Meeting Title:	**Subcommittee (SC) on Antimicrobial Susceptibility Testing (AST)**	**Contacts:**	mhackenbrack@clsi.org Egomez@clsi.org
Meeting Dates and Times:	**Plenary 1:** Monday, 4 June 2021, 10:00 AM – 1:00 PM Eastern (US) time **Plenary 2:** Monday, 4 June 2021, 3:00 – 6:00 PM Eastern (US) time **Plenary 3:** Tuesday, 5 June 2021, 12:00 – 3:00 PM Eastern (US) time **Plenary 4:** Thursday, 17 June 2021, 10:00 AM – 1:00 PM Eastern (US) time		
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 (ed).		
Requested Attendee(s):	SC Chairholder, Vice-chairholder, Members, Advisors, and Reviewers; Expert Panel on Microbiology Chairholder and Vice-chairholder; 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 Medical School**
Jean B. Patel, PhD, D(ABMM) Expert Panel on Microbiology Chairholder	**Beckman Coulter, Inc.**
Members:	
Sharon K. Cullen, BS, RAC	Beckman Coulter, Inc. Microbiology Business
Marcelo F. Galas	Pan American Health Organization
Howard Gold, MD, FIDSA	Beth Israel Deaconess Medical Center
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
Tony Mazzulli, MD, FACP, FRCP(C) (Both)	Sinai Health System
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
Members Absent	
Plenaries 1 and 2 (June 7) Audrey N. Schuetz, MD, MPH, D(ABMM)	Mayo Clinic (Rochester, MN)
Plenaries 3 (June 8) and 4 (June 17)	None
Advisors Present	
Tanaya Bhowmick, MD	Rutgers Robert Wood Johnson Medical School
April M. Bobenchik, PhD, D(ABMM), MT(ASCP)	Lifespan Academic 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
Tanis Dingle, PhD, D(ABMM), FCCM	Alberta Precision Laboratories
George M. Eliopoulos, MD	Beth Israel Deaconess Medical Center
German Esparza, MSc	Proasecal SAS
Christian G. Giske, MD, PhD	Karolinska University Hospital

Advisors Present (cont.)	
Janet A. Hindler, MCLS, MT(ASCP), F(AAM)	Los Angeles County Department of Public Health
Elizabeth Hirsch, PharmD	University of Minnesota College of Pharmacy
Maria Karlsson, PhD	Centers for Disease Control and Prevention
Joe Kuti, PharmD, FIDP	Hartford Hospital
Joseph D. Lutgring, MD	Centers for Disease Control and Prevention
Linda A. Miller, PhD	CMID Pharma Consulting LLC
Greg Moeck, PhD	Venatorx Pharmaceuticals, Inc.
Stephanie L. Mitchell, PhD, D(ABMM)	Cepheid, Inc.
Navaneeth Narayanan, PharmD, MPH	Rutgers University
Robin Patel, MD	Mayo Clinic
Virginia M. Pierce, MD	Massachusetts General Hospital
Ribhi M. Shawar, PhD, D(ABMM), F(AAM)	FDA Center for Devices and Radiological Health
Barbara L. Zimmer, PhD	Beckman Coulter
Reviewers and Guests Present: See the attached attendence sheet	
Staff Present:	
Kathy Castagna, MS, MT(ASCP)CT, MB	CLSI
Glen Fine, MS, MBA, CAE	CLSI
Emily Gomez, MS, MLS(ASCP)MB	CLSI
Marcy L. Hackenbrack, MCM, M(ASCP)	CLSI
Christine Lam, MT(ASCP)	CLSI

EXECUTIVE SESSION AND PLENARY AGENDAS All times are Eastern (US) Time All presentation can be accessed through on the CLSI Website: AST Meeting Files				
Working Group Virtual Meeting Time/Date	**Length**	**Chairholder(s)**	**Objectives (Use links to go directly to each report)**	
Plenary: Part 1 **Monday, 7 June 2021 10:00 AM - 1:00 PM**	3 h	**J. Lewis** (Chairholder) **M. Weinstein** (Vice-Chairholder)	Opening Remarks: Dr. Lewis	5 min.
			CLSI Update: Mr. Fine	10 min.
			Vet AST Update: Mr. Bowden	5 min.
			M23 WG Report: Dr. Wikler	5 min.
			QC WG Report: Ms. Cullen and Ms. Traczewski	60 min.
			Break	5 min.
			Table 1 WG Report: Dr. Simner	90 min.
Plenary: Part 2 **Monday, 7 June 2021: 3:00 - 6:00 PM**	3 h		Breakpoint WG Report (Part 1): Dr. Satlin and Dr. Mathers • Aminopenicillin (A4)	90 min.
			Break	5 min.
			Outreach WG Report: Ms. Hindler/Dr. Schuetz	15 min.
			Methods Application and Interpretation WG Report: Dr. Kirn/Dr. Limbago	60 min.
Plenary: Part 3 **Tuesday, 8 June 2021:12:00 - 3:00 PM**	3 h		Breakpoint WG Report (Part 2): Dr. Mathers and Dr. Satlin • Piperacillin-tazobactam	90 min.
			Break	5 min.
			Breakpoint WG Report (Part 3): Dr. Mathers and Dr. Satlin • Ceftolozane-tazobactam disk and comment	85 min.
Plenary: Part 4 **Thursday, 17 June 2021: 10:00 AM - 1:00 PM**	3 h		Breakpoint WG Report (Part 4): Dr. Mathers and Dr. Satlin • Finish Part 3 (as needed)	20 min.
			Joint CLSI-EUCAST WG Report: Ms. Hindler/Dr. Matuschek	20 min.
			Text and Tables WG Report: Dr. Bobenchik and Dr. Campeau	20 min.
			Break	5 min.
			Methods Development WG Report: Dr. Zimmer and Dr. Hardy	2 hrs.

Upcoming AST Meetings:

- **January 2022: In person (as allowed), Sunday - Tuesday, 23-25 January 2022**
  - St. Bonaventure Hotel, Ft. Lauderdale, Florida
  - All ad Hoc WG meetings must be held virtually in December 2021 and early January 2022.
  - Agenda requests and background material due for submission by **Monday, 13 December 2021**.
- **June 2022: In person (as allowed), Sunday - Tuesday, 26 - 28 June 2022**
  - Lowe's Chicago, Rosemont, Illinois
  - All ad Hoc WG meetings must be held virtually in May 2021 and early June 2022.
  - Agenda requests and background material due for submission by **Wednesday, 1 June 2021**.

Summary of Voting Decisions and Action Items

Summary of Passing Votes			
#	Motion Made and Seconded	Results[a]	Page[b]
1.	To approve the MIC QC ranges for meropenem-QPX7728 (fixed 8 µg/mL) for *K. pneumoniae* ATCC BAA-2814 (0.015/8-0.06/8 µg/mL) as the recommended routine QC strain and *P. aeruginosa* PA5257 (1/8-4/8 µg/mL) listed as an additional QC strain.	11-0-1-1	9
2.	To approve the MIC QC ranges for meropenem with *A. baumannii* NCTC 13304 (32-128 µg/mL)(integrity check), *E. coli* 13353 (0.015-0.06 µg/mL), *P. aeruginosa* PA5257 (128-1024 µg/mL) (integrity check).	11-0-1-1	10
3.	To approve the MIC QC ranges for QPX9003 with *A. baumannii* NCTC 13304 (0.06-0.5 µg/mL), *E. coli* 25922 (0.06-0.25 µg/mL) (routine), *E. coli* 13353 (0.03-0.25 µg/mL), *K. pneumoniae* ATCC BAA-2814 (0.015-0.12 µg/mL), *P. aeruginosa* 27853 (0.06-0.25 µg/mL)(routine), and *P. aeruginosa* PA5257 (0.12-0.5 µg/mL).	11-0-1-1	11
4.	To approve the agar dilution QC ranges for tebipenem with *B. fragilis* ATCC 25285 (0.03-0.25 µg/mL), B. *thetaiotaomicron* ATCC 29741 (0.12-0.5 µg/mL), *E. lenta* ATCC 43055 (0.06-0.25 µg/mL), and *C. difficile* ATCC 700057 (0.5-2 µg/mL).	11-0-1-1	12
5.	To approve the MIC QC ranges for MRX-8 with *E. coli* ATCC 25922 (0.06-0.5 µg/mL), *P. aeruginosa* ATCC 27853 (0.25-1 µg/mL), *E. coli* NCTC 13846 (2-16 µg/mL).	11-0-1-1	13
6.	To approved MIC QC ranges for *N. gonorrhoeae* ATCC 49226 (4-16 µg/mL).	11-0-1-1	14
7.	To approve the QC ranges for colistin with *E. coli* NCTC 13846 (1-4 µg/mL) and *E. coli* CDC AR (0349 1-4 µg/mL).	11-0-1-1	14
8.	To approve the revision of the QC range with *E. coli* ATCC 25922 for imipenem to 0.06-0.5 µg/mL and to expand the range for imipenem/relebactam to 0.06/4-0.5/4 µg/mL (4 dil) to match imipenem.	11-0-1-1	17
9.	To approve the revision of the QC range for *K. pneumoniae* ATCC 700603 with imipenem to 0.06-0.5 µg/mL.	11-0-1-1	17
10.	To approve the Table 2A Enterobacterales comment (4A) that breakpoints for ampicillin apply to parenteral ampicillin dosage of 2g q 4-6h or parenteral amoxicillin dosage of 1-2g q 6h. Breakpoints for oral ampicillin apply only to treatment of uncomplicated UTIs caused by *E. coli* and *P. mirabilis*, or shigellosis and salmonellosis. The revised comment is to be harmonized, as needed, with other comments in M100.	10-0-1-2	31
11.	To add an Enterobacterales ampicillin-sulbactam dosing comment: Breakpoint is based on dosage of 3 g administered parenterally every 6 hours.	11-0-1-1	32
12.	To approve the Enterobacterales comment for amoxicillin-clavulanate: “Breakpoint for oral amoxicillin/clavulanic acid is based on doses of either 875/125 q12h or 500/125 q8 in the setting of uncomplicated UTI or completing therapy for systemic infection. Breakpoint for parenteral formulation is based on a dosage regimen of 1.2 g intravenously administered every 6 hours.	11-0-1-1	33
13.	To approve suggested changes to Table 2D for ampicillin including a revised and a new comment: (Revised) “Rx Combination therapy with high dosage parenteral ampicillin, amoxicillin, penicillin …” and (New) “Breakpoints for ampicillin apply to parenteral ampicillin dosage of 2g q 4-6 h or parenteral amoxicillin 1-2g q 6 h. Breakpoints for oral ampicillin or oral amoxicillin apply only to treatment of uncomplicated UTIs”.	11-0-1-1	34
14.	To approve the dosage comment for ampicillin: “The dosage correlating with this breakpoint for meningitis is 2g IV given every 4 hrs.	11-0-1-1	35
15.	To add colistin for *Hafnia alvei* intrinsic resistance with footnote regarding *Hafnia paralvei* in Appendix B.	11-0-1-1	39

Summary of Passing Votes			
#	**Motion Made and Seconded**	**Results[a]**	**Page[b]**
16.	To approve the revised Piperacillin-Tazobactam BPs for Enterobacterales as ≤8 (S), 16 (SDD), and ≥ 32 (R) with the comment "Based on a dose of 4.5 grams q6h administered as a 3-hr infusion or 4.5 grams q8h administered as a 4-hr infusion" (FDA and "assuming normal renal function" removed) and with piperacillin alone being reassessed comment.	11-0-1-1	43
17.	To approve the revised amoxicillin-clavulanate MIC BPs for *H. influenzae* as S ≤2/1, I =4/2, R ≥8/4 with dosing comment (Breakpoint is based on a dose of either 875/125 mg q12h or 500/125 mg q8h given orally) contingent upon review of disk correlates.	12-0-0-1	43
18.	To approve the FDA approved ceftolozane-tazobactam disk breakpoints for Enterobacterales (≥22 S/ 19-21 I/ ≤18 R).	11-0-1-1	44
19.	To approve the proposed ceftolozane-tazobactam dosing comment (Breakpoints are based on a dosage regimen of 3 g administered every 8 hours) for *H. influenzae*.	11-0-2-0	45
20.	To approve the proposed ceftolozane-tazobactam dosing comment (Breakpoints are based on a dosage regimen of 3 g administered every 8 h for pneumonia and 1.5 g administered every 8 h for other indications) for Enterobacterales and *P. aeruginosa*.	11-0-2-0	45
21.	To approve proposed disk correlates for piperacillin-tazobactam of S ≥25 mm/ I 21-24 mm/R ≤20 mm (2.2% VME and 13.4% mE).	10-2-0-1	46
22.	To approve the addition of recommended process protocol for sponsors to work with the Joint CLSI-EUCAST WG for setting disk content (potency) to M23S.	13-0-0-0	47
23.	To include general surrogate testing comment with β-lactam combination agents and remove combination-specific comments.	10-2-0-1	49
24.	To recommend performing QC for the direct DD method from positive blood cultures according to standard methods (as per M02 as stated in the 1st bullet in the proposal).	13-0-0-0	52
25.	To approve the proposed ciprofloxacin 8-10 hr (early direct DD reads) zone cutoffs (S ≥23; I 18-22; R ≤ 17) for P. aeruginosa.	13-0-0-0	53
26.	To approve the current tobramycin zone cutoffs (S ≥15; I 13-14; R ≤ 12) for 8-10 hr (early direct DD reads) for *P. aeruginosa*.	13-0-0-0	53
27.	To approve the current ceftazidime zone cutoffs (S ≥18; I 15-17; R ≤ 14) for 16-18 hr direct DD reads for *P. aeruginosa*.	11-1-0-1	53
Electronic Votes			
28.	To approve the test/report placement of cefiderocol in Group B Tables 1 and Tables 2 for Enterobacterales, *P. aeruginosa*, *Acinetobacter*, and *Stenotrophomonas* with the plan to reassess when the revised Tables 1 are approved. **NOTE:** The sponsor has been notified and the both the BPWG and SC members approved unanimously.	13-0-0-0	N/A
29.	To approve the reassessment of breakpoints for Aminoglycosides.	In progress	
30.	To approve disk correlates for amoxicillin-clavulanate for *H. influenzae*.	TBD	

[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.

NOTE: The information contained in these minutes represents a summary of the discussions from a CLSI committee meeting, and do not represent approved current or future CLSI document content. These summary minutes and their content are considered property of and proprietary to CLSI, and as such, are not to be quoted, reproduced, or referenced without the expressed permission of CLSI. Thank you for your cooperation.

NOTE: Discussions recorded in this summary may be paraphrased.

2021 SUMMER AST MEETING SUMMARY MINUTES PLENARY 1: MONDAY, 7 JUNE 2021 – 10:00 AM – 1:00 PM EASTERN (US) TIME	
#	**Description**
1.	**OPENING REMARKS (Dr. Lewis)** • Dr. Lewis opened the meeting at 10:00 AM Eastern (US) time by welcoming the participants and thanking them for their time and dedication.
2.	**CLSI UPDATE (Mr. Fine)** • The organization has managed well during the pandemic. – CLSI staff has been working remotely for the last 15 months and is expected to remain remote until Summer 2022. – The office building was sold in 2020 and no new space has been leased. Mr. Fine noted that the virtual office is working well and, by working virtually, CLSI been able to save money that can be applied to member benefits and to CLSI's mission and activities. Staffing has been very stable. • The plan is to return to in-person meetings in January 2022 (23 – 25 January 2022 in Ft. Lauderdale). The meeting is expected to be in some form of hybrid format. CLSI is working on the logistics and mechanics of conducting the hybrid meetings. • The sales of standards have been fluctuating but are normalizing overall. • Mr. Fine expressed his gratitude to all the volunteers who have continued to dedicate their time and expertise to CLSI during a difficult time.
3.	**VAST UPDATE (Mr. Bowden)** • The VAST SC is expected to meet in the fall of 2021. • The VAST SC has nine active working groups (WG) covering different VAST areas and VAST is responsible for eight documents. • Recent VAST WG recommendations approved by the VAST SC include: – The Bovine Mastitis WG decided that existing breakpoints (BPs) for kanamycin/cephalexin will be placed in a new table in VET01S. – The VAST Editorial/Breakpoint (BP) Table Approvals o Recommendations to remove body site designations from dog, cat, and horse BPs. o Formation of an *Enterococcus* subgroup to investigate and propose revisions to current testing recommendations and ampicillin BPs. – The Generic Drug WG recommendation for cat urine "S" BPs of ≤8 µg/mL (MIC) and ≥17mm (disk diffusion) for *E. coli* and *Staphylococcus* spp. have been approved and "I" and "R" BPs are in discussion. – For Doxycyline, the SC approved the following recommendations from the Generic WG. o Canine BPs of ≤ 0.12 S / 0.25 I / ≥ 0.5 R (*E. coli* and *Staphylococcus* spp.) o Addition of a Table 2A comment that isolates of Enterobacterales are expected to test resistant. o Removal of human BPs for tetracyclines from VET01S Table 2A

2021 SUMMER AST MEETING SUMMARY MINUTES PLENARY 1: MONDAY, 7 JUNE 2021 – 10:00 AM – 1:00 PM EASTERN (US) TIME	
#	**Description**
4.	**M23 WG REPORT (Dr. Wikler)** **WG Roster:** Avery Goodwin, Matt Wikler (Co-Chairholders); Romney Humphries (Secretary); Timothy Bensman, Mariana Castanheira, Patricia Conville, Sharon Cullen, Eileen Kim, Linda Miller, Stephanie Mitchell, Greg Moeck, Margaret Ordonez Smith de Danies, Mike Satlin, Simone Shurland, Hui Wang (Members). **M23 Revision Status.** • **Volunteers who contributed significantly to the project and provided extraordinary leadership and efforts were recognized.** • **Timeline** – The draft was submitted for editing in preparation for the proposed draft and is expected to begin editing in mid- to late- June. – The draft is expected to be posted for a 45-day proposed draft vote in mid- to late-August. – Any comments will be resolved by the Chairholders, CLSI staff, and WG members and the draft revised as needed. – The approved draft will be edited for final vote and submitted to Consensus Council for approved. – M23 is expected to publish by March 2022. • **Revisions to the document include:** – Updated pharmacokinetics/pharmacodynamic (PK/PD) related definitions – Addition of new subchapter with rationale for, and factors to be assessed in, studies to assess reproducibility of reference broth microdilution (BMD) and disk diffusion (DD) assays. – Removal of disk content (potency) guidance that has been published in M23S. – Clarified the importance of the four cutoffs used to establish clinically relevant BPs. – Clarified the methods and guidance on targets, number of isolates to test, etc. – Clarified the clinical exposure-response cutoff information. – Added information regarding the presentation of outcomes, including discordances between clinical and microbiological outcomes and evaluating minimal inhibitory concentration (MIC increases between baseline and post-baseline isolates. – Added a sponsor checklist for CLSI BP proposals. – Added Appendix B (Example of a Reference Broth Microdilution Reproducibility Study) and Appendix C (Example of a Disk Diffusion Reproducibility Study).

5. **QUALITY CONTROL WORKING GROUP (WG) REPORT (Ms. Cullen)**

WG Roster: Sharon Cullen, Maria Traczewski (Co-Chairholders); Mike Huband (Secretary); Alexandra Bryson, Patricia Conville, Dana Dressel, Janet Hindler, David Lonsway, Erika Matuschek, Stephanie Mitchell, David Paisey, Elizabeth Palavecino, Chris Pillar, Susan Thomson, Katherine Young (Members).

Dr. Lewis announced the retirement of Maria Traczewski.

- He praised Maria for her many contributions to CLSI. He noted that during his association with CLSI, Ms. Traczewski along with Ms. Cullen have provided the detailed data used in making QC decisions. He commented on the amount of work needed to collect, organize, and present the data.
- He also noted that Maria has been very much involved with the Joint CLSI-EUCAST WG and their efforts to harmonize with EUCAST.
- He expressed his appreciation and congratulations for all her efforts and that she will be missed.

TIER 2 QC DATA AND WG RECOMMENDATIONS

- **Meropenem-QPX728 MIC QC ranges**

Drug: Meropenem-QPX7728 (fixed 8 µg/mL)	**Abbreviation (Glossary II & III)**: None (pending QPX7728 name)	**Previous ID**: None
Solvent (Table 6A): Water	**Diluent (Table 6A)**: Water	**Preparation (Table 6C combination agents)**: Pending
Route of administration (Glossary II): IV	**Class (Glossary I & II)**: ß-lactam combination agents	**Subclass (Glossary I & II)**: none
Study Report by: JMI	**Pharma Co**: Qpex Biopharma	**Control Drug**: Meropenem

Additional Information (M23 requirements)	• Tier 1 Impact Assessment (stability, inoculum, reading, incubation time, cations, zinc, surfactants, etc): Not conducted yet. Sponsor plans to conduct these prior to publication of QC ranges. • **Equivalency of agar dilution to broth dilution**: Not yet established. Sponsor plans to conduct these prior to publication of QC ranges. • **ISO/TS 16782 assessment of Tier 2 study materials**: Confirmed.
Footnotes:	• **Recommendations for Troubleshooting Guide (Table 4D Disk or 5G MIC):** NA
Discussion	• Meropenem was used as the control drug since the most applicable combination comparators were all proprietary and not commercially available (eg, imipenem-relebactam, meropenem-vaborbactam, and meropenem-nacubactam).

Drug Name: Meropenem-QPX7728 (fixed 8 µg/mL): Votes: 12/0/1/2 (For, Against, Absent, Abstain)

QC Strain	Range	% In	Mode	Dil	Shoulder	Media Mode	Lab Mode	M23 Range	Range Finder	Comments
K. pneumoniae **ATCC BAA-2814**	0.015/8-0.06/8	99.3%	0.03/8	3	31.3%@0.06	2@0.03/81@0.06/8	9@0.03/8	0.015/8-0.06/8, 99.3%	0.015/8-0.06/8, 99.3%	Media variability. Small shoulder. No lab variability. (Routine QC strain)

***P. aeruginosa* ATCC 27853**	0.06.8-0.5/8	99.3%	0.12/8	4	71.7%@0.25/8	2@0.12/8 1@0.12/8-0.25/8	1@0.06/8, 6@0.12/8, 1@0.12/8-0.25/8, 1@0.25/8	0.06.8-0.5/8, 99.3%	0.06.8-0.5/8, 99.3%	Media variability. Some lab variability. Large shoulder.
***P. aeruginosa* PA5257**	1/8-4/8	99.6%	2/8	3	56.6%@1/8	3@2/8	3@1/8, 5@2/8, 1@4/8	1/8-4/8, 99.6%	1/8-4/8, 99.6%	Lab variability. No significant media variability. Shoulder 56.6%.

- *K. pneumoniae* ATCC BAA-2814 (KPC producer) is recommended for routine QC of meropenem-QPX7728 (fixed 8 µg/mL) (12/0/1/1).
- *P. aeruginosa* (PA5257) will be listed as an additional QC strain in a footnote. Qpex Biopharma will complete the stability studies and paperwork required to submit PA5257 to the American Type Culture Collection (ATCC).
- **SC Discussion:** No discussion was needed.

A motion to approve the MIC QC ranges for meropenem-QPX7728 (fixed 8 µg/mL) for *K. pneumoniae* ATCC BAA-2814 (0.015/8-0.06/8 µg/mL) as the recommended routine QC strain and *P. aeruginosa* PA5257 (1/8-4/8 µg/mL) listed as an additional QC strain was made (T. Simner) and seconded (S. Sharp) was made and seconded. Vote: 11 for, 0 against, 1 abstain, 1 absent (Pass).

- **Meropenem MIC QC Ranges**

Drug: Meropenem	**Abbreviation (Glossary II & III)**: MEM	**Previous ID**: NA
Solvent (Table 6A): Water	**Diluent (Table 6A):** Water	**Preparation(Table 6C combination agents):**
Route of administration (Glossary II): IV	**Class (Glossary I & II):**Carbapenems	**Subclass (Glossary I & II):** NA
Study Report by: JMI	**Pharma Co**: Qpex Biopharma	**Control Drug**: meropenem
Additional Information (M23 requirements)	• **Tier 1 Impact Assessment** (stability, inoculum, reading, incubation time, cations, zinc, surfactants, etc): Completed. • **Equivalency of agar dilution to broth dilution**: Completed. • **ISO/TS 16782 assessment of Tier 2 study materials**: Confirmed.	
Footnotes:	• **Recommendations for Troubleshooting Guide (Table 4D Disk or 5G MIC):** NA	
Discussion	• No change to currently approved QC ranges. Study established expected ranges for additional strains including 2 options for QC strain integrity when testing combination beta lactam agents.	

Drug Name:	Meropenem					Votes:	12/0/1/1 (For, Against, Absent, Abstain)			
QC Strain	Range	% In	Mode	Dil	Shoulder	Media Mode	Lab Mode	M23 Range	Range Finder	Comments
A. baumannii NCTC 13304	32 -128	99.6%	64	3	40.7%@32	3@64	8@64, 1@32	32-128 99.6%	32-128 99.6%	QC integrity strain
E. coli ATCC 25922	0.008-0.06	99.6%	0.015	4	39.5%@0.03	1@0.15-0.03, 2@0.15	6@0.015, 3@0.03	0.008-0.03 97.8%	NA	Current range/control drug. Small shoulder but lab & media variability
E. coli NCTC 13353	0.015-0.06	98.9%	0.03	3	<30% (5.8%)	3@0.03	9@0.03	0.015-0.06, 98.9%	0.015-0.06, 98.9%	Not required for routine QC
K. pneumoniae ATCC BAA-2814	32-256	100%	64	4	41.6%@128	3@64	1@32, 7@64, 1@128	32-128, 98.9%		Current range/control drug. Small shoulder, some lab variability
P. aeruginosa ATCC 27853	0.12-1	99.6%	0.25	4	36.5%@0.5	3@0.25	8@0.25, 1@0.5	0.12-0.5, 98.1%	NA	Current range/control drug. Small shoulder, minimum variability
P. aeruginosa PA5257	128-1024	100%	512	4	64.4%@256	2@512, 1@256	4@256, 5@512	128-1024, 100%	128-1024, 100%	Lab & Media variability Highest dil tested 512. None @ >512, supports high end @ 1024. QC integrity strain

- **Current interpretive criteria for meropenem**: R ≥4 for Enterobacterales, ≥ 8 for *P. aeruginosa* and *Acinetobacter* spp.
- **Orange highlight on M100 Table 5A-2**: Meropenem with *A. baumannii* NCTC 13304 and *P. aeruginosa* PA5257 as QC integrity strains.
- **SC Discussion: Main points**
  - **ATCC number for *P. aeruginosa* PA5257 (unfamiliar strain):** The combination drug has not been officially named; therefore, the QC ranges will not be added to M100 until the name is designated. The QC ranges for *P. aeruginosa* PA5257 will not be added for meropenem (alone) until the combination drug is named and added to M100.
  - **Rationale for adding *A. baumannii* NCTC 13304 vs using current recommendations for *K. pneumoniae* BAA-1705 for QC integrity:** Any integrity stain can be used and not all need to be used. Since this strain was tested for the combination agent, the data was provided for the strain.
  - **Recommendations for routine QC**: Recommendations for routine QC are in progress. The QCWG is working on streamlining the QC for the single agents and plan to work on this for 2022.

A motion to approve the MIC QC ranges for meropenem with *A. baumannii* NCTC 13304 (32-128 µg/mL)(integrity check), *E. coli* 13353 (0.015-0.06 µg/mL), *P. aeruginosa* PA5257 (128-1024 µg/mL) (integrity check) was made (A. Mathers) and seconded (T. Mazzulli). Vote: 11 for, 0 against, 1 abstain, 1 absent (Pass).

- **QPX9003 MIC QC Ranges**

Drug Name:	QPX9003	Votes:	12/0/1/1 (For, Against, Absent, Abstain)

QC Strain	Range	% In	Mode	Dil	Shoulder	Media Mode	Lab Mode	M23 Range	Range Finder	Comments
***A. baumannii* NCTC 13304**	0.06-0.5	99.6%	0.12-0.25	4	98.5%@0.12	1@0.12, 2@0.25	3@0.12, 1@0.12-0.25, 5@0.25	0.06-0.5, 99.6%	0.06-0.5, 99.6%	Bimodal (and represents 99.3% of all results), Both media and lab variability.
***E. coli* ATCC 25922**	0.06-0.25	100%	0.12	3	31.1%@0.06	3@0.12	1@0.06, 1@0.06-0.12, 7@0.12	0.06-0.25, 100%	0.06-0.25, 100%	Small lab variability. Small shoulder Routine QC
***E. coli* NCTC 13353**	0.03-0.25 or 0.06-0.25	100%or 98.9%	0.12	4 or 3	60.3% @ 0.06	1@0.06, 2@0.12	2@0.06, 1@0.06-0.12, 6@0.12	0.03-0.25, 100%	0.06-0.25, 98.9	Media and lab variability. Shoulder 60.3%
***K. pneumoniae* ATCC BAA-2814**	0.015-0.12	99.3%	0.03	4	83.2%@0.06	2@0.03, 1@0.06	5@0.03, 4@0.06	0.015-0.12, 99.3%	0.015-0.12, 99.3%	Media and lab variability. Shoulder 83%
***P. aeruginosa* ATCC 27853**	0.06-0.25	99.6%	0.12	3	51.5%@0.25	2@0.12, 1@0.25	7@0.12, 2@0.25	0.06-0.25, 99.6%	0.06-0.25, 99.6%	Media and lab variability. Shoulder 51.5% Routine QC
***P. aeruginosa* PA5257**	0.12-0.5	97.4%	0.25	3	37.6%@0.12	1@0.12, 2@0.25	2@0.12, 7@0.25			Media and lab variability. Shoulder 37.6%

  - *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 are recommended for routine QC (any of the QC strains will work).
  - Discussed potential to create a separate table for additional strains with expected ranges that can be used for other purposes (eg, research, various types of studies, drug development, manufacturer's QC). This will be explored in 2022.
  - **SC Discussion:** No discussion was needed.

A motion to approve the MIC QC ranges for QPX9003 with *A. baumannii* NCTC 13304 (0.06-0.5 µg/mL), *E. coli* 25922 (0.06-0.25 µg/mL) (routine), *E. coli* 13353 (0.03-0.25 µg/mL), *K. pneumoniae* ATCC BAA-2814 (0.015-0.12 µg/mL), *P. aeruginosa* 27853 (0.06-0.25 µg/mL)(routine), and *P. aeruginosa* PA5257 (0.12-0.5 µg/mL) was made (B. Limbago) and seconded (A. Mathers). Vote: 11 for, 0 against, 1 abstain, 1 absent (Pass).

- **Tebipenem Agar Dilution QC Ranges**

Drug Name:	Tebipenem – Agar dilution	Votes:	12/0/1/1 (For, Against, Absent, Abstain)

QC Strain	Range	% In	Mode	Dil	Shoulder	Media Mode	Lab Mode	M23 Range	Range Finder	Comments
B. fragilis **ATCC 25285**	0.03-0.25	94.6% (all data) 100% (excluding Lab F)	0.06	4	87.5%@0.12 (all data)	2@0.06, 1@0.12	5@0.06, 1@0.06-0.12, 2@0.12	0.03-0.25, 94.6%	0.03-0.25, 94.6%	Lab F potential outlier (not per RangeFinder criteria). Doesn't change range, impacts % in range. Lab F 13@0.15, mode@0.06 Media and lab variability.[a] Shoulder 87.5%
B. thetaiotaomicron **ATCC 29741**	0.12-0.5	100%	0.25	3	<30% (15.1%)	3@0.25	7@0.25, 1@0.5	0.12-0.5, 100%	0.12-0.5, 100%	Control drug notes: Ertapenem control mode @ 1 (top of range). Metronidazole mode in middle of range.
Eggerthella lenta (formerly Eubacterium lentum) **ATCC 43055**	0.06-0.25	100%	0.12	3	<30%@0.25 (20.0%)	3@0.12	7@0.12, 1@0.25	0.06-0.25, 100%	0.06-0.25, 100%	
Clostridioides (formerly Clostridium) difficile **ATCC 700057**	0.5-2	100%	1	3	<30% (22.1%)	3@1	1@0.5, 6@1, 1@2	0.5-2, 100%	0.5-2, 100%	Lab variability

[a.] Labs made the agar dilution plates with materials provided so there is more potential variability or errors than a centrally provided broth microdilution.

- **SC Discussion: Main points**
  - **Using QC ranges for methods other than agar dilution**: It is unsure if this agent is going to be used for broth dilution. It will be noted in the table that this is for agar dilution and if to be used for BMD, verification is needed.

A motion to approve the agar dilution QC ranges for tebipenem with *B. fragilis* ATCC 25285 (0.03-0.25 µg/mL), *B. thetaiotaomicron* ATCC 29741 (0.12-0.5 µg/mL), *E. lenta* ATCC 43055 (0.06-0.25 µg/mL), and *C. difficile* ATCC 700057 (0.5-2 µg/mL) was made (A. Mathers) and seconded (R. Humphries). Vote: 11 for, 0 against, 1 abstain, 1 absent (Pass).

- **MRX-8 MIC QC Ranges**

Drug: MRX-8	**Abbreviation (Glossary II & III):** TBD	**Previous ID:** NA
Solvent (Table 6A): Water	**Diluent (Table 6A):** Water	**Preparation (Table 6C combination agents):** Not applicable
Route of administration (Glossary II): IV infusion	**Class (Glossary I & II):** Polymyxin	**Subclass (Glossary I & II):** none
Study Report by: IHMA	**Pharma Co:** MicuRx Pharmaceuticals, Inc.	**Control Drug:** colistin, polymyxin B
Additional Information (M23 requirements)	• Tier 1 Impact Assessment (stability, inoculum, reading, incubation time, cations, zinc, surfactants, etc): Per sponsor, Tier 1 impact assessment has been performed for inoculum, cations, and surfactant. • **Equivalency of agar dilution to broth dilution**: Per sponsor, agar vs. broth equivalency has been performed.	

	• **ISO/TS 16782 assessment of Tier 2 study materials**: Confirmed
Footnotes:	• Recommendations for Troubleshooting Guide (Table 4D Disk or MIC): NA
Discussion	• Future discussion needed on which strains to recommend for routine QC.

Drug Name:	MRX-8	**Votes:**	12/0/1/1 (For, Against, Absent, Abstain)

QC Strain	Range	% In	Mode	Dil	Shoulder	Media Mode	Lab Mode	M23 Range	Range Finder	Comments
E. coli **ATCC 25922**	0.06-0.5	100%	0.25	4	75%@0.12	1@0.12, 2@0.25	4@0.12, 5@0.25	0.12-0.5	0.06-0.5	Media and lab variability. Shoulder 75% Note: Colistin & Polymyxin controls: mode at bottom of range.
P. aeruginosa **ATCC 27853**	0.25-1	95.9%	0.5	3	44%@0.5	1@0.25, 2@0.5	9@0.5	0.25-1, 95.9%	0.12-1, 100%	Media variability but minimal lab variability. Should 44%. Note: Colistin controls: mode at bottom of range.
E. coli **NCTC 13846**	2-16	100%	4	4	64.5%@8	3@4	5@4, 4@8			Media mode@4 but 2 lots with high frequency @ 8, 1 lot with high frequency @2. Lab variability. Shoulder 64.5%

- Future discussion is needed on which strains to recommend for routine QC.
- **SC Discussion:** No discussion was needed.

A motion to approve the MIC QC ranges for MRX-8 with *E. coli* ATCC 25922 (0.06-0.5 µg/mL), *P. aeruginosa* ATCC 27853 (0.25-1 µg/mL), *E. coli* NCTC 13846 (2-16 µg/mL) was made (B. Limbago) and seconded (A. Mathers). Vote: 11 for, 0 against, 1 abstain, 1 absent (Pass).

- **Gentamicin Agar Dilution QC Range for *N. gonorrheoae***

Drug: Gentamicin	**Abbreviation (Glossary II & III)**: no change	**Previous ID**: NA
Solvent (Table 6A): no change	**Diluent (Table 6A):** no change	**Preparation(Table 6C combination agents):** no change
Route of administration (Glossary II): no change	**Class (Glossary I & II):** no change	**Subclass (Glossary I & II):** no change
Study Report by: CDC	**Pharma Co**: NA	**Control Drug**: Spectinomycin MICs

Drug Name:	Gentamicin – Agar dilution	**Votes:**	12/0/3/0

QC Strain	Range	% In	Mode	Dil	Shoulder	Media Mode	Lab Mode	M23 Range	Range Finder	Comments

***N. gonorrhoeae* ATCC 49226**	4-16	100%	8	3	<30% @16	3@8	9@8, 1@8-16	4-16, 100%	4-16, 100%	No significant media or lab variability. Spectinomycin control mode@32, top of current CLSI range

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

A motion to approve MIC QC ranges for *N. gonorrhoeae* ATCC 49226 (4-16 µg/mL) was made (A. Mathers) and seconded (S. Sharp). Vote: 11 for, 0 against, 1 abstain, 1 absent (Pass).

- **Colistin QC Ranges as a control for MRX-8**

Drug Name:	Colistin: IHMA Study control for MRX-8 (3 lots of media included)	**Votes:**	12/1/1/1 (For, Against, Absent, Abstain)

QC Strain	Range	% In	Mode	Dil	Shoulder	Media Mode	Lab Mode	M23 Range	Range Finder	Comments
***E. coli* NCTC 13846**[a]	1-4	99.3%	2	3	54.4%@4	3@2	8@2, 1@4	1-4, 99.3%	1-4, 99.3%	Minimal media & lab variability. Shoulder 54.4%
***E. coli* CDC AR 0349**[b]	1-4	100%	2	3	36%@1	1@1, 2@2	9@2	1-4, 100%	1-4, 100%	Some media variability. Shoulder only 36%.
***E. coli* ATCC 25922**	0.25-2	100%	0.25	4	<30%	1@0.25	9@0.25	NA	NA	Current range/control drug. Mode at bottom of range
***P. aeruginosa* ATCC 27853**	0.5-4	100%	0.5	4	<30%	1@0.5	8@0.5	NA	NA	Current range/control drug. Mode at bottom of range

[a.] *E. coli* NCTC 13486: EUCAST target 4, with occasional 2 or 8 (based on limited data)
[b.] ***E. coli*** CDC AR Bank #0349 ≤1-4 range with target of two established for Colistin broth disk elution (CBDE) and Colistin agar test (CAT). *P. aeruginosa* ATCC 27853 range ≤1-4. (follow up pending)

- **NOTE:** QC strains *E. coli* ATCC 25922 and *P. aeruginosa* 27853 are not the best for colistin QC.
- Further investigation suggested for difference in mode with *E. coli* NCTC 13846 in CLSI Tier 2 study and EUCAST.
- Modes for *E. coli* 25922 and *P. aeruginosa* ATCC 27853 were at bottom on the range in multiple labs. This will be added to Tier 3 and reassessed.
- Future discussion is needed on which strains to recommend for routine QC.
- Footnote needed in Table 5A-1: "Additional ranges provided by *E. coli* NCTC 13846 and *E. coli* CDC AR Bank #0349"?
- **SC Discussion: Main points**
  - **Ranges for *E. coli* 25922 and *P. aeruginosa* 27853 at the low end of the range:** Current Tier 3 data are also being requested.
  - **Source for colistin used in the preparation of media in the IHMA study (all one lot?): V**ariability is an issue with colistin and should be considered when testing.

A motion to approve the QC ranges for colistin with *E. coli* NCTC 13846 (1-4 µg/mL) and *E. coli* CDC AR (0349 1-4 µg/mL) was made (R. Humphries) and seconded (M. Galas). Vote: 11 for, 0 against, 1 abstain, 1 absent (Pass).

- **Colistin QC ranges as control for QPX9003: No QC ranges could be established for new strains.**

Drug Name:	Colistin: JMI study-control for QPX9003	**Votes:**	0/0/0/0 (For, Against, Absent, Abstain)

QC Strain	Range	% In	Mode	Dil	Shoulder	Media Mode	Lab Mode	M23 Range	Range Finder	Comments
***A. baumannii* NCTC 13304**	0.25-1	100%	0.5	3	<30%@1	NA	1@0.5-1, 8@0.5	NA	NA	Only 1 media lot. Insufficient to establish range.
***E. coli* NCTC 13353**	0.25-1	100%	0.5	3	<30%@0.25	NA	1@0.25-0.5, 8@0.5	NA	NA	Only 1 media lot. Insufficient to establish range.
***E. coli* ATCC 25922**	0.25-2	100%	0.5	4	<30% @0.25	NA	2@0.25, 7@0.5			Current range/control drug.
***K. pneumoniae* ATCC BAA-2814**	0.12-0.5	98.9%	0.25	3	<30%@0.5	NA	7@0.25, 2@0.5	NA	NA	Only 1 media lot. Insufficient to establish range.
***P. aeruginosa* ATCC 27853**	0.5-4	100%	0.5	4	57.9%@1	NA	6@0.5, 1@0.5-1, 2@1	NA	NA	Current range/control drug. Mode a bottom of range. No results at 2-4
***P. aeruginosa* PA5257**	0.5-2	100%	1	3	<30%@0.5	NA	1@0.5, 8@1	NA	NA	Only 1 media lot. Insufficient to establish range.

  - *E. coli* NCTC ATCC 13486 range established by EUCAST, CDC AR Bank #0349 range established for CBDE and CAT
  - Consider separate table with additional strains for other purposes vs routine QC or publish in a footnote.
  - Add *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853. to Tier 3 list since QC is at the lower end of approved range.

TIER 3 MIC QC DATA AND WG RECOMMENDATIONS

- **Active Tier 3**
  - **Data requests and continued monitoring**

QC Strain (ATCC)	Antimicrobial Agent	Current Range	Action Recommended	Concern
E. coli NCTC ATCC 13486 and/or CDC AR Bank #0349	Colistin	1-4 (2) 1-4 (2)	Summer 2021 Part 1 meeting: Approved ranges for BMD with new Tier 2 Study. Recommendations for which QC strains to test routinely is pending. See slides for combined data from 2 studies.	***E. coli* NCTC 13486**: EUCAST target 4, with occasional 2 or 8 (based on limited data) ***E. coli* CDC AR Bank #0349**: CLSI target 2, range 1-4 for CBDE and AD (June 2019 with limited disk & media data). Additional discussion/assessment needed: Assess difference in EUCAST and CLSI mode for NCTC 13486.
E. coli ATCC 25922	Colistin	0.25-2	Request feedback and additional /reassess range	Mode at bottom of range in 2 studies (control drug for QPX9003 [1 media lot] and MRX-8 [full 3-lot study])
P. aeruginosa ATCC 27853	Colistin	0.5-4	Request feedback and additional data/reassess range	Mode at bottom of range in 2 studies (control drug for QPX9003 [1 media lot] and MRX-8 [full 3-lot study])

- The issue will be revisited during the January 2022 meeting.
- It was noted that the stock preparation and length of storage may play a role in the issues.

QC Strain (ATCC)	Antimicrobial Agent	Current Range	Action Recommended	Concern
S. pneumoniae ATCC 49619	Levofloxacin	0.5-2	Request additional data, consider expanding to include 0.25	Mode 0.5 USCAST data (86% of 1,520). Tier 3: 120 results, mode 0.5, 4% out at 0.25.
K. pneumoniae ATCC 700603	Ampicillin/ Sulbactam	8/4 - 32/16	Request feedback	Report from one lab with results at 64/32
E. coli ATCC 25922	Piperacillin/ Tazobactam	1/4 - 4/4	Monitor/request feedback (Added Jan 2021, added some data June 2021)	Control drug in Ceftibuten/VNRX-5236 Tier 2 Jan 21 Mode at 4/4 µg/ml (2 media lots) at top of range. 4% out high at 8/4
E. coli ATCC 25922	Ceftibuten	0.12-0.5	Monitor/request feedback (Added Jan 2021)	Control drug Ceftibuten/VNRX-5236 Tier 2 Jan 21 Mode 0.25 with 83% shoulder at 0.5, Mode for one media at 0.5 (3 lots). 100% in range.
E. coli ATCC 25922	Aztreonam/ avibactam	0.03/4-0.12/4	Request feedback (Added June 2021)	Report from one lab with 44% at top of range and 4% out high with one media mfg
K. pneumoniae ATCC 700603	Piperacillin/ Tazobactam	8/4-32/4	Request feedback (Added June 2021)	Report from one lab with results at bottom of range with some out low.

- **Items to be removed from Tier 3 monitoring in 2022 if no new data is submitted.**

QC Strain (ATCC)	Antimicrobial Agent	Current Range	Action Recommended	Concern
H. influenzae ATCC 49247	Moxifloxacin	0.008-0.03	Monitor-request feedback	80.0% at upper extreme (0.03 µg/mL) of MIC range (results were from only one study, Table 3-29) Refer to USCAST Quinolone report V1.2.
E. faecalis ATCC 29212	Amikacin	64-256	Monitor-request feedback	CDC reported out low when testing gram-neg. panels, other strains in range.
S. aureus ATCC 29213	Ciprofloxacin	0.12-0.5	Monitor/request feedback	"bi-modal" MIC distribution noted from three studies. Consider revising range to 0.12-1. (Table 3-28). Refer to USCAST Quinolone report V1.2.
S. aureus ATCC 29213	Rifampin	0.004 to 0.016	Monitor-request feedback	One report of *S. aureus* out low
K. pneumoniae ATCC BAA-1705	Imipenem/relebactam	0.03/4-0.25/4	Monitor-request feedback	Results at high end with one lab.

- **Voting Requests for revised QC Ranges**

QC Strain (ATCC)	Antimicrobial Agent	Current Range	Action Recommended	Concern
E. coli ATCC 25922	Imipenem	0.06-0.25	Revise to 0.06-0.5 (4 dilutions). QCWG approved 11/1/3/0 See slides	Tier 3 with >900 results from 5+ labs Mode 0.12 with shoulder 69% at 0.25 Lab mode: 5@0.12, 2@0.12-0.25, 3@0.25. <1% at 0.06, 3% out of range high at 0.5. 0.06-0.5 supported by M23 and RangeFinder analysis. Unable to get Tier 2 data. **Note:** Deterioration of potency is best detected with *P. aeruginosa* ATCC 27853.
E. coli ATCC 25922	Imipenem/ relebactam	0.06/4-0.25/4	Expand to 0.06/4-0.5/4 (4 dil) to match proposal for Imipenem (0.06-0.5) QCWG approved 11/1/3/0 See slides	Tier 2 mode 0.12, 32% shoulder at 0.25, only 2% @0.06/4 Not a routine QC strain Tier 3: 5 labs, >900 results. Mode 0.12 with 42% shoulder at 0.25. Only 4% out of range high at 0.5/4,

				Only 2% at 0.06/4 (low end of range) Not required for routine testing. Can report AST results based on routine QC with *K. pneumoniae* ATCC 700603. RangeFinder & M23: 0.06/4-0.25/4, 3 dil, Tier 3 & 2+3.

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

A motion to approve the revision of the QC range with *E. coli* ATCC 25922 for imipenem to 0.06-0.5 µg/mL and to expand the range for imipenem/relebactam to 0.06/4-0.5/4 µg/mL (4 dil) to match imipenem was made (A. Mathers) and seconded (H. Gold). Vote: 11 for, 0 against, 1 abstain, 1 absent (Pass).

QC Strain (ATCC)	Antimicrobial Agent	Current Range	Action Recommended	Concern
K. pneumoniae ATCC 700603	Imipenem/ relebactam	0.03/4-0.25/4	Revise to 0.06-0.5 (4 dil, 98.7%) (QCWG approved 12/0/3/0) RangeFinder & M23: 0.06/4-0.5/4 (Tier 3 98.7% and Tier 2+3, 98.6%) See slides	Tier 2: mode 0.12/4, 61% shoulder @0.06/4, only 1 result at 0.03/4 Media mode: 1 @ 0.06/4, 2@ 0.12/4, Lab mode: 2@0.06/4, 6@0.12/4, 1@ 0.25/4, Tier 3 data: >900 results from 5+ labs, Mode 0.12/4, 48.8% shoulder @ 0.25 Lab mode: 7@ 0.12/4, 1@0.12/4-0.25/4, 2@ 0.25/4, Only 0.2% @ 0.03/4 and 0.9% @ 0.06/4 5.6% out high at 0.5/4, Only 93.7% in current range. Tier 2+3 mode 0.12/4, 44.8% shoulder @ 0.25/4, However only 93.7% within current range & variability in lab modes **Note:** K. pneumoniae ATCC BAA-1705 or 2814 are recommended for routine QC

A motion to approve the revision of the QC range for *K. pneumoniae* ATCC 700603 with imipenem to 0.06-0.5 µg/mL was made (A. Mathers) and seconded (H. Gold). Vote: 11 for, 0 against, 1 abstain, 1 absent (Pass).

TIER 3 DISK DIFFUSION QC DATA AND WG RECOMMENDATIONS

QC Strain	Antimicrobial Agent	Method	Current Range	Action Recommended	Concern	Date Reported
S. aureus ATCC 25923	Fluroquinolones	Disk		Request additional data Assess possibility of harmonizing reading instructions with EUCAST	Fuzzy zone edges results in too small zones (also observed for ATCC 29213). Inner zone visible depending on the lighting and angle.	May 2021
P. aeruginosa ATCC 27853	Cefiderocol	Disk	22-31	Collect additional data (prefer non-European labs) with multiple media manufacturers Potential to narrow the range	Major media differences observed in M23 study resulting in 10 mm range (22-31). EUCAST QC range is 23-29 mm. New European data fit with EUCAST range. All Tier 3 Data (n=249) are within the EUCAST range. Suggest changing the CLSI range to 23-29 or 22-29.	Jan 2021
E. coli ATCC 25922	Minocycline	Disk	19-25	Monitor and collect additional data.	Values at the top of the range and above range for 1lab.	Jan 2021

	MISCELLANEOUS TOPICS • **Troubleshooting and Footnotes** – *K. pneumoniae* ATCC 700603 may demonstrate multiple colony types that demonstrate the same AST results. o Suggest adding footnote to tables 4A-2 and 5A-2 for *K. pneumoniae* ATCC 700603: Strain may demonstrate two colony morphologies: 1) opaque and cream colored; and 2) translucent. o Add similar observation to Appendix C in the row for *K. pneumoniae* ATCC 700603 • **QC Data Storage and Access** – Proposal to create a repository for QCWG summaries on CLSI website with AST SC access. – The WG is discussing the best approach for organizing the data (eg, by agent, by key groups, by methods, etc.) and hope to include historical data. – The WG is discussing logistics and concerns with CLSI staff regarding making the data available with the ability to filter the data. – An example demonstration can be viewed at https://sites.google.com/view/alexandrashiny/home. • **CLSI/EUCAST Harmonization and QC Improvements:** This topic will be discussed during the Joint CLSI-EUCAST WG report.
6.	**TABLE 1 WG REPORT (Dr. Simner)** **WG Roster:** Patricia Simner, George Eliopoulos (Co-Chairholders); Virginia Pierce (Secretary); Tanaya Bhowmick, April Bobenchik, Carey-Ann Burnham, Joseph Lutgring, Barth Reller, Sandy Richter, Lauri Thrupp, Matt Wikler (Members) **Status of the Table 1 Revisions** • **The intent of Tables 1**: Suggested grouping of antimicrobial agents that should be considered for testing (not requirements) • **Update on previous decisions** – Fall 2020: The WG suggested adding a new group (B2) which was approved by the AST SC. – Winter 2021: Decision to replace "groups" with "tiers" and to transition to a horizontal format from a vertical format. – Spring 2021 (pre-AST meeting): WG developed the horizontal format and reviewed the antimicrobial agents for potential re-classification into tiers. • **New Tier definitions** – **Tier 1 (Group A)** - Antimicrobial agents that are considered appropriate for routine, primary testing, as well as for routine reporting of results. – **Tier 2 (Group B1)** – Antimicrobial agents that warrant primary testing but can be reported selectively such as when the organism is resistant to agents of the same antimicrobial class, as in Tier 1, or may be reported routinely per institution-specific guidelines. – **Tier 3 (NEW: Group B2)** – Antimicrobial agents that may warrant primary testing in institutions that harbor endemic or epidemic strains resistant to key primary drugs in Tiers 1 and 2 (Groups A and B1), but should be reported selectively on such multi-drug resistant strains per institution-specific guidelines (ie, report selectively). – **Tier 4 (Group C)** – Alternative or supplemental antimicrobial agents that may require testing and reporting for treatment of patients allergic to primary drugs or for reporting to infection control as an epidemiological aid (ie, by request only). **NOTE: The tables have not yet been formatted with separate boxes and with "or' where necessary.**

- **Enterobacterales:** Tier 1 agent is resistant, cascade to the Tier 2 agents, then to Tier 3 etc.

Tier 1	Tier 2	Tier 3	Tier 4
Ampicillin			
Cefazolin	Cefuroxime		
Cefotaxime or ceftriaxone	Cefepime → Ertapenem, Imipenem, Meropenem	Ceftazidime-Avibactam, Meropenem-Vaborbactam, Imipenem-Relebactam, Cefiderocol	
Amoxicillin-clavulanate, Ampicillin-sulbactam Piperacillin-tazobactam			
Gentamicin	Tobramycin → Amikacin		
Ciprofloxacin, Levofloxacin			
Trimethoprim-Sulfamethoxazole			
	Cefotetan, Cefoxitin		
	Tetracycline, Minocycline, Doxycycline		
			Aztreonam
			Ceftaroline
			Ceftazidime
			Ceftolozane-Tazobactam
Urine			
Cefazolin (surrogate for uUTI)			
Nitrofurantoin			
		Fosfomycin (*E. coli*)	
			Sulfisoxazole
			Trimethoprim

Testing Tiers & Cascade Reporting Between Tiers

- WG discussions and decisions
  - The WG discussed if agents should be separated out based on intrinsic resistance. It was decided to use footnotes to discuss intrinsic resistance.
  - Tetracyclines were retained as placed in the original tables.
  - Ceftazidime and ceftolozane-tazobactam were placed in Tier 4 since they are anti-pseudomonal drugs and would be discouraged for use with Enterobacterales.
  - Chloramphenicol and colistin/polymyxin B were removed as they are "O" agents.
  - *Salmonella* and *Shigella* were moved to a separate table.

- **SC Discussion**
  - **Question:** Agents with similar activities have previously been placed in a box but the example doesn't seem to adhere to those rules. Is the definition of agents placed in a box changed? **Answer:** Standard conventions for placing agents in a box will be followed. This table has not yet been formatted except for which agents are in which tier and will be addressed.
  - **Comment:** Tier 1 and 2 combines for Enterobacterales includes 22 agents. This amount is usually not included in a single panel. So there are concerns about laboratories thinking they 'need' to primary test all of these as recommended. It is suggested that the tables be formatted so

that laboratories understand that they only need to test a dozen or so agents. **Answer:** This should be addressed when standard conventions (eg, or) are added.
  - **Question:** Why not keep *Salmonella* and *Shigella* in the Enterobacterales table and use footnotes to explain differences. **Answer:** The WG believed that the primary agents tested are different from those tested for most Enterobacterales.
  - **Question:** Countries outside the US often have issues accessing newer antimicrobial agents and rely on the polymyxins and colistin. With new methods now available for testing, it might become an issue by removing them from the table. Could a footnote be added for those countries that test them frequently? Also, in Latin America, aztreonam is used frequently for those organisms with NDMs. Should aztreonam be included? **Answer:** Omission of the polymyxins and aztreonam was initially based on those recognized by the FDA and used in the US; however, these agents should be reviewed and perhaps placed in a regional-specific table. The WG will consider this option.
  - **Question:** Concern was raised regarding the Tier placement when looking for guidance on testing *Serratia*, *Pseudomonas*, Indole-positive *Proteus*, *Citrobacter*, and *Enterobacter* (SPICE). Is there going to be additional guidance for testing these with the 3rd-generation cephalosporins? **Answer:** The WG will reconsider additional guidance for these organisms.
  - **Comment**: It was questioned if cefazolin should be a Tier 1 due to difficulty with testing and the BP not being recognized by the FDA. It was suggested that is belongs in Tier 2 as a practical testing issue. There was concern that it will not be used of listed in Tier 2.
  - **Comment:** The final formatted table needs to be available for review before any decisions are made.
  - **Comment:** There was confusion regarding the use of the table, especially the urine drugs. There are drugs not listed under the urine section that may need to be used for urine isolates**. Answer:** This issue will be considered by the WG.
  - **Comment:** Suggest providing guidance regarding testing one agent but reporting another.
  - **Comment:** There was disagreement regarding the definition of Tier 4. **Answer:** The WG will look at expanding and clarifying the definition of Tier 4.
  - It was decided that the table was not ready for a vote. The WG will address the issues discussed.

- ***Salmonella* and *Shigella*** (see the Enterobacterales table for Tier definitions and cascading arrow)

Tier 1	Tier 2	Tier 3	Tier 4
Ampicillin			
Ciprofloxacin, Levofloxacin			
Trimethoprim-sulfamethoxazole			
Ceftriaxone		Ertapenem, meropenem, imipenem	
	Azithromycin		
			Tetracycline, Minocycline, Doxycycline

  - **WG discussions and decisions**
    - The WG decided to pull *Salmonella* and *Shigella* out of the Enterobacterales table.
    - It was decided that ceftriaxone as a Tier 1 in case there is an extraintestinal isolate (primary testing).
    - Cefepime was omitted from the table due to lack of data.
  - **SC Discussion**
    - **Question**: It was questioned if the carbapenems should be included. **Answer**: The WG believed that the intracellular activity may be similar to ceftriaxone although there is a lack of data. Testing for the carbapenems is being requested and the table provides the laboratories some guidance. A comment may be added to clarify carbapenem use.
    - **Question:** Was there consideration for moving azithromycin to Tier 1? **Answer:** Moving azithromycin was not considered to Tier 1 because the WG was trying to align with the comments currently in Table 1. Keeping it in Tier 2 lets laboratories make the decision on testing and reporting.

A motion to approve the new table 1 for *Salmonella* and *Shigella* for Tier 1 and Tier 2 only and remove carbapenems until there is further discussion was made (R. Humphries) and seconded (M. Satlin). 8 for, 2 against, 1 abstain, 2 absent (Fail).

- The votes against the motion (A. Mathers, T. Kirn) were due to concerns for only approving parts of the Table.
- It was suggested that the vote should be postponed until the carbapenem issue can be resolved.
- Issues regarding intestinal and extraintestinal *Salmonella* and *Shigella* also need to be addressed.

- ***Pseudomonas aeruginosa***

Tier 1	Tier 2	Tier 3	Tier 4
Ceftazidime Cefepime Piperacillin-tazobactam	Imipenem, Meropenem	Ceftolozane-Tazobactam, Ceftazidime-Avibactam, Imipenem-Relebactam, Cefiderocol	
Gentamicin, Tobramycin	Amikacin		
Ciprofloxacin, Levofloxacin			
	Aztreonam		

  - **WG Discussions and Decisions**
    - It was decided to have the carbapenems cascade from ceftazidime, cefepime, and piperacillin-tazobactam.
    - Colistin and Polymyxin B were not included as they are considered to be "Other" drugs and not routinely tested.
  - **SC Discussion**
    - **Question:** Carbapenems can be resistant to the carbapenems but susceptible to the other agents. How did the WG envision handling this issue? **Answer:** The WG didn't discuss putting the carbapenems in Tier 1 but believed that Tier 2 agents can be tested and reported.
    - **Comment:** Several suggestions were made for moving aztreonam to Tier 4 as it probably shouldn't be using it frequently due to penicillin allergies and endemic resistance.

NOTE: The remainder of the Table 1 WG presentation was completed during Plenary 2 but is recorded here.

- During the break between Plenary 1 and Plenary 2, Dr. Simner addressed some of the issues discussed during the earlier session.
  - **Revised definition of Tier 4 (changes in red):** Alternative or supplemental antimicrobial agents that may require testing and reporting by clinician request in certain scenarios such as for treatment of patients allergic to primary drugs, for treatment of unusual organisms, polymicrobial infections or for reporting to infection control as an epidemiological aid, among others.
  - **Note:**
    - These are suggestions.
    - All decisions should be made with the antimicrobial stewardship group and follow institutional guidelines.
    - Patient-specific factors for use of an agent (eg, age, body site) should be considered.
    - Always report unexpected resistance.

- **Summary**

	Tier 1	Tier 2	Tier 3	Tier 4
TEST	X	X	If MDR common	By clinician request
REPORT	X	Test if R to Tier 1 of the same class	Test if R to Tier 1 and 2	

X = Test and/or Report

- ***Staphylococcus* spp.**

Tier 1	Tier 2	Tier 3	Tier 4
Azithromycin or clarithromycin or erythromycin			
Clindamycin			
Oxacillin Cefoxitin (surrogate test for oxacillin)		Ceftaroline	
Tetracycline, Doxycycline, Minocycline			
Trimethoprim-Sulfamethoxazole			
Vancomycin			
		Rifampin	
		Daptomycin	
		Linezolid, Tedizolid	
		Lefamulin	
		Penicillin	
			Ciprofloxacin, levofloxacin, moxifloxacin
			Gentamicin
			Dalbavancin, Oritavancin, Telavancin
Urine			
Nitrofurantoin			
			Sulfisoxazole
			Trimethoprim

  - **SC Discussion**
    - **Comment:** Penicillin placement was questioned due to its lack of use. Suggested it be moved to Tier 4.
    - **Question:** Should delafloxacin be added to Tier 1? **Answer:** CLSI does not currently have BPs for delafloxacin; therefore, it was not included.
    - **Question:** What about including daptomycin and rifampin? **Comment:** Daptomycin is a primary therapy for invasive *S. aureus* and should be Tier 2. Believe that rifampin and ceftaroline can be retained as Tier 3. Answer: The WG will revisit the placement of these agents.

- ***Enterococcus* spp.**

Tier 1	Tier 2	Tier 3	Tier 4
Ampicillin, Penicillin			
	Vancomycin		
	Gentamicin (high-level resistance testing only)		
		Streptomycin (high-level resistance testing only)	
		Daptomycin	
		Linezolid, Tedizolid	
			Oritavancin
			Dalbavancin, Telavancin
Urine			
Nitrofurantoin			
	Ciprofloxacin, Levofloxacin		
		Fosfomycin	
		Tetracycline (Not Doxycyline or minocycline see comment below – remove footnote or add a new one here)	

  - **WG Discussions and Decisions**
    - The WG decided to move streptomycin, linezolid, and tedizolid to Tier 3 since if more resistant strains they would be selectively reported.
  - **SC Discussion**
    - **Comment:** There were multiple suggestions to move linezolid and daptomycin to Tier 2 for *Enterococcus* due to VRE being common isolates. It is less clear that Tier 3 agents need to be tested routinely. **Response:** The suggestion will be considered.

- ***Acinetobacter* spp.**

Tier 1	Tier 2	Tier 3	Tier 4
Ampicillin-sulbactam			
Ceftazidime Cefepime	Imipenem, Meropenem	Cefiderocol	
Ciprofloxacin, Levofloxacin			
Gentamicin, Tobramycin	Amikacin		
	Piperacillin-tazobactam		
	Trimethoprim-sulfamethoxazole		
	Minocycline		Doxycycline
			Cefotaxime, Ceftriaxone
			Colistin
Urine			
Tetracycline			

- **WG Discussion and Decisions**
  - It was agreed that imipenem and meropenem should cascade from ceftazidime and cefepime.
  - It was agreed that cefiderocol should cascade from imipenem and meropenem.
  - It was decided to include colistin as they are a big component of treatment guidelines.
- **SC Discussion**
  - **Question:** Is there any consideration to remove BPs for ceftriaxone and cefotaxime? They have high MICs for the wild-typi (WT) which are above PK-PD cutoffs. **Answer:** BPs for these agents need to be revisited as the question is accurate.

- ***Burkholderia cepacia* complex**

Tier 1	Tier 2	Tier 3	Tier 4
Levofloxacin			
Meropenem			
Ceftazidime			
Minocycline			
Trimethoprim-sulfamethoxazole			

- **WG Discussion and Decisions**: Chloramphenicol was removed and there were no other revisions made.
- **SC Discussion**: No discussion was needed.

- ***Stenotrophomonas maltophilia***

Tier 1	Tier 2	Tier 3	Tier 4
Levofloxacin		Cefiderocol	
Minocycline			
Trimethoprim-sulfamethoxazole			
	Ceftazidime		

- **WG Discussions and Decisions**
  - Cefiderocol will cascade from all the drugs in Tiers 1 and 2.
  - Uncertainties regarding ceftazidime were discussed.
  - **SC Discussion:** It was suggested that ceftazidime be moved to Tier 4.

- **Other Non-Enterobacterales**

Tier 1	Tier 2	Tier 3	Tier 4
Ceftazidime	Cefepime, Imipenem, Meropenem		
Gentamicin, Tobramycin	Amikacin		
Piperacillin-tazobactam			
Trimethoprim-sulfamethoxazole			
	Aztreonam		
	Ciprofloxacin, levofloxacin		
	Minocycline		
			Cefotaxime, Ceftriaxone

Urine			
Tetracycline			
			Sulfisoxazole

- **WG Discussion and Decisions**
  - Minocycline was added as a Tier 2 agent and chloramphenicol was removed.
  - The possibility of moving BPs for these organisms to M45 was discussed.
- **SC Discussion**
  - **Comment:** This needs to be assessed species by species. It was agreed that it should be determined if these BPs need to be in M45.
  - Chloramphenicol placement will be revisited for all tables.

- ***Haemophilus influenzae***

Tier 1	Tier 2	Tier 3	Tier 4
Ampicillin	Cefotaxime or ceftazidime or ceftriaxone	Meropenem	Ertapenem or imipenem
	Ampicillin-sulbactam		
	Amoxicillin-clavulanate		
	Ciprofloxacin or levofloxacin or moxifloxacin		
	Trimethoprim-sulfamethoxazole		
			Ceftolozane-tazobactam
			Lefamulin
			Azithromycin Clarithromycin
			Aztreonam
			Cefaclor Cefprozil
			Cefdinir or cefixime or cefpodoxime
			Ceftaroline
			Cefuroxime
			Rifampin
			Tetracycline

- **WG Discussion and Decisions**
  - Ampicillin-sulbactam and amoxicillin-clavulanate were moved to Tier 2.
  - Discussed reviewing the footnotes associated with this table to determine whether revisions are needed and revisit comment 5 in Table 2E and Table 1 footnotes.
- **SC Discussion:** No discussion was needed.

- ***Neisseria gonorrhoeae***

Tier 1	Tier 2	Tier 3	Tier 4
Azithromycin			
Ceftriaxone, Cefixime			
Ciprofloxacin			
Tetracycline			

  - **Discussion and Decisions**: No changes were recommended by the WG and no SC discussion was needed.

- ***Streptococcus pneumoniae***

Tier 1	Tier 2	Tier 3	Tier 4
Erythromycin			
Penicillin			Amoxicillin, Amoxicillin-clavulanate
Trimethoprim-sulfamethoxazole			
Cefotaxime, Ceftriaxone			Cefepime, Ceftaroline
	Meropenem		Ertapenem, Imipenem
	Clindamycin		
	Tetracycline, Doxycycline		
	Levofloxacin, Moxifloxacin		
	Vancomycin		
			Lefamulin
			Linezolid
			Cefuroxime
			Rifampin

  - **WG Discussions and Decisions**
    - Place levofloxacin and moxifloxacin in Tier 2 to provide flexibility to decide whether or not to report the fluoroquinolones.
    - Place linezolid in Tier 4 since the need for linezolid AST results seems to fit in with the definition for Tier 4.
    - Move cefepime to Tier 4 since it is rarely used especially if cefotaxime or ceftriaxone are tested routinely.
    - Place lefamulin in Tier 4 for reasons similar to those for linezolid.
  - **SC Discussion**: No discussion was needed.

- ***Streptococcus* spp. ß-Hemolytic Group**

Tier 1	Tier 2	Tier 3	Tier 4
Clindamycin			
Erythromycin			
Penicillin or ampicillin		Cefotaxime or ceftriaxone	Cefepime, Ceftaroline
	Tetracycline	Vancomycin	
			Linezolid, Tedizolid
			Daptomycin
			Levofloxacin
			Dalbavancin, Oritavancin, Telavancin

- **WG Discussion and Decisions**
  - Move cefepime to Tier 4 with ceftaroline as it does not need to be primarily tested.
  - Request input from the SC regarding inclusion of the tetracyclines in the table.
- **SC Discussion**
  - **Comment:** It was strongly suggested that tetracycline should be included in the table. **Response:** Tetracycline is currently listed as an "O' agent and not currently included in the Table 1 for *Streptococcus* spp. Tetracycline will be included and a footnote regarding Doxycyline being tested for tetracycline will be added.

- ***Streptococcus* spp. Viridans Group**

Tier 1	Tier 2	Tier 3	Tier 4
Ampicillin, Penicillin			
Cefotaxime, Ceftriaxone		Cefepime	
	Vancomycin		
		Linezolid, Tedizolid	
			Ceftolozane-tazobactam
			Clindamycin
			Erythromycin

- **WG Discussion and Decisions**
  - Place cefepime in Tier 3.
- **SC Discussion**
  - **Comment:** It was suggested that ceftolozane-tazobactam be removed as it seems out of place. **Response:** It is currently in M100 as a "C" drug.
  - **Comment:** It was questioned if cefepime should be in the table. **Response:** It is in the table to provide useful information from testing in hematology-oncology patients when penicillin is not highly susceptible.

- **Gram-negative Anaerobes**

Tier 1	Tier 2	Tier 3	Tier 4
Amoxicillin-clavulanate Ampicillin-sulbactam Piperacillin-tazobactam			
Clindamycin			
Ertapenem, Imipenem, Meropenem			Imipenem-relebactam
Metronidazole			
			Penicillin, Ampicillin
			Cefotetan, Cefoxitin
			Ceftizoxime, Ceftriaxone
			Moxifloxacin

- **WG Discussion and Decisions**
  - The WG noted that in M100, Table 1 for anaerobes, there are only Groups A and C. Therefore, it was decided to place all Group A agents into Tier 1 and Group C agents in Tier 4.

- **SC Discussion**
  - **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.

- **Gram-positive Anaerobes**

Tier 1	Tier 2	Tier 3	Tier 4
Ampicillin, Penicillin			
Amoxicillin-clavulanate Ampicillin-sulbactam Piperacillin-tazobactam			
Clindamycin			
Ertapenem, Imipenem, Meropenem			Imipenem-relebactam
Metronidazole			
			Cefotetan, Cefoxitin
			Ceftizoxime, Ceftriaxone
			Moxifloxacin
			Tetracycline

- **WG Discussion and Decisions**
  - Place imipenem-relebactam and moxifloxacin in Tier 4.
- **SC Discussion**
  - **Comment:** It was suggested that the sponsor be contacted for rationale as to why an agent should be included in the table. If there is an FDA indication and BPs, the sponsor would be contacted for a potential response. Response: It was noted that when the results for a particular drug are known, there is no reason to test an agent.

- The WG will continue to meet and address concern raised during the discussion. The Tables will be formatted as they should be in M100. The plan will be to discuss these tables again in January 2022 and add them to the 33rd edition (2023) of M100.

Adjournment (Dr. Lewis): Dr. Lewis thanked the participants for their time. The meeting was adjourned at 1:00 PM Eastern (US) time.

2021 SUMMER AST MEETING SUMMARY MINUTES PLENARY 2: MONDAY, 7 JUNE 2021 – 3:00 – 6:00 PM EASTERN (US) TIME	
Item #	**Description**
	NOTE: See Plenary 1 for the full Table 1 WG report.
7.	**OUTREACH WG REPORT (Ms. Hindler)** **WG Roster:** Janet Hindler, Audrey Schuetz (Co-Chairholders); Stella Antonara (Secretary); April Abbott, April Bobenchik; Romney Humphries, Andrea Ferrell, Graeme Forrest, Shawn Lockhart, Rianna Malherbe, Nicole Scangarella-Oman, Paula Snipps-Vagnone, Priyanka Uprety, Lars Westblade (Members) • **Recent and upcoming webinars and presentations** – The new attendee orientation program is now available on demand. – Over 1000 registrants attended the 2021 AST Update provided by Romney Humphries, Audrey Schuetz, and Janet Hindler – The CLSI-SIDP ACCP Annual Webinar is scheduled for Summer of 2021. – A webinar presented by April Abbott and Romney Humphries on "Practical Advice for Bench Techs – How to Recognize Unusual AST Patterns" is scheduled for Fall 2021. – Romney Humphries and Navaneeth Narayanan will be presenting at the ASM Virtual World Microbe Forum on "Antimicrobial Testing Meets Antimicrobial Stewardship: What Works and What's Needed?" • **CLSI AST New Updates** – Most recent news update was published in April 2021. Content included: o A feature article and case study on Intermediate^ (I^). o Hot topic on Imipenem-relebactam and aztreonam-avibactam. o An overview of the changes in M100, 31st edition. – The next newsletter edition is expected in the Fall 2021. Content is expected to include: o A feature article on direct disk diffusion from blood cultures o Practical tips for *H. influenzae*. o A hot topic related to Antifungal susceptibility testing. – The WG is seeking volunteers to write articles, suggest content, and to translate the update into Spanish. • **AST SC Meeting Workshops:** Being planned for the in-person meeting in January 2022. The tentative topic for the next meeting is "Updating Breakpoints" – The Concerns and "Solutions" • **Development of an M100 Education Program** – The program will consist of an interactive video on how to use M100. The plan is to update the video for each edition. – The program is being developed with the assistance of an educational software designer. – The program will provide 1 hour of CEUs and will be free of charge. – The target for completion is June 30, 2021 with a preview date of June 17th.

PLENARY 2 (continued)

Item #	Description
8.	**BREAKPOINT WG REPORT – PART 1 (Dr. Mathers/Dr. Satlin)** **WG Roster:** Amy Mathers, Mike Satlin (Co-Chairholders); Karen Bush (Secretary); George Eliopoulos, Marcelo Galas, Romney Humphries, Navaneeth Narayanan, Robin Patel, Simone Shurland, Lauri Thrupp, Hui Wang, Barbara Zimmer (Members); Matt Wikler (Advisor) **Aminopenicillin (A4) WG Report (Dr. Mathers)** **AHWG Roster:** Paul Edelstein (UPenn), Nav Narayanan (Rutgers)(Co-chairholders); Eric Wenzler (U Illinois at Chicago)(Recording secretary); Christian Giske (Karolinska Univ Hosp and Institutet, EUCAST), Amy Mathers (U. Virginia), Nicholas Moore (Rush Univ Medical Center), Rodrigo Mendes (JMI labs), Matt Wikler (Industry)(Members)

- **BPs presented for SC discussion and decisions included:**

Table	Organism	Ampicillin	Amoxicillin	Amox/clavulanate	Amp/Sulbactam
2A	Enterobacterales	8/32	amp surrogate	8/32	8/32
2D	Enterococci	8/16	ampicillin or penicillin surrogates		
2E	*Haemophilus*	1/2/4	amp surrogate	4/8	2/4

- **Ampicillin (Amoxicillin) for Enterobacterales**
  - Current CLSI and EUCAST BPs

	S	I	R
CLSI M100-31 ampicillin	≤ 8	16	≥ 32
CLSI M100-31 amoxicillin	Ampicillin surrogate		
EUCAST 11.0 Jan 2021 (amp & amox)	≤ 8 (IV admin only)	--	≥ 16 (IV admin only)
EUCAST dosage amp	2g q6 to 8h		
EUCAST dosage amox	1-2 g q4 to 8h		

  - Historically, no rationale for setting CLSI BPs was found in early CLSI records (1980 and later) and modern data is limited. Ampicillin has both oral and parenteral dosages that vary widely. A single BP for various dosages is problematic without specifying site.
  - PK data were reviewed. Conclusions were:
    - Oral amoxicillin 500 mg has 0% target attainment (TA) at BP
    - IV amoxicillin dosages of 2g q6h has >90% TA at fT>MIC 40% at MIC of 8 µg/ml (BP)
    - IV amoxicillin dosages of 1g q6h has >90% TA at fT>MIC 30% at MIC of 8 µg/ml (BP)
  - Clinical data were reviewed. Conclusions were:
    - BPs for *E. coli* not achievable by standard oral dosing except for uncomplicated UTI
    - Enteric infection BPs are difficult to evaluate, and may be appropriate, but ampicillin is inferior to other therapies for shigellosis.
    - Comment 2 in Table 2A should include warning regarding possible amoxicillin failure for *Shigella*.
  - WG Suggestions
    - Specify dosage for oral ampicillin and amoxicillin for uncomplicated UTI
    - Retain BPs, specifying that treatment for systemic infections requires high dosage IV therapy (ampicillin and amoxicillin)

- Modify comment 2 based on potential inferiority of amoxicillin vs ampicillin
- Add specified dosages to Appendix E

– **WG requested SC votes on the following (all approved by the WG):**
- **Revise comment (4) (new text in red) in Table 2A:** Results of ampicillin testing can be used to predict results for amoxicillin. (4A) Breakpoints for ampicillin apply to parenteral ampicillin dosage of 2 g q 4-6 h or parenteral amoxicillin 1-2 g q 6 h. Breakpoints for oral ampicillin apply only to treatment of uncomplicated UTIs caused by *E. coli* and *P. mirabilis*, or shigellosis and salmonellosis, based on oral ampicillin dosage of 500 mg q 6 h; or oral amoxicillin 250 mg q 8 h or 500 mg q 12 h. See general comment (2).
- **Revise general comment (2) (new text in red) in Table 2A:** When fecal isolates of *Salmonella* and *Shigella* spp. are tested, only ampicillin, a fluoroquinolone, and trimethoprim-sulfamethoxazole should be reported routinely. There are conflicting data regarding whether amoxicillin should be used to treat shigellosis. When reporting ampicillin results state that treatment of shigellosis with amoxicillin might not be comparable to ampicillin with poorer efficacy. In addition, for extraintestinal isolates of *Salmonella* spp., a 3rd-generation cephalosporin should be tested and reported, and chloramphenicol may be tested and reported if requested. Susceptibility testing is indicated for typhoidal *Salmonella* (*S. enterica* ser. Typhi and *S. enterica* ser. Paratyphi A–C) isolated from extraintestinal and intestinal sources. Routine susceptibility testing is not indicated for nontyphoidal Salmonella spp. isolated from intestinal sources. In contrast, susceptibility testing is indicated for all *Shigella* isolates.
- Add dosage regimen to Appendix E:

Antimicrobial Agent	Breakpoints and Interpretive Categories	
	Susceptible	
	MIC	Dose
Table 2A. Enterobacterales		
Ampicillin	≤ 8 µg/mL	500 mg administered orally every 6h (uncomplicated UTI)
		2 g administered IV every 4-6h (systemic infections other thanmeningitis)
Amoxicillin	≤ 8 µg/mL	250 mg administered orally every 8h or 500 mg every 12h (uncomplicated UTI)
		1-2 g administered IV every 6h (systemic infections other than meningitis)

– **SC discussion**
- Suggested to note in M100 that the BPs have been reviewed and reassessed. Options: New table below the BP changes table or include a comment about the review in the BP changes since 2010 table.

A motion to approve the Table 2A Enterobacterales comment (4A) that breakpoints for ampicillin apply to parenteral ampicillin dosage of 2g q 4-6h or parenteral amoxicillin dosage of 1-2g q 6h. Breakpoints for oral ampicillin apply only to treatment of uncomplicated UTIs caused by *E. coli* and *P. mirabilis*, or shigellosis and salmonellosis. The revised comment to be harmonized, as needed, with other comments in M100 was made (R. Humphries) and seconded (M. Satlin). Vote: 10 for, 0 against, 1 abstain, 2 absent (Pass).

- A vote was not needed to add the revised dosages for ampicillin to Appendix E as shown in the table above.

- **Ampicillin-sulbactam BPs for Enterobacterales**

Current BPS	S≤	I	R≥	Dosage
CLSI	8/4	16/8	32/16	none
EUCAST	8		16	2/1 q6 to q8 IV

- History
  - BP adopted in 1987 with no rationale stated and comment to reassess ampicillin and ampicillin-sulbactam BPs with data correlating clinical responsiveness and *in vitro* data are available.
  - Uncontrolled clinical trial data were presented without MICs, dosage or outcome by MIC or susceptibility
  - Studies in diabetic foot, community-acquired pneumonia, aspiration pneumonia, pelvic infections and gonorrhea all show efficacy
  - Ampicillin/sulbactam was an independent risk factor for failure in lower GI intraabdominal infections in two studies vs moxifloxacin and ertapenem. The study data was insufficient to determine cause of difference
  - There was a lack of robust clinical data assessing outcome by MIC.
- **WG Conclusions**
  - The current BP is reasonable.
  - ECVs differ between target organisms, and for *K. pneumoniae* BP is in WT distribution
  - WG Suggestions and Request for vote.
  - Retain the current BPs
  - Include a dosage comment in Table 2A: "Breakpoint is based on dosage of 3 g administered parenterally every 6 hours."
  - Add dosage comment to Appendix E
- **SC Discussion**
  - Concern was raised regarding discordance between the dose for ampicillin alone and for ampicillin-sulbactam. The point was considered valid; however, this is the dose that the BP is based on and may not be the dosage used clinically.

A motion to add an Enterobacterales ampicillin-sulbactam dosing comment: "Breakpoint is based on dosage of 3 g administered parenterally every 6 hours" was made (M. Satlin) and seconded (H. Gold). Vote: 11 for, 0 against, 1 abstain, 1 absent (Pass).

- **<u>Amoxicillin-clavulanate for Enterobacterales</u>**
  - Current CLSI BPs

Drug	S	I	R
Ampicillin/sulbactam	≤ 8/4	16/8	≥ 32/16

  - Current EUCAST BPs

Drug	S	R	Dosages
Amox/clav IV	≤ 8	≥ 16	1/0.2 to 2/0.2q6-8h
Amox/clav PO (UTI only - currently under revision)	≤32	≥64	875/125 q8

  - History
    - 1983: PK/PD for amoxicillin in combination were shown to be the same as for amoxicillin only. The MIC correlate (≤8 µg/ml) for the disk diffusion susceptible BP of ampicillin was chosen as the MIC susceptible BP. The BPs were considered tentative.
    - 1989: The BPs were reassessed and no changes were made.
    - Issues with current BPs: PK/PD showed insufficient TA at the current BP and there is insufficient FDA-submitted data to support the primary use of oral amoxicillin-clavulanate for skin and soft tissue infections caused by Enterobacterales.

- **Summary of Data Review**
  - Amoxicillin-clavulanate effectiveness on ß-lactamase (+) *E. coli* and *K. pneumoniae* depends on concentrations of both amoxicillin and clavulanate.
  - Modern data showed that the time above MIC is insufficient for the BP with the oral dose.
  - TA time above MIC with an IV dosage is acceptable for the BP.
  - Clinical data looked good for various non-urinary infections but were rarely caused by Enterobacterales.
  - Clinical data for UTI showed reasonable outcomes but the data for response by MIC were not robust. A large study did not demonstrate that there was inferiority compared to other agents.
  - The susceptibility category did not matter in three-day treatment failures.
  - Amoxicillin-clavulanate appears to work well as a "step-down therapy".
- **Summary and BPWG Discussion**
  - Monte carlo simulations showed low TA with common oral dosing.
  - There is a strong clinical outcome for >90% or oral dosing for UTI but no clear MIC response.
  - The combination agent is used almost exclusively as outpatient treatment but clinical outcomes were no correlated with MIC.
  - Clinical data support the MIC is the correct BP for parenteral.
  - The WG agreed that there is insufficient data to revise the BP.
  - The oral dosing regimen needs to be clarified.
  - It needs to be clarified that oral usage can be used for "mop up" therapy.
  - Need to emphasize that the dose needs to be higher for non-UTI indications
  - The WG proposed to retain the BP as is and add a comment to Table 2A: "**Breakpoint for oral amoxicillin/clavulanic acid is based on doses of either 875/125 q12h or 500/125 q8 in the setting of uncomplicated UTI or completing therapy for systemic infection. Breakpoint for parenteral formulation is based on a dosage regimen of 1.2 g intravenously administered every 6 hours.**"
- **SC Discussion:** No discussion was needed.

A motion to approve the Enterobacterales comment for amoxicillin-clavulanate: "Breakpoint for oral amoxicillin/clavulanic acid is based on doses of either 875/125 q12h or 500/125 q8 in the setting of uncomplicated UTI or completing therapy for systemic infection. Breakpoint for parenteral formulation is based on a dosage regimen of 1.2 g intravenously administered every 6 hours" was made (M. Satlin) and seconded (T. Mazzulli). Vote: 11 for, 0 against, 1 abstain, 1 absent (Pass).

- **Ampicillin for *Enterococcus***
  - Current BPs

	S	I	R	Infers	Drug Route
CLSI - ampicillin	≤8		≥16	Amox, amox/clav, amp/sulbact	None specified
EUCAST ampicillin, amox, amp/sul or amox/clav	≤4	8	≥16	Amp infers amox but not others	All BPs pertain to parenteral administration except when treating UTI

- **History**
  - Pre-1980: S≤8, R≥32 with no information regarding rationale for selecting these BPs
  - 1987: Change of "S" to "MS" (moderately susceptible) and MS ≤8, R≥16. No rationale for changing the "R" BP
  - Pre-1990: (M100-S4): S≤8, R≥16
  - 1992: Language added for high dosage ampicillin combination therapy with aminoglycoside and method to test for synergy
  - PK Data were reviewed. Conclusions were:
    - Oral & IV ampicillin 500 mg q 6hrs has 0% target attainment for BP of 8, using 30% fT>MIC
    - Variability of 2g IV PK studies, but all three support minimum dosages of 2g Q4 hrs to 2g q 6 hrs for TA of 30% fT>MIC for BP of 8
    - Dosages as low as ampicillin 0.5 g q 6h have high likelihood of target attainment for uncomplicated enterococcal UTI
- **Conclusions from clinical data were:**
  - Oral ampicillin at conventional dosages will not achieve sufficient exposure for the treatment of systemic enterococcal infections
  - Parenteral ampicillin at dosages of 2g every 4 to 6 hrs likely to achieve adequate target attainment
  - Current breakpoint is acceptable, but should include warning that oral ampicillin treatment should be confined to uncomplicated UTI
- **The WG suggested and approved the following for *Enterococcus*:**
  - Retain the current BP
  - Revise comments in Table 2D
  - Current (revisions in red): Rx Combination therapy with high dosage parenteral ampicillin, amoxicillin, or penicillin …
  - New: Breakpoints for oral ampicillin and amoxicillin apply only to treatment of uncomplicated UTI and are based on dosage of oral ampicillin 500 mg q 6 h or oral amoxicillin 250 mg q 8 h or 500 mg q 12 h.
- **SC Discussion**
  - **Question:** Should these particular oral ampicillin BPs only apply to uncomplicated UTIs? It was noted that higher BPs have been used successfully. **Answer**: The available data supports this BP.
  - It was noted that there are publications and clinical data showing good efficacy with MICs as high at 512 if it's a UTI. (https://pubmed.ncbi.nlm.nih.gov/28666756/; https://journals.asm.org/doi/full/10.1128/AAC.01817-15; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6363309/)
  - **Question:** Why are there no "I" BPs? **Answer:** There is no historical data for an "I" category.
  - Setting a urine-only BP may be discussed in the future.
  - **Question:** Clarification was requested for the 2nd sentence in the new comment regarding uncomplicated UTIs. **Answer:** The statement is to explain that the oral ampicillin and oral amoxicillin should only be applied to those infections but not to other types of infections.

A motion to approve the suggested changes to Table 2D for ampicillin including a revised comment and a new comment: (Revised) "Rx Combination therapy with high dosage parenteral ampicillin, amoxicillin, penicillin …" and (New) "Breakpoints for ampicillin apply to parenteral ampicillin dosage of 2g q 4-6 h or parenteral amoxicillin 1-2g q 6 h. Breakpoints for oral ampicillin or oral amoxicillin apply only to treatment of uncomplicated UTIs" was made (M. Satlin) and seconded (M. Satlin). Vote: 11 for, 0 against, 1 abstain, 1 absent (Pass).

- **Ampicillin and amoxicillin-clavulanate for *Haemophilus influenzae***
  - Current CLSI and EUCAST BPs

Table	Organism	Ampicillin	Amoxicillin	Amox/clavulanate	Amp/Sulbactam
CLSI	*H. influenzae, H.parainfluenzae*	1/2/4 (to be presented)	amp surrogate	4/8 (to be presented)	S ≤2/1 R≥ 4/2 (Presented Feb 2021, no Δ bp, dosage specified 3g q 6 to 8 h)
EUCAST	*H. influenzae, (H. parainfluenzae)*	1/2 IV*** (No meningitis BP)	2/4 IV; 0.001/4 PO	2/4 IV***; 0.001/4 PO (No meningitis BP)	S ≤1 R≥ 2 IV

  - **History:** Ampicillin and Amoxicillin-clavulanate BPs for *H. influenzae*
    - ≤1980: Ampicillin S≤2, R≥4 (no rationale available)
    - 1987: Ampicillin no change, Amox-clav susceptible only ≤4 (no rationale but may be based on population distribution)
    - 1988 to 1992: Ampicillin changed S≤1, R≥4. Amox clav R≥8 (no rationale available)
    - 1992 to present – no additional changes
    - Before 2006, M100 tables specified *Haemophilus* spp.; After 2006, species specified (*H. influenzae* and *parainfluenzae*)
    - The PK/PD data is very old and there was limited clinical data available.
  - **Ampicillin**
    - BP appears to be correct for *H. influenzae* pneumonia
    - Limited clinical data for MIC of 1 and most data is for MIC of 0.5
    - There is no clinical or animal data for *H. parainfluenzae*. It was suggested that *H. parainfluenzae* belongs in M45.
    - The WG suggested retaining the BP but add a dosage comment: "The dosage correlating with this breakpoint for meningitis is 2g IV given every 4 hrs."

A motion to approve the dosage comment for ampicillin: "The dosage correlating with this breakpoint for meningitis is 2g IV given every 4 hrs was made (T. Kirn) and seconded (A. Mathers). Vote: 11 for, 0 against, 1 abstain, 1 absent (Pass).

  - **Amoxicillin-clavulanate**
    - MIC affected by β-lactamase
      - MIC and effective clinical activity depend on both amoxicillin and clavulanate concentrations
      - Minimal concentration of clavulanate that inhibits the β-lactamase depends on the concentration of amoxicillin and differs according to amoxicillin concentration and bacterium
      - β-lactamase (+) *H. influenzae* minimum effective clavulanate concentration ≈0.125 mg/L; Enterobacterales minimum effective clavulanate concentration ≈0.5 mg/L
      - %fT>effect clavulanate concentration ≥ ≈20
    - Clinical data doesn't appear to provide any signal for treatment failure
    - WG Conclusions
      - Amoxicillin-clavulanate BP is too high based on population PK data for oral dosing of doses ≤ 875/125g q8 hrs
      - Lowering breakpoint to S ≤2 will be at the ECV.
      - Clinical trials show efficacy in pneumonia of 875/125g bid or tid, but MIC reports available show MICs ≤1
      - No clinical or animal data for *H. parainfluenzae*. It was suggested that this should really be in M45.

	○ **WG Suggestions** ▪ Change the current **BP to S ≤2/1, I=4/2, R ≥8/4** and add comment for the associated dosage; "Breakpoint based on oral dosage 875/125 mg q 12 h ▪ Use an "I" category to allow for higher dosage with 2000/125XR q 12h orally and parenteral therapy with IV formulation ▪ Will require the determination of zone size disk correlated for MIC BP change. ▪ Original data is available and a more recent study is in process. ○ **SC Discussion** ▪ The disk correlate data will be reviewed off-line and voted on at a later date. ▪ It was noted that there are other MIC BPs that don't have disk correlates.
	Adjournment (Dr. Lewis) Dr. Lewis thanked the participants for their time and attention. The meeting was adjourned at 6:00 PM Eastern (US) time.

2021 SUMMER AST MEETING SUMMARY MINUTES PLENARY 3: TUESDAY, 8 JUNE 2021 – 12:00 – 3:00 PM EASTERN (US) TIME	
Item #	**Description**
	GEORGE ELIOPOULOS RETIREMENT Dr. Lewis announced the retirement of Dr. George Eliopoulos. He noted some of Dr. Eliopoulos accomplishments. • Dr. Eliopoulos has been an active member of the AST Subcommittee since at least 1995. • He was the lead author on the second edition of M23, has been active on a variety of WGs, and Co-Chaired the BPWG for many years. • He was awarded the CLSI Excellence in Standards Development in 2019. Dr. Lewis and Dr. Weinstein expressed their gratitude to Dr. Eliopoulos for his wisdom, expertise, clinical judgement, and dedication to CLSI. Meeting participants added their well-wishes to the chat. Dr. Eliopoulos thanked everyone for their greetings and was happy to see the new volunteers following in his footsteps.
9.	**METHODS APPLICATION AND INTERPRETATION WG REPORT (Dr. Kirn) (Presented on Tuesday, 8 June)** **WG Roster:** Brandi Limbago, Tom Kirn (Co-Chairholders); Kristie Johnson (Secretary); Darcie Carpenter, Steve Jenkins, Joseph Kuti, Samir Patel, Virginia Pierce, Sandra Richter, Susan Sharp, Trish Simner **Intermediate^ (I^)** • The I^ definition is confusing to users and only applies to drugs that accumulate in urine. • The MAIWG agreed that the information is useful but needs to be presented more clearly. The WG recommended that the definition be revised to clarify that I^ is informational only and laboratories should consult with the infectious diseases and antimicrobial stewardship groups. • Two options for revised wording in the Overview of Changes was presented. – **Option 1: NOTE:** An I with a "^" in Tables 2 indicates agents that have the potential to concentrate in the urine. The I^ is for informational use only. Thus, the necessity (alternate: decision) to report I^ for patient care is a decision best made by each laboratory based on institution-specific guidelines in consultation with the infectious diseases and pharmacy practitioners, the pharmacy and therapeutics and infection prevention committee of the medical staff and/or the antimicrobial stewardship team. – **Option 2: NOTE:** An I with a "^" in Tables 2 indicates agents that have the potential to concentrate in the urine. The I^ is for informational use only. The decision to report I^ is best made by each laboratory based on institution-specific guidelines and in consultation with appropriate medical personnel. • The same options were presented for the general comments section of Tables 2 where I^ is used. • **SC Discussion** – It was suggested to keep the language (either version) consistent where used in M100. – There was concern that accumulation in the urine doesn't distinguish between kidney and bladder urine. Since the comment steers users to consult with infectious diseases, this issue should be covered. – It was noted that M39 incorporated information on I^ that might be used for M100. – It was decided that a vote was not needed for the revision of this comment.

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Item #	**Description**
	INTRINSIC RESISTANCE WG (IRWG) REPORT **AHWG Roster:** Barbara Zimmer (Chairholder); Susan Butler-Wu, Rafael Canton, German Esparza, Mark Fisher, Sandy Richter, Rosemary She, Carole Shubert (Members) **Reminder – Intrinsic resistance definition**: Intrinsic resistance is defined as inherent or innate (not acquired) antimicrobial resistance, which is reflected in wild-type antimicrobial patterns of all or almost all representatives of a species. Intrinsic resistance is so common that susceptibility testing is unnecessary. ***Hafnia alvei* and Colistin/Polymyxin B** • This issue was raised in 2019 because EUCAST considers *Hafnia alvei* as resistant to colistin and polymyxin B while CLSI does not. – The IRWG considered harmonizing with EUCAST. – Two publications were reviewed but the data was not strong enough for the IRWG to consider and preferred to collect more data before making any recommendations to the MAIWG and SC. – Primary study reviewed: Jayol A et al. J Antimicrob Chemother. 2017; 72: 2507- 2511. – Additional data was needed to make a decision • A study performed at Massachusetts General Hospital (MGH) (Virginia Pierce in collaboration with Sarah Turbett [MGH] Ryan Bronson, Colin Worby, Ashlee Earl (Broad Institute Bacterial Genomics Group) was reviewed. – 119 total isolates of *H. alvei* from US international travelers and MGH clinical specimens – All identified by MALDI-TOF and phenotypic automated methods with 96 identified by whole genome sequencing. – AST performed for colistin using BMD – The modal MIC was used for analysis. – ID Results o Phenotypic IDs: *H. alvei*, *H. paralvei*, *H. alvei*/*H. paralvei* split, *Obesumbacterium proteus*, Novel *Hafniaceae* spp. o MALDI-TOF MS: *H. alvei*/*O. proteus* split, *H. alvei*/*H. paralvei*/*O. proteus* split, *O. proteus*, Novel *Hafniaceae* spp. o Whole genome sequencing showed the isolates were not clonal. – AST Results o Traveler isolates all tested as resistant o Clinical isolates all test as resistant except 2 – Study conclusions o MGH routine ID methods were unable to consistently distinguish between *H. alvei*, *H. paralvei,* and *O. proteus*. o 98.3% of the *Hafniaceae* isolates had colistin MICs ≥ 4 µg/mL o MIC distributions for both traveler and clinical isolates were similar o Mean modal colistin MIC was 8.3 µg/mL for *H. alvei* and 5.6 µg/mL for *H. paralvei*. o MIC Distributions were similar to the Sentry *Hafnia* spp. and EUCAST *H. alvei* distributions.

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Item #	**Description**
	○ The genetic diversity among study isolates did not suggest a small number of resistant clones. • **IRWG Proposal** – In Appendix B, add an "R" to colistin/polymyxin B for *H. alvei*. It was noted that the R could also apply to *H. paralvei* but would require confirmation for the other agents in the row. – **MAIWG Vote:** Include colistin IR for *H. alvei* along with a footnote indicating that this also applies to *H. paralvei* (Approved 8-0-0-3) • **SC Discussion** – It was questioned if it was considered to include the two isolates with susceptible isolates as these would not be IR. It was discussed if IR had to be 100% resistant or the vast majority and it was concluded that it only had to be the vast majority. – It was noted that in M100 Appendix B that with IR, a small percentage (1% to 3%) may appear susceptible due to method variation, mutation, or low levels of resistance expression.
	A motion to add colistin for *Hafnia alvei* intrinsic resistance with footnote regarding *Hafnia paralvei* in Appendix B was made (A. Mathers) and seconded (S. Sharp). Vote: 11 for, 0 against, 1 abstain, 1 absent (Pass).
	ANAEROBE AHWG REPORT **AHWG Roster:** Darcie Carpenter (Chairholder); Karen Anderson (retiring), Marc-Christin Domingo (new), Joanne Dzink-Fox, Meredith Hackel, Steve Jenkins, Cindy Knapp, Laura Koeth, Audrey Schuetz, Samantha Shannon (members) • Summary of Discussions – Metronidazole: Plan to present new data at the January 2022 meeting. – Working on identifying QC organisms for fidaxomin – Working on an update to Appendix D antibiogram – Plan to work with EUCAST on disk testing – M56 (*Principles and Procedures for Detection of Anaerobes in Clinical Specimens*) revision in progress: Darcie Carpenter and Audrey Schuetz are Co-Chairholders of the document development committee. **ONGOING MAIWG PROJECTS** • Progress in resolving contradictions between M100 and IDSA guidance regarding ESBLs. Planning to create an AHWG to review and revise Appendix H as well as current statements throughout M100 regarding testing and reporting of carbapenemases only (maybe other ESBLs later) and make recommendations for revision (if deemed necessary). • *Burkholderia* AHWG: Draft manuscript on *Burkholderia* available. Data will be presented at the next meeting. • It was suggested that the WG consider discussing the issue of AmpC resistance at the next meeting.

Item #	Description
10.	**BREAKPOINT WG REPORT – PARTS 2 AND 3 (Dr. Mathers/Dr. Satlin)** WG Roster: See Plenary 2

PIPERACILLIN-TAZOBACTAM AHWG REPORT

AHWG Roster: Pranita Tamma, Romney Humphries (Co-Chairholders); Patrick Harris, Amy Mathers, Eric Wenzler (Members).

- The AHWG was formed to investigate whether piperacillin-tazobactam (PTZ) breakpoints for the Enterobacterales need to be revised.
  - The current CLSI BPs were published in 1992.
  - M23 criteria have been met for a revision: Clinical signal, updated PK/PD, modern day use changes and emerging resistance.

- Current PTZ BPs (tazobactam fixed at 4 µg/mL)

	Susceptible (µg/mL)	Intermediate (µg/mL)	Resistant (µg/mL)
CLSI	≤16	32 – 64	≥128
FDA	≤16	32 – 64	≥128
EUCAST	≤8	–	>8

- Primary concerns
  - Clinical laboratory AST method data resulted in very major errors (VME) compared to reference broth microdilution (BMD)
  - Clinical data: Patients infected with Enterobacterales that have PTZ MICs >16 have higher 30-day mortality than those with MICs <16
  - Modern PK/PD data suggest low PTA using package label does if the MIC ≥16

- FDA approved Dosing

Renal function (creatinine clearance, mL/min)	All Indications (except nosocomial pneumonia)	Nosocomial pneumonia
>40 mL/min	3.375g q6h	4.5g q6h
20-40 mL/min	2.25g q6h	3.375g q6h
<20 mL/min	2.25g q8h	2.25g q6h
Hemodialysis, peritoneal dialysis	2.25g q12h	2.25g q8h

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- Commonly used PTZ dosages are lower than anticipated (infusion time unknown)

- **Accuracy of PTZ MICs: Testing issues with commercial platforms**
  - Clinical data derived from the Merino trial
    - Randomized clinical trial on the effect of PTZ vs Meropenem on 30-day mortality for patients infected with *E. coli* for *K. pneumoniae* bloodstream infections and ceftriaxone resistance
    - 30-day mortality was higher with the PTZ group (12%) than with the meropenem group (4%)
    - BMD: 94% within range (≤16 µg/mL)
    - Overall essential agreement between Vitek 2 and BMD was 87%. Of the 18 PTZ resistant isolates by BMD, 12 were considered susceptible by local Vitek 2
    - Disk correlates: 44% VME
  - Other studies showed that commercial panels had been reformulated in the past to correct errors
  - BMD showed better reproducibility
  - Whole genome sequencing (WGS) of bloodstream isolates:
    - Isolates exhibited various ß-lactamase genes
    - Isolates with OXA plus ESBL genes had higher modal PTZ MICs vs ESBL alone (8 µg/mL vs 2 µg/mL; P < .001)
  - Summary
    - There are issues with PTZ MICs by non-reference BMD methods used in laboratories.
    - Appears to be partly related to co-production of ESBL genes and bla_{OXA-1} genes which increase the PTZ MIC
    - Vitek2, ETEST, and BMD studies in controlled environments show reasonable validity and reproducibility, including in isolates with ESBL genes and bla_{OXA-1}
    - ECOFF for PTZ and *E. coli* and *K. pneumoniae* is 8µg/mL
- **Clinical Signal: Increased mortality with MICs >16 µg/mL**
  - Review of multiple published clinical studies showed the same mortality rates
  - Clinical data indicate that PTZ MIC cutoff of >16 µg/mL associated with increased 30-day mortality
  - Using current CLSI resistance criteria of ≥128 µg/mL, clinical outcomes data suggest lowering the resistance criteria might improve patient outcomes
- **Low PTA with package-insert compliant dosing with PTZ MIC ≥16 µg/mL**
  - Data from multiple PK/PD studies were reviewed.
    - Initial studies (pre-2006) evaluating only PK (± estimating subject-level %fT>MIC) after intermittent infusions of ≤1 hour primarily in healthy volunteers with normal renal function (CrCl ≤120 mL/min) suggest:
      - 3.375g q6h or 4.5g q8h over 30 min adequate for MIC ≤8 µg/mL
      - 3.375g q4h or 4.5g q6h over 30 min adequate for MIC ≤16 µg/mL
    - Later studies (2004-onward) using popPK and/or Monte-Carlo simulation and evaluating intermittent and/or extended infusions of 3-4 hrs primarily in patients with normal renal function (CrCl ≤120 mL/min) suggest:

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- 3.375g q6h or 4.5g q6h over 30 min. adequate for MIC ≤8 µg/mL
- 3.375g q8h over 4h or 4.5g Q8h over 4h adequate for MIC ≤8 µg/mL
- 4.5g q8h over 4h or 4.5g q6h over 3h adequate for MIC ≤16 µg/mL

  - No study suggests an MIC >16 µg/mL is achievable with normal renal function (CrCl >40 mL/min) regardless of dose or infusion

- **Summary data for BP change**
  - ECV for *E. coli* and *K. pneumoniae* is 8 µg/mL
  - Nonclinical PK-PD cutoff: Extensive new data using modern day methods reviewed showed that an MIC >16 µg/mL is not achievable using standard dosing.
  - Clinical exposure-response cutoff data: N/A
  - Clinical cutoff: Mortality increase seen >16 µg/mL

- **AHWG Proposal (unanimous)**

	Susceptible µg/mL	Susceptible Dose-dependent µg/mL	Resistant µg/mL
CLSI	≤16	32 – 64	≥128
FDA	≤16	32 – 64	≥128
EUCAST	≤8	–	>8
Proposal	**≤8 (Based on FDA dosing)**	**16 (Based on a dose of 4.5 grams q6h as a 3-hr infusion or 4.5 grams q8h as a 4-hr infusion, assuming normal renal function)**	**≥32**

  - **BPWG Discussion**
    - Agreed that the PK/PD and clinical data is fairly strong
    - Discussed the use of and SDD vs I category based on both technical variability and dosing change
    - Change will greatly affect both labs and manufacturers, and a rationale document was recommended
    - There was debate regarding the infusion comment
    - Testing variability is primarily related to non-BMD methods and there are issues with the disk correlates
    - Disk correlates need to be reviewed and the sponsors need to be notified (**NOTE:** Both the original sponsor [now Pfizer] and primary generic manufacturers have been notified by email by CLSI staff.)
    - The BPWG approved the AHWG proposal: 10-0-1-1
  - A preliminary review of the disk correlate data was provided and will be needed for the MIC change. More detailed data to be reviewed in more detail at Plenary 4.

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Item #	**Description**
	• **SC Discussion (Decisions will be contingent upon the review of the disk correlates at Plenary 4)** – It was noted that piperacillin alone also needs to be addressed. A comment about this discrepancy may be added to address. – It was noted that piperacillin is not available in the US or S. America. It is available in some European countries. – It was questioned if these BPs apply to all Enterobacterales or just *E. coli*. In the Merino trial, cure rates in both arms were high for 30 minute infusion but the severity rating may have been lower. 30-minute infusion of 4.5 g may not cover more severe infections. – Treating *Enterobacter* with PTZ may be problematic but the WG did not look closely at the data for *Enterobacter*. – It was recommended that an SDD BP would work well for this agent. Extended infusions in severely ill patients is best when the MIC is not yet known. Education is going to be needed. – It was noted that 3-5% of isolates in the US have BPs for 16 which would change the interpretation from S to SDD. **A motion to accept the revised Piperacillin-Tazobactam BPs for Enterobacterales as ≤8 (S), 16 (SDD), and ≥ 32 (R) with the comment "Based on a dose of 4.5 grams q6h administered as a 3-hr infusion or 4.5 grams q8h administered as a 4-hr infusion" (FDA and "assuming normal renal function" removed) and with piperacillin alone being reassessed comment was made (H. Gold) and seconded (T. Simner). Vote: 11-0-1-1 (Pass).** – **NOTE:** This decision is contingent on the disk correlate review during Plenary 4. – It was questioned if the data for piperacillin alone will be available for a decision at the next plenary. There is limited MIC distribution data for modern isolates with piperacillin. – It was suggested that any data regarding the disk correlates or piperacillin alone is available should be provided for review before Plenary 4. **Amoxicillin-Clavulanate BPs for *H. influenzae* (data for vote revisited)** • WG Proposal (Approved by BPWG) – Change current BP to S ≤2/1, I =4/2, R ≥8/4 – Add comment (8C): "Breakpoint is based on a dose of either 875/125 mg q12h or 500/125 mg q8h given orally." – **NOTE:** This decision is contingent on the disk correlate review during Plenary 4. • **SC Discussion**: No discussion was needed **A motion to accept the revised amoxicillin-clavulanate BPs for *H. influenzae* as S ≤2/1, I =4/2, R ≥8/4 with dosing comment (Breakpoint is based on a dose of either 875/125 mg q12h or 500/125 mg q8h given orally) contingent upon review of disk correlates was made (B. Limbago) and seconded (S. Sharp). Vote: 12 for; 0 against; 0 abstain; 1 absent (Pass).** **Ceftolozane-tazobactam Disk BPs** • Introduction – Ceftolozane-tazobactam recently FDA approved for the treatment of HABP/VABP but FDA and CLSI MIC BPs were not changed – FDA disk zone BPs were shifted down 1 mm for Enterobacterales only. Resulted in a decreased VME and mE between BMD MICs and disk zones

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- Sponsor requests that CLSI disk BPs be updated to match the FDA
- There were no changes to the BPs for *P. aeruginosa*.
- New FDA disk BPs for Enterobacterales: **≥22/21-19/≤18 mm**
- Current CLSI disk BPs for Enterobacterales: **≥21/20-18/≤17 mm**

- Conclusions from the presented HABP/VABP study data
  - The ceftolozane-tazobactam FDA disk BP (1 mm shift compared to CLSI) for Enterobacterales decreased the number of VME and mEs. The main cause for errors were *K. pneumoniae* isolates with OmpK35 disruption.
  - Proposal for ceftolozane-tazobactam disk BP revisions for Enterobacterales (BPWG approved)
- SC Discussion: No discussion was needed.

Breakpoint type	Current CLSI DD breakpoints for Enterobacterales (S / I / R)	Proposed: FDA DD breakpoints for Enterobacterales (S / I / R)
Disk diffusion (mm)	≥21 / 18-20 / ≤17	≥22 / 19-21 / ≤18
MIC (µg/mL)	≤2-4 / 4-4 / ≥8-4	≤2-4 / 4-4 / ≥8-4

A motion to approve the FDA ceftolozane-tazobactam disk breakpoints for Enterobacterales (≥22 S/ 19-21 I/ ≤18 R) was made (B. Limbago) and seconded (T. Simner). Vote: 11 for; 0 against; 1 abstain; 1 absent (Pass)

Ceftolozane-tazobactam Dosing Comment

- Proposal to revise the current dosing comment for Enterobacterales, *P. aeruginosa*, *H. influenzae*, and *H. parainfluenzae* as causes of pneumonia.
  - **Current comment:** "Breakpoints are based on a dosage regimen of 1.5 g administered every 8 h".
  - **Proposed new comment:** "Breakpoints are based on a dosage of 3 g administered every 8 h for pneumonia and 1.5 g administered every 8 h for other indications".

- BPWG Discussion and Decisions
  - Vote to change comment for *H. influenzae* (no breakpoint for H. *parainfluenzae*): S-only MIC breakpoint of ≤0.5 µg/mL
    - **Proposed comment**: "Breakpoints are based on a dosage regimen of 3 g administered every 8 hours"
    - **Passed:** Yes (10), No (0), Abstain (1), Absent (1)
  - Vote for Enterobacterales and *P. aeruginosa*
    - **Proposed comment**: "Breakpoints are based on a dosage regimen of 3 g administered every 8 h for pneumonia and 1.5 g administered every 8 h for other indications.
    - **Passed:** Yes (10), No (0), Abstain (1), Absent (1)

2021 SUMMER AST MEETING SUMMARY MINUTES PLENARY 3: TUESDAY, 8 JUNE 2021 – 12:00 – 3:00 PM EASTERN (US) TIME	
Item #	**Description**
	• SC Discussion: No discussion was needed. **A motion to approve the proposed ceftolozane-tazobactam dosing comment (Breakpoints are based on a dosage regimen of 3 g administered every 8 hours) for *H. influenzae* was made (S. Sharp) and seconded (B. Limbago). Vote: 11 for; 0 against; 2 abstain; 0 absent (Pass).** **A motion to approve the proposed ceftolozane-tazobactam dosing comment (Breakpoints are based on a dosage regimen of 3 g administered every 8 h for pneumonia and 1.5 g administered every 8 h for other indications) for Enterobacterales and *P. aeruginosa* was made (H. Gold) and seconded (R. Humphries). Vote: 11 for; 0 against; 2 abstain; 0 absent (Pass)** **PLAZOMICIN AHWG REPORT** • Plazomicin AHWG provided feedback of their BP proposal to the sponsor. Sponsor is working on preparing a revised presentation for January 2022. • Discussed a potential review of aminoglycoside BPs as a class and publish any revisions along with new plazomicin BPs. The WG will follow M23 guidelines and discuss with sponsors. • SC Discussion – It was noted that it may be difficult to find older data for the aminoglycosides. It does appear that there is some PK/PD data and some clinical outcome data. **FINAL A4 WG DISCUSSION** • It was questioned if BPs for ampicillin-sulbactam vs. *Acinetobacter* should be reassessed. The WG thought this might be out of scope for the A4 AHWG because it is based on sulbactam, not an A4 drug. • ß-lactamase inhibitor disk content and ratio for MIC testing (ie, fixed inhibitor vs fixed ratio). • It was questioned if *H. parainfluenzae* should be moved to M45 considering all the data is from *H. influenzae*. • Work is being done to evaluate *Haemophilus* disk correlates for amoxicillin-clavulanate. • SC Discussion – It was noted that the M45 WG would be meeting soon to discuss the revision of M45 and *H. parainfluenzae* discussion can start there. The other non-Enterobacterales will be discussed as well. – It was suggested that *Acinetobacter* does need to be reassessed and the ampicillin-sulbactam should also be reviewed.
	Adjournment (Dr. Lewis): The meeting was adjourned at 3:10 PM Eastern (US) time.

Item #	Description
11.	**BREAKPOINT WG REPORT – PART 4 (Dr. Mathers/Dr. Satlin)** **WG Roster:** See list under Plenary 2 **Piperacillin-tazobactam Disk Correlates** • During the piperacillin-tazobactam report, it was noted that disk correlates were needed to support the MIC BP revision. • Disk correlate data were presented and included: – Original 1992 clinical trial data from isolates with less resistance (622 total) – Data from 2004 provided by IHMA for 632 isolates including ESBL-positive *E. coli*, *K. pneumoniae*, and *Enterobacter* spp. – Manual analysis of combined data showed BPs of ≥25 mm / 22-24 mm/≤21mm with VMEs of 2.2%. This is 0.2% outside M23 acceptable limits for the error-rate bound method. – dBets analysis of combined data showed BPs of ≥19 mm / 20-22 mm/≤21mm with VMEs of 6% and mEs of 27.8%. It was noted that the 2 mm intermediate zone is problematic and errors are unacceptable. – Alternatives for all combined data included consideration for BPs of ≥24 mm / 21-23 mm/≤20 with 4.9% VME and 10.8% mEs or BPs of ≥25 mm / 21-24 mm/≤20 mm with 2.2% VME and 13.4% mE. – The results of the manual analysis was considered to be the best option (BPs of ≥25 mm / 22-24 mm/≤21mm). • SC Discussion – It was suggested that these should be considered as provisional and that the disk content needs to be reassessed. – Concern was raised about the narrow intermediate zone (2 mm). – Since the DD zones need to correlate with the new MIC BPs and the new MIC BPs are a critical need, the DD BPs should be approved and work continue on the disk. – It was noted that occasionally the AST SC has strayed from the normal errors rates (based on M23) when it is necessary. **A motion to approve proposed disk correlates of S ≥25 mm/ I 21-24 mm/R ≤20 mm (2.2% VME and 13.4% mE) was made (T. Simner) and seconded (B. Limbago). Vote: 10 for; 2 against; 0 abstain; 1 absent (Pass).** – Votes against were related to the absence of a cautionary comment. **Electronic votes will be distributed for the following:** • Reassessment of Aminoglycoside BPs • Amoxicillin-clavulanate disk correlates for *H. influenzae*
12.	**JOINT CLSI-EUCAST WG REPORT (Ms. Hindler/Dr. Matuschek)** **WG Roster:** Janet Hindler, Erika Matuschek (Co-Chairholders); Mariana Castanheira, Sharon Cullen, Christian Giske, Gunnar Kahlmeter, Laura Koeth, Maria Traczewski, John Turnidge, Mandy Wootton **Process Protocol for Developing Harmonized Disk Content** • The process protocol for submitting and approving disk content was reviewed and a vote was requested. – The process for sponsors to submit disk data for review was presented in January 2021 and was recently distributed by email for review.

Item #	Description
	– The plan is to add the process protocol to M23S (*Procedure for Optimizing Disk Contents [Potencies] for Disk Diffusion Testing of Antimicrobial Agents Using Harmonized CLSI and EUCAST Criteria*).
	NOTE: Since this information is needed in the near future and M23, 2nd edition can likely not publish until 2022, this protocol will be published as a 2nd supplement to M23 (M23S-2) and will be incorporated into M23S during its next revision.
	• Protocol summary – Sponsor contacts the Joint WG and submits Phase 1 data. Data required for submission to the WG is listed in Attachment A of the protocol. – A group of four WG members (2 each from CLSI and EUCAST) review the data and work with the sponsor. – Data accepted by the small group is sent to the full Joint WG for review. If accepted, the WG instructs the sponsor to proceed to Phase II. If the data are unacceptable, the small group works with the sponsor until the data are approved and work moves to Phase II. – Phase II data is reviewed in the same manner as Phase I data until it is accepted by the full Joint WG. – The Joint WG reports on the completed Phase II work to the AST SC (informational). The Joint WG decision is final. – A series of questions and answers will also be included with the protocol. • SC Discussion – Dr. Matuschek noted that EUCAST has approved the SOP. – It was noted that the same process could be used to reassess older disk contents (potencies) but more discussion is needed for looking at older drugs.
	A motion to approve the addition of recommended process protocol for sponsors to work with the Joint CLSI-EUCAST WG for setting disk content (potency) to M23S was made (S. Cullen) and seconded (T. Mazzulli). Vote: 13 for, 0 against, 0 abstain, 0 absent.
	<u>Harmonization of QC between CLSI and EUCAST</u> • The Joint CLSI-EUCAST WG has been working to harmonize QC between the two organizations. Discussions have been ongoing regarding the information need to harmonize ranges included: – Amount of data needed (number results, laboratories etc) and method for selecting QC range (statistical applications or other) – Criteria for identification and elimination of outlying data – Establishing target, media, and/or mode criteria, acceptable QC range, and when such additional criteria might be used – Additional measures to ensure DD "quality" (eg, MHA) – Differences between CLSI and EUCAST QC strains, disk contents (potencies), and processes for establishing QC ranges – Challenges in setting ranges when different media and/or manufacturers are used. • Future Plans – Start with harmonization of QC ranges for new agents. Existing ranges will be discussed later – Aim to harmonize QC processes and work with the best practices for both groups. – The plan is to begin with a more comprehensive Tier 1 protocol and to investigate possible media differences before starting a Tier 2 study – An Ad Hoc WG led by Sharon Cullen will be formed to work on the details and will report to the Joint CLSI-EUCAST WG and QCWG.

Item #	Description
13.	**TEXT AND TABLES WG REPORT (Dr. Bobenchik/Dr. Campeau)** **WG Roster:** April Bobenchik, Shelley Campeau (Co-Chairholders); Carey-Ann Burnham (Secretary); Suki Chandrasekaran, Nicolynn Cole, Andrea Ferrell, Janet Hindler, Melissa Jones (retiring), Jean Patel, Barth Reller, Felicia Rice, Flavia Rossi, Dale Schwab, Maria Traczewski, Nancy Watz (Members); Darcie Carpenter (MAIWG), Sandy Richter, Barbara Zimmer (MDSWG) (Liaisons) **Cefiderocol Comment Edits** • ***S. maltophilia* MIC and DD BP revisions and comments** – SC voted to add a comment regarding the origin of the susceptible-only MIC BP – **Suggested comment revision (new in red):** Breakpoints are based on a dosage regimen of 2 g every 8 h administered over 3 h. Breakpoints are based on PK/PD properties, MIC distributions, and limited clinical data. • ***Acinetobacter* spp. and DD BP revisions and comments** – SC voted to approve a comment regarding evaluation of zone sizes ≤14 mm. – **Suggested comment revision (new in red):** Breakpoints are based on a dosage regimen of 2 g every 8 h administered over 3 h. Disk diffusion zone diameters of ≤ 14 mm should not be interpreted, and an MIC test is recommended. • SC Discussion – There was discussion regarding how to word the comment regarding zone diameters ≤ 14 mm. There was concern that users will interpret "zone diameters of ≤ 14 mm" as NS (non-susceptible). It was suggested that the phrase "should not be interpreted" should be changed "should not report an interpretive category" or "should not be interpreted or reported". – It was suggested that language similar to that used for *S. pneumoniae* and oxacillin be used: "zone diameters ≤19 mm occur with penicillin-resistant, -intermediate, or certain-susceptible strains. For isolates with oxacillin zones ≤19 mm, do not report penicillin as resistant without performing an MIC test." – It was agreed that similar language should be used for *Acinetobacter* spp. (eg, For isolates with cefiderocol disk diffusion zone diameters of ≤ 14 mm, do not report cefiderocol as resistant without performing an MIC test.") – The TTWG will also consider adding a species specific comment for *Acinetobacter* since the FDA BPs for *A. baumannii* complex. – It was noted that the test/report group needs to be revised from INV for both organisms since the FDA now has BPs for cefiderocol. It was decided to address this issue off-line (**Note:** An electronic vote to place cefiderocol in Group B pending Table 1 revision has been distributed.) **Nonsceptible Definition Revision** • The TTWG discussed revising the definition of nonsusceptible for clarification. • Suggested revision to the 1st sentence: "nonsusceptible (NS) – a category used for isolates for which only a susceptible breakpoint is designated because of the absence or rare occurrence of resistant strains or because performance indicates only susceptible results are reliable. • Suggested additional text: Note 3: In rare cases, there is only a susceptible breakpoint because the test cannot reliably categorize isolates that have MICs or zone diameters beyond the susceptible breakpoint. When needed, "not susceptible" should be applied in these cases. • SC Discussion – Concern was expressed for issues related to reporting limitations with laboratory and hospital information systems. – It was suggested that a definition of "not susceptible" is also needed. The TTWG will consider the suggestion. – It was noted that the terms are too different to be combined in one definition.

Item #	Description

- It was suggested that instead of "not susceptible" in this case, a definition that conveys the actual issue (eg, testing unreliable, zone diameters not appropriate, or something else) would be more appropriate.
- Care needs to be taken to not confuse AST performance (ability to obtain accurate results) with treatment success.
- It was decided that additional discussion and clarity regarding "not susceptible" and nonsusceptible is needed.

Surrogate Testing Comments

- M100, 31st ed. includes a comment for imipenem-relebactam: "Organisms that test susceptible to imipenem are also considered susceptible to imipenem-relebactam. However, organisms that test susceptible to imipenem-relebactam cannot be assumed to be susceptible to imipenem."
- During the Winter meetings, it was discussed whether a similar comment for other single agents and combo agents would apply. It was also discussed whether the definition of "surrogate" needs to be clarified.
- TTWG Discussion
  - It was suggested to add a general comment that applies to all combination agents to the header above the combination agents in Tables 2.
  - It was suggested that the comment may not be needed since it should be intuitive, that including it with a specific drug makes better sense but that including it for all combination agents doesn't add value, and that the comment may be misleading.
  - The TTWG requested input from the BPWG and the SC on whether the comment is needed. If not, the TTWG proposed removing the comment and references to it in each table.
- SC Discussion
  - It was suggested that the comment is generally not needed except maybe in the anaerobe table. I was noted that for anaerobes, relebactam does not add anything.
  - It was noted that users need to understand that they shouldn't report the combination agent when the primary agent alone is susceptible. Retaining the comment may provide clarity.
  - It was suggested that this might be a good topic for education.
  - There was support for including the general comment at the beginning of the combination agents.

A motion to include general surrogate testing comment with ß-lactam combination agents and remove combination-specific comments was made (R. Humphries) and seconded (T. Simner). Vote: 10 for; 2 against, 0 abstain, 1 absent (Pass)

- The reasons for the negative votes included:
  - Dr. Sharp and believed that the comment is more noticeable in the comment column rather than above the ß-lactam combination agent section and preferred that it be retained there.
  - Dr. Schuetz agreed with Dr. Sharp and she noted that some laboratories may not be able to test for the primary agent without the combination agent.

Surrogate Definition

- The TTWG reviewed the current definition of "surrogate" and proposed revisions. On further review of the whole document, it was determined that the definition needs more consideration since the term is used for various applications.
- **Action Item**: TTWG will review all applications where "surrogate" is used and either expand current surrogate definition or explore creation of a new definition.

Item #	Description
	Language Regarding *Enterococcus* "low-level" Ampicillin/Penicillin Resistance • Comments submitted during draft review questioned the meaning of "low-level resistance" for ampicillin/penicillin and there were requests to edit comments in Table 3K (HLAR in *Enterococcus* spp.) • The TTWG suggested revisions to the comment: **"Strains of enterococci with ampicillin and penicillin MICs ≥ 16 µg/mL are categorized as resistant. However, enterococci with penicillin MICs ≤ 64 µg/mL or ampicillin MICs ≤ 32 µg/mL may be susceptible to synergistic killing by these penicillins in combination with gentamicin or streptomycin …(retain rest of the comment)"(TTWG approved)** • SC Discussion: No discussion was needed. **Direct Disk Blood Culture AST: Edits to Tables 2 and 3** • New tables to accommodate direct DD expansion with additional incubation times and additional BPs are being considered. Revisions to the current methods table to incorporate new incubation times and *P. aeruginosa* (depending on approvals) are also under consideration. • Options for new BP tables to be added to Table 3E (TTWG preferred Option 2) – Option 1: Uses column header to separate the 8-10 h vs 16-18 h BPs – Option 2: Uses a new column ("Incubation") to delineate 8-10 h vs 16-18 h BPs • The general comment in Tables 2 regarding using positive blood culture broth as an inoculum will be revised for those organisms and BPs that are approved. **M02/M07 Revision Update** • Council has approved the revisions of M02 and M07 • AHWG Leadership – Overall Chairholder: Barb Zimmer – M02 Vice-Chairholder: German Esparza – M07 Vice-Chairholder: Darcie Carpenter • WG members have been approved • Inaugural meeting scheduled for June 30th, 2021

Item #	Description
14.	**METHODS DEVELOPMENT AND STANDARDIZATION WG REPORT (Dr. Hardy/Dr. Zimmer)** WG Roster: Dwight Hardy, Barbara Zimmer (Co-Chairholders); Katherine Sei (Secretary); Kevin Alby, Jennifer Dien Bard, Susan Butler-Wu, Tanis Dingle, German Esparza, Laura Koeth, Ribhi Shawar **Direct Blood Cultures (BC)** **AHWG Roster:** Shelley Campeau, Audrey Schuetz (Co-Chairholders); April Bobenchik (Secretary); April Abbot, Eileen Burd, Dwight Hardy, Romney Humphries, Kristie Johnson, Tom Kirn, Niki Litchfield, Robin Patel, Susie Sharp, Lauri Thrupp, Mel Weinstein, Barbara Zimmer; Sharon Cullen, Special Advisor • Disk study overview – Five clinical sites performing disk diffusion (DD) on clinical isolates of gram-negative bacilli from positive blood culture bottles – 500 isolates total, with 45 evaluable *P. aeruginosa* – Objectives ○ Evaluate performance of direct DD test performed using positive blood culture broth and read at 16-18h of incubation ○ Evaluate performance of direct DD test performed using positive blood culture broth and read at 8-10h of incubation – A seeded study was also performed due to a limited number of certain isolates in the disk study. – The primary comparator was standard reference DD. • A study on early QC reads was performed to support antimicrobial agents approved at the winter meeting for early reads – Three QC organisms tested: *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, and *E. coli* ATCC 35218 – Standard reference method using Mueller-Hinton agar was performed – QC isolate tested depended on the specific antimicrobial agent • General QC Results – All 16-18 hr (overnight) QC readings were within acceptable limits – 8-10 hr (early) QC readings for some antimicrobials differed from 16-18 hr reads and were generally lower for the 8-10 hr reads. • General QC Conclusions – The overnight QC is acceptable and shows that components of the test are working. – Need to provide some indication that test as performed was working for early reads. • Study showed that early reads for Enterobacterales QC with aztreonam, ceftriaxone, and ceftazidime showed similar QC results. • MDSWG Proposed QC Recommendations – Perform QC according to standard DD QC procedures (per M02; eg, daily or weekly) using QC ranges in M100 Tables 4A-1 and 4A-2 to confirm quality of the testing materials and procedures. – When implementing the early read method (Direct DD method from positive blood culture broth), recommend that QC is performed with standard DD testing as per M02 but read results at 8-10 hours to validate the procedure and materials with these early read times. CLSI has established provisional QC ranges for reading DD at 8-10 hours for *E. coli* ATCC 25922. This DD QC procedure is performed mainly to validate the implementation of the new procedure but can be used periodically to reassess performance. – A footnote to be added to the early read QC table: “The QC ranges were established with disks and media from a limited number of manufacturers and are considered provisional until additional data are evaluated by CLSI and shown to meet M23 guidelines.”

Item #	Description
	• SC Discussion – The MDSWG voted to include QC for early reads to verify the procedure (9-4-1-0). Once verified, the early read QC would not have to be performed except to reassess performance. – A number of participants believed that early read QC is not needed and that the routine QC is sufficient as it tests for the conditions of the test (ie, media, disks, etc). – It was suggested to make the early read QC available but note that it is not required (for verification and quality assurance only) (QC ranges are provided for use to verify the implementation of the new method (early reads) in individual labs) – It was suggested that a reading guide would be helpful.
	A motion to recommend performing QC for the direct DD method from positive blood cultures according to standard reference methods (as per M02 as stated in the 1st bullet in the proposal) was made (B. Limbago) and seconded (A. Mathers). Vote: 13 for, 0 against, 0 abstain, 0 absent (Pass).
	A motion to provide early read QC (8-10 hr) QC ranges for *E. coli* ATCC 25922 for the direct DD method from positive blood cultures as part of the verification process, training personnel, etc. for the method (language from 2nd bullet in the proposal to be word smithed) was made (B. Limbago) and seconded (A. Schuetz). Vote: 7 for, 6 against, 0 abstain, 0 absent (Fail). • SC Discussion on 2nd motion (bullet 2) – Concern was expressed regarding if this process is sufficient to verify the performance of the test. It was noted that this would provide some information an establish ranges for verification but would not be considered a full verification. Language can be added for clarification. – The participants were reminded that early reads on some organism/agent combinations were approved at the last meeting contingent upon QC ranges for early reads and this needs consideration. – Votes against the motion were primarily due to the opinion that the early QC reads are not needed and that standard (16-18 hr) QC is sufficient. Others believed that verification should be performed using spiked blood culture bottles. – It was agreed that the recommendation will be to perform QC for the direct DD method from positive blood cultures according to standard methods as per M02 as stated in the first bullet. This would cover the early reads that have already been voted on. • An overview of a seeded study for *P. aeruginosa* was provided. – Main comparator of direct DD data is DD performed at site and DD performed at reference lab – MIC data included in presentation for background information – Zone cutoffs were assessed by applying different zone cutoffs based on direct reads vs standard DD and then examining those cutoffs vs MIC and reference DD. • **Ciprofloxacin and *P. aeruginosa* (early reads)** – Proposed early read zone cutoffs: QC was acceptable and both WGs approved

Item #	Description

Proposed new zone cutoffs (mm)		
S	I	R
≥23	18-22	≤17

- SC Discussion: No discussion was needed.

A motion to approve the early read proposed ciprofloxacin 8-10 hr (early direct DD reads) zone cutoffs (S ≥23; I 18-22; R ≤ 17) for *P. aeruginosa* was made (M. Satlin) and seconded (S. Sharp). Vote: 13 for; 0 against; 0 abstain; 0 absent (Pass).

- **Tobramycin and *P. aeruginosa* (early reads)**
  - Proposed early read zone cutoffs: QC was acceptable and both WGs approved

Proposal to accept current DD (mm)		
S	I	R
≥15	13-14	≤12

  - SC Discussion: No discussion was needed.

A motion to accept the current tobramycin zone cutoffs (S ≥15; I 13-14; R ≤ 12) for 8-10 hr (early direct DD reads) for *P. aeruginosa* was made (S. Sharp) and seconded (A. Mathers). Vote: 13 for; 0 against; 0 abstain; 0 absent (Pass).

- **Ceftazidime and *P. aeruginosa* (overnight reads: 16-18 hr)**
  - Proposed early read zone cutoffs: QC was acceptable and both WGs approved

Proposal to accept current DD (mm)		
S	I	R
≥18	15-17	≤14

  - SC Discussion

A motion to accept the current ceftazidime zone cutoffs (S ≥18; I 15-17; R ≤ 14) for 16-18 hr direct DD reads for *P. aeruginosa* was made (M. Satlin) and seconded (A. Schuetz). Vote: 11 for; 1 against; 0 abstain; 1 absent (Pass).

- Concern was raised for comparing the direct DD reads to reference DD when the original DD correlates compared to MIC are in question.
- The vote against was in regard to the previous comment.
- It was suggested that a footnote regarding poor correlation with MIC should be added.
- It was noted that the error rate is acceptable as per M23.

Item #	Description

- **Cefepime and *P. aeruginosa* (early reads)**
  - Proposed early read zone cutoffs: QC was acceptable and both WGs approved.
  - It was noted that while the comparison to standard DD, the standard DD correlates to MIC were problematic.

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

  - SC Discussion
    - Concern was raised for comparing the direct DD reads to reference DD when the original DD correlates compared to MIC are in question. There may be a signal with the original zone/MIC correlates are a problem.
    - The VME was based on only two isolates and may not be a cause for concerned.
    - It was noted that all CLSI BPs are based on MICs and the zone ranges are based on DD correlates. The SC did vote to a disk to disk comparison and not to MIC.
    - It was also noted that will always be occasional discrepancies and laboratories will need to learn to deal with it.

A motion to approve the current cefepime zone cutoffs (S ≥18; I 14-17; R ≤ 13) for 16-18 hr direct DD reads for *P. aeruginosa* was made (M. Satlin) and seconded (S. Sharp). Vote: 8 for; 5 against; 0 abstain; 0 absent (Fail).

- The votes against primarily related to concerns about the lack of correlation between zone and MIC BPs. One negative would have been changed to approve if a comment was included regarding poor correlation with MIC.
- A second motion was made but it was suggested that the term poor should be used. It was noted that the two VMEs were within one MIC dilution of intermediate and one zone size of intermediate.

A motion to accept the current cefepime zone cutoffs (S ≥18; I 14-17; R ≤ 13) for 16-18 hr direct DD reads for *P. aeruginosa* with note of caution regarding poor disk correlation (to be word smithed) with MIC was made (A. Schuetz) and seconded (S. Sharp). Vote: 7 for; 5 against; 0 abstain; 1 absent (Fail).

- The votes against were related to the previous issues.

- Options for how to present the information in M100. Text and tables will work on drafting the tables.

Tedizolid Disk Diffusion Study

- A disk diffusion method for tedizolid is being developed.
- Harmonization between CLSI and EUCAST has been attempted but has not been achieved due to the discrepant (lower) BPs obtained during studies.
- The studies are ongoing and data will be presented at the January 2022 meeting.

2021 SUMMER AST MEETING SUMMARY MINUTES PLENARY 4: THURSDAY, 17 JUNE 2021 – 10:00 AM – 1:00 PM EASTERN (US) TIME	
Item #	**Description**
	Cefazolin High Inoculum Study • PHASE 1: Assess the prevalence of CIE phenotype in MSSA isolates in contemporary US strains (Completed) • PHASE 2: Evaluate a rapid CIE assay in a multi-center study. If assay performs well, develop CLSI guidance on testing CIE in clinical laboratories. • Update Summer 2021: Positive CziE isolates from Phase 1 study have been forwarded to Cesar Arias for whole genome sequencing. • An abstract has been submitted to World Microbe Forum on Phase 1 study. **Update: Proposed study for *H. influenzae* AST using Mueller Hinton-Fastidious media (MH-F)** • The goal of the study was to compare the performance of *Haemophilus* Test Media and MH-F using BMD and DD for assessing *H. influenzae* susceptibility. • The study was postponed from 2020 due to competing priorities during the pandemic and will be performed mostly asynchronously as sites are available to do the testing. • Update Summer 2021: Testing has begun at JMI and CDC. There have been issues with shipping agar powder INS in Colombia. Preliminary data should be available to review in January 2022. **Update from the *mecA*-mediated β-Lactam Resistance AHWG (CoNS AHWG)** • Published an article about the evaluation of surrogate testing for the presence of *mecA*-mediated methicillin resistance in *S. capitis*, *S. haemolyticus*, *S. hominis*, and *S. warneri*. – Suggested a terminology change from CoNS to staphylococci other than *S. aureus* (SoSA). – Proposed a SoSA BP change for oxacillin: S ≤0.5; R ≥1 • Updates: – Studies to evaluate phenotypic methods for detecting *mecA/C*-mediated β-lactam resistance in *S. saprophyticus*. – Study to determine the prevalence of SoSA recovered from clinical specimens in North America.
	Adjournment (Dr. Lewis) Dr. Lewis expressed his gratitude to the members, advisors, reviewers, WGs, and guests for their time and attention. The meeting was adjourned at 3:15 Eastern (US) time.

Respectfully submitted,
Marcy L. Hackenbrack, MCM, M(ASCP)
Senior Project Manager

NOTE: The following AST SC Reviewers and Guests attended at least one of the four plenary sessions.

Full Name	Organization/Company Name
Allison Tsan	UCLA
Amanda Kuperus	Microbiologics
Andrea Ferrell	BD
Antonieta Jimenez	Inciensa
Beth P Goldstein	Beth Goldstein Consultant
Cecilia G. Carvalhaes	JMI Laboratories
Chris Pillar	Microbiologics
Dale A Schwab	Quest Diagnostics
Darcie Carpenter	IHMA, Inc.
Dawn Sievert	CDC
Dee Shortridge	JMI Labs
Diane Anastasiou	Paratek Pharmaceuticals
Dubraska Diaz-Campos	The Ohio State University
Elaine Duncan	Beckman Coulter
Elizabeth Palavecino	Wake Forest Baptist Health
Erika Matuschek	EUCAST Development Laboratory
Gina Ewald-Saldana	Beckman Coulter, MicroScan
Helio Sader	JMI Laboratories
James Karlowsky	Shared Health Manitoba/University of Manitoba
Jane E. Ambler, PhD	ContraFect
Jean Patel	Beckman Coulter
Jekia Cox	BD
Jennifer Boyer	BD
Jennifer Slaughter	bioMerieux, Inc.
Joseph Daniel Lutgring	Centers for Disease Control and Prevention
Karen Bush	Indiana University
Kerian Grande Roche	FDA/CDER
Larry Friedrich	Spero Therapeutics
Linda Otterson	self
Linda Schuermeyer	bioMerieux
Marcelo Fabian Galas	Pan American Health Organization
Mark Fisher	ARUP/U. of Utah
Matthew A. Wikler, MD, MBA, FIDSA	Infectious Disease Technology Development Consulting

Full Name	Organization/Company Name
Michael Huband	JMI Laboratories
Nancy Watz	Stanford Health Care
Natasha Griffin	FDA
Nicole E Scangarella-Oman	GlaxoSmithKline
Nicolynn Cole	Mayo Clinic
Nilia M Robles Hernandez	BioMerieux
Patricia Conville	FDA
Paul Edelstein	Univ Penn
Paula Snippes Vagnone	Minnesota Department of Health
Robert Bowden	Beth Israel Deaconess Medical Center
Ron Master	Quest Diagnostics
Simone Shurland	FDA-CDER
Stephanie Mitchell	Cepheid (Danaher)
Sukantha Chandrasekaran	UCLA
Susan Cusick	Venatorx Pharmaceuticals
Susan Thomson	MAST GRP
Tiffany Keepers White	Paratek
William Brasso	Consultant