Meeting Title:	**Subcommittee on Antimicrobial Susceptibility Testing (AST)**	**Contact:**	mhackenbrack@clsi.org egomez@clsi.org
Meeting Dates and Times: All times are Eastern (US) time.	**Plenary 1:** Monday, 31 January 2022, 3:00 – 6:00 PM **Plenary 2:** Tuesday, 1 February 2022, 3:00 – 6:00 PM **Plenary 3:** Monday, 7 February 2022, 2:00 – 5:00 PM **Plenary 4:** Thursday, 10 February 2022, 2:00 – 5:00 **Plenary 5:** Friday, 11 February 2022, 1:00 – 4:00 PM		
Meeting Purpose:	The purpose of this meeting is to review and discuss AST WG and SC business in preparation for publication of the next edition of M100 (33rd).		
Requested Attendee(s):	SC Chairholder, Vice-chairholder, Members, Advisors, and Reviewers; Expert Panel on Microbiology Chairholder and Vice-chairholder; Other Interested Parties; CLSI Staff (see SC roster)		

Attendee(s):	
James S. Lewis, PharmD, FIDSA AST Subcommittee Chairholder	**Oregon Health and Science University**
Melvin P. Weinstein, MD AST Subcommittee Vice-Chairholder	**Robert Wood Johnson University Hospital**
Jean B. Patel, PhD, D(ABMM) Expert Panel on Microbiology Chairholder	**Beckman Coulter, Inc.**
Members Present (for all plenaries):	
Sharon K. Cullen, BS, RAC	Beckman Coulter, Inc. Microbiology Business
Tanis Dingle, PhD, D(ABMM), FCCM	Alberta Precision Laboratories
Marcelo F. Galas	Pan American Health Organization
Romney M. Humphries, PhD, D(ABMM)	Vanderbilt University Medical Center
Thomas J. Kirn, MD, PhD	Rutgers Robert Wood Johnson Medical School
Brandi Limbago, PhD	Centers for Disease Control and Prevention
Amy J. Mathers, MD, D(ABMM)	University of Virginia Medical Center
Virginia M. Pierce, MD	Massachusetts General Hospital
Sandra S. Richter, MD, D(ABMM), FCAP, FIDSA	Mayo Clinic (Jacksonville, Fl)
Michael Satlin, MD, MS	New York Presbyterian Hospital
Audrey N. Schuetz, MD, MPH, D(ABMM)	Mayo Clinic (Rochester, MN)
Susan Sharp, PhD, D(ABMM), F(AAM)	Copan Diagnostics, Inc.
Patricia J. Simner, PhD, D(ABMM)	Johns Hopkins School of Medicine, Department of Pathology
Advisors Present	
Tanaya Bhowmick, MD	Rutgers Robert Wood Johnson Medical School
April M. Bobenchik, PhD, D(ABMM), MT(ASCP)	Penn State Hershey Medical Center
Carey-Ann Burnham, PhD, D(ABMM)	Washington University School of Medicine
Shelley Campeau, PhD, D(ABMM)	Accelerate Diagnostics, Inc.
Mariana Castanheira, PhD	JMI Laboratories
Sanchita Das, MD, D(ABMM)	National Institutes of Health
German Esparza, MSc	Proasecal SAS
Christian G. Giske, MD, PhD	Karolinska University Hospital
Howard Gold, MD, FIDSA	Beth Israel Deaconess Medical Center
Janet A. Hindler, MCLS, MT(ASCP), F(AAM)	Los Angeles County Department of Public Health
Dmitri Iarikov, MD, PhD	FDA Center for Drug Evaluation and Research
Joe Kuti, PharmD, FIDP	Hartford Hospital
Joseph D. Lutgring, MD	Centers for Disease Control and Prevention
Linda A. Miller, PhD	CMID Pharma Consulting LLC
Stephanie L. Mitchell, PhD, D(ABMM)	Cepheid, Inc.
Greg Moeck, PhD	Venatorx Pharmaceuticals, Inc.
Navaneeth Narayanan, PharmD, MPH	Rutgers University

Robin Patel, MD Samir Patel Ribhi M. Shawar, PhD, D(ABMM), F(AAM) Eric Wenzler, PharmD, BCPS, AAHIVP Barbara L. Zimmer, PhD	Mayo Clinic FDA Center for Devices and Radiological Health University of Illinois at Chicago Beckman Coulter
Reviewers and Guests (Non-SC-roster attendees): See list below	
Staff:	
Kathy Castagna, MS, MT(ASCP)CT, MB Glen Fine, MS, MBA, CAE Emily Gomez, MS, MLS(ASCP)MB Marcy L. Hackenbrack, MCM, M(ASCP) Christine Lam, MT(ASCP) Lori Selden, MS, MT(ASCP)	CLSI CLSI CLSI CLSI CLSI CLSI

EXECUTIVE SESSION AND PLENARY AGENDAS All times are Eastern (US) Time All presentation can be viewed using this link: 2022 Winter Plenary Presentations				
Working Group Virtual Meeting Time/Date	**Length**	**Chairholder(s)**	**Objectives**	
Executive Session **(By Invitation Only)** **Monday, 31 January 2022** **12:00 - 2:00 PM**	2 hr.	**J. Lewis** (Chairholder) **M. Weinstein** (Vice-Chairholder)	Review and discuss subcommittee issues associated with the upcoming plenaries	Page
Plenary: Part 1 **Monday, 31 January 2022** **3:00 - 6:00 PM**	3 h		**Opening Remarks:** Dr. Lewis	6
			CLSI Update: Mr. Fine	6
			Vet AST Update: Mr. Bowden	7
			M23 Update: Dr. Wikler	7
			QCWG	8
			Break	
			MAIWG	14
			TTWG	17
Plenary: Part 2 **Tuesday, 1 February 2022** **3:00 - 6:00 PM**	3 h		**Table 1 WG Report**	19
			Break	
			M45 Update	23
			M39 Update: Ms. Hindler and Dr. Simner	25
			Outreach WG	25
			Joint CLSI-EUCAST WG	27
			M02/M07 WG update	17
Plenary: Part 3 **Monday, 7 February 2022** **2:00 - 5:00 PM**	3 h		**BPWG Part 1**	28
			Break	
			BPWG Part 2	28
Plenary: Part 4 **Thursday, 10 February 2022** **2:00 - 5:00 PM**	3 h		**EUCAST Update:** Dr. Giske	34
			BPWG Part 3	35
			Break	
			BPWG Part 4	35
Plenary: Part 5 **Friday, 11 February 2022** **1:00 - 4:00 PM**	3 h		**MDSWG Part 1**	41
			Break	
			MDSWG Part 2	41

Summary of Voting Decisions and Action Items

Summary of Passing Votes			
#	Motion Made and Seconded	Results[a]	Page[b]
1.	To approve the tebipenem MIC QC ranges for *S. pneumoniae* ATCC 49619 (0.004-0.03 µg/mL) and *H. influenzae* ATCC 49766 (0.06-0.25 µg/mL) (with the proposed media comment for *H. influenzae* QC ranges were established with a limited number of media manufacturers).	12-0-0-1	8
2.	To approve the MIC QC ranges for ceftibuten-avibactam for *E.coli* ATCC 25922 (0.016/4 -0.12/4 µg/mL), *E.coli* NCTC 13353 (0.03/4 -0.12/4 µg/mL), *K. pneumoniae* ATCC 700603 (0.06/4 -0.25/4 µg/mL), *K. pneumoniae* ATCC BAA-1705 (0.03/4 -0.25/4 µg/mL), and *K. pneumoniae* ATCC BAA-2814 (0.12/4 -0.5/4 µg/mL) with the comment regarding equivalency (MIC ranges were established using broth microdilution only).	12-0-0-1	10
3.	To approve the MIC QC ranges for ceftibuten alone for *E. coli* ATCC 25922 (0.12-1 µg/mL), *K. pneumoniae* ATCC 700603 (0.25-1 µg/mL)	12-0-0-1	11
4.	To approve the addition of orange shading (integrity check) to the previously approved ranges for *E. coli* NCTC 13353, *K. pneumoniae* ATCC BAA-1705, and *K. pneumoniae* ATCC BAA-2814	13-0-0-0	11
5.	To approve the three new MIC QC ranges for ceftazidime-avibactam: *E. coli* NCTC 13353 (0.12/4 –0.5/4 µg/mL), *K. pneumoniae* ATCC BAA-1705 (0.25/4 – 2/4 µg/mL), *K. pneumoniae* ATCC BAA-2814 (1/4 - 4/4 µg/mL) (with no shading)	13-0-0-0	11
6.	To approve the addition of the lack of established equivalency comment for tebipenem, ceftibuten-avibactam, ceftazidime-avibactam, and ceftibuten (MIC ranges were established using broth microdilution only. Equivalency data for agar dilution are not available.) and removal when equivalency is provided. Also to add a general note to Tables 5A-1, 5A-2, and 5B to reflect current status (MIC ranges apply to both broth microdilution and agar dilution unless otherwise specified.).	12-0-0-1	12
7.	To approve the WG proposal to change the QC range for colistin for *E. coli* NCTC 13486 (1-8 µg/mL) with a comment Bimodal 2-4. Investigate if frequent MICs of 1 or 8 are obtained. regarding frequent MICs of 8 and to add modes for both QC organisms. Add comment for *E. coli* BAA-3170, mode 2.	13-0-0-0	13
8.	To adopt the new horizontal format with four Tiers (categories) and new individual organism or group tables for Tables 1.	13-0-0-0	22
9.	To approve Tables 1D through 1N as presented.	13-0-0-0	22
10.	To approve Table O with levofloxacin and cefepime in Tier 4 and dirithromycin deleted from footnote (e).	13-0-0-0	22
11.	To approve the PTZ BPs for *P. aeruginosa* (≤16 [S]; 32 [I]; ≥64 [R]) with a comment regarding extended infusions (Based on dosing of 4.5g q6h as a 30 minute infusion or 4.5g q6h as a 3-hour infusion) and issues with the intermediate category (to align the comment with the current definition of "I" in M100)	11-2-0-0	30
12.	To approve the proposed PTZ disk (100/10 µg disks) BPs (S: ≥22 mm; I: 18–21 mm; R: ≤17 mm)	13-0-0-0	30
13.	To approve the piperacillin BPs (Disk: S ≥22 mm; I 18-21 mm; R ≤17 mm and MIC: S ≤16 µg/mL; I 32 µg/mL; R ≥64 µg/mL)	13-0-0-0	31
14.	To approve plazomicin MIC BPs for Enterobacterales same as FDA (S ≤2, I 4, R ≥8) with a comment similar (with wordsmithing) to #12 (imipenem-relebactam) in Table 2A in M100 (Breakpoints do not apply to the family Morganellaceae, which includes but is not limited to the genera *Morganella*, *Proteus*, and *Providencia*) and not publishing the plazomicin BPs until older aminoglycosides are re-evaluated	11-1-1-0	39

Summary of Voting Decisions and Action Items (continued)

Summary of Passing Votes (continues)			
#	**Motion Made and Seconded**	**Results**[a]	**Page**[b]
15.	To approve the plazomicin disk diffusion BPs (zone diameter in mm) for Enterobacterales (S ≥18, I 15-17, R ≤14) with same comment regarding *Morganellaceae*	11-1-1-0	39
16.	To approve MH-F as an alternative to HTM for broth microdilution AST of *H. influenzae*	13-0-0-0	42
17.	To add comments regarding MH-F data not being currently available for *H. parainfluenzae* and a comment analogous to that for *S. pneumoniae* (excluding disk diffusion) that states that the two media types are equivalent (*For disk diffusion, results using MHA with 5% sheep blood and MH-F agar were equivalent when disk contents, testing conditions, and zone diameter breakpoints in Table 2G were used. Disk diffusion QC ranges for S. pneumoniae ATCC® 49619 in Table 4B apply to testing using either MHA with 5% sheep blood or MH-F agar*)	13-0-0-0	42
18.	To approve the direct read from positive blood culture (PBC) bottles for Enterobacterales and meropenem at 16-18 hrs. reading proposed zone cutoffs (mm) as S ≥22, I 19-21, R ≤18	13-0-0-0	43
19.	To approve the direct read results from PBC bottles for Enterobacterales and meropenem at 8-10 hrs. with proposed zone cutoffs (mm) as S ≥22, I 20-21, R ≤19	12-0-0-1	43
20.	To approve the direct read results from PBC bottles for Enterobacterales and ampicillin at 8-10 hrs. with proposed zone cutoffs (mm) as S ≥16, I 12-15, R ≤11	12-0-0-1	44
21.	To approve direct DD reads from PBC for Enterobacterales (excluding *Salmonella*) with ciprofloxacin at 8 – 10 hrs. with proposed zone cutoffs (mm) as S ≥21, I 18-20, R ≤17 and with a warning to determine identification before reporting the AST results	13-0-0-0	44
22.	To approve direct read from PBC for Enterobacterales (excluding Salmonella) with ciprofloxacin at 16 – 18 hrs. with proposed zone cutoffs (mm) as S ≥21, I 18-20, R ≤17	11-2-0-0	45
23.	To approve the direct 8-10 hr reads from PBC with *P. aeruginosa* and meropenem with proposed zone cutoffs (mm) of S ≥19, I 16-18, R ≤15	13-0-0-0	45

[a] Key for voting: X-X-X-X = For-against-abstention-absent

[b] Page links can be used to go directly to the related topic presentation and voting discussions.

2022 WINTER AST MEETING SUMMARY MINUTES PLENARY 1: MONDAY, 31 JANUARY – 3:00 – 6:00 PM EASTERN (US) TIME	
#	**Description**
1.	**OPENING REMARKS (J. LEWIS)** **Dr. Lewis opened the meeting at 3:00 PM Eastern (US) time by welcoming the participants.** • The agenda was reviewed. It was noted the M23 report originally scheduled for this meeting will be postponed to Plenary 3. • It is hoped that the next meeting in Chicago in June will be able to be held in person with a virtual component.
2.	**CLSI UPDATE (G. FINE)** **Mr. Fine provided a brief update on the status of CLSI. The main points included:** • The staff continues to work in a virtual environment and will for the foreseeable future. The inability to travel internationally has somewhat hampered the global health group but work has still been carried out in a virtual environment. • The organization is weathering the pandemic financially. • He expressed his gratitude to all the volunteers for continuing their work on CLSI projects even though the pandemic has taken so much of their time. • Ms. Hackenbrack will be retiring as of March 1, 2022. Management of the AST subcommittee and M100 will transition to Emily Gomez and Chris Lam, respectively. • Mr. Fine will retire as of June 30th, 2022, and expects to assist the new CEO acclimate to the position before he retires. • The current plan is for the June meeting to be held in person in Chicago, Illinois with a virtual component (hybrid format). • Mr. Fine presented the Excellence in Standards Development to Dr. Barbara Zimmer and provided and overview of her many accomplishments. He expressed his and CLSI's gratitude for her many years of involvement with the AST SC and CLSI Board of Directors.

3.	**VET SUBCOMMITTEE (VAST) UPDATE (R. BOWDEN)** **Mr. Bowden provided and update on the activities of the Subcommittee on Veterinary Antimicrobial Susceptibility testing. The following items are in progress:** • ***Enterococcus* spp.** – Development of dog and cat urine breakpoints (BPs) for ampicillin and non-urine ampicillin IV BPs for dogs – Investigate chloramphenicol PK/PD targets for development of vet-specific BPs – Delete text regarding low-level ampicillin resistance and aminoglycoside synergy as it is not applicable to vet species – Add clarifying text regarding treatment of uncomplicated UTIs with β-lactams and excluding certain antimicrobial agents when treating non-food producing animals • **Revisions to VET01S** – Deletion of body site designation for generic BPs – Expansion of vet-specific BPs from species to families – Creation of new tables for bovine mastitis BPs with newly approved BPs – Added new BPs for linezolid for *Staphylococcus* and *Enterococcus* spp. – Addition of urine BPs for ampicillin and amoxicillin-clavulanate with *Enterococcus* spp. for dogs and cats • **Other activities** – Revision of VET05, *Generation, Presentation, and Application of Antimicrobial Susceptibility Test Data for Bacteria of Animal Origin* – Revision of VET06, *Methods for Antimicrobial Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria Isolated From Animals* – Working to standardize the targets to be examined for all future BP revisions
4.	**M23 WG REPORT (M. WIKLER)** (Note: This report was provided during Plenary 3) **Dr. Wikler provided an update on the M23 Revision** • The M23 draft has completed proposed draft vote and has been approved to continue in the consensus process by the SC members, Expert Panel on Microbiology, and the CLSI member delegates. • The comment submitted during review are being addressed by the WG. • Once all comments are resolved, the resolutions will be distributed to the reviewers for a 15-day appeal period. • When the appeal period is completed, CLSI staff will prepare the draft to submit for preparation for Final vote by the Consensus Council (15 days). • The approved draft will then be submitted to the editorial staff to prepare for publication. • Publication is expected during the Summer of 2022. **SC Discussion** • It was questioned if there is text in M23 that states that it can be demonstrated that BMD and agar dilution are comparable when new drugs are developed. It was noted that if this is not already in the document, it can be added before the draft is published. • This has been added to the standard report for setting QC ranges. If comparability is not established, footnotes will be added to the QC table.

5. **QUALITY CONTROL WG (QCWG) REPORT (S. CULLEN)**

WG Roster

- Maria Traczewski and Patricia Conville have officially retired.
- Chris Pillar has been appointed as the new Co-Chairholder on the WG.

TIER 2 QC STUDIES

- **Tebipenem**

Drug: Tebipenem	**Abbreviation (Glossary II & III):** TBP*	**Previous ID:** NA
Solvent (Table 6A): Water*	**Diluent (Table 6A):** Water*	**Preparation(Table 6C combination agents):** NA
Route of administration (Glossary II): PO*	**Class (Glossary I & II):** Penems*	**Subclass (Glossary I & II):** Carbapenems*
Study Report by: IHMA (#3919 in 2021)	**Pharma Co:** Spero Therapeutics	**Control Drug:** Meropenem
Additional Information (M23 requirements)	• **Tier 1 Impact Assessment** (stability, inoculum, reading, incubation time, cations, zinc, surfactants, etc): No issues. • **Equivalency of agar dilution to broth dilution:** Not available/known at this time. • **ISO/TS 16782 assessment of Tier 2 study materials:** Confirmed	
Footnotes:	• **Recommendations for Troubleshooting Guide (Table 4D Disk or 5G MIC):** No additional recommendations	

QC Strain	Range	% In	Mode	Dil	Shoulder	Media Mode	Lab Mode	M23 Range	Range Finder	Comments: WG approved 12/0/0/1
S. pneumoniae **ATCC 49619**	0.004-0.03	100%	0.016	4	69% @ 0.008	0.008 (1), 0.016 (2)	0.008 (4), 0.016 (5)	0.004-0.03 100%	0.008-0.03 99.6%	Media and lab variability. Shoulder >60% Control drug: 100% in range, mode 0.06
H. influenzae **ATCC 49766**	0.06-0.25	100%	0.12	3	19%@ 0.06	0.12 (3)	0.12 (8) 1 bimodal 0.06-0.12	0.06-0.25 100%	0.06-0.25 100%	Lot 1&2 same manufacturer, mode at 0.12. Lot 3 different manufacturer: 0.12 mode with shoulder 48% @ 0.06 Control drug 100% in range – bimodal 0.03-0.06 (bottom half of range) Approved: 13/0/0/0 Footnote: QC ranges were established with a limited number of media manufacturers.

- SC Discussion: No discussion was needed.

A motion to approve the tebipenem MIC QC ranges for *S. pneumoniae* ATCC 49619 (0.004-0.03 µg/mL) and *H. influenzae* ATCC 49766 (0.06-0.25 µg/mL) (with the proposed media comment for *H. influenzae* QC ranges were established with a limited number of media manufacturers.) was made and seconded. VOTE: 12 for, 0 against, 0 abstain, 1 absent (Pass).

- **Ceftibuten-avibactam**

Drug: Ceftibuten-avibactam (fixed 4µg/ml)	**Abbreviation (Glossary II & III)**: CBA	**Previous ID**: NA
Solvent (Table 6A): Ceftibuten: Phosphate buffer pH 8.0 0.1 M, * Avibactam: Water	**Diluent (Table 6A)**: Ceftibuten: Phosphate buffer pH 8.0 0.1 M, * Avibactam: Water	**Preparation(Table 6C combination agents)**: Proposed addition: Ceftibuten-avibactam (fixed 4µg/ml), Fixed concentration of avibactam at 4 µg/mL, Same as aztreonam-avibactam.
Route of administration (Glossary II): Oral	**Class (Glossary I & II)**: ß-lactam combination agents	**Subclass (Glossary I & II)**: NA
Study Report by: JMI	**Pharma Co**: Pfizer	**Control Drug**: ceftazidime-avibactam, ceftibuten

Additional Information (M23 requirements)	• **Tier 1 Impact Assessment** (stability, inoculum, reading, incubation time, cations, zinc, surfactants, etc): No significant issues • **Equivalency of agar dilution to broth dilution**: Not yet established (studies in process) • **ISO/TS 16782 assessment of Tier 2 study materials**: Confirmed
Footnotes:	• **Recommendations for Troubleshooting Guide (Table 4D Disk or 5G MIC):** • No additional footnotes needed. Similar to other ß-lactam combination agents – MIC too low or susceptible for single ß-lactam agent; in range for combination ß-lactam agent: Spontaneous loss of the plasmid encoding the ß-lactamase – MIC too high or resistant for both the single ß-lactam agent and the combination ß-lactam agent
Discussion	• M100 31 & 32Ed indicate 1/10 volume of DMSO as solvent and water as diluent. This study used a different option. • *Sponsor request to add second option to Table 6A: Phosphate buffer pH 8.0, 0.1M for solvent and diluent

QC Strain	Range	% In	Mode	Dil	Shoulder	Media Mode	Lab Mode	M23 Range	Range Finder	Comments/ QCWG votes 12/0/0/1 for ranges 13/0/0/0 for Routine QC
E.coli ATCC 25922	0.016/4 - 0.12/4	100%	0.03/4	4	88.1%@ 0.06/4	0.03/4 (1) 0.03/4-0.06/4 (1) 0.06/4 (1)	0.03/4 (3) 0.06 (4) 0.06/4-0.12/4 (1)	0.015/4 - 0.12/4, 100%	0.015/4 - 0.12/4, 100%	Media and lab variability. Shoulder >60%. QC range is lower than for Ceftibuten only. See comments on next slide.
E.coli NCTC 13353	0.03/4 - 0.12/4	100%	0.06/4(3)	3	15%@ 0.03/4	0.06/4	0.06/4	0.03/4 - 0.12/4	0.03/4 - 0.12/4	No significant media or lab variability CLSI Ceftibuten range: 16-64 Highlight green as Routine QC
K. pneumoniae ATCC 700603	0.06/4 - 0.25/4	98.8%	0.12-4	3	10%@ 0.25/4	0.12/4 (3)	0.12/4 (8)	0.06/4 - 0.25/4, 100%	0.06/4 - 0.25/4, 100%	No significant media or lab variability Proposed Ceftibuten range: 0.25-1 (none at 0.25, see details) Don't highlight as Routine QC. Listed as routine QC strain for CZA, but range overlaps Ceftibuten range.

K. pneumoniae ATCC BAA-1705	0.03/4 - 0.25/4	100%	0.12/4	4	70.0%@0.06/4	0.06/4 (3)	0.06/4 (3) 0.12/4 (5)	0.03/4 - 0.25/4, 100%	0.03/4 - 0.25/4, 100%	Some media & lab variability, Shoulder >60% CLSI Ceftibuten range: 4-32 Highlight green as Routine QC
K. pneumoniae ATCC BAA-2814	0.12/4 - 0.5/4	99.6%	0.25/4	3	12%@0.12/4	0.25/4 (3)	0.12/4- 0.25/4 (1) 0.25/4 (7)	0.12/4 - 0.5/4, 99.6%	0.12/4 - 0.5/4, 99.6%	No significant media or lab variability CLSI Ceftibuten range: 8-32 Highlight green as Routine QC

- It was noted that equivalency has not been established; therefore, the approved comment regarding lack of equivalency will be included as a footnote.
- SC Discussion
  - It was questioned if equivalency has been shown for the phosphate-buffered saline (PBS) as a solvent.
  - It was noted that studies have been done using both solvents and it was shown that ceftibuten will only go into solution with PBS.

A motion to approve the MIC QC ranges for ceftibuten-avibactam for *E.coli* ATCC 25922 (0.016/4 -0.12/4 µg/mL), *E.coli* NCTC 13353 (0.03/4 -0.12/4 µg/mL), *K. pneumoniae* ATCC 700603 (0.06/4 -0.25/4 µg/mL), *K. pneumoniae* ATCC BAA-1705 (0.03/4 -0.25/4 µg/mL), and *K. pneumoniae* ATCC BAA-2814 (0.12/4 -0.5/4 µg/mL) with the comment regarding equivalency (MIC ranges were established using broth microdilution only) was made and seconded. VOTE: 12 for, 0 against, 0 abstain, 1 absent (Pass).

- **Ceftibuten (Alone)**

QC Strain	Range	% In	Mode	Dil	Shoulder	Media Mode	Lab Mode	M23 Range	Range Finder	Comments
E. coli ATCC 25922	0.12-0.5	100%	0.25	3	88.1% @ 0.5	0.25 (2) 0.5 (1)	0.25 (6) 0.5 (2)	0.12-1, 100%	NA	Range previously approved & published in 32nd Ed. (EUCAST same.) Tier 3: Recommend expanding range to 4 dilutions (0.12-1). WG Approved 13/0/0/
K.pneumoniae ATCC 700603	0.25-1	99.2%	0.5	3	54.5%@1	0.5 (3)	0.5 (6) 1 (2)	0.25-1, 99.2%	0.25-1, 99.2%	SHV-18, OXA-2, Mutations in OmpK35 and OmpK37. No EUCAST range Some media and lab variability. Add QC range with no color highlight Vote 12/0/0/1

QC Strain	Range	% In	Mode	Dil	Shoulder	Media Mode	Lab Mode	M23 Range	Range Finder	Comments
E.coli NCTC 13353	16-64									QC range previously approved and published in 32nd Ed (with no color highlights) Add orange highlight as QC integrity check when Ceftibuten/avibactam is added to Table 5A-2.
K. pneumoniae ATCC BAA-1705,	4-32									QC range previously approved and published in 32nd Ed (with no color highlights) Add orange highlight as QC integrity check when Ceftibuten/avibactam is added to Table 5A-2.

K. pneumoniae ATCC BAA-2814	8-32									QC range previously approved and published in 32nd Ed (with no color highlights) Add orange highlight as QC integrity check when Ceftibuten/avibactam is added to Table 5A-2.

- **SC Discussion**: No discussion was needed.

A motion to approve the MIC QC ranges for ceftibuten alone for *E. coli* ATCC 25922 (0.12-1 µg/mL), *K. pneumoniae* ATCC 700603 (0.25-1 µg/mL) was made and seconded. VOTE: 12 for , 0 against, 0 abstain, 1 absent (Pass).

A motion to approve the addition of orange shading (integrity check) to the previously approved ranges for *E. coli* NCTC 13353, *K. pneumoniae* ATCC BAA-1705, and *K. pneumoniae* ATCC BAA-2814 was made and seconded. VOTE: 13 for , 0 against, 0 abstain, 0 absent (Pass).

- **Ceftazidime-avibactam (new ranges)**

QC Strain	Range	% In	Mode	Dil	Shoulder	Media Mode	Lab Mode	M23 Range	Range Finder	Comments/Vote 12/0/0/1 Add new QC ranges as indicated with no highlight (since no range for ceftazidime alone).
E. coli NCTC 13353	0.12/4 -0.5/4	100%	0.25/4	3	31%@ 0.12/4	0.25/4 (3)	0.12/4 (1) 0.25/4 (7)	0.12/4 - 0.5/4, 100%	0.12/4 -0.5/4, 100%	Some lab variability, minimal media variability. No EUCAST range. Add range, no highlight
K. pneumoniae ATCC BAA-1705	0.25/4 -2/4	100%	1/4	4	76.6%@- 0.5/4	0.5/4 (1) 1/4 (2)	0.5/4 (4) 1/4 (4)	0.25/4 - 2/4, 100%	0.25/4 -2/4, 100%	Lab variability. Some media variability. No EUCAST range Add range, no highlight
K. pneumoniae ATCC BAA-2814	1/4 - 4/4	100%	2/4	3	24.5%@1/4	2/4 (3)	1/4 (1) 2/4 (7)	1/4 - 4/4, 100%	1/4 - 4/4, 100%	Minimal variability (lab) No EUCAST range Add range, no highlight

- SC Discussion: No discussion was needed.

A motion to approve the three new MIC QC ranges for ceftazidime-avibactam: *E. coli* NCTC 13353 (0.12/4 -0.5/4 µg/mL), *K. pneumoniae* ATCC BAA-1705 (0.25/4 – 2/4 µg/mL), *K. pneumoniae* ATCC BAA-2814 (1/4 - 4/4 µg/mL) (with no shading) was made and seconded. VOTE: 13 for, 0 against, 0 abstain, 0 absent (Pass).

ADDRESSING BROTH AND AGAR EQUIVALENCY ON QC TABLES 5A-1, 5A-2, AND 5B

- The QCWG raised the issue that it hasn't consistently been confirmed that equivalency studies have been performed.
- This is considered best practice but is not required by M23 but are expected for FDA-NDA submissions.
- Proposal
  - Add checklist item to summary slide for all future Tier 2 studies
  - Add notes to the tables 5A-1, 5A-2, and 5B to address current status.

- Add future footnotes when needed if equivalency is not established and remove when equivalency is provided.

- WG approved footnotes:
  - General Note to be added to Tables 5A-1, 5A-2, and 5B to address current status of other QC ranges: "MIC ranges apply to both broth microdilution and agar dilution unless otherwise specified."
  - Specific comments may be added for specific situations. Examples include the following. MIC ranges were established using broth microdilution only. Equivalency data for agar dilution are not available.
  - SC Discussion: No discussion was needed.

A motion to approve the addition of the lack of established equivalency comment for tebipenem, ceftibuten-avibactam, ceftazidime-avibactam, ceftibuten-avibactam and ceftibuten (*MIC ranges were established using broth microdilution only*. *Equivalency data for agar dilution are not available)* and removal when equivalency is provided was made and seconded. Also general note to be added to Tables 5A-1, 5A-2, and 5B to address current status of other QC ranges "MIC ranges apply to both broth microdilution and agar dilution unless otherwise specified". VOTE: 12 for, 0 against, 0 abstain, 1 absent (Pass).

TIER 3 QC

- *E. coli* NCTC ATCC 13486 and/or E. coli BAA 3170 (formerly AR Bank # 0349) for colistin
  - Current ranges for both QC strains (1 – 4 µg/mL) approved by SC
  - WG recommended expanding the range for *E. coli* NCTC ATCC 13486 to 4 dilutions (1 – 8 µg/mL) and adding a footnote to Table 5A-1: "Bimodal 2-4. Investigate if frequent MICs of 1 or 8 are obtained." (WG Vote: 13/0/0/0).
  - For *E. coli* BAA 3170, retain QC range (1-4 µg/mL) but add a footnote to Table 5A-1 indicating the mode of 2. (WG Vote: 13/0/0/0).
  - The WG suggested that a table be created for Table 3D to implement changes to the current footnote with changes from this meeting (see example).

	MIC ranges, µg/mL	Mode, µg/mL	Comments
E. coli NCTC 13486	1-8	2-4	Investigate if frequent MICs of 1 µg/mL or 8 µg/mL are observed.
E. coli ATCC® BAA-3170™	1-4	2	

- SC Discussion (main points)
  - There was concern that different laboratories would interpret "frequent MICs of 8" differently and that some guidance should be provided on what to consider as "frequent"
  - It was suggested that guidance when and how to investigate if frequent MICs of 8 are seen.
  - The WG suggested that for the future, to publish modes for all QC ranges and indicated that they are also working on guidance for identifying frequent MICs of 8 and how and when to investigate.
  - It was suggested that guidance for colistin be added to M02 and M07.

A motion to approve the WG proposal to change the QC range for E. coli NCTC 13486 (1-8 µg/mL) with a comment regarding frequent MICs of 8 and to add modes for both QC organisms was made and seconded. The motion also included adding guidance on interpretation of "frequent" and how to investigate. VOTE: 13 for, 0 against, 0 abstain, 0 against (Pass).

- The WG also suggested that an additional footnote be added for colistin and *E. coli* NCTC 13486: "*Colistin results are significantly impacted by preparation and handling of reagents/testing materials including stock solutions, test medium, testing container (tube/panel) etc. and may differ from the established CLSI QC ranges if methods other than CLSI reference methods described in M07 and M100 are used.*" The comment will be clarified and presented at the June AST meeting. It was suggested to add a reference to provide additional information on the considerations when manufacturing colistin broth microdilution.

- The WG pointed to the list of Tier 3 MIC and disk diffusion active discussions lists and requested that any data be sent to the WG.
  - Tier 3 disk data for P. aeruginosa ATCC 27853 and cefiderocol 30 µg.The WG is looking at the media to see if a tighter range can be proposed and to see if the range can be harmonized with EUCAST.The WG is looking at S. aureus ATCC 29523 and fluoroquinolones. It has been noted that zones in the lower part of the range or below range for all fluoroquinolone disks on Mueller-Hinton from two manufacturers. It was recommended that reading guidance be added to M02.

- The WG noted that colistin and polymyxin B disk diffusion QC ranges (*E.coli* ATCC 25922 and *P. aeruginosa* ATCC 27853) are still in Table 4A even though BPs were removed from Tables 2.
  - An SC vote to remove the disk QC ranges from Table 4A and move them to the archived QC range table was requested.
  - SC Discussion
    - There was concern that labs use colistin disks for certain identifications. It was suggested that the disk QC ranges be retained but to add a footnote about use. The disks are also used for the disk elution test.
    - The WG will reassess how to address the disk QC ranges and provide recommendations at the June meeting.

- Disk Diffusion reading variation
  - M02 states in Chapter 4 (QC) that zone measurement readings from several individuals should not vary more than ± 2 mm. Should this be changed to ± 3 mm as stated in M23?
  - Expectations differ if this is applied to testing by a single lab and a single lot of disks versus 2 individuals reading a single zone.
  - The WG recommended that the language in M02 be clarified. This issue will be forwarded to the M02 WG.

- Streamline QC
  - Susie Sharp will assist with this group.
  - Suggestions for streamlining QC included:
    - Clarify and streamline language in the QC boxes in Tables 2.
    - Use IQCP and the troubleshooting guide to define QC processes
    - Harmonize with EUCAST if possible

6. **METHODS APPLICATION AND INTERPRETATION WG (MAIWG) REPORT (T. KIRN)**

All presentations are informational.

ESBL/AMPC/CARBAPENEMASE GUIDANCE MODIFICATIONS

- The CLSI susceptibility testing and reporting guidance and IDSA treatment guidance for multiple drug resistant organisms (MDRO) do not align
  - CLSI applies current BPs and reports MIC as tested. Resistance mechanism testing is not routinely performed.
  - IDSA guidance is based on whether the mechanism testing is performed or not. Recommended treatment is based on the mechanism of resistance.
  - The goal is to align more closely with IDSA by providing more guidance on mechanism testing

- CAP Checklist addressing the application of updated BPs
  - M100 still refers to M100-S20 BPs if laboratories have not updated to current BPs. Many CAP accredited labs are still using outdated BPs.
  - The WG suggested removing this guidance to encourage labs to update to new BPs. In January 2024, CAP will require labs to update to new or revised BPs.

- ESBL Treatment Guidance
  - ESBL-E refers to presumed (ceftriaxone MIC: ≥ 2 mcg/mL) or confirmed ESBL-producing *E. coli*, *K. pneumoniae*, *K. oxytoca*, or *P. mirabilis*.
  - Antibiotic treatment selection can be based on susceptibility testing results if a locally validated ESBL phenotypic test does not indicate ESBL production
  - The WG recommended revising the 1st paragraph in the carbapenem Tables by deleting the 1st two sentences and the last two sentences and revising the middle sentences. **Example:** *"When using the current breakpoints, routine ESBL testing is not necessary before reporting results. If ESBL testing is performed at your institution the results may be used to guide therapeutic management, or for epidemiological or infection prevention purposes."* (add IDSA reference).
  - The WG also recommended to revise the introduction to Table 3A (Test for ESBLS) to align with the comments in Tables 2. All references to the old BPs would be deleted.
  - The WG will work to finalize the comments for presentation at the June meeting.

- AmpC Treatment Guidance
  - The WG recommended revising and updating the guidance in inducible AmpC comments in Tables 2 to better align with the IDSA recommendations.
  - The same revisions would also affect comments in the revised Tables 1.
  - The WG will work to finalize the comments for presentation at the June meeting.

- Guidance for Carbapenem Resistant Enterobacterales
  - IDSA bases treatment recommendations on carbapenemase detection.
  - The WG recommended additional revisions to the carbapenemase comments for Enterobacterales in Table 2A and in the introductions to Tables 3B and 3C to encourage mechanism testing.
  - The WG also recommended that Tables 3B-1 and 3C-1 be deleted.

- SC Discussion (main points)
  - There was agreement that the old breakpoints should be deleted.
  - There was concern regarding being too proscriptive on ESBL guidance. Many of the tests have limitations that are not totally understood.
  - Education is going to be key to inform labs on how to handle these resistance mechanisms.
  - The guidance should be different based on the type of infection.
  - There was concern that there is an overlap of ESBLs and KPCs with automated interpretation so there needs to be guidance on how to discern between the two.
  - It was agreed that the limitations with the phenotypic testing that should be emphasized. Better methods are needed and should be investigated.

APPENDIX H MODIFICATIONS

- The WG recommended that the title and column headers of Appendix H be revised for clarity: Resistance Mechanism Detection to include molecular testing but certain types of phenotypic testing that are provided in the appendix.
- The recommendations will also be aligned with the changes to the comment already discussed for resistance testing and reporting.

RIFAMYCINS

- Treatment of staphylococcal prosthetic joint infections is currently managed with irrigation and debridement with rifampin combination therapy; however, up to 30% of patients are unable tolerate rifampin or may have drug interactions.
- Activity of rifabutin and rifapentine has been shown against *S. aureus* and *S. epidermidis* (Antimicrob Agents Chemother 2019;63(11). pii: e00959-19. doi: 10.1128/AAC.00959-19).
- It was suggested that rifabutin and rifapentine might be repurposed for use in treating these and that QC ranges be established and/or use rifampin as a surrogate.
- SC Discussion (main points)
  - It was agreed that this is an important issue and should be pursued.
  - The path to a surrogate would be the most practical route to take.
  - It was decided that the MAIWG will provide an update at the June meeting.

AZTREONAM + CEFTAZIDIME-AVIBACTAM DISK ELUTION METHOD

- Background
  - Metallo-ß-lactamases (MBL) hydrolyze all ß-lactams except aztreonam and avibactam inhibits production of other ß-lactamases
  - Aztreonam + Ceftazidime-avibactam is recommended for treatment of certain organisms (MBL-producing CRE and *P. aeruginosa* and *S. maltophilia*)
  - RUO methods are available as well as testing at ARLN (CDC) laboratories; however, access can be difficult

- Disk Elution Method Rationale
  - Develop an easy method using aztreonam and ceftazidime-avibactam disks added to broth which related to specific concentrations.
  - Look for growth (not susceptible) vs no growth (susceptible).

- Study Summary
  - 3 testing sites working in two phases

	– Phase 1: Compare aztreonam & ceftazidime-avibactam (A & C-A) Disk Broth Elution Test to CDC BMD aztreonam & ceftazidime-avibactam AST results – Phase 2: Each site to test additional MBL producing Enterobacterales, *P. aeruginosa* and *S. maltophilia* clinical isolates at each site compared to reference BMD (single well aztreonam 6ug/ml, ceftazidime 6 ug/ml, avibactam 4 ug/ml) • Next steps – Complete and compile the multicenter data – Define the QC studies needed – Compare disks and broths from multiple manufacturers • SC Discussion (main points) – It was agreed that more resistant isolates need to be included in the studies.

7. **TEXT AND TABLES WG (TTWG) REPORT (A. BOBENCHIK)** (**NOTE:** THIS REPORT WAS PROVIDED DURING PLENARY 2)

- **M02/M07 WG UPDATE**
  - WG working on three parts: M02 unique text, M07 unique text, text common to both documents
  - Reviews of each part has been completed
  - The revisions to Tables 1 will be incorporated into the appropriate subchapter of both documents
  - First revision drafts for each part are expected by summer 2022.
  - Publication expected with M100 in January 2024.

- **PROPOSED REVISIONS AND/OR CLARIFICATIONS FOR M100**
  - Definitions and formatting
    - Define "antibiogram" vs "antimicrobial susceptibility profile" and harmonize with M39.
    - Harmonize selective, suppression, and cascade with M39.
    - Separation of the BP additions and revisions into two separate tables was proposed. Mocked-up tables will be presented in June.
  - Mismatches between Tables 1 and Tables 2
    - All comments between Tables 1 and 2, Tables 3 and the Appendixes will be reviewed and harmonized.
  - ß-lactam combination agent and tetracycline comments
    - Clarify and harmonize the comments regarding susceptibility to the ß-lactam agent alone and the ß-lactam combination agent in all appropriate tables.
    - Clarify and harmonize the statements regarding susceptibility to the tetracycline agents (minocycline, doxycycline) in all appropriate tables
    - Review and harmonize both comment types between Tables 1 footnotes, Tables 2 general comments, Tables 2 antimicrobial agent/organism specific comments and Appendixes.
  - Dosage comment standardization in Tables 2 and Appendix E
    - The placement of dosage comment and possible options were reviewed.
    - What the dosage comments can and cannot be used will be clarified.
    - The text for dosage comment will be standardized.
    - The placement of the dosage comments was also discussed and proposals will be made during the June meeting.
  - Use of R_x Comments
    - The therapy comments and when and what they are used for will be clarified.
  - Use of Meningitis and Non-Meningitis comments
    - The use of "meningitis" and "non-meningitis" labels cases will be reviewed and clarified.
    - Options for revision included:
      - Keeping the non-meningitis labels as IV formulation may be available outside the US but Is not for meningitis

	▪ Provide a reference to the Warning box in each of Tables 2 (eg, The susceptibility of CSF isolates should not be reported for some drugs. See Warning notes in Instructions for Use") – Reporting comments in Tables 3 (methods tables) o Work with the MDSWG to determine if BMD and the agar oxacillin screen are still useful for detecting *mecA* in *Staphylococcus* spp. other than *S. aureus*. o The single dilution screening test is not generally adequate for the *Staphylococcus* spp. other than *S. aureus*. o Determine if this group of organisms should be removed from Table 3G-2. – Inconclusive vs Indeterminate vs Intermediate o There are inconsistencies in the use of these terms and creates confusion. This especially true for Tables 3C and 3K in use of the terms. o A single word for both tables will be considered. o Definitions for terms will be added to the Instructions for Use. • **SC DISCUSSION (MAIN POINTS)** – It was noted that many related agent BPs were approved using a single FDA approved standard dosage regimen. It was suggested that only those BPs that are based on multiple dosage regimens be listed. It was noted that for drugs having different dosage regiments outside the US, listing that dosage might be useful. – Dr. Schuetz noted that a group has been formed to work on standardizing terminology across professional societies (eg, ASM), laboratory groups, and industry. She can provide a contact if needed.
8.	**ADJOURNMENT** Dr. Lewis thanked the participants for their attention. The meeting was adjourned at 5:45 PM Eastern (US) time.

2022 WINTER AST MEETING SUMMARY MINUTES PLENARY 2: TUESDAY, 1 FEBRUARY – 3:00 – 6:00 PM EASTERN (US) TIME	
#	**Description**
1.	**TABLE 1 REVISION AD HOC (AHWG) REPORT (P. SIMNER)** **BACKGROUND** • June 2019: Proposed re-assignment of agents presented. • Fall 2020: Approval of an additional group • Winter 2021: Groups replaced by Tiers and approval of replacement of vertical horizontal formatting with horizontal formatting. • Summer 2021: Addition of a 4th Tier and new antimicrobial agent placement was presented • Fall and Winter 2021: AHWG met and incorporated SC feedback into newly formatted horizontal tables which were also separated into specific organism groups resulting in Tables 1A – 1Q. Instructions for Use (IFU) were revised with assistance of Janet Hindler. **INSTRUCTIONS FOR USE OF TABLES REVISIONS (SECTION 1 – SELECTING ANTIMICROBIAL AGENTS FOR TESTING AND REPORTING)** • A. Appropriate Agents for Routine Testing – Text was streamlined and updated to reflect the new tables (1A-1Q). – The recommendations for selecting, testing, and reporting guidelines were called out in a box and streamlined. • B. Equivalent Agents – The meaning of agents in the same box or in the same box with an “or” were clarified. – Same box: Similar interpretive categories and clinical efficacy – Same box with an “or”: Agents with cross-susceptibility or cross-resistance • C. Test/Report Tiers – Definitions for the Tiers were provided. – The WG recommended adding a new table titled, “Antimicrobial Agent Test and Report Tiers and Additional Considerations”. The table would include the tier definitions, how to test (routine and/or by request), how to report (routine vs cascade vs cascade and/or selectively report or by request), and additional testing and reporting considerations.

- D. Selective and Cascade Reporting
  - The definitions of selective reporting and cascade reporting within tiers and between tiers were revised and clarified.
  - The WG recommended including an example figure that explains the concept of cascading.

- Introduction to Tables 1A-1Q
  - The introduction was revised and clarified to indicate that these are recommendations and are not required to be implemented in laboratories.
  - The goal was to be directed towards drugs approved by the FDA. Additional region-specific tables could be added to guide laboratories outside the US.
  - The introductory text included the Warning regarding agents that should not be reported on organisms isolated from CSF.

TABLES 1 REVIEW (1A – 1Q): REVISIONS MADE TO THE TABLES SINCE THE SUMMER 2021 MEETING WERE HIGHLIGHTED. FOOTNOTES APPLICABLE TO THE AGENTS IN THE TABLE WERE INCLUDED.

- Table 1A. Enterobacterales (not including Inducible AmpC producers & *Salmonella/Shigella*)
  - AmpC producers are described in Table 1B.
  - Ceftazidime is included in Tier 4 since it is generally reserved for *P. aeruginosa* and as a screen for ESBLs.
  - The urine agents were listed as urine only but it is noted that these agents are not just limited to testing on urine isolates but can be tested through Tiers 1-3 as appropriate.
  - Trimethoprim and sulfasoxazole as single agents were deleted since they are not used for clinical use in the US.
  - SC comment: It was requested that the AmpC producers be specifically identified.

- Table 1B. Inducible AmpC-Producing Enterobacterales (New since Summer 2021)
  - A footnote was defined which Enterobacterales species are included in this table.
  - Most discussion concentrated on the placement of ceftriaxone, cefotaxime, and piperacillin-tazobactam. The WG attempted to align with the IDSA guidelines. It decided to retain the drugs in Tier 1 but add a footnote to clarify that reporting should be based on institutional guidelines.
  - The other discussion was related to placement of cefotaxime, cefoxitin, and cefotetan. It was retained as in Table 1A but a footnote was included for clarification.
  - SC Discussion (Main Points)
    - There was concern regarding the plan for educating bench techs about the AmpC Enterobacterales which may have a different testing panel than the non-AmpC Enterobacterales.
    - It was noted that rules can be added to most commercial system expert rules. The commercial system manufacturers could assist with this.
    - It was suggested that a footnote be added for intrinstic resistance for ampicillin-sulbactam.

- Table 1C. *Salmonella* and *Shigella* spp.: The WG opted to retain the carbapenems Tier 3 and azithromycin in Tier 2.

- Table 1D. *P. aeruginosa*
  - Language was added to the IFU to address unusual resistance (eg, resistant to the carbapenems but susceptible to other ß-lactams).
  - Aztreonam was moved to Tier 4 to be consistent with the definition of Tier 4 and placement for Enterobacterales.

- Table 1E. *Staphylococcus* spp.
  - Daptomycin and linezolid were moved to Tier 2 from Tier 3.
  - Penicillin was also moved to Tier 2, as it is still an option for ß-lactamase non-producers. A footnote was added stating to report penicillin if the absence of ß-lactamase has been confirmed.

- Table 1F. *Enterococcus* spp.: Linezolid and daptomycin were moved to Tier 2.

- Table 1G. *Acinetobacter* spp.: Cefotaxime and ceftriaxone were retained until it is determined through further investigation if the data shows they should be removed.

- Table 1H. *Burkholderia cepacia* complex: There were no changes to the table but it was noted that a WG has been formed to review *B. cepacia* complex BPs.

- Table 1I. *S. maltophilia:* Ceftazidime was moved to Tier 4 based on the recent IDSA recommendations.

- Table 1J. Non-Enterobacterales**:** No revisions were made since the Summer 2021 meeting; however, the M45 and Non-Enterobacterales WGs are looking at this table and revisions could be made based on the WG recommendations.

- There were no changes to the following tables:
  - Table 1K. *H. influenzae* and *H. parainfluenzae*
  - Table 1L. *N. gonorrheoae*
  - Table 1M. *S. pneumoniae*

- Table 1N. *Streptococcus* spp. ß-Hemolytic Group: Tetracycline was included in Tier 2.

- Table 1O. *Streptococcus* spp. Viridans Group
  - Cefepime was added to Tier 3 as it is used selectively empirically for pathogens of concern and is frequently used in oncology patients.
  - It was suggested that levofloxacin be added as it is frequently used for neutropenic patients.
  - Chloramphenicol was removed from the table as oral dosages are no longer available in the US. **NOTE:** IV chloramphenicol is still available.
  - Cefotaxime was retained as it can still be obtained in the US.
  - It was suggested that levofloxacin be added to the table in Tier 4 as it is tested routinely in some cancer centers.

- Table 1P. Gram-Negative Anaerobes and Table 1Q. Gram-Positive Anaerobes
  - Imipenem-relebactam was removed from both tables.
  - SC Discussion (Main points)
    - It was questioned as to why imipenem-relebactam was removed from Tables 1P and 1Q. It was noted that the agent is still listed with BPs in Tables 2.
    - It was noted that there was a discussion regarding imipenem-relebactam during the Summer 2021 plenary: "Comment: It was noted that although the sponsor requested a BP for imipenem-relebactam, there is no real need to test it. It was suggested that it doesn't need to be in Table 1. Response: There is a comment in M100 regarding imipenem-relebactam being susceptible if imipenem is susceptible. It was agreed that imipenem-relebactam can be removed."

- SC Discussion (Main points)
  - It was suggested that the Tables 1 information could be incorporated into Tables 2 rather than separate. This suggestion will be considered.
  - It was suggested that a footnote be added to the anaerobe tables regarding activity of imipenem-relebactam against anaerobes. It was agreed that this would be considered.

A motion to adopt the new horizontal format with four Tiers (categories) and new individual organism or group tables was made and seconded. Vote: 13 for, 0 against, 0 abstain, 0 absent (Pass)

- It was emphasized that the education will be critical for laboratories.
- It was suggested that the Outreach WG consider development of programs for education.
- It was suggested that testing and reporting as per institutional guidelines be emphasized in the Tier definitions.

A motion to approve Tables 1D through 1N as presented was made and seconded. Vote: 13 for, 0 against, 0 abstain, 0 absent (Pass).

A motion to approve Table O with levofloxacin and cefepime in Tier 4 and dirithromycin deleted from footnote (e) was made and seconded. Vote: 13 for, 0 against, 0 abstain, 0 absent (Pass).

- It was suggested that a footnote be added to Tables 1P and 1Q to imipenem that states that imipenem susceptibility can be used to predict imipenem-relebactam.
- A motion to accept Tables 1P and 1 Q was withdrawn.
- It was agreed that Tables 1A – 1C and Tables 1P – 1Q will be revisited at a later plenary or at the June meeting.

2. **M45 UPDATE (P. SIMNER AND R. HUMPHRIES)**

High-level items under consideration for the next edition included:

- Evaluate disk diffusion correlates for *Aerococcus* spp., *Pasteurella* spp., and *Achromobacter* and other non-*P. aeruginosa* isolates.
- Consider new BPs for:
  - Ciprofloxacin and *Aerococcus* spp.
  - Carbapenems for *Campylobacter* spp.
  - *Helicobacter pylori*
  - Vancomycin and *Listeria* spp.
- Revise existing BPs for fluoroquinolones and *Aeromonas* spp. and penicillin and *Corynebacterium* spp.
- Investigate growth failures for *Aerococcus* spp.
- Consider addition of tables for new organisms including:
  - *Campylobacter upsaliensis*, *C. lari*, *C. fetus*, *C. hyointestinalis*
  - *Actinomyces* split from *Corynebacterium* spp.
  - *Weissella* spp.
  - *Kocuria*, *Nesterkonia*, *Dermacoccus*, *Kytococcus* (*Micrococcus*)
  - Non-catarrhalis *Moraxella* spp.
  - *Bacillus cereus* serovar *anthracis*
- Consider adding an intrinsic resistance table

The WG requested that data and/or isolates be submitted for the following:

Isolates	Data (ideally MICs from BMD or agar dilution and/or disk diffusion testing)
Aerococcus spp. for disk:MIC studies	*Abiotrophia* / *Granulicatella* MIC data
Aeromonas spp. for carbapenemase test evaluation	*Leuconostoc* spp. MIC data
Catalase negative GPC for methods evaluation	*Bacillus* spp. MIC data
Pasteurella spp. for disk:MIC evaluation	*Corynebacterium* spp. and related genera
Achromobacter spp.	*Gemella* spp. MIC data
Non-*aeruginosa Pseudomonas* spp.	*Weisella* spp. MIC data
	Moraxella (non-catarrhalis spp)

- Please include ID method, test method (media brand, disk/strip brand), MIC dilution range tested, and any testing notes.

	The WG presented the following topics for discussion. • Consider moving the Non-Enterobacterales table from M100 to M45 • Consider making M45 freely available online **SC Discussion (main points)** • The M45 and Non-Enterobacterales WG will meet off-line to discuss the disposition of the Non-Enterobacterales table. • CLSI management will be approached regarding including M45 as a free online document. • It was noted that many of the "BPs" in M45 were approved without meeting M23 requirements. • There are practical issues regarding testing isolates in M45. Most BPs are based on BMD and not commercial systems. The WG will be investigating disk correlates and gradient diffusion.

3.	**M39 AND OUTREACH WG UPDATE (J. HINDLER) (NOTE: THIS PRESENTATION WAS MADE DURING PLENARY 3)** **Ms. Hindler provided an update from the Outreach and M39 WGs.** • The new AST attendee orientation has been updated and is available on the CLSI website. It can also be accessed through YouTube. • **Webinars for 2021 and 2022** – **CLSI-SIDP ACCP Annual Webinar:** The Evolving Value a Laboratory - Stewardship Partnership: Cases in Susceptibility Testing, Rapid Diagnostics and More (completed) – **CAP-CLSI Annual Webinar Breakpoints Matter:** Understanding CLSI Efforts and New CAP Requirements to Ensure Appropriate Antimicrobial Treatment for all Patients (completed) – **CLSI Annual Update (19th):** What's New in the 2022 CLSI Standards for Antimicrobial Susceptibility Testing (AST)? – March 22 – 23, 2022 (R. Humphries and A. Schuetz) – M39 Antibiograms – April 28, 2022 (S. Erdman and T. Simner) – CLSI-SIDP ACCP Annual Webinar is being planned as well as a possible Webinar on Practical Advice for Bench Techs – How to Recognize Unusual AST Patterns • **M39, 5th edition:** Analysis and Presentation of Cumulative Antimicrobial Susceptibility Test Data published January 25, 2022. A JCM mini-review, a CLSI webinar, and an ASM Microbe symposium are being planned • **ASM Microbe 2022 presentations** – The status of Antibiograms in 2022 (T. Simner) – Antibiograms in Healthcare: What they tell us and what they don't (S. Erdman) – Piperacillin-tazobactam Clinical and Susceptibility Review (P. Tamma) • **A new educational program in Using M100 is now available on the CLSI website was reviewed.** – This is freely available without Pace credits – 1.5 hours of CEU can be obtained for $30. • **Other publications:** JCM, Mini-review of M100, 31st edition • **CLSI Newsletter Update** – Most recent published in April 2021. These have been translated into Chinese and Spanish. – Planned topics for the Winter 2022 edition include: o A feature on Direct Disk Diffusion testing from blood cultures o A case study on *Shigella* and azithromycin o Practical tips for *S. epidermidis* and *S. marcescens* o Hot topic on Amphotericin B and *C. auris* o News regarding Webinars, new documents, updated ASM IQCP guidance, and a summary of the Joint CLSI-EUCAST WG efforts • **AST SC Meeting Workshops:** It is expected to be held during the next in-person meeting (Updating Breakpoints –The Concerns and Solutions) • **New ORWG Projects** – JCM minireview for M100, 32nd edition – Reorganize customer questions and answers by topic and assign volunteers to specific topic questions – Reassess the newsletter format – Develop a list of optional report comments

	– M23 tutorial • **ORWG Volunteer Opportunities** – Suggest content and/or write articles for the newsletter – Sign up to be an expert for customer questions and answers – Work on the M23 tutorial – Suggest content and/or present topics for new webinars

4.	**JOINT CLSI-EUCAST WG REPORT (J. HINDLER) (NOTE: THIS PRESENTATION WAS MADE DURING PLENARY 3)** **UPDATE ON THE WG'S ACTIVITIES (J. HINDLER)** • **WG roster:** Maria Traczewski has retired and Dana Dressel has replaced her as an industry member. • **WG Goals** – Describe a method for disk content determination which can be used early in the drug development process to avoid having different disk contents in the CLSI and EUCAST standards. Completed with the publication of M23-S, *Procedure for Optimizing Disk Contents (Potencies) for Disk Diffusion Testing of Antimicrobial Agents Using Harmonized CLSI and EUCAST Criteria* and M23-S2, *Process to Submit Disk Content (Potency) Data for Joint CLSI-EUCAST Working Group Review and Approval*. o One disk content in progress: ceftibuten-avibactam o To be presented at the June 2022 meeting – Discuss differences between CLSI and EUCAST QC criteria, methods for establishing QC criteria and the possibility of harmonizing CLSI and EUCAST QC criteria. **OVERVIEW OF THE PLAN FOR HARMONIZING CLSI AND EUCAST QC PROCESSES (S. CULLEN).** • **Background** – A comparison between CLSI and EUCAST QC some processes showed differences in sample sizes and approach for the following but generally both processes considered the same factors: o Number of laboratories or independent evaluations o Number of media lots o Number of replicates required o Number of disk lots o Total data points needed o Data analysis o Media manufacturers • **Plan for QC standardization** – M23S and EUCAST SOP 11.0 provide identical requirements for media standardization – The plan is to develop a protocol to be performed after the disk potency has been decided and before QC studies begin with a goal to provide data sufficient for both organizations to establish QC ranges and hopefully harmonize the QC ranges. The main focus will be to improve the assessment of media lots for disk diffusion (and include media commonly used in Europe). – The procedure will be developed by a sub-group of the Joint WG with 1-2 members representing Susceptibility Testing Manufacturer's Association (STMA). – The protocol will be presented to the SC at the next meeting. – The WG suggested development of a joint CLSI-EUCAST QC study once disk content has been approved
5.	**M02/M07 WG REPORT:** See the Text and Tables WG report
6.	**ADJOURNMENT** Dr. Lewis thanked the participants for their attention. The meeting was adjourned at 5:55 PM Eastern (US) time.

#	Description
1.	**BPWG REPORT (PARTS 1 AND 2) (A. MATHERS AND M. SATLIN)**

PIPERACILLIN-TAZOBACTAM (PTZ) AND PIPERACILLIN BP REVIEW FOR *P. AERUGINOSA* (A. MATHERS)

Background

- In 2021, an ad hoc (AHWG) was formed to review and revise PTZ BPs for Enterobacterales. In light of BP changes for Enterobacterales, the AHWG was asked to review PTZ BPs for *P. aeruginosa*. Also reviewed:
  - Disk correlates for all potential changes
  - BPs for piperacillin alone

- Current BPs for PTZ

	Enterobacterales				*P. aeruginosa*		
	Susceptible (µg/mL)	Susceptible Dose-Dependent (µg/mL)	Resistant (µg/mL)		Susceptible (µg/mL)	Susceptible Dose-Dependent (µg/mL)	Resistant (µg/mL)
Previous CLSI	≤16	32 to 64	≥128		≤16	32 to 64	≥128
FDA	≤16	32 to 64*	≥128		≤16	32 to 64*	≥128
EUCAST	≤8	-	>8		≤0.001	-	>16
CLSI 2021	≤8[1]	16[2]	≥32				

1. Based on dosing of 3.375g or 4.5g q6h over 30 minutes
2. Based on a dose of 4.5g q6h as a 3-hour infusion or 4.5g q8h as a 4-hour infusion
* FDA does not recognize Susceptible Dose-Dependent as an interpretive category.

Data review

- The epidemiological cutoff value (ECV) for PTZ and *P. aeruginosa* is 16 µg/mL (EUCAST data) (ECV for Enterobacterales is 8 µg/mL.)
- Clinical outcome data were reviewed.
  - Several retrospective studies suggested that *P. aeruginosa* isolates with PTZ MICs ≥32 µg/mL resulted in poorer outcomes.
  - Clinical data do not inform appropriate antibiotic dosing, frequency, or infusion times for *P. aeruginosa* infections with PTZ MICs ≤16 µg/mL.
  - Revisions to the CLSI susceptibility criteria for PTZ against *P. aeruginosa* will primarily be informed by PK/PD data.
- PK/PD data were reviewed.
  - Older PK/PD data showed that infusions of more than 1 hour can achieve PK-PD targets for an MIC of 8 and possibly 16 µg/mL
  - Lodise TP, et al. (Antimicrob Agents Chemother. 2004; 48(12):4718-24) concluded that 3.375g q6h achieves PK-PD targets for an MIC up to 8 µg/mL.
  - DeRyke CA, et al. (Diag Micro Infect Dis. 2007;58:337-344) concluded that 3.375g q6h and 4.5g q6h achieves PK-PD targets for MICs up to 8 µg/mL; PD-derived BP for PTZ is 8 µg/mL for Enterobacterales and *P. aeruginosa*.
- Data from multiple evaluations of extended PTZ infusions were reviewed

Study Reference	Conclusion
Burgess DS, et al. (Clin Ther 2002; 24: 1090-104.)	3.375g q6h covers MICs up to 8 µg/mL and 13.5g continuous infusion covers MICs up to 16 µg/mL
Li C, et al. (J Antimicrobial Chemother 2005; 56:388-95)	3.375g q6h covers MIC up to 8 µg/mL and 13.5g daily as continuous infusion covers MIC up to 16 µg/mL
Felton TW, et al. (Antimicrob Agents Chemother 2012; 56: 4087-94)	3.375g q6h over 3 hours covers MICs up to 8 µg/mL, 4.5g q6h as an extended infusion needed to target MICs up to 16 µg/mL
Thabit AK, et al. (J Pharm Pract 2017; 30: 593-9.)	In patients with normal renal function, 3.375g q6h and 4.5g q6h covers MICs up to 8 µg/mL; extending the infusion covers MICs up to 16 µg/mL
El-Haffaf I, et al. (Clin Pharmacokinet 2021;60:855-875)	• 4.5g q6h as a standard infusion covers MICs up to 8 µg/mL • 4.5g q6h extended over 3 hours covers MICs up to 16 µg/mL

- 3.375g q6h, 4.5g q6h, or 4.5g q8h as a **standard infusion** appears adequate for organisms with MICs up to 8 µg/mL
- Extending the infusion of PTZ over 3 hours and administered every 6 hours generally necessary to target PTZ MIC up to 16 µg/mL; not clear if there is a benefit with 4.5g dosing versus 3.375g dosing

- In several studies, tazobactam was shown to have no significant role in PTZ activity on *P. aeruginosa*.

AHWG proposal to the BPWG

	Susceptible (µg/mL)	SDD (µg/mL)	Resistant (µg/mL)
CLSI current	≤16	32 to 64	≥128
Proposal	≤8[a]	16[b]	≥32

[a]Based on a dose of 3.375g or 4.5g Q6-8h as 3-4h extended infusion
[b]Based on a dose of 4.5g Q6h as an extended infusion over 3h

- BPWG Discussion
  - There was concern that the intermediate would split the wild-type distribution and make testing a bigger challenge.
  - Suggested potential comments regarding technical uncertainty.
  - Motion passed: 9-1-1-0

BPWG Proposal to SC

	Susceptible	Intermediate	Resistant
Current CLSI	≤16	32 to 64 (SDD)	≥128
New Proposed BP	≤16[1]	32[2]	≥64

[1]Based on dosing of 4.5g q6h as a 30 minute infusion or 4.5g q6h as a 3-hour infusion
[2]Intermediate category based on technical uncertainty with MIC testing

- SC Discussion
  - PK/PD data don't support a susceptible breakpoint of 16 with a standard dose and infusion of PTZ. 16 is based on a prolonged infusion.
  - Although the clinical data are imperfect, the data are better and more consistent than for other CLSI BPs.

- There was concern that not all hospitals have the capability of doing extended infusions (increased exposure). This is also an issue internationally.
- It was suggested that the comment regarding intermediate being based on technical uncertainty (technical variability) should be better aligned with the current definition in M100.

A motion to approve the PTZ BPs for P. aeruginosa (≤16 [S]; 32 [I]; ≥64 [R]) with a comment regarding extended infusions (Based on dosing of 4.5g q6h as a 30 minute infusion or 4.5g q6h as a 3-hour infusion) and issues with the intermediate category (to align the comment with the current definition of "I" in M100) was made and seconded. Vote: 11 for, 2 against, 0 abstain, 0 absent (Pass).

- Dr. Limbago's opposition was based on attaining 16 with a standard dose.
- Dr. Schuetz's opposition was based on concerns between 32 and 64 and difficulty reading the test results. She would like to see a dosage associated with intermediate.

Disk Correlates for PTZ

- The BPWG proposed the following PTZ disk correlates:
  - S: ≥ 22 mm; I: 18–21 mm; R: ≤17 mm
  - The disk correlate data for these BPs fit the M23 requirements.
  - The BPWG approved the disk correlates: 9-1-1-0

A motion to approve the proposed PTZ disk (100/10 µg disks) BPs (S: ≥22 mm; I: 18-21 mm; R: ≤17 mm) was made and seconded. Vote: 13 for, 0 against, 0 abstain, 0 absent (Pass).

Piperacillin-Only Disk BPs for *P. aeruginosa*

- Current Piperacillin-only BPs: S: ≥ 21; I: 15-20, R: ≤14
  - With the lowering of the PTZ BPs and using modern PK/PD for piperacillin alone, it was suggested that piperacillin along should be lowered as well.
  - It was reiterated that tazobactam has no significant role in PTZ activity against *P. aeruginosa*.
  - The ECV for PTZ is identical to that for piperacillin alone.
  - There is limited recent disk correlate data for piperacillin alone

- **BPWG proposal:** Revise the piperacillin only BP (MIC and DD) to align with PTZ BP for *P. aeruginosa*

Antimicrobial Agent	Disk Content	Interpretive Categories and Zone Diameter Breakpoints, nearest whole mm			Interpretive Categories and MIC Breakpoints, µg/mL		
		S*	I	R	S	I	R
Piperacillin	100 µg	≥22	18-21	≤17	≤16	32	≥64

*Based on a dose of 4 gm q6h as a 30-minute or 3-h infusion, assuming normal renal function.
Intermediate accounts for some technical uncertainty in test reproducibility in the range of 32 µg/mL. Would not anticipate that 32 µg/mL would be achievable in serum at any approved dose of piperacillin.

- BPWG approved: 9-1-1-0 motion to align the piperacillin BP with the amended PTZ BP (with the caveat that no disk correlate data were presented for piperacillin alone)

A motion to approve the piperacillin BPs (Disk: S ≥22 mm; I 18-21 mm; R ≤17 mm and MIC: S ≤16 µg/mL; I 32 µg/mL; R ≥64 µg/mL) was made and seconded. Vote: 13 for, 0 against, 0 abstain, 0 absent (Pass)

***STENOTROPHOMONAS MALTOPHILA* BPs**

- **History**
  - Opportunistic environmental gram-negative bacilli increasing causing infections in immunocompromised patients.
  - Specific BPs for *S. maltophilia* were established in the early 2000s although little PK/PD data were available at that time.
  - There are considerable differences in BPs between CLSI, EUCAST, and FDA
  - M23 criteria for BP review is met for this organism with new PK/PD data available.

- **New PK/PD Data available from a study by the Center for Anti-Infective Research & Development (funded by FDA)**
  - Data were presented to the FDA who requested it be reviewed by CLSI.
  - Potential AHWG was formed to review the data
  - Antmicrobial agents studied: Levofloxacin, minocycline, trimethoprim-sulfamethoxazole
  - Levofloxacin
    - Data suggested that the susceptible BP could be lowered to 0.5 µg/mL (consistent with Enterobacterales), which would result in ≈21% susceptibility or to 1 µg/mL (consistent with *P. aeruginosa*), which would result in ≈57% susceptibility.
    - Both BPs based on dosage regimen of 750mg q24h.
  - Minocycline
    - *In vivo* efficacy studies of a minocycline HSR 100mg q12h against 17 *S. maltophilia* support CFU reductions of approximately 1 log10 at MICs ≤ 0.5 µg/mL
    - No kill was observed for isolates with MICs ≥ 1 µg/mL, well below the current CLSI susceptible breakpoint of 4 µg/mL
    - Monte Carlo simulation of minocycline 200mg q12h demonstrated PTA of 97.3% for 1 log10 kill thresholds at MIC of 0.5 µg/mL, which would result in ≈64% susceptibility
  - Trimethoprim-sulfamethoxazole
    - Generally considered to be the drug of choice.
    - Rodent animal models can't be used for studies due to higher concentrations of thymidine in plasma
    - Time-kill and chemostat models were used for the studies.
    - Based on observations from the studies, the investigators recommended that *S. maltophilia* be defined as intermediate for all isolates ≤2/38 µg/mL based on ≥10 mg/kg/daily dosing regimen with Warning about need for combination therapy as currently done for colistin.

- **BPWG Discussion**
  - It was generally agreed that M23 criteria had been met; however, additional data are needed to formally review the BPs for most agents.
  - It was questioned what type of data will be needed going forward.
  - The BPWG proposed that the AHWG be formally charged with reviewing the *S. maltophilia* BPs.

- The SC agreed that the AHWG should move forward with review of the BPs. IDSA guidelines should be take into consideration going forward.

CEFIDEROCOL MIC AND DISK ZONE CORRELATES FOR *A. BAUMANNII* (M. SATLIN)

Background

- BPs approved at the Winter 2021 meeting

	MIC breakpoints (µg/mL)			Disk diffusion breakpoints (mm)		
	S	I	R	S	I	R
Enterobacterales	≤4	8	≥16	≥16	9-15	≤8
Pseudomonas aeruginosa	≤4	8	≥16	≥18	13-17	≤12
Acinetobacter spp.	≤4	8	≥16	≥15	--	--
Stenotrophomonas maltophilia	≤1	--	--	≥15	--	--

  - Set from combined data from multiple trials, multiple labs, with different broth and agar manufacturers.
  - Sponsor requested to generate additional disk data to help establish an intermediate disk zone BP

Data Review: *Acinetobacter* spp. MIC vs Disk Correlation Studies (IHMA and Shionogi)

- IHMA and Shionogi tested 261 and 197 isolates that had elevated cefiderocol MICs (respectively) in triplicate. These were from the original data set and new isolates.
- IHMA data showed frequent major errors, MICs changed on re-test, and disks zones frequently had colonies in the inhibition zone
- Shionogi re-tested 197 isolates that IHMA had tested and results did not compare well.
  - There was a trailing phenomenon in the BMD study
  - A majority of isolates tested by disk show colonies in the inhibition zone
  - There was no strong relationship between trailing and colony observations.

Conclusions

- Poor reproducibility in both disk zone and MIC for 197 *A. baumannii* isolates which showed high cefiderocol MIC (>2 µg/mL)
- Many high MIC isolates showed trailing phenomenon in broth and/or the appearance of colonies in the disk zone by disk diffusion method.
- Shionogi conducted additional studies on inoculum size and media with BMD and disk diffusion.

Evaluation of inoculum effect

- 10 isolates with cefiderocol MIC >4 µg/mL and showed colony appearance in the disk zone + 10 isolates with cefiderocol MIC of ≤1 µg/mL
- The disk zone was consistent for all 20 isolates irrespective of medium and/or inoculum size.
- In the 10 high MIC isolates, variations in BMD MICs were observed between inoculum dilutions in ID-CAMHB
- No MIC variations were seen in 10 isolates with cefiderocol MIC of ≤1 µg/mL
- Conclusions
  - Isolates with low cefiderocol MICs (≤ 1 µg/mL) correlated with disk zone diameters, demonstrated reproducibility both by ID-CAMHB and ID-ISB, showed no significant differences based on inoculum size

	– Isolates with higher cefiderocol MICs (≥ 2 µg/mL) showed that small colonies made it difficult to accurately read and interpret disk diffusion sizes, there was low reproducibility of MIC and disk studies, there was a noted inoculum effect for ID-CAMHB. **Plan Forward – Studies to be Performed** • BMD vs disk diffusion by using low inoculum size • Characterization of microcolony-producing isolates for heteroresistance • *In vivo* activity in mouse thigh infection models under humanized PK **BPWG Discussion (members of both Methods Groups were in attendance)** • It was questioned if the MIC and disk zone reproducibility concerns extends to other organism groups. The sponsor stated that these issues were not seen with Enterobacterales or *P. aeruginosa*. • It was also questioned if there are patient safety concerns with keeping the current BPs. It was noted that the issues only seem to occur with a select group of isolates with high MICs and that the agents are only being used when there are limited or no alternatives. **SC Discussion** • EUCAST also had issues with reproducibility. • The BPWG requested that anyone interested in investigating the issue, let the WG know. • It was suggested that isolates from countries with high carbapenem resistance be included in further studies. • It was suggested that there be clear reading instructions provided to the users. It was noted that Appendix I in M100 provides recommendations for reading cefiderocol results. • It would be helpful to look at the iron-concentrations.
2.	**Adjournment** Dr. Lewis thanked the participants for their attention. The meeting was adjourned at 5:05 PM Eastern (US) time.

2022 WINTER AST MEETING SUMMARY MINUTES PLENARY 4: THURSDAY, 10 FEBRUARY – 2:00 – 5:00 PM EASTERN (US) TIME	
#	**Description**
1.	**EUCAST UPDATE (C. GISKE)** **An update on EUCAST activities was provided.** • The committee extended the tenure with one year for Gian Maria Rossolini (Italy) and Jorge Sampaio (Brazil). • There are 3 standing subcommittees (Antifungal, Vet, and Antimycobacterial) and 5 ad hoc WGs currently in progress. • EUCAST BPs and guidelines have been implemented in most European countries. The same countries also have national AST committees in place. • BP consultations in 2021 included: – *Vibrio* spp. – Colistin (bracketed) – BPs and disk diffusion methodology for rapidly growing anaerobes (eg, *Bacteroides* spp., *Prevotella* spp., *C. perfringens* etc.) – Aminopenicillin BPs for Enterobacterales • Planned activities for 2022 include: – Fosfomycin IV – Chloramphenicol (meningitis) – Pediatric dosing – Dosing of cephalosporins and staphylococcal penicillins in methicillin-susceptible *S. aureus*.

2. **BPWG REPORTS (PARTS 3 AND 4)(M. SATLIN)**

AMINOGLYOSIDE AHWG REPORT (M. SATLIN FOR THE AHWG)

Background

- The AHWG (lead by Dr. Navaneeth Narayanan and Dr. Susan Butler-Wu) was formed to re-evaluate aminoglycoside BPs for gram-negative bacilli. Recent PK/PD data shows that the current BPs may not be appropriate.
- Current CLSI BPs were established pre-1980 and primarily based on toxicity concerns.

CLSI-FDA (µg/mL)				
Agent	**Organisms**	**S**	**I**	**R**
Gentamicin	Enterobacterales	≤4	8	≥16
	Pseudomonas	≤4	8	≥16
	Acinetobacter	≤4	8	≥16
Tobramycin	Enterobacterales	≤4	8	≥16
	Pseudomonas	≤4	8	≥16
	Acinetobacter	≤4	8	≥16
Amikacin	Enterobacterales	≤16	32	≥64
	Pseudomonas	≤16	32	≥64
	Acinetobacter	≤16	32	≥64

More Recent Data

- New PK/PD data from Sujata Bhavnani (USCAST) became available and presented in a USCAST report.
- Craig WA, et al. J Antimicrob Chemother. 1991 May;27 Suppl C:29-40) showed that AUC/MIC ration seems to correlate best with killing in the neutropenic thigh model.
- Stasis models have been developed for non-clinical PK/PD targets including thigh and lung depending on the organism.
- Studies of population PK models have been published. Selection criteria included:
  - Developed in adults
  - Relevant covariates assessed (CL – renal function; volume – body size)
  - Structural and statistical model reproducible from original publication
  - Patient population generalizable to patients with a broad set of indications
- Clinical constructs were developed for selecting bacterial reduction endpoints for non-clinical PK/PD targets
- Data for gentamicin, tobramycin, and amikacin were reviewed.
- Summary: Aminoglycoside *in Vitro* Susceptibility test interpretive criteria

Organism/Antimicrobial	MIC breakpoints in µg/mL by criteria organization Susceptible/Resistant			
	CLSI[a]	US-FDA[b]	EUCAST[c]	USCAST[d]
Enterobacteriaceae				
Amikacin	≤16 / ≥64	≤16 / ≥64	≤8 / >8[e]	≤4 / ≥8
Gentamicin	≤4 / ≥16	≤4 / ≥16	≤2 / >2[e]	≤2 / ≥4
Gentamicin – pneumonia				≤1 / ≥4
Plazomicin	-	≤2 / ≥8	-	≤4 / ≥8[f]
Tobramycin	≤4 / ≥16	≤4 / ≥16	≤2 / >2[e]	≤ 2 / ≥4
Tobramycin - pneumonia				≤ 1 / ≥4
Pseudomonas spp.				
Amikacin	≤16 / ≥64	≤16 / ≥ 64	≤16 / >16[e]	≤2 /≥ 8
Gentamicin	≤4 / ≥16	≤4 / ≥16	-	-
Tobramycin	≤4 / ≥16	≤4 / ≥16	≤2/ >2[e]	≤1 / ≥2

a. CLSI M100-ED31 (2021) interpretive criteria. http://em100.edaptivedocs.net/GetDoc.aspx?doc=CLSI%20M100%20ED31:2021&scope=user
b. FDA 2021 interpretive criteria https://www.fda.gov/drugs/development-resources/fda-recognized-antimicrobial-susceptibility-test-interpretive-criteria
c. EUCAST 2021 breakpoint tables. https://www.eucast.org/clinical_breakpoints/
d. Based primarily on the assessment of high dose, extended interval regimens and the assumption of combination therapy.
e. For the treatment of urinary tract infections. For treatment of systemic infections, aminoglycosides should be used in combination with an active agent.
f. For monotherapy of complicated urinary tract infection (including acute pyelonephritis).

- MIC Distribution data for Enterobacterales and *P. aeruginosa* was provided.
- Preliminary clinical data were reviewed
  - Meta-analysis of 37 randomized trials comparing aminoglycoside monotherapy to one or more non-aminoglycoside antibiotic regimens was performed
  - For UTI: Aminoglycosides equally effective to comparator antibiotics in achieving clinical improvement
  - Rate of bacteriological failure increased at end of treatment, but not at 30 d
  - Adverse events were less with aminoglycosides overall compared to ß-lactams, except nephrotoxicity was increased; discontinuation rates similar
  - Paucity of data from RCTs, and based on data available from non-randomized trials, AGs not to be given as monotherapy if other agents available. Exception: UTI/pyelonephritis.
- AHWG Ideas for future strategies
  - Systemic BP with caveat on combination therapy
  - Urine only BP (aminoglycosides listed as alternative treatment options for ESBL-E and CRE UTIs in IDSA guidelines)
  - Systemic BP that cut into the WT distribution
  - Separate BP by site (systemic/serum vs. urine vs. lung)
- BPWG Discussions
  - There was concern that if the BP was set based on PK-PD data, the BP would bisect the wild-type population
  - Suggestion: Assess aminoglycoside MIC distributions for strains without aminoglycoside-modifying enzymes (true “wild-type”)
  - Each aminoglycoside different in which enzymes they are inactivated by

- AME detection may be part of next-generation rapid diagnostic assays
- There was a comment that using combination therapy empirically isn't really combination therapy, it's to rely on the aminoglycoside in case the organism is resistant to the ß-lactam

- SC Discussions
  - It was noted that combination therapy needs to be active rather than empirical therapy.
  - M23 states a one-log drop is required rather than stasis and this should be resolved. Drug developers do work toward the one-log drop.
  - It was noted that the same criteria are planned to be used for the aminoglycosides and plazomicin. The same endpoint should be used for the entire class of drugs.
  - It was suggested that different BPs might be set for different body sites.
  - Molecular characterization of acquired resistance mechanisms may become important in better understanding what is considered to be the wild type.
  - There was concern regarding the BP cutting the wild-type distribution as the drug could not be testing using an MIC method. It was suggested to look at the drug-exposure data rather than the MIC.
  - The AHWG will consider proposals to present at the June 2022 meeting.

PLAZOMICIN BPs FOR ENTEROBACTERALES

Background

- Agent developed to treat infections caused by ESBL-producing and carbapenem-resistant Enterobacterales.
- Structure protects it from degradation by most aminoglycoside-modifying enzymes (AMEs), the most common AG resistance mechanism.
- FDA approved plazomicin in June 2018 for treatment of complicated urinary tract infections (cUTI), including acute pyelonephritis (AP), caused by susceptible *E. coli, K. pneumoniae*, *P. mirabilis* and *E. cloacae* (15 mg/kg q24h over 30 min).

Data Review

- PK properties
  - Predictable, linear PK
  - Low protein binding (20%)
  - Half-life: 4-5 hours
  - Mean AUC in cUTI patients: 234 mg*h/L
  - >97% of dose eliminated by kidneys as unchanged drug
  - Low potential for drug-drug interactions
- AUC/MIC ratio is the PK/PD driver of efficacy for plazomicin
- Conclusions: Clinical efficacy has been shown in cUTI/AP
  - Drug is non-inferior to meropenem for cUTI/AP, with higher composite cure rates and microbiologic eradication at test-of-cure
  - High rates of clinical and microbiologic success vs. Enterobacterales at MICs up to 4 µg/mL
  - Slight increased risk of nephrotoxicity compared to meropenem
  - Outcomes supported plazomicin benefit for patients with cUTI with limited or no alternative treatment options (FDA approval based on this)
- Randomized Clinical Trials showed favorable outcomes
- Justification for sponsor BP proposal: Susceptible: ≤4 µg/mL; Resistant: ≥8 µg/mL

- MIC distributions: >99% of Enterobacterales have MIC values ≤4 µg/mL
- PK-PD target attainment: >90% probability of achieving stasis targets for cUTI/AP patients at an MIC of 4 µg/mL
- Clinical evidence: High rate of composite cure for cUTI/AP and high rate of microbiological eradication in cUTI/AP patients infected with Enterobacterales with MICs ≤4 µg/mL

- Proposed disk correlates: ≥ 17 mm (S) and ≤ 16 (R)

AHWG Discussion

- FDA's BPS may be more appropriate because they align with the 1-log kill PK/PD target that is often desired for systemic infections
- Only 6 patients with MIC of 4 µg/mL in cUTI trial, although all had cure (4 of 6 were *P. mirabilis*)
- Preferred to have an intermediate category to allow for testing variability
- Vote: 4-0 for FDA breakpoints of: Susceptible: ≤2; Intermediate: 4; Resistant: ≥8 (µg/mL)

BPWG Discussion

- MIC BPs
  - *Proteus*, *Providencia*, *Morganella* spp. had elevated MICs.
  - No additional clinical or PK/PD data were available since presentation to FDA
  - BPWG Vote Passed: Vote passed: Yes (9), No (0), Abstain (1), Absent (1)

MIC BPs	Susceptible	Intermediate	Resistant	Comment
Plazomicin (µg/mL)	≤2 µg	4 µg	≥8 µg	Add comment about higher MICs with *Proteus*, *Providencia*, and *Morganella*

- Disk Correlates
  - The data met the M23 criteria.
  - MIC to disk correlate data included the data presented to FDA plus additional data from JMI
  - Thought error rates would improve if excluded *Proteus*/*Morganella*: 3 VMEs with *M. morganii*
  - Requested to see data with exclusion of *Proteus*, *Providencia*, *Morganella*
  - Vote Passed: Yes (8), No (1), Abstain (1), Absent (1) (No vote: Preferred to see data with the omission of problematic organisms)

DD BPs	Susceptible	Intermediate	Resistant	Proposed Comment
Plazomicin (mm)	≥18 mm	15-17 mm	≤14 mm	Increased number of minor errors are observed with the *Morganellaceae* family, which includes but it is not limited to the genera *Morganella*, *Proteus*, and *Providencia*.

SC Discussion

- It was agreed that if the plazomicin BPs are approved, they should not be published until the reassessment of the older aminoglycosides is completed.
- There was concern regarding the handling of the problematic organisms (*Morganella*, *Proteus*, *Providencia*). These organisms have high MICs and will go beyond the wild type. There was a similar situation with imipenem-relebactam. The mechanism leading to the high MICs is not definitely known but likely relates to permeability issues. It was noted that *Proteus* is in the package insert for treatment. It was suggested that the comment needs to stronger than the proposed one.

A motion to approve plazomicin MIC BPs for Enterobacterales same as FDA (S ≤2, I 4, R ≥8) with a comment similar (with wordsmithing) to #12 (imipenem-relebactam) in Table 2A in M100 (Breakpoints do not apply to the family *Morganellaceae*, which includes but is not limited to the genera *Morganella*, *Proteus*, and *Providencia*) and not publishing the plazomicin BPs until older aminoglycosides are re-evaluated was made and seconded. Vote: 10 for, 2 against, 1 abstain, 0 absent (Pass).

- The votes against approval related to limited clinical data and issues related to device manufacturers (A. Schuetz and S. Cullen).

A motion to approve the plazomicin disk diffusion BPs (zone diameter in mm) for Enterobacterales (S ≥18, I 15-17, R ≤14) with same comment regarding *Morganellaceae* was made and seconded. Vote: 11 for, 1 against, 1 abstain, 0 absent (Pass).

- The vote against approval was regarding voting on BPs for disk correlates for MIC that she did not approve.

AMOXICILLIN-CLAVULANATE NEW DISK CORRELATE DATA FOR *H. INFLUENZAE*

Background

- New MIC BPs were approved in 2021 and published in M100, 32nd edition.
- Disk correlate data for new MIC BPs were insufficient to approve new disk correlates and the disk BPs were deleted from the 32nd edition.

Reanalysis of disk correlate data (Doern GV et al. European J of Clin Micro Inf Dis. 1990; 9(5):329-336)

- Data were analyzed using dBETs software and run against the approved, revised MIC BPs.
- The data were taken from a historical isolate collection which was weighted towards strains lacking TEM-1 ß-lactamase with higher ampicillin MICs. Few were resistant to amoxicillin-clavulanate.
- Historical data did not meet M23 criteria.

MIC/Disk Diffusion Data obtained for *H. influenzae* tested with amoxicillin-clavulanate during Mueller-Hinton Fastidious (MH-F) media study

- Study to compare *Haemophilus* Test Media (HTM) vs MH-F media which included testing 100 isolates against amoxicillin-clavulanate.
- Isolate collection
  - Represented all capsule types
  - Susceptibility was determined using broth microdilution (BMD) and disk diffusion.
  - ß-lactamase activity was determined by a nitrocefin-test.
- Three options for amoxicillin-clavulanate disk correlates were presented for all data combined (BMD vs disk).
  - Option 1: S ≥20, R ≤19 (Old BPs)
  - Option 2: S ≥21, I 19-20, R ≤18
  - Option 3: S ≥20, I 18-19, R ≤17

BPWG Discussion

- Neither data set meets M23 criteria for setting a disk correlate.
- There were few resistant isolates in the set.
- Questions arose regarding the rates of ß-lactamases present in the resistant isolates.
- There are still too many minor errors.
- It was suggested that a disk test is needed for international sites where BLNAR *H. influenzae* is present.

- No vote was taken by the BPWG and no additional data are forthcoming.

SC Discussion

- It was questioned if the error-rate bound method was used to analyze the data as the data might meet M23 criteria if this was done.
- It might be helpful to look for PBP3 mutations.
- It was noted that M100 already has a comment stating the rare ß-lactamase negative ampicillin-resistant strains should be considered resistant to amoxicillin-clavulanate.
- The use of the ß-lactamase test is critical and should be emphasized. It was suggested that the comment does address the issue and perhaps it could be reinforced.
- Path forward
  - Rework the ß-lactamase test comment.
  - Look at data from the third lab that weren't available for this meeting.
- Ms. Cullen noted that it might be possible to resolve the one very major error that exceeded the M23 criteria. Looking at the option on slide 62, 16.7% VMJ was observed in the study. Upon further assessment of the MICs obtained at the 3 sites, the consensus result of the MIC would be 4 which is intermediate. Therefore the VMJ discrepancy was resolved (since it would be considered minor instead of VMJ) and resulting in meeting M23 criteria. She suggested that a motion to accept could be made. The motion would include the current comment regarding ß-lactamase.
- It was noted that this would not be the first time that disk correlates were accepted without meeting M23 criteria (ie, fluoroquinolones).
- There was concern that the disk is not performing very well and that not all resistant isolates will be captured.
- There was concerned that BLNAR strains are increasing in the US. The population studies may not include enough data to show what the true VME rate is. These BLNAR strains don not behave well in disk diffusion tests and a test specifically for these strains may be needed.
- Not clear that there is going to be additional data any time soon and thus if no disk correlates established from this data it could be a while before this would be possible.

A motion to accept the *H. influenzae* disk correlates (S ≥21, I 18-20, R ≤17) including careful documentation with what occurred with isolate and emphasize ß-lactamase testing and clarify the "rare" comment was made and seconded. Vote: 3 for, 10 against, 0 abstain, 0 absent (Fail)

- The votes against related to:
  - Discomfort with "massaging the data" to fit.
  - The need to see additional data.
  - The study wasn't designed to look at resistant isolates so a study is needed that specifically looks at resistant isolates. The current ß-lactamase test can serve as a practical solution until appropriate data are available.
  - The need to understand the resistant mechanisms better and perhaps develop a specific test to detect the resistance.
  - The lack of confidence in the current method.

ADJOURNMENT

Dr. Lewis thanked the participants for their attention. The meeting was adjourned at 5:05 PM Eastern (US) time.

2022 WINTER AST MEETING SUMMARY MINUTES PLENARY 5: FRIDAY, 11 FEBRUARY – 1:00 – 4:00 PM EASTERN (US) TIME	
#	**Description**
1.	**METHODS DEVELOPMENT AND STANDARDIZATION WG REPORT (D. HARDY)** **AST OF *H. INFLUENZAE* USING MH-F BROTH** **Background** • Multi-laboratory study to compare AST results of MH-F broth to HTM. Disk diffusion testing will be discussed in June. • Objectives – Compare HTM and MH-F performance using BMD reference method and disk diffusion (DD) for assessing *H. influenzae* susceptibility. – Assess the possible need for changes in the approved QC ranges for the designated QC organisms on MH-F agar and MH-F broth. – Assess the potential need for guidance regarding a "substantially inhibited growth phenotype" when interpreting β-lactam MICs on *H. influenzae* BMD panels. • Three QC strains (20 replicates each) and a collection of 100 *H. influenzae* isolates were studied. • Three HTM and two MH-F manufacturer's media were used. • Antimicrobial agents tested included: ampicillin, amoxicillin-clavulanate, cefotaxime, cefuroxime, clarithromycin, chloramphenicol, levofloxacin, meropenem, rifampicin, tetracycline, and trimethoprim-sulfamethoxazole. **QC Study Summary** • QC replicates on HTM and on MH-F were within the acceptable (>95%) CLSI ranges for all 12 drugs for all testing laboratories. • It was concluded that the CLSI QC ranges were acceptable and the same between the two media. **MIC Testing Study Summary** • Isolate summary: All agents showed HTM/MH-F consensus in overall essential agreement (OEA) of at least 94%. • EA and categorial agreement (CA) summary: All agents showed EA range and CA range among all sites of at least 85%.

Conclusions

- MICs determined in MH-F broth and HTM broth correlate very well for both QC organisms and clinical isolates and MICs in MH-F broth are often much easier to read than MICs in HTM.
- The CLSI-approved MIC QC ranges for HTM are acceptable for MH-F broth.
- It was recommended that HTM users disregard trailing growth and where endpoints should be selected and that photographs be added.

MDSWG Discussion

- MDSWG voted 9-0-1 to approve the addition of MH-F to testing media for *H. influenzae* for BMD for these antimicrobial agents pending bias calculation is less than or equal to ± 30%.
- A motion to approved MH-F as an alternative to HTM for AST of *H. influenzae* was requested.

SC Discussion

- It was questioned as to how this media will be viewed going forward: replacement, equivalent, alternative etc. It was noted that MH-F has already been approved for use in testing *S. pneumoniae* (HTM or MH-F) and it was suggested to use the same language for *H. influenzae*.
- It was questioned if MH-F is for *H. influenzae* only or applicable to *H. parainfluenzae*.

A motion to approve MH-F as an alternative to HTM for broth microdilution AST of *H. influenzae* was made and seconded. Vote: 13 for, 0 against, 0 abstain, 0 absent (Pass).

- It was noted that there are additional *H. parainfluenzae* data that can be reviewed at a later date.

A motion to add comments regarding MH-F data not being currently available for *H. parainfluenzae* and a comment analogous to that for S. pneumoniae (excluding disk diffusion) that states that the two media types are equivalent (*For disk diffusion, results using MHA with 5% sheep blood and MH-F agar were equivalent when disk contents, testing conditions, and zone diameter breakpoints in Table 2G were used. Disk diffusion QC ranges for S. pneumoniae ATCC® 49619 in Table 4B apply to testing using either MHA with 5% sheep blood or MH-F agar*) was made and seconded. Vote: 13 for, 0 against, 0 abstain, 0 absent (Pass).

- It was noted by EUCAST that the two media are in some cases not equivalent for *Haemophilus*.

DIRECT BLOOD DISK DIFFUSION TESTING (see presentation 2022_Winter_AST_MDSWG_Presentation_Final)

Background

- AHWG goals were to define DD BPs at 16-18 hr (overnight) and 8-10 hr (early) for applicable gram-negative bacilli directly from positive blood culture (PBC) broth
- Data from the Antibacterial Resistance Leadership Group (ALRG) disk study and seeded isolated testing were reviewed.
- A number of early and overnight reads for Enterobacterales have been approved by the SC and will be published in M100, 32nd ed.
- An update on the progress of the study and an overview was provided. The participants were reminded that the SC has already approved the main comparator method as standard disk diffusion performed at the site.
- The goal for the meeting was to review and vote on 5 new cutoffs for Enterobacterales and to vote on applying current cutoffs for *P. aeruginosa* and meropenem (early reads).

Enterobacterales Data

- Meropenem direct from PBC (16-18 hr reads): Proposed adding new zone cutoffs
  - Corrected for a technical error with *Providencia stuartii* and re-analyzed
  - Changing zone cutoffs improved CA vs standard DD at the testing site to 92.9%
  - Changing zone cutoffs improved CA vs MIC to 94.3%
  - Changing zone cutoffs improved CA vs reference DD to 94.5%
  - The MDSWG voted to approve the new zone cutoffs (9-0-1)

Current DD (mm)			Proposed zone cutoffs (mm)		
S	I	R	S	I	R
≥23	20-21	≤19	≥22	19-21	≤18

- SC Discussion
  - Outliers in the data were questioned. It was noted that these outlier species are rare and shouldn't detract from the results of the more commonly isolated and tested species.
  - It was suggested that these outlier species be studied in more detail going forward.

A motion to approve the direct read from positive blood culture bottles for Enterobacterales and meropenem at 16-18 hrs. reading proposed zone cutoffs (mm) as S ≥22, I 19-21, R ≤18 was made and seconded. Vote: 13 for, 0 against, 0 abstain, 0 absent (Pass).

- Meropenem PBC (8-10 hr reads): Proposed to add new zone cutoffs
  - Changing zone cutoffs improved CA vs standard DD at the site to 89.7%.
  - Changing zone cutoffs improves CA vs MIC to 91.0%
  - Changing zone cutoffs improves CA vs reference DD to 91.3%
  - The MDSWG voted to approve the zone cutoffs (9-0-1)

Current DD (mm)			Proposed zone cutoffs (mm)		
S	I	R	S	I	R
≥23	20-22	≤19	≥22	20-21	≤19

- SC Discussion
  - There was concern regarding the major errors seen. It was questioned if these were resistant isolates but were noted to be random errors.
  - It was questioned if the intermediate zone was too small. The AHWG discussed the issue and decided that it shouldn't be an issue.
  - It was suggested that it be noted as to which MIC systems were used in the studies. It was noted that a publication is in progress. Manufacturer names cannot be listed in M100 but can be in a publication. The ORWG will also present guidance in the next newsletter.

A motion to approve the direct read results from positive blood culture bottles for Enterobacterales and meropenem at 8-10 hrs. with proposed zone cutoffs (mm) as S ≥22, I 20-21, R ≤19 was made and seconded. Vote: 11 for, 0 against, 0 abstain, 1 absent (Pass).

- Ampicillin PBC (8-10 hr): Proposed new zone cutoffs
  - 16-18 hrs. have already been approved by the SC.
  - Changing zone cutoffs improves CA vs standard DD at the site to 93%.
  - Changing zone cutoffs improves CA vs MIC to 95.2%.
  - Changing zone cutoffs improves CA vs reference DD to 93.5% (Note: 3 organisms with technical errors were excluded)
  - The MDSWG vote to approve the zone cutoffs (9-0-1).

Current DD (mm)			Proposed zone cutoffs (mm)		
S	I	R	S	I	R
≥17	14-16	≤13	≥16	12-15	≤11

- SC Discussion: No discussion was needed.

A motion to approve the direct read results from positive blood culture bottles for Enterobacterales and ampicillin at 8-10 hrs. with proposed zone cutoffs (mm) as S ≥16, I 12-15, R ≤11 was made and seconded. Vote: 12 for, 0 against, 0 abstain, 1 absent (Pass).

- Ciprofloxacin PBC (8-10 hr): Proposed zone cutoff (**excludes *Salmonella* spp**).
  - Changing zone cutoffs improves CA vs standard DD at the site to 90%.
  - Changing zone cutoffs improves CA vs MIC to 90.4%.
  - Changing zone cutoffs improves CA vs reference DD to 90.2%.
  - The MDSWG vote to approve the zone cutoffs (9-0-1) with a warning regarding the need to determine the identification before reporting the result.

Current DD (mm)			Proposed zone cutoffs (mm)		
S	I	R	S	I	R
≥26	22-25	≤21	≥21	18-20	≤17

- SC Discussion
  - It was noticed that these disk zones have the largest differences in changing to the proposed zone cutoffs compared to all the drugs. It was noted that this issue will also be seen in future data sets.
  - It was suggested that this drug reacts differently resulting in the larger differences.
  - There was concern that the test did not compare well to MIC. The SC was reminded that comparison to the standard disk diffusion test was approved by the SC.
  - It was noted that the error rates were in acceptable ranges as per M23.

A motion to approve direct DD reads from PBC for Enterobacterales (excluding *Salmonella*) with ciprofloxacin at 8 - 10 hrs. with proposed zone cutoffs (mm) as S ≥21, I 18-20, R ≤17 and with a warning to determine identification before reporting the AST results was made and seconded. Vote: 13 for, 0 against, 0 abstain, 0 absent (Pass).

- Ciprofloxacin PBC (16-18 hrs.): Proposed new zone cutoffs to match 8-10 hrs. (**excludes *Salmonella* spp**).
  - Changing zone cutoffs improves CA vs standard DD to 90.1%
  - Changing zone cutoffs improves CA vs MIC to 95.6%, VMJ 4%
  - Changing zone cutoffs improves category agreement to 90.6%
  - MDSWG approved the proposed zone cutoffs (9-0-1)

Current DD (mm)			Proposed zone cutoffs (mm)		
S	I	R	S	I	R
≥26	22-25	≤21	≥21	18-20	≤17

- SC Discussion
  - Questions regarding time of set up after flagging positive (within 8 hrs. of flagging) and if colony counts were done. Colony counts were done in the pilot study and those data are published.

A motion to approve direct read from PBC for Enterobacterales (excluding *Salmonella)* with ciprofloxacin at 16 – 18 hrs. with proposed zone cutoffs (mm) as S ≥21, I 18-20, R ≤17 was made and seconded. Vote: 11 for 2 against, 0 abstain, 0 absent (Pass).

  - The votes against approval related to the large shift in BPs (S. Richter and R. Humphries). It was suggested that it continue to be studied with data going forward. It was noted that the study was set up as close to real world as possible.

***P. aeruginosa* Data**

- Meropenem PBC (8-10 hrs.): Apply current zone cutoffs
  - 16-18 hr reads were approved previously
  - Applying the current zone cutoffs vs standard DD at the site showed CA of 91.0%
  - Applying the current zone cutoffs vs MIC showed CA of 92.3%
  - Applying the current zone cutoffs vs reference DD showed CA of 94.7%
  - The MDSWG vote to approve the zone cutoffs (9-0-1).

Current DD (mm) for vote		
S	I	R
≥19	16-18	≤15

- SC Discussion: No discussion was needed.

A motion to approve the direct 8-10 hr reads from PBC with *P. aeruginosa* and meropenem with proposed zone cutoffs (mm) of S ≥19, I 16-18, R ≤15 was made and seconded. Vote: 13 for, 0 against, 0 abstain, 0 absent (Pass).

- Cefepime PBC (16-18 hrs.): Proposed zone cutoffs
  - **NOTE:** Approach when performance to disk is within acceptable limits but performance compared to MIC is not within acceptable limits, and standard DD to MIC correlates are not acceptable with this dataset.

- Changing zone cutoffs improves CA vs standard DD at site to 92.5%
- Changing zone cutoffs does not change CA vs reference DD of 97.8%.
- There was low CA vs. MIC, and minor errors. Changing zone cutoffs decreases CA vs MIC to 86.1%
- Proposed zone cutoffs show good performance vs. Std DD (CA=92.5%) and REF DD (CA=97.8%), but performance vs. MIC was not acceptable.
- MDSWG voted against this 4-5-1 (Fail). It was questioned of this is a signal to re-evaluate DD to MIC for cefepime.
- The SC was reminded that although the results vs MIC were not good, the SC has already approved standard DD as the comparator for this study.

Current DD (mm)			Proposed zone cutoffs (mm)		
S	I	R	S	I	R
≥18	15-17	≤14	≥18	14-17	≤13

- SC Discussion
  - It was questioned if there is a list of problematic agents that may need to be re-evaluated for broth vs disk. It was noted that this drug may be showing a signal and there are others that may also be showing a signal. Data on other drugs can be presented at a future meeting.
  - It was noted that these studies were done at different labs, by different techs, at different times etc. and errors could be related to site.
  - It was noted that the dose is different than FDA or EUCAST and resistance could be under called.
  - It was reported that the vote within the AHWG was unanimous. Although the comparison to MIC were not good, the main comparator was agreed to be standard DD which looked good. Because this is an important drug/organism combination, the AHWG weighed the advantages and disadvantages and opted to move forward with approving the BPs.
  - The WG questioned if the disk vs MIC for cefepime needs to be looked at. If so, the AHWG will need guidance on how to proceed.
  - The group was reminded that disk to disk comparison is what was approved and it worked for this drug and organism.

A motion to approve the direct 16-18 hr reads from PBC with *P. aeruginosa* and cefepime with proposed zone cutoffs (mm) of S ≥18, I 14-17, R ≤13 was made and seconded. Vote: 5 for, 6 against, 1 abstain, 1 absent (Fail).

- The vote against approval were related to discomfort with disagreement with MIC (R. Humphries, T. Dingle, S. Richter, M. Galas, P. Simner, V. Pierce).
- The group was reminded that by basing the disapproval on the difference between disk and MIC with differences in inoculum sets an important precedent and was not what the study was supposed to look at. By questioning the comparator method, the BPs that have already been approved are put into question and the AHWG can't move forward. The AHWG agreed that consistency is needed, comparing disk diffusion to disk diffusion performed at the same site.
- There was concern if what has already been approved needs to be revisited and/or if the rules already set down need to be changed. The AHWG requested guidance and how to move forward.
- It was agreed that this issue needs to be reassessed and it is possible that direct disk for PBC and cefepime may have to be tabled.

RANGEFINDER QC RANGES FOR TOBRAMYCIN AND CIPROFLOXACIN FOR EARLY READS

- The charge was to analyze the remaining QC ranges for tobramycin and ciprofloxacin with early reads using RangeFinder.
  - *E. coli* ATCC 25922 at 8-10 hrs. for Ciprofloxacin: CLSI QC range 29-38 mm. 228/231 (98.7%) within range per Range Finder

- *E. coli* ATCC 25922 at 8-10 hrs. for Tobramycin: CLSI QC range 18-26 mm. 185/187 (98.9%) within range per Range Finder.

- Additional Discussion
  - Some of the remaining Enterobacterales and *P. aeruginosa* organism-antimicrobial combinations have been analyzed, do not show good performance, and will not be pursued (Enterobacterales with ampicillin-sulbactam (overnight and early reads); *P. aeruginosa* with aztreonam (overnight and early reads)
  - Acinetobacter data
- The AHWG is seeking a laboratory to perform additional seeding studies.

TOPICS DEFERRED TO THE JUNE 2022 MEETING

- Tedizolid and Linezolid Disk Diffusion and CLSI/EUCAST Harmonization
- Reformation of the Non-Enterobacterales AHWG
- Formation of an AHWG to review M100 Table 6A, Solvents and Diluents for Preparing Stock Solutions of Antimicrobial Agents
- Update from the Cefazolin High Inoculum Ad-Hoc Working Group
- Updates to Table 1 coming out of Plenary 3

ADJOURNMENT

Dr. Lewis expressed his gratitude to the participants for their time, efforts, and patience during the five plenaries. The meeting was adjourned at 4:05 PM Eastern (US) time.

REVIEWER AND GUEST ATTENDEES

Plenary 1	Plenary 2	Plenary 3	Plenary 4	Plenary 5
Pranita Tamma	Dwight Hardy	Matt Wikler	Matt Wikler	Dwight Hardy
Melissa Boddicker	Natasha Griffin	Pennie.baptie	Dwight Hardy	Beth Goldstein
Mary Motyl	Paul Edelstein	Emily Snavely	Samantha Shannon	Lauri Thrupp
John Breton	Robert Bowden	Ron Master	Laura Koeth	Jekia Cox
M. Sfeir	Kerian Grande Roche	Mark Redell	Kimberley Lewis	Amity Roberts
John Fissel	M. Sfeir	Scott Killian	Sandra McCurdy	Gina Ewald-Saldana
Linda Schuermeyer	Gina Ewald-Saldana	Sukantha Chandrasekaran	Helio Sader	Patricia Bradford
James Jorgensen	Nancy Watz	Holly Huse	Boudewijn DeJonge	Rod Mendes
Susan O'Rourke	Charles Jakielaszek	Linda Schuermeyer	Luiz Lisboa	CHEUNG YEE
Nilia Robles-Hernandez	Chris Pillar	Nicolynn Cole	Amanda Kuperus	Paula Snippes Vagnone
Jennifer Smart	Linda Schuermeyer	Niki Litchfield	Karen Bush	Natasha Griffin
Tam Van	Diane Anastasiou	L. Barth Reller	Deborah Butler	Niki Litchfield
Ron Master	Beth Goldstein	Rachael Liesman	William Brasso	Nancy Watz
Gregory Stone	Jennifer Boyer	Nicole Scangarella-Oman	Faiza Benahmed	Sandra McCurdy
Nancy Watz	Helio Sader	Faiza Benahmed	Francis Arhin	Elide Herrera
Thao Truong	Dale Schwab	Jason Bryowsky	Stella Antonara	Sarah Alsamarai
Sarah Leppanen	Rebecca Weingarten	Nicholas Moore	lauri thrupp	Susan Thomson
Laura Stewart	Michael Huband	Natasha Griffin	Charles Jakielaszek	Linda Otterson
Rita Hoffard	Patricia Bradford	Beth Goldstein	Nicole Scangarella-Oman	Elaine Duncan
Rachel Britt	Davina Campbell	Animesh Dhara	Simone Shurland	David Hilbert
Patricia Conville	James Jorgensen	John Breton	Dee Shortridge	Zabrina Lockett
Deborah Butler	David Hilbert	Robert Bowden	Beth Goldstein	Paul Edelstein
Andrew Fuhrmeister	Sukantha Chandrasekaran	Michael Huband	David Hilbert	Megan Klatt
Barb Gancarz	Keith DeDonder	Laura Koeth	Maryann Brandt	Susan Kircher
Lawrence Friedrich	Andrew Fuhrmeister	Paula Snippes Vagnone	Keith DeDonder	Karen Bush
Dee Shortridge	Ron Master	Alexandra Bryson	Patricia Bradford	L. Barth Reller
Sukantha Chandrasekaran	Elaine Duncan	Camille Hamula	Scott Killian	Rachael Liesman
Dale Schwab	Karri Sutter	Francis Arhin	Mark Redell	Sukantha Chandrasekaran
Helio Sader	Harley Parker	Zabrina Lockett	Cecilia Carvalhaes	Flavia Rossi
Charles Jakielaszek	Xian-Zhi Li	Susan Kircher	Nicolynn Cole	David Lonsway
Susan Kircher	Rita Hoffard	Elizabeth Hirsch	Edwin Kamau	Yesenia Morales
Zabrina Lockett	Linda Otterson	Brian Johnson	Rod Mendes	Boudewijn DeJonge

Keith DeDonder	Alisa Serio	Margaret Ordonez Smith de Danies	Amity Roberts	Andrew Fuhrmeister
Animesh Dhara	Kerian Grande Roche	Lindsay Donohue	Emily Snavely	Robert Bowden
Jean Whichard	Animesh Dhara	Nancy Watz	Jennifer Slaughter	Animesh Dhara
Tomefa Asempa	Emily Snavely	James Jorgensen	Jolyn Tenllado	Lara Rajeev
Boudewijn DeJonge	Mary Motyl	Daniel Timko	Kerian Grande Roche	Francis Arhin
Mark Fisher	William Brasso	Morgan Pence	Antonieta Jimenez	Mark Fisher
Allison Eberly	Mark Fisher	Mary Motyl	Darcie Carpenter	Darcie Carpenter
Chris Pillar	Jeffrey Pearson	Cheung Yee	Susan Thomson	Dee Shortridge
Alisa Serio	Luiz Lisboa	Jennifer Slaughter	Melissa Boddicker	Melissa Jones
Ellen Kersh	Francis Arhin	Rebecca Brady	Judith Steenbergen	Helio Sader
Amelia Bhatnagar	Helio Sader	Melissa Jones	Mozna Khraiwesh	Fred Tenover
Sandra McCurdy	Fred Tenover	Yoshinori Yamano	Flavia Rossi	Matt Wikler
Fred Tenover	Mark Redell	Cecilia Carvalhaes	Elaine Duncan	Maryann Brandt
Patricia Bradford	Tomefa Asempa	Amity Roberts	Natasha Griffin	Samia Naccache
Susan Cusick-Pevear	Jennifer Slaughter	Paul Edelstein	Roger Echols	Cecilia Carvalhaes
Diane Anastasiou	Melissa Jones	Patricia Bradford	Paul Edelstein	Simone Shurland
Edwin Kamau	Jane Ambler	Sarah McLeod	Animesh Dhara	Joseph Lutgring
Lisa Leung	Cecilia Carvalhaes	Karen Bush	Mary Motyl	Nicole Scangarella-Oman
Beth Goldstein	Amanda Kuperus	Samantha Shannon	Daniel Timko	John Bonnewell
Robert Bowden	John Fissel	Gina Ewald-Saldana	Gina Ewald-Saldana	Lynn Yaolin
Paula Snippes Vagnone	Scott Killian	Linda Otterson	Kerian Grande Roche	Luiz Lisboa
Darcie Carpenter	Jennifer Johnson	Dee Shortridge	Nancy Watz	Nicolynn Cole
Lindsay Donohue	Amelia Bhatnagar	Kimberley Lewis	Lawrence Friedrich	Laurie Flemming
Dmitri Iarikov	Dee Shortridge	Fred Tenover	Marc Scheetz	Jane Ambler
Susan Butler-Wu	Jennifer O'Connor	Ellen Kersh	Kerian Grande Roche	Linda Schuermeyer
Kimberley Lewis	Ribhi Shawar	Jekia Cox	Sukantha Chandrasekaran	L. Barth Reller
Natasha Griffin	Lawrence Friedrich	William Brasso	L. Barth Reller	Scott Killian
Morgan Pence	Katherine Young	Jennifer Smart	Zabrina Lockett	Lindsay Donohue
Robert Bowden	Sandra McCurdy	Rita Hoffard	Linda Schuermeyer	Daniel Timko
Melissa Gitman	lauri thrupp	Keith DeDonder	mervat elanany	Jennifer Smart
Jennifer Johnson	Patricia Conville	Darcie Carpenter	Brian Johnson	Kimberley Lewis
Kerian Grande Roche	Sarah Leppanen	Frank Kung	Archana Angrup	Melissa Gitman
Jekia Cox	Allison Eberly	Jane Ambler	Niki Litchfield	Isabella Martin

Chris Pillar	Isabella Martin	Chris Pillar	Patricia Conville	Elide Herrera
Gregory Stone	Sukantha Chandrasekaran	Lawrence Friedrich	Mozna Khraiwesh	Marc Scheetz
Jekia Cox	Melissa Gitman	Laura Stewart	Meredith Hackel	Christian Gill
Margaret Ordonez Smith de Danies	Samia Naccache	Tam Van	Jolyn Tenllado	Melissa Boddicker
Lynn Yaolin	Elizabeth Palavecino	Isabella Martin	Sarah Sabour	Sujata Bhavnani
Stella Antonara	Graeme Forrest	Edwin Kamau	Ellen Kersh	Rita Hoffard
Luiz Lisboa	Erene Mina	Helio Sader	Elaine Duncan	Susan Cusick-Pevear
Anna Zhou	Andre Hsiung	Karri Sutter	Tam Van	Margaret Ordonez Smith de Danies
Katherine Young	Yesenia Morales	Elaine Duncan	Cecilia Carvalhaes	Mary Motyl
Andrea Ferrell	Morgan Pence	mervat elanany	Jennifer Slaughter	Alice Gray
Sarah Alsamarai	Timothy Bensman	Gunnar Kahlmeter	davina	Lisa Meyers
Elizabeth Palavecino	Susan Thomson	Tsigereda Tekle	Ron Master	Antonieta Jimenez
Collette Wehr	Lara Rajeev	Boudewijn DeJonge	M. Sfeir	Nicholas Moore
Niki Litchfield	Darcie Carpenter	Rod Mendes	Jennifer Johnson	Antonieta Jimenez
Maryann Brandt	Jean Whichard	Antonieta Jimenez	Amanda Kuperus	Maryann Brandt
Melissa Jones	Susan Kircher	Alisa Serio	Jane Ambler	Alexandra Bryson
Laura Stewart	Stella Antonara	Diane Anastasiou	James Jorgensen	Edwin Kamau
Jane Ambler	Lynn McCloskey	Liang Li	Gregory Stone	Simone Shurland
Tam Van	Linda Schuermeyer	Jolyn Tenllado	Samantha Shannon	Lynn Yaolin
Rebecca Yee	Susan Weir	Brian Johnson	M Sfeir	Tam Van
Sujata Bhavnani	Matt Wikler	Samia Naccache	Mary Motyl	Andrea Ferrell
Dee Shortridge	Sarah Alsamarai	Susan Thomson	John Bonnewell	Antonieta Jimenez
Zabrina Lockett	Edwin Kamau	Elide Herrera	Susan Kircher	Liang Li
Chris Pillar	Antonieta Jimenez	John Bonnewell	Nilia Robles-Hernandez	Elizabeth Palavecino
Elaine Duncan	Jennifer Slaughter	David Hilbert	Niki Litchfield	Xian-Zhi Li
Ashley Dahlquist	Thao Truong	lauri thrupp	Barb Gancarz	Tomefa Asempa
Isabella Martin	Judith Steenbergen	Maria Burgos-Garay	Karri Sutter	Faiza Benahmed
Rod Mendes	Collette Wehr	Katherine Young	James Jorgensen	Kerian Grande Roche
Erene Mina	Karen Bush	Jennifer Boyer	Chris Pillar	Yesenia Morales
Jane Ambler	Laura Koeth	Simone Shurland	Thao Truong	Mimi Precit
Nicolynn Cole	Diane Anastasiou	Lara Rajeev	Gunnar Kahlmeter	Sarah Sabour
Melissa Gitman	Laurie Flemming	Susan Cusick-Pevear	Robert Bowden	Jennifer Johnson

Elaine Duncan	Samantha Shannon	Maryann Brandt	Linda Otterson	Davina Campbell
Elizabeth Hirsch	Maryann Brandt	Kevin Alby	Tomefa Asempa	Lawrence Friedrich
Jennifer O'Connor	Daniel Timko	Laurie Flemming	Megan Klatt	Lisa Meyers
Marc Scheetz	Jennifer Smart	Dubraska Diaz-Campos	Isabella Martin	Nilia Robles-Hernandez
Jennifer Boyer	Jolyn Tenllado	Andrea Ferrell	Susan Cusick-Pevear	Rebecca Yee
Francis Arhin	Michael Sidlak	Maryann Brandt	Mark Fisher	Tam Van
Elizabeth Church	Boudewijn DeJonge	Judith Steenbergen	Katherine Sei	Melissa Henry
Paul Edelstein	Holly Huse	Robert Hamilton	Susan Kircher	Victoria Campodonico
Nicholas Moore	Nicole Scangarella-Oman	Jennifer O'Connor	Jennifer Smart	Gunnar Kahlmeter
Anna Klavins	Nicolynn Cole	Charles Jakielaszek	Lynn Yaolin	Andrea Ferrell
Maryann Brandt	Alexandra Bryson	M. Sfeir	Michael Huband	Emily Snavely
Lisa Meyers	Marc Scheetz	Lynn Yaolin	Andrew Fratoni	Karri Sutter
Linda Otterson	Stella Antonara	Luiz Lisboa	Lara Rajeev	Dev Ranjit
Amanda Kuperus	John Breton	Alice Gray	Jennifer Boyer	Michael Huband
Laurie Flemming	Rod Mendes	Marc Scheetz	Xian-Zhi Li	
Alexandra Bryson	Ellen Kersh	Melissa Gitman	Morgan Pence	
Simone Shurland	Susan O'Rourke	Xian-Zhi Li	Yesenia Morales	
Dubraska Diaz-Campos	Linda Otterson	Erene Mina	Melissa Gitman	
Xian-Zhi Li	Nicholas Moore	Sujata Bhavnani	Rachael Liesman	
Meredith Hackel	Elizabeth Hirsch	Samia Naccache	Rebecca Yee	
Graeme Forrest	Yesenia Morales	Lisa Meyers	Margaret Ordonez Smith de Danies	
Gerald Capraro	Elaine Duncan	Hari Dwivedi	Andrew Fuhrmeister	
Emily Snavely	Linda Otterson	Jane Ambler	Charles Jakielaszek	
Pragya Singh	Jennifer Slaughter	Mark Fisher	Jekia Cox	
Davina	Lisa Meyers	Edwin Kamau	Lindsay Donohue	
Besarta Mullalli	Zabrina Lockett	Dev Ranjit	L. Barth Reller	
Antonieta Jimenez	Heike Kaspar	Andrew Fratoni	Fred Tenover	
Karri Sutter	Elaine Duncan	Jennifer Smart	John Breton	
Kevin Alby	Stephen LaVoie	Kerian Grande Roche	Robert Hamilton	
Nicole Scangarella-Oman	Dev Ranjit	Tomefa Asempa	Susan Butler-Wu	
Luiz Lisboa	Lynn Yaolin	Ellie Sukerman	Laura Stewart	
Jennifer Smart	Susie Sharp	Barb Gancarz	Thao Truong	
Jeff Alder	Nicholas Moore	Jennifer Johnson	Melissa Jones	

Cecilia Carvalhaes	Amelia Bhatnagar	Liang Li	Paula Snippes Vagnone	
Robert Hamilton	Chris Pillar	Stephen LaVoie	Gina Ewald-Saldana	
Barb Gancarz	Tam Van	Amanda Kuperus	Zabrina Lockett	
Kamisha Gray	Yesenia Morales	Karri Sutter	Elizabeth Palavecino	
Stella Antonara	Elaine Duncan	Niki Litchfield	Daniel Timko	
Liang Li	Navaneeth Narayanan	Sujeet Govindan	Dev Ranjit	
Graeme Forrest	Cheung Yee	Antonieta Jimenez	Sujata Bhavnani	
Susan Thomson	mervat elanany	Maryann Brandt	Christian Gill	
Laura Koeth	Heike Kaspar	Xian-Zhi Li		
Samia Naccache	Andrew Fuhrmeister	Collette Wehr		
Karen Bush	Jean Whichard	M Sfeir		
Alice Ngo	Melissa Jones	Amelia Bhatnagar		
Holly Huse	Margaret Ordonez Smith de Danies	Holly Huse		
Charles Jakielaszek	Holly Huse	Camille Hamula		
Melissa Jones	James Jorgensen	Jason Bryowsky		
Laura Bio	Nicole Scangarella-Oman	Jennifer Smart		
Mark Redell	Fred Tenover	Elaine Duncan		
Stephen LaVoie	Graeme Forrest	lauri thrupp		
Rebecca Yee		Rachael Liesman		
Mervat Elanany		Elaine Duncan		
Harley Parker				
Jennifer O'Connor				
Barb Gancarz				
Susan Kircher				
Cheung Yee				
Dev Ranjit				
Sophie Arbefeville				
John Bonnewell				