Meeting Title:	**Subcommittee on Antimicrobial Susceptibility Testing (AST)**	**Contact:**	Emily Gomez egomez@clsi.org
Meeting Location:	St. Louis, Missouri, USA (with virtual live streaming)		
Meeting Dates and Times: All times are Central (US) time.	**Plenary 1:** Monday, 5 June 2023, 7:30 AM – 12:00 PM **Plenary 2:** Monday, 5 June 2023, 1:00 – 5:30 PM **Plenary 3:** Tuesday, 6 June 2023, 7:30 AM – 12:00 PM		
Meeting Purpose:	The purpose of this meeting is to review and discuss AST WG and SC business in preparation for publication of the next edition of M100 (34th).		
Requested Attendee(s):	SC Chairholder, Vice-Chairholder, Secretary, Members, Advisors, and Reviewers; Expert Panel on Microbiology Chairholder and Vice-Chairholder; Other Interested Parties; CLSI Staff		

Attendee(s):	
James S. Lewis, PharmD, FIDSA **AST** Subcommittee Chairholder	**Oregon Health and Science University**
Amy J. Mathers, MD, D(ABMM) AST Subcommittee Vice-Chairholder	**University of Virginia Medical Center**
Alexandra L. Bryson, PhD, D(ABMM) AST Subcommittee Secretary	**Virginia Commonwealth University Health**
Jean B. Patel, PhD, D(ABMM) Expert Panel on Microbiology Chairholder	**Beckman Coulter, Inc.**
Members Present:	
Sharon K. Cullen, BS, RAC	Beckman Coulter, Inc. Microbiology Business
Tanis Dingle, PhD, D(ABMM), FCCM	Alberta Precision Laboratories
Marcelo F. Galas, BSc	Pan American Health Organization
Romney M. Humphries, PhD, D(ABMM), FIDSA	Vanderbilt University Medical Center
Thomas J. Kirn, MD, PhD	Rutgers Robert Wood Johnson Medical School
Brandi Limbago, PhD	Centers for Disease Control and Prevention
Virginia M. Pierce, MD, FIDSA	University of Michigan Medical School
Sandra S. Richter, MD, D(ABMM), FIDSA	Mayo Clinic (Jacksonville, FL)
Michael Satlin, MD	Weill Cornell Medicine
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 University School of Medicine, Department of Pathology
Pranita D. Tamma, MD, MHS	John Hopkins University School of Medicine, Department of Pediatrics
Melvin P. Weinstein, MD	Robert Wood Johnson University Hospital
Advisors Present (In-person and Virtual):	
Amelia S. Bhatnagar, MPH	Centers for Disease Control and Prevention
April M. Bobenchik, PhD, D(ABMM), MT(ASCP)	Penn State Hershey Medical Center
Shelley Campeau, PhD, D(ABMM)	Scientific and Medical Affairs Consulting, LLC
Mariana Castanheira, PhD	JMI Laboratories
German Esparza, MSc	Proasecal SAS
Christian G. Giske, MD, PhD	Karolinska University Hospital
Howard Gold, MD, FIDSA	Beth Israel Deaconess Medical Center
Natasha Griffin, PhD	FDA Center for Devices and Radiological Health
Janet A. Hindler, MCLS, MT(ASCP), F(AAM)	Los Angeles County Department of Public Health
Dmitri Iarikov, MD, PhD	FDA Center for Drug Evaluation and Research
Joe Kuti, PharmD, FIDP	Hartford Hospital
Joseph D. Lutgring, MD	Centers for Disease Control and Prevention
Linda A. Miller, PhD	CMID Pharma Consulting LLC

Stephanie L. Mitchell, PhD, D(ABMM)	Cepheid, Inc.
Greg Moeck, PhD	Venatorx Pharmaceuticals, Inc.
Navaneeth Narayanan, PharmD, MPH	Rutgers University
Kiyofumi Ohkusu, PhD	Tokyo Medical University
Elizabeth Palavecino, MD	Wake Forest Baptist Medical Center
Robin Patel, MD	Mayo Clinic
Eric Wenzler, PharmD, BCPS, AAHIVP	University of Illinois at Chicago
Barbara L. Zimmer, PhD	Beckman Coulter
Reviewers and Guests (Non-SC-roster attendees): see Plenary Attendee List below	
Staff:	
Jennifer Adams, MT(ASCP), MSHA	CLSI
Katie Barnett	CLSI
Kathy Castagna, MS, MT(ASCP)CT, MB	CLSI
Emily Gomez, MS, MLS(ASCP)MB	CLSI
Barb Jones, PhD	CLSI
Christine Lam, MT(ASCP)	CLSI

Plenary Agendas

PLENARY AGENDA: Session 1 Monday, 5 June 2023 (In-person with virtual live streaming) 7:30 AM – 12:00 PM Central Standard (US) Time			
Time	**Item**	**Presenter**	**Page**
7:30 AM – 7:40 AM (10 min)	Opening Remarks	J. Lewis	7
7:40 AM – 7:50 AM (10 min)	CLSI Welcome and Update	J. Adams	7
7:50 AM – 8:00 AM (10 min)	CLSI Awards	B. Jones	8
8:00 AM – 8:10 AM (10 min)	EUCAST Update	C. Giske	8
8:10 AM – 8:40 AM (30 min)	Outreach WG	J. Hindler A. Schuetz	9
8:40 AM – 9:40 AM (1 hr)	Methods Application and Interpretation WG	T. Kirn	13
9:40 AM – 10:00 AM (20 min)	Break		
10:00 AM – 11:00 AM (1 hr)	Quality Control WG	S. Cullen C. Pillar	20
11:00 AM – 12:00 PM	Text and Tables WG	A. Bobenchik S. Campeau	35

PLENARY AGENDA: Session 2 Monday, 5 June 2023 (In-person with virtual live streaming) 1:00 PM – 5:30 PM Central Standard (US) Time			
Time	**Item**	**Presenter**	**Page**
1:00 PM – 3:00 PM (2 hr)	Breakpoints WG: Part 1	N. Narayanan M. Satlin	42
3:00 PM – 3:20 PM (20 min)	Break		
3:20 PM – 5:30 PM (2 hr)	Breakpoints WG: Part 2	N. Narayanan M. Satlin	42

PLENARY AGENDA: Session 3 Tuesday, 6 June 2023 (In-person with virtual live streaming) 7:30 AM – 12:00 PM Central Standard (US) Time			
Time	**Item**	**Presenter**	**Page**
7:30 AM – 8:00 AM (30 min)	Joint CLSI-EUCAST WG	J. Hindler	67
8:00 AM – 10:00 AM (2 hr)	Methods Development and Standardization WG	T. Dingle	71
10:00 AM – 10:20 AM (20 min)	Break		
10:20 AM – 11:20 AM (1 hr)	M45 WG	T. Simner	82
11:20 AM – 11:30 AM (10 min)	Table 1 AHWG	T. Simner	88
11:30 AM – 12:00 PM (30 min)	Disk Diffusion Reference Method Discussion	J. Hindler R. Humphries	92
12:00 PM	Closing Remarks	J. Lewis	94

Summary of Voting Decisions and Action Items

Summary of Passing Votes			
#	**Motion Made and Seconded**	**Results**[a]	**Page**[b]
1.	To remove *Burkholderia cepacia* complex disk breakpoints from M100 for all antibiotics and to add a comment stating, "Disk diffusion breakpoints were removed due to suboptimal correlation with reference broth microdilution and will be reevaluated when more data are available."	13-0-0-1	16
2.	To approve adding a comment for *Burkholderia cepacia* complex stating, "Testing should be performed using a broth microdilution or agar dilution method."	12-1-0-1	16
3.	To approve the changes in red to Table H3 for the detection of carbapenem resistance in Enterobacterales and add a comment stating "Cefepime S/SDD results should be suppressed or reported as R for isolates that demonstrate carbapenemase production (see Table H3)." to Table 2A for cefepime.	11-2-0-1	18
4.	To approve the revision of CLSI M11.	13-0-0-1	19
5.	To approve the meropenem/KSP-1007 QC ranges for *Acinetobacter baumannii* NTCC 13304 (0.5/8-4/8 µg/mL), *E. coli* ATCC 25922 (0.008/8 – 0.03/8 µg/mL), *K. pneumoniae* BAA-1705 (0.008/8 – 0.03/8 µg/mL), and *P. aeruginosa* ATCC 27853 (0.12/8 – 1/8 µg/mL).	13-0-0-1	21
6.	To approve the OMN6 QC ranges for *Acinetobacter baumannii* NTCC 13304 (4-16 µg/mL) and *E. coli* ATCC 25922 (8-32 µg/mL) pending the MDSWG approval of the modified reference method.	13-0-0-1	23
7.	To approve the Exebacase QC range for *S. aureus* ATCC 29213 (0.25-2 µg/mL) for the incubation conditions of ambient air for 16-20 hours and 5% CO2 for 20-24 hours and to add a comment stating, "QC ranges reflect MICs obtained when incubated in ambient air conditions for 16-20 hours or 5% CO2 for 20-24 hours (mode 0.5-1 µg/mL). Data with incubation for 5% CO2 and 20-24 hours was collected with limited Mueller Hinton media manufacturers."	14-0-0-0	24
8.	To delete the colistin QC range for *E. coli* ATCC 25922 (0.25-2 µg/mL), revise the colistin QC range for *P. aeruginosa* ATCC 27853 (0.25-2 µg/mL), and to add a comment stating, "If frequently at 0.25 test E. coli NCTC 13846 or *E. coli* ATCC BAA-3170."	14-0-0-0	29
9.	To revise the aztreonam QC range for *K. pneumoniae* ATCC 700603 (> 8 µg/mL).	14-0-0-0	30
10.	To revise the aztreonam QC range for *E. coli* ATCC 25922 (0.06-0.5 µg/mL).	14-0-0-0	31
11.	To approve the proposed revisions to Table 4A-2 and 5A-2 for combination beta lactams with footnote f stating, "Any one strain in green may be used for routine QC of this antimicrobial agent."	14-0-0-0	34
12.	To create a new introduction section to Tables 2 and move Appendix E to below Tables 2.	10-2-0-2	38
13.	To remove two middle columns (Breakpoints and Interpretive Categories) and revise the last column "Dose" to be "Dosage Susceptible Breakpoint Is Based On" to delineate S vs SDD in Appendix E.	12-0-0-2	38
14.	To revise *Enterococcus* footnote b in Table 1I to state "Rx: Combination therapy with high-dosage parenteral ampicillin, amoxicillin, penicillin, or vancomycin, plus an aminoglycoside, may be indicated for serious enterococcal infections, such as endocarditis, unless high-level resistance to both gentamicin and streptomycin is documented; such combinations are predicted to result in synergistic killing of enterococci. Refer to Table 3K for high-level aminoglycoside resistance testing."	13-0-0-1	39

Summary of Passing Votes			
15.	To remove *Serratia marcescens* tobramycin footnote g from Appendix B1 and have the Intrinsic Resistance Ad Hoc Working Group review.	13-0-0-1	40
16.	To accept the sulbactam-durlobactam MIC breakpoints for *Acinetobacter* spp. (S≤4/4, I 8/4, R≥16/4 µg/mL).	13-0-0-1	44
17.	To accept the sulbactam-durlobactam disk breakpoints for *Acinetobacter* spp. (S≥17, I 14-16, R≤13 mm).	13-0-0-1	44
18.	To place sulbactam-durlobactam in Table 1A tier 3.	10-3-0-1	44
19.	To not revise the trimethoprim-sulfamethoxazole MIC breakpoint for *Stenotrophomonas maltophilia* and to add a comment stating, "Trimethoprim-sulfamethoxazole should not be used alone for antimicrobial therapy."	10-3-0-1	50
20.	To accept the minocycline disk breakpoints for *Stenotrophomonas maltophilia* (S≥26, I 21-25, R≤20 mm).	11-0-0-3	56
21.	To not revise the cefepime MIC breakpoints for Enterobacterales and to add a comment stating, "The susceptible breakpoint is based on a dose of 2g Q12h or 1g Q8h and SDD is based on 2g Q8h as a 3h infusion."	13-0-0-1	59
22.	To not revise the meropenem-vaborbactam breakpoints for Enterobacterales and to add a comment to Table 2A next to meropenem-vaborbactam stating, "Enterobacterales that harbor OXA-48-family enzymes may test susceptible to meropenem-vaborbactam but may not respond to this therapy *in vivo*. If OXA-48 is detected, suppress or report as resistant."	13-0-0-1	62
23.	To accept the linezolid disk breakpoints for *Staphylococcus* spp. (S≥26, I 23-25, R≤22 mm) with reflected light.	13-0-0-1	65
24.	To move the *Salmonella* and *Shigella* breakpoints into a separate table in Table 2.	13-0-0-1	65
25.	To add the cefiderocol text, "The positive control should show strong growth in the form of a button of >2 mm or heavy turbidity. The MIC of cefiderocol is read as the first well in which the growth corresponds to a button of <1 mm or the presence of light haze/faint turbidity is observed." with corresponding pictures.	12-1-0-1	73
26.	To accept the tobramycin direct blood disk breakpoints for Enterobacterales (S≥17, I 13-16, R≤12 mm) and *P. aeruginosa* (S≥19, I 13-18, R≤12 mm) for 16-18h and 8-10h reading times.	12-0-0-2	77
27.	To accept the standard disk breakpoints for *Acinetobacter* ampicillin-sulbactam (16-18h), cefepime (16-18h and 8-10h), ceftriaxone (8-10h), ciprofloxacin (16-18h and 8-10h), meropenem (16-18h and 8-10h), tobramycin (16-18h and 8-10h), and trimethoprim-sulfamethoxazole (16-18h and 8-10h) as the direct blood disk breakpoints for the indicated reading times.	12-0-0-2	79
28.	To accept the ceftazidime direct blood disk breakpoints for *Acinetobacter* (S≥17, I 15-16, R≤14 mm) for a 16-18h reading time.	12-0-0-2	80
29.	To accept the ceftriaxone direct blood disk breakpoints for *Acinetobacter* (S≥20, I 13-19, R≤12 mm) for a 16-18h reading time.	12-0-0-2	80
30.	To accept the proposed *Neisseria meningitidis* Table 1.	10-0-0-4	89
31.	To accept the proposed combined anaerobe Table 1 with the modification of ampicillin and penicillin in tier 1 for gram-positives and ampicillin and penicillin in tier 4 for gram-negatives.	11-0-0-3	90

[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.

2023 JUNE AST MEETING SUMMARY MINUTES PLENARY 1: Monday, 5 June 2023 (In-person with virtual live streaming) 7:30 AM – 12:00 PM Central Standard (US) Time	
#	**Description**
1.	**OPENING REMARKS (J. LEWIS)** Dr. Lewis opened the meeting at 7:30 AM Central Standard (US) time by welcoming the participants to the CLSI meeting in St. Louis, Missouri. He announced Alexandra Bryson as the new AST Subcommittee Secretary.

2.	**CLSI WELCOME AND UPDATE (J. ADAMS)**
	Ms. Adams provided an update on CLSI activities. The main points included:
	• Announcement of newly published CLSI documents and resources.
	  ○ M100-33rd edition and M24S
	  ○ Micro Free website that includes M100, M45, M23, M27M44S, and the M23 supplements
	  ○ Breakpoint Implementation Toolkit
	• Thank you to the work and contributions from the AST Subcommittee volunteers.
	• Thank you to the CLSI staff.

3.	**CLSI AWARDS (B. JONES)** Dr. Jones presented CLSI awards to: • Janet Hinder – M39 Co-Chairholder • Trish Simner – M39 Co-Chairholder • Romney Humphries – MR-14 Contributions

4.	**EUCAST UPDATE (C. GISKE)**
	Dr. Giske provided an update on the activities of EUCAST. The main points included:
	• Revision of fosfomycin breakpoints
	  ○ Revision of fosfomycin MIC breakpoints for *E. coli* (S≤8 mg/L, R>8 mg/L) and *S. aureus* (S≤(32) mg/L, R>(32) mg/L) for the daily dose of at least 16g.
	  ○ Post consultation agreed that no bracketed breakpoints would be used for *S. aureus*. Instead ECOFFs will be listed for some species including *S. aureus*.
	• Completed revision of chloramphenicol MIC breakpoints for Enterobacterales, *Staphylococcus* spp., *Streptococcus* groups A, B, C, G, and *S. pneumoniae*.
	• Cephalosporins vs *S. aureus*
	  ○ New guidance document on cefotaxime and ceftriaxone for *S. aureus* infection published in January 2023.
	  ○ Recommendation is that for MSSA, susceptibility can be inferred for:
	  ▪ Cefotaxime, provided dosages of 2g x 3-4 are used
	  ▪ Ceftriaxone, provided dosages of 2g x 2 iv or 4g x 1 iv are used, and preferably only as stepdown therapy after initial response to other more established antistaphylococcal agents
	  ○ There are no specific staphylococcal breakpoints for these agents, and testing of individual isolates for clinical purposes, including MIC determination by eg, gradient diffusion, is strongly discouraged.
	• New guidance on the implementation of revised aminopenicillin breakpoints for Enterobacterales published in January 2023
	• Upcoming consultations
	  ○ Viridans group streptococci – breakpoints and MIC vs zone
	  ○ Overlook of the breakpoint tables to adapt to requirements in endocarditis (previously such breakpoints were published in national endocarditis guidelines)
	  ○ *Nocardia* spp. – AST methodology and breakpoints
	  ○ EUCAST dosing tab adapted to pediatric use
	• EUCAST Development Lab
	  ○ Investigation of alternative media for disk diffusion of fastidious organisms
	  ○ Development of a disk diffusion method for *N. gonorrhoeae*
	  ○ Investigation of alternative disks for determining the benzylpenicillin susceptibility in *Streptococcus pneumoniae* (to avoid the frequent need for MIC testing)
	  ○ Evaluation of AST methods for cefiderocol (reference BMD, disk diffusion, and commercially available)

5. **OUTREACH WORKING GROUP (A. SCHUETZ AND J. HINDLER)**

WEBINARS/PRESENTATIONS

- CLSI Annual Update (20th)
  - What's New in the 2023 CLSI Standards for Antimicrobial Susceptibility Testing (AST)?
  - April 5 and 6, 2023
  - April Bobenchik, PhD, D(ABMM) and Romney Humphries, PhD, D(ABMM)
  - >1000 registrants between the two days with 673 live attendees
- CAP-CLSI Annual Webinar
  - What's New in Susceptibility Testing of Mycobacteria?
  - May 4, 2023
  - Barbara Brown-Elliot and Marie-Claire Rowlinson, PhD, D(ABMM)
- CLSI-SIDP-ACCP Annual Webinar
  - Date TBD
  - Content: Table 1, aminoglycoside breakpoint updates, EBSL/carbapenemase updates
- CLSI Webinar
  - Aim for September 2023
  - Implementation of new AST panels introduced by manufacturers with updated breakpoints
- Attendee Orientation to Antimicrobial Subcommittees available on CLSI website and YouTube

ASM MICROBE 2023

- CLSI Tables for Antimicrobial Reporting- A New Look!
  - June 16, 2023
  - Virginia Pierce, MD
- Adoption of Antifungal ECVs into Clinical Practice
  - June 18, 2023
  - Philippe Dufresne, PhD
- ASM Microbe 2024 Topic Submission
  - Newer Antimicrobials and When to Report
  - Extent of services offered by primary laboratories for newer antimicrobials to fulfill stakeholders needs
  - Laboratory, clinical, and public health

M100 EDUCATIONAL PROGRAM

- Available on the CLSI website
- No fee
- Provides 1.5-hour CEU ($30)
- Will not be updated to 33rd edition
- Will be updated for 34th Edition (2024)

ORWG NEWS UPDATE

- June 2023 Edition
  - Feature: Aminoglycosides breakpoints
  - Case: Aminoglycosides use
  - Practice Tips: Cefiderocol testing
  - Hot Topic: Intrinsic resistance – antifungals
- News Update background information is on CLSI website in a separate page

AST SC MEETING EDUCATION SESSIONS

- June 2023
  - Standard Reference Methods for AST: Perspectives From Various Stakeholders
  - Mariana Castanheira, PhD, Jean B. Patel, PhD, and Kevin Alby, PhD
  - Will be available on-demand viewing and CE credit
- January 2024
  - Speakers from AST, Antifungal, and Veterinary Subcommittees
  - Topic suggestion: MDRO, reporting comments, and body site source reporting

PUBLICATIONS

- CLSI updates (Janet Hindler, April Bobenchik, Andrea Ferrell, April Abbott). JCM. Cover 2022 and 2023 changes.
- Point counterpoint on cascade reporting of antimicrobials. JCM.
- Mini review – use of cefazolin as a surrogate for the treatment of uncomplicated cystitis (Alexandra Bryson and Amira Bhalodi). JCM.
- CoNS updates. JCM.
- Summary of the Clin Micro Open discussion. JCM.
- Instruction for labs on how to implement breakpoints.
- AST systems (Graeme Forrest to discuss format of document). CMR.

ORWG PROJECTS

- 2023-2024 Summary Project
  - Collation of report comments helpful for laboratories
  - Some comments are FYI, some should be added to a report, some helpful to know for testing
  - Follow-up from April Abbott's past Education Session presentation Jan 2020 (Beyond SIR)
  - Collaboration with Text and Tables Working Group
  - Possible publication and a webinar
- Webinars
  - CLSI-SIDP-ACCP Annual Webinar
  - CLSI-CAP Annual Webinar
- Annual M100 Update
- Update M100 Educational program for 2024
- Mini review of M100 for JCM

- News Update second half of 2023
- Other programs
  - January 2024 AST SC meeting workshop
  - ASM Microbe 2024
- More for Breakpoint Implementation Working Group

BREAKPOINT IMPLEMENTATION AD HOC WORKING GROUP REPORT

- Goals
  - Identify needs of clinical laboratories to ensure they are using current CLSI, FDA and/or EUCAST breakpoints (BPs)
  - Provide resources to assist clinical laboratories to determine:
    - What BPs are currently used in their laboratory at the AST instrument, LIS and EHR levels
    - Which BPs require updating
    - A plan for updating BPs
  - Develop ongoing mechanism for communicating with clinical laboratories any new information about BPs.
- Meetings
  - March 2022
    - Organized as part of ORWG
  - June 2022
    - Posted BP in use template on CLSI website
    - Modify BP Additions/Revisions Table in M100 into two separate sections
    - Updating BP article in June 2022 CLSI News Update – CAP requirements
    - Workshop at AST SC Meeting
    - Updating Breakpoints - Challenges and Solutions for Various Stakeholders
  - January 2023
    - Finalize 2023 Breakpoint Implementation Toolkit (BIT) for posting
    - Review CDC FDA AR Bank status of isolates for validations
    - Revise “commercial AST system – BP” discussion in front of M100
    - Discuss proposal for CLSI validation guideline
  - June 2023
    - Launch 2023 BIT!
- Next steps
  - Post audio instructions of all BIT parts
  - Webinar in September 2023
  - Validation of disk diffusion?
  - Validation of updated BPs for gram-positives

VOLUNTEER OPPORTUNITIES

- News Update
  - Provide feedback on content, delivery, and structure

	○ Suggest content ○ Partner with others to write articles (case studies and more) • Other Publications ○ Assorted topics • Webinars / Workshops / Lectures ○ Suggest content ○ Speakers

6. **METHODS APPLICATION AND INTERPRETATION WORKING GROUP (T. KIRN)**

BURKHOLDERIA CEPACIA COMPLEX AST AD HOC WORKING GROUP REPORT

- Issues with *B. cepacia* complex (BCC) AST
  - Discrepancies in recommendations for AST:
    - EUCAST does not recommend routine AST of BCC organisms because: No evidence relating MIC and clinical outcomes in people with cystic fibrosis (CF) and poor performance of AST methods
  - The Antimicrobial Resistance in CF International Working Group does not recommend routine AST because it does not predict clinical outcomes
  - Issue:
    - Some labs are performing routine AST for BCC
    - Some clinicians use AST to guide therapy and eligibility for lung transplant in individuals with CF
- Review of Previous Studies
  - Wootton et al. study (2020)
    - 155 isolates from individuals with CF
    - Poor reproducibility of BMD at 35°C (< 95%)
    - Poor correlation of BMD at 30°C, agar dilution (AD), gradient strip (GS), and DD with BMD at 35°C
    - EUCAST recommendation: no routine AST for BCC
  - Fehlberg et al. study (2016)
    - 82 isolates, n=47 from individuals with CF
    - DD performance acceptable for meropenem (MEM) and minocycline (MIN) (ceftazidime [CAZ], levofloxacin [LVX], and trimethoprim-sulfamethoxazole [TMP-SMX] fail)
    - ETEST performance acceptable for MEM, MIN, and TMP-SMX (CAZ and LVX fail)
  - AHWG on BCC AST study: 100 CF isolates tested at the Clinical Microbiology Institute (CMI)
    - Acceptable BMD reproducibility for MEM and MIN (≥ 95%)
    - Poor BMD reproducibility for CAZ, LVX, TMP-SMX (< 95%)
    - Poor DD reproducibility using a 3 mm cut-off
    - Acceptable DD performance for MEM compared to BMD
    - Overall: poor performance of AST methods except for MEM
    - Limitations:
      - All isolates from people with CF
      - Only MHA from Remel was tested
      - Used *P. aeruginosa* DD breakpoints for LVX
- Addressing Limitations from Previous Studies
  - In collaboration with Dr. Romney Humphries' lab at Vanderbilt University Medical Center (VUMC):
    - Test 105 isolates obtained from people without CF (non-CF isolates)
    - For 100 CF isolates tested at CMI:
      - Perform BMD in triplicate at VUMC
      - Perform DD using MHA from Remel, Hardy, and BD
      - Estimate DD breakpoints for LVX using disk-to-MIC correlations generated by diffusion Breakpoint Estimation Testing Software (dBETS)

- Compare CF and non-CF isolates
- For non-CF isolates: compare respiratory to non-respiratory isolates

- Conclusions
  - Drugs tested: CAZ, MEM, MIN, LVX, TMP-SMX
  - BMD reproducibility:
    - All isolates together, CAZ does not meet ≥ 95% acceptance criteria
    - Non-CF: all drugs meet acceptance criteria
    - CF: MIN meets ≥ 95%, other drugs failed at either CMI or VUMC
    - Overall: good reproducibility for non-CF isolates, poor reproducibility for CF isolates except MIN
    - Expand acceptance criteria to ≥ 90% and +/- 2 log2 dilutions: all drugs pass
  - DD vs. BMD:
    - In general, must drugs do not pass due to unacceptably high mE and VME rates > false susceptibility
    - In general, no significant differences between 3 MHA brands
    - Exception: non-CF, non-respiratory isolates had slightly better data: CAZ, MEM, MIN (Hardy and Remel) passed
- Study Limitations
  - Mostly isolates of *B. cenocepacia* and *B. multivorans*
  - BMD reproducibility, CF isolates, VUMC: 34 isolates in triplicate, 1 isolate in duplicate, 65 isolates, single replicates
  - CF and non-CF isolates tested at different times
    - CF isolates: ThermoFisher BMD panels
    - Non-CF isolates: custom BMD panels
    - Different lot #s of MHAs for CF and non-CF isolates
  - Only 1 site for non-CF isolates
  - Other AST methods (agar dilution, Etest) not evaluated
  - Modification to CLSI methods not tested (inoculum, incubation times)
- AHWG Discussion and Recommendations
  - Clinically, what does this mean?
    - Dr. John LiPuma, University of Michigan: In CF, acknowledges that routine AST does not correlate with clinical outcomes; uses AST under extreme circumstances and looks for drugs that are I or S or with low MICs
    - Dr. Ajai Dandekar, University of Washington: always takes an empirical approach over a susceptibility-guided approach in CF; in favor of ending routine AST
    - Dr. Eileen Burd, Emory: quit routine testing of BCC from CF, required a phone call to set up testing; no requests
  - Recommendations that were discussed:
    - Remove DD breakpoints
    - Add comment: routine AST not recommended for CF isolates
    - Perform BMD reference method only with no breakpoints and just report an MIC
    - Concerns about how many labs could perform this testing and how to validate tests with no breakpoints
    - Perform BMD for blood isolates only, since BMD is more reproducible for blood than for other sources
    - Is Etest worth pursuing?
      - Poor performance in EUCAST study
      - Acceptable for MEM, MIN, and TMP-SMX in Fehlberg et al. study

- Analysis of contemporary *P. aeruginosa* isolates: EA < 90% but due mostly to mEs

- MAIWG Discussion and Recommendation
  - Remove *Burkholderia cepacia* complex disk breakpoints from M100 for all antibiotics. WG Vote: 7-1-0-3.
  - Add a comment: "DD BPs were removed due to suboptimal correlation with reference BMD and will be reevaluated when more data are available". WG Vote: 8-0-0-3.
  - Add a comment: "Testing should be performed using a reference MIC method". WG Vote: 8-0-0-3.
  - Consider moving *Burkholderia cepacia* complex to M45. WG Vote: 8-0-0-3.
  - Other recommendations
    - Use current data set to determine revised breakpoints/DD correlates
    - Present data to M45 committee

SC DISCUSSION (MAIN POINTS)

- Cystic Fibrosis physicians were wishy-washy over AST, but the ID physicians really want AST. There is a larger issue for the immunocompromised patients because they need AST. CLSI needs to get support to help get out the message that AST for *Burkholderia cepacia* complex is not necessary; however, we can expect some physicians will be upset with the discontinuation of testing.
- *Burkholderia* is slow growing with large zones with colonies in the zone of inhibition. Additionally, the ECOFF is above the breakpoint. The MIC breakpoints do not make sense, so why use the disk data? Even though the BP is in the WT distribution, the MIC data was reproducible. The disk data looked bad.
- There is more variability in the MIC in CF vs. non-CF patients. A suggestion was made to salvage some of the disk breakpoints for non-CF patients.

A motion to remove *Burkholderia cepacia* complex disk breakpoints from M100 for all antibiotics and to add the comments stating "Disk diffusion breakpoints were removed due to suboptimal correlation with reference broth microdilution and will be reevaluated when more data are available. Testing should be performed using a reference MIC method." was made and seconded. Vote: 8 for, 5 against, 0 abstain, 1 absent (Fail)

Against Vote Reasoning:

- Not practical.
- Requiring a reference BMD does not work for labs.
- Comment is not needed.
- Reference labs do not necessarily use a CLSI reference method so many labs will not have a way to test.
- Commercial MIC panels would not count as a reference method.
- Suggestion to remove the word "reference".

A motion to remove *Burkholderia cepacia* complex disk breakpoints from M100 for all antibiotics and to add the comments stating "Disk diffusion breakpoints were removed due to suboptimal correlation with reference broth microdilution and will be reevaluated when more data are available. Testing should be performed using a MIC method." was made and seconded. Vote: 4 for, 9 against, 0 abstain, 1 absent (Fail)

Against Vote Reasoning:

- There is an issue with the last comment.

- Do not want people to be pushed to use Etests.

A motion to remove *Burkholderia cepacia* complex disk breakpoints from M100 for all antibiotics and to add a comment stating, "Disk diffusion breakpoints were removed due to suboptimal correlation with reference broth microdilution and will be reevaluated when more data are available." was made and seconded. Vote: 13 for, 0 against, 0 abstain, 1 absent (Pass)

SC DISCUSSION (MAIN POINTS)

- Suggestion was made to state testing should be performed by BMD and agar dilution.
- Do not know if commercial systems work.
- It was stated that Microscan has lots of VMEs.
- Suggestion was made to state to not use a MIC test strip.
- Suggestion was made to state to validate methods other than BMD.

A motion to approve adding a comment for *Burkholderia cepacia* complex stating, "Testing should be performed using a broth microdilution or agar dilution method." was made and seconded. Vote: 12 for, 1 against, 0 abstain, 1 absent (Pass)

Against Vote Reasoning:

- There is no agar dilution data.

CEFEPIME VS CARBAPENEM ENTEROBACTERALES AST INTERPREATION (TABLE H3 AND TABLE 2A)

- Challenging CRE Cases
  - Recent case of CRE isolates that are also cefepime susceptible or susceptible-dose dependent
  - Does susceptible equal success?
  - Barnes-Jewish Hospital, St. Louis, MO
    - 149 KPC-producing CRE isolates were identified with 14% of isolates testing as cefepime S or SDD despite carbapenem resistance.
    - Susceptibility testing at this site was conducted via disk diffusion
    - Report cefepime as resistant
  - The Johns Hopkins Hospital, Baltimore, MD
    - 209 KPC-producing CRE isolates were identified with 28% of isolates testing as cefepime S or SDD despite carbapenem resistance.
    - Susceptibility testing at this site was conducted via BD Phoenix automated susceptibility system
    - Suppress/hide cefepime results
- *In vivo* Study Results Summary
  - Among CRE isolates that test as cefepime-S or cefepime-SDD
    - Significant blunting of cefepime *in vivo* activity among CP-CRE isolates vs non-CP CRE despite having similar MICs and receiving the same cefepime 2g q8h human-simulated regimen (HSR)
    - Cefepime antimicrobial activity in CRE does not meet 1-log kill threshold indicative of clinical efficacy
  - Among non-CRE (ESBL-like) isolates that test as cefepime-S or cefepime-SDD
    - In contrast to CRE isolates, administration of cefepime 2g q8h HSR resulted in >2 log kill among non-CRE isolates with cefepime-S indicative of clinical efficacy

- However, similar activity was observed among non-CRE and non-CP CRE isolates that tested as cefepime-SDD

- MAIWG Discussion and Recommendation
  - Add to or modify current Appendix H to encourage suppression/conversion to R of cefepime results for CREs. WG Vote: 10-0-0-0.
  - Add a comment to Table 2 to encourage suppressing/conversion to R cefepime for CREs. WG Vote: 10-0-0-0.
  - Proposed Table H3 Revisions (in red). WG Vote: 8-0-0-3.

Table H3. (Continued)

Indication	Resistance Mechanism	Method	Specimen Type	Results		Suggestions for Resolution	Report as:	Comments[a]
				Resistance Mechanism Detected	AST (if tested)			
Detection of carbapenem resistance in Enterobacterales (Continued)	KPC, OXA-48-like, VIM, NDM, or IMP carbapenemases	NAAT, microarray, phenotypic methods such as those described in Tables 3b and 3c	Colony, blood culture	Any carbapenemase(s)	Susceptibility (S or SDD) to cefepime	If this is an unexpected phenotype in your institution, consider repeating resistance mechanism test(s) and AST.	If the discrepancy is not resolved, cefepime should be suppressed or reported as R. Note: Current evidence suggests cefepime therapy may not be effective against carbapenemase-producing strains. Most of these data are based on studies investigating KPC producing CREs.	1-4, 12-14

  - Proposed Table 2A Comment for Cefepime: Cefepime S/SDD results should be suppressed or reported as R for isolates that demonstrate carbapenemase production (see Table H3). WG Vote: 6-2-0-3.

SC DISCUSSION (MAIN POINTS)

- There is a difference in kill between carbapenemase-producing and non-carbapenemase-producing CRE for cefepime.
- The WG wants to encourage suppression/conversion of cefepime to R for carbapenemase-producing CRE.
- Suggestion was made to state that cefepime should not be reported unless carbapenemase testing is performed.
- Suggestion was made to state carbapenemase other than OXA-48.
- Question was asked if lateral flow assay for carbapenemase is allowed. Answer is yes.
- Per CAP, 60% of labs perform carbapenemase testing.

- The OXA-48 and cefepime clinical outcomes data is not available, so there was concern that it is inaccurate to state OXA-48 can be treated with cefepime.
- Suggestion to remove OXA-48 for the resistance mechanism.

A motion to approve the changes in red to Table H3 for the detection of carbapenem resistance in Enterobacterales and add a comment stating "Cefepime S/SDD results should be suppressed or reported as R for isolates that demonstrate carbapenemase production (see Table H3)." to Table 2A for cefepime was made and seconded. Vote: 11 for, 2 against, 0 abstain, 1 absent (Pass)

Against Vote Reasoning:
- Cefepime is a valid treatment for OXA-48 producers.

ANAEROBE AD HOC WORKING GROUP REPORT

- Current Projects
  - Disk testing with EUCAST efforts
    - EUCAST has released a guidance document and publication of the data on fastidious anaerobe agar
    - Review of EUCAST materials
    - Planning small pilot of EUCAST disk diffusion method
  - M11 to be revised
    - AHWG Vote: 7-0-0. WG Vote: 8-0-0-3.
    - Include wording about EUCAST methods with disks
  - Antibiogram – Appendix D
    - Nothing new to update
- Pilot of EUCAST Disk Diffusion Method
  - Three sites (Mayo, IHMA and Public Health Wales)
    - Complete before October 2023
    - Present results in January 2024 CLSI meeting
  - Methods
    - Disk diffusion - Fastidious Anaerobe Agar base (Read at 18+ 2hrs.) – per EUCAST methods
    - Agar Dilution – Fastidious Anaerobe Agar base (Read 48 hrs.) – per EUCAST methods
    - Agar Dilution - Brucella Blood Agar base (Read 42-48 hrs.) – per CLSI methods
  - All three methods set-up on same day, one media manufacturer/one lot of FAA plate
  - Organisms
    - 27 clinical isolates (10 from Public Health Wales Challenge Set)
      - *Bacteroides* spp., *Prevotella* spp., *Fusobacterium necrophorum*, *Clostridium perfringens*, *Cutibacterium acnes* and *Clostridioides difficile*
    - 4 QC organism
      - *Bacteroides fragilis* ATCC 25285, *Clostridium perfringens* ATCC 13124, *Clostridium perfringens* DSM 25589 (anaerobic conditions – Unique to EUCAST), *Clostridioides difficile* ATCC 700057 (Unique to CLSI)
      - Antibiotics (ThermoFisher donating disks)

- Meropenem (10 mg) – 0.007 – 2 mg/ml
- Metronidazole (5 mg) – 0.125 - 8 mg/ml – no CLSI disk concentration
- Clindamycin (2 mg) – 0.06 – 8 mg/ml

SC DISCUSSION (MAIN POINTS)

- Question on what the M11 revision will include. The M11 revision will review and update the MALDI and species names and will evaluate the EUCAST disk diffusion method.
- Question if it matters to use anaerobic jars vs chambers for anaerobe DD assessment. This is a pilot and for now the study will not evaluate these conditions.
- Brucella Blood Agar base will also be added to the disk diffusion study.

A motion to approve the revision of CLSI M11 was made and seconded. Vote: 13 for, 0 against, 0 abstain, 1 absent (Pass)

7. **QUALITY CONTROL WORKING GROUP (S. CULLEN)**

TIER 2 QC

MEROPENEM/KSP-1007

- Background

Drug: Meropenem/KSP 1007 (fixed 8 µg/mL)	**Abbreviation (Glossary II & III)**: TBD	**Previous ID**: NA
Solvent (Table 6A): Meropenem: Sterile distilled water, KSP-1007: Sterile distilled water with equimolar sodium carbonate	**Diluent (Table 6A):** Sterile distilled water	**Preparation (Table 6C combination agents)**: **TBD**
Route of administration (Glossary II): IV	**Class (Glossary I & II): β-lactam combination agents**	**Subclass (Glossary I & II): NA**
Study Report by: JMI	**Pharma Co**: Sumitovant Biopharma, Inc.	**Control Drugs**: Meropenem
Additional Information (M23 requirements)	• **Tier 1 Impact Assessment** (stability, inoculum, reading, incubation time, etc): pending. Action: Stability report needed in future to determine if there is a need to include as indicators of deterioration in consideration as routine QC for streamlined QC.. • **ISO/TS 16782 assessment of Tier 2 study materials**: Yes	
Footnotes:	• **Recommendations for Troubleshooting Guide (Table 4D Disk or 5G MIC):** None at this time	
Discussion	Note: media tested included BD, Difco, Oxoid	

- Proposed QC Ranges

Drug Name:	Meropenem/KSP 1007 (fixed 8 µg/mL)	Votes:	9/0/4/1 (For, Against, Absent, Abstain)

QC Strain	Range	% In	Mode	Dil	Shoulder	Media Mode	Lab Mode	M23 Range	Range Finder	Comments
Acinetobacter baumannii NCTC 13304	0.5/8 - 4/8	94.7%	1/8	4	65.9% @ 2/8	3@ 1/8	2@0.5/8, 4@1/8, 1@2/8, 1@4/8	0.5/8 - 4/8, 94.7%, 4	No proposed QC range	Media: no variability Lab: variability, Lab C (mode 4/8) and E (mode 2/8) had higher MICs than other labs. Routine QC (Meropenem range 32-128)
Escherichia coli ATCC 25922	0.008/8 - 0.03/8	100%	0.016/8	3	<30%	2@ 0.016/8	8@ 0.016/8	0.008/8 - 0.03/8, 100%, 3	0.008/8 - 0.03/8, 100%, 3	
Klebsiella pneumoniae ATCC BAA-1705	0.008/8 - 0.03/8	97.9%	0.016/8	3	<30%	3@ 0.016/8	8@ 0.016/8	0.008/8 - 0.03/8, 97.9%, 3	0.008/8 - 0.03/8, 97.9%; 3	Routine QC (Meropenem range 8-64)
P. aeruginosa ATCC 27853	0.12/8 - 1/8	100%	0.25/8	4	<30%	3@ 0.25/8	7@0.25/8 1@1/8	0.12/8 - 0.5/8, 94.2%, 3	0.12/8 - 1/8, 100%, 4	Lab C was statistical outlier for mode (typically exclude with outlier for 2 parameters). Propose 0.12/8-1 to be consistent with Meropenem alone range 0.12-1
)P. aeruginosa ATCC 27853 (minus Lab C)	0.12/8 - 0.5/8	99.5%	0.25/8	3	<30%	See above	See above	0.12/8 - 0.5/8, 99.5%, 3	0.12/8 - 0.5/8, 100%, 3	Lab C mode 1/8. 7@0.12/8, 8@0.25/8, 2@0.5/8, 13@1/8. Meropenem 12@0.12, 5@0.5, 13@1.

A motion to approve the meropenem/KSP-1007 QC ranges for *Acinetobacter baumannii* NTCC 13304 (0.5/8-4/8 µg/mL), *E. coli* ATCC 25922 (0.008/8 - 0.03/8 µg/mL), *K. pneumoniae* BAA-1705 (0.008/8 - 0.03/8 µg/mL), and *P. aeruginosa* ATCC 27853 (0.12/8 - 1/8 µg/mL) was made and seconded. Vote: 13 for, 0 against, 0 abstain, 1 absent (Pass)

OMN6

- Background

Drug: OMN6	**Abbreviation (Glossary II & III):**	**Previous ID**: 9/0/4/1
Solvent (Table 6A): sterile distilled water	**Diluent (Table 6A): sterile distilled water**	**Preparation (Table 6C combination agents)**: NA
Route of administration (Glossary II): IV	**Class (Glossary I & II):** novel antimicrobial peptide	**Subclass (Glossary I & II):** None specified
Study Report by: JMI	**Pharma Co**: Omnix Medical	**Control Drugs**: colistin, meropenem

Additional Information (M23 requirements)	• **Tier 1 Impact Assessment** (stability, inoculum, reading, incubation time, etc): Completed cations, pH, urine, and serum. Pending stability, incubation and inoculum. • **ISO/TS 16782 assessment of Tier 2 study materials**: CAMHB lots yes. NAMHB N/A • 9/0/4/1 for actions and footnotes below
Footnotes:	• **Recommendations for Troubleshooting Guide (Table 4D Disk or 5G MIC):** Observation: MICs too high. Cause: Combined Ca and Mg >15 mg/L or use of CAMHB. • **Footnote:** QC ranges reflect MICs obtained with non-adjusted Mueller Hinton Broth NAMHB with a combined Ca and Mg concentration <15 mg/L. NAMHB is Mueller Hinton Broth without addition or adjustment of cation concentration.
Discussion	Target organism is multi-drug resistant and carbapenem-resistant *A. baumannii* Media included Difo, Oxoid, Sigma Millipore Action: Complete Tier 1 studies before publication, may need additional data on NAMHB or stability in future to determine if one or both QC are needed. Inclusion in Table 5A-1 is dependent on approval of modified reference method by Methods Working Group. Presentation Slide 5: Checkerboard *A. baumannii* NCTC 13304 testing concentrations of calcium and magnesium. MICs higher with current CAMHB concentrations, decreased 1-3 dilutions with lower concentrations. Report page 4: Mean and modal OMN6 MIC values against *A. baumannii* NCTC 13304 and E. coli ATCC 25922 increased by 8-fold when tested in CAMHB as compared to NAMHB (Tables 1, 2, 7, and 8) and in the JMI Laboratories report 22-OMX-03, suggesting that the MIC increase is likely due to higher cation levels in CAMHB.

- Proposed QC Ranges

Drug Name:	OMN6	Votes:	9/0/4/1 (For, Against, Absent, Abstain)

QC Strain	Range	% In	Mode	Dil	Shoulder	Media Mode	Lab Mode	M23 Range	Range Finder	Comments
Acinetobacter baumannii NCTC 13304	4 –16	98.9%	8	3	<30%	3@8	8@8	4 –16, 98.8, 3	4 –16, 98.8, 3	
Escherichia coli ATCC *25922*	8-32	100%	16	3	<30%	3@16	8@16	8-32, 100%, 3	8-32, 100%, 3	

- QC Strain Selection
  - Proposed *A. baumannii* QC strain as this is the target organism.
  - Due to novel mechanism of action of this peptide, *E. coli* mcr-1 is not needed and *E. coli* ATCC 25922 can be used.
- QCWG Discussion and Recommendation
  - Only publish if modified reference method is approved by MDSWG.
  - List both *E. coli* ATCC 25922 and *A. baumannii* NCTC 13304 until more information is available.

A motion to approve the OMN6 QC ranges for *Acinetobacter baumannii* NTCC 13304 (4-16 µg/mL) and *E. coli* ATCC 25922 (8-32 µg/mL) pending the MDSWG approval of the modified reference method was made and seconded. Vote: 13 for, 0 against, 1 abstain, 0 absent (Pass)

EXEBACASE QC

- Objectives
  - Review QC data for incubation conditions recommended for coagulase negative staphylococci (5% CO2, 20-24 hours) – CLSI approved modified incubation for CNS June 2022.
  - Determine if current range (established using ambient, 16-20 hours) can be applied to both incubation conditions.
  - Review options and decide on proposed QC table footnote changes.
- Data Observations
  - Tier 2 (see next slide from Jan 2017) : Media mode variability (Lot 1 Difco 0.5, Lot 2 BBL 0.5-1, Lot 3 Oxoid 1). Overall mode 0.5-1 (0.5 with 95% shoulder at 2).
  - Data with 5% CO2 and 20-24 hours incubation: Most data collected with BBL (middle of range in Tier 2). Mode shifts higher to 1 but all within the current CLSI QC range 0.5-2.
- Comments/Questions
  - Is QC testing *S. aureus* 29213 in ambient conditions for 16-20 hours sufficient or test both incubation times/conditions with QC *S. aureus* 29213 if testing both *S. aureus* and CNS?
    - Range OK for both, QC testing recommendations pending.
    - Testing will be mainly for surveillance, not routine clinical labs. Sponsor is testing both, can be determined in future.

- Are data equivalent to Tier 2 or adequate as Tier 3 to modify the QC table comment?
  - Yes, but only 1 media manufacturer.
  - Additional data: 213 replicates, 6 individual labs, >3 lots of BBL media, multiple lots of horse serum (now >250)
  - Tier 2 requirements: 210 total, 3 media manufacturers, 7 labs (as a retrospective/compiled vs prospective)
  - Tier 3 requirements: 250 total, 3 labs, 2 media manufacturers (at least 50 from each)
- Do we ask for data with other media manufacturers (Oxoid and Difco)?
  - Not at this time (testing limited to research/surveillance not routine clinical). Add footnote regarding limited data.

- Proposed *S. aureus* ATCC 21913 QC Ranges and Footnote

Incubation: 5% CO_2 20-24 hours

Data Set	n	Exebacase MIC (µg/mL)				
		0.25	0.5	1	2	4
Consolidated all studies: Jan. 2023	92		6	83	3	
Consolidated all studies: Current	**213**		**17**	**188**	**8**	
				↑ mode		

Incubation: ambient 16-20 hours

Data Set	n	Exebacase MIC (µg/mL)				
		0.25	0.5	1	2	4
Tier 2	240	17	107	102	12	2
Consolidated all other studies	527	17	334	173	3	0
ALL DATA TOTAL	**767**	**34**	**441**	**275**	**15**	**2**
			↑ mode			

QCWG vote: Add footnote

QC ranges reflect MICs obtained when incubated in ambient conditions for 16-20 hours or 5% CO_2 for 20-24 hours (mode 0.5-1 µg/mL). Data with incubation for 5% CO_2 and 20-24 hours was collected with limited Mueller Hinton media manufacturers.

A motion to approve the Exebacase QC range for *S. aureus* ATCC 29213 (0.25-2 µg/mL) for the incubation conditions of ambient air for 16-20 hours and 5% CO_2 for 20-24 hours and to add a comment stating, "QC ranges reflect MICs obtained when incubated in ambient air conditions for 16-20 hours or 5% CO_2 for 20-24 hours (mode 0.5-1 µg/mL). Data with incubation for 5% CO_2 and 20-24 hours was collected with limited Mueller Hinton media manufacturers." was made and seconded. Vote: 14 for, 0 against, 0 abstain, 0 absent (Pass)

TIER 3 MIC QC

- Discussion and Decision Requests

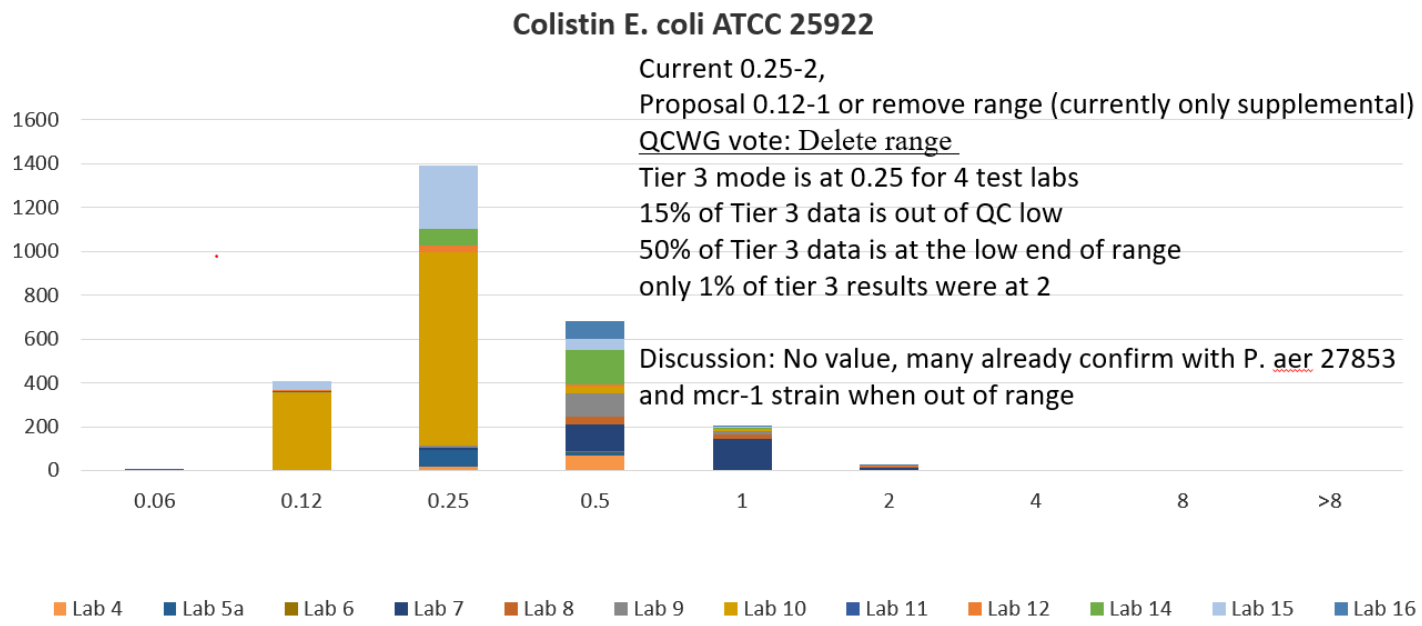
QC Strain (ATCC)	Antimicrobic	Current Range	Action Recommended	Concern	Reported
S. pneumoniae ATCC 49619	Levofloxacin	0.5-2	Discussed changing range to 0.25-2 or 0.25-1 No change 9/1/4/0	Including USCAST data (Mode @ 0.5; 86% of 1,520) and data from new lab we have sufficient data to make a decision. Tier 3: 1655 results, 4 labs, mode @ 0.5 for 3/4 labs, 1% out at 0.25. 1/1655 Tier 3 results at 2. June 2023: new data from 1 lab and incorporation of USCAST data into Tier 3 analysis	18-Jan
E. faecalis ATCC 29212	Amikacin	64-256	Recommend archiving	CDC reported out low when testing gram-neg. panels, other strains in range. Dec 2021-Jun 2023: no new data	18-Jan
S. aureus ATCC 29213	Ciprofloxacin	0.12-0.5	Discussed widening range to 0.12-1 No change 10/0/4/0	"bi-modal" MIC distribution noted from three studies. Consider revising range to 0.12-1. (Table 3-28). USCAST quinolone report data and new data added in June 2022 support this. (N=2143 from 5 labs, bimodal with a mode of 0.5 having 54% of total results) Jun 2023: USCAST data incorporated into analysis	18-Jan
K. pneumoniae BAA-1705	Imipenem/ relebactam	0.03/4-0.25/4	Request additional data	Results at high end with one lab Dec 2021: Added 1 lab with limited 2021 data. Only 2% out high @ 0.5/4 µg/ml for all Tier 3 (n=1147 results). Available data supports current range. Jan 2022-Jun 2023: no new data Dec 2021: Added 1 lab with limited 2021 data. Only 2% out high @ 0.5/4 µg/ml for all Tier 3 (n=1147 results). June 2022: no new data	19-Jan
S. aureus ATCC 29213	Rifampin	0.004 to 0.016	Recommend archiving	One report of S. aureus out low Dec 2021-Jun 2023: no new data; data only from one lab	19-Dec

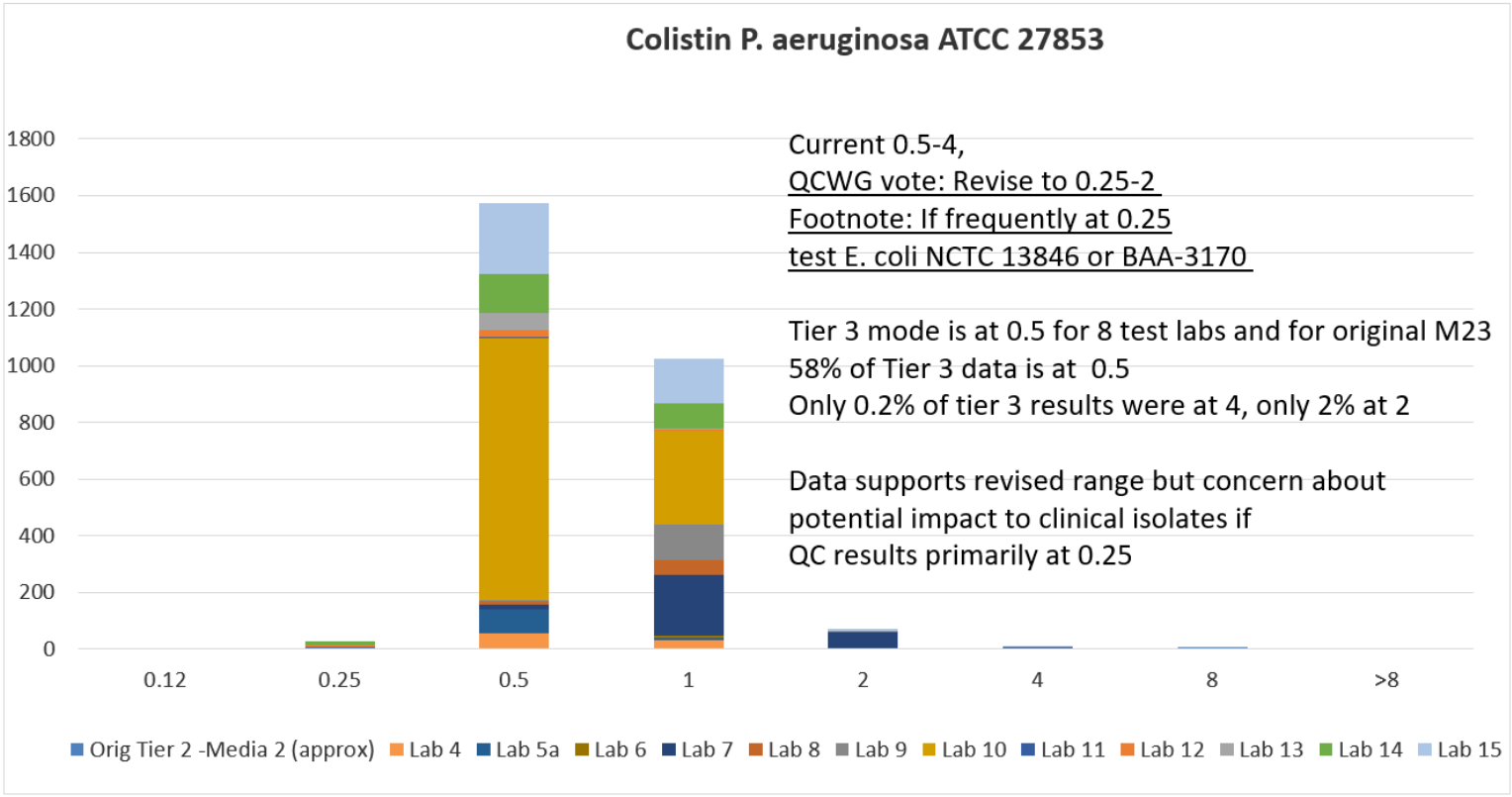
QC Strain (ATCC)	Anti-microbic	Current Range	Action Recommended	Concern	Reported
K. pneumoniae ATCC 700603	Pip/Tazo	8/4-32/4	Request additional data	Tier 2 data available. Data from 3 additional labs added June 2022. Data available from 6 labs total (N=735). Apart from two labs with less than 10 datapoints where one was bimodal at the low end of range and one had a mode at the low end of the range, data supports current range. Jan - Jun 2023: no new data	21-Jun
K. pneumoniae ATCC 700603	Amp/ sulbactam	8/4-32/16	Request additional data	Data from 2 additional labs added June 2022. Data available from 6 labs total (N=1587). Data supports current range. Jan - Jun 2023: no new data	21-Jun
E. coli ATCC 25922	Colistin	0.25-2	Discuss adjusting range to 0.12-1 or removing 25922 (currently CLSI supplemental). Delete range 8/1/4/1	Data available from >10 labs (N=2719; 1274 from one lab with mode at low end of range and high frequency out of QC low; three other lab with mode at low end of range and one with high frequency out of QC low results; overall 15% out of QC). Jun 2023: data from 3 new labs and adding in data from Jan 2022 tier 2 and Jun 2023 study when tested as control Inform EUCAST (currently test either 25922 or 27853 plus mcr-1 strain).	21-Jun
P. aeruginosa ATCC 27853	Colistin	0.5-4	Discuss if frequently at 0.5 test NCTC 13846 or BAA-3170. 8/1/4/1 revise range to 0.25-2	Data available from >10 labs (N=2771; 1262 from one lab with mode at low end of range; four other labs + original Tier 2 with mode at low end of range and out of QC low results). Jun 2023: data from 4 new labs and adding in data from Jan 2022 tier 2 study when tested as control. 9/0/4/1 Add to footnote. If MICs at low end of range, also test mcr-1 QC strain.	21-Jun
E. coli ATCC 25922	Aztreonam/ avibactam	0.03/4-0.12/4	Request additional data	Additional data June 2022 from 1 lab (multiple years) and Jan 2023 data from 1 lab. Tier 3 mode at 0.06/4, with 1% out high; 57% shoulder at 0.12/4. Jun 2023: no new data (data supplied didn't test over qc range)	21-Jun

QC Strain (ATCC)	Antimicrobic	Current Range	Action Recommended	Concern	Reported
K. pneumoniae ATCC 700603	Aztreonam	8-64	Discussed shifting to 16-128 or >8 to address mode at 32 and shoulder at 64 Revised to >8 mg/L 10/0/4/0	New signal. Concern is too many results at high end of range. Results from 5 labs available for analysis (N=1219). Two labs had mode at the high end, the others and the original tier 2 at 32 with no significant shoulder; overall shoulder at 64 is >60%. Out of QC largely associated with one lab; only 1/1219 at 8 for tier 3. June 2023: data from 2 new labs QC integrity strain only.	22-Aug
E. coli ATCC 25922	Aztreonam	0.06-0.25	Expand to 0.06-0.5 10/0/4/0	New signal. Concern is too many results at high end of range. The Tier 3 distribution is nearly biomodal. Results from original Tier 2 and 4 labs available for analysis (N=956). Two labs had modes at the high end, the other at 0.12 with a 50% shoulder and the original Tier 2 (from 1987) had a mode at the low end. June 2023: data from 2 new labs	22-Dec
S. pneumoniae ATCC 49619	Ceftriaxone	0.03-0.12	Request additional data	Signal reported from one lab that there may be an issue with MICs frequently observed at the upper end of the range. Data based on freeze-dried panels, need reference data to determine whether this is in fact a signal for the reference method.	22-Nov
K. pneumoniae BAA-1705	Imipenem	4-16	New request for data	Signal from Tier 2 study showed a mode at 16 (70% of total results) and out of QC results at 32 (6.7%).	23-Jan
K. pneumoniae BAA-2814	Imipenem	16-64	New request for data	Signal from Tier 2 study showed a mode at 64 (67% of total results) and out of QC results at 128 (24.8%).	23-Jan
S. pneumoniae ATCC 49619	Doxycycline	0.016-0.12	New request for data	Signal from EDL 5 lab dried panel study where nearly 70% of results tested at 0.12, the high end of the range; requesting frozen reference method data to see if further monitoring or adjustment is warranted	23-Jun

COLISTIN

- Background and QCWG Recommendation

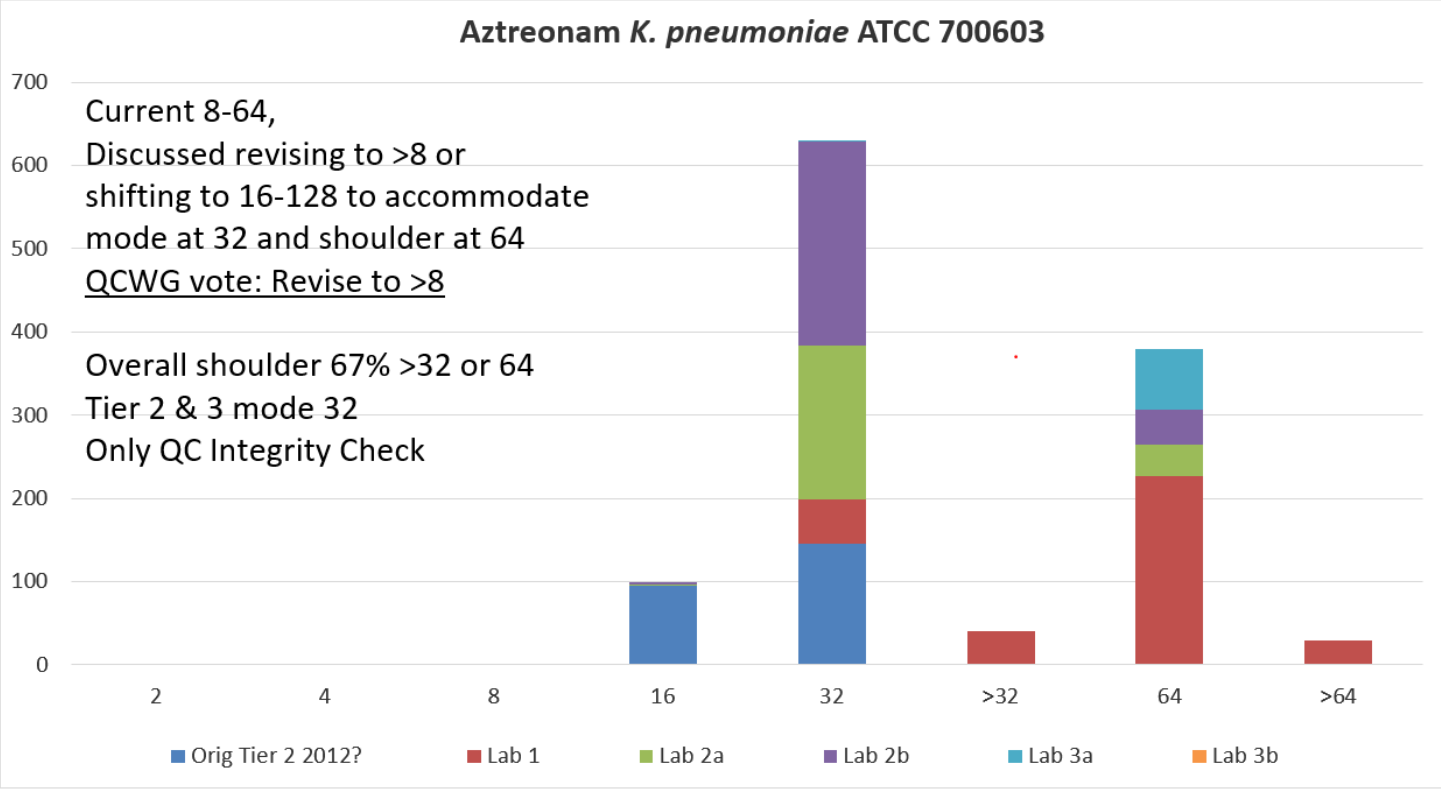

Colistin E. coli ATCC 25922
Current 0.25-2,
Proposal 0.12-1 or remove range (currently only supplemental)
QCWG vote: Delete range
Tier 3 mode is at 0.25 for 4 test labs
15% of Tier 3 data is out of QC low
50% of Tier 3 data is at the low end of range
only 1% of tier 3 results were at 2
Discussion: No value, many already confirm with P. aer 27853 and mcr-1 strain when out of range
1600
1400
1200
1000
800
600
400
200
0
0.06
0.12
0.25
0.5
1
2
4
8
>8
Lab 4
Lab 5a
Lab 6
Lab 7
Lab 8
Lab 9
Lab 10
Lab 11
Lab 12
Lab 14
Lab 15
Lab 16



A motion to delete the colistin QC range for *E. coli* ATCC 25922 (0.25-2 µg/mL), revise the colistin QC range for *P. aeruginosa* ATCC 27853 (0.25-2 µg/mL), and to add a comment stating, "If frequently at 0.25 µg/mL test *E. coli* NCTC 13846 or *E. coli* ATCC BAA-3170." was made and seconded. Vote: 14 for, 0 against, 0 abstain, 0 absent (Pass)

AZTREONAM *K. PNEUMONIAE* ATCC 700603

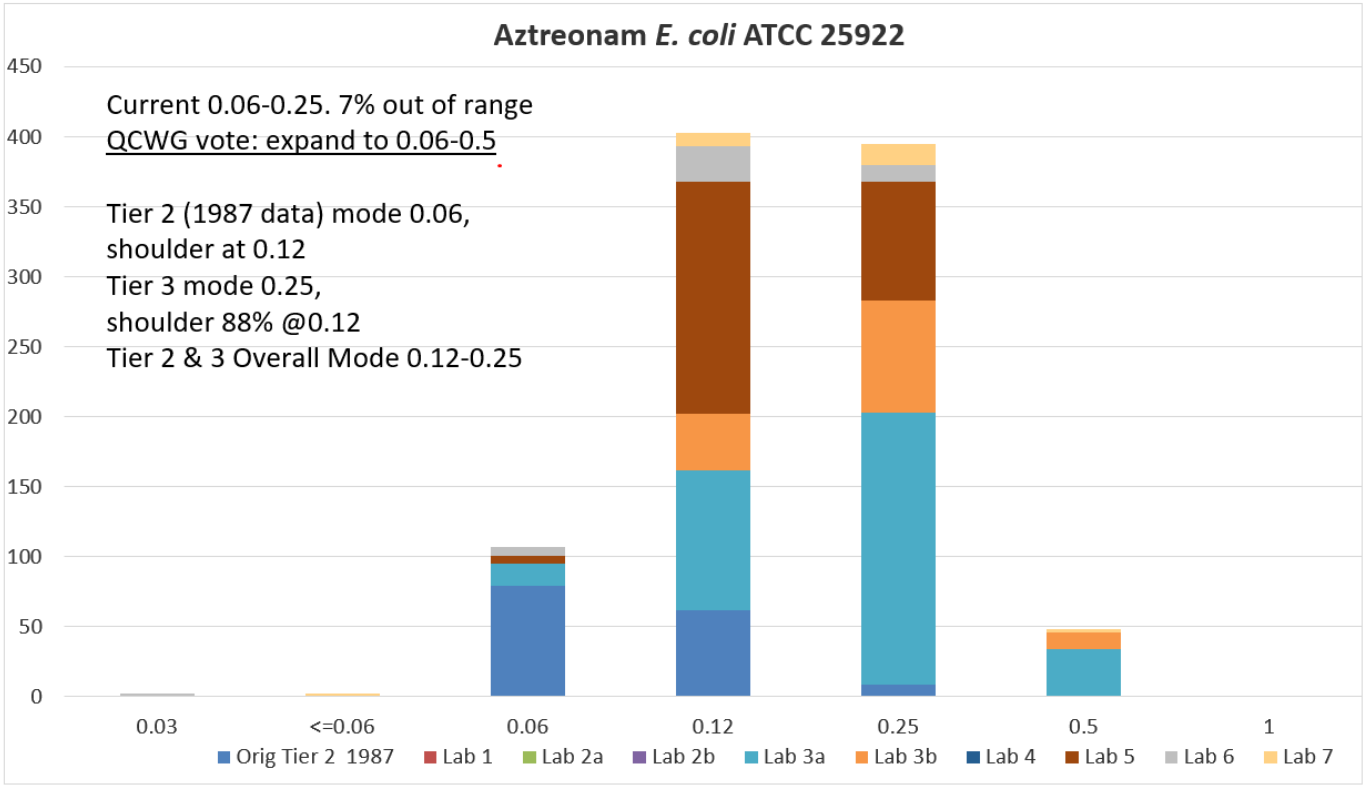
- Background and QCWG Recommendation



A motion to revise the aztreonam QC range for *K. pneumoniae* ATCC 700603 (> 8 µg/mL) was made and seconded. Vote: 14 for, 0 against, 0 abstain, 0 absent (Pass)

AZTREONAM *E. COLI* ATCC 25922

- Background and QCWG Recommendation



A motion to revise the aztreonam QC range for *E. coli* ATCC 25922 (0.06-0.5 µg/mL) was made and seconded. Vote: 14 for, 0 against, 0 abstain, 0 absent (Pass)

TIER 3 DISK DIFFUSION QC

- Discussion and Decision Requests

QC Strain (ATCC)	Antimicrobic	Current Range	Action Recmd	Concern	Update	Date Reported
S. aureus ATCC 25923	Ciprofloxacin 5 µg Levofloxacin 5 µg Moxifloxacin 5 µg Ofloxacin 5 µg Norfloxacin 10 µg	22-30 25-30 28-35 24-28 17-28	Suggested action: Archive and refer to reading guide group	Fuzzy zone edges results in too small zones (also observed for S. aureus ATCC 29213).	June 2023: Comparative data added for ATCC 29213 (EUCAST recoemmended strain).	May-21
P. aeruginosa ATCC 27853	Cefiderocol 30 µg	22-31	Suggested action: Archive??	Major media differences observed in M23 study, which resulted in a 10 mm range. EUCAST QC range is set to 23-29 mm.	June 2023: Additional data on BBL, Remel and Hardy MH added. The new data show the same trends with smaller zones for BBL and larger for Hardy and Remel.	Jan-21
E. coli ATCC 25922	Minocycline 30 µg	19-25	Suggested action: Continue to monitor until January 2024. Request additional data.	Values at top of range and above range from one lab.	June 2023: Data from one source added. The new data is well within the existing range.	Jan-21
N. gonorrhoeae ATCC 49226	Spectinomycin	23-29	Suggested action: Continue to monitor until June 2025. Request additional data.	QC study out high	June 2023: No additional data. June 2022: Observations in gentamicin QC study, especially with one lab and media	June-22

CEFIDEROCOL

- Cefiderocol discussion from virtual QCWG meeting
  - EUCAST has some data where VME associated with larger QC zone sizes (shared with MDSWG).
  - Hardy is asking for feedback from CLSI whether to pursue media formulation improvements (that give smaller zones for Cefiderocol with no impact to other agents).
  - Disk variation smaller than media variation. Other comments include can vary between days, Remel (ThermoFisher) OK at ThermoFisher but some clinical labs get larger zones, larger zones also obtained with BioRad.
  - Recommendation: Depending on recommendation from MDSWG, consider narrower range and ask media manufacturers pursue formulation refinement if tighter (or smaller) zone sizes are important to correlate with *in vivo* or MIC correlates.

SC DISCUSSION (MAIN POINTS)

- Question if the QCWG will review a better cefiderocol QC organism. The WG is open to the suggestion but currently does not have a plan to review.

ROUTINE/STREAMLINED QC

- Current State and Issues
  - Table 2s QC recommendations – future improvement; readdress in 2024
    - Not clear/consistent
    - Many have off-scale results and provide minimal value for user QC (eg, *E. coli* ATCC 25922)
  - Table 4A-2 and 5A-2 for combination beta lactams

        - Confusion regarding strains not listed as “routine QC”. These strains do not assess potency of the beta lactamase inhibitor.
    - Other QC tables have similar but may be fewer issues – review in future
    - AST QC may represent a large proportion of ASTs performed in a laboratory where volume of ASTs is low - Can we reduce QC% of AST testing? – See plans, report outcome Jan 2023
        - Small numbers of ASTs (eg, patient office labs, small hospitals, reference labs doing limited AST)
        - Small numbers of one type of AST (eg, anaerobes, enterococci)
        - Can have multiple backup ASTs for select organisms/AST methods
        - Testing newer B-lactam/ß-lactamase combinations, up to 8 QC strains if all agents are tested
- QC Table Improvements -Potential Options for Future
    - Replace *E. coli* 35128 with *K. pneumo* 700603 which covers 10 agents including labile inhibitor clavulanate
        - Commercial AST requires 510(k) to add QC strains and ranges
        - Discuss least burdensome options with FDA
    - Revise to support streamlined QC
        - Add guidance for streamlined QC to Table 4C and 5F
        - Add to troubleshooting guide (as appropriate from Jan 2023 superuser and July 2023 user surveys)
        - Revise QC recommendations in Tables 2, 3, 4, 5 as needed
- Next Steps
    - Distribute Survey (end June/early July), send reminder message then compile results after 3 weeks
        - CLSI AST meeting registrants, ASM Clin Micro Net, Div C
    - Based on survey results, refine options to define a streamlined routine QC approach (eg, frequency, number or rotation of QC strains)
    - Mock-up revisions to QC tables and footnotes, etc.
        - Table 2’s Routine QC Recommendation box
        - Table 4A-2 and 5A-2 (QC for Beta lactam combination agents)
            - Address single agents: remove ranges, remove from table (archive on CLSI website), revise comments?
        - Troubleshooting Guide: update from survey, enhance critical indicator information
        - Potential new M100 Table (Table 4D, 5F) to address options for streamlined routine QC
            - Apply to reference, commercial methods, or both? Currently includes commercial methods.
    - Share with CMS/CAP for feedback and request support for inspector guidance
        - Suggest using IQCP for labs to make and document decisions.
        - Updated CLSI tables and guidance provided for technical justification.
        - Could use M50 approach for lab to retrospectively review QC data for justification
    - White Paper to explain rationale and process. Allows for earlier communication (not dependent on M100 annual publications; address methods other than CLSI reference methods).
    - Outreach Working Group – proposed topic for educational session

SC DISCUSSION (MAIN POINTS)

- Consider including guidance for large labs that might store data on multiple computers or have multiple instruments when developing streamlined QC.
- Question on the motivation of the WG to look at streamlining QC. Labs were doing a lot of unnecessary QC that really does not add much benefit.
- There was support for making the QC as relevant as possible and reducing workload for laboratories.

- Positive praise was given with the way the streamlined QC is moving forward. New agents are coming that have additional QC, so labs will have more work in the future.

TABLE 4A-2 AND 5A-2 REVISIONS

- Revisions for Table 4A-2 and 5A-2 for combination beta lactams
  - Move footnote f to definition for green highlight:
    - "Any strain highlighted in green may be used for routine QC of this antimicrobial agent." WG vote: 9-0-4-0
  - Add footnote and/or header to QC strains normally used for single agents (*E. coli* 25922, *P. aeruginosa* 27853, *S. aureus* 29213, *S. aureus* 25923, *E. faecalis* 29212). WG Vote: 9-0-4-0.
    - Not recommended for QC of ß-lactam combination agents
    - Consider removing from Combination ß-lactam table in future
  - Add green highlight for routine QC for Ceftibuten-ledaborbactam
    - *E. coli* NCTC 13353, *K. pneumo* BAA-1705, *K. pneumo* BAA-2814

A motion to approve the proposed revisions to Table 4A-2 and 5A-2 for combination beta lactams with footnote f stating, "Any one strain in green may be used for routine QC of this antimicrobial agent." was made and seconded. Vote: 14 for, 0 against, 0 abstain, 0 absent (Pass)

8. **TEXT AND TABLES WORKING GROUP (S. CAMPEAU)**

M02/M07 AD HOC WORKING GROUP REPORT

- On schedule for January 2024 publication with M100 34th ed.
- Documents are currently with CLSI editors being prepared for Proposed Draft Vote
- Proposed Draft Vote scheduled to occur in mid-June
- Major change that impacts M100 is the addition of cefiderocol methods to M07 and subsequent removal from M100 Appendix I. May need to retain some information in M100 depending on upcoming cefiderocol AHWG discussions at this meeting.
- Quick Guides for reading are also being updated

DOSAGE COMMENT REMOVAL

- Dosage Comment Mini Group Discussions
  - Importance of having this information up where breakpoints are located was expressed by pharm/clinical colleagues on call
  - Three main suggestions were made to
    - Option 1: Put organism-group-specific dosages in front of each of Tables 2 within general comments sections
    - Option 2: Consider putting back into Tables 2 but in a way that would not detract from other important testing/reporting comments
    - Option 3: Put dosages (all of Appendix E content) up in front of Tables 2 so not in back of the document
  - Emphasis was made on preventing redundancy within the document to help avoid errors when updates occur; preference would be to keep to one location and not continue maintaining in 2 locations
  - Mockups were created and sent to the group
  - Mockups and mini group feedback were reviewed/discussed by TTWG with vote
- TTWG Recommendation (Option #3)
  - New section before Tables 2
  - Move all of Appendix E content ahead of Tables 2
  - This option was preferred by most as a middle-ground solution between the other two options
  - WG Vote: 8-0-0-4.
  - Section placement

Contents (Continued)

- New Introduction to Tables 2

Introduction to Tables 2A-2J. Zone Diameter and MIC Breakpoints

Tables 2A through 2J: tables for each organism group that contain:

- Recommended testing conditions
- Routine QC recommendations (also see Chapter 4 in M02[1] and M07[2])
- General comments for testing the organism group and specific comments for testing particular agent/organism combinations
- Agents that should be considered for routine testing and reporting by medical microbiology laboratories, as specified in Tables 1A **through 1P** (test/report **Tiers 1, 2, 3, and 4), including agents reported only on organisms isolated from the urinary tract (designated by "U").**
- **Agents** that are appropriate for the respective organism group but **are not listed in Tables 1 and** would generally not warrant routine testing by a medical microbiology laboratory in the United States (**designated with an asterisk as** "other"; **designated with "Inv."** for "investigational" [not yet FDA approved]), **including agents reported only on organisms isolated from the urinary tract (designated by "U").**
- Zone diameter and minimal inhibitory concentration (MIC) breakpoints

Recently approved susceptible or susceptible-dose dependent (SDD) breakpoints for a number of agents have been based on a specific dosage regimen(s); these dosage regimens are listed in the table preceding Tables 2A-2J. This information should be shared with pharmacists, infectious diseases staff, and others making dosing recommendations for the institution.

- New Format of Appendix E

Dosage Regimens Used to Establish Breakpoints

The evolving science of pharmacokinetics-pharmacodynamics has become increasingly important in recent years in determining minimal inhibitory concentration (MIC) breakpoints. Recently approved susceptible or susceptible-dose dependent (SDD) breakpoints for a number of agents have been based on a specific dosage regimen(s); these dosage regimens are listed in the table below. Proper application of the breakpoints necessitates drug exposure at the site of infection that corresponds to or exceeds the expected systemic drug exposure at the dose listed in adult patients with normal renal function. This information should be shared with pharmacists, infectious diseases staff, and others making dosing recommendations for the institution.

Antimicrobial Agent	Breakpoints (µg/mL) and Interpretive Categories		Dose
Table 2A. Enterobacterales			
Amikacin	≤ 4	S	15 mg/kg administered every 24 h
Ampicillin (used to predict results for amoxicillin)	≤8	S	Ampicillin: 2 g parenterally administered every 4-6 h or Amoxicillin: 1-2 g parenterally administered every 6 h
Ampicillin (used to predict results for amoxicillin; salmonellosis, shigellosis, and uncomplicated UTIs due to *E. coli* and *P. mirabilis*.	≤8	S	Ampicillin: 500 mg orally administered every 6 h or Amoxicillin: 250 mg orally administered every 8 h or 500 mg every 12 h
Amoxicillin-clavulanate	≤8/4	S	1.2 g administered parenterally every 6 h 875/125 mg orally administered every 12 h or 500/125 mg every 8 h (only for uncomplicated UTIs or when completing therapy for systemic infection)
Ampicillin-sulbactam	≤8/4	S	3 g parenterally administered every 6 h
Azithromycin (*Salmonella enterica* ser. Typhi and *Shigella* spp.)	≤16	S	500 mg administered daily
Aztreonam	≤4	S	1 g administered every 8 h
Cefazolin (*E. coli*, *K. pneumoniae*, and *P. mirabilis* for infections other than uncomplicated UTIs only) Cefazolin (*E. coli*, *K. pneumoniae*, and *P. mirabilis* for uncomplicated UTIs only)	≤2 ≤16	S	2 g administered every 8 h 1 g administered every 12 h
Ceftaroline	≤0.5	S	600 mg administered every 12 h
Cefepime	≤2	S	1 g administered every 12 h
	4	SDD	1 g administered every 8 h or 2 g administered every 12 h
	8 or zone diameter: 19-24 mm	SDD	2 g administered every 8 h (Because it is not possible to correlate specific zone diameters with specific MICs, an isolate with a zone diameter in the SDD range should be treated as if it might be an MIC of 8 µg/mL.)
Cefiderocol	≤4	S	2 g every 8 h administered over 3 h
Cefotaxime	≤1	S	1 g administered every 8 h
Ceftriaxone	≤1	S	1 g administered every 24 h
Cefoxitin	≤8	S	8 g per day (eg, 2 g administered every 6 h)
Cefuroxime	≤8	S	1.5 g administered every 8 h
Ceftazidime	≤4	S	1 g administered every 8 h

SC DISCUSSION (MAIN POINTS)

- There was concern with putting the Appendix E below the introduction and having the breakpoints repeated twice. It is duplicative.
- Pharmacy colleagues like having the breakpoint near the dose.

- From the laboratory perspective, the table should be below Table 2 because most people using this document are laboratories. The labs do not need dosing data daily.

A motion to create a new introduction section to Tables 2 and move Appendix E to below Tables 2 was made and seconded. Vote: 10 for, 2 against, 0 abstain, 2 absent (Pass)

Against Vote Reasoning:
- Appendix E will get lost by putting below Tables 2.

SC DISCUSSION (MAIN POINTS)
- Suggested name for the new table: "Doses used to establish breakpoints".
- Suggestion to look at EUCAST for an example to make the data less duplicative.
- The long list of "S, S, S" is taking up space. Consider removing the "S" column and/or the two middle columns. There can be special examples for cefepime.
- It is best practice for standards to only have a single table with all the information in one place, instead of having repeated information because it can easily confuse people.

A motion to remove two middle columns (Breakpoints and Interpretive Categories) and revise the last column "Dose" to be "Dosage Susceptible Breakpoint Is Based On" to delineate S vs SDD in Appendix E was made and seconded. Vote: 12 for, 0 against, 0 abstain, 2 absent (Pass)

ENTEROCOCCUS **AND LOW-LEVEL RESISTANCE DEFINITION AND COMMENT**
- Background
- Previous comment (30th ed and earlier):

(8) ***Rx:*** Combination therapy with ampicillin, penicillin, or vancomycin (for susceptible strains only), plus an aminoglycoside, is usually indicated for serious enterococcal infections, such as endocarditis, unless high-level resistance to both gentamicin and streptomycin is documented; such combinations are predicted to result in synergistic killing of the *Enterococcus*. For strains with low-level penicillin or ampicillin resistance when combination therapy with a β-lactam is being considered, also see additional testing and reporting information in Table 3J.[4]

- Current comment:

(9) ***Rx:*** Combination therapy with high-dosage parenteral ampicillin, amoxicillin, penicillin, or vancomycin (for susceptible strains only), plus an aminoglycoside, is usually indicated for serious enterococcal infections, such as endocarditis, unless high-level resistance to both gentamicin and streptomycin is documented; such combinations are predicted to result in synergistic killing of enterococci.

- TTWG Discussion and Recommendation
  - Confusion that the '(for susceptible strains only)' applied to beta-lactams but only for vancomycin.
  - The last sentence is not needed but perhaps can be reinstated in part for reference to Table 3K.

- Proposed comment: (9) *Rx*: Combination therapy with high-dosage parenteral ampicillin, amoxicillin, penicillin, or vancomycin ~~(for susceptible strains)~~, plus an aminoglycoside, is usually indicated for serious enterococcal infections, such as endocarditis, unless high-level resistance to both gentamicin and streptomycin is documented; such combinations are predicted to result in synergistic killing of enterococci. Refer to Table 3K for high-level aminoglycoside resistance testing.

SC DISCUSSION (MAIN POINTS)

- Consider minimizing comments that suggest treatment. Should refer people to institutional or national guidelines. There is a comment overhaul taskforce being discussed. Perhaps this can be a future task for them. This specific comment has been there for a long time along with other Rx comments.
- Most of the field has moved to ceftriaxone as a combination agent, so it seems a little prescriptive. It is not common to use ampicillin and an aminoglycoside for *Enterococcus*. The problem is that we do not want to suggest using an aminoglycoside alone, but you must test it for synergy.
- Consider recommending combination therapy with a high dosage beta lactam or vancomycin plus an aminoglycoside.
- The laboratory needs background knowledge that synergistic testing for high level resistance should be done.
- Suggestion to change "usually" to "may be" in the comment. Do not want the comment to sound like it is indicating the standard or usual treatment.

A motion to revise *Enterococcus* footnote b in Table 1I to state "Rx: Combination therapy with high-dosage parenteral ampicillin, amoxicillin, penicillin, or vancomycin, plus an aminoglycoside, may be indicated for serious enterococcal infections, such as endocarditis, unless high-level resistance to both gentamicin and streptomycin is documented; such combinations are predicted to result in synergistic killing of enterococci. Refer to Table 3K for high-level aminoglycoside resistance testing." was made and seconded. Vote: 13 for, 0 against, 0 abstain, 1 absent (Pass)

REVISE TOBRAMYCIN/*S. MARCESCENS* COMMENT

- Background
  - June 2022 summary minutes indicated that a suggestion was made to include *Serratia* and include a comment like *Proteus, Providencia,* and *Morganella*. SC agreed to include *Serratia marcescens* tobramycin MIC breakpoints with a comment.
  - M100 33rd edition comment (Appendix B footnote g) added that stated "*Serratia marcescens* may have elevated MICs to tobramycin. Isolates that test susceptible should be reported as susceptible."
  - Proposed comment revision: Tobramycin MICs for wild-type strains of *Serratia marcescens* tend to be higher than gentamicin MICs. Isolates may test intermediate or resistant to tobramycin but susceptible to gentamicin.
  - Discussed adding comment to Table 1A to tobramycin in tier 2.

SC DISCUSSION (MAIN POINTS)

- The MIC is reported as tested, so *S. marcescens* should not be in the tobramycin intrinsic resistance table. Labs are confused by gentamicin susceptible and tobramycin resistant, which is the reasoning behind the comment.
- There are lots of resistance mechanisms in Enterobacterales that test gentamicin susceptible and tobramycin resistant.
- The comment belongs in Table 2 because it is not intrinsically resistant.
- Note that in the SENTRY database 70% *Serratia* are susceptible by new breakpoints. Also, gentamicin susceptible and tobramycin resistant is seen in other Enterobacterales.
- *Serratia* is in the package insert for tobramycin.
- *Serratia* can have *aac* resistance gene which is specific to tobramycin; therefore, while on therapy patients may develop resistance. Counterpoint was made that just because the organism has *aac* does not make it resistant.

	• The Antifungal Subcommittee is dealing with a similar issue, and working on how to note organisms with high MICs where the definition of intrinsic resistance is not truly met. Consider discussing how they decided to handle these scenarios. • *Serratia* is tested and reported as tested, so there is no need for a comment. It is not intrinsic resistance. • Suggestion to inform labs when this AST profile is acquired to not perform repeat testing. • Suggestion to remove the comment. The comment is not being removed because it is untrue. • Good opportunity to educate labs that there can be modifying enzymes specific to tobramycin and gentamicin. • Some physicians do not believe tobramycin resistant and gentamicin susceptible phenotype, and regularly ask for AST to be repeated.
	A motion to remove *Serratia marcescens* tobramycin footnote g from Appendix B1 and have the Intrinsic Resistance Ad Hoc Working Group review was made and seconded. Vote: 13 for, 0 against, 0 abstain, 1 absent (Pass)
	OTHER CHANGES TO M100-34TH EDITION • Addition of a Breakpoint Additions Table in Table 3E-1 to include direct disk breakpoint changes. • Modifications to Table 3G to clarify *mecA* and PBP2a testing. • Revisions to consolidate all methicillin (oxacillin) resistant information into a single comment/location in Table 2C. • Add "lower" before respiratory tract in relevant locations. • Update Table 1M footnote b, Table 2H comment 16, and Table 3I footnote b to match The American College of Obstetricians and Gynecologists guidelines for *Streptococcus* spp. ß-hemolytic group. • Harmonization of language for the development of resistance and frequency of testing isolates where relevant. **POTENTIAL FUTURE CHANGES** • Addition of new *Salmonella*/*Shigella* Table 2. • Renumbering of Tables 1 to align with Tables 2 • Move the placement of procedures with modifications to the reference method to M02/M07 or as M100 Appendixes. • Consolidation of the anaerobe Tables 1O and 1P into one anaerobe table.
9.	**ADJOURNMENT** Dr. Lewis thanked the participants for their attention. The meeting was adjourned at 12:00 PM Central (US) time.

2023 JUNE AST MEETING SUMMARY MINUTES PLENARY 2: Monday, 5 June 2023 (In-person with virtual live streaming) 1:00 PM – 5:30 PM Central Standard (US) Time	
#	**Description**
1.	**OPENING** Dr. Lewis opened the meeting at 1:00 PM Central Standard (US) time.

2. **BREAKPOINTS WORKING GROUP (N. NARAYANAN AND M. SATLIN)**

SULBACTAM-DURLOBACTAM AD HOC WORKING GROUP REPORT

- Sulbactam-durlobactam is a targeted antibiotic for treatment of HABP/VABP caused by *Acinetobacter baumannii-calcoaceticus* complex.
- Summary of Data
  - ECV for combined surveillance and clinical trial isolates was sulbactam-durlobactam MIC of 4 µg/mL, which includes 98.1% of all isolates.
  - SUL-DUR exposure in plasma and ELF exceeds a PK/PD efficacy target of 1-log10 kill at an MIC ≤ 4 µg/mL.
  - Clinical cutoff was a sulbactam-durlobactam MIC of 4 µg/mL for isolates from patients treated with sulbactam-durlobactam in Part A.
  - Disk correlates for the proposed MIC breakpoints that minimized the error rates were ≥17 mm for susceptible and ≤13 mm for resistant.
- Proposed Interpretive Criteria of Intermediate Susceptibility
  - The proposed intermediate MIC value of 8 µg/mL includes the ECV for the clinical trial isolates
  - PTA for SUL-DUR MIC = 8 µg/mL based on durlobactam (AUC/MIC ≥ 10) across renal function categories ranges from 72.2% – 97.9% for free drug in plasma and 58.9% - 94.5% for total drug in ELF
  - 4 of 4 patients treated with SUL-DUR with baseline active bacterial core (ABC) isolates testing with sulbactam-durlobactam MIC = 8 µg/ml survived to 28 days
  - 3 of 4 demonstrated clinical cure at TOC
  - 2 of 4 demonstrated microbiologic eradication at TOC
- Sponsor Proposed Breakpoints for *Acinetobacter* spp.

	MIC (µg/mL)			Zone Diameter (mm)		
Pathogen	S	I	R	S	I	R
Acinetobacter spp.	≤4/4	8/4	≥16/4	≥17	14-16	≤13

S = susceptible; I = intermediate; R = resistant

Proposed Table 1 Placement:

- *Tier 1: antimicrobial agents that are appropriate for routine, primary testing and reporting*
- **Tier 2: antimicrobial agents that are appropriate for routine, primary testing but may be reported following cascade reporting rules established at each institution**

- AHWG Discussion and Recommendation
  - There were no significant concerns noted with the proposed MICs cutoffs of ≤4, S; 8, I; and ≥16, R.
  - There was discussion over cutoff for disk diffusion breakpoints.
  - The cutoffs fall within the M23 guidance.
  - The proposed cutoff led to an additional very major error as well as several isolates with MICs of 16 and 32 mg/L in the intermediate zone.

- Since sulbactam-durlobactam already retains high rates of activity against *Acinetobacter*, the working group felt there may be discussion regarding the trade-off to capture the entire cohort of susceptible MICs.
- Suggested that the sponsor may consider placing Sul-Dur in the tier 3 category instead of tier 2.
- Suggested to include data on the reproducibility of MICs, especially in the 4-8 mg/L range between the S and I cutoff.

- BPWG Discussion and Recommendation
  - Question of reproducibility concerns for QC strains (Sharon Cullen said there were none)
  - DD breakpoints
    - Discrepancy noted in the way DD error rates are calculated between CLSI M23, M52, and the FDA
    - 19/14 mm performed better than FDA-approved DD BP (17/13 mm)
  - Why did FDA favor 17/13 mm?
    - Lack of concern with only one additional VME with 17/13 mm – stressing selecting optimal breakpoint
    - Both 19/14 mm and 17/13 mm meet M23 criteria
  - ELF exposure
    - Higher ELF penetration in mice (vs humans) -> lower AUC/MIC threshold for kill
    - Only ELF data in healthy volunteers (no patients)
  - Motion to accept proposed MIC breakpoints of 4/4, 8/4, 16/4 mg/L. WG Vote: 8-0-1-2.
  - Motion to accept DD breakpoint of 17/13 mm. WG Vote: 8-0-1-2.
  - Motion for tier 2 placement for Table 1. WG Vote: 8-0-1-2.
  - Discussion: concern to put novel agent (designed specifically for *A. baumannii*) in tier 3 given limited number of new drugs available for this pathogen; better efficacy against colistin

SC DISCUSSION (MAIN POINTS)

- Question: What does the Intermediate category mean? The percent target attainment (PTA) is below 90% and only 4 patients in the study has this MIC. Does the intermediate category mean technical variability, or does it pertain to exposure? Should the breakpoint be 4/8 µg/mL without an intermediate category? Every time CLSI sets a breakpoint without an intermediate category, it is regretted later. There is agreement that there is significant PK/PD target attainment drop off at an MIC of 8 µg/mL. PTA was built on simulated patients per renal category. The phase 3 simulated clinical trial patient population shows that a target attainment of >90% at an MIC of 8 µg/mL was achieved. CLSI's definition of intermediate fits perfectly with this scenario: "A category defined by a breakpoint that includes isolates with MICs or zone diameters within the intermediate range that approach usually attainable blood and tissue levels, and for which response rates may be lower than susceptible isolates."
- Concerns about drug placement in tier 2. What about hospitals with a carbapenem resistant *Acinetobacter baumannii* (CRAB) problem? Institutions with a CRAB problem can primary test; however, there is not an easy way for labs to test this drug in house. It would be confusing to place it in tier 2 at this time. It best fits in tier 3 for now.
- Tier placement for drugs is important for future development of commercial systems to include new drugs.
- 2019 SENTRY data on drug susceptibility rates suggest that there are not many drug options against *Acinetobacter*. Cefepime: 50% susceptible; Meropenem: 58% susceptible; Pip/tazo: 50% susceptible.
- Based on the tier definitions, this belongs in tier 3. It does not preclude labs from choosing to perform primary testing.
- SENTRY data says 13,000 of 22,000 *Acinetobacter baumannii* isolates are XDR.
- Some individual labs here do not see many CRAB.

- There is concern that providers will use colistin against *Acinetobacter baumannii* because they do not know this drug is available. It should go in tier 2 to promote better awareness.
- Cefiderocol is in tier 3, so people may argue this new drug also belongs in tier 3. However, sulbactam-durlobactam is a drug specifically designed for *Acinetobacter baumannii*, and has clinical trial data specifically for this indication, which makes it different from cefiderocol. It belongs in tier 2.
- Question: How to we reconcile this breakpoint with the ampicillin-sulbactam breakpoint? Does the ampicillin-sulbactam breakpoint need to be re-evaluated? New data going to be presented at ASM Microbe that the large ampicillin-sulbactam dose recommended by IDSA does not really have much of an effect. Possible future direction for the BPWG is to look at ampicillin-sulbactam breakpoint.
- Question: How come durlobactam does not improve the activity of imipenem when the two drugs are used in combination? Sponsor has data showing MICs of sulbactam-durlobactam look better than MICs of imipenem plus durlobactam, so there could be another mechanism of resistance such as porins or efflux pumps that are contributing to the poor performance of imipenem in addition to beta-lactamases. It was a surprise to the sponsor too.
- Question: What did FDA say with regards to not adding a comment about combination treatment with imipenem? This drug was tested in combination with high dose imipenem. PK/PD data shows sulbactam-durlobactam can cover MICs of 4 µg/mL. *In vitro* MIC data says sulbactam-durlobactam is doing the heavy lifting.
- The sharp PTA drop off starting at MICs of 4 µg/mL and 8 µg/mL are concerning and precision of laboratories ability to test is going to be important. Isolates with an MIC of 8 are PBP mutants and the sponsor will soon publish data showing there is a benefit to adding a carbapenem in these specific strains.
- One reason the working group favored the more conservative breakpoints is because there is not a lot of data on disk diffusion reproducibility. Do not want to call an 8 µg/mL as susceptible.

A motion to accept the sulbactam-durlobactam MIC breakpoints for *Acinetobacter* spp. (S≤4/4, I 8/4, R≥16/4 µg/mL) was made and seconded. Vote: 13 for, 0 against, 0 abstain, 1 absent (Pass)

A motion to accept the sulbactam-durlobactam disk breakpoints for *Acinetobacter* spp. (S≥17, I 14-16, R≤13 mm) was made and seconded. Vote: 13 for, 0 against, 0 abstain, 1 absent (Pass)

SC DISCUSSION (MAIN POINTS)

- If ampicillin-sulbactam is susceptible, then suppress sulbactam-durlobactam.
- Concerns with trusting ampicillin-sulbactam. There are testing issues.
- Suggestion for the cascade testing to be based off a carbapenem.
- Industry does not care about tier placement. This drug meets an important need and that will drive customer demand.

A motion to place sulbactam-durlobactam in Table 1A tier 3 was made and seconded. Vote: 10 for, 3 against, 0 abstain, 1 absent (Pass)

Against Vote Reasoning:

- Preferred tier 2 placement because of the paucity of drugs with reliable *in vitro* activity against *A. baumannii*.

SC DISCUSSION (MAIN POINTS)

- There was discussion around what triggers the cascade: carbapenem or ampicillin-sulbactam. There was uncertainty on the cascading.

- The discussion was made to place sulbactam-durlobactam in tier 3 without any cascading.

STENOTROPHOMONAS MALTOPHILIA AD HOC WORKING GROUP REPORT

- Differences in Recognized Breakpoints for *Stenotrophomonas maltophilia*

	CLSI			EUCAST		FDA	
	Category	MIC (µg/mL)	DD (mm)	MIC (mg/L)	DD (mm)	MIC (µg/mL)	DD (mm)
Ticarcillin-clavulanate	O	S ≤16/2, I 32/2-64/2, R ≥128/2	---	XX	XX	XX	XX
Ceftazidime	B	S ≤8, I 16, R≥32	---	XX	XX	S ≤8, I 16, R≥32	--
Cefiderocol#	B	S ≤1	S ≥15	S ≤ 0.001 mg/L "off scale" breakpoint (IE).	≥20 mm corresponds with MIC≤2	XX	XX
Minocycline	A	S ≤4, I 8 R ≥16	S ≥19, I 15-18, R ≤14	XX	XX	XX	XX
Levofloxacin	A	S ≤2 I 4 R ≥8	S ≥17, I 14-16, R ≤13	XX	XX	XX	XX
Trimethoprim-sulfamethoxazole	A	S ≤2/38, R≥4/76	S ≥16 I 11-15 R ≤10	S=0.001, I ≤2, R>4 mg/L*	S>50 mm* I16-50 R<16 mm	XX	XX
Chloramphenicol	C	S ≤8, I 16, R≥32	---	XX	XX	XX	XX

* Breakpoints are based on PK/PD properties, MIC distributions, and limited clinical data. *Reading guide provided trimethoprim component only. MICs ≤2 as intermediate, which requires the use of a higher dosing regimen, 240 mg (trimethoprim component) intravenously every 12 hours

Slide courtesy of Amy Mathers

- Summary of Breakpoint Changes to Date
  - June 2022:
    - Levofloxacin presented
    - AHWG advocated for BP change from ≤2 S; 4 I; ≥8 R to ≤1 S; 2 I; ≥4 R
    - Did not pass; no changes made
  - January 2023:
    - Ceftazidime breakpoint removed in light of historical data, low AST reproducibility, L1/L2 beta-lactamases
    - Minocycline breakpoint lowered from ≤4 S; 8 I; ≥16 R to ≤1 S; 2 I; ≥4 R

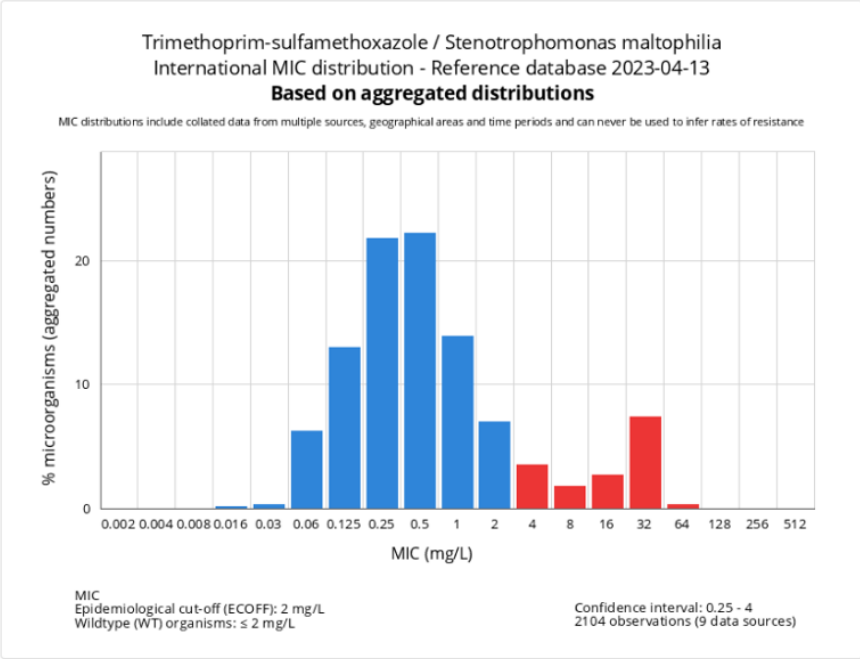
TRIMETHOPRIM-SULFAMETHOXAZOLE

- TMP/SMX PK/PD Analysis Summary and Conclusions
  - Limited dose response was observed for TMP/SMX against *S. maltophilia* in the *in vitro* chemostat PD model (IVM) and time kill studies
  - At most, clinically equivalent AUC exposures achieved only stasis to 0.5 log10 CFU reductions

- A 1 log10 CFU reduction threshold was not identified; however, the stasis threshold was 67.4 in the IVM and not identified in the time kill studies
- In contrast, *E. coli* at the same MIC and TMP/SMX AUC exposure demonstrated CFU reductions consistent with current CLSI susceptibility breakpoints (≤2/38 µg/mL)
- Monte Carlo simulation demonstrates static exposures are achievable up to an 0.5/9.5 µg/mL using ≥10 mg/kg/daily doses
- *In vivo* neutropenic rabbit pneumonia model demonstrated reductions in organism burden compared to untreated controls but did not measure PK concentrations so translation of 5 mg/kg IV q12h dosing is unknown (hopefully future work with this model!)

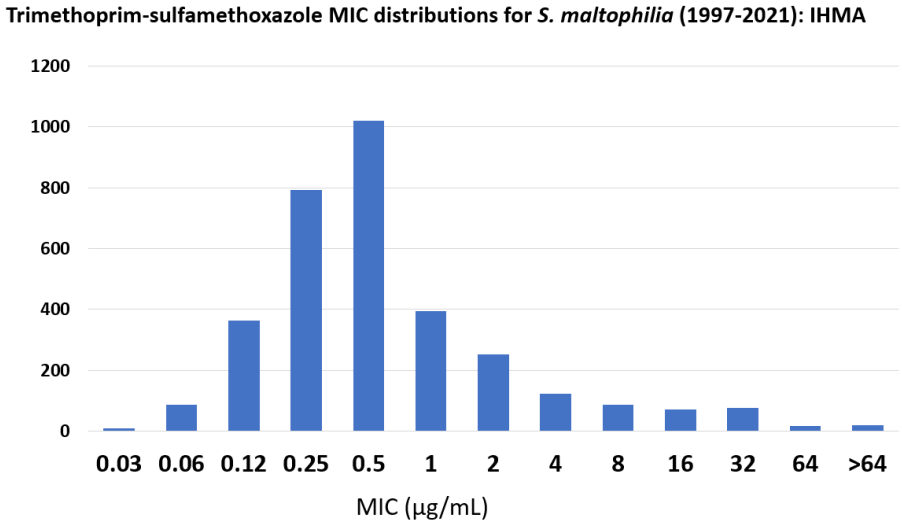
- TMP/SMX Clinical Outcomes Analysis
  - TMP/SMX vs Levofloxacin Summary
    - Meta-analysis of 12 studies prior to 2018 comparing LVX and TMP/SMX showed no difference in outcomes
    - One single center study of monomicrobial *S. maltophilia* infection (predominantly pneumonia [PNA]), no difference in treatment groups, but more emergence of resistance to LVX
    - One single center study of monomicrobial *S. maltophilia* BSI showed trend towards better outcomes with LVX-containing regimens when active
  - TMP/SMX vs Minocycline Summary
    - One single center study of *S. maltophilia* infection (predominantly PNA) found minocycline had a lower potential outcome mean 30-day mortality as compared to TMP/SMX: 5.5% vs 15%, p = 0.011
    - One single center study of *S. maltophilia* infections found no differences between TMP/SMX and minocycline
- TMP/SMX Microbiology Analysis

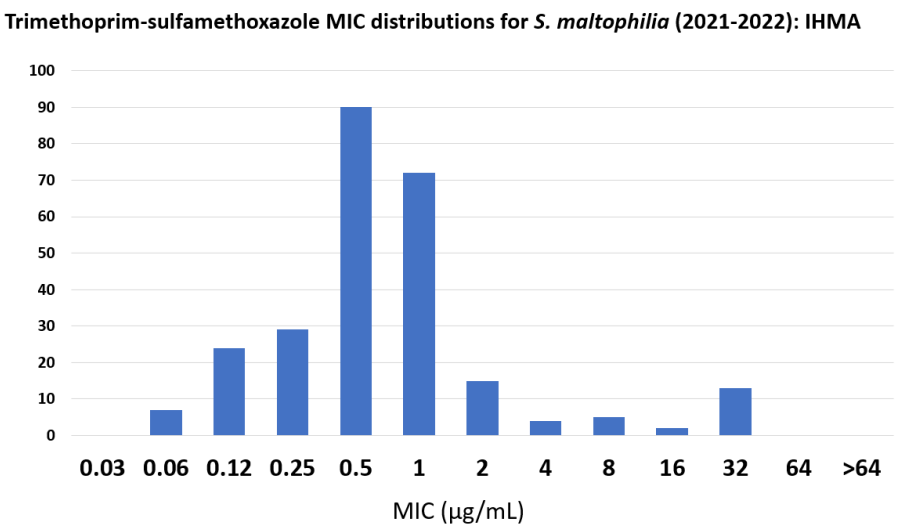
EUCAST: TMP/SMX MIC Distribution



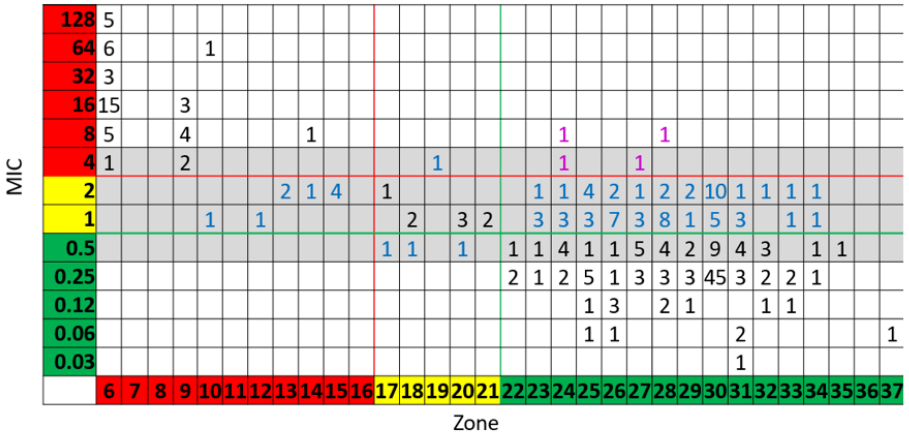
Note: We also saw a difference for EUCAST Minocycline MIC distribution compared to JMI and IHMA data last meeting. The JMI and IHMA data matched, so we believe the data from JMI and IHMA is representative of modern populations.

	Percent of Distribution	
MIC	JMI	EUCAST
> 4	3.3	12.1
4	1.3	3.5
2	2.2	6.9
1	3.1	13.9
≤0.5	90.1	63.6
Total	100	100.0





IHMA data also indicate a likely ECV of 2 µg/mL, similar to EUCAST.



Isolates		
Total	Susceptible	Resistant
261	128	51

	Data Source	
	2003 CLSI	Khan/Humphries
# Isolates	152	109

Agreement / Errors	Percent	Raw numbers
VME	8%	4/51
ME	0%	0/128
MI	30%	78/261
CA	69%	179/261

MIC Range 2-dilution intermediate	Number in MIC Range	VME	ME	MI
≥I +2	45	2/45 (4%)	N/A	0/45 (0%)
I +1 to I - 1	128	2/128 (1.6%)	0/128 (0%)	78/128 (60%)
≤I -2	88	N/A	0/88 (0%)	0/88(0%)

MIC Range	Acceptable Discrepancy Rates M23 6.3.2 Table 7		
Dilution Intermediate	VME	ME	MI
≥I +2	<2%	N/A	<5%
I + 1 to I - 1	<10%	<10%	<40%
≤ I -2	N/A	<2%	<5%

- AHWG Discussion and Recommendation
  - Four options discussed:
    - Option 1: Keep BP the same, but add comment about combination therapy only
    - Option 2: Remove BP in entirety given lack of cidal activity across studies and lack of robust clinical trials
    - Option 3: Change BP to 'I' only ≤2/38, R≥4/76 with combination therapy recommended for serious infections based on lack of any dose response for isolates between 0.25 and 2 mg/L, in contrast to *E. coli* which behaves as expected
    - Option 4: Introduce intermediate category and change BP to ≤ 0.5/9.5 (S), 1/19 – 2/38 (I), ≥ 4/76 mg/L (R)
  - AHWG recommended option 4. AHWG Vote: 7-0-2-1.
    - Rationale in support:
    - 90% of isolates have MIC of ≤ 0.5 mg/L
    - *In vitro* chemostat model stasis target can reach 90% PTA using 5 mg/kg q12h dose
    - We see a decrease in mortality with active therapy, but can push providers away from use with higher MIC values so hopefully can improve outcomes
    - Rationale Against: Not all the commercial systems have the lower dilution; however, several do.
- BPWG Discussion and Recommendation
  - Why differences in EUCAST MIC distributions? Inflated for clinical isolates – not surveillance.

- What does Intermediate mean for option #4?
- Feelings about option #1 (contrasting to levofloxacin BP). M100 levofloxacin has comment not to use alone for therapy.
- Need to based changes to breakpoint on outcomes data
- All drugs lack the data needed to meet standards for setting/revising breakpoints – caution in changing breakpoint based on *in vitro* model
- What dosing is option #4 based on?
- Motion to accept proposal 4 as listed. WG Vote: 7-1-0-4.
- Motion to add same comment from levofloxacin about not using alone (Rx: Levofloxacin should not be used alone for antimicrobial therapy.). WG Vote: 8-0-0-4.
- Motion to accept disk correlates as is even with error rates. WG Vote: 8-0-0-4.

SC DISCUSSION (MAIN POINTS)

- Concern stated with how the intermediate range will be decided and what it is based on.
- Option 4 is a good compromise. Worry about combination therapy dosing.
- AHWG was cautious about the intermediate range with having one set of MIC values from location. Intermediate range provides a little bit of buffer. With additional MIC distribution data, there are more isolates in 1-2 range.
- For the PTA analysis, there were not a lot of pharmacokinetics data.
- A study showed that those patients that received the appropriate therapy did better than not having active therapy. Active therapy was not well defined, but it could have been somewhere in the susceptible or intermediate range. Because indications were seen that combination therapy would be more beneficial, if physicians seeing an I might be more likely to use combination therapy than if there was an S in a comment alone.
- The increasing of exposure does not help with killing of the organism. Lowering of the breakpoint does not make sense.
- EUCAST has intermediate only. Suggestion to handle like colistin.
- Combination therapy potentially helps. It is important to educate that when treating for *Stenotrophomonas* more than one drug needs to be used.
- Suggestion to add similar comment used for tobramycin for *Pseudomonas* stating that "the breakpoints were based on Pk/PD target attainment analysis with an endpoint of net bacterial stasis".
- AHWG and BPWG did not review the new data from IHMA and there is concern with the new data that option 4 does not work because lowering the susceptible breakpoint to ≤0.5/9.5 µg/mL would cut into the wild-type distribution.
- Concern that it if the breakpoints are lowered it is going to be harder to test the MIC. The disk diffusion data is not great, and lowering is making it worse.
- Interest in the AHWG generating new disk data and not removing the disk breakpoint at this time.
- Not confident that the S breakpoint meets CLSI definitions.
- Concerns with international treatment of patients with only I and R breakpoints.

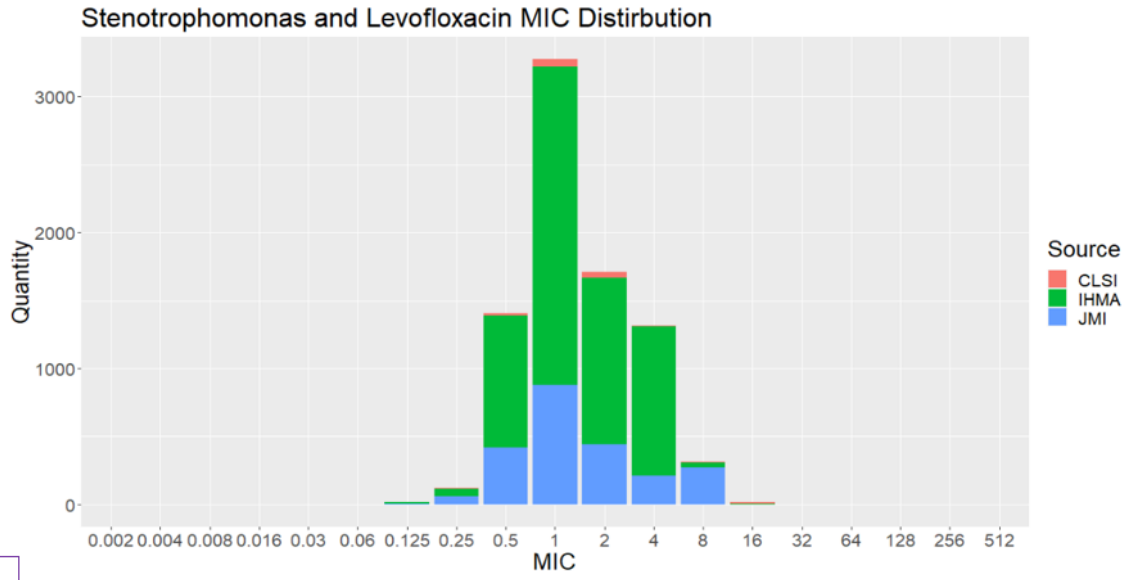
A motion to not revise the trimethoprim-sulfamethoxazole MIC breakpoint for *Stenotrophomonas maltophilia* and to add a comment stating, "Trimethoprim-sulfamethoxazole should not be used alone for antimicrobial therapy." was made and seconded. Vote: 10 for, 3 against, 0 abstain, 1 absent (Pass)

Against Vote Reasoning:

- Liked the I and R only breakpoints option.
- Intermediate only sends a clear message that it is not optimal therapy, and it is an extra push for combination therapy.

	LEVOFLOXACIN
	• Rationale for Revisiting
	  ○ Breakpoint changes:
	  ▪ Removed ceftazidime BP
	  ▪ Lowered minocycline BP
	  ▪ Proposed to lower TMP/SMX BP
	  ○ Do not want to push prescribers to favor levofloxacin in light of:
	  ▪ Fratoni/Kuti data suggest breakpoint of 0.5 mg/L (96% PTA), or 1 mg/L (72% PTA) would be appropriate
	  ▪ CLSI breakpoints did not discriminate patients based on risk-adjusted mortality outcome in multi-center study, but some limitations (Sarzynski S et al.)
	  ▪ Retrospective studies with heterogenous patient populations, study goals, and outcomes
	  ▪ Very limited data on outcomes according to MICs
	• Presented in June 2022 did not pass.
	  ○ Concern about proposed BPs cutting into the WT distribution
	  ○ Current BP of 2 mg/L already splits the WT distribution
	• *Stenotrophomonas* Levofloxacin MIC Distribution

- ihma: 2017 – 2021
  - 7,340 isolates
- JMI: 2015 – 2020
  - 2,293 isolates
  - MICs >4 were all merged into 8
- CLSI: 2003
  - 152 isolates
  - 5labs (~30 isolates each)



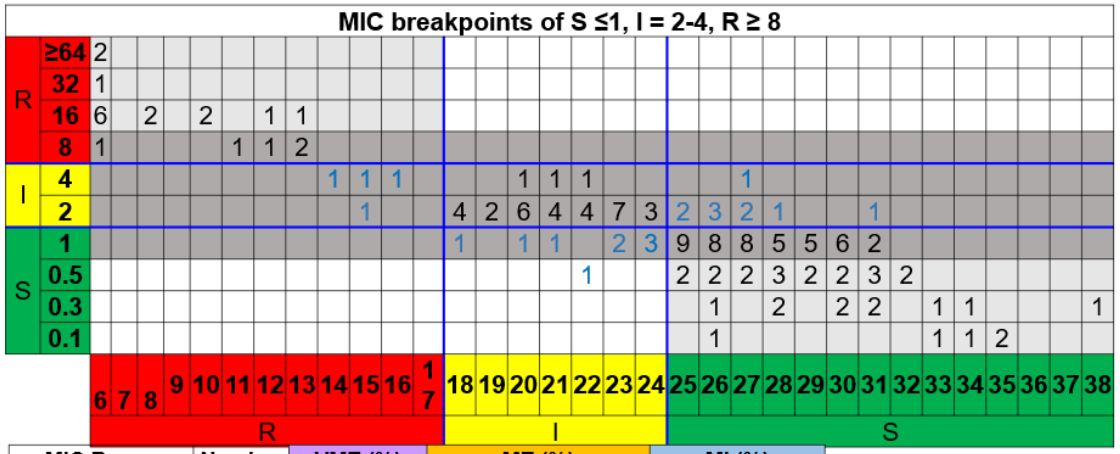
Note: Due to the scale of the y-axis, low frequency MIC counts are not visible on this figure

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

- AHWG MIC Discussion and Recommendation
  - Option 1: Lower breakpoint to ≤1 mg/L (≤1 S; 2 I; ≥4 R). AHWG Vote: 4-5-0-1.
    - Rationale for yes votes:
    - PK/PD data support lowering the breakpoint
    - Global data don't support leaving it at 2 mg/L
    - Mortality outcomes are increased across the board
    - Rationale for no vote:
    - Clinical data do not demonstrate a signal that mortality is improved with a breakpoint of 1 rather than 2 mg/L but retrospective data have limitations
    - Lowering to 1 will likely push providers to use more SXT which is potentially harmful to patients, based on one thigh infection model study
    - Will split the WT distribution
  - Option 2: Lower breakpoint to ≤1 mg/L (≤1 S; 2-4 I; ≥8 R). AHWG Vote: 7-2-0-1.
    - Rationale for yes votes:
    - R BP stays where it is, but lowering BP still achieved but hopefully less cutting into the WT distribution

- Might not push more SXT use, but also may lead to increased cefiderocol use
- Still leaves levo as an option but perhaps pushes toward more combination therapy and/or additional drug approval
- Rationale for no vote:
- Clinical data do not demonstrate a signal that mortality is improved with a breakpoint of 1 rather than 2 mg/L but retrospective data have limitations
- Lowering to 1 will likely push providers to use more SXT which is potentially harmful to patients, based on one thigh infection model study
- Will split the WT distribution
- Need more data using pulmonary model to feel confident in PK/PD assessment

- *Stenotrophomonas* Levofloxacin Disk Diffusion Breakpoints



2003 CLSI Data	
Isolates Category	Number
Total Isolates	152
Total Resistant	20
Total Susecptible	85
Total Intermediate	47

Agreement/ Errors	Percent	Raw numbers	CLSI Acceptable Criteria
VME	0.0%	0/20	<3%
ME	0.0%	0/85	<3%
MI	15.1%	23/152	<10%
CA	84.9%	129/152	>90%

MIC Range	Number	VME (%)	ME (%)	MI (%)
≥I +2	15	0/15 (0%)	N/A	0/15 (0%)
I + 1 to I - 1	103	0/103 (0%)	0/103 (0%)	22/98 (21%)
≤ I -2	34	N/A	0/34 (0%)	1/34 (2.9%)

MIC Range	Acceptable Discrepancy Rates M23 6.3.2 Table 7		
2- Dilution Intermediate	VME	ME	MI
≥I +2	<2%	N/A	<5%
I + 1 to I - 1	<10%	<10%	<40%
≤ I -2	N/A	<2%	<5%

Proposed Disk Breakpoint	**Vote:**
≤ 17 is Resistant	Yes: 9
18-24 is Intermediate	No: 0
≥ 25 is Susceptible	Absent: 1

Used dBETS error-rate bounded method

- BPWG MIC Discussion and Recommendation

- Creating 2 dilution intermediate range does not solve bisecting WT distribution problem
- Class comment about combo therapy and lack of necessary data
- Move *Stenotrophomonas* to M45?
- Motion to accept proposal #2 for 1/2-4/8 – no second – motion died

MINOCYCLINE

- Minocycline *Stenotrophomonas* Disk Diffusion Breakpoints History
  - January 2023: Minocycline breakpoint lowered
    - Old: ≤4 S; 8 I; ≥16 R
    - New: ≤1 S; 2 I; ≥4 R
  - Breakpoints WG asked for new data to be generated based on concerns from the committee's personal experience for minocycline disk diffusion
- Data and Proposed Breakpoints

Minocycline Disk Diffusion Breakpoint

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

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

Vote:
Yes: 9
No: 0
Absent: 1

Analysis – meets CLSI requirements (6.3.1)

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

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

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

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

Note: 70% of VMEs are from one media type

144

- BPWG Discussion and Recommendation
  - Motion to accept disk BPs (S≥26, I 21-25, R≤20). WG Vote: 8-0-0-4.

SC DISCUSSION (MAIN POINTS)

- Question: For the media with the very major errors was there any indication there was a problem with the QC? QC (*E. coli* 25922) was on the higher side for all laboratories with one media type. Any time the QC did not pass the replicates associated were not included in the data. QCWG will look at minocycline disk QC in January. May need to add a statement about media differences and the association with very major errors. The media manufacturers have not been made aware yet of the study's findings, but the AHWG plans to communicate to them.

A motion to accept the minocycline disk breakpoints for *Stenotrophomonas maltophilia* (S≥26, I 21-25, R≤20 mm) was made and seconded. Vote: 11 for, 0 against, 0 abstain, 3 absent (Pass)

CEFEPIME ENTEROBACTERALES BREAKPOINT AD HOC WORKING GROUP REPORT

- Current Cefepime Enterobacterales MIC Breakpoints

Organization	Susceptible	Intermediate		Resistant
CLSI (1999)	≤8	16		≥32
CLSI (2014)	**≤2** 1g every 12h	**4** (susceptible dose-dependent) 1g every 8h or 2g every 12h	**8** (susceptible dose-dependent) 2g every 8h	**≥16** -
EUCAST	**≤1** 1g every 8h or 2g every 12h	--		**≥8**
FDA	**≤2** -	**4-8** "For isolates of Enterobacterales with intermediate susceptibility, use a dose of 2g every 8 hours in patients with normal renal function."		**≥16** -

- M100-S33 Appendix E

Breakpoints and Interpretive Categories				
	Susceptible		SDD	
	MIC	Dose	MIC	Dose
Cefepime	≤2 µg/mL	1g every 12 h	4 µg/mL	1 g every 8 h or 2 g every 12 h
			8 µg/mL	2 g every 8 h

- Cefepime MIC Distributions for Enterobacterales Summary
  - Using EUCAST data, the epidemiological cutoff value for cefepime against Enterobacterales is 0.125 µg/mL
  - Using US SENTRY data, most Enterobacterales isolates have cefepime MICs of ≤0.5 µg/mL
  - Unless cefepime susceptibility criteria is set at ≤1 µg/mL, it is unlikely to bisect the wild type cefepime MIC distribution for Enterobacterales
  - The portion of Enterobacterales isolates with cefepime MICs of 4-8 ug/mL is approximately <3%
- Cefepime PK/PD Summary
  - Cefepime-specific %fT>MIC thresholds differ between pre-clinical and clinical outcomes studies
  - Cefepime PTA is impacted primarily by %fT>MIC threshold, renal function, and dosing regimen
  - 1g Q12h over 0.5h does not achieve >90% PTA against all susceptible MICs (≤2 mg/L)
  - 2g Q12h or 1g Q8h over 0.5h achieve >90% PTA against all susceptible MICs (≤2 mg/L)
  - 2g Q8h is necessary to achieve >90% PTA against SDD MICs (4-8 mg/L)
  - Extended infusion over 3-4h necessary to ensure adequate PTA at 8 mg/L
- Cefepime Clinical Outcomes Data
  - No clear clinical signals indicating patients infected with Enterobacterales isolates with cefepime MICs of 4-8 µg/mL have poorer outcomes than patients with cefepime MICs of ≤2 µg/mL
  - Data insufficient to adequately investigate the most effective cefepime dose or dosing strategy associated with optimal outcomes for patients infected with Enterobacterales isolates with cefepime MICs of 4-8 µg/mL
  - The one observational study that did compare high-dose extended infusion vs standard infusion demonstrated a benefit with extended-infusion cefepime
  - Several observational studies suggest that clinical outcomes are worse with cefepime compared to carbapenems for the treatment of ESBL-producing infections
- ESBL Issue
  - Low ECV (0.125 mg/L) for cefepime against the Enterobacterales results in some ß-lactamase-producing strains, including ESBL, being categorized as susceptible or SDD. Would not be significantly impacted by breakpoint change.
  - Pre-clinical and clinical PK/PD data demonstrate efficacy of cefepime is based on %fT>MIC, regardless of underlying resistance mechanism

- CLSI no longer recommends routine ESBL screening and reporting rules allow cefepime to be reported as susceptible even if ESBL identified pheno or genotypically
- Ultimately, laboratories should adopt the current breakpoints and discuss with appropriate stakeholders (ie, antimicrobial stewardship) how these results should be reported for patient care at their respective institutions

- CLSI Reporting Recommendations
  - Q: If we are still doing extended-spectrum ß-lactamase (ESBL) testing and implement the new cefepime breakpoints, do we change a susceptible or SDD result to resistant for ESBL-positive isolates?
  - A: No. When CLSI changed the other cephem breakpoints in 2010, the recommendation to perform routine ESBL testing was eliminated. When using the new cefepime breakpoints, there is no need to perform routine ESBL testing for patient reporting purposes. However, ESBL testing might be done for infection control or epidemiological purposes.
  - The revised breakpoints eliminate the need to perform ESBL screen and confirmatory tests for making treatment decisions. Phenotypic tests for ESBL detection and confirmation are less accurate when multiple enzymes are present (eg, false-negative results occur when isolates express both ESBLs and AmpC-type enzymes) (13) and the presence of multiple enzymes are more common in contemporary isolates (4, 8). The MIC of an isolate correlates better with clinical outcome than knowledge of resistance mechanisms (eg, ESBLs) (16).
- M100 ED33:2023: Table 3A, Appendix H, and Table H3
  - Detecting a resistance marker does not necessarily predict therapeutic failure of an antimicrobial. Conversely, the absence of a genetic marker does not necessarily indicate susceptibility
  - Reporting Results From Extended-Spectrum ß-Lactamase Resistance and Molecular Tests for Enterobacterales:
  - Detection of SHV, TEM, or CTX-M ESBL target:
    - Variable resistance to 3rd- and 4th-generation cephalosporins (eg, S or R to ceftriaxone, cefotaxime, ceftazidime, and/or cefepime)
    - Expected phenotype for some ESBL strains. Check cefepime using a reference method if S
    - Report phenotypic results as found, including reference cefepime result; consider reporting presence of molecular target per institutional protocol
  - Comments:
    - 2) Molecular assays can detect the presence of specific ß-lactamase genes but cannot exclude the presence of other ß-lactamase genes or resistance mechanisms, or novel variants with changes in primer or probe annealing sites. Therefore, phenotypic resistance should always be reported.
    - 3) Isolates with phenotypic susceptibility despite the presence of a resistance determinant may indicate the potential for resistance to emerge during therapy.
    - 6) Susceptibility of ESBL-carrying strains to cefepime is variable.
- EUCAST Expert Rules v 3.2 on Enterobacterales
  - The cephalosporin breakpoints for Enterobacterales will detect all clinically important resistance mechanisms (including ESBL and plasmid mediated AmpC). Some isolates that produce beta-lactamases are susceptible to 3rd or 4th generation cephalosporins with these breakpoints and should be reported as tested, ie, the presence or absence of an ESBL does not in itself influence the categorization of susceptibility. ESBL detection and characterization are recommended for public health and infection control purposes
- AHWG Discussion and Recommendation
  - Options:
    - Option 1: No changes
    - Option 2: Change to 2/4/8 µg/mL or 1/2-4/8 µg/mL (EUCAST)

- Option 3: Change SDD (ie, 4-8 µg/mL) to 2 g every 8 hours over 30 minutes
- Option 4: Change SDD to extended-infusion dosing

- All 5 members voted to leave breakpoints where they are
- For cefepime susceptible isolates (ie, MICs ≤2 µg/mL) add comment such as "MICs based on a cefepime dose of 1 g every 8h or 2 g every 12h over 30 minutes"
- For cefepime SDD isolates (ie, 4-8 µg/mL) add comment such as "MICs based on a cefepime dose of 2 g every 8h as a 3-hour infusion"
- Add some version of "Caution is advised with prescribing cefepime if the isolate is known to be producing an ESBL enzyme"

	S µg/mL	SDD µg/mL	R µg/mL
CLSI	≤2	4-8	≥16
FDA	≤2	4-8	≥16
EUCAST	≤1	--	≥8
Proposal	≤2	4-8	≥16

- BPWG Discussion and Recommendation
  - May need to change cascade reporting rules in Table 1 for carbapenem resistant organism (CRO)-NS isolates and cefepime susceptibility
  - Concern regarding the use of cefepime for ESBLs and deferring to labs to decide how to handle reporting of cefepime for ESBLs without CLSI providing explicit enough guidance
  - There are often one or more other enzymes present in these isolates such as OXA-1 which would not be detected by current molecular tests
  - Motion to keep current BPs with comment that S BP is based on a dose of 2g Q12h or 1g Q8h and SDD is based on 2g Q8h over 0.5h or >/=3h
    - Was in favor of 'or' as extended infusion may not be necessary in all patients
    - Consensus from the group was that dosing used to base BPs on should be based on available data therefore extended infusion should be recommended for SDD MICs
    - Failed 1-7-0-4
  - Motion to keep current BPs with comment that S BP is based on a dose of 2g Q12h or 1g Q8h and SDD is based on 2g Q8h as a 3h infusion. WG Vote: 8-0-0-4.
  - Request from BPWG that Table 1 WG evaluate the ESBL issue with cascade reporting

SC DISCUSSION (MAIN POINTS)

- The working group wants to keep the breakpoint, but change the dosing based on PTA.
- The recommended dose is still in line with FDA dosing, just adding an infusion time. There should not be an impact on labs or manufacturers.

A motion to not revise the cefepime MIC breakpoints for Enterobacterales and to add a comment stating, "The susceptible breakpoint is based on a dose of 2g Q12h or 1g Q8h and SDD is based on 2g Q8h as a 3h infusion." was made and seconded. Vote: 13 for, 0 against, 0 abstain, 1 absent (Pass)

MEROPENEM-VABORBACTAM OXA-48 AD HOC WORKING GROUP REPORT

- Challenges with certain new ß-lactam/ß-lactamase Inhibitors vs. OXA-48-producing Enterobacterales
  - Relebactam and vaborbactam do not inhibit OXA-48 carbapenemase
  - Meropenem-vaborbactam (MEM-VAB) susceptible breakpoint is 2 dilutions higher than meropenem alone
  - Based on higher dose (2 g q8h vs. 1 g q8h) AND prolonged infusion (over 3 hours instead of 30 minutes)
  - Strains can test susceptible to MEM-VAB, but intermediate or resistant to meropenem
- Current CLSI Breakpoints

	CLSI Breakpoints, mg/L		
	Susceptible	Intermediate	Resistant
Ceftazidime	≤ 4	8	≥16
Ceftazidime/avibactam	≤ 8/4	-	≥ 16/4
Imipenem	≤ 1	2	≥4
Imipenem/relebactam	≤ 1/4	2/4	≥4/4
Meropenem	≤ 1	2	≥4
Meropenem/vaborbactam	≤ 4/8	8/8	≥16/8

- Concern: Ineffective therapy with meropenem-vaborbactam vs. OXA-48-producing Enterobacterales?
  - OXA-48-producing Enterobacterales often have meropenem-vaborbactam (MEM-VAB) MICs of 2/8-4/8 µg/mL
  - Labs may not know a carbapenem-resistant Enterobacterales (CRE) isolate is an OXA-48-producer and report these isolates as susceptible
  - Patients may be treated with MEV for OXA-48-producing Enterobacterales with MICs of 2/8-4/8 µg/mL
  - Is MEV effective *in vivo* for OXA-48-producing isolates with MIC values of 2/8-4/8 µg/mL?
- AHWG Discussion and Recommendation
  - Clinical relevance to problem:
    - OXA-48-producing Enterobacterales becoming more prevalent in USA
    - 4.6% of all CRE 2019-2021 from JMI data (8.2% in 2021)
    - Most labs don't perform testing to determine presence of and type of carbapenemase
    - Similar issue could apply to imipenem-relebactam (poor *in vitro* activity in neutropenic thigh model) but don't have different imipenem breakpoints like with MEM-VAB/MEM
  - Concern about lowering MEM-VAB breakpoints:
    - Could remove an effective drug for patients with KPC-producing Enterobacterales with MICs of 2-4 µg/mL (no *in vivo* data with strains like this)
    - Lack of consistency if make same breakpoint for MEM and MEM-VAB given:
    - Higher dosage of meropenem in MEM-VAB
    - Prolonged infusion with MEM-VAB
  - *In vivo* findings of concern only from a single lab with no confirmatory clinical data
  - Consensus that labs should be testing CRE isolates for carbapenemase
    - Lateral flow assays are relatively inexpensive
    - Many clinical labs in the USA have the capacity and resources to test for carbapenemase type -> should be encouraged
    - Patrick Harris noted that this is routine in Australia

- Option 1: Add comment in Table 2A at ß-lactam combination agents: "Testing for carbapenemase type is recommended for carbapenem-resistant Enterobacterales isolates to inform the optimal use of ß-lactam/ß-lactamase inhibitors."
  - General support for this option.
  - Thought that this will help spur labs to perform this testing.
- Option 2: Add comment in Table 2A on row of meropenem-vaborbactam: "Enterobacterales that harbor OXA-48-family enzymes may test susceptible to meropenem-vaborbactam but may not respond to this therapy *in vivo*. These organisms typically have similar meropenem and meropenem-vaborbactam MIC values because vaborbactam does not inhibit OXA-48 enzymes."
  - Might need wordsmithing.
  - Provide a warning signal for labs if don't do carbapenemase testing (but would prefer carbapenemase testing).
  - MBLs would also have same MEM and MEM-VAB MICs but not an issue because test resistant to MEM-VAB
- No enthusiasm or motions for lowering the MEM-VAB/Enterobacterales breakpoints to account for OXA-48
- Enthusiasm for recommending increased use of tests to detect and differentiate carbapenemase
- 65% of labs used these tests in a CAP survey
- Disagreements on the last part of the sentence "to inform the optimal use of ß-lactam/ß-lactamase inhibitors" ("too vague")

- BPWG Discussion and Recommendation
  - Proposed comment: "Testing for carbapenemase type is recommended for carbapenem-resistant Enterobacterales isolates ~~to inform the optimal use of ß-lactam/ß-lactamase inhibitors~~."
  - Vote taken for first part of sentence with second part to be worked out later. WG Vote: 8-0-0-4.
- Table 2 Draft Comment Post BPWG Meeting: "Determining the presence and type of carbapenemase is recommended for any carbapenem non-susceptible Enterobacterales to inform optimal use of the beta-lactam combination agents with potential activity against carbapenemase-producing organisms (ie, meropenem-vaborbactam, ceftazidime-avibactam, imipenem-relebactam). Report carbapenemase type and susceptibility test results. Laboratories should discuss testing and reporting strategies with the antimicrobial stewardship team and other relevant institutional stakeholders."
- Table 1 Draft Post BPWG Meeting: Recommended B-lactam combination agents to test and report, based on carbapenemase type

	CAZ-AVI	MEM-VAB	IMI-REL
KPC	Y	Y	Y
NDM	N	N	N
VIM	N	N	N
IMP	N	N	N
OXA-48	Y	N	N

SC DISCUSSION (MAIN POINTS)

- Meropenem-vaborbactam does not work well for OXA-48.
- The working group would like to add a comment to encourage laboratories to determine which carbapenemase is present to better guide which new beta-lactam combination agents are used to treat patients. Initially, thought they would put this comment in the beta-lactam combination agent section before it lists all the different inhibitors.
- Maybe the comment should note that not all carbapenemase detection assays have a clinical indication for guiding therapy in their package insert.

- Make sure to include antigen testing in the allowed carbapenemase detection methods. Technically antigen testing is phenotypic.
- Do not hold up reporting patient test results to get the carbapenem mechanism.
- There are issues with detecting OXA carbapenemase, they do not all test as carbapenem resistant.
- Consider "not susceptible" over "carbapenem resistant" because there are some OXAs that could test as "I" to meropenem or ertapenem.
- mCIM does not help us with defining a mechanism.
- Meropenem-Vaborbactam is not going to work against OXA-48, so labs should just test the drug directly and report the results.
- Prefers "carbapenem not susceptible". For example, one laboratory tests isolates with low MICs for carbapenemase and find OXAs. Their lab then looks for carbapenemase if the meropenem MIC is ≥0.12 and Ertapenem ≥1.
- The intent here is to say that labs need to figure out what type of carbapenemase is present.
- For the *in vivo* meropenem-vaborbactam study, there was MIC variability. In the USA, 40% of these OXAs are testing as susceptible. This drug was never designed to treat OXA. If breakpoint is moved down, still will not get all the OXAs. There are a lot of underrecognized OXAs.
- Asking labs to do molecular testing is not feasible.

A motion to not revise the meropenem-vaborbactam breakpoints for Enterobacterales and to add a comment to Table 2A next to meropenem-vaborbactam stating, "Enterobacterales that harbor OXA-48-family enzymes may test susceptible to meropenem-vaborbactam but may not respond to this therapy *in vivo*. If OXA-48 is detected, suppress or report as resistant." was made and seconded. Vote: 13 for, 0 against, 0 abstain, 1 absent (Pass)

CARBAPENEMASE DEFINITION (PRESENTED ON 6 JUNE 2023)

- Current Wording in Table 2A for Enterobacterales (under carbapenems): "Institutional treatment guidelines, infection prevention procedures, or epidemiological investigations may necessitate identification of carbapenemase-producing Enterobacterales. Isolates with elevated carbapenem MICs (intermediate or resistant) can be tested for carbapenemase production by a phenotypic and/or a molecular assay (refer to Tables 3B and 3C for methods). See Appendix H, Table H3 regarding suggestions for reporting when mechanism of resistance-based testing (molecular and phenotypic methods) is discordant with phenotypic AST."
- Now we want to recommend testing to detect and identify carbapenemase to provide important information to help treatment.
- Carbapenemase detection: for which resistance profiles?
    - Nothing will be perfect
    - Option #1: CDC definition of CRE: resistance to any carbapenem (except *Proteus*/*Providencia*/*Morganella* (PPM and imipenem)
    - Option #2: meropenem or imipenem intermediate or resistant (except PPM and imipenem)

SC DISCUSSION (MAIN POINTS)

- There is concern for detecting OXA 48 with either definition.
- This is a breakpoint issue, not a reporting issue.
- Note that the CDC definition is a surveillance definition. National Notifiable Diseases Surveillance System definition was updated to carbapenemase producing organisms (CPO) in the reportable diseases case definitions. Consider not worrying about the CDC definition because it is for a different purpose.
- Option 1 reduces the testing burden on labs.
- Need to help guide labs on what to do and what drugs to test or not test based on a specific mechanism.

- EUCAST has a different way to identify possible carbapenemase. They use a low ECV.
- Option 2 is beneficial because the goal here is to increase testing.
- Suggestion to have separate comments for therapy vs. infection control because there are two different indications for testing.
- Concern to align to indication for use for a device. Using for clinical practice vs. instruction for use.
- It is probably a wash between options 1 and 2 because an ertapenem resistant isolate could be S to meropenem and imipenem and be missed.
- "Should" means "must" from the reader perspective so careful with wording.
- If this is clinically important need to say "should" to justify the cost.
- Carbapenem not susceptible leaves a lot of room for lab flexibility.
- Suggestion to provide some information in the box next to the drugs about what laboratories should do next in Tables 1.
- Point against CDC definition is labs will do too much testing on ertapenem R isolates. Sensitivity is 50% for ertapenem.
- Several members feel CLSI is rushing this decision; however, others believe it is very important to push laboratories to start testing for carbapenemase ASAP.
- CLSI need to think about this wording throughout the document to harmonize.
- No decision was made. This topic will be discussed further at future meetings.

STAPHYLOCOCCI LINEZOLID BREAKPOINTS WITH REFLECTED LIGHT

- Background
  - Need for linezolid disk correlates for *Staphylococcus*
  - Method for reading disk diffusion results for tedizolid and linezolid changed from transmitted light to reflected light because easier to read and more reproducible
  - In January 2023: revised disk diffusion breakpoints for linezolid and *S. aureus* approved: Susceptible: ≥26 mm; Intermediate: 23-25 mm; Resistant: ≤ 22 mm
  - However, data for coagulase-negative staph (CoNS) not available
  - Objective: To obtain, evaluate, and propose disk diffusion breakpoints for linezolid against *Staphylococcus* spp.
- Proposed Linezolid Breakpoints Data

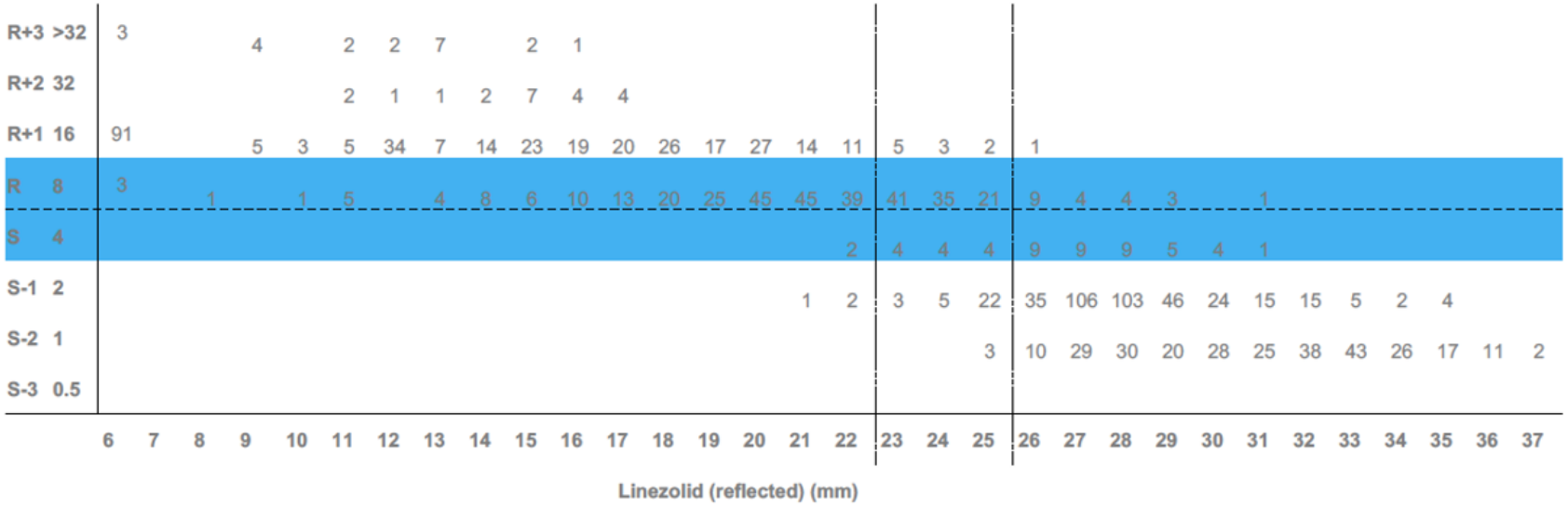


Table 8. Guideline Acceptable Discrepancy Rates (Without Intermediate Range)

MIC Range	Discrepancy Rates		
No Intermediate Range	Very Major	Major	Minor
≥R+1	<2%	N/A	<5%
R+S	<10%	<10%	<40%
≤S−1	N/A	<2%	<5%

Abbreviations: MIC, minimal inhibitory concentration; N/A, not applicable; R, resistant; S, susceptible.

MIC range	Number	Very major (%)	Major (%)	Minor (%)
≥R+1	369	1 (0.3)	N/A	10 (2.7)
S+R	394	21 (5.3)	2 (0.5)	109 (27.7)
≤S-1	670	N/A	3 (0.4)	33 (4.9)
Total	1,433	22 (1.5)	5 (0.3)	152 (10.6)

- BPWG Discussion and Recommendation
  - No CoNS isolates available with linezolid MICs of 4 or 8 µg/mL for MIC/disk correlate testing. These isolates are very rare.
  - Noted that an intermediate disk breakpoint but no intermediate MIC breakpoint. Precedent for this noted (eg, TMP-SMX or CAZ-AVI vs. Enterobacterales).
  - Should the types of CoNS be clarified (eg, no S. lugdunensis in MIC/disk correlate data).
  - Motion to accept the proposed linezolid breakpoints for Staphylococci with reflected light: S≥26, I 23-25, R≤22. WG Vote: 8-0-1-2.

SC DISCUSSION (MAIN POINTS)

- *S. lugdunensis* was not included in the study, the WG did not see a reason it would be different from the other *Staph* results.

	A motion to accept the linezolid disk breakpoints for *Staphylococcus* spp. (S≥26, I 23-25, R≤22 mm) with reflected light was made and seconded. Vote: 13 for, 0 against, 0 abstain, 1 absent (Pass)

	TABLE 2 FOR *SALMONELLA/SHIGELLA*
	• Background
	  ○ *Salmonella* and *Shigella* are different than other Enterobacterales
	  ▪ Aminoglycosides, 1st and 2nd-generation cephalosporins, and cephamycins are not effective vs. *Salmonella* and *Shigella*
	  ▪ Azithromycin breakpoints are only for these organisms
	  ▪ *Salmonella* has its own fluoroquinolone breakpoints
	  ○ CDC's NARMS program was contacted
	  ▪ They approved the idea of a new Table 2 for *Shigella/Salmonella*
	  ▪ Had suggestions for revisions to Table 1B
	  ○ Ask to BPWG: what additional information is needed?
	• BPWG Discussion and Recommendation
	  ○ Motion to separate *Salmonella* and *Shigella* into own table with Table 2. WG Vote: 9-0-0-2.
	
	SC DISCUSSION (MAIN POINTS)
	• *Salmonella* is an intracellular organism and do not know how the carbapenems will behave, so a comment might be needed. There is a comment in Table 1B to address carbapenem and *Salmonella/Shigella* already. Consider moving or copying the sentence to the new *Salmonella/Shigella* Table 2.

	A motion to move the *Salmonella* and *Shigella* breakpoints into a separate table in Table 2 was made and seconded. Vote: 13 for, 0 against, 0 abstain, 1 absent (Pass)
3.	**ADJOURNMENT** Dr. Lewis thanked the participants for their attention. The meeting was adjourned at 6:30 PM Central Standard (US) time.

2023 JUNE AST MEETING SUMMARY MINUTES PLENARY 3: Tuesday, 6 June 2023 (In-person with virtual live streaming) 7:30 AM – 12:00 PM Central Standard (US) Time	
#	**Description**
1.	**OPENING** Dr. Lewis opened the meeting at 7:30 AM Central Standard (US) time.

2. **JOINT CLSI-EUCAST WORKING GROUP (J. HINDLER)**

WG GOALS

- Describe a method for disk content determination which can be used early in the drug development process to avoid having different disk contents in the CLSI and EUCAST standards. Completed July 2021.
- Discuss differences between CLSI and EUCAST QC criteria, methods for establishing QC criteria and the possibility of harmonizing CLSI and EUCAST QC criteria.

DISK CONTENT SELECTION IN PROGRESS

WG Assigned Study #	Agent	Sponsor	Notes
JWG-2022-2	Contezolid	MicuRX	Phase 2 completed; present Summer 2023
JWG-2022-3	Imipenem-XNW4107 (Funobactam) (fixed at 8 mg/L)	Evopoint Biosciences [a]	Phase 1 & 2 completed
JWG-2022-4	~~RG6006~~ Zosurabalpin	Roche	Ongoing studies for BMD reference method
JWG-2022-5	Aztreonam-nacubactam (1:1) and Cefepime-nacubactam (1:1)	Meiji	Phase 1 complete; some difficulties
JWG-2022-9	Zoliflodacin	Nobelex	Phase 1 planning
JWG-2023-1	BWC0977	Evopoint Biosciences [a]	Phase 1 completed
JWG-2023-1	Piperacillin-tazobactam (reassessment)	CLSI/EUCAST	Evaluating (µg) 100/10 (CLSI); 30/6 (EUCAST); 20/5 and ???

[a] formerly Sinovent Pharmaceuticals

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MHA AGAR EVALUATIONS IN PROGRESS

WG Assigned Study #	Agent	Sponsor	Notes
JWG-2022-6	Debio 1452	Debiopharm	Disk manufacturers report no problems with low content disks.
JWG-2022-7	Cefepime-enmetazobactam	AdvanZ	Present Summer 2023
JWG-2022-8	Ceftazidime-avibactam	Pfizer	Projected Spring 2023

PUBLICATIONS

- ECCMID Poster April 2023
- M23S June 2020 – Updates soon to add detail for selecting content for combination agents
- M23S2 July 2021 – Updates soon to add first step suggesting Joint WG discuss project with sponsor to Phase 1
- M23S3 June 2023

QC HARMONIZATION

- Looking further at use of statistical options for evaluation of QC data
- Examine previous raw data from QC studies

CONTEZOLID DISK POTENCY STUDY PHASE 2

- Study Layout
  - 2-4 disks (commercially prepared or two lots of in-house prepared disks)
  - Media from two manufacturers
  - 30 isolates per species / 60 per organism group
- Materials and Methods
  - Disk diffusion was performed according to CLSI and EUCAST methodology
    - Contezolid 2, 5 and 10 µg disks
    - Linezolid 10 and 30 µg as control disks
  - BMD for contezolid and linezolid was performed in parallel
    - Standard CAMHB for staphylococci and enterococci
    - CAMHB with 5% lysed horse blood for streptococci
    - MICs were read according to CLSI and EUCAST recommendations (ignoring pinpoint growth)

- QC with strains recommended by CLSI and/or EUCAST
  - At least 3 repeats per media and strain

- Results Summary
  - QC results and results for the comparative agent (linezolid) were all approved/as expected.
  - There were only minor differences between reading zones with reflected and transmitted light when testing non-fastidious organisms.
  - For fastidious organisms, there were no differences between MH-F (EUCAST) and MH + sheep blood (CLSI).
  - NWT isolates could not be found for *S. pneumoniae* and beta-hemolytic streptococci.
  - Data is presented separately for *E. faecalis* and *E. faecium*, since there was a difference in overlap between WT and NWT isolates for these species.
  - Contezolid 2 µg
    - Too weak for *Enterococcus* spp. and viridans group streptococci, for which several isolates with MICs 1-2 mg/L have no zone.
  - Contezolid 5 and 10 µg
    - Zone diameters for WT isolates between 15 and 35 mm for most species with both 5 and 10 µg disks.
    - Good separation between WT and NWT isolates for *S. aureus*, CoNS, *E. faecium* and viridans group streptococci.
    - Overlap between WT and NWT isolates for *E. faecalis*. MICs were repeated three times with the same results for isolates in the overlap area.
    - 5 µg disk: Some isolates with MICs 1-2 mg/L have still no zone.
    - 10 µg: The same isolates have zones of 9-14 mm, but cannot be separated from isolates with >2 mg/L.
- Sub-group Recommendation
  - The sub-group suggests the contezolid 5 µg disk to be the most optimal choice since this disk better separates between susceptible and resistant isolates for important species. Also, the contezolid 5 µg disk correlates well with linezolid resistance.
  - The sub-group suggests reading contezolid zone diameters for non-fastidious organisms with reflected light (=standard reading instruction) since there was no clear advantage with transmitted light.

MEDIA EVALUATION STUDY FOR CEFEPIME-ENMETAZOBACTAM

- Study Layout
  - 4 relevant QC strains + 2 clinical isolates with elevated MICs for cefepime-enmetazobactam
  - Mueller-Hinton agar from 4 manufacturers: BBL, Bio-Rad, Oxoid and Remel
  - Cefepime-enmetazobactam 30-20 µg disks from 3 manufacturers + ceftolozane-tazobactam as control disk
- Conclusions
  - Media-related differences were small.
    - 2 MH agars among the 4 tested will be selected for MIC-zone diameter correlation studies.
  - Cefepime-enmetazobactam disks from manufacturer C produced larger zones than manufacturers A and B for the two clinical isolates with elevated MICs.
    - A re-calibrated lot of disks from manufacturer C showed results equal with manufacturers A and B.
    - Disks from all three manufacturers (re-calibrated lot for manufacturer C) will be used for MIC-zone diameter correlation studies.

JOINT WG - WHAT IS NEXT?

- Continue with disk diffusion content selection and MHA (for QC) acceptability studies

	• Launch M23S3 • Complete edits on M23S and M23S2 • Harmonization of QC (VET QC ranges) • Harmonization of disk diffusion and BMD reading guide

3. **METHODS DEVELOPMENT AND STANDARDIZATION WORKING GROUP (T. DINGLE)**

CEFIDEROCOL BROTH MICRODILUTION UPDATES

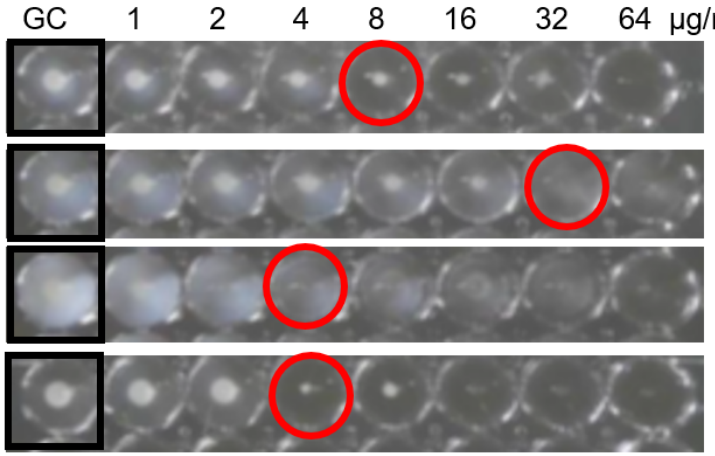
- Methodology
  - MIC determinations by broth microdilution for 85 isolates with MIC values "validated" with *in vivo* efficacy experiments using iron-depleted cation-adjusted Mueller-Hinton Broth (ID-CAMHB)
    - 4 different brands (1 lot for each brand) of (CA)MHB: BD BBL, BD Difco, Oxoid, and Merck
    - Perform testing over 3 days (three separate inoculum)
    - 10 replicates* per isolate per media per day (same inoculum)
    - Total of 30 or 9* MIC determinations for each brand of (CA)MHB (120 or 36* total per strain)
  - Preparation of ID-CAMHB
    - Stir (CA)MHB with Chelex 100 (analytical grade, 100–200 mesh, sodium form) for 6 hours
    - Filter and replenish medium with Ca^{2+} (22.5 mg/L), Mg^{2+} (11.25 mg/L) and Zn^{2+} (0.65 mg/L)#
    - Adjust pH to 7.2 - 7.4 if needed
    - Confirm final iron concentration ≤0.03 mg/L (VISOCOLOR HE Iron)
  - 7 *E. coli*, 17 *K. pneumoniae*, 14 *P. aeruginosa* and 47 *A. baumannii*
    - Historical cefiderocol MIC ranges from 0.25 - 64 µg/mL
  - Bacterial inoculum (0.5 McFarland) controlled by nephelometer
  - Assessed reproducibility of MIC determinations (mode ±1 dilution) amongst and across media
- Conclusions
  - New procedure to generate ID-CAMHB resulted in reproducible MIC values for each ID-CAMHB
  - Differences in MIC values were observed across the different ID-CAMHB. Differences cannot be attributed to differences in iron content.
  - MIC values generated with ID-CAMHB from BD-BBL and Difco correlated the best with the *in vivo* pharmacology response. BD-BBL and Difco ID-CAMHB recommended for use in cefiderocol broth microdilution susceptibility testing.
  - Enterobacterales and *P. aeruginosa* showed clear endpoints, while trailing was observed with some *A. baumannii* isolates for all media
  - Trailing complicates determination of clear MIC endpoint and improved reading guidance with example pictures are recommended to include in M100 to improve consistency across laboratories
  - Set of isolates available for testing to third parties for validation
- MDSWG Discussion and Recommendation
  - A reminder that the data presented is challenge set of isolates
  - How to handle differences between media manufacturers
    - Identify a supplemental QC organism(s) that can be used as an indicator of successful iron-depletion
    - Review QC data for range differences and systematic differences between media
    - State that there are differences between broth manufacturers and provide a reference
  - The QC strain work will be taken on by the Cefiderocol AHWG

CEFIDEROCOL M100 READING GUIDELINES

- Proposed Revisions
  - The positive control should show strong growth in the form of a button of >2 mm or heavy turbidity

- The MIC of cefiderocol is read as the first well in which the reduction of growth corresponds to a button of <1 mm or is replaced by the presence of light haze/faint turbidity
- New guidance is in line with current guidance, but more quantitative, harmonization with EUCAST, and additional representative pictures

- Suggested Additional Pictures



MIC is read at first well corresponding to a button of <1 mm; 8 µg/mL

MIC is read at the first well corresponding by the presence of light haze/faint turbidity; 32 µg/mL

MIC is read at the first well corresponding by the presence of light haze/faint turbidity; 4 µg/mL

MIC is read at first well corresponding to a button of <1 mm; 4 µg/mL

Examples of *A. baumannii* growth patterns. GC (black box) is positive control showing strong growth with either a button of >2 mm or heavy turbidity. MIC is indicated by red circle

- MDSWG Discussion and Recommendation
  - General consensus that even these pictures are difficult to read
  - EUCAST (Erika Matuschek)
    - Button is easier to read than the haze
    - Trailing is not only common for *Acinetobacter baumannii*, but also *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia*
    - Suggest finding a QC strain with trailing to help labs read those results
  - AHWG will work on obtaining as many pictures as possible to help labs with reading – make sure pictures are true to scale/include a size legend
  - How realistic is it for labs to measure buttons of growth? Limited to labs that perform BMD.
  - A few mentioned being in favor of aligning reading with EUCAST
  - Recommendations:
    - Addition of reading guidelines to M100 (and M07) to align with EUCAST
    - The positive control should show strong growth in the form of a button of >2 mm or heavy turbidity
    - The MIC of cefiderocol is read as the first well in which the reduction of growth corresponds to a button of <1 mm or the presence of light haze/faint turbidity is observed

SC DISCUSSION (MAIN POINTS)

- This is a difficult drug to read. What is being proposed is not different or changing anything. It is just being more specific and improving guidance for reading.
- The drug sponsor (Shionogi) needs to provide the high-quality photos for the reading guide.
- JMI (Mariana Castanheira) has images for the reading guide.
- The 1 mm guidance for a BMD button size is challenging for labs because some technologists will be very strict with the cutoff whereas others will not. It is more helpful to have images and an interactive training guide with multiple examples rather than listing 1 mm.
- The M07 says "small" or "tiny" for reading BMD buttons, so changing this to 1 mm is more specific.
- The M02 and M07 AHWG generated an internal reading guide and images can be shared with MDSWG.
- Maria Machado had additional images.
- Additional concern with the 1 mm because users might read it too literally and measure every button. Practice, photos, and training are most important in reading the MICs.
- Suggestion to send the photos in the reading guide to labs in a blinded fashion and see how the photos are interpreted to ensure clear and user-friendly ones are selected.
- Need to make sure there is M100 and M07 alignment. TTWG had originally wanted to remove the cefiderocol from the M100 appendix to M07. It was meant to be a temporary appendix and will not be aligned with M07.
- It is probably too much to take out of M100 now. It may be worth removing from M07.
- Barb Zimmer can share photos. She will make sure the AHWG reviews and aligns all the photos.
- Make images for reading disk diffusion a high priority as well.
- The wording proposed by the AHWG needs to clarify if it is it 1 mm reduction in the button or if the button should be 1 mm.
- Concern about what to do for isolates that do not make a button of 2 mm for the control. If there is not 2 mm control growth, the test results cannot be read.
- Question about the methods for preparing the media. Clarification needed that the instructions state chelation takes approximately 6 hours. Multiple different media types were looked at and it was determined that 6 hours worked well across all media types. Suggestion to change the wording to ">6 hours" instead of "around 6 hours" to make it easier for laboratories to implement.

A motion to add the cefiderocol text, "The positive control should show strong growth in the form of a button of >2 mm or heavy turbidity. The MIC of cefiderocol is read as the first well in which the growth corresponds to a button of <1 mm or the presence of light haze/faint turbidity is observed." with corresponding pictures was made and seconded. Vote: 12 for, 1 against, 0 abstain, 1 absent (Pass)

Against Vote Reasoning:

- The comment is confusing and needs more work and input from experts.

CEFIDEROCOL DISK DIFFUSION UPDATES

- Additional disk diffusion data for a challenge set of *E. coli*, *P. aeruginosa* and *A. baumannii* isolates
  - Results were reproducible regardless of media or disks used
  - Reading for *E. coli* and *P. aeruginosa* was straightforward

- *A. baumannii* isolates with elevated MIC values frequently showed colonies in the inhibition zones
  - Phenomenon was not reproducible, so larger variation of inner inhibition zones was observed compared to outer inhibition zones
  - No clear correlation with trailing effect and appearance colonies in zone of inhibition
  - Good categorical agreement with broth microdilution MIC when outer zones of inhibition were used (>90%), but those introduced very major errors
  - Categorical agreement decreased (80-85%) if inner zones were used
- *In vivo* correlation data were also presented
- MDSWG Discussion and Recommendation
  - EUCAST (Erika Matuschek)
    - Colonies within the zones tend to happen more commonly with specific media
    - Isolated colonies may be able to be ignored
    - More reluctant to ignore growth if the inner zone growth is more confluent
  - Discussion on removal of *Acinetobacter baumannii* disk breakpoints due to accuracy concerns
    - The data presented was a challenge set
    - Original data and any additional data need to be reviewed
    - EUCAST only has PK/PD MIC breakpoints for *Acinetobacter baumannii*
  - Request to Cefiderocol AHWG
    - To evaluate use of inner or outer zones of inhibition in disk diffusion evaluations, when microcolonies or a less turbid disk zone are apparent and re-examine inhibition zone cut-offs
    - EUCAST recommends ignoring microcolonies for several cell wall acting antibiotics (temocillin, fosfomycin)
    - Correlation to *in vivo* data should trump reproducibility data

SC DISCUSSION (MAIN POINTS)

- A request to the sponsor was made to provide an iron deplete control.
- Suggestion to add a comment in M07 about differences seen among the performance of different media manufacturers with a reference to a published data set. Cannot call out specific manufacturers in CLSI documents.
- Need an interactive training guide, video, and quiz examples.
- Suggestion for Outreach WG to assist in making training material.
- EUCAST does not have a disk diffusion breakpoint for *Acinetobacter*. Surprised there is not more discussion about removing the cefiderocol breakpoint for *Acinetobacter*. This was discussed at the MDSWG meeting, and they did not feel there was enough data at the time to truly address this question.

CEFIDEROCOL AD HOC WORKING GROUP REPORT

- Chairholder: Barb Zimmer
- Goals:
  - Reproducible means of testing cefiderocol by broth microdilution or disk diffusion for Enterobacterales, *Pseudomonas aeruginosa*, *Acinetobacter* and *Stenotrophomonas maltophilia*, and appropriate quality control to ensure testing method is accurate
  - Ease of reading and guidance for reading, especially with *Acinetobacter* (skips, trailing, pinpoint colonies)

DIRECT BLOOD DISK DIFFUSION AD HOC WORKING GROUP REPORT

- Goals
  - Define disk diffusion breakpoints for applicable gram-negative rods direct from positive blood culture bottle broth
  - 16-18 hour (overnight reads) and 8-10 hour (early reads)
  - Review data from:
    - Direct Susceptibility Testing of Gram-negative Rods from Blood Cultures (ARLG DISK Study)
    - Seeded isolate testing (performed Fall 2020 to Spring 2021)
  - Progress as of June 2023

	Enterobacterales 8-10h	Enterobacterales 16-18h	PA 8-10h	PA 16-18h	*Acinetobacter* 8-10h	*Acinetobacter* 16-18h
Ampicillin	AST SC approved new zone cutoffs 2/2022	AST SC approved current zone cutoffs 6/2020	N/A	N/A	N/A	N/A
Amp-sul	Unable to set zone cutoffs	Unable to set zone cutoffs	N/A	N/A		Ad hoc approved current zone cutoffs 5/2023
Aztreonam	AST SC approved current zone cutoffs 2/2021	AST SC approved current zone cutoffs 6/2020	Unable to set zone cutoffs	Unable to set zone cutoffs	N/A	N/A
Cefepime				AST SC approved current zone cutoffs 1/2023	Ad hoc approved current zone cutoffs 5/2023	Ad hoc approved current zone cutoffs 5/2023
Ceftazidime	AST SC approved current zone cutoffs 2/2021	AST SC approved current zone cutoffs 6/2020		AST SC approved current zone cutoffs 6/2021		Ad hoc approved new zone cutoffs 5/2023
Ceftriaxone	AST SC approved current zone cutoffs 2/2021	AST SC approved current zone cutoffs 6/2020	N/A	N/A	Ad hoc approved current zone cutoffs 5/2023	Ad hoc approved new zone cutoffs 5/2023
Ciprofloxacin	AST SC approved new zone cutoffs 2/2022	AST SC approved new zone cutoffs 2/2022	AST SC approved new zone cutoffs 6/2021	AST SC approved current zone cutoffs 2/2021	Ad hoc approved current zone cutoffs 5/2023	Ad hoc approved current zone cutoffs 5/2023
Ertapenem			N/A	N/A	N/A	N/A
Meropenem	AST SC approved new zone cutoffs 2/2022	AST SC approved new zone cutoffs 2/2022	AST SC approved current zone cutoffs 2/2022	AST SC approved current zone cutoffs 2/2021	Ad hoc approved current zone cutoffs 5/2023	Ad hoc approved current zone cutoffs 5/2023
Pip-tazo	Unable to set zone cutoffs	Unable to set zone cutoffs	Unable to set zone cutoffs	Unable to set zone cutoffs		
Tobramycin	Ad hoc approved current zone cutoffs 4/2023	Ad hoc approved current zone cutoffs 4/2023	Ad hoc approved current zone cutoffs 4/2023	Ad hoc approved current zone cutoffs 4/2023	Ad hoc approved current zone cutoffs 5/2023	Ad hoc approved current zone cutoffs 5/2023
Trimeth-sul		AST SC approved current zone cutoffs 6/2020	N/A	N/A	Ad hoc approved current zone cutoffs 5/2023	Ad hoc approved current zone cutoffs 5/2023

Peach = pending further *Ad hoc* review of data
Blue = recently voted up and passed by *Ad hoc* WG
Gray font = passed by AST SC
N/A = not applicable

- Comparison of Disk to Disk
  - Both disk and MIC results for Direct DISK study
  - After much discussion Winter 2021, MDSWG voted to compare direct DISK results to standard DD at the study site (STD DD SITE)-primary comparison
  - Secondary comparison would be DISK results to REF DD (performed at reference lab)
  - Discussed and agreed at AST Subcommittee Winter 2021

- Testing Procedure Comparison

DISK Study

1. Set up disk diffusion testing within 8 h of flagging positive
2. Four drops of blood culture broth (from a venting needle) applied to two Mueller-Hinton agar (MHA) plates
3. Subculture of the blood broth inoculated to blood agar plate
4. Plates incubated at 35°C in ambient air
5. Plates read at 8-10h
6. Plates read again at 16-18h
7. Standard disk diffusion was performed on isolated colonies at the study site (**Std DD Site**)
8. Isolates were shipped to reference lab for DD (**Ref DD**)

Seeded Study

1. Set up disk diffusion testing within 8 h of flagging positive
2. Four drops of blood culture broth (from a venting needle) applied to two Mueller-Hinton agar (MHA) plates
3. Subculture of the blood broth inoculated to blood agar plate
4. Plates incubated at 35°C in ambient air
5. Plates read at 8-10h
6. Plates read again at 16-18h
7. Standard disk diffusion was performed on isolated colonies at the study site (**Std DD Site**)
8. No Ref DD performed.

- Seeded Study
  - Undertaken due to limited number of certain isolates in DISK study
  - Completed testing
    - 50 additional *P. aeruginosa*
    - 25 additional Enterobacterales (resistant to a variety of antimicrobials). Not applicable to the tobramycin data reviewed.
    - 100 *Acinetobacter*
  - Seeded studies performed by BD and Accelerate

TOBRAMYCIN FOR ENTEROBACTERALES AND *P. AERUGINOSA*

- New standard DD breakpoints published in M100 33rd ed.
- Reassess cutoffs for direct DD testing from positive blood cultures
- Prior M100 32nd ed. (now obsolete) standard DD cutoffs for tobramycin had been applied to direct DD testing
  - Enterobacterales and *P. aeruginosa* for overnight and early reads
- No prior DD cutoffs for piperacillin-tazobactam had been applied for Enterobacterales or *P. aeruginosa*
  - Categorical agreements were too low for setting piperacillin-tazobactam zone cutoffs using the new breakpoints as well
- Tobramycin Direct DD vs. Standard DD at Site

	Time of reading	CA		VME		ME		mE	
Enterobacterales	16-18h	342/368	92.9%	0/33	0	2/320	<1%	24/386	6.5%
Enterobacterales	8-10h	344/369	93.2%	0/32	0	2/324	<1%	23/369	6.2%
P. aeruginosa	16-18h	90/93	96.8%	0/25	0	0/63	0	3/93	3.2%
P. aeruginosa	8-10h	73/79	92.9%	0/21	0	0/55	0	6/79	7.6%

- Proposed breakpoints of standard DD zone cutoffs for direct blood DD testing

Enterobacterales

Standard zone cutoffs (mm)		
S	I	R
≥17	13-16	≤12

P. aeruginosa

Standard zone cutoffs (mm)		
S	I	R
≥19	13-18	≤12

A motion to accept the tobramycin direct blood disk breakpoints for Enterobacterales (S≥17, I 13-16, R≤12 mm) and *P. aeruginosa* (S≥19, I 13-18, R≤12 mm) for 16-18h and 8-10h reading times was made and seconded. Vote: 12 for, 0 against, 0 abstain, 2 absent (Pass)

ACINETOBACTER

- Study
  - Performed seeding study due to lack of adequate numbers of Acinetobacter isolates from DISK study
  - Standard DD testing performed at testing site
  - No DD testing performed at reference lab
- Direct DD vs. Standard DD

	Time of reading	CA		VME		ME		mE	
Ampicillin-sulbactam	16-18h	101/107	94.4%	0/9	0	0/89	0	6/107	5.6%
Cefepime	16-18h	96/107	89.7%	0/18	0	1/85	1.2%	10/107	9.3%
Cefepime	8-10h	98/106	91.6%	0/18	0	1/84	1.2%	7/106	6.6%
Ceftriaxone	8-10h	99/107	92.5%	0/29	0	0/4	0	8/107	7.5%
Ciprofloxacin	16-18h	106/107	99.1%	0/25	0	0/80	0	1/107	<1%
Ciprofloxacin	8-10h	104/107	97.2%	0/25	0	0/80	0	3/107	2.8%
Meropenem	16-18h	103/107	96.3%	0/16	0	0/87	0	4/107	3.7%
Meropenem	8-10h	103/107	96.3%	0/16	0	0/87	0	4/107	3.7%
Tobramycin	16-18h	106/107	99.1%	0/14	0	0/90	0	1/107	<1%
Tobramycin	8-10h	105/107	98.1%	0/14	0	0/90	0	2/107	1.9%
Trimethoprim-sulfamethoxazole	16-18h	103/107	96.3%	0/22	0	0/82	0	4/107	3.7%
Trimethoprim-sulfamethoxazole	8-10h	104/107	97.2%	0/22	0	0/82	0	4/107	2.8%

- Proposed breakpoints of standard DD zone cutoffs for direct blood DD testing
  - Ampicillin-sulbactam 16-18h
  - Cefepime 16-18h and 8-10h
  - Ceftriaxone 8-10h
  - Ciprofloxacin 16-18h and 8-10h
  - Meropenem 16-18h and 8-10h
  - Tobramycin 16-18h and 8-10h
  - Trimethoprim-sulfamethoxazole 16-18h and 8-10h

SC DISCUSSION (MAIN POINTS)

- The calculations for performance used the more conservative error calculations (the standard calculations, not the error-bounded rate method). The VME denominator included the total number of resistant isolates and the ME denominator include the total number of susceptible isolates.
- Suggestion to remove ceftriaxone breakpoint for *Acinetobacter* because they all have MICs above the PK/PD attainment targets. There were serious reservations about ceftriaxone and *Acinetobacter* and more data is expected soon.
- Question: What is the terminology for "standard zone cutoff" instead of a breakpoint? Trying to avoid confusion in the laboratory with standard disk diffusion breakpoints in Table 2 vs. the zone cutoffs in Table 3 for direct disk testing from blood. There are some differences between the cutoff and breakpoint values.
- Given that the 8-10h and 16-18h read times are both approved, do labs need to read at 8-10 then confirm at 16-18h? A lab does not need to do any confirmation testing. Labs may choose if they prefer to use the 8-10h read time or the 16-18h time.

A motion to accept the standard disk breakpoints for *Acinetobacter* ampicillin-sulbactam (16-18h), cefepime (16-18h and 8-10h), ceftriaxone (8-10h), ciprofloxacin (16-18h and 8-10h), meropenem (16-18h and 8-10h), tobramycin (16-18h and 8-10h), and trimethoprim-sulfamethoxazole (16-18h and 8-10h) as the direct blood disk breakpoints for the indicated reading times was made and seconded. Vote: 12 for, 0 against, 0 abstain, 2 absent (Pass)

CEFTAZIDIME FOR *ACINETOBACTER*

- 16-18h vs. Standard DD for Proposed Zone Cutoffs

	Std DD			
16-18 hr	S	I	R	Grand Total
S	82	3		85
I		2		2
R	1		19	20
Grand Total	83	5	19	107

CA	103/107	96.3%
VME	0/19	0
ME	1/83	1.2%
mE	3/107	2.8%

- Proposed breakpoints of DD zone cutoffs for direct blood DD testing

Proposed zone cutoffs (mm)			Current zone cutoffs (mm)		
S	I	R	S	I	R
≥17	15-16	≤14	≥18	15-17	≤14

A motion to accept the ceftazidime direct blood disk breakpoints for *Acinetobacter* (S≥17, I 15-16, R≤14 mm) for a 16-18h reading time was made and seconded. Vote: 12 for, 0 against, 0 abstain, 2 absent (Pass)

CEFTRIAXONE FOR *ACINETOBACTER*

- 16-18h vs. Standard DD for Proposed Zone Cutoffs

	Std DD			
16-18 hr	S	I	R	Grand Total
S	3			2
I	1	74	5	72
R			24	33
Grand Total	4	74	29	107

CA	101/107	94.3%
VME	0/29	0
ME	0/4	0
mE	6/107	5.6%

- Proposed breakpoints of DD zone cutoffs for direct blood DD testing S>=20, I 13-19, R <=12. Current zone cutoffs S>=21, I 14-20, R <=13.

A motion to accept the ceftriaxone direct blood disk breakpoints for *Acinetobacter* (S≥20, I 13-19, R≤12 mm) for a 16-18h reading time was made and seconded. Vote: 12 for, 0 against, 0 abstain, 2 absent (Pass)

OMN6 BROTH MICRODILUTION METHOD

- Background
  - Phase 1 completed Phase 2 (US/EU) is in preparation
  - Effective against gram-negative bacteria, non-toxic to human cells
  - Omnix is targeting multi-drug resistant and carbapenem-resistant *Acinetobacter baumannii*

- A designated Qualified Infectious Disease Product status by the US FDA for HABP/VABP, BSI, and cUTI
- Method development work showed OMN6 was generally more active and more consistent in NA-MHB compared to the standard CA_MHB method

- Tier-2 M23 QC and cation checkboard studies completed
- Summary
  - OMN6 demonstrates good activity against multi-drug resistant *A. baumannii* isolates
  - OMN6 is more consistent and generally more active in NA-MHB than CA-MHB
  - Recommended for testing is to use NA-MHB with a total Ca^{2+} and Mg^{2+} divalent cation concentration that does not exceed 15 mg/L
- MDSWG Discussion and Recommendation
  - Modifications to reference methods are discouraged unless absolutely necessary since this makes testing/materials more challenging (and potentially not feasible) when testing multiple agents
  - Why is the change necessary? Why does the MIC need to be lower?
    - Comparing MICs to other drugs
    - Dynamic range of activity needed
  - Dose response data (*in vivo* and/or *in vitro*) needed to show that the MIC method can separate responders from non-responders
  - Reproducibility data needed for both CA-MHB and NA-MHB
  - MDSWG will work to get the sponsor a list of asks to move this forward

SC DISCUSSION (MAIN POINTS)

- Phase 2 study in progress for this antimicrobial peptide targeting MDR and carbapenem resistant *Acinetobacter baumannii*.
- The MICs for this peptide are high in cation adjusted Mueller Hinton broth, so the sponsor wants to use Mueller Hinton Broth instead because the MICs are lower in that media.
- There is cation adjusted Mueller Hinton broth and Mueller Hinton broth, so why is this called non-adjusted Mueller Hinton broth? The sponsor was concerned that users would get confused with existing media called Mueller Hinton 2, which is cation adjusted. The goal is to avoid unnecessary confusion.
- A high MIC does not sway providers. The MIC is the MIC. A separate method is extremely hard for labs to test, so we need to be very cautious with this. The reality of drug development is that it is harder to get funding for drugs with higher MICs. Also, so providers choose antibiotics with lower MICs over ones with higher MICs even if both options are classified as susceptible.
- This is a small molecule, a peptide, it deserves its own category and considerations.
- Most commercial AST systems use cation adjusted Mueller Hinton broth, so it will be difficult for manufacturers to include this new drug in existing panels.

4. **M45 WORKING GROUP (T. SIMNER)**

- Process for setting M45 "Breakpoints"
  - Literature review on MIC distributions, PK-PD, antimicrobial resistance mechanisms, cases studies/series and clinical outcomes
  - Accumulate MIC data from publications and reference laboratories
  - Prioritize reference methods
  - Evaluate all data including all non-reference method data
  - Run data through ECOFF Finder
  - Create histograms with MIC data and compare to current M45 breakpoints, breakpoints from related organisms, any PK-PD/clinical data (rarely available) and EUCAST non-species-specific PK-PD breakpoints
  - Complete template
  - Update/create M45 tables
  - Consideration of intrinsic resistance tables for M45 organisms
  - Provide next steps for future M45 updates
  - Transparency about data utilized to set "breakpoints" with follow-up publications on MIC distributions/ posting on the CLSI website
- Organism-specific areas for evaluation

Table	Potential revisions/needs
Table 2. *Aerococcus*	Growth failures with current method; add disk diffusion breakpoints
Table 3. *Aeromonas*	FQ failures / low level resistance (update breakpoint?); mCIM testing to detect *cphA* as carbapenem breakpoint low already
Table 3. *Bacillus* spp.	Assess impact of adding related genera in last edition; Address penicillin resistance-revisited *B. anthracis* breakpoints
Table 5. *Campylobacter jejuni/coli*	Look at other species, add a meropenem breakpoint and disk correlates
Table 6. *Corynebacterium* spp.	Revisit penicillin BP with aerotolerant *Actinomyces*
Table 7. *Gemella* spp.	Add other catalase negative GPC; Study to evaluate adding daptomycin and linezolid
Table 9. HACEK	Assess differences with EUCAST Impact of testing methods added in last edition
Table 10. *Helicobacter pylori*	Assess differences with EUCAST; Time for breakpoints?
Table 12. *Lactococcus* spp.	Add doxycycline; Add a comment about endocarditis with penicillin → apply viridans strep breakpoints despite essentially placing all MICs in the intermediate category
Table 13. Leuconostoc	Add linezolid and daptomycin breakpoints; consider adding *Weisella* spp
Table 15. *Micrococcus* spp.	Test nitrocefin & penicillin; Separate out *Kocuria* spp?
Table 16. *Moraxella catarrhalis*	Expand to *Moraxella* spp.
Table 17. *Pasteurella* spp.	Re-evaluate disk correlates

Table	Additions
Capnocytophaga species	ARUP data using custom lyophilized sensititre panel, BHI + LHB, 35°C, elevated CO_2, 24-120h incubation. Consider recommending β-lactamase test at minimum to laboratories as media may be difficult for laboratories to obtain
Non-*aeruginosa Pseudomonas*	Perform a BMD study to define MIC distribution, define intrinsic resistance, disk-to-MIC, evaluate gradient diffusion & mCIM (include CRO subset); evaluate FQ breakpoints
Achromobacter species	Perform a BMD study to define MIC distribution, define intrinsic resistance, disk-to-MIC, evaluate gradient diffusion & mCIM (include CRO subset); evaluate FQ breakpoints
Non-Enterobacterales	Move to M45 – At minimum, the non-Enterobacterales tables should be reviewed to potentially align with the updated *Enterobacterales/P. aeruginosa* breakpoints.

- Table 5: *Campylobacter jejuni/coli*
  - Can breakpoints be extended to species beyond *C. coli/jejuni*?
    - Consensus to expand to other *Campylobacter* species based on MIC distributions
    - Provide guidance on what antimicrobials to test based on specimen source under Testing Guidance (akin to *Salmonella* in M100)
  - Meropenem breakpoint
    - Proposing S only breakpoint of ≤0.25 ug/mL based on new MIC distributions
    - Disk diffusion breakpoint S ≥ 36mm based on dBETs
    - This susceptible breakpoint fits well with PK data for meropenem
  - Azithromycin breakpoint
    - Adding S only breakpoint of ≤0.5 ug/mL based on new MIC distributions
    - Aligns well with the EUCAST ECOFFs (*C. jejuni* 0.25ug/mL; *C. coli* 0.5ug/mL; although method different)
  - Ciprofloxacin
    - Current CLSI breakpoint of S ≤1ug/mL looks good from an MIC distribution perspective
    - PK/PD data suggests you can't achieve that level
    - Adjust breakpoint to be more aligned with the Enterobacterales breakpoint?
- Table 8: *Gemella* and Other Catalase Negative Gram-Positive Cocci
  - MIC distribution data was reviewed for *Gemella, Facklamia, Globicatella, Dolosigranulum*
  - *Globicatella* and *Gemella* typically demonstrate elevated MICs to ceftriaxone and low MICs to penicillin
    - Leave ceftriaxone breakpoint <1, add comment *Gemella, Facklamia,* and *Globicatella* have elevated MICs to ceftriaxone
  - *Facklamia* demonstrates elevated MICs to penicillin, ceftriaxone and meropenem
  - Consider eliminating the erythromycin BP?
  - Proposed BP for doxycycline S<0.25, linezolid <1, and daptomycin <2

- Ongoing study: Perform LHB BMD and evaluate linezolid and daptomycin
  - Evaluate CA-MHB as an alternative media type

- Table 16: *Moraxella catarrhalis*
  - Expand to other *Moraxella* species
  - N: 1,300
  - *M. osloensis*, *M. nonliquefaciens*, etc
  - Breakpoints look good for other *Moraxella* species
    - Recommend beta-lactamase testing for non-*catarrhalis* species as beta-lactamases are not as common among these species
    - Need to review additional beta-lactamase data
  - Maybe add meropenem breakpoints?
  - Add lefamulin for *M. catarrhalis* only
    - AST meeting Jan 2021: To accept S/NS BPs for lefamulin with *M. catarrhalis* (MIC-S: 0.5 µg/mL and NS: ≥1 µg/mL; DD-S: ≥19 mm and NS: ≤18 mm) to be added to M45.

- Table 21: Potential Bacterial Agents of Bioterrorism

Organisms	Suggested Updates
***Brucella* species**	• Clarify that the BPs are for *B. meletensis*, *B. suis* and *B. abortus* • Add a statement that these BPs do not apply to *Ochrobactrum* species or other previous *Brucella* species (that are now designated as other genera) • Emphasize importance of pH for methods • Add rifampin BP (S ≤ 2ug/mL) with appropriate monotherapy comment
Bacillus anthracis	• No changes to current breakpoints • No new reports of antimicrobial resistance • Add footnote for *Bacillus cereus* serovar *anthracis* which causes an anthrax type illness. CDC currently in conversations about how to deal with this organism. There are some differences between this strain's MICs versus *B. anthracis* • Need to add QC recommendations for amoxicillin; CDC use *E. coli* 25922 and *S. aureus* 29213
Yersinia pestis	• Add moxfloxacin or use ciprofloxacin/levofloxacin as a surrogate for moxifloxacin or add footnote?
Francisella tularensis	• Add moxfloxacin or use ciprofloxacin/levofloxacin as a surrogate for moxifloxacin or add footnote?

Organisms	Suggested Updates

Burkholderia pseudomallei; B. mallei	• Changes suggested for ceftazidime S≤8;R≥16 (remove intermediate category)
	• Changes suggested to meropenem S≤2;R≥4 (remove intermediate category)
	  • Concern raised about removing intermediate categories because of potential for testing issues.
	  • May not be an issue since most of these organisms are only tested at reference laboratories by reference methods.
	  • Potential concern for changing a breakpoint that is recognized by the FDA (especially for dropping the intermediate breakpoint for ceftazidime).
	• Add moxfloxacin or use ciprofloxacin/levofloxacin as a surrogate for moxifloxacin or add footnote?

- Follow-Up Items
  - Now that M45 is freely available. What should be moved from the M100 to the M45?
    - Non-Enterobacterales?
    - Anaerobes?
    - *Burkholderia cepacia* complex?
    - *Stenotrophomonas maltophilia*?
    - Any others?
  - Should M45 be renamed?
  - Publication date: January 2025?
  - Create a M45 working group that reports to an established working group
  - Can M45 become a "living" document?
- Criteria for M100 (standard) vs M45 (guideline)

	Data Required	Available for M45	Available for M100
Breakpoint	• ECV • Non clinical PK-PD cutoff • Clinical exposure-response cutoff • Clinical cutoff	No	Yes
ECV	• Collecting & merging data from a range of sources to define the upper-limit of the WT distribution • Need to use a recognized reference method • Data from ≥ 3 labs • MICs should be on scale	Maybe (but usually "No")	Yes
MIC distribution data with or without a reference method	• Data from one or more laboratories • Data may be generated using non reference MIC methods (e.g., lyophilized MIC panels) or using a non-standard method (e.g. *Capnocytophaga* species)	Yes	Not applicable; as ECVs usually available

- Studies Underway

Panels	# of panels	Location of Panels	Organisms	# of Isolates	Study	# of testing sites	# of panels for testing	# of panels for QC
GNB CAMHB panel (IHMA)	550	JHU	*Achromobacter* species	100	Disk-to-MIC & GD & mCIM, include CRO subset; FQ	1	200	10
			Non-*aeruginosa Pseudomonas*	100	Disk-to-MIC & GD & mCIM, include CRO subset; FQ*	1	200	10
			Aeromonas species	50	Disk-to-MIC & mCIM, FQ	1	100	20
LHB panel (IHMA)	450	VUMC	*Aerococcus* species	100	Disk-to-MIC	1	200	20
			Pasteurella spcies	50	Disk-to-MIC	1	100	10
			Gamella species & other catalase negative GPC	?	Add linez/dapto BPs	1		
			Leuconostoc species	?	Add linez/dapto BPs	1		
			Weisella species	?		1		
GP CAMHB (Thermo)	350	VUMC	*Micrococcus* species	?	Test nitrocefin & penicillin	1		
			Kocuria, Dermacoccus,	?	Eval as alternative media type?	1		
			Kytococcus, etc	100	Eval as alternative media type?	1		
			Aerococcus speices	50		1		
			Pasteurella species					

SC DISCUSSION (MAIN POINTS)

- Question: Do we need to re-define/rename the M45 as the document for BPs with less data? Yes, should rename this document. Also need to define what criteria are needed for breakpoints to be set in M100.
- Need to make sure the next publication of the M45 would match with M100. Perhaps a January 2025 publication date. There is also a talk of making this more of a living document, which can be updated more readily. Could use a model similar of the Manual of Clinical Microbiology, where it is published in print every 4 years, but updated online every year.
- CLSI needs to address PK/PD breakpoints. Eric Wenzler would like to be involved in the process.
- What is the process for approval of all these new tables? CLSI needs to plan for this large amount of data. The current chairholder would like to hear from previous chairholders of the working group. In the past, this document did not go through an extensive review process by the subcommittee
- There should be more feedback and oversight moving forward and need to plan how to have these future discussions.
- There is support for living documents in the field of infectious diseases, so it would be good for CLSI to also move this direction.
- Suggestion to remove the old drugs that are no longer clinically relevant or safe. Move them to someplace else, so they are not in the main document.
- *Neisseria gonorrhoeae* also does not have a lot of PK/PD data, so perhaps it should be considered for M45.
- The WG may want to add M45 breakpoints to CLSI vs. the FDA spreadsheet in the tool kit.
- This is a good opportunity to make a checklist to define ECV, PK/PD, and other metrics to need to determine if data should be in the M100 or M45. There was agreement in making a check list.

	• Need to have guidelines set so we can move older breakpoints that do not have all the modern necessary data into M45. Right now, these older breakpoints cannot be updated because they do not have and will never have the necessary data to update them by M100 standards. • There are difficulties in finding the perfect breakpoint. All of the components need to line up to tell you what it is versus a breakpoint. For example, what the PK/PD data says is different from the MIC distribution data, and the clinical data says something else. That is a decision to make about what goes in the M100. There is a difference between absence of data vs. conflicting data. The M45 would be for an absence of data, not as much for conflicting data. There was agreement for this statement. • Possible document title: Infrequently isolated and limited data • Suggestion to work with FDA to offer MIC only reporting. If we establish performance, can we report MIC only? If we establish essential agreement and bias, can we have the ability to report MIC only? • CLSI did start to plan an AHWG for PK/PD breakpoints under the Breakpoints working group. • A committee or WG need to define the M45 guidelines first so there is a reason for what goes where and why. There was agreement; however, this is such a large group of organisms that the group will not have data to keep them all in there. If they are moved out, then can bring some specific organisms back into M100 as data is collected. • There is a Non-Enterobacterales AHWG that currently exists so it either needs to be disbanded or this needs to be sent to this group. • Agreement to create a checklist and define M100 and M45 data. In general, there was agreement with where the working group is going (moving the Non-Enterobacterales to the M45), so the working group can continue forward down this path. But do need to define M100 and M45 placement before voting to move organism groups in M45. • There already is an M100 definition for what data is required, so please look at the existing definition. • MDSWG did get a report from the Non-Enterobacterales AHWG last year, so check for that existing data. • Jim Lewis nominated Trish Simner to head up defining the M100 and M45 definitions. The BPWG also needs to work on defining this. Darcie Carpenter and Linda Miller also volunteered. • The M45 final draft needs to be ready in February 2024 to get into the 2025 publication date.

5. **TABLE 1 AD HOC WORKING GROUP (T. SIMNER)**

***NEISSERIA MENINGITIDIS* TABLE**

- Proposed Table

Tier 1 - Antimicrobial agents that are appropriate for routine, primary testing and reporting	**Tier 2** - Antimicrobial agents that are appropriate for routine, primary testing but may be reported following cascade reporting rules established at each institution.	**Tier 3 -** Antimicrobial agents that are appropriate for routine, primary testing in institutions that serve patients at high risk for multidrug-resistant organisms (MDROs) but should only be reported following cascade reporting rules established at each institution.	**Tier 4** - Antimicrobial agents that may warrant testing and reporting by clinician request if antimicrobial agents in other Tiers are not optimal because of various factors.
Penicillin			
Cefotaxime or Ceftriaxone			Meropenem
			Azithromycin[a]
			Ciprofloxacin[a] Levofloxacin[a]
			Minocycline[a]
			Trimethoprim-sulfamethoxazole[b]
			Rifampin[a]

[a] May be appropriate only for prophylaxis of meningococcal case contacts. These breakpoints do not apply to therapy of patients with invasive meningococcal disease. **Antimicrobial susceptibility testing may be warranted to guide post-exposure prophylaxis.**

[b] Trimethoprim-sulfamethoxazole is the preferred disk for detection of sulfonamide resistance. Trimethoprim-sulfamethoxazole testing predicts susceptibility and resistance to trimethoprim-sulfamethoxazole and sulfonamides. Sulfonamides may be appropriate only for prophylaxis of meningococcal case contacts.

- *Neisseria meningitidis* Additional Footnotes
  - Important: For complete information on safety precautions, see Biosafety in Microbiological and Biomedical Laboratories. 6th ed. Washington, DC: US Department of Health and Human Services; 2020. Accessed 10 January 2023. http://www.cdc.gov/biosafety/publications/bmbl5/
  - (1) Recommended precautions: Perform all AST of *N. meningitidis* in a BSC. Manipulating N. meningitidis outside a BSC is associated with increased risk for contracting meningococcal disease. Laboratory-acquired meningococcal disease is associated with a case fatality rate of

50%. Exposure to droplets or aerosols of *N. meningitidis* is the most likely risk for laboratory-acquired infection. Rigorous protection from droplets or aerosols is mandated when microbiological procedures (including AST) are performed on all *N. meningitidis* isolates.

- (2) If a BSC is unavailable, manipulation of these isolates should be minimized, limited to Gram staining or serogroup identification using phenolized saline solution, while wearing a laboratory coat and gloves and working behind a full-face splash shield. Use BSL-3 practices, procedures, and containment equipment for activities with a high potential for droplet or aerosol production and for activities involving production quantities or high concentrations of infectious materials. If BSL-2 or BSL-3 facilities are not available, forward isolates to a referral or public health laboratory with a minimum of BSL-2 facilities.

A motion to accept the proposed *Neisseria meningitidis* Table 1 was made and seconded. Vote: 10 for, 0 against, 0 abstain, 4 absent (Pass)

COMBINED ANAEROBE TABLE 1J

- Proposed Table

Proposed Table 1J Combined Anaerobes

Tier 1: Antimicrobial agents that are appropriate for routine, primary testing and reporting	**Tier 2:** Antimicrobial agents that are appropriate for routine, primary testing but may be reported following cascade reporting rules established at each institution	**Tier 3:** Antimicrobial agents that may warrant routine testing or tested by request in institutions that serve patients at high risk for MDRO but should only be reported following cascade or selective reporting rules	**Tier 4:** Antimicrobial agents that may warrant testing and reporting by request if antimicrobial agents in other Tiers are not optimal because of various factors
Ampicillin[a,b] Penicillin[a,b,c]			
Amoxicillin-clavulanate Ampicillin-sulbactam Piperacillin-tazobactam			
Clindamycin			
Ertapenem Imipenem[d] Meropenem			Imipenem-relebactam[d]
Metronidazole[e]			
			Cefotetan Cefoxitin
			Ceftriaxone
			Moxifloxacin
			Tetracycline

Abbreviation. MDRO, multi-drug resistant organism

- Combined Footnotes

Footnotes

a. Ampicillin and penicillin are recommended for primary testing and reporting for gram-positive anaerobes (Tier 1) because most of them are ß-lactamase negative, but not for gram-negative anaerobes because many are ß-lactamase positive. For gram-negative anaerobes, ampicillin and penicillin are Tier 4 agents.

b. If ß-lactamase positive, report as resistant to penicillin and ampicillin. Be aware that ß-lactamase-negative isolates may be resistant to penicillin and ampicillin by other mechanisms.

c. Penicillin retains good *in vitro* activity against most *Fusobacterium* species and may be considered for primary testing and reporting with this genus.

d. 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.

e. Many non-spore-forming, gram-positive anaerobic rods are resistant to metronidazole (see Appendix D).

NOTE 1: Most anaerobic infections are polymicrobial, including both ß-lactamase-positive and ß-lactamase-negative strains. Testing may not be necessary for isolates associated with polymicrobial anaerobic infections. However, if susceptibility testing is requested, only the organism most likely to be resistant (eg, *Bacteroides* spp. and *Parabacteroides* spp.) should be tested and results reported (see Appendix D).

NOTE 2: Specific *Clostridium* spp. (eg, *Clostridium septicum, Clostridium sordellii*) may be the singular cause of infection and are typically susceptible to penicillin and ampicillin. Penicillin and clindamycin resistance have been reported in *Clostridium perfringens*. Agents in Tier 1 of Table 1J should be tested and reported for *Clostridium* spp.

SC DISCUSSION (MAIN POINTS)

- Approved by Anaerobe AHWG and TTWG
- Question: Why did the working group default to putting drugs in the tier that refers to gram-positive anaerobes? For ampicillin and penicillin, have tier 1 with a parenthesis indicating for gram-positives and then have it in tier 4 with a parenthesis indicated it is for gram-negatives. Then the footnote can be removed. This will be helpful because if it stays as a footnote, users could easily miss the footnote.
- Suggestion to keeping the footnote to provide an explanation for the gram-positive and gram-negative parentheses notations.

A motion to accept the proposed combined anaerobe Table 1 with the modification of ampicillin and penicillin in tier 1 for gram-positives and ampicillin and penicillin in tier 4 for gram-negatives was made and seconded. Vote: 11 for, 0 against, 0 abstain, 3 absent (Pass)

EDUCATION EFFORTS

- Annual M100 webinar – April Bobenchik
- Updates to the M100 Education Module to reflect the updated Tables 1– Janet Hindler
- JCM Minireview - Virginia Pierce, Tanaya Bhowmick, Trish Simner
- ASM Microbe symposia – Virginia Pierce

	DEVELOP TABLES FOR OTHER GEOGRAPHIC REGIONS
	• Start to work with PAHO to revise for South American countries
	• Presented at the first Latin American and Caribbean Network for AMR Surveillance (ReLAVRA+) webinar on March 28th, 2023
	• Attend conference in Medellin, Colombia July 11-13th to work on adapting the tables
	
	NEXT STEPS
	• Address new changes suggested at this meeting
	  ○ Enterobacterales
	  ○ Cascade from third generation cephalosporins to cefepime: add a footnote for ESBL producers
	• Discuss inclusion of ASP reporting comments
	• Provide further guidance on testing and reporting when antimicrobial resistance testing is performed
	• Should we provide a cutoff for resistance above which laboratories should consider primary testing tier 3 agents?
	• Further guidance around antimicrobial resistance testing and implications on testing and reporting guidance

6.	**DISK DIFFUSION REFERENCE METHOD (J. HINDLER)** **OBJECTIVES** • Request an ad hoc committee be formed to address disk diffusion as a reference method and think about defining future "reference methods" • Decide on what to do with "the box" (box shown below) **AD HOC WORKING GROUP CHARGES** • Define "future" state of disk diffusion as "reference" vs "standardized" method • Draft language to clarify across CLSI documents and FAQ for labs • Evaluate future "reference method" requirements **"THE BOX"** • Disk diffusion manufacturers are not updating BPs in IFU • M100 is suggesting use of an off-label test (disk diffusion) to validate another off-label test

CLSI Reference Methods vs Commercial Methods and CLSI vs US Food and Drug Administration Breakpoints

It is important for users of M02,[1] M07,[2] and M100 to recognize that the standard methods described in CLSI documents are reference methods. These methods may be used for routine antimicrobial susceptibility testing of patient isolates, for evaluating commercial devices that will be used in medical laboratories, or by drug or device manufacturers for testing new agents or systems. Results generated by reference methods, such as those included in CLSI documents, may be used by regulatory authorities to evaluate the performance of commercial susceptibility testing devices as part of the approval process. Clearance by a regulatory authority indicates the commercial susceptibility testing device provides susceptibility results that are substantially equivalent to results generated using reference methods for the organisms and antimicrobial agents described in the device manufacturer's approved package insert.

CLSI breakpoints may differ from those approved by various regulatory authorities for many reasons, including use of different databases, differences in data interpretation, differences in doses used in different parts of the world, and public health policies. Differences also exist because CLSI proactively evaluates the need for changing breakpoints. The reasons why breakpoints may change and the manner in which CLSI evaluates data and determines breakpoints are outlined in CLSI document M23.[4]

Following a decision by CLSI to change an existing breakpoint, regulatory authorities may also review data to determine how changing breakpoints may affect the safety and effectiveness of the antimicrobial agent for the approved indications. If the regulatory authority changes breakpoints, commercial device manufacturers may have to conduct a clinical trial, submit the data to the regulatory authority, and await review and approval. For these reasons, a delay of one or more years may be needed if a breakpoint and interpretive category change is to be implemented by a device manufacturer. In the United States, it is acceptable for laboratories that use US Food and Drug Administration (FDA)-cleared susceptibility testing devices to use existing FDA breakpoints. Either FDA or CLSI susceptibility breakpoints are acceptable to laboratory accrediting organizations in the United States. Policies in other countries may vary. Each laboratory should check with the manufacturer of its antimicrobial susceptibility test system for additional information on the breakpoints and interpretive categories used in its system's software.

Following discussions with **the antimicrobial stewardship team and other relevant institutional** stakeholders, newly approved or revised breakpoints may be implemented by laboratories. Following verification, CLSI disk diffusion test breakpoints may be implemented as soon as they are published in M100. If a device includes antimicrobial test concentrations sufficient to allow interpretation of susceptibility and resistance to an agent using the CLSI breakpoints, a laboratory could choose to, after appropriate verification, interpret and report results using CLSI breakpoints.

SC DISCUSSION (MAIN POINTS)

- Question if the box belongs in M100. There is consideration to remove this.
- Manufacturers are not able to update disk diffusion breakpoints and disk instructions for use until a legacy disk breakpoint update protocol is cleared by the FDA by the 510K process is available. No one was aware of any disk manufacturers which have achieved submission and clearance for this yet.
- This box also exists in M02 and M07.
- The last paragraph in this box is currently incorrect.
- This whole box is talking about reference methods, but users are incorrectly using disk diffusion to validate commercial MIC methods. Perhaps this section needs to be clarified that it does not apply to disk diffusion.
- A suggestion was made to use broth microdilution as the gold standard comparison to update new breakpoints.

	• Suggestion to remove the last paragraph. • The top sentence in red is OK to stay. • The FDA is working on a pathway for manufacturers to update disk diffusion breakpoints on legacy devices. • Taking out disk diffusion as a reference method is going to be a big deal for clinical laboratories because broth microdilution is not widely available in laboratories. • If removed from M100, the box should also come out of M02 and M07 documents as well to keep harmonization. • Verification vs. validation is incorrect. Disk manufacturers also need to get clearance for updated breakpoints but that was not clear. • This box does provide value because it says that just because CLSI publishes a breakpoint change does not mean that the device has been FDA cleared for use. Consider changing the word "verification" to "validation", then leave it as it is for now, and do additional cleanup later. • A clinical lab can do their own validation of disk breakpoints to update. Disk diffusion is like any other commercial manufacturer. • The disk method cannot be used as a reference method for validation of an MIC method. • Updating a CLSI breakpoint requires either clearance by the disk manufacturer or validation of the off-label use by the laboratory. • Suggestion to delete the last sentence in red, and then change the last sentence to say validation instead of verification. • In the 3rd paragraph, it discusses commercial devices. If labs need to validate disk diffusion breakpoint changes, it should be consistent and say that labs need to validate commercial devices to update breakpoints as well. • Since this is an FDA recognized document, it is not recommended to include the word validation. This is an FDA recognized document, and validating off label use is not supported by the agency. • The following group of volunteers to work offline for the box wording and discuss disk diffusion as a reference method versus standard method: Janet Hindler, Sharon Cullen, Sandy Richter, Darcie Carpenter, Barb Zimmer, Elizabeth Palavecino, Virginia Pierce, Natasha Griffin, and the TTWG.
7.	**ADJOURNMENT** Dr. Lewis thanked the participants for their attention. The meeting was adjourned at 12:00 PM Central Standard (US) time.

PLENARY ATTENDEES

Plenary 1	Plenary 2	Plenary 3
April Abbott	April Abbott	April Abbott
Rebecca Abelman	Rebecca Abelman	Rebecca Abelman
Egla Agalliu	Egla Agalliu	Egla Agalliu
Iftikhar Ahmed	Iftikhar Ahmed	Iftikhar Ahmed
Julia Alaniz	Julia Alaniz	Julia Alaniz
Kevin Alby	Kevin Alby	Kevin Alby
Jeff Alder	Jeff Alder	Jeff Alder
Anna Karina Algustie	Anna Karina Algustie	Anna Karina Algustie
Jane Ambler	Jane Ambler	Jane Ambler
Diane Anastasiou	Diane Anastasiou	Diane Anastasiou
Archana Angrup	Archana Angrup	Archana Angrup
Stella Antonara	Stella Antonara	Ruth Appleby
Sophie Arbefeville	Sophie Arbefeville	Nicolas Arab
Mari Ariyasu	Mari Ariyasu	Sophie Arbefeville
Tomefa Asempa	Tomefa Asempa	Mari Ariyasu
Robyn Atkinson Dunn	Robyn Atkinson Dunn	Tomefa Asempa
Rocio Balbuena	Rocio Balbuena	Robyn Atkinson Dunn
Meagan Barber	Pennie Baptie	Habeeb Baig
Faiza Benahmed	Meagan Barber	Rocio Balbuena
Amira Bhalodi	Faiza Benahmed	Meagan Barber
Amelia Bhatnagar	Amira Bhalodi	Faiza Benahmed
Kelley Black	Amelia Bhatnagar	Amira Bhalodi
April Bobenchik	Kelley Black	Amelia Bhatnagar
Malcolm Boswell	April Bobenchik	Kelley Black
Robert Bowden	Malcolm Boswell	April Bobenchik
Jennifer Boyer	Robert Bowden	Malcolm Boswell
Patricia Bradford	Jennifer Boyer	Robert Bowden
Makena Brand	Patricia Bradford	Jennifer Boyer
Maryann Brandt	Makena Brand	Patricia Bradford
John Breton	Maryann Brandt	Makena Brand
Rebecca Brock	John Breton	Maryann Brandt
Jay Bryowsky	Jay Bryowsky	John Breton
Alexandra Bryson	Alexandra Bryson	Jay Bryowsky

Maria Burgos-Garay
Carey-Ann Burnham
Deborah Butler
Dr. Umeshkumar.C
Davina Campbell
Shelley Campeau
Rafael Canton
Darcie Carpenter
Cecilia Carvalhaes
Mariana Castanheira
Michelle Cecilia
Sukantha Chandrasekaran
Shelley Chang
YAMIN CHEN
Katherine Cicala
Nicolynn Cole
Jekia Cox
Hannah Creager
Edith Csiki-Fejer
Sharon Cullen
Dmitri Debabov
Boudewijn DeJonge
Dubraska Diaz-Campos
Jennifer Dien Bard
Tanis Dingle
Lindsay Donohue
Dana Dressel
Rebekah Dumm
Elaine Duncan
Allison Eberly
Paul Edelstein
GERMAN ESPARZA
Sandy Estrada
Marianna Fedorenko

Maria Burgos-Garay
Carey-Ann Burnham
Deborah Butler
Dr. Umeshkumar.C
Davina Campbell
Shelley Campeau
Rafael Canton
Darcie Carpenter
Cecilia Carvalhaes
Mariana Castanheira
Michelle Cecilia
Sukantha Chandrasekaran
Shelley Chang
YAMIN CHEN
Katherine Cicala
Nicolynn Cole
Jekia Cox
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Karen Bush
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Dr. Umeshkumar.C
Davina Campbell
Shelley Campeau
Rafael Canton
Darcie Carpenter
Cecilia Carvalhaes
Katharine Castagna
Mariana Castanheira
Michelle Cecilia
Sukantha Chandrasekaran
Shelley Chang
YAMIN CHEN
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Allison Eberly
Paul Edelstein
GERMAN ESPARZA

Erica Fernandez
Andrea Ferrell
Andrea Feßler
Laura Filkins
Kelly Flentie
Andrew Fratoni
Lawrence Friedrich
Marcelo Galas
Barb Gancarz
Rahul Garg
Darcy Gill
Melissa Gitman
Heather Glasgow
Melissa Godwin, MLS
Howard Gold
Beth Goldstein
Rebecca Gordon
Alice Gray
Kamisha Gray
Natasha Griffin
Carlos Gutierrez
Meredith Hackel
Camille Hamula
Christine Hanks
Dwight Hardy
Krystal Hennerbichler
Esther Hernandez
Janet Hindler
Elizabeth Hirsch
Rita Hoffard
Henry Carl Hosea
Michael Huband
Romney Humphries
Lauren Hunt

Andrea Ferrell
Andrea Feßler
Laura Filkins
Kelly Flentie
Andrew Fratoni
Lawrence Friedrich
Marcelo Galas
Barb Gancarz
Rahul Garg
Darcy Gill
Melissa Gitman
Heather Glasgow
Melissa Godwin, MLS
Howard Gold
Beth Goldstein
Rebecca Gordon
Alice Gray
Kamisha Gray
Natasha Griffin
Carlos Gutierrez
Meredith Hackel
Camille Hamula
Christine Hanks
Dwight Hardy
Esther Hernandez
Janet Hindler
Elizabeth Hirsch
Rita Hoffard
Henry Carl Hosea
Michael Huband
Romney Humphries
Lauren Hunt
Holly Huse
Dmitri Iarikov

Sandy Estrada
Marianna Fedorenko
Erica Fernandez
Andrea Ferrell
Andrea Feßler
Laura Filkins
Kelly Flentie
Andrew Fratoni
Lawrence Friedrich
Marcelo Galas
Barb Gancarz
Rahul Garg
Darcy Gill
Melissa Gitman
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Henry Carl Hosea
Michael Huband
Romney Humphries

Holly Huse
Dmitri Iarikov
Mitsutaka Iguchi
Sophonie Oyeniran
Antonieta Jimenez
Brian Johnson
Kristie Johnson
James Jorgensen
Sarah Jung
Gunnar Kahlmeter
Maria Karlsson
Haziq Khalid
Edson Kimario
Susan Kircher
Thomas Kirn
Anna Klavins
Cynthia Knapp
Amanda Kuperus
Joseph Kuti
Kajal Larson
Stephen LaVoie
Carlo Ledesma
Blaine Leppanen
Autumn Lewis
James Lewis
Rachael Liesman
Brandi Limbago
Christopher Longshaw
David Lonsway
Joseph Lutgring
Maria Jose Machado
iman mahmood khudhur
Rianna Malherbe
Michelle Malysa
Sophonie Oyeniran
Antonieta Jimenez
Brian Johnson
Kristie Johnson
James Jorgensen
Sarah Jung
Gunnar Kahlmeter
Maria Karlsson
Haziq Khalid
Edson Kimario
Susan Kircher
Thomas Kirn
Anna Klavins
Cynthia Knapp
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Michelle Malysa
Naveen Gopi Manakkadan
Isabella Martin
Ron Master
Lauren Hunt
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Mitsutaka Iguchi
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Maria Karlsson
Haziq Khalid
Edson Kimario
Susan Kircher
Thomas Kirn
Anna Klavins
Cynthia Knapp
Amanda Kuperus
Joseph Kuti
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Stephen LaVoie
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James Lewis
Rachael Liesman
Brandi Limbago
Christopher Longshaw
David Lonsway
Joseph Lutgring
Maria Jose Machado
iman mahmood khudhur
Rianna Malherbe

Naveen Gopi Manakkadan
Isabella Martin
Ron Master
Amy Mathers
Erika Matuschek
Pinku Mazumdar
Sandra McCurdy
Sarah McLeod
Rod Mendes
Alita Miller
Linda Miller
Will Miller
Crystal Minchew
Ruel Mirasol
Stephanie Mitchell
Greg Moeck
Nicholas Moore
Mary Motyl
Bhavik Nana
Navaneeth Narayanan
Sean Nguyen
David Nicolau
John O'Donnell
Susan O'Rourke
Kiyofumi Ohkusu, Ph.D.
Margaret Ordonez Smith de Danies
John Otero
Jennifer Ott
Linda Otterson
Elizabeth Palavecino
Utsav Pandey
Jean Patel
Robin Patel
Tammy Payne

Amy Mathers
Pinku Mazumdar
Sandra McCurdy
Sarah McLeod
Rod Mendes
Alita Miller
Linda Miller
Will Miller
Crystal Minchew
Ruel Mirasol
Stephanie Mitchell
Greg Moeck
Nahid Mohamed Salih
Nicholas Moore
Mary Motyl
Bhavik Nana
Navaneeth Narayanan
Sean Nguyen
David Nicolau
John O'Donnell
Susan O'Rourke
Kiyofumi Ohkusu, Ph.D.
FREDRICK ODOYO ONDIEK
Margaret Ordonez Smith de Danies
John Otero
Jennifer Ott
Linda Otterson
Elizabeth Palavecino
Jean Patel
Robin Patel
Tammy Payne
Morgan Pence
Elizabeth Jean Picardal Lucas
Laura Tatiana Picón Moncada

Michelle Malysa
Naveen Gopi Manakkadan
Isabella Martin
Ron Master
Amy Mathers
Mira Maximos (she/her/hers)
Shelly Maximov
Pinku Mazumdar
Sandra McCurdy
Sarah McLeod
Rod Mendes
Linda Miller
Will Miller
Crystal Minchew
Ruel Mirasol
Stephanie Mitchell
Greg Moeck
Nicholas Moore
Mary Motyl
Bhavik Nana
Navaneeth Narayanan
Sean Nguyen
David Nicolau
John O'Donnell
Susan O'Rourke
Kiyofumi Ohkusu, Ph.D.
Margaret Ordonez Smith de Danies
John Otero
Jennifer Ott
Linda Otterson
Elizabeth Palavecino
Jean Patel
Robin Patel
Tammy Payne

Morgan Pence
Elizabeth Jean Picardal Lucas
Laura Tatiana Picón Moncada
Jessica Pierce
Virginia Pierce
Chris Pillar
Kelsey Pischel
Anna Poettker
Dakota Poirrier
Abigail Pride
Sachidevi Puttaswamy
David R
Mark Redell
L. Barth Reller
Felicia Rice
Sandra Richter
Kristen Roberts
Flavia Rossi
William Rotunno
Deana Sabuda
Michael Satlin
Nicole Scangarella-Oman
Marc Scheetz
Linda Schuermeyer
Audrey Schuetz
Alisa Serio
Susan Sharp
Ribhi Shawar
Jingzi Sherman
Kileen Shier
Sharon Shinn
Simone Shurland
Patricia Simner
Christine Slover
Jessica Pierce
Virginia Pierce
Chris Pillar
Kelsey Pischel
Anna Poettker
Dakota Poirrier
Abigail Pride
Sachidevi Puttaswamy
Mark Redell
L. Barth Reller
Felicia Rice
Sandra Richter
Kristen Roberts
Stephanie Robinson
Flavia Rossi
William Rotunno
Deana Sabuda
Michael Satlin
Nicole Scangarella-Oman
Marc Scheetz
Linda Schuermeyer
Audrey Schuetz
Alisa Serio
Susan Sharp
Ribhi Shawar
Jingzi Sherman
Kileen Shier
Sharon Shinn
Simone Shurland
Patricia Simner
Christine Slover
Jillian Socea
Brittany Spindler
Jeff Starkey
Morgan Pence
Elizabeth Jean Picardal Lucas
Laura Tatiana Picón Moncada
Jessica Pierce
Virginia Pierce
Chris Pillar
Kelsey Pischel
Anna Poettker
Dakota Poirrier
Abigail Pride
Sachidevi Puttaswamy
Mark Redell
L. Barth Reller
Felicia Rice
Sandra Richter
Kristen Roberts
Stephanie Robinson
Flavia Rossi
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Pranita Tamma
Nicole Tarlton
Robert Taylor
Jolyn Tenllado
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