>8 ug/mL R	
Tigecycline	>8 ug/mL R	
Tobramycin	>8 ug/mL R	
Trimethoprim-Sulfamethoxazole	>2/38 ug/mL R	

Susceptibility

	Pseudomonas aeruginosa		
	MIC	BP	KB
Amikacin	>32 ug/mL R		
Ampicillin			
Aztreonam	>16 ug/mL R		
Cefepime	>16 ug/mL R		
Cefiderocol			R
Ceftazidime	>16 ug/mL R		
Ceftazidime-Avibactam	>8/4 ug/mL R		
Ceftolozane-Tazobactam	>8/4 ug/mL R		
Ciprofloxacin	>2 ug/mL R		
Clindamycin			
Colistin		<=1 ug/mL I[1]	
Daptomycin			
Erythromycin			
Gentamicin	>8 ug/mL R		
Imipenem-relebactam			R
Linezolid			
Meropenem	>8 ug/mL R		
Oxacillin			
Piperacillin-Tazobactam	>64/4 ug/mL R		
Quinupristin-Dalfopristin			
Tetracycline			
Tobramycin	>8 ug/mL R		

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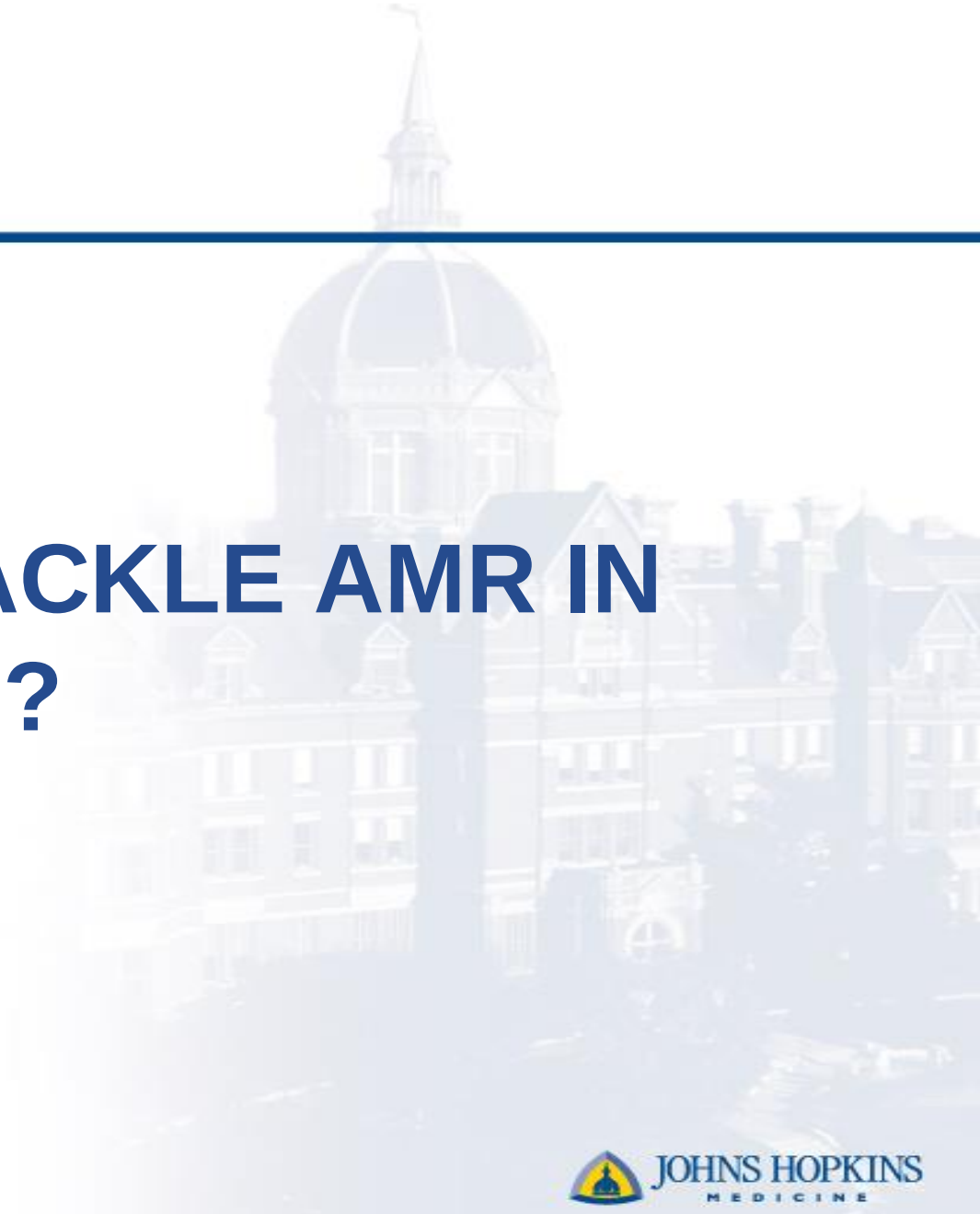
WHAT CAN WE DO TO TACKLE AMR IN LABORATORY MEDICINE?



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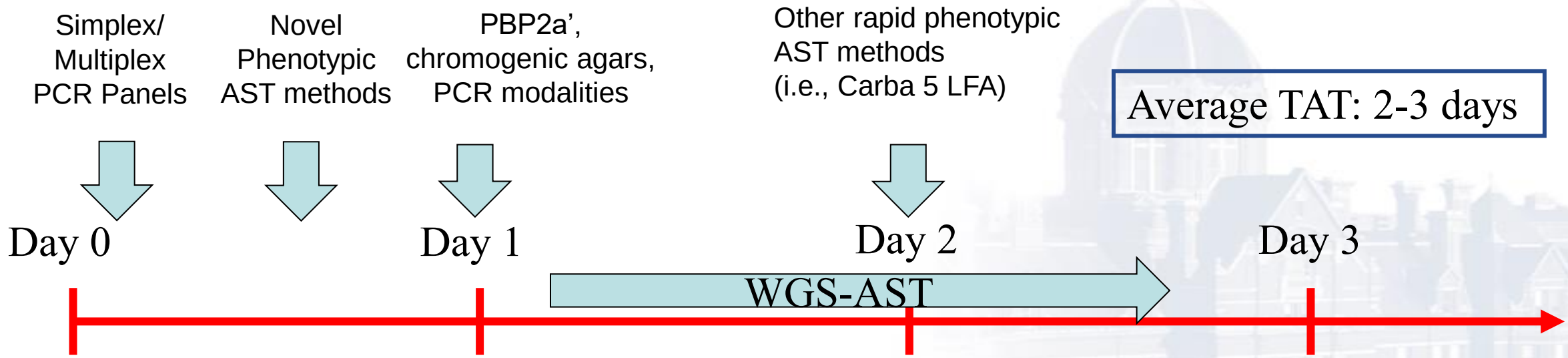
Current Paradigm for ID & AST



Collection and plating of specimen in the lab

Isolation of your organism on solid media
- MALDI-TOF MS ID
- Set up of AST panels

Standard AST panel results available
- Setup of additional antimicrobials

Additional AST results

Empiric Treatment | **Narrowed Treatment** | **Targeted Treatment**

AST: antimicrobial susceptibility testing; ID: identification; whole genome sequencing-AST: WGS to predict AST

Breakpoints = Stop Light Approach to Guide Therapy

- **The most critical step in AST involves interpretation of results!**
  - **Susceptible (S):** Isolates are inhibited by usually achievable concentrations of drug and dosing for that particular site of infection
    - **Resulting in likely clinical efficacy**
  - **Susceptible-Dose Dependent (SDD):** MIC/zone diameter for the isolate is dependent on the dosing regimen that is used in this patient
    - **Increasing the dose (if PK/PD parameters allow) increases the likelihood of clinical efficacy**
  - **Intermediate (I):** MICs/zone diameters for that isolate approach the usually achievable concentration of drug
    - Addresses ambiguity in testing methods
    - **Response may be lower than for susceptible isolates**
  - **Resistant (R):** Isolates are not inhibited by usually achievable concentrations of drug
    - **Resulting in a likely unfavorable outcome**

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Who Sets Breakpoints in the United States?

- Set by 2 groups in the U.S.:
  - Clinical Laboratory Standards Institute (CLSI)
    - Global standard
    - Published annually in the M100 standard
      - https://clsi.org/standards/products/free-resources/access-our-free-resources/
  - U.S. Food and Drug Administration (FDA)'s Center for Drug Evaluation and Research (CDER)
    - Prior to 2017: Published in the drugs prescribing information
    - 2017: Published on the FDA STIC website
      - https://www.fda.gov/drugs/development-resources/fda-recognized-antimicrobial-susceptibility-test-interpretive-criteria
  - Outside the U.S.:
    - European Committee on Antimicrobial Susceptibility Testing (EUCAST)
    - U.S. Committee of Antimicrobial Susceptibility Testing: USCAST affiliated with & reports to EUCAST

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21st Century Cures Act – Changes to FDA BP Recognition

Humphries, Ferraro & Hindler, Impact of 21st Century Cures Act on Breakpoints and Commercial Antimicrobial Susceptibility Testing Test Systems: Progress and Pitfalls, JCM, 2018.

1972 CLSI initiates publication of breakpoints (BP)
1980-1990s FDA-recognized BP are printed in the drug label
Pre-2006 **FDA permits AST clearance with CLSI and/or FDA BP**
2005 CLSI votes to approve revision of cephalosporin BP for Enterobacterales
2006 **FDA enforces restrictions of cAST labeling to include only FDA BP (list 1 organisms)**
2006 CLSI submits citizen petition to FDA to allow CLSI BP for cAST clearance
2007 FDA rejects CLSI petition
2007 FDAAA enacted, allowing FDA process to update BP in drug label
2009 FDA publishes guidance for industry on approach to comply with FDAAA
2010 CLSI publishes revised Enterobacterales BPs
2013 FDA updates drug label for Enterobacterales
2015 CLSI publishes ECV if insufficient data are available for clinical breakpoints
2016 **21st Century Cures Act Signed into law**
2017 **FDA establishes AST Interpretive Criteria website, recognizing CLSI BP**

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cAST: commercial AST device

Example From the FDA STIC Website:
Ciprofloxacin Oral, Injection Products

	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (zone diameter in mm)		
Pathogen	S	I	R	S	I	R
Enterobacteriaceae	M100 standard is recognized					
Salmonella spp.	M100 standard is recognized					
Pseudomonas aeruginosa	M100 standard is recognized					
Staphylococcus spp.	M100 standard is recognized					
Enterococcus spp.	M100 standard is recognized					
Haemophilus influenzae and *parainfluenzae*	M100 standard is recognized					
Neisseria gonorrhoeae	M100 standard is recognized					
Streptococcus pneumoniae	≤1	2	≥4	≥21	16-20	≤15
Streptococcus spp. β-Hemolytic Group	≤1	2	≥4	≥21	16-20	≤15
Bacillus anthracis	M45 standard is recognized			-	-	-
Yersinia pestis	M45 standard is recognized			-	-	-

- Allows the FDA to more rapidly update breakpoints
- Recognize most CLSI breakpoints but not all
  - M100, M45, M62 and M60
- Automated AST device manufacturers are required by current law to apply FDA breakpoints to the data generated by their systems at the time of clearance
  - Not required to update BPs after FDA clearance
  - Most automated AST labs rely on CLSI standards to inform clinical practice

https://www.fda.gov/drugs/development-resources/ciprofloxacin-oral-injection-products

Many New CLSI Breakpoint Revisions Since 2019

Antimicrobial Agents	Organisms	FDA Recognized ?
Amoxicillin-clavulanate	*Haemophilus influenzae & H. parainfluenzae*	No
Cefiderocol	Enterobacterales (disk only), *Acinetobacter baumannii* (disk only), *Stenotrophomonas maltophilia*	Yes, No, No
Ceftaroline	*Staphylococcus aureus*	No
Ceftolozane-tazobactam	Enterobacterales (disk only)	Yes
Ciprofloxacin, levofloxacin	Enterobacterales, *Pseudomonas aeruginosa*	Yes
Colistin, polymyxin B (MIC only)	*P. aeruginosa*, *Acinetobacter* spp.	No
Daptomycin (MIC only)	*Enterococcus* spp.	Y, *E. faecalis*; No, all other *Enterococcus* spp., including no FDA BP for *E. faecium*
Lefamulin	*H. influenzae, Streptococcus pneumoniae* (disk only)	No
Oxacillin	*Staphylococcus epidermidis* (disk only), *Staphylococcus* spp. except *S. aureus* and *S. lugdunensis* (MIC only)	Yes
Piperacillin-tazobactam	Enterobacterales	No

M100-S32, CLSI, 2022. FDA STIC website.

Why Do Breakpoints Need To Be Changed?

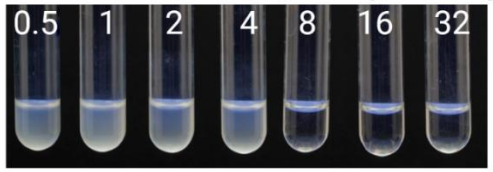
- Initial BP:
  - Extensive studies are performed to determine breakpoints
  - Based on CLSI M23 guidance

- Over time, signals may appear that the breakpoints no longer meet clinical need
  - Investigation is performed to see if a breakpoint revision is in order

M23, CLSI, 5th Edition, 2018. Humphries et al, Impact of 21st Century Cures Act on Breakpoints and Commercial Antimicrobial Susceptibility Testing Test Systems: Progress and Pitfalls, JCM, 2018.

Why Is It Important to Apply Updated Breakpoints?

Antimicrobial Susceptibility Testing



MIC: 8 ug/ml

Ceftriaxone

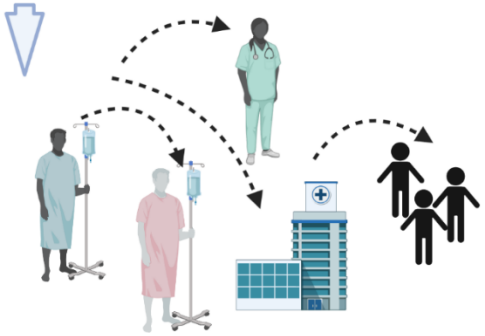
Interpreting MIC Result Using Obsolete Breakpoints

	Susceptible	Intermediate	Resistant
Ceftriaxone	≤ 8	16-32	≥64

Reporting results in the patient chart

Antimicrobial	Interpretation
Amikacin	S
Ampicillin	R
Ampicillin-Sulbactam	R
Cefazolin	R
Cefepime	SDD
Ceftriaxone	**S**
Ciprofloxacin	S
Ertapenem	S
Gentamicin	S
Meropenem	S
Piperacillin-tazobactam	S
Tobramycin	S
Trimethoprim-Sulfamethoxazole	S

Ineffective antimicrobials perscribed



Further transmission of AMR

Interpreting MIC Result Using Current Breakpoints

	Susceptible	Intermediate	Resistant
Ceftriaxone	≤ 1	2	≥4

Reporting results in the patient chart

Antimicrobial	Interpretation
Amikacin	S
Ampicillin	R
Ampicillin-Sulbactam	R
Cefazolin	R
Cefepime	SDD
Ceftriaxone	**R**
Ciprofloxacin	S
Ertapenem	S
Gentamicin	S
Meropenem	S
Piperacillin-tazobactam	S
Tobramycin	S
Trimethoprim-Sulfamethoxazole	S

Effective antimicrobials persecribed with recovery of the patient.

CAP Supplemental Questions: D-B 2019

"For MIC testing, has your laboratory updated breakpoints to current CLSI/FDA breakpoints by performing in-lab validation/verification studies?"

2,296 laboratories in June 2019 (1,873 U.S. laboratories and 423 international laboratories)

Supplemental Questions, cont'd

Organism Group	Antimicrobial agent	Current Breakpoint (µg/mL) S	I	R	Previous Breakpoint (µg/mL) S	I	R	Answer	Primary test system used in your laboratory for AST*
Enterobacteriaceae	Ceftazidime	≤ 4	8	≥ 16	≤ 8	16	≥ 32	010 ○ 100 Yes ○ 101 No ○ 695 Not tested ○ 696 Unsure/Other: 020	030 ○ 1685 Agar Dilution ○ 1465 BD Phoenix ○ 1686 Broth Tube or Macrodilution ○ 1181 Gradient diffusion strips (eg, Etest, MTS) ○ 1035 M2 (Kirby-Bauer) ○ 1021 Microdilution - In House Prepared ○ 1093 MicroScan ○ 1690 Sensititre (TREK) ○ 1703 Vitek ○ 2179 Vitek 2 ○ 0010 Other, specify: 040
Enterobacteriaceae	Meropenem	≤ 1	2	≥ 4	≤ 4	8	≥ 16	050 ○ 100 Yes ○ 101 No ○ 695 Not tested ○ 696 Unsure/Other: 060	070 ○ 1685 Agar Dilution ○ 1465 BD Phoenix ○ 1686 Broth Tube or Macrodilution ○ 1181 Gradient diffusion strips (eg, Etest, MTS) ○ 1035 M2 (Kirby-Bauer) ○ 1021 Microdilution - In House Prepared ○ 1093 MicroScan ○ 1690 Sensititre (TREK) ○ 1703 Vitek ○ 2179 Vitek 2 ○ 0010 Other, specify: 080

Supplemental Questions, cont'd

Organism Group	Antimicrobial agent	Current Breakpoint (µg/mL) S	I	R	Previous Breakpoint (µg/mL) S	I	R	Answer	Primary test system used in your laboratory for AST*
Pseudomonas aeruginosa	Piperacillin-tazobactam	≤ 16	32 - 64	≥ 128	≤ 64	-	≥ 128	010 ○ 100 Yes ○ 101 No ○ 695 Not tested ○ 696 Unsure/Other: 020	030 ○ 1685 Agar Dilution ○ 1465 BD Phoenix ○ 1686 Broth Tube or Macrodilution ○ 1181 Gradient diffusion strips (eg, Etest, MTS) ○ 1035 M2 (Kirby-Bauer) ○ 1021 Microdilution - In House Prepared ○ 1093 MicroScan ○ 1690 Sensititre (TREK) ○ 1703 Vitek ○ 2179 Vitek 2 ○ 0010 Other, specify: 040
Acinetobacter baumannii	Imipenem	≤ 2	4	≥ 8	≤ 4	8	≥ 16	050 ○ 100 Yes ○ 101 No ○ 695 Not tested ○ 696 Unsure/Other: 060	070 ○ 1685 Agar Dilution ○ 1465 BD Phoenix ○ 1686 Broth Tube or Macrodilution ○ 1181 Gradient diffusion strips (eg, Etest, MTS) ○ 1035 M2 (Kirby-Bauer) ○ 1021 Microdilution - In House Prepared ○ 1093 MicroScan ○ 1690 Sensititre (TREK) ○ 1703 Vitek ○ 2179 Vitek 2 ○ 0010 Other, specify: 080

Answer Options:

- Yes
- No
- Not tested
- Unsure/Other

Responses were collated in the D-A 2020 participant summary

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Open Forum Infectious Diseases

MAJOR ARTICLE

Raising the Bar: Improving Antimicrobial Resistance Detection by Clinical Laboratories by Ensuring Use of Current Breakpoints

Patricia J. Simner,[1] Carol A. Rauch,[2] Isabella W. Martin,[3] Kaede V. Sullivan,[4] Daniel Rhoads,[5] Robin Rolf,[6] Rosemary She,[7] Rhona J. Souers,[6] Christina Wojewoda,[8] and Romney M. Humphries[9]

[1]Johns Hopkins Medical Institute, Baltimore, Maryland, USA, [2]Vanderbilt University, Nashville, Tennessee, USA, [3]Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire, USA, [4]Temple University Hospital, Philadelphia, Pennsylvania, USA, [5]Cleveland Clinic, Cleveland, Ohio, USA, [6]College of American Pathologists, Chicago, Illinois, USA, [7]University of Southern California, Los Angeles, California, USA, [8]University of Vermont Medical Center, Burlington, Vermont, USA, and [9]Vanderbilt University Medical Center, Nashville, Tennessee, USA

Evaluated 7 Organism/Antimicrobial Agent Combinations

Organism/Organism Group	Antimicrobial Agent	Year Updated by CLSI
Enterobacterales	Ceftazidime	2010
Enterobacterales	Ceftriaxone	2010
Enterobacterales	Ciprofloxacin	2019
Enterobacterales	Levofloxacin	2019
Enterobacterales	Meropenem	2010
Pseudomonas aeruginosa	Piperacillin-tazobactam	2012
Acinetobacter baumannii	Imipenem	2014

Response Rate

- 1,490 laboratories (65%) provided responses to the supplemental questionnaire
  - 1,258 (67%) from the U.S. and 232 (55%) from international locations

AST Methods Applied By Labs

Table 2. Use of automated antimicrobial susceptibility test methods among participant laboratories in this study.

Organism	Antimicrobial Agent	United States		International	
		Total no. of labs	% Automated method	Total no. of labs	% Automated method
Enterobacterales	Ceftazidime	1018	98.6	194	93.3
Enterobacterales	Ceftriaxone	1101	98.8	180	92.2
Enterobacterales	Ciprofloxacin	1022	97.4	198	92.9
Enterobacterales	Levofloxacin	977	97.1	153	88.9
Enterobacterales	Meropenem	944	97.4	180	91.7
Pseudomonas aeruginosa	Piperacillin/tazobactam	1029	96.7	186	91.4
Acinetobacter baumannii	Imipenem	743	95.3	154	89.5

≥90% of laboratories apply an automated AST system as their primary AST method

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Current Breakpoint Usage

Table 3. Current breakpoint usage by laboratory location (U.S. versus international)

Organism	Antimicrobial Agent	U.S.		International		
		Total no. of labs	Current Breakpoints No. (%)	Total no. of labs	Current Breakpoints No. (%)	Difference between U.S. and International *P* value
Enterobacterales	Ceftazidime	1046	620 (59.3)	201	164 (81.6)	<0.001
Enterobacterales	Ceftriaxone	1124	694 (61.7)	186	153 (82.3)	<0.001
Enterobacterales	Ciprofloxacin	1058	312 (29.5)	206	122 (59.2)	<0.001
Enterobacterales	Levofloxacin	1019	306 (30.0)	160	90 (56.3)	<0.001
Enterobacterales	Meropenem	982	610 (62.1)	187	149 (79.7)	<0.001
Pseudomonas aeruginosa	Piperacillin/ tazobactam	1064	559 (52.5)	197	150 (761)	<0.001
Acinetobacter baumannii	Imipenem	784	367 (46.8)	182	139 (76.4)	<0.001

Use of current breakpoints:

- ~30 – 62% of U.S. laboratories
- 56 – 82% of international laboratories
  - (p<0.001)

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Current Breakpoint Usage by Automated AST System

Table 4. Use of current breakpoint by laboratory location and automated AST system

Organism	Agent	System	U.S.[a]		International[b]	
			Total no. of labs	Current breakpoint No. (%)	Total no. of labs	Current breakpoint No. (%)
Enterobacterales	Ceftazidime	Phoenix	63	49 (77.8)	36	30 (83.3)
		MicroScan	347	182 (52.4)	19	15 (78.9)
		Vitek 2	572	354 (61.9)	122	102 (83.6)
Enterobacterales	Ceftriaxone	Phoenix	70	62 (88.6)	37	34 (91.9)
		MicroScan	360	214 (59.4)	14	10 (71.4)
		Vitek 2	638	391 (61.3)	111	91 (82.0)
Enterobacterales	Ciprofloxacin	Phoenix	63	22 (34.9)	35	23 (65.7)
		MicroScan	332	50 (15.1)	19	9 (47.4)
		Vitek 2	579	204 (35.2)	127	80 (63.0)
Enterobacterales	Levofloxacin	Phoenix	63	23 (36.5)	33	20 (60.6)
		MicroScan	307	51 (16.6)	18	10 (55.6)
		Vitek 2	555	195 (35.1)	81	45 (55.6)
Enterobacterales	Meropenem	Phoenix	65	57 (87.7)	36	33 (91.7)
		MicroScan	322	180 (55.9)	19	16 (84.2)
		Vitek 2	507	321 (63.3)	107	82 (76.6)
Pseudomonas aeruginosa	Piperacillin/ tazobactam	Phoenix	65	55 (84.6)	35	31 (88.6)
		MicroScan	353	189 (53.5)	19	14 (73.7)
		Vitek 2	553	266 (48.1)	113	86 (76.1)
Acinetobacter baumannii	Imipenem	Phoenix	49	38 (77.6)	33	29 (87.9)
		MicroScan	258	115 (44.6)	17	12 (70.6)
		Vitek 2	381	161 (42.3)	101	79 (78.2)

The WHY? Reasons Provided for Not Updating Breakpoints

Table 5. Comment summary for laboratories unsure of the breakpoints they applied or if they used obsolete breakpoints by location

Reason	All n=918 (%)	U.S. n=835 (%)	International n=83 (%)
Efforts to use or implement current breakpoints underway	**405 (44.1)**	**372 (44.6)**	**33 (39.8)**
Plan to update, in progress	188 (46.4)	181 (48.7)	7 (21.2)
Not applicable because do not report, use alternate method, or send to reference lab	128 (31.6)	102 (27.4)	26 (78.8)
Changing panels or instruments	55 (13.6)	55 (14.8)	0 (0.0)
Validation testing not completed but underway	34 (8.4)	34 (9.1)	0 (0.0)
Ongoing use of obsolete breakpoints, no current revisions in progress	**513 (55.9)**	**463 (55.4)**	**50 (60.2)**
Manufacturer-related issues	263 (51.3)	232 (50.1)	31 (62.0)
Resource limitations of staff, time, organisms, guidance, laboratory information system issues, cost	120 (23.4)	112 (24.2)	8 (16.0)
Overlooked or unaware of breakpoint change or need to update	68 (13.3)	57 (12.3)	11 (22.0)
Facility does not support	30 (5.8)	30 (6.5)	0 (0.0)
Not done, under review for a variety of concerns	28 (5.4)	28 (6.0)	0 (0.0)
Do not want or intend to update	4 (0.8)	4 (0.8)	0 (0.0)

Study Conclusions

- These data demonstrate a significant gap in the ability to detect antimicrobial resistance in the U.S., and to a lesser extent internationally

- Improved application of current breakpoints by clinical laboratories will require combined action from regulatory agencies, laboratory accreditation groups and device manufacturers

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What is Driving This?

Stakeholder	Regulatory Agencies (eg, CMS, FDA)	Industry	Clinical and Public Health Laboratories	Accreditation Bodies
Barriers	• Lack of regulatory oversight of BPs after initial clearance of the device • Little knowledge of BPs applied by devices after initial clearance	• Large financial burden to update BPs for AST devices • Significant opportunity cost, slowing the development of more rapid and accurate tests	• Misconceptions about BPs applied by automated AST systems • Lack of awareness of the need to update clinical BPs • Lack of resources & support to update BPs	• Lack of oversight on BPs used to interpret AST results

BP: breakpoint

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What is the Process Outside the US?

- Manufacturers may update breakpoints on AST devices without seeking additional formal approval from regulatory bodies

- European Medicines Agency (EMA) granted breakpoint setting authority to EUCAST -> single, unified set of breakpoints which further streamline the process

What Are the Solutions & Opportunities?

Stakeholder	Government (eg, CMS, FDA)	Industry	Clinical and Public Health Laboratories	Accreditation Bodies
Potential Solutions & Opportunities	• Develop a framework that requires AST device manufacturers to apply updated clinical BP to their devices after initial clearance of the device • Establish a community collaborative	• Develop a streamlined regulatory process to update AST device breakpoints within a defined period of a BP being updated • Allow the application of SDO and FDA BPs or apply ISO 20776-1 standard	• Create educational tools and resources to relieve the burden of implementing updated BPs on clinical laboratories • Advocate for additional resources and support from all levels within each individual hospital system, regional and state public health	• Develop requirements for clinical laboratories to apply updated clinical breakpoints (similar to CAP checklist items)

BP: breakpoint

CAP Checklist MIC.11380 (Revised)

REVISED* ***09/22/2021***

MIC.11380 **Antimicrobial Susceptibility Test Interpretation Criteria** **Phase II**

For antimicrobial susceptibility testing systems, there are written criteria for determining and interpreting minimal inhibitory concentration (MIC) or zone diameter sizes as susceptible, intermediate, resistant, non-susceptible, or susceptible dose-dependent. These criteria are reviewed annually.

- **Key points:**
  - You must know which breakpoints are in use in your laboratory.
  - You may choose to use CLSI, EUCAST, or FDA breakpoints.
  - You must review the breakpoints applied by your laboratory annually.

Previously MIC.21930 (Susceptibility Test Endpoint Determination)

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CAP Checklist MIC.11385

***NEW** 09/22/2021

MIC.11385 Current Antimicrobial Susceptibility Test Interpretation Breakpoints Phase I

Effective January 1, 2024, the laboratory uses current breakpoints for interpretation of antimicrobial minimum inhibitory concentration (MIC) and disk diffusion test results, and implements new breakpoints within three years of the date of official publication by the FDA or other standards development organization (SDO) used by the laboratory.

- **Key points:**
  - Effective January 1, 2024 laboratory must use current breakpoints for MIC and disk diffusion tests.
  - Minimum requirement = FDA breakpoint (US laboratories); may also use current CLSI or EUCAST BPs.
  - UNACCEPTABLE to use breakpoints no longer recognized by CLSI, EUCAST, FDA .

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The CAP Process

Identify (MIC 11380)

Determine which breakpoints are applied by lab for MIC and disk diffusion tests

Document this as your “baseline”

Update (MIC 11385)

Identify obsolete breakpoints.

Make plan and update.

Maintain (MIC 11380 & 11385)

Perform & document annual review

Identify updates in breakpoints.

Implement within 3 years of FDA.

Jean Patel & Romney Humphries, CAP-CLSI Webinar, 2022.

Many Resources Coming Down the Pipeline

- CAP Microbiology Committee, CLSI Breakpoint Implementation Ad Hoc Committee, APHL and ASM are working on resources to address the new CAP checklist item and education on updating breakpoints
  - CLSI Breakpoints in Use Template – Free!
  - CLSI M100 Breakpoint Addition/Revision Tables
  - CAP FAQs
  - Breakpoint Implementation Toolkits
  - Educational Webinars

CLSI Breakpoints In Use Template

Freely available

Includes instructions, template & demo data

Notes About "Breakpoints in Use" CLSI

The instructions, Breakpoints (BPs) in Use Template, and examples ("Demo Data") provided here are suggestions for documenting BPs in use. The template and examples can be downloaded by clicking the button below.

Access Here ▸

Each laboratory should edit the form or use terminology that differs from th

Procedure for completing "BPs in Use" Form:

1. Arrange a meeting with an appropriate IT staff member in your facility instrument software) BPs may be currently stored and applied at your into the LIS and/or EHR.
2. If using a commercial AST system, ask your system's AST technical rep breakpoints being applied on your system or refer to your instrument,
3. For drugs currently tested within your lab, compare BPs being used by Flag the BPs being used in your lab that differ from the current CLSI M
4. Cross-check BPs that are flagged in #3 with susceptibility test interpreti to see if CLSI BPs = FDA BPs.
   a. If CLSI BPs = FDA BPs but are different from those in use in your la Develop a plan for implementing updated BPs. This might inv program (ASP) team to prioritize updates (if multiple BP updat needs for the drug(s).
   b. If CLSI BPs ≠ FDA BPs: Meet with your ASP to discuss which BPs are appropriate for y
5. Develop a plan (including timeline) to update any BPs in use that do n STIC (BPs).

Notes about variables suggested in columns in the "BPs in Use template" sh

Column: Location of BP

Automated instruments likely house BPs that will automatically interpret M Disk diffusion measurements may be interpreted manually prior to entry int the SOP.

Disk diffusion measurements may be interpreted automatically in the LIS or Interpretive results for some drugs generated with an instrument may be ov LIS; in this case, source of BPs is likely referenced in the SOP.

Column: BP Matches Current M100 as of Date of Lab Review?

The current edition of M100 is the most recent edition listed on CLSI's website.

BPs listed match those published in the current edition of M100.

Column: BP Matches FDA STIC as of Date of Lab Review?

Current FDA BPs are found here.

BPs listed match those published on the FDA STIC website on the Date of Lab Review.

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Abbreviations

ASP	antimicrobial stewardship program
BPs	breakpoints
EHR	electronic health record where final laboratory reports are posted
LIS	laboratory information system
SOP	standard operating procedure (laboratory procedure)
STIC	susceptibility test interpretive criteria (FDA terminology for breakpo
ZD	zone diameter

CLSI Version 1.0. This was last updated on 9 Working Group.

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Antimicrobial Agent	Organism/Group	Test System	Interpretive Categories and MIC BPs (μg/mL) or Zone Diameter BPs (mm)				Location of BP (instrument/ LIS/SOP/EHR)	BP matches current M100 as of lab review date?	BP matches FDA STIC as of lab review date?	Date BPs implemented in lab	Date of lab review
			Susceptible, MIC ≤ or ZD ≥	Susceptible Dose-Dependent	Intermediate	Resistant, MIC ≥ or ZD ≤					
Cefepime	Enterobacterales	Commercial automated device	2	4-8	n/a	16	LIS	Yes	No	Pre-2021	5/12/2022
Cefepime	Enterobacterales	Disk diffusion	25	19-24	n/a	18	EHR	Yes	No	Pre-2021	5/12/2022
Cefepime	*P. aeruginosa*	Commercial automated device	8	n/a	16	32	LIS	Yes	No	Pre-2021	5/12/2022
Cefepime	*P. aeruginosa*	Disk diffusion	18	n/a	15-17	14	EHR	Yes	No	Pre-2021	5/12/2022
Ceftazidime	Enterobacterales	Commercial automated device	8	n/a	16	32	LIS	No	No	Pre-2021	5/12/2022
Ceftazidime	Enterobacterales	Disk diffusion	21	n/a	18-20	17	EHR	Yes	Yes	Pre-2021	5/12/2022
Ceftazidime	*P. aeruginosa*	Commercial automated device	8	n/a	16	32	LIS	Yes	No	Pre-2021	5/12/2022
Ceftazidime	*P. aeruginosa*	Disk diffusion	18	n/a	15/17	14	EHR	Yes	No	Pre-2021	5/12/2022

https://clsi.org/standards/products/microbiology/companion/bpiu/

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M100 Breakpoint Addition/Revision Table

CLSI Breakpoint Additions/Revisions Since 2010

Previous breakpoints can be found in the edition of M100 that precedes the document listed in the column labeled "Date of Addition/Revision (M100 edition)." For example, previous breakpoints for aztreonam are listed in M100-S19 (January 2009).

Antimicrobial Agent	Date of Addition/Revision (M100 edition)	Disk Diffusion Breakpoints		MIC Breakpoints		Comments
		New[a]	Revised[b]	New[a]	Revised[b]	
Enterobacterales						
Azithromycin	January 2015 (M100-S25)	X		X		*S. enterica* ser. Typhi only
	March 2021 (M100-Ed31)	X		X		*Shigella* spp. Previously assigned an ECV
Aztreonam	January 2010 (M100-S20)		X		X	
Cefazolin (parenteral)	January 2010 (M100-S20)				X	Removed disk diffusion breakpoints January 2010 (M100-S20)
	January 2011 (M100-S21)	X			X	
	January 2016 (M100-S26)	X		X		For uncomplicated UTIs
Cefazolin (oral)	January 2014 (M100-S24)	X		X		Surrogate test for oral cephalosporins and uncomplicated UTIs
Cefepime	January 2014 (M100-S24)		X		X	Revised breakpoints include SDD
Cefiderocol	January 2019 (M100, 29th ed.)			X		
	January 2020 (M100, 30th ed.)	X				
	February 2022 (M100-Ed32)		**X**			
Cefotaxime	January 2010 (M100-S20)		X		X	
Ceftaroline	January 2013 (M100-S23)	X		X		
Ceftazidime	January 2010 (M100-S20)		X		X	
Ceftazidime-avibactam	January 2018 (M100, 28th ed.)	X		X		
Ceftizoxime	January 2010 (M100-S20)		X		X	
Ceftolozane-tazobactam	January 2016 (M100-S26)			X		
	January 2018 (M100, 28th ed.)	X				
	February 2022 (M100-Ed32)		**X**			
Ceftriaxone	January 2010 (M100-S20)		X		X	

CLSI, M100-S32

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Resources to Verify/Validate Breakpoints

- APHL CRO Breakpoint Implementation Toolkit (BIT)
- Universal Breakpoint Implementation Toolkit
  - Creation of CDC-FDA AR Bank Isolate Panels to address multiple breakpoint updates (e.g., piperacillin-tazobactam, aminoglycosides)
  - Formatted excel templates with pre-populated calculations including essential agreement, categorical agreement and error calculations
  - Verification/Validation report outline

https://www.aphl.org/programs/infectious_disease/Pages/CRO-Breakpoint-Implementation-Toolkit.aspx

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Educational Webinars

On-Demand CLSI and CAP Webinar 2022

ASTEDUJune22WR

June 2022 AST Education Session: Updating Breakpoints—Challenges and Solutions for Various Stakeholders

Organized by the C

Moderated by:

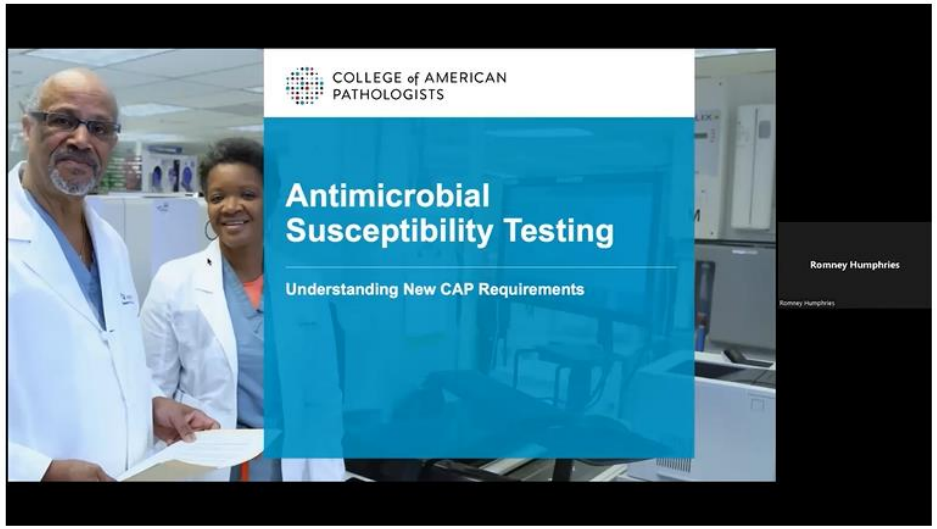
- **Janet Hindle** *Angeles, CA*
- **Jean B. Pate** *CA*

Presenters:

- **Romney M. H** *University Me*
- **Jean B. Pate** *CA*
- **Dimitri Iarik** *Administrati*
- **Natasha Grif** *Administrati*

Introduction: Microbiology Breakpoints

Dr. Humphries discusses AST requirements.



https://clsi.org/standards/products/microbiology/education/astcap22wr/

https://clsi.org/standards/products/microbiology/education/astedujune22wr/

https://documents-cloud.cap.org/appdocs/learning/LAP/FFoC/MicroBreakpoints/index.html#/

DIFFERENT APPROACHES TO BREAKPOINT UPDATES

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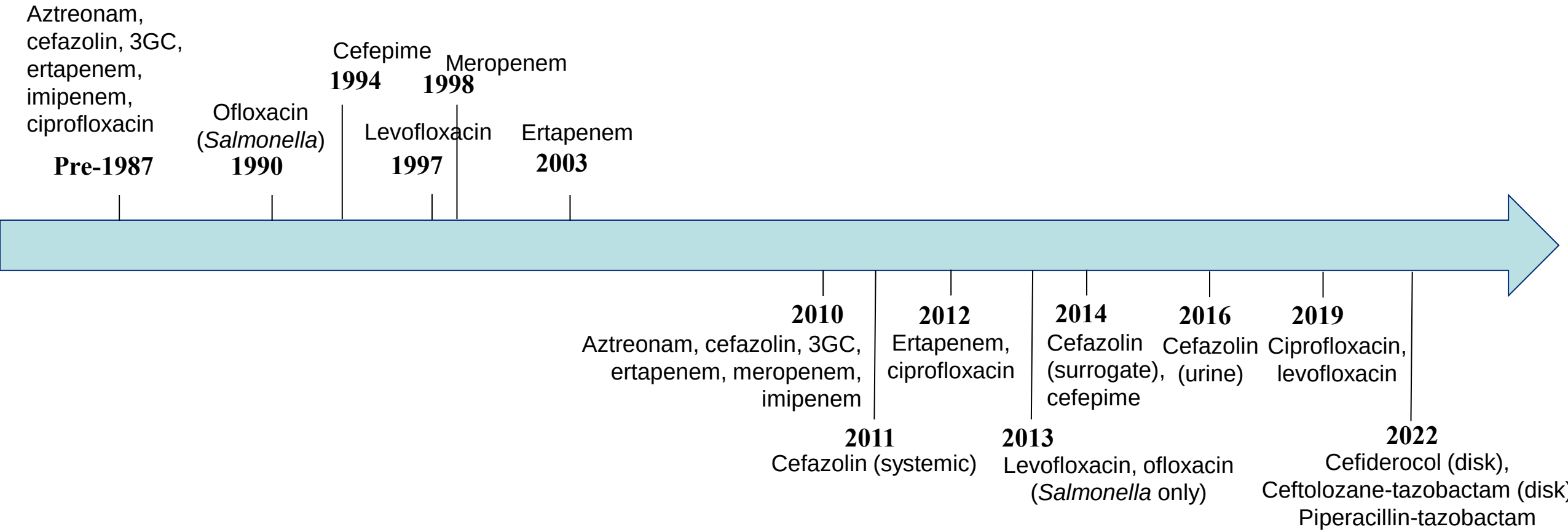
Changes To Enterobacterales CLSI Breakpoints Since 2010

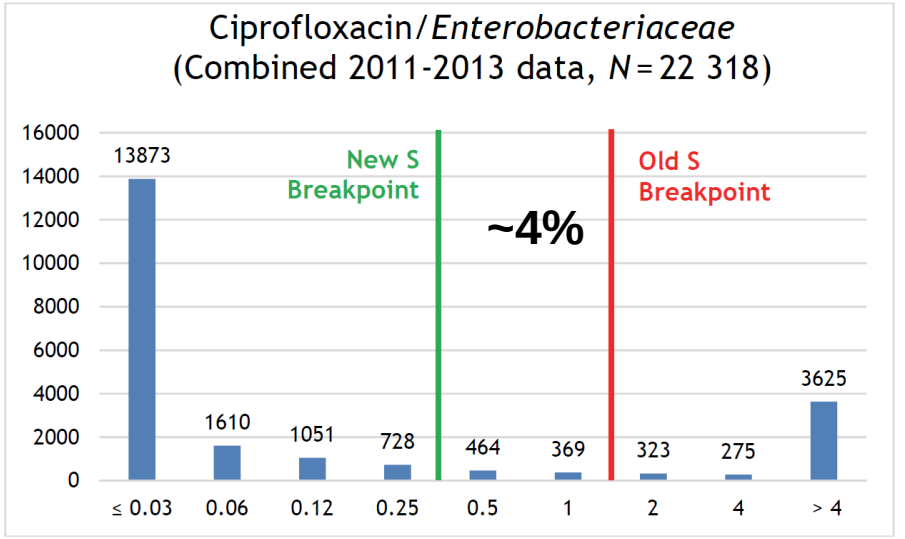


M100-S32, CLSI, 2022. Humphries *et al*, Understanding and Addressing CLSI Breakpoint Revisions: a Primer for Clinical Laboratories, JCM, 2019.

Example 1: Updated Fluoroquinolone (FQ) Breakpoints

- New pharmacokinetic/pharmacodynamic (PK/PD) data indicated breakpoint was set too high
- Enterobacterales & *Pseudomonas aeruginosa*

Enterobacterales	Susceptible (µg/ml)	Intermediate (µg/ml)	Resistant (µg/ml)
M100-S28			
Ciprofloxacin	≤1	2	≥4
Levofloxacin	≤2	4	≥8
M100-S29			
Ciprofloxacin	≤0.25	0.5	≥1
Levofloxacin	≤0.5	1	≥2



Abbreviations: MIC, minimal inhibitory concentration; S, susceptible.

Figure 1. MIC Distribution for *Enterobacteriaceae* and Ciprofloxacin[10]

Verified Breakpoints on a New Panel

- Our initial panels did not have doubling dilutions that were low enough to validate the updated breakpoint
  - Ciprofloxacin: 0.5 -2 µg/ml
  - Levofloxacin: 1- 4 µg/ml
- AST volumes were too high to perform manual testing
- Reached out to our automated AST manufacturer
  - Identified panels with appropriate dilutions & software update to implement current FQ breakpoints
  - Emerge panels for which novel agents were included
- Verified the new panels & the updated FQ breakpoints at the same time

Panel Contents		
Antimicrobic	**Code**	**Conc. Range (µg/mL)**
Amikacin	AN	8 - 32
Amoxicillin-clavulanate	AMC	4/2 - 16/8
Ampicillin	AM	4 - 16
Ampicillin-sulbactam	SAM	1/0.5 - 16/8
Aztreonam	ATM	2 -16
Cefazolin	CZ	1 - 16
Cefepime	FEP	1 - 16
Cefoxitin	FOX	4 - 16
Ceftaroline	CPT	0.25 - 1
Ceftazidime	CAZ	2 - 16
Ceftazidime-avibactam	CZA	0.25/4[a] - 8/4
Ceftolozane-tazobactam	CT	1/4 - 8/4
Ceftriaxone	CRO	1 - 32
Cefuroxime	CXM	4 - 16
Ciprofloxacin	CIP	0.25 - 2
Confirmatory ESBL	ESBL	YES
CPO detect	CPO 9-well	N/A
Ertapenem	ETP	0.25 - 2
Gentamicin	GM	2 - 8
Levofloxacin	LVX	0.5 - 4
Meropenem	MEM	0.5 - 8
Meropenem-vaborbactam[a]	MEV	2/8 - 16/8
Minocycline	MI	1 - 8
Moxifloxacin	MXF	1 - 4
Nitrofurantoin	FM	16 - 64
Piperacillin-tazobactam*	TZP	2/4 - 64/4
Tetracycline	TE	2 - 8
Tigecycline	TGC	1 - 8
Tobramycin	NN	2 - 8
Trimethoprim-sulfamethoxazole	SXT	0.5/9.5 - 2/38

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Example 2: Updated Piperacillin-Tazobactam Breakpoints for Enterobacterales

- Revised breakpoint based on extensive clinical and pharmacokinetic/pharmacodynamic (PK/PD) data that previous breakpoint was set to high
- Randomized control trial demonstrated increased mortality with MICs ≥32µg/ml

CLSI Guideline	Susceptible (µg/ml)	Susceptible Dose Dependent (µg/ml)	Intermediate (µg/ml)	Resistant (µg/ml)
M100-S31	≤16/4		32/4 – 64/4	≥128/4
M100-S32	≤8/4	16/4		≥32/4

Humphries et al, JCM, 2022.

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Validating the Breakpoint on An Existing Panel

- BD Phoenix™ (PHX) MIC to Disk Diffusion
  - Categorical agreement: 40%
    - Minor errors: 55%
    - Major errors: 9%
- BD Phoenix™ MIC to Etest MIC
  - CA: 76%
    - Minor errors: 23%
  - EA: 97%
- BD Phoenix™ MIC to BMD MIC
  - CA: 87%
    - Minor errors: 13%
  - EA: 97%

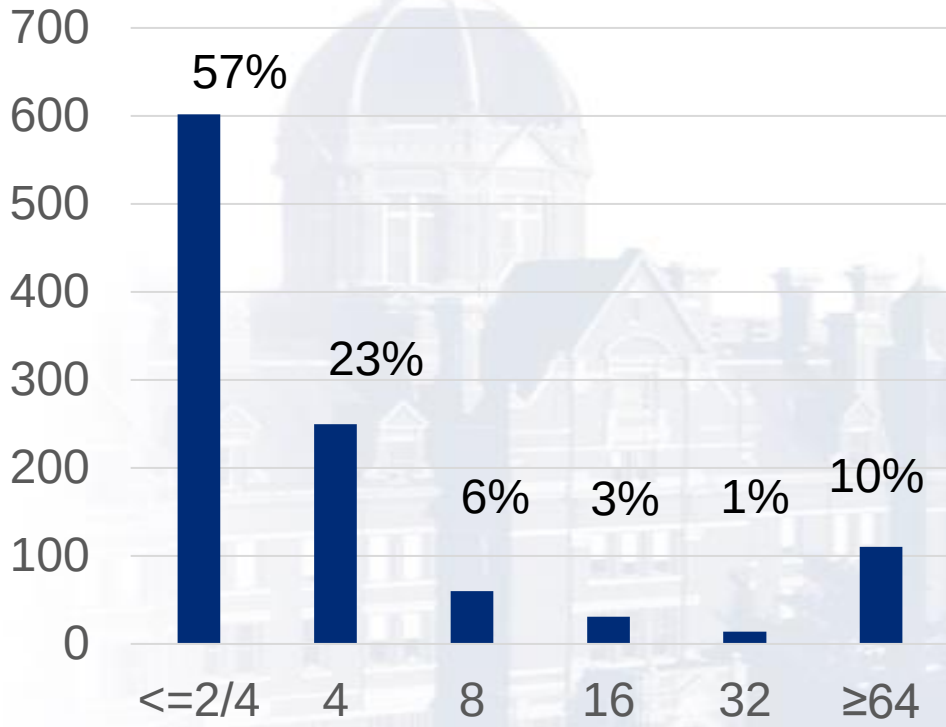
PHX MIC NMIC-306 (µg/ml)	# of Isolates	Disk Diffusion (DD) Susceptible	DD SDD	DD Resistant
≤2/4	6 (17%)	6		
4/4	8 (22%)	1	7	
8/4	9 (24%)	1	6	2
16/4	6 (17%)	1		7
32/4	1 (3%)			1
≥64/4	6 (17%)			6

Disk-to-MIC correlates used to establish the updated CLSI disk breakpoints (Humphries et al, JCM, 2022)

MIC (µg/ml)	# of Isolates	# with VME	# with ME	# with mE
≤4	667	NA	9 (1.3)	83 (12.4)
8-32	318	4 (1.6)	4 (1.3)	97 (30.5)
≥64	267	6 (2.2)	NA	36 (13.4)
All	1,252	10 (3.3)	13 (1.5)	216 (17.3)

What Approach Should You Take?

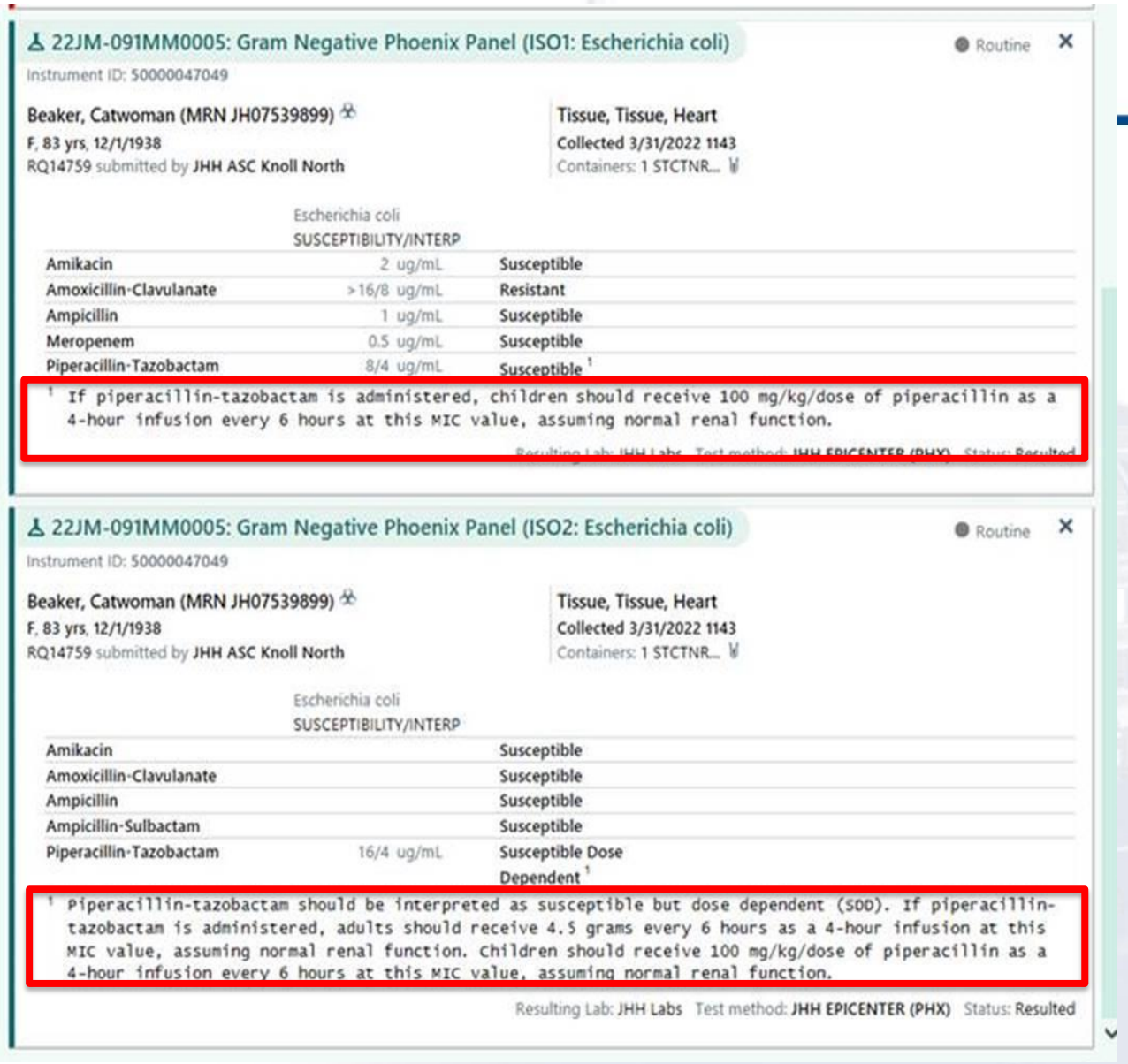
- Determine your normal distribution of P-T MICs are for Enterobacterales
- Calculate the distribution of isolates required at each dilution for your validation (eg - N: 30)
- Proceed with validation



Selection of Isolates N (%)						
MIC (µg/mL)	**≤ 2**	**4**	**8**	**16**	**32**	**≥64**
Initial – Challenged the BP	6 (17)	8 (22)	9 (24)	6 (17)	1 (3)	6 (17)
Normal Distribution	17 (57)	7 (23)	2 (6)	1 (3)		3 (10)

How Do We Handle Reporting SDD?

- What dosing are we going to recommend for adults? What about pediatrics?
- Discussed at our Microbiology/Antimicrobial Stewardship Program/Infection Control Meeting to devise comments



22JM-091MM0005: Gram Negative Phoenix Panel (ISO1: Escherichia coli) — Routine

Instrument ID: 50000047049

Beaker, Catwoman (MRN JH07539899)
F, 83 yrs, 12/1/1938
RQ14759 submitted by JHH ASC Knoll North

Tissue, Tissue, Heart
Collected 3/31/2022 1143
Containers: 1 STCTNR...

	Escherichia coli	SUSCEPTIBILITY/INTERP
Amikacin	2 ug/mL	Susceptible
Amoxicillin-Clavulanate	>16/8 ug/mL	Resistant
Ampicillin	1 ug/mL	Susceptible
Meropenem	0.5 ug/mL	Susceptible
Piperacillin-Tazobactam	8/4 ug/mL	Susceptible [1]

[1] If piperacillin-tazobactam is administered, children should receive 100 mg/kg/dose of piperacillin as a 4-hour infusion every 6 hours at this MIC value, assuming normal renal function.

Resulting Lab: JHH Labs Test method: JHH EPICENTER (PHX) Status: Resulted

22JM-091MM0005: Gram Negative Phoenix Panel (ISO2: Escherichia coli) — Routine

Instrument ID: 50000047049

Beaker, Catwoman (MRN JH07539899)
F, 83 yrs, 12/1/1938
RQ14759 submitted by JHH ASC Knoll North

Tissue, Tissue, Heart
Collected 3/31/2022 1143
Containers: 1 STCTNR...

	Escherichia coli	SUSCEPTIBILITY/INTERP
Amikacin		Susceptible
Amoxicillin-Clavulanate		Susceptible
Ampicillin		Susceptible
Ampicillin-Sulbactam		Susceptible
Piperacillin-Tazobactam	16/4 ug/mL	Susceptible Dose Dependent [1]

[1] Piperacillin-tazobactam should be interpreted as susceptible but dose dependent (SDD). If piperacillin-tazobactam is administered, adults should receive 4.5 grams every 6 hours as a 4-hour infusion at this MIC value, assuming normal renal function. Children should receive 100 mg/kg/dose of piperacillin as a 4-hour infusion every 6 hours at this MIC value, assuming normal renal function.

Resulting Lab: JHH Labs Test method: JHH EPICENTER (PHX) Status: Resulted

What Other Tools That Can be Implemented to Address Antimicrobial Resistance?

- Reporting comments
- AST Suppression rules
- AST Cascade reporting

- *Enterobacter cloacae* complex, *Klebsiella* (formerly *Enterobacter*) *aerogenes* and *Citrobacter freundii* complex may quickly develop resistance during therapy with 3rd-generation cephalosporins (e.g., ceftriaxone, ceftazidime) due to production of AmpC beta-lactamases. This does not apply to cefepime. Refer to the JHH/BMC Antibiotic Guidelines for Antibiotic Use Apps for adults or the Pediatric Antibiotic Guidelines for children for further guidance.

Susceptibility

	Klebsiella (Enterobacter) aerogenes MIC	Klebsiella pneumoniae complex MIC
Amikacin	<=8 ug/mL S	<=8 ug/mL S
Ampicillin	>16 ug/mL R	>16 ug/mL R
Ampicillin-Sulbactam	>16/8 ug/mL R	8/4 ug/mL S
Aztreonam	<=2 ug/mL S	<=2 ug/mL S
Cefazolin	>16 ug/mL R	2 ug/mL S
Cefepime	<=1 ug/mL S	<=1 ug/mL S
Cefoxitin	>16 ug/mL R	<=4 ug/mL S
Ceftazidime		<=2 ug/mL S
Ceftriaxone		<=1 ug/mL S
Ciprofloxacin	<=0.25 ug/mL S	<=0.25 ug/mL S
Gentamicin	<=2 ug/mL S	<=2 ug/mL S
Meropenem	<=0.5 ug/mL S	<=0.5 ug/mL S
Piperacillin-Tazobactam	4/4 ug/mL S	4/4 ug/mL S
Tobramycin	<=2 ug/mL S	<=2 ug/mL S
Trimethoprim-Sulfamethoxazole	<=0.5/9.5 u... S	<=0.5/9.5 u... S

Coming soon- Updates to M100 Tables 1

Table 1A: Enterobacterales

Tier 1: Antimicrobial agents that are appropriate for routine, primary testing and reporting	**Tier 2:** Antimicrobial agents that are appropriate for routine, primary testing but may be reported following cascade reporting rules established at each institution	**Tier 3:** Antimicrobial agents that may warrant routine testing or be tested by request in institutions that serve patients at high risk for MDRO but should only be reported following cascade or selective reporting rules	**Tier 4:** Antimicrobial agents that may warrant testing and reporting by request if antimicrobial agents in other Tiers are not optimal because of various factors
Ampicillin			
Cefazolin	Cefuroxime		
Cefotaxime or Ceftriaxone	Cefepime		
	Ertapenem Imipenem Meropenem	Cefiderocol Ceftazidime-avibactam Imipenem-relebactam Meropenem-vaborbactam	
Amoxicillin-clavulanate Ampicillin-sulbactam			
Piperacillin-tazobactam			
Gentamicin	Tobramycin Amikacin		
Ciprofloxacin Levofloxacin			
Trimethoprim-Sulfamethoxazole			
	Cefotetan Cefoxitin		
	Tetracycline[b]		
			Aztreonam
			Ceftaroline
			Ceftazidime
			Ceftolozane-tazobactam
Urine only			
Cefazolin (surrogate for uUTI)[c]			
Nitrofurantoin			
		Fosfomycin[d] (*Escherichia coli*)	

Testing Tiers & Cascade Reporting Between Tiers

Coming soon – M100-S33; draft version depicted

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Many New Toys in The Clinical Microbiology Laboratory That Help Address AMR

Proteomic Based ID: MALDI-TOF MS

Moderately Complex Closed Systems- Sample- to-Answer devices
Syndromic Multiplex Molecular Panels

Sophisticated Advanced NGS Technologies

CLIA waived PCR POC devices

Total Laboratory Automation

Rapid Phenotypic AMR or AST Methods

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Now Let's Fast Forward to 2050

- What if we encounter Mrs. Anne Miller 2.0 with multidrug-resistant gram-negative bloodstream infection?
  - Will we have an antibiotic to treat her?
  - Will it be a story of success?
- We need to return our focus to tackling AMR globally, nationally and institutionally
  - We need to lobby to obtain the resources to tackle this important threat

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Summary

- AMR is a global public health concern that requires collective action
- Conventional antimicrobial susceptibility testing is the primary method used to detect AMR globally
- Applying updated clinical breakpoints needs to be emphasized as a priority to improve patient safety and to limit the spread of AMR

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Thank-you!

- Questions?
  - Feel free to e-mail me: psimner1@jhmi.edu
  - Twitter @SimnerLab

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