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Meeting Title:	**Subcommittee (SC) on Antimicrobial Susceptibility Testing (AST)**	**Contact:**	mhackenbrack@clsi.org
Meeting Date:	3 – 5 June 2018		
Start Time:	3 June – 8:00 AM 4 June – 8:00 AM 5 June - 8:00 AM	**End Time:**	5:00 PM 5:00 PM 12:00 PM
Meeting Purpose:	The primary purpose of this meeting is to review and discuss AST WG and SC business in preparation for publication of the next edition of M100 (29th).		
Requested Attendee(s):	SC Chairholder, Vice-chairholder, Members, Advisors, and Reviewers; Expert Panel on Microbiology Chairholder and Vice-chairholder; CLSI Staff		

Attendee(s):

Melvin P. Weinstein, MD **Chairholder**	**Rutgers Robert Wood John Medical School**
Jean B. Patel, PhD, D(ABMM) **Vice-chairholder: AST Subcommittee and Expert Panel on Microbiology**	**Centers for Disease Control and Prevention**

Members Present:

Sharon K. Cullen, BS, RAC	Beckman Coulter, Inc. Microbiology Business
Marcelo F. Galas	Pan American Health Organization
Howard Gold, MD, FIDS	Harvard Medical Faculty Physicians, BIDMC
Romney M. Humphries, PhD, D(ABMM)	Accelerate Diagnostics, Inc.
Thomas J. Kirn, MD, PhD	Rugers Robert Wood Johnson Medical School
James S. Lewis, PharmD	Oregon Health and Science University
Brandi Limbago, PhD	Centers for Disease Control and Prevention
Amy J. Mathers, MD, D(ABMM)	University of Virginia Medical Center
Tony Mazzulli, MD, FACP, FRCP(C)	Mount Sinai Hospital
Sandra S. Richter, MD, D(ABMM), FCAP, FIDSA	Cleveland Clinic
Michael Satlin, MD	New York Presbyterian Hospital
Audrey N. Schuetz, MD, MPH, D(ABMM)	Mayo Clinic
Pranita D. Tamma, MD, MHS	Johns Hopkins University School of Medicine

Advisors

Vanessa G. Allen,. MD	Public Health Ontario
Tanaya Bhowmick, MD	Rutgers Robert Wood Johnson Medical School
April Bobenchik, PhD, D(ABMM)	Lifespan Academic Medical Center
Mariana Castanheira, PhD	JMI Laboratories
Sheila Farnham, MT(ASCP)	bioMérieux, Inc.
Graeme Forrest, MBBS	Oregon Health Sciences University
Janet A. Hindler, MT(ASCP), MCLS	UCLA Medical Center
Elizabeth Hirsch, PharmD	University of Minnesota College of Pharmacy
Stephen G. Jenkins, PhD, D(ABMM), F(AAM)	Weill Cornell Medicine
Linda A. Miller, PhD	CMID Pharma Consulting
Greg Moeck, PhD	VenatoRx Pharmaceuticals
Sumathi Nambiar, MD	FDA Center for Devices and Radiological Health
Navaneeth Narayanan, PharmD	Ernest Mario School of Pharmacy, Rutgers University
David P. Nicolau, FCCP, FIDSA, PharmD	Hartford Hospital
Virginia M. Pierce, MD	Massachusetts General Hospital
Ribhi M. Shawar, PhD, D(ABMM)	FDA Center for Devices and Radiological Health
Patricia J. Simner, PhD, D(ABMM)	Johns Hopkins Hospital - Pathology
Kazuhiro Tateda, MD	Toho University School of Medicine

Barbara L. Zimmer, PhD	Beckman Coulter – West Sacramento
Reviewers	
Jane E. Ambler, PhD	Wockhardt, Morton Grove Pharmaceuticals
Robert Bowden, BS	University of Florida's Veterinary Diagnostic Laboratories
Lynn Boyer, BA, MT(HEW), MLT(ASCP)	Beckman Coulter Diagnostics
Willliam B. Brasso, BS	BD Diagnostic Systems
Linda C. Bruno, MA, MT(ASCP)	ACL Laboratories
Kendall Bryant, PhD, D(ABMM)	Kaiser Permanente
Karen Bush, PhD	Indiana University
Susan Butler-Wu, PhD, D(ABMM), SM(ASCP)	LACUSC Medical Center
Shelley Campeau, PhD, D(ABMM)	Accelerate Diagnostics
Darcie E. Carpenter, PhD, CIC	International Health Management Associates, Inc.
Karen C. Carroll, MD	Johns Hopkins Medical Institutions
Diane M. Citron, BS	R.M. Alden Research Laboratory
Patricia S. Conville, MS, MT(ASCP)	FDA Center for Devices and Radiological Health
Ian A. Critchley, PhD	Spero Therapeutics
Jennifer Dien Bard, PhD, D(ABMM), F(CCM)	Children's Hosptial Los Angeles; University of Southern California
Tanis Dingle, PhD, D(ABMM), FCCM	Provincial Laboratory for Public Health
Michael J. Dowzicky	Pfizer, Inc.
Michael N. Dudley, PharmD	The Medicine Company
Paul Edelstein, MD	Hospital of the University of Pennsylvania
German Esparza, BSc	Proasecal SAS Colombia
Gina L. Ewald-Saldana, MT(ASCP)	Beckman Coulter, Inc.
Mary Jane Ferraro, MPH, PhD	Massachusetts General Hospital and Harvard Medical School
Andrea L. Ferrell, MLScm(ASCP)	Becton Dickinson
Robert K. Flamm, PhD	JMI Laboratories
Avery Goodwin, MS, PhD	FDA Center for Devices and Radiological Health
Meredith Hackel, PhD	International Health Management Associates, Inc.
Dwight J. Hardy, PhD	University of Rochester Medical Center
Michael D. Huband, BS	JMI Laboratories
Kristie Johnson, PhD, D(ABMM)	University of Maryland, Baltimore
Ronald N. Jones, MD	JMI Laboratories
James H. Jorgensen, PhD	University of Texas Health Science Center
Asa Karlsson	bioMérieux, Inc.
Susan M. Kircher, MS, MT(ASCP)	BD Diagnostics Systems
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Peggy Kohner, BS, MT(ASCP)	Mayo Clinic
Kevin Krause, BS	Achaogen, Inc.
Dyan Luper, BS, MT(ASCP)SM, MB	BD Diagnostic Systems
Sandra McCurdy, MS	Melinta Therapeutics, Inc.
Ian Morrissey, PhD	IHMA Europe Sàrl
Susan D. Munro, MT(ASCP), CLS	USA
Elizabeth Papavecino, MD	Wake Forest Baptist Medical Center
Samir Patel, PhD, FCCM, D(ABMM)	Public Health Ontario
Chris Pillar, PhD	Micromyx, LLC
L. Barth Reller, MD	Duke University School of Medicine
Helio S. Sader, MD	JMI Laboratories
Nicole Scangarella-Oman, BS	GlaxoSmithKline
Jeff Schapiro, MD	The Permanente Medical Group
Dale A. Schwab, PhD, D(ABMM)CM	Quest Diagnostics Nichols Institute

Katherine Sei, BS	Beckman Coulter, Inc.
Susan Sharp, PhD	Copan Diagnostics, Inc.
Dee Shortridge, PhD	JMI Laboratories
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Susan Thomson	MAST Group
Lauri D. Thrupp, MD	University of California Irvine Medical Center
Maria M. Traczewski, BS, MT(ASCP)	The Clinical Microbiolgy Institute
Nancy E. Watz, MS, MT(ASCP), CLS	Stanford Health Care
Mary K. York, PhD, D(ABMM)	MKY Microbiology Consulting
Katherine Young, AB	Merck & Company
Guests (Non-SC-roster attendees)	
Victoria Anikst	UCLA Health
Mari Ariyasu	Shionogi, Inc.
Donald Biek	Geom Therapeutics
Malcolm Boswell	Accerlerate Diagnostics
Jeffrey Brocious	FDA Center for Devices and Radiological Health
Ashanti Brown	BD Diagnostics
Jason Bryowsky	Achaogen
Timothy Carrothers	Allergan
Chulhun Chang	Pusan National University Yangsan Hospital
Susan Cusick	VenatoRx
Zhixia Y. Danielsen	Food and Drug Administration
Andrew DeRyke	Merck Research Labs
Dana Dressel	IHMA, Inc.
Elaine Duncan	Beckman Coulter
Roger Echols	Shionogi & Company
David Fam, PharmD	Shionogi, Inc.
Jerome Ferrari	bioMérieux, Inc.
Cindy Fowler	bioMérieux, Inc.
Andrew Fuhrmeister	JMI Laboratories
Momoko Fujisaki	Eiken Chemical
Barbara Gancarz	bioMérieux, Inc.
Alice Gray	bioMérieux, Inc.
Jennifer Hammond	Pfizer
Nilia M. Robles Hernández	bioMérieux, Inc.
Rita Hoffard	Becton Dickinson
Ann Howell, PharmD, MS	Shionogi, Inc.
Olga Lomovskaya	The Medicines Company
Audrey Manalo, M(ASCP), PHM	Los Angeles Public Health Laboratory
Ron Master	Quest Diagnostics
Sarah McLeod	Entasis Therapeutics
Lisa Meyers	bioMérieux, Inc.
Ruel B. Mirasol	UCLA Health
Ross Mulder	bioMérieux, Inc.
Kiyofumi Ohkusu, PhD	Tokyo Medical University
John Otero	Shionogi, Inc.
Nick Pankau	IHMA, Inc.
Susan Raber	Pfizer
Janet Raddatz	Merck Research Labs

Eric Ransom	APHL - CDC
Mark Redell	Melinta Therapeutics
Jen-Yves Ressot	bioMérieux, Inc.
Mike Rinaldi	Melinta Therapeutics
Barbara Schenk	Becton Dickinson
Alisa Serio	Achaogen
Kimiyo Shono, MBA	Shionogi, Inc.
Laura Stewart	Becton Dickinson
Jolyn Tenllado	bioMérieux, Inc.
Masakatsu Tsuji, PhD	Shionogi & Co., Inc.
Tam Van	Harbor-UCLA Medical Center
Yang Yang, CLS II	Los Angeles Public Health Laboratory
Yoshie Yuhara	Eiken Chemical
Staff:	
Kathy Castagna, MS, MT(ASCP)CT, MB	CLSI
Glen Fine, MS, MBA, CAE	CLSI
Marcy L. Hackenbrack, MCM, M(ASCP)	CLSI
Megan Scanlon	CLSI

OPENING PLENARY AGENDA Monday, 4 June 2018								
Item #	**Item Title**	**Start**	**End**	**Length (Min)**	**Category**	**Presenter**	**Folder**	**Page**
1.	Opening Remarks	11:00 AM	11:10 AM	10	Remarks	Dr. Weinstein	N/A	7
2.	CLSI Update	11:10 AM	11:20 AM	10	Update	Mr. Fine	N/A	7
3.	Updates to Disclosure of Interest Summary	11:20 AM	11:25 AM	5	Update	Dr. Weinstein	3	7
4.	June 2017 Meeting Summary Minutes	11:25 AM	11:30 AM	5	VOTE	Dr. Weinstein	2	7
5.	Methods Development and Standardization WG	11:30 AM	12:30 PM	60	Report	Dr. Zimmer Dr. Hardy	7	8
	Luncheon – 12:30 – 1:30 PM (Garden Terrace 4)							
6.	Breakpoint WG Report (Part 1)	1:30 PM	3:30 PM	120	Report Votes?	Dr. Lewis Dr. Eliopolous	5	13
	Break (3:30 – 3:45 PM)							
7.	Outreach WG Report	3:45 PM	4:00 PM	15	Report	Dr. Schuetz Ms. Hindler	8	19
8.	Methods Application and Interpretation WG Report	4:00 PM	5:00 PM	60	Report Votes?	Dr. Limbago Dr. Kirn	6	21
9.	M39 WG Report	5:00 PM	5:30 PM	30	Report	Ms. Hindler Dr. Simner	13	29
10.	Testing for susceptibility using using physiologic media other than Mueller-Hinton	5:30 PM	6:00 PM	30	Report	Dr. Nizet	N/A	29
	Adjournment	6:00 PM				Dr. Weinstein		N/A

CLOSING PLENARY AGENDA Tuesday, 5 June 2018								
Item #	**Item Title**	**Start**	**End**	**Length (Min)**	**Category**	**Presenter**	**Folder**	**Page**
1.	Opening Remarks	7:30 AM	7:35 AM	5	Remarks	Dr. Weinstein	N/A	N/A
2.	Breakpoint WG Report (Part 2)	7:35 AM	8:35 AM	60	Report Votes?	Dr. Lewis Dr. Eliopolous	5	31
3.	M23 WG Report	8:35 AM	9:00 AM	25	Report	Dr. Wikler	12	N/A
	Break (9:00 – 9:15 AM)							
4.	Quality Control WG Report	9:15 AM	10:00 AM	45	Report Vote?	Ms. Cullen Ms. Traczewski	9	36
5.	Text and Tables WG Report	10:00 AM	10:30 AM	30	Report	Dr. Campeau Ms. Swenson	10	44
6.	Veterinary AST Liaison Report	10:30 AM	10:45 AM	15	Report	Mr. Bowden	N/A	46
7.	ADDED: GCWG Report				Report	Dr. Ferraro	13	46
8.	Meeting Wrap-up/Plans for next meeting	10:45 AM	11:00 AM	15		Dr. Weinstein	N/A	N/A
	Adjourn	11:00 AM						

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SUMMARY MINUTES	
#	**Description**
Monday, 4 June 2018 (NOTE: All presentations from the plenary sessions are now available on the CLSI Website (2018 June AST Plenary Presentations)	
1.	**Opening Remarks: Dr. Mel Weinstein** Dr. Weinstein opened the meeting at 11:00 AM by thanking the attendees for their participation in the working group sessions and continued efforts. Updates on subcommittee activities included: • Significant progress has been made on the drafting of rationale documents for drug/microorganisms combinations where CLSI breakpoints differ from Food and Drug Administration (FDA) breakpoints. He expressed his gratitude to Dr. Romney Humphries for taking the lead on this project. – The colistin rationale document is in the final editing process and should be available soon. – The fluoroquinolone rationale document for *Enterobacteriaceae*, *Pseudomonas* spp, and *Acinetobacter* spp. is next in the queue. – A rationale document for *Acinetobacter* spp. and the imipenem and doripenem is in progress. • Dr. Weinstein announced that Dr. Mary Jane Ferraro will be awarded the Sonnenwirth Award for Leadership in Clinical Microbiology and Dr. Trish Simner will be awarded the Diagnostic Young Investigator Award at the ASM Microbe meeting in Atlanta, Georgia. He congratulated both on their fine accomplishments.
2.	**CLSI Update: Mr. Glen Fine** • Mr. Fine welcomed the attendees to San Diego on behalf of the CLSI Board of Directors and staff. He expressed his gratitude to the Subcommittee volunteers for their hard work and continued support of CLSI. • He recognized and expressed thanks to all the new AST attendees. There are 25 first-time attendees at this meeting and hope that they will continue with CLSI. • The statistics regarding the use of M100 and related standards was reviewed. There are three ways to access M100: through document sales, through the cloud-based Eclipse product, and through free availability on the CLSI website. – Compared to the last package (ie, revised M100, M02, and M07) year (2015), sales for this package year (2018) are within 2% of those in 2015. – Those member organizations subscribing to Eclipse have access to all CLSI documents and "hits" for M100 on Eclipse has increased by 20% in the last year. – "Hits" and the free version of M100, M60 (antifungal breakpoints), and the VET01 supplement (soon to be replace by VET08) has increased by about 20%.
3.	**Updates to Disclosure of Interest Summary: Dr. Weinstein (Folder 3)** • Dr. Weinstein requested any updates to the disclosure of interest summary included in the agenda material. • There were no updates reported.
4.	**Vote: January 2018 Meeting Summary Minutes (Folder 2)**
	A motion to accept the summary minutes from the January 2018 subcommittee meeting was made and seconded. VOTE: 13 for – 0 against (Pass).
	The approved summary minutes have been posted on the CLSI website using the following link to the 2018 January AST Meeting Files.

SUMMARY MINUTES

#	Description
5.	**Methods Development and Standardization Working Group (MDSWG) Report: Dr. Dwight Hardy (Folder 7)** **WG Roster**: Co-chairholders – Dwight Hardy and Barbara Zimmer (co-chairholders); Secretary – Katherine Sei; Members – Bill Brasso, Susan Butler-Wu, Jennifer Dien-Bard, Tanis Dingle, Romney Humphries, Laura Koeth, and Ribhi Shawar. **Coagulase-Negative Staphylococcus (CoNS) AdHoc WG (AHWG) Report - (Vote)** **CoNs AHWG Roster**: Co-chairholders – Jennifer Dien-Bard and Lars Westblade; Members – Shelley Campeau, Paul Edelstein, Romney Humphries, and Jana Swenson • Laboratories are now better able to identify CoNS isolates to the species level using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS). As a result, the AHWG was charged to investigate whether the current breakpoints for oxacillin against CoNS are appropriate for contemporary *Staphylococcus epidermidis* isolates. Current breakpoints in Table 2C of M100 are listed below.

Organism	Oxacillin Breakpoint				Cefoxitin Breakpoint			
	DD (mm)		MIC (ug/ml)		DD (mm)		MIC (ug/ml)	
	S	R	S	R	S	R	S	R
S. aureus/*S. lugdunensis*	-	-	≤2	≥4	≥22	≤21	≤4	≥8
CoNS (except *S. lugdunensis*, *S. pseudintermedius*, *S. schlieferi)*	-	-	≤0.25	≥0.5	≥25	≤24	-	-
S. pseudintermedius, S. schlieferi	≥18	≤17	≤0.25	≥0.5	-	-	-	-

- The study plan to evaluate oxacillin and cefoxitin tests (disk diffusion [DD] and broth microdilution [BMD]) for detection of *mecA*-mediated ß-lactam resistance in *S. epidermidis* was reviewed.
  - 3 institutions participated in the study
  - 100 isolates were studied and were isolated from a variety of specimen sources (eg, blood, cerebrospinal and synovial fluids, catheter etc).
  - 48 isolates were *mecA* positive and 52 were *mecA* negative
  - For broth microdilution (BMD) test, frozen panels were used with cation-adjusted Mueller-Hinton broth (CAMHB) from 3 manufacturers.
  - For the disk diffusion (DD) test, Mueller-Hinton agar (MHA) from 3 different manufacturers was used.
  - QC – BMD: *Staphylococcus aureus* ATCC® 29213; DD: *S. aureus* ATCC® 25923; PBP2a and PBP2': *S. aureus* ATCC® 25923 and *S. aureus* ATCC® 43300
- Based on the results, it was concluded that the oxacillin DD interpreted by the breakpoints (S = ≥18 mm and R = ≤17 mm) reliably detected *mecA* positive and *mecA* negative *S. epidermidis* isolates.
  - The WG voted (8-0-2) to include oxacillin DD for *S. epidermidis* with breakpoints (S = ≥18 mm and R = ≤17 mm).
  - The WG also proposed that Table 2C in M100 and its associated tables be revised to include *S. epidermidis* in the row for oxacillin.
  - The cefoxitin row will remain unchanged.
  - Current comment (15) will be revised to clarify that either oxacillin or cefoxitin disk test can be performed (Text and tables to revise).

SUMMARY MINUTES	
#	Description
	A motion to accept the WG proposal as presented was made and seconded. VOTE: 13 for – 0 against (Pass). **Comparison of CLSI and EUCAST Reference Media for *S. pneumoniae* Disk Diffusion** **AHWG Roster**: Chairholder – Jennifer Dien Bard; Members – Susan Butler-Wu, Tanis Dingle, Dwight Hardy, Lesley McGee • Differences exist between CLSI recommended media (MHA supplemented with 5% sheep blood) and EUCAST recommended media Mueller-Hinton fastidious (MHF) (MHA supplemented with 5% mechanically defibrinated horse blood and β-NAD [20 mg/L]). Because of the differences, a study was performed to determine if MHF can be used to perform disk diffusion using CLSI disk breakpoints and QC ranges. • The AHWG objective was to determine whether these media differences impact susceptibility test results. • The phase II study design was reviewed. – 100 CDC isolates were tested at 3 sites. 10 clinical isolates a day were tested over 10 days with 10 total QC results. – All 3 sites used the same lots of reagents, media, and disks and tested the same isolates and QC organism (*S. pneumoniae* ATCC® 49619). – Results were read at 20 hrs. and 24 hrs. and interpreted using CLSI breakpoints. • The study results were reviewed and showed good categorical agreement and only one very major error. • The QC data for 20 and 24 hr. reads were reviewed. CLSI QC ranges were used for both media types. – 2 of the 3 test sites showed good agreement . – The 3rd site showed significant discrepancies with the other 2 sites for multiple drugs on both media types. • Conclusions and proposals – For the tested agents, the WG concluded that CLSI media and EUCAST media for DD testing of *S. pneumoniae* yield equivalent results, pending investigation of QC results. (At WG, QC data by site were not available.) WG Vote: 9-0-1. – It was proposed that a statement regarding the equivalence of the media be added to the next editions of M100 and to M02 and M07. • Discussion – A number of attendees expressed concerns about the out-of-range QC results from one site (#2). – It was suggested that the data from Site 2 be excluded from the total to see if the issue is resolved. – It was suggested that the out-of-range results from site 2 and for levofloxacin be investigated. **NOTE**: A request for QC data on levofloxacin will be submitted by the QC WG. – Although the CLSI and EUCAST QC ranges are different, the WG still concluded that the media are equivalent. It was suggested that a notation about the media equivalency be made in the test conditions box in the appropriate table in M100. – It was agreed that the issue regarding QC being out of range needs to be addressed before the media can be accepted as equivalent. It was proposed that the data be reworked to remove the site 2 data and with the correct levofloxacin QC ranges. The EUCAST QC media ranges will also be reviewed. • The data with Site 2 failed QC data excluded were reviewed. – For the two laboratories, all QC data was within range. – Based on the data, the WG concluded that the MHF media is equivalent to MHA with 5% sheep blood using CLSI breakpoints and QC ranges.

SUMMARY MINUTES	
#	Description
	• SC Discussion – It was noted that the disk mass's are different and it is desirable to generate additional QC data. – It was also suggested that the data from the Site 2 (failed QC) needs to be addressed. – It was noted that the failed QC ranges in the remaining sites were only off by millimeters. – It was suggested that including the media in M100 would be confusing to users; however, pending future study, the media may not be used just for *S. pneumoniae* but also for *Haemophilus*.
	A motion to accept the proposal that the CLSI and EUCAST media are equivalent with a follow-up on the Site 2 QC issue and draft text to add to the testing conditions box for the *S. pneumoniae* table was made and seconded. Vote: 11 for - 2 against (Pass).
	– The opposition votes were in response to the issues with the QC failures. **<u>Ceftazidime-avibactam Disk Breakpoints: S</u>ubmitted by Eric Wenzler, PharmD, BCPS, AAHIVP** • The objective was to determine the correlation of the current DD breakpoints with MIC breakpoints using various new data sets. • Current CLSI-approved breakpoints for ceftazidime/avibactam are: – BMD MIC breakpoints: S = ≤ 8/4 µg/ml; R = ≥16 µg/ml – DD breakpoints: S = ≤ 21 mm; R = ≤ 20 mm • The data sets for the analysis were reviewed. – 476 *Enterobacteriaceae* and 56 *P. aeruginosa* (NDA submission) – 74 carbapenem resistant *Enterobacteriaceae* (CRE) (published in Journal of Clinical Microbiology) – 102 gram negative bacilli (Wenzler study) • The analysis results were reviewed. – The analysis showed that based on the current breakpoints there is a cluster of isolates categorized as susceptible by MIC but resistant by DD. – Potential for patients to be denied treatment when the drug may be the only alternative. • It was proposed that the DD breakpoints be revised and a comment added. This will decrease the number of major errors. – S ≤ 20 mm – I = 18 – 19 mm – R ≥ 17 mm – Suggested comment: "Isolates with zones of 18-19 mm may test susceptible by MIC, confirmatory testing is indicated." • Discussion – Concerns were raised about the data set being derived from a single disk manufacturer. – It was suggested that more data may be needed and that the issue should be passed to the Breakpoint (BP WG). – It was noted that if a decision is not made now, the revision will have to wait until 2020. – This would be a short tem strategy (do an MIC with and intermediate results) with plans for a long-term strategy.

SUMMARY MINUTES	
#	Description
	A motion to accept the revised susceptible breakpoint (≤ 20 mm) and intermediate zone (18-19 mm) for *Enterobacteriaceae* and include a comment about confirming the results with an MIC test was made and seconded. This will continue to be evaluated and more data will be collected. VOTE: 3 – 10 (Fail). **An alternative motion to retain the current DD breakpoints (no intermediate) and include a comment recommending that when DD results are in the 18 – 20 mm range, a confirmatory MIC test should be performed was made and seconded. The comment will be bold in M100-29. VOTE: 13 for –0 against (Pass).** • **Action Item**: An AHWG under the BPWG will be formed to further study and discuss the issues in January 2019. **AST Methods for Colistin** **AHWG Roster**: Chairholder – Romney Humphries; Members – Chris Doern, Dan Green, Andre Hsiung, Stephen Jenkins, Christopher Massey, Shelley Campeau, Audrey Schuetz, Katherine Sei, Trish Simner • Currently, there is no practical method for testing for colistin susceptibility. • Updates to M100, 28th edition – DD breakpoints deleted. – Comment added to refrain from testing by gradient or disk diffusion. – Breakpoints for *P. aeruginosa* and *Acinetobacter* revised (rationale document with FDA) – Recommend testing colistion to predict polymyxin B susceptibility • Method to be presented: Colistin Broth Disk-elution (CBDE) method • Methods under study include: – EDTA-CBDE method – Broth macrodilution – Agar dilution – Polymxyin NP (deemed impractical) • The procedure for the CBDE method was reviewed. – 0, 1, 2, and 4 disks containing 10 µg of colistin are added to 4 separate 10 mL tubes of CAMHB. – The tubes are incubated for 30 minutes. – 50 µL of a 0.5 McFarland inoculum is added to the 4 tubes, vortexed, and incubated for 18 – 20 hrs. at 35°C. – The tubes are visually read for turbidity. • The results of the two-site evaluation and reproducibility testing were reviewed. – The two-site evaluation compared with BMD (reference method) showed 98% categorial agreement and 99% essential agreement. – The WG concluded that the procedure was easy to perform and provided good reproducible results.

SUMMARY MINUTES	
#	Description
	• The WG proposed that CBDE be recommended as a screening method (excluding *Enterobacter cloacae* due to heteroresistance) and included in M100, 29th ed. pending confirmation of the QC strain (NCTC 13846). – A comment would be included with the method that states that isolates with MICs >1 µg/mL should be confirmed using an *mcr-1* test or BMD. – Although it is not a full CLSI study, the data looks acceptable. The WG voted to approve the test as a provisional screening method: 9-0-1 – A three laboratory study to confirm the methods is planned. • Discussion and comments – The method appears to be acceptable for screening for emerging resistance. – There are still issues with disk content; however, the variability doesn't appear to affect the results. – QC ranges is still being investigated. Dr. Humphries and Ms. Cullen are working to confirm the QC ranges. A comment regarding the lack of large studies as noted in M45 may be added. – It was suggested an MIC of ≥ 2 rather than >1 trigger confirmation. – It was suggested that multiple lots of CAMHB be studied. – There is no current criteria to call susceptible or resistant and would only be reported as WT or NWT. • **Action Item:** A motion was made to continue the QC studies and develop appropriate language and then circulate both for electronic vote. The voting members agree to the motion via a poll of the SC voting members. **Coordinated Development of Antimicrobials and AST Systems Report** **AHWG Roster**: Chairholder – Romney Humphries; Recording Secretary – Jane Amber; Members – Robert Badal, Sheila Farnham, Janet Hindler, Susan Kircher, Kevin Krause, Amy Mathers, Jean Patel, Ribhi Shawar, Dee Shortridge, Audrey Schuetz • The WG is still working on their charges. • Two articles regarding methods and best practices for assessing AST methods have been authored by WG members have been published. • Ways in which CLSI can help were discussed. **Direct Blood Culture AST AHWG Report** **AHWG Roster**: Co-chairholders - Shelley Campeau and Audrey Schuetz; Recording Secretary – April Bobenchik; Members - Eileen Burd, Dwight Hardy, Romney Humphies, Kristie Johnson, Tom Kirn, Dyan Luper, Robin Patel, Lauri Thrupp, Mel Weinstein, Barbara Zimmer • An update on the progress of a multicenter study assessing direct DD from positive blood culture bottles for gram-negative bacteria was provided. • Hypothesis and Outcome Measures – Direct-from-blood culture DD test read at 16-18 hrs performs at or above CLSI standards as compared to standard DD and to reference BMD. – Direct-from-blood culture DD test read at 8-10 hrs performs at or above CLSI standards as compared to standard DD and to reference BMD. • Study progress and updates were reviewed. – The Direct Blood Culture AST WG will meet in the fall of 2018 to discuss progress and future plans – The final report from Antibacterial Resistance Leadership Group on a DISK trial will be presented at January 2019 CLSI meeting.

SUMMARY MINUTES	
#	**Description**
6.	**Breakpoint WG Report – Part 1: Dr. Jim Lewis** **BPWG Roster**: Co-chairholders – George Eliopoulos (absent) and Jim Lewis; Recording secretary – Karen Bush; Members – Marcelo Galas, Amy Mathers, David Nicolau, Mike Satlin, Simone Shurland, Lauri Thrupp, Barbara Zimmer; Members absent – Robin Patel, Kerry Snow; Advisors (non-voting); Matthew Wikler, Hui Wang (absent) **Meropenem-Vaborbactam Breakpoint Proposal (Folder 5; 7a – 7i)** • The mechanism of action and kinetics of KPC inhibition of vaborbactam were reviewed. The agent is primarily for treatment of CRE and KPC producers. • Data on the activity of meropenem-vaborbactam against various isolates of key *Enterobacteriaceae*, CRE and KPC-producing CRE, *P. aeruginosa*, *Acinetobacter*, *Stenotrophomonas*, and *Burkholderia* were reviewed and summarized. – Vaborbactam inhibits Class A ß-lactamases, notably KPC, and restores meropenem activity against KPC-producing *Enterobacteriaceae*. – Vaborbactam does not potentiate meropenem activity against OXA-48- and MBL-containing strains. – Meropenem-vaborbactam activity against *P. aeruginosa* and *A. baumannii* is similar to that of meropenem alone. – Vaborbactam does not decrease the activity of meropenem against meropenem-susceptible organisms. – The *in vitro* potency of meropenem-vaborbactam is not reduced in the presence human serum, lung surfactant, or urine. – Reduced susceptibility to meropenem-vaborbactam in laboratory-derived mutants and in clinical isolates is associated with the previously described meropenem resistance mechanisms (eg, porin inactivation, increase in *blaKPC* gene copy number, increased efflux). There is not a single mechanism responsible for meropenem-vaborbactam MICs at or above proposed breakpoints. – Isolates that are resistant to ceftazidime-avibactam due to mutations in *blaKPC* are often susceptible to meropenem-vaborbactam. • The majority of strains tested in the efficacy studies were KPC producing. • The results of the efficacy studies were reviewed. The data showed that: – There was a change in log CFU/thigh over 24 Hours in neutropenic mice infected with various KPC-producing *Enterobacteriaceae* strains when treated with exposures equivalent to meropenem 2 g and vaborbactam 2 g administered every 8 hrs. by 3 hr. infusion in humans (Mer, 300 mg/kg and Vab, 50 mg/kg, Q2) showed that meropenem MICs determined with vaborbactam at 8 mg/L are predictive of efficacy at human equivalent exposures. – Meropenem-vaborbactam at human equivalent exposures produces bacterial killing against all strains with meropenem-vaborbactam (8 mg/L) MIC ≤8 mg/L • The pharmacokinetic (PK) data on vaborbactam were reviewed and summarized. – There are dose proportional exposures and linear PK for doses of 250 – 2000 mg. – Vaborbactam PK matched meropenem PK and has no effect on meropenem PK (and vice-versa). – Protein binding is low (≈ 33%). – There is a low potential for metabolic drug-drug interactions (no CYP450-dependent metabolism and no inhibition or induction of CYP450 enzymes). – Elimination is mainly through renal excretion (dose adjustment is needed in patients with moderate and severe renal impairment)

SUMMARY MINUTES	
#	Description
	• The results of the completed Phase 3 studies were reviewed. – **Tango I**: Site/Indication Focus: Complicated UTI (cUTI) o FDA primary endpoint: Proportion of subjects in the m-MITT population who achieve overall success (clinical cure or improvement and eradication of baseline pathogen to < 10^4 CFU/ml) at the end of IV therapy visit. o EMA-proportion of subjects in the co-primary m-MITT and ME populations who achieve a microbiologic outcome of eradication (eradication of baseline pathogen to < 10^3 CFU/ml) at the TOC visit. o All key efficacy endpoints met the non-inferiority margin. o The data showed overall success at end of IV therapy at 98.4%. o Pathogen-specific clinical cure rates were acceptable. o Clinical cure and eradication rates showed low MICs. – **Tango II:** Pathogen-Focused: CRE Infections (cUTI, acute pyelonephritis [AP], hospital-aquired/ventilator-associated pneumonia [HABP/VABP], bacteremia or complicated intra-abdominal infections [cIAI]) o Study patients received meropenem-vaborbactam monotherapy (2g/2g every 8hr via 3-hr infusion) or best available therapy (BAT)(7-14 days) o Study design summary ▪ Inclusion criteria: Known or suspected CRE pathogen requiring ≥7 days IV therapy for confirmed cUTI/AP, HABP/VABP, bacteremia, or cIAI. ▪ Clinical cure: Complete resolution of signs/symptoms and no further antimicrobial therapy needed. ▪ Clinical cure assessed at end of treatment (EOT) and test of cure (TOC). ▪ The most common baseline pathogen was *K. pneumoniae* (86%) and the most common molecular mechanism of carbapenem resistance was KPC carbapenemase (80%) production. • The Tango II Study data were reviewed. – Meropenem-vaborbactam outcomes were improved compared to the BAT (reduced mortality and higher clinical cure at EOT and TOC). – There was no obvious cutoff in meropenem-vaborbactam MIC that discriminated between clinical or microbiological successes and failures. – There was a higher clinical cure at EOTand TOC meropenem-vaborbactam compared to BAT. – Benefits were evident in important patient subgroups of HABP/VABP, bacteremia, renal impairment, and immunocompromised. – There were fewer treatment-related adverse events with meropenem-vaborbactam and decreased nephrotoxicity. – There was no changes in susceptibility to meropenem-vaborbactam, but resistance to ceftazidime-avibactam observed in the few patients treated with this agent. – PK-PD data showed good target attainment by MIC. • The discussions and assessment by the AHWG was reviewed. – Based on the data, the AHWG preferred the FDA MIC breakpoints with MIC of 8 as Intermediate due to the absence of any clinical data on outcomes with MICs of 8 and a drop-off in PK-PD in probability of target attainment at an MIC of 8. – The AHWG agreed that there was no strong evidence to modify the FDAs MIC breakpoint recommendations. – The AHWG unanimously voted in favor of the FDA MIC breakpoints for *Enterobacteriaceae* (S = ≤4/8; I = 8/8; R = 16/8) with dosage regimen of 4 g (2 g meropenem + 2 g vaborbactam every 8 hr over 3 hrs.

SUMMARY MINUTES	
#	Description
	– The AHWG unanimously voted in favor of modified DD breakpoints for *Enterobacteriaceae* (S = ≥ 18mm; I = 15-17mm; R = ≤14mm) with the same dosage regimen. – They supported the sponsors' request for placement in Table 1A for *Enterobacteriaceae* in Group B. • The Breakpoint WG voted to accept the AHWG breakpoint proposal (6 for – 0 against – 3 abstentions). **Note:** No vote on table placement was held by the BPWG.
	A motion to accept the AHWG breakpoint proposal for *Enterobacteriaceae* (MIC: S = ≤4/8; I = 8/8; R = ≥ 16/8 and DD: S = ≥ 18mm; I = 15-17mm; R = ≤14mm) was made and seconded. Vote: 12 for – 0 against - 1 abstention (Pass). Note: The abstention was due to the member's participation in research and consultation with the sponsor.
	A motion to place the drug in Table 1A for *Enterobacteriaceae* in Group B was made and seconded. 12 for – 0 against - 1 abstention (Pass). Note: The abstention was due to the member's participation in research and consultation with the sponsor.
	A motion to place meropenem-vaborbactam, ceftazidime-avibactam, and ceftolozane-tazobactam in three separate boxes in Table 1A, Group B and place the other three ß-lactam combination agents together in the same box for *Enterobacteriaceae* was made and seconded. Vote: 13 for - 0 against (Pass).
	Ciprofloxacin-levofloxacin Disk Correlates for *Enterobactericeae* and *Pseudomonas* Breakpoints (Folder 5, 6a-6b) Submitted by Romney Humphries, Keith Schaffer, Janet Hindler, Shelley Campeau, Dulini Gamage, Erika Matuschek • In 2017 and 2018, AST SC approved revisions to ciprofloxacin and levofloxacin MIC breakpoints for *Enterobacteriaceae* and *P. aeruginosa* pending establishment of disk correlates. – Some data available in Jan. 2017 did not meet M23 criteria for the number of isolates test with levofloxacin. – New data presented in June 2017 demonstrated performance that did not meet M23 criteria for acceptance. – Additional studies were performed at three sites. • The analysis of the data was reviewed. – MIC ranges were truncated to consistent data sets across all sources on values where the lower end of the range was high were discarded. – Analyzed data was compared to EUCAST breakpoints and analyzed by dBET software. • *Enterobacteriaceae* summary – For ciprofloxacin, the analysis software provided a 4 mm range with 0 very major errors, 7 major errors, 60 minor errors – For levofloxacin, the analysis software provided 0 very major errors, 2 major errors and 34 minor errors • *Enterobacteriaceae* breakpoint proposal for M100, 29th edition

SUMMARY MINUTES

#	Description

		Disk (mm)			MIC (µg/mL)		
Organism Group	Antimicrobial Agent	S	I	R	S	I	R
Enterobacteriaceae	Ciprofloxacin	≥26	22-25	≤21	≤0.25	0.5	≥1
	Levofloxcin	≥21	17-20	≤16	≤0.5	1	≥2

- *P. aeruginosa* summary
  - The disk breakpoints were evaluated using the BETs software.
  - For ciprofloxacin, there was 1 major error, 0 major errors, and 7 minor errors
  - For levofloxacin, there were 0 very major or major errors, and 11 minor errors.

- *P. aeruginosa* proposal

		Disk (mm)			MIC (µg/mL)		
Organism Group	Antimicrobial Agent	S	I	R	S	I	R
P. aeruginosa	Ciprofloxacin	≥25	19-24	≤18	≤0.5	1	≥2
	Levofloxcin	≥22	15-21	≤14	≤1	2	≥4

- The BPWG proposed to accept the breakpoints as shown.

		Zone diameter in mm		
		Susceptible	Intermediate	Resistant
Enterobacteriaceae	Ciprofloxacin	≥26	22-25	≤21
	Levofloxacin	≥21	17-20	≤16
Pseudomonas aeruginosa	Ciprofloxacin	≥25	19-24	≤18
	Levofloxacin	≥22	15-21	≤14

NOTE: The susceptible zone size for *P. aeruginosa* and ciprofloxacin is incorrect in the final presentation shown at the plenary (ie, ≥23). The above table is correct (ie, ≥25).

A motion to accept the *P. aeruginosa* disk correlates for ciprofloxacin as shown (ciprofloxacin: ≥25 [S]; 19-24 [I]; ≤18[R]) was made and seconded. Vote: 13 for – 0 against (Pass).

SUMMARY MINUTES	
#	Description
	A motion to accept the disk correlates for ciprofloxacin and levofloxacin with *Enterobacteriaceae* and *P. aeruginosa* with levofloxacin as shown was made and seconded. Vote: 13 for – 0 against (Pass).

Reassessment of Piperacillin-tazobactam Breakpoints for *Enterobacteriaceae* (Folder 5, 8a – 8i)
Submitted by German Esparza

- Data on the clinical utility of piperacillin-tazobactam for ESBL therapy is conflicting. The current CLSI and EUCAST breakpoints are different and some publications point to EUCAST breakpoints as being more accurate for predicting clinical efficacy.
- Data from multiple publications and from a European Congress of Clinical Microbiology and Infectious Diseases Conference (Merino trial) presentation (currently unpublished) was reviewed. The study presented the primary outcome of mortality was unfavorable for piperacillin-tazobactam compared to meropenem.
- The BPWG proposed that an AHWG be formed to evaluate piperacillin-tazobactam for ESBL and enterics in general. Points discussed:
  - This is an important issue for antimicrobial stewardship.
  - May cause SC to need a review of the breakpoints and ESBLs in general.
  - It was suggested that the formation of the AHWG be postponed until the Merino data is published and available in a peer-reviewed form and there is additional data.
- It was agreed that the AHWG will be formed at a later date when sufficient data becomes available.

Azithromycin Breakpoints for *Neisseria gonorrhoeae* (GC) (Folder 13, 4a, 4c, 5, 8h)
AHWG Roster: Co-chairholders – Mary Jane Ferraro and Vanessa Gray; Members – Carey Ann Burnham, Marcelo Galas, Ellen Kersh, Jean Patel, Nicole Scangarella-Oman

- Justification for setting a susceptible azithromycin breakpoint for GC at ≤ 1 were presented.
  - The recommended treatment for ucomplicated gonorrhea includes azithromycin and a second agent (ceftriaxone or cefixime or gentamycin).
  - US MIC distribution surveillence data and EUCAST data showed:
    - 8.4% of the 15,495 US surveillance isolates (2014 – 2016) were at an MIC of 1 or above (≈1,300 isolates)
    - Overall, 468,514 gonorrhea cases were reported to CDC in 2016 and no treatment failures were reported. National guidance is to contact CDC in case of suspected treatment failure.
    - CDC reported that 81% of patients with gonorrhea received the recommended regimen in 2016, based on data from the STD Surveillance Network (Weston et al, MMWR 2018)
- The WG proposed setting an azithromycin breakpoint at ≤1. Rationale included:
  - Absence of a breakpoint causes problems because MIC result interpretation cannot be reported clinically.
    - As a result, laboratories do not offer the test and patient care is less than it could be if it were based on laboratory results.
    - FDA is hampered in its ability to approve novel tests and devices (eg, gradient diffusion for azithromycin is not FDA approved for gonorrhea, although it provides comparable data to AST in CDC's evaluation).

SUMMARY MINUTES	
#	Description
	– ≤ 1 is appropriate because: o The ECV supports it. o No treatment failures have occurred as surveillance data in the US and Canada has shown. o A lower MIC (as per EUCAST) may lead to over-diagnosis of non-susceptible gonorrhea. A lower breakpoint could also result in unnecessary use of higher azithromycin doses (more side effects; higher cost). o More broad spectrum antibiotics may be used (eg, ertapenem) without any evidence of additional clinical benefit. o A lower susceptible breakpoint may cause the surveillance numbers of non-susceptible cases to artificially increase leading to calls for treatment recommendation changes. – Limited PK-PD data showed: o Median azithromycin exposure in mononuclear and polymorphonuclear leukocytes after a 5-day or 3-day regimen was greater than a 1000-fold and 800-fold greater than in serum, respectively. o Azithromycin concentrates well in affected tissues (eg, tonsils and cervix). o A multicenter study showed a 95% cure rate. • The proposals by the AHWG were to: – Establish a breakpoint for azithromycin and GC that is consistent with the current ECV (S ≤ 1). – Add a comment to Table 2F stating, "This breakpoint presumes that azithromycin (1 gm single dose) is used in an approved regimen that includes an additional antimicrobial agent (ie, ceftriaxone 250mg IM single dose)." – Delete the ECV currently listed in Appendix G2. – Add azithromycin to Table 1B, Group A. – The Breakpoint WG approved the motion: 7 for – 1 against – 1 abstention (Pass). • Discussion – It was questioned whether a resistant breakpoint should be set and that a susceptible-only breakpoint is usually reserved in cases where there are no resistant isolates; however, GC does show resistance. It was noted that a susceptible-only breakpoint is also used when resistance is rare which seems to be the case. It was also reported that there is insufficient data to definitely set a resistant breakpoint. – It was noted that most of the data for the breakpoint is based on treatment with ceftriaxone. Other agents will be revisited at a later date. – For Table 1B, the drug should be listed in a box separate from tetracycline.
	A motion to accept the AHWG proposal to establish a S breakpoint for GC and azithromycin at ≤ 1, include the proposed comment in Table 2F, and to place azithromycin for GC in Table 1B, Group A **was made and seconded. Vote: 13 for - 0 against (Pass).**
	Polymyxin Susceptibility Issues Submitted by Jim Lewis • Despite progress in limiting antimicrobials use in animals, inappropriate antimicrobial agent use in animals is still a common practice resulting in increasing resistance. – Colistin is still being used to promote growth in India.

SUMMARY MINUTES	
#	Description
	– Currently, there are no *Enterobacteriaceae* CLSI breakpoints for colistin, only ECVs (1). Laboratories are using the ECV as a breakpoint. – There are continuing PK-PD concerns about the drug. • Data reviewed from multiple published studies showed that target attainment is extremely difficult to reach even using combination therapy and that treatment with the drug results in high failure and mortality rates. • Conclusions: – Colistin is not an effective drug and the issue needs to be addressed. – It was suggested that CLSI reach out to the joint EUCAST/CLSI WG to revisit the issue. – Suggested options included: o Report as intrinsically resistant o Report as resistant only o Discontinue reporting the ECV • Discussion – It was agreed that the drug is marginally useful; however, in some cases, colistin is the only option and may or may not be better than no treatment. – In some countries, it is the only drug available for multiply-resistant organisms. – Some laboratories use the EUCAST breakpoints because CLSI breakpoints are not available. – It was suggested that intermediate or resistant only be reported as some patients do respond when there is no other option. – A proposal to revisit the discussion with EUCAST to convince them to remove their breakpoint, not to set one for CLSI was made. – If the drug is used, treatment must be discussed with an infectious disease specialist and used in combination therapy. • The WG requested guidance on the next best steps. Suggested proposal: – Consider creating new breakpoints: I = ≤ 2; R = ≥ 4 with no "S" for all organisms. – It was noted that this does not meet the definition of intermediate (eg, not technical variability, not using a higher does, not effective at a particular site). It was suggested to call the result indeterminate. – May not be pratical to recommend discontinuing the drug at this time but would be desirable. • It is agreed that action is needed but the clinicians need to be educated in addition to changing the laboratory recommendations. It was decided to continue the discussion at a later time.
7.	**Outreach WG Report: Dr. Audrey Schuetz (Folder 8)** **WG Roster:** Co-chairholders – Janet Hindler and Audrey Schuetz; Recording secretary – Stella Antonara; Members – April Abbott, April Bobenchik, Mariana Castanheira, Graeme Forrest, Angie Charnot-Katsikas, Romney Humphries, Nicole Scangarella-Oman, Paula Snippes Vagnone, Lars Westblade • The June 2018 Newsletter has been released. • The Fall 2018 newletter is in progress and information will include: – A feature article on dosing antibiotics – A case study on cefazolin testing for *Enterobacteriaceae* – Practical tips on when perform yeast AST

SUMMARY MINUTES	
#	Description
	– A hot topic on cefazolin and methicillin-susceptible *S. aureus* – Formatting improvements • New activities for first time AST SC meeting attendees were planned including: – Providing a packet to first time registrants – Identifying the new attendees with green ribbons – Holding a welcome gathering before the Sunday evening reception – Designating dedicated tables at meal functions • The WG has been collaborating with the CLSI marketing group to streamline and improve the AST portion of the CLSI Website. Goals were to: – Reorganize the meeting materials – Provide enhanced access to high value materials (eg molecular tables; electronic M100 and M60) – Make it searchable • Recent Webinars presented included: – The annual 2018 AST Webinar on M100, M02, and M07 – A webinar on current recommendations for AST on Enterococcus spp. – A free webinar on the available CLSI AST documents • Upcoming Webinars include: – Preparation, Presentation, and Promotion of Cumulative Antibiogram to Support Antimicrobial Stewardship Programs – Resources for Implementation of MALDI-TOF MS in the Microbiology Laboratory • Presentations being given at the upcoming ASM Microbe meeting were reviewed. – How are the newest and revised clinical breakpoints and ECVs impacting healthcare decisions (Mike Satlin) – Newer CLSI pursuits to assist the lab, clinician and other in combatting AR in 2018 (April Abbott) – Sonnenwirth award for leadership in clinical microbiology award lecture: a brief history of the CLSI AST subcommittee: a personal take on “then” and “now” (Mary Jane Ferraro) • The WG requested ideas and suggestions for the next AST educational session (January 2019). • Continuing and new projects were reviewed. – Explore reorganization of AST SC meeting proceedings – Potential for a workshop on intermediate/SDD technical uncertainty – Practical recommendations for testing and reporting newer drugs – Understanding intrinsic resistance (for clinicians and for laboratories) – “Right to report” initiative – Coagulase-negative staphylococci issues – Education regarding updated taxonomy changes for *Bacteroides* and *Parabacteroides*

SUMMARY MINUTES

#	Description
8.	**Methods Application and Interpretation WG (MAIWG) Report:** Dr. Tom Kirn (Folder 6) **WG Roster**: Co-chairholders – Brandi Limbago and Tom Kirn; Recording secretary – Trish Simner; Members – Darcie Carpenter, Sandra Richter, J. Kristie Johnson, Joseph Kuti, Susan Sharp, Samir Patel, Virginia Pierce, Stephen Jenkins **Intermediate vs Susceptible-Dose dependent (SDD) AHWG Report** **AHWG roster**: Co-chairholders - Susan Sharp and Tom Kirn; Members – Avery Goodwin, Alice Grey, Romney Humphries, Kristie Johnson, Joseph Kuti, Stephanie Mitchell, Lauri Thrupp • The interpretation of the intermediate category is misunderstood and laboratories are unsure of how it is being used. The intermediate category is used: – To account for test variability – To accommodate organisms/drug combinations where dosing impacts interpretation (alternate dosing, alternate administration, physiologic concentration of the drug). • There is a recent trend toward avoiding the establishment of an intermediate or SDD category despite evidence of MIC variability or improved outcomes if the dosage is increased. • There are differing CLSI vs EUCAST philopsophies.

EUCAST (S-I-R)	CLSI (S-I-SDD-R)
Dosing • S = Susceptible, standard dose • I = Susceptible, increased exposure • R = Resistant	**Susceptible Dose Dependent** • Increased dose (state explicitly) • Alternate dosing • Physiological concentration
Technical Uncertainty • Repeat test • Repeat with an MIC method • Do not report • Report at resistant • Push a consultation	**Intermediate:** Accounts for technical variation and increased exposure

• AHWG Concerns and Discussion
– Lack of harmonization adds additional confusion regarding the use of the terms.
– There is confusion regarding which term to use for drugs that are physiologically concentrated or that have both dosing and technical variability.
– It was questioned how SDD would be used in practice and whether it can be reported in a laboratory information system. Education is needed.
– If intermediate is eliminated, device manufacturers will have difficulty validating their devices.

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AHWG Charge

Make recommendations regarding the continued use, discontinuation, modification, or replacement of “Intermediate” category for AST reporting
Provide 2 or more options with pros and cons for consideration

AHWG Decisions

All drugs should have 3 categories which consider testing variability.
It does not appear that there are any antibiotic/organism combination for which inherent testing variability does not exist. The limited number of results in the borderline (“I”) range should be communicated to the clinician.

The AHWG options were presented.

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<tr><th>S-I-R</th><th>S-I-R or S-SDD-R</th></tr>
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Keep current S and R definitions, but eliminate SDD.
Keep intermediate definition but add two new footnotes to Tables 2 to denote:

alternate dosing possible, or
anatomic site concentration.

Isolates with an “I” result approach susceptible if exposures are maximized by alternative dosing regimens. An “*” in M100 Tables 2 indicates antibiotics where “I” implies the potential for an increased/alternative dosing regimen.
Isolates with “I” result approach susceptible if infection is at an anatomical location where the drug concentrates (ie, urine) but alternate dosing regimens not feasible. An “^” in M100 Tables 2 indicates antibiotics where “I” has the potential for concentration at an anatomical site.
“I” results also provide a buffer zone for inherent variability in AST. Isolates with an “I” result could be “S” or “R”; proceed with caution.

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Keep the current S and R definitions.
Intermediate definition will no longer include drugs for which higher dosage or exposure can be used (now SDD).
I definition:

Isolates with “I” result approach susceptible if infection is at an anatomical location where the drug concentrates (ie, urine). An “^” in M100 Tables 2 indicates agents where “I” has the potential to concentrate at an anatomical site (as above).
Provides a buffer zone for inherent variability in AST. Isolates with “I” result could be “S” or “R” – proceed with caution.

SDD definition:

Considered susceptible if higher exposure or doses can be used if FDA approved or supported by literature and reviewed by CLSI.
Provides a buffer zone for inherent variability in AST (as does “Intermediate”).

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<tr><th colspan="2">PROS</th></tr>
<tr><td>

Retains current “I” definition and a historical comfort level.
Consistent with proposed EUCAST nomenclature (but not necessarily the definition).
As most clinicians do not understand what SDD means or the difference between the inherent variability in testing from drugs that can be dosed higher or those that concentrate at certain body sites, the “*” and “^” in Tables 2 may help to clarify these differences.

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SDD is already used for cefepime for AST and azoles for Antifungal.
Clearly identifies drugs that can be dosed using alternate regimens with reasonable expectation of safety and efficacy.
Inherent variability is covered by both SDD and I definitions.
Encourages increased SDD drug use (with continued education) rather than broader antibiotics (eg, carbapenems).
Daptomycin/*E. faecium* BPWG proposal is an example of ideal application of SDD where an increased dosage is needed (supported

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SUMMARY MINUTES	
#	Description

• No need to make accommodations in LIS, HIS and instruments to report SDD. • Retaining the "I" category enables instrument manufacturers to achieve FDA clearance under current requirements. • Incorporates the buffer zone for inherent test variability and allows for both the possibility of increased exposures or of anatomic concentration while indicating the differences in Tables 2.	by literature and society guidelines) to treat many VRE infections. Without SDD, ≈80% of VRE (*E. faecium*) could be categorized as "I" based on proposed BPs, which could discourage use for VRE. • Leaves an option for new antibiotic developers considering indications for two different doses (eg, ceftolozane/tazobactam). • Additional SDD designations (eg, cefepime/*Pseudomonas)* would create enhanced awareness of the clinical/stewardship value of SDD.
CONS	
• Routine "I" results reported by individual laboratories may not differentiate drugs that can be dosed higher or those that concentrate at certain body sites. • "I" definition will differ from EUCAST's. • A path for redefining breakpoints for drugs with only S/R or S/NS may need to be determined. • Clinicians may still be reluctant to use drugs reported as "I" (lack of confidence with I), leading to increased use of broader spectrum antibiotics (eg, increased carbapenem use for ESBLs that fall in cefepime 4-8 µg/L range). The primary purpose of the SDD concept would be lost. • The new "*" or "^" footnotes in Tables 2 may not be communicated to the clinician unless individual laboratories (or LIS) choose to do so. • CLSI may cause some confusion if SDD is dropped, since it remains in the Fungal Guidance and was adopted after extensive discussion.	• Disagrees with proposed EUCAST nomenclature. • SDD with cefepime has not been widely accepted nor understood. • Continued SDD use may result in the need to evaluate all drugs for which SDD is a possibility to define alternative dosing strategies. • CLSI responsible for conforming with the FDA (21st Century Cures Act). Some drugs may have an SDD option (eg, carbapenems, daptomycin for *Enterococcus* spp.) but no corresponding FDA dose that defines SDD. • Optimal SDD reporting may require significant changes to LIS, HIS, and instruments. • FDA only recognizes the SDD category for antifungals. If FDA does decide to recognize SDD, depending on how it is classified, this could lead to errors being categorized as Major or Very Major. This would likely decrease the ability of device manufactures to develop a test that will get approval. M23 would need revision to address calculation of minor errors (inclusive of SDD).

- **AHWG Vote**: 6 for S-I-R or S-SDD-R; 4 for S-I-R (no consensus)
- **MAIWG Vote**: 6 for S-I-R or S-SDD-R; 3 for S-I-R
- SC Discussion
  - The FDA does not have an issue with the term SDD but needs to review the data used to determine the alternate dose.
  - Clinicians still don't understand what SDD means.
  - Recommendations for alternate dosing is constrained by the FDA approved dosage.
  - SDD doesn't necessarily mean treating with the highest safe dose and some drugs have multiple doses.
  - Safety of a higher dose may not be known. SDD would be used in limited circumstances when the data are strong.
  - It was noted that although this may not fit with the FDA, the document is intended to be global and some doses may be approved in other countries that are not approved in the United States.

SUMMARY MINUTES	
#	Description
	A motion to accept the S-I-R or S-SDD-R option for all newly approved drugs having 3 categories (none with only 2 categories but with an S-only would be acceptable) was made and seconded. The drugs currently in the document would stay the same. Vote: 9 for - 4 against (Pass).

- Rationale for opposition votes
  - Concerns about calling something SDD and misinterpreting and being close to the R.
  - Prefer the S-I-R as it seems to cover better what is trying to be accomplished.
  - Dosing issue is important and if a comment is going to be attached to an "I", then the dosing issue is being accomplished.

Anaerobe WG Report

AHWG Roster: Chairholder – Darcie Carpenter; Member – Karen (Kitty) Anderson, Diane Citron, Joanne Dzink-Fox, Meredith Hackel, Stephen Jenkins, Cindy Knapp, Laura Koeth, Audrey Schuetz, Hannah Wexler

- Informational topics were presented.
  - Current *B. fragilis* group nomenclature is outdated. In the new edition of M11, *B. fragilis* group will be changed to *Bacteroides* spp. and *Parabacteroides* spp. which consists primarily of members of the formerly defined *B. fragilis* group.
  - An article on piperacillin-tazobactam MIC susceptibility for anaerobes has been published. Clinical failures have been noted with the old breakpoints.
  - The potential for changing breakpoint for other agents is being reviewed.
    - Metronidazole (January 2019)
    - B-lactamase inhibitors: ECVs for anaerobes. To date, no funding is available for data collection.
  - No progress has been made on drafting an antibiogram manuscript based on the most recent antibiogram.
  - The M11 revision is in progress. Proposed draft comments are in the process of being resolved.
  - Inclusion of MICs generated by gradient diffusion in the anaerobe antibiogram was discussed. The plan is to include MICs generated by gradient diffusion and document that not all data was generated with the reference method in accordance with device indications with future versions of the anaerobe antibiogram. The WG has concerns that enough data will not be available for the next version if it is restricted to the CLSI agar dilution method due the reduction in the number of laboratories who are actively using this method.

- Rifampin AST for *Cutibacterium* (*Propionibacterium*).
  - The WG proposed adding a comment to the antibiogram table (Appendix Table D2) regarding *Cutibacterium* (*Propionibacterium*) entries.
  - Footnote would state, "**80 isolates of *Cutibacterium* (*Propionibacterium*) *acnes* from two of the sites generated MIC values for rifampin ≤0.03µg/mL using the agar dilution method. There are no interpretive breakpoints for this organism/antimicrobial agent combination.**" **Note:** The Text and Tables WG will ensure the grammar is correct.
  - A vote by the SC was requested.

SUMMARY MINUTES	
#	Description
	A motion to approve addition of the proposed footnote to the anaerobe antibiogram for *Cutibacterium* (*Propionibacterium*) *acnes* in Appendix D2 was made and seconded. Vote: 13 for – 0 against (Pass). **Intrinsic Resistance (IR) WG Report** **AHWG Roster**: Chairholder – Barbara Zimmer; Secretary – Dyan Luper; Members – Jeff Alder, Susan Butler-Wu, Rafael Canton, German Esparza, Mark Fisher, Sandy Richter, Susan Sharp, Rosemary She, Carole Shubert, Tom Thomson • *Acinetobacter* and ampicillin-sulbactam footnote – A question was submitted to the ASM Division C list serv regarding a comment for *A. baumannii/calcoaceticus* complex in the IR table for non-*Enterobacteriaceae* which states "may appear to be susceptible to ampicillin-sulbactam due to the activity of sulbactam with this species". The commenter questioned the phrase "may appear" as they rarely isolate *calcoaceticus*. – The WG discussed whether the comment is still needed or if it should be moved from the IR table to Table 2B-2. – The IRWG decided to delete the comment from the IR table and the MAIWG approved the deletion (9-0-0). Ampicillin would be retained. **A motion to delete the ampicillin-sulbactam comment (Footnote a) from the *A. baumannii/calcoaceticus* complex row in the IR table was made and seconded. Vote: 13 for - 0 against (Pass).** • IR of *Burkholderia cepacia* complex – A presentation from June 2017 and the EUCAST IR table were reviewed (discrepancies exist). – Recent publications have reported that not all the drugs listed as IR in the IR table are testing as resistant. – The definition of IR was reviewed. – The IRWG previously decided to delete cefepime and imipenem from the IR table and are reviewing other drugs. Current data suggests that the following drugs be reconsidered for deletion due to lack of conclusive data for IR: o Piperacillin-tazobactam o Aztreonam o Ceftriaxone o Trimethoprim o Ertapenem o All ß-lactams – WG Discussion o It was agreed that *B. cepacia* complex still needs to be in the IR table. o Data on ertapenem was not included in the reviewed papers. o It was suggested that if the "R" is removed for specific drugs, a comment may be needed. o It was agreed that other organism/antibacterial agents in the table should also be reviewed. – It was proposed that the "R" be retained for ertapenem and deleted for: o Piperacillin-tazobactam

SUMMARY MINUTES	
#	Description

- Cefotaxime
- Ceftriaxone
- Cefepime
- Aztreonam
- Imipenem
- Aminoglycosides
- Trimethoprim

– A comment to be added states (or with similar language): **"*B. cepacia* complex isolates have chromosomal genes that encode resistance mechanisms that may not be expressed, resulting in susceptible or low MIC testing results. Recall, intrinsic resistance implies the presence of resistance mechanisms in natural or wild-type strains that result in phenotypic resistance for all or nearly all strains. Environmental *B. cepacia* complex strains have low MICs to many antimicrobials whereas clinical strains, such as those from cystic fibrosis patients, have very high MIC values to most antimicrobials. There is insufficient clinical evidence to confirm whether or not strains that test susceptible, despite the presence of chromosomal resistance genes, will be eradicated *in vivo*. Therefore, the Intrinsic Resistance Working Group was unable to confirm strains as intrinsically resistant." Note:** The comment may be edited.

A motion to delete the "R" in the IR table for *B. cepacia* and the designated drugs and include the proposed comment was made and seconded. Vote: 12 for – 1 against (Pass).

– The opposition vote was due to concerns that testing may not be reliable.

Fosfomycin Susceptibility Testing AHWG Report

AHWG Roster: Co-chairholders – Amy Mathers and Robert Flamm; Members – Karen (Kitty) Anderson, Betsy Hirsch, Laura Koeth, Kiofumi Ohkusu, Virginia Pierce, Lauri Thrupp, Mandy Wootton.

- The AHWG reviewed and finalized a recommendation for interpreting *E. coli* disk diffusion tests when colonies are within the zone.
  – Information reviewed:
    - Data on inner colonies
    - Fitness related to inner colonies
    - Data and decisions from EUCAST
    - Guidance images
  – Discussion summary
    - Inner colonies with *E. coli* are relatively infrequent.
    - Most inner colonies are related to mutations which confer a fitness cost for the bacteria.
    - There was concern that guidance regarding ignoring inner colonies in *E. coli* would be extrapolated to other species where the data are less clear.

SUMMARY MINUTES	
#	Description
	– A motion to retain the document as is without additional comment regarding ignoring colonies within the zone was made. The AHWG and MAIWG agreed to make no changes. • Clarification of language in M100, Table 2A on fosfomycin testing recommendations for non-*E. coli Enterobacteriaceae* and *P. aeruginosa*. – Laboratories are frequently asked to test fosfomycin against non-*E.coli* isolates. The clinical impact is unknown and PK-PD data is lacking. – The current comments in Table 2A in M100 include: o (44) For testing and reporting of E. coli urinary tract isolates only. o (45) The 200-µg fosfomycin disk contains 50 µg of glucose-6-phosphate. o (46) The only approved MIC method for testing is agar dilution using agar media supplemented with 25 µg/mL of glucose-6-phosphate. Broth dilution MIC testing should not be performed. **NOTE**: The comment numbers listed in the plenary presentation (16, 17, and 18) were incorrect. – It was recommended that comment (44) be strengthened provide additional clarification for <u>not</u> performing fosfomycin testing non-*E. coli*. o New proposed comments: ▪ (44a) "Disk diffusion testing is appropriate for testing and reporting of *E. coli* urinary tract isolates only." ▪ (44b) "Interpretive criteria apply only to *E. coli* urinary tract isolates and should not be extrapolated to other species of *Enterobacteriaceae*." **Note:** the numbering of the comments will be adjusted. o The MAIWG approved the comments (10-0).
	A motion to accept the revised Fosfomycin comments as presented with understanding that the numbering will be corrected was made and seconded. Vote: 11 for – 0 against; 2 absent (Pass).
	• Next steps for the AHWG include: – Provide additional education to clinical laboratories regarding the recommendation to not test non-*E.coli Enterobacteriaceae* – Revisit the urine breakpoint – Closely review all data about glucose-6-phosphate. – Collect PK-PD animal data to understand other species and breakpoints. – Review clinical trial data. – Discuss availability of Fosfomycin IV in United States **<u>ESBL testing recommendations for *Raoutella* (former *Klebsiella*)</u>** • *Raoutella* is infrequently isolate and rarely needs ESBL testing. • Data showing the presence of ESBL in this species AND performance of ESBL tests before any recommendations can be made are needed. • No recommendations for testing was made.

SUMMARY MINUTES	
#	Description
	Reporting IR for drugs that aren't tested Submitted by Susan Butler-Wu, Janet Hindler, Romney Humphries, Audrey Schuetz • Guidance on reporting "R" results for an antimicrobial agent to which an isolate has IR but is not tested is unclear. – Reasons for reporting: o Patient may be receiving the drug o Clinicians may lack awareness of the drug's activity resulting in a patient safety issue. o To enhance antimicrobial stewardship – There are questions regarding how the results for IR should be reported: o Drug listed in the panel with an "R" (no MIC) o Add comment to the AST report regarding IR of the organism to the drug – The SC decided to leave language as is and suggested that additional education should be provided. • Table 1A footnote "n" and Table 2D, Comment (5) for *Enterococcus*. – The current comment in M100 states: "The results of ampicillin susceptibility tests should be used to predict the activity of amoxicillin. Ampicillin results may be used to predict susceptibility to amoxicillin-clavulanate, ampicillin-sulbactam, and piperacillin-tazobactam among non-ß-lactamase-producing enterococci. Ampicillin susceptibility can be used to predict imipenem susceptibility, providing the species is confirmed to be *E. faecalis*." – Update on ampicillin as a predictor of imipenem and piperacillin for *E. faecalis* was provided. o Two reports were presented in January that showed that penicillin was a better predictor of piperacillin and imipenem than ampicillin o This may be due to an emerging resistance mechanism and it was suggested that data be collected to understand the degree of the issue. o Anecdotal information: There may be more penicillin-R ampicillin-S isolates on the West Coast. – Submission of penicillin-R/ampicillin-S data and/or isolates was requested. **Contact:** Amy Mathers (AJM5B@hscmail.mcc.virginia.edu) • Issues submitted to Text and Tables – Strengthen recommendation for inducible clindamycin resistance testing for staphylococci – How to interpret differences in reported significant digits

SUMMARY MINUTES

#	Description
9.	**M39 WG Report (Folder 13)** **WG Roster**: Co-chairholders – Janet Hindler and Trish Simner; Secretary – April Abbott; Members – See below

Team #1	Team #2	Team #3
Review current M39 - Expand specific ways to use local antibiogram for ASP and include guidance for LTCF	Antimicrobial Resistance Surveillance Program Design	IT – Data extraction & presentation
Erdman, Sharon - LEAD	Redell, Mark - LEAD	Das, Sanchita - LEAD
Hindler, Janet - Coordinator	Simner, Patricia - Coordinator	Abbott, April - Coordinator
Johnson, Kristie	Benahmed, Faiza	Ferrell, Andrea
Master, Ron	Morrissey, Ian	Mehta, Jimish
Neuhauser, Melinda	Sader, Helio	Nowak, Michael
Bhowmick, Tanaya	Sievert, Dawn	Stelling, John
	Snippes-Vignone, Paula	

- The format of the revised document was provided.
  - Part 1: The routine cumulative antibiogram
  - Part 2: Enhanced "Special" antibiogram
  - Part 3: Antimicrobial Resistance Surveillance Programs
  - Part 4: Use of Local Antibiogram and Surveillance Data (Infection control, Antimicrobial Stewardship, Clinical Microbiology, Public Health)
- Details of each team's approaches and plans for revision were provided (refer to the posted presentation).
- The next steps for the project were provided.
  - The teams have started to draft their sections.
  - A completed draft will be submitted for the January 2019 meeting.
  - Companion articles for each section will be drafted following the completion of M39.

10.	**Is AST in standard bacteriologic media sufficient to guide management of certain highly multiple-drug resistant organisms in critically-ill patients?: Dr. Victor Nizet** • Dr. Nlzet provided an overview of research performed to seek alternatives to classical antibiotics (especially very broad-spectrum agents) that kill bacteria or block their growth (refer to posted presentation). – Drugs to block specific pathogen immune resistance factors – Modulation of innate immunity to treat bacterial infections

SUMMARY MINUTES	
#	**Description**
	– Explore repurposing existing drugs for the above properties – Synergy between pharmaceutical and endogenous antibiotics • No actions by the SC were needed.
11.	Dr. Weinstein thanked the attendees for their attention and reported that the closing plenary would begin at 7:00 AM on Tuesday, 5 June 2018. The meeting was adjourned a 6:15 PM.

SUMMARY MINUTES	
#	**Description**
Tuesday, 5 June 2018	
1.	Dr. Weinstein opened the meeting at 7:00 AM Eastern (US) time.
2.	**<u>Breakpoint WG Report – Part 2:</u> Dr. Jim Lewis** **<u>Reassessment of Daptomycin Breakpoints for Enterococci (Folder 5, 5a – 5f)</u>** **AHWG Roster:** Co-chairholders – Jim Jorgensen and Mike Satlin; Members – German Esparza, Amy Mathers, Linda Miller, Elizabeth Palavecino, Robin Patel, Katherine Young, Barbara Zimmer; Advisors – Cesar Arias, Shelley Campeau, Romney Humphries, Joe Kuti, David Nicolau • In January 2018, revised breakpoints were proposed with comments. – Susceptible: ≤1 µg/mL*; Susceptible-Dose Dependent: 2-4 µg/mL**; Resistant: ≥ 8 µg/mL o *Based on a dosage regimen of 6 mg/kg/day in adults o **Increased daptomycin doses of 10-12 mg/kg are recommended for infections caused by these organisms, with potential consideration of combination therapy. o **Votes:** Approved by the AHWG (5-0-0-4) and BPWG (11-0-1-1) but not by the SC (7-6-0-0) – Concerns were raised by those opposed o Safety issues: Are recommending higher doses of daptomycin than what is in the FDA label o Should *E. faecium* breakpoints be separated from other enterococci? If so, should there just be S-DD and R (instead of S, S-DD, and R)? o It was questioned if these breakpoints would be for all infections including urinary tract infections. o There was a lack of clarity around "combination therapy". • Microbiologic data for *E. faecium* were presented. – MIC distributions showed that the ECV is at 4 µg/mL for *E. faecium*. – Multiple publications show that outcomes seem to improve with higher daptomycin doses (≥ 8mg/kg vs 6 mg/kg) especially for *E. faecium*. • Limited safety data with high-dose daptomycin were reviewed. – High-dose daptomycin is currently being used without any increase in safety issues. – Observational studies show no increase in rhabdomyolysis, myositis, myalgia, or myopathy. Eosinophilic pneumonia incidence does not appear to be a dose-dependent adverse reaction. – IDSA currently recommends and supports high-dose daptomycin for: o MRSA bacteremia and endocarditis o Persistent MRSA bacteremia and vancomycin treatment failures o Native valve endocarditis caused by staphylococci o Endocarditis caused by ampicillin-resistant and vancomycin-resistant enterococci • PK-PD data were reviewed. – Daptomycin did not perform well in the original animal studies.

#	Description

- The data were reanalyzed to try to determine a PK-PD signal.
- Data from published observational were acquired and the estimated exposures to correlate with clinical outcomes were modeled.
- Estimated *f*AUC/MIC targets that were correlated with microbiologic clearance and survival were identified.

Outcome	Survival (Monotherapy)	Survival (Combo therapy)	Microbiologic response
fAUC/MIC target	27.4	20.0	12.3

- Targets were similar to those seen in animal models.
- Monte Carlo simulations showed that the susceptible breakpoint changes with higher doses.
- With 6 mg/kg dosing, susceptible breakpoint should be 1 or 2 µg/mL.
- With 10-12 mg/kg dosing, susceptible breakpoint should be 2 or 4 µg/mL.

- Resolutions of concerns reviewed.
  - Safety of higher doses:
    - Minor increases in CK elevations cannot be ruled out, but this potential small toxicity risk is minor compared to a likely mortality benefit
    - Eosinophilic pneumonitis not dose-related
    - IDSA Guidelines frequently recommend these doses
  - Separation of *E. faecium* from other enterococci was not preferred as laboratories may not always be able to reliably speciate enterococci
    - Don't want to recommend high doses for infections with other enterococci
    - Data supporting this high dose are only for *E. faecium* with MICs 2-4 µg/mL
- Proposal for daptomycin breakpoints and comments for enterococci
  - Breakpoints
    - Susceptible: ≤1 µg/mL*
    - Susceptible-Dose Dependent: 2-4 µg/mL**
    - Resistant: ≥ 8 µg/mL
  - Comments to be included
    - *Based on a dosage regimen of 6 mg/kg/day in adults.
    - **The S-DD category is based on a dosage regimen of 8-12 mg/kg in adults and is intended for serious infections due to Enterococcus spp. Consultation with an infectious diseases specialist is recommended.
  - **Voting results**: AHWG – unanimous approval; BPWG – 8-0-1
- SC Discussion
  - Currently, only a susceptible breakpoint at ≤4 µg/mL and it seems outdated and not useful.
  - Need method for communicating the need for higher doses for MICs of 2 and 4.

#	Description
	– It is believed that the data available are all that will be generated. – On separation of *E. faecium* from other enterococci, there are other species that have high MICs and would benefit from higher doses. Also, the MICs appear to separate out *E. faecium* from other species that do not need higher doses (or would be treated with other drugs) so that the concern that laboratories cannot speciate enterococci is not an issue. The SDD range provides a conservative option. – It was suggested that the dose range be 10-12 mg/kg. It was decided that a separation between 6 and 10 (ie, 8 mg/kg) would cause confusion.
	A motion to accept the WG's proposed *Enterococcus* breakpoints for daptomycin as presented with the inclusion of the proposed comments was made and seconded. Vote: 13 for – 0 against (Pass).
	<u>Evaluation of Ceftaroline Breakpoints for *S. aureus*</u>: Submitted by Helio Sader (Folder 5, 1a – 1g) • Conclusions from the January 2018 meeting were reviewed. – Current breakpoint (1 µg/mL) is very close to the wild-type distribution. Many isolates show higher breakpoints (2 and 4) in other parts of the world. – It was questioned whether there a direct correlation between disk-MIC discrepancy rates and the proportion of ceftaroline nonsusceptible isolates. – Error rates are elevated (>10% Mi and/or >1% VM) when the collection had >15% ceftaroline-nonsusceptible isolates. – Current CLSI/US FDA disk breakpoints (≥24 mm/≤20 mm for S/R) appeared appropriate to reduce discrepancy errors. – An optimal correlation between disk and BMD methods cannot be achieved with current MIC breakpoints in geographic regions/medical centers with >15% ceftaroline-nonsusceptible MRSA isolates. • The potential for increasing dosage to deal with higher MICs was discussed. There were safety concerns about the higher dose. • Data collected after establishment of the current CLSI/FDA breakpoints were reviewed. – Efficacy of the ceftaroline fosamil 600 mg q8h with 2hr infusion conducted in patients with more considerable disease or system upset was studied. – Data suggest that the current breakpoint for *S. aureus* bisects the normal distribution which impacts the 5 µg disk. – Dose ranging hollow fibre study data provide a more robust definition of PK-PD targets with a revision of stasis, 1-log and 2-log kill PK-PD targets for *S. aureus*. – Data from cSSTI patients were used to update the population model and probability of target attainment analysis with the revised PK-PD targets. – Ceftaroline fosamil doses at 600 mg q8h with 2 h infusion achieves >95% and >90% PTA agains new 1-log kill and 2-log kill targets respectively for *S. aureus* up to an MIC of 4 µg/mL. • Clinical data were reviewed. – Clinical efficacy data in patients with cSSTI and *S. aureus* with ceftaroline MICs of ≥2µg/L are limited. – It is difficult to enroll patients with pathogens at the upper end of the MIC distribution.

#	Description

- Relying only on clinical data causes breakpoint to lag behind emergence of more resistant pathogens; therefore, guidance to clinicians may be lacking for treating patients at greatest need.

- Current EUCAST breakpoints were reviewed. EUCAST has developed indication-level breakpoints (pneumonia, non-pneumonia, and complicated skin and skin structure) and many countries are already are treating at the higher dose.
- The AHWG proposed that the breakpoints be revised. AHWG approved the proposal (6-0).

Organism	MIC breakpoints (µg/L)		
	Susceptible	SDD[a]	Resistant
S. aureus	≤1	2-4	≥8

Organism	Zone diameter breakpoints (mm)		
	Susceptible	SDD[a]	Resistant
S. aureus	≥25	20-24	≤19

[a] SDD is based on 600 mg q8h infused over 2 hours in adults.

- The AHWG also proposed that Outreach WG be contacted to promote education around the reasoning for this change and its applicability outside the US. (Passed 6-0).
- The BPWG approved the proposed breakpoints (6-2-1).

- SC Discussion
  - Two BPWG opposition votes were related to concern about a lack of clinical data and 5-minute infusion used in the US.
  - It was suggested that the comment be added to the comment currently in M100.
  - In the US, the drug is used off-label and it was agreed that the targets are conservative.

A motion to accept the ceftaroline MIC and DD breakpoint revisions as proposed was made and seconded. Vote: 10 for – 3 against (Pass).

- The opposition votes were due to the issues at a MIC of 4 µg/mL and the implementation challenges (AST devices and reporting implications).

SUMMARY MINUTES	
#	Description
	<u>Cefiderocol Breakpoint Request (</u>Folder 5, 3a – 3i) • Cefiderocol is a siderofore that does not appear to have an adaptive resistance problem. – The drug has better stability against serine- and metallo-type carbapenemases than carbapenems and cephalosporins. – There was no clear relationship between specific carbapenemase production and cefiderocol resistance. – A high MIC trend was observed for NDM producers. – MIC distributions showed that 99.6% of all isolates were susceptible to cefiderocol at ≤4 µg/mL. – The drug performed very well *in vitro*. – It has a short room temperature stability. • The PK-PD model data were reviewed. – Dose fractionation studies using murine thigh infection models showed that $T_{>MIC}$ was an appropriate PK-PD index to predictive efficacy. 75% showed a 1-$\log_{10}$ reduction. – The Percent target attainment (PTA) for 75% free time above MIC ($\%fT_{>MIC}$) against up to 4 µg/mL at the dose regimens was >90% for all renal function groups. • The non-clinical PD evaluation under human PK data were reviewed (Rat lung and murine thigh). – Simulated PK and protein binding lined up. – Animal model studies showed a good response rates with MICs at 4 µg/mL or lower for the tested organisms. • The clinical study data were reviewed. – Population included: o Hospitalized subjects with either cUTI with or without pyelonephritis or acute uncomplicated pyelonephritis (AUP) (limited to 30%). o Patients could be immunosuppressed or in mild to moderate renal failure. – Patients excluded: o Positive urine culture of gram-negative uropathogen resistant to imipenem. o More than 2 baseline uropathogens or confirmed fungal UTI o Patient receiving hemodialysis or peritoneal dialysis – In a modified intent to treat (MITT) population, the drug performed well at test of cure (TOC)]. – The breakpoints (see table below) were proposed by the AHWG and they deferred to the BPWG for a vote. – A motion was made and seconded by the BPWG to accept provisional MIC breakpoints proposed by the sponsor (see below). The BPWG approved the breakpoint proposal (5-0-3). – The BPWG also requested additional data before final breakpoints could be approved: clinical data for pneumonia and Monte Carlo simulations for *Acinetobacter* using 88 % T>MIC.

#	Description

	MICs (µg/ml)		
	Susceptible	Intermediate	Resistant
Enterobacteriaceae	≤4	8	≥16
Pseudomonas aeruginosa	≤4	8	≥16
Acinetobacter baumannii	≤4	8	≥16
Stenotrophomonas maltophilia	≤4	8	≥16

- SC Discussion
  - The drug is not yet FDA approved but will undergo a streamlined approval process (smaller database).
  - Since the drug has not been approved and is not on the market, it was questioned if these breakpoints would be considered provisional and kept out of M100 until available.
  - Concern was raised about the drug's safety and whether it is necessary to publish the breakpoints before FDA approval. It was noted that there is a precedent for approving breakpoints as provisional and placing them in the tables as investigational (INV).
  - Concern was also raised that clinical data in patients is not yet available and that there is no data for the proposed indication (pneumonia).
  - It was suggested that the AHWG continue to review the data and that the Table 1 placement should wait until the drug is approved.
- Options for action on the drug were reviewed.
  - Table the breakpoint approval until the next meeting.
  - Approve all or some of the breakpoints as provisional and do not publish them in M100.
  - Approve the breakpoints as provisional and place them in Tables 2 (only) with and INV designation.
- Discussion of options
  - It was noted that ertapenem breakpoints were published in M100 with provisional breakpoints. The breakpoints did not change once approved.
  - Historically, this type of approval used was common until there was an FDA policy change. There is language in M23 that encourages sponsors to come forward early before the drug is FDA approved.
  - It may be beneficial to publish the breakpoints as provisional for those rare patients that have pan-resistant organisms.
  - Guidance should be provided to the AHWG and the sponsor on types of data needed and to be reviewed. This includes *Acinetobacter* data and information on the special needs for preparing the media needed to perform AST.
  - Any new data that are produced after this presentation needs to be reviewed.
  - Differences in methodology for testing needs to be communicated (iron depletion issue). Information on the media needed to test needs to be added to the testing box in Tables 2. The appropriate text is already associated with the QC ranges.
  -

#	Description
	A motion to approve the proposed MIC breakpoints as provisional and place them in the appropriate Tables 2 only with a designation of INV and continue to review data as they become available was made and seconded. Vote: 12 for – 1 against (Pass).
3.	**Due to unforeseen circumstances, the M23 WG meeting was cancelled. The WG will meet by conference call in the near future.**
4.	**Quality Control (QC) WG Report: Ms. Sharon Cullen and Ms. Maria Traczewski (Folder 9)** **QCWG Roster**: Co-chairholders: Sharon Cullen and Maria Traczewski; Secretary – Michael Huband; Members – Patricia Conville, Dana Dressel, Janet Hindler, Denise Holliday (absent), Erika Matuschek (absent), Susan Munro, David Paisey (absent), Elizabeth Palavecino, Chris Pillar, Mary York **Tier 2 QC Studies** • **Cefpodoxime-ETX1317 (1:2) MIC QC ranges**

QC Strain	Range	% In	Mode	dil	Comments
E. coli ATCC 25922	**0.03/0.06-0.12/0.25**	100%	0.06/0.12	3	
E. coli ATCC 5218	**0.03/0.06-0.12/0.25**	100%	0.06/0.12	3	
E. coli NCTC 13353	**0.06/0.12-0.25/0.5**	100%	0.12/0.25	3	Add footnote to explain not to use for routine QC.
K. pneumoniae ATCC 700603	**0.03/06-0.25/0.5**	99.2%	0.12/0.25	4	Shoulder 87% @ 0.06/0.12 Recommended routine QC strain for combination

- Footnotes
  - Highlight *K. pneumoniae* ATCC 700603 on Table 5A-2 as routine QC strain.
  - Cefpodoxime-ETX1317 (1:2): "ETX1317 has demonstrated intrinsic activity against *E. coli*; therefore, *K. pneumoniae* ATCC 700603 should be used for routine QC testing of cefpodoxime-ETX1317 (1:2) as this strain can QC both components of the cefpodoxime-ETX1317 (1:2) combination."
  - Highlight on Table 5A-2, *E. coli* NCTC 13353 and *K. pneumoniae* ATCC 700603 for QC integrity check.
- Discussion within WG
  - Footnote needed to ensure *E. coli* NCTC 13353 is not used for routine QC since it appears in the MICs for the combination and single drug that this strain could also be a candidate for routine QC.
  - Included strains with ranges in I-R category as QC integrity check.
  - QCWG will review Table 4A-2 and 5A-2 in January 2019 to determine if footnotes or guidance should be added for others.
  - WG Vote: 9-0-0-1 (Pass)

A motion to accept the cefpodoxime-ETX1317 (1:2) MIC QC ranges as presented (highlighted in yellow) was made and seconded. Vote: 11 for – 0 against – 1 abstention; 1 absent (Pass)

- **Cefpodoxime MIC QC ranges**

QC Strain	Range	% In	Mode	dil	Comments
E. coli ATCC 25922	**0.25-1**	100%	0.5	3	Currently approved range
E. coli ATCC 35218	**0.12-0.5**	99.6%	0.25	3	
E. coli NCTC 13353	**32-128**	100%	64	3	100% of results at mode (64) Identify as QC integrity strain*
K. pneumoniae ATCC 700603	**4-32**	100%	16	4	Identify as QC integrity strain*

  - No footnotes
  - QCWG vote: 9-0-0-1 (Pass)

A motion to accept the cefpodoxime MIC QC ranges as presented (highlighted in yellow) was made and seconded. Vote: 13 for - 0 against (Pass)

- **Gepotidacin Disk Diffusion (DD) QC Ranges**

QC Strain	Range	% In	Median	mm
N.gonorrhoeae 49226	32-40	98.5%	36	9

  - **No footnotes**
  - **QCWG vote: 9-0-0-1**

A motion to accept the gepotidacin DD QC ranges as presented (highlighted in yellow) was made and seconded. Vote: 13 for - 0 against (Pass)

- **Imipenem-Relebactam (DD) QC ranges**

QC Strain	Range	% In	Median	mm	Comments
E. coli ATCC 25922	**27-33**	99.4%	30	7	Lab 7 mode outlier
P. aeruginosa ATCC 27853	**26-31**	100%	29	6	

K. pneumoniae ATCC 700603	**26-32**	100%	29	7	
K. pneumoniae ATCC BAA-1705	**23-29**	98.5%	26	7	Routine QC strain
K. pneumoniae ATCC BAA-2814	21-28 22-28	99.6% 96.5%	25	8 7	Lab 3 mode outlier. Approved smaller range for better control. Routine QC strain

- Footnotes
  - Add to footnote: "QC ranges for (drug name) were established using data from only one disk manufacturer. Disks from other manufacturers were not available at the time of testing."
  - Highlight *K. pneumoniae* ATCC BAA-1705 and *K. pneumoniae* BAA-2814 on Table 4A-2 as QC strains for routine QC for imipenem-relebactam.
  - Highlight *K. pneumoniae* ATCC BAA-1705 on Table 4A-2 for QC integrity check for imipenem.
- QCWG Discussion
  - Study objective was to add QC strains for imipenem-relebactam and Imipenem alone
  - Table 6 and Glossary information previously added.
  - **Note:** Abbreviation needs to be added to M100 29th Ed. in Glossary II.
  - Routine QC strains are same as those identified for MIC on Table 5A-2.
  - QC integrity check: Not needed for *K. pneumoniae* BAA-2814. Need to address reading when breakthrough colonies that are seen with single drug during QC integrity check.
  - QCWG vote: 7-2-0-1 (ranges); 9-0-0-1 (routine QC strain)

- **Imipenem (DD) QC ranges**

QC Strain	Range	% In	Median	mm
K. pneumoniae ATCC BAA-1705	**11-22**	98.1%	16	12
K. pneumoniae ATCC BAA-2814	**6-14**	95.7%	10	9

- Footnote: Read inner colonies for zone diameter
- QCWG Discussion
  - 7/1/0/1 (ranges)
  - 10/0/0/0 (change cefepime description of QC ranges to be consistent)
    - *E. coli* ATCC 13353 from ≤15 to 6-15 mm
    - *baumannii* NCTC 13304 from ≤16 to 6-16 mm

A motion to accept the DD QC ranges for imipenem-relebactam and imipenem as presented (both highlighted in yellow) was made and seconded. Vote: 13 for - 0 against (Pass)

#	Description

- **Tebipenem DD QC ranges**

QC Strain	Range	% In	Median	mm
E. coli ATCC 25922	**30-37**	99.3%	33	8
P. aeruginosa ATCC 27853	**19-27** **20-26**	99.4% 96.5	23	9 7
K. pneumoniae ATCC 700603	**26-32**	99.2%	29	7

  - Footnotes
    - Add to Table 4A-1,
    - QC range for *K. pneumoniae* ATCC 700603 with tebipenem is 26-32 and is considered a supplemental QC strain and is not required for routine QC of tebipenem MIC tests.
  - QCWG Discussion
    - PO administration as SPR994, pa pivoxil prodrug of SPR859
    - Ranges were established for *K. pneumoniae* ATCC 700603 as supplemental for use in various studies since the drug is targeting ESßLs but not needed for routine QC.
  - QCWG Votes
    - 8/0/0/1 for *E. coli* ATCC 25922
    - 8/0/0/1 Changed range for *P. aeruginosa* ATCC 27853 to 7 mm
    - 8/0/0/1 *K. pneumoniae* ATCC 700603
    - 8/0/0/1 *S. aureus* ATCC 25923 (no range approved)

A motion to accept the DD QC ranges for tebipenem as presented (highlighted in yellow) was made and seconded. Vote: 13 for - 0 against (Pass)

Tier 3 MIC QC Monitoring: Data and Feedback Request

- Monitor and look for signals that there is an issue.
- Request to submit data and/or feedback to Sharon Cullen (SKCULLEN@beckman.com) or Erika Matuschek (erika.matuschek@kronoberg.se)
- *S. pneumoniae* ATCC 49619 has been on the list for a while and may be removed from the list if no feed back is provided.

QC Strain (ATCC)	Antimicrobial Agent	Current Range
S. pneumoniae ATCC 49619	Levofloxacin	0.5-2
S. aureus ATCC 29213	Ciprofloxacin	0.12-0.5

#	Description

H. influenzae ATCC 49247	Moxifloxacin	0.008-0.03
E. faecalis ATCC 51299	Gentamicin HLAR	Resistant
S. pneumoniae ATCC 49619	Cefuroxine	0.25-1

- List of organisms from 2013 – 2015 reports will be removed unless new information is reported.

QC Strain (ATCC)	Antimicrobic	Current Range	Action Recmd	Concern	Date Reported
K. pneumoniae 700603	Imipenem/ relebactam	0.03-0.25	Monitor/request feedback	>5% out high reported with one lab	Jan-18
K. pneumoniae BAA-2814	Imipenem/ relebactam	0.06-0.25	Monitor/request feedback	>5% out high reported with one lab. (BAA-2814 or BAA-1705 used for routine QC)	Jan-18
E. faecalis 29212	Amikacin	64-256	Monitor/request feedback	CDC reported out low when testing gram neg panels, other strains in range.	Jan-18
E. coli NCTC 13486	Colistin	NA	Potential QC organism	MICs in range likely tested (e.g., MIC = 4 µg/ml) Potentially more reproducible than current QC	Jan-2017
E. faecalis 29212	Gentamicin	4-16	Monitor/request feedback	Some out low. Cations, pH in range	Jan-2015
E. faecalis 29212	Tobramycin	8-32	Monitor/request feedback	Some out low. Cations, pH in range	Jan-2015
P. aeruguginosa 27853	Etrapenem	2-8	Monitor	Out low with some labs	NA
E. faecalis 29212	Minocycline	1–4	Monitor/request feedback	Mode at low end at 16 hrs, bimodal at 18 hrs, at middle of range at 20 hrs	NA
S. aureus 29213	Minocycline	0.06–0.5	Monitor/request feedback	Mode at low end of current range regardless of read time 16-20 hr	Jun-2013
B. fragilis 25285	Pip/tazo	0.12-1	Monitor/request feedback	Out low (control M23 study Jan 2010)	Jun-2013

Tier 3 DD QC Monitoring: Data and Feedback Request

- Additional data or analysis needed for the January 2019 meeting especially from the United States
- Perform normal statistics

#	Description

QC Strain (ATCC)	Antimicrobic	Current Range	Action Recmd	Concern	Date Reported
P. aeruginosa 27853	Imipenem	20-28	Consider tightening range to 20-26 (98% in range), or 20-27 (99% in range). Analyze by gavan and rangefinder	Zones in the lower part or below range reported (1600 results, including 480 from 2001 M23)	Dec-15
E. coli 25922	Pefloxacin	25-33	EUCAST range 26-32 (07% in range). CLSI 25-33 (100% in range). Clearer reading instructions (inner or outer zone diameters, pictures) and/or address in troubleshooting guide.	Is there a better way to QC this agent? Varies by manufacturer.	Jan-17
P. aeruginosa ATCC 27853	Ceftriaxone	17-23	Request data, reassess range or troubleshooting information.	Colonies within zone causing, out of range	Jun-17
P. aeruginosa ATCC 27853	Amikacin	18-26	Suggest changing to 20-26. Aligns with changes to Gentamicin and Tobramcyin. Is data from original M23 available? Analyze by gavan and rangefinder	Out high for many labs, 781 results. No results at 18-19	Jan-18

Miscellaneous Requests

QC Strain (ATCC)	Antimicrobic	Current Range	Action Recmd	Concern	Date Reported
K. pneumoniae 700603	B-lactam/ B-lactamase inhibitors	No range	Request ranges for single and combination agents (eg, amoxicillin, ampicillin, ampcillin-sulbactam (2:1), cefepime, ceftaroline)	Alternative for E. coli 35218	NA
S. aureus 25923	Tedizolid	NA	Request Tier 2 study to establish QC ranges. (Methods Working Group).	Need new Tier 2 study for QC range if disk mass is changed from 20 to 2 µg	Jan-17
S. aureus 25923	Linezolid	NA	Request Tier 2 study to establish QC ranges. (Methods Working Group).	Need new Tier 2 study for QC range if disk mass is changed from 30 to 10 µg.	Jan-17

Revisions to Table 5G MIC Troubleshooting Guide

- It was proposed to revise general comment (1) to read, "QC organism maintenance: Avoid repeated subcultures. Retrieve new QC strain from stock (refer to M07,1 Subchapter 4.4). If using lyophilized strains, follow the maintenance recommendations of the manufacturer. ~~Store *E. coli* ATCC®* 35218, and *K. pneumoniae* ATCC® 700603 stock cultures at –60°C or below and prepare working cultures weekly.~~

#	Description

- Similar revisions will be made to the DD troubleshooting guide.
- It was proposed that the following text (highlighted in yellow) be deleted from Table 5G and replaced with text in the table below (highlighted in orange).

Antimicrobial Agent	QC Strain	Observation	Probable Cause	Comments/Suggested Actions
Β-LACTAMS				
Amoxicillin-clavulanate Ticarcillin-clavulanate	*E. coli* ATCC® 35218 *K. pneumoniae* ATCC® 700603	MIC too high	Clavulanate is labile. Antimicrobial agent is degrading.	Use alternative lot. Check storage conditions and package integrity.
Aztreonam Cefotaxime Cefpodoxime Ceftazidime Ceftriaxone	*K. pneumoniae* ATCC® 700603	MIC too low	Spontaneous loss of the plasmid encoding the β-lactamase	See general comment (1) on QC organism maintenance.

- It was proposed that the text in the rows below replace the text in the rows above in Table 5G.

Antimicrobial Agent	QC Strain	Observation	Probable Cause	Comments/Suggested Actions
Β-LACTAMS				
Combination β-Lactam agents	*A. baumannii* ATCC 13304 *E. coli* ATCC 35218, *E. coli* ATCC 13353, *K. pneumoniae* ATCC 700603, *K. pneumoniae* ATCC BAA-1705,	MIC too low or susceptible for single β-lactam agent, in range for combination β-lactam agent	Spontaneous loss of the plasmid encoding the beta-lactamase	Obtain new frozen or lyophilized stock culture. Use other routine QC strain (if available). These strains should be stored at -60°C or below and avoid frequent subcultures. Note: *K. pneumoniae* BAA-2814 is stable and doesn't require QC integrity check.

#	Description

Combination β-Lactam agents	*A. baumannii* ATCC 13304 *E. coli* ATCC 35218, *E. coli* ATCC 13353, *K. pneumoniae* ATCC 700603, *K. pneumoniae* ATCC BAA-1705, *K. pneumoniae* ATCC BAA-2814	MIC too high or resistant for both the single β-lactam agent and the combination β-lactam agent	Antimicrobial agent is degrading	Use alternative lot of test materials. Check storage and package integrity. Imipenem and clavulanate are especially labile.

A motion to accept the revisions to the troubleshooting guide (Table 5G) as proposed was made and seconded. Vote: 13 for – 0 against (Pass).

- It was proposed that Q & A for combination agents be added for QC. The QCWG agreed with the concept but did not yet take a vote.
  - The Q & A will be added to the next edition of M100.
  - It was agreed that a SC vote was not needed.

5. **Text and Tables WG (TTWG) QG Report: Dr. Shelley Campeau (Folder 10)**

TTWG Roster: Co-chairholders – Jana Swenson and Shelley Campeau; Secretary – Carey-Ann Burnham; Members present – Andrea Ferrell, Janet Hindler, Peggy Kohner, Susan Munro, Barth Reller, Dale Schwab, Maria Traczewski, Nancy Watz, Mary York; Members absent – Melissa Jones, Dyan Luper, Linda Mann, Flavia Rossi, Richard Thomson

Inducible clindamycin testing language revision

- Language change suggested in response to a TTWG comment submitted during the spring review of M100.
- **Current Table 2C, Comment (29):** "Inducible clindamycin resistance can be detected by disk diffusion using the D-zone test or by broth microdilution (see Table 3G, Subchapter 3.9 in M021, and Subchapter 3.12 in M07)."
- **Revising the comment with stronger language was proposed**: "For isolates that test erythromycin resistant and clindamycin susceptible or intermediate, testing for inducible clindamycin resistance is required before reporting clindamycin. See Table 3G, Subchapter 3.9 in M02,2 and Subchapter 3.12 in M07." This revision will apply to Table 2 comments where inducible clindamycin resistance is mentioned [Table 2C, comment (29), Table 2G, comment (23), and Table 2H-1 – comment (14)].
- There seems to be a lack of understanding by clinicians regarding erythromycin and inducible clindamycin testing. The TTWG also agreed that there are other comments in Table 3G which are soft in their recommendations and need to be reviewed and potentially revised.
  - It was suggested that volunteers from the TTWG to review the language throughout the document regarding inducible clindamycin testing and reporting.
  - The TTWG also suggested this may be a good topic for discussion in the Outreach WG newsletter.
- SC Discussion
  - It was questioned whether the same recommendation should be made for erythromycin intermediate isolates as well.

#	Description
	– It was questioned whether this also applies to ß-streptococci and *S. pneumoniae*. It was noted that the soft language was in the document to account for organisms other than *Staphylococcus*. – The TTWG will reach out to other volunteers to assist with the review if needed. **<u>Addition of text regarding reporting 0.125 µg/mL as 0.12 µg/mL.</u>** • The MAIWG submitted a comment to the TTWG regarding reporting 0.125 as 0.12 throughout M100. Others noted that there are international guidelines that suggest 0.125 rather than 0.12 and it create confusion. • Language regarding this issue is already in Table 2H-2 for *Streptococcus* spp. (Comment 6) and Table 7. It would be helpful to add stronger language in other parts of the document. • It was suggested in M100 that language similar to that in Table 2H-2 and Table 7 be added to the instructions for use in a new section D (MIC Reporting Concentrations):
	D. MIC Reporting Concentrations **When serial twofold dilution minimal inhibitory concentrations are being prepared and tested, the actual dilution scheme is, for example:** **16, 8, 4, 2, 1, 0.5, 0.25, 0.125, 0.0625, 0.03125 µg/mL, etc. (See Table 7 for additional dilutions)** **For convenience only, and not because these are the actual concentrations tested, it was decided to use the following values in these tables:** **16, 8, 4, 2, 1, 0.5, 0.25, 0.12, 0.06, 0.03 µg/mL, etc.** **The values that appear in the tables are equivalent to the actual values tested, eg, 0.12 µg/mL = 0.125 µg/mL, and laboratories should report an MIC of ≤0.125 µg/mL as ≤0.12 µg/mL.**
	• The SC agreed that the addition makes sense and that no vote was needed. **<u>Tetracycline comment clarification</u>** • A comment posted on the ASM, Division C listserv was forwarded to the TTWG that stated: "For ß-hemolytic strep and tetracyclines comment 13 (Table 2H-1), we have a physician requesting doxycycline sensitivities on a ß-strep isolate. Tetracycline is on our panel and tested "R". So does that mean you can interpret isolates "R" to tetracycline to also be "R" to doxycycline? Or this only works for "S" results? • The current Table 2H-1, comment (13) states: "Organisms that are susceptible to tetracycline are also considered susceptible to doxycycline and minocycline."

#	Description
	• It was proposed that additional clarifying language be added to comment (13): "Organisms that are susceptible to tetracycline are also considered susceptible to doxycycline and minocycline. However, resistance to doxycycline and minocycline cannot be inferred from tetracycline resistance." The comment would be revised wherever it appears in the document. • The SC agreed that this is an issue, the additional language is acceptable, and no vote was needed. **Options for revising Table 2C (*Staphylococcus* spp.)** • The goal of the TTWG is to improve the table formatting as testing recommendations continue to become more complicated, particularly with oxacillin and non-*S. aureus* spp. • Three versions of the table were presented. – Version 1: Table 2C-1 *S. aureus* only and Table 2C-2 Other staphylococci with option to group species based on testing recommendations – Version 2: Keep Table 2C but add a column for specific indications – Version 3: Table 2C-1 with oxacillin/cefoxitin and vancomycin *Staphylococcus* only and Table 2C-2 with all other antimicrobials ○ Option 1: Add new column for species indications ○ Option 2: Separate MIC and DD and list species indications • The TTWG preferred some version of Version 3. • **Action Item**: Version 3, Options 1 and 2 will be drafted and circulated for review before the formal TTWG M100 review.
6.	**Subcommittee on Veterinary Antimicrobial Susceptiblity Testing (VAST) Report: Mr. Robert Bowden** • An update on the activities of the VAST SC was provided. – There are currently 10 WG managed by VAST that are working on different aspects of veterinary microbiology. – VET01 is in the process of being revised. This document is the veterinary equivalent of M02 and M07. ○ A committee was appointed in August 2016 to perform an extensive revision on the document. ○ The revision includes a new VET01 informational supplement which will be renumbered as VET08 (equivalent to M100). ▪ The SC plans to release future editions of VET08 biennially. ▪ New content has been adapted from M100 for veterinary applications and with veterinary-specific breakpoints. ▪ The current supplement has been freely available on the CLSI website (VET01) with with 80% of users being from outside the US. ○ The new editions are expected to publish by the end of June 2018. – VET09, *Understanding Antimicrobial Susceptibility Test Data in Veterinary Settings* ○ This is a report with a primary target audience of veterinarians and laboratorians. ○ A document development committee was formed in November 2017 to develop the document. ○ Publication is expected in August 2019.
7.	**GCWG Report – Table 2F Discussion: Dr. Mary Jane Ferraro** • It was proposed that the *Neisseria gonorrhoeae* (GC) table (2F) be "cleaned up" to remove drug breakpoints that are no longer, or have never been validated (investigational only) and are not in use for treating GC.

SUMMARY MINUTES	
#	Description
	• It was suggested that the following drugs be deleted from Table 2F. – Cefoxitin – Cefuroxime – Cefmetazole – Cefotetan – Ceftazidime – Cefetamet – Enofloxacin – Lomefloxacin – Ofloxacin – Fleroxacin • It was also proposed that the following drugs be considered for deletion if it is determined that they are not still in clinical use. – Cefepime – Ceftizoxime – Cefpodoxime • It was questioned whether the drugs meet the criteria for being deleted. – It was noted that they can be added to the archived drug table on the CLSI website (Archived drugs). – It was also suggested that the ß-lactam comments be reviewed. – It was noted that in the past, drugs have been deleted from tables due to: o Lack of availability o No longer marketed in any part of the world o No longer useful for the indication
	A motion to delete the 4 quinolones (Enofloxacin, Lomefloxacin, Ofloxacin, and Fleroxacin) from Table 2F and move them to the archive table on the website was made and seconded. Vote: 12 for – 0 against; 1 absent (Pass).
	– These drugs are currently not available for the indication and there may be a surrogate for testing (eg, ciprofloxacin).
	A motion to delete the 6 cephalosporins (Cefoxitin, Cefuroxime, Cefmetazole, Cefotetan, Ceftazidime, Cefetamet) from Table 2F and move them to the archive table on the website was made and seconded. Vote: 12 for – 0 against; 1 absent (Pass).
	– Cefepime is being retained due to its better activity. – Cefepime, Ceftizoxime, and Cefpodoxime would be retained as they are used frequently in other countries and their usage needs to be researched more extensively. – The ß-lactamase comments will be reviewed for consideration for revision.

SUMMARY MINUTES	
#	**Description**
	NOTE: Based on input received from the Centers for Disease Control after the summary was distributed for review indicating that cefotetan and cefoxitin are still included in the clinical recommendations for treatment of *N. gonorrheoae*, both drugs have been retained in Table 2F in M100, 29th edition.
8.	**Adjournment** • Dr. Weinstein reviewed the upcoming meeting schedule and thanked the participants for their hard work and attention. • The meeting was adjourned at 11:30 AM.

Upcoming Meetings of the Subcommittee on Antimicrobial Susceptibility Testing:

27 – 29 January 2019 at the Renaissance World Golf Village, St. Augustine, Florida, USA
16 – 18 June 2019 at the Westin Galleria, Dallas, Texas, USA
26 – 28 January 2020 at the Tempe Mission Palms Hotel, Tempe, Arizona, USA
14 – 16 June 2020 at the Hyatt Regency Baltimore Inner Harbor, Baltimore, Maryland, USA

ACTION ITEMS		Responsible
1.	Form an ad Hoc WG under the BPWG to continue to study the issues regarding ceftazidime-avibactam disk breakpoints.	SC
2.	Continue the QC studies for the Colistin broth-disk elution test, develop appropriate language, and circulate both for electronic vote.	Colistin WG
3.	Draft a mock-up of Version 3, options 1 and 2, of Table 2C (*Staphylococcus*) and circulate both for review and comment.	TTWG

Summary of Passing Votes			
#	**Motion Made and Seconded**	**Results***	**Page**
1.	To approve the summary minutes from the January 2018 subcommittee meeting.	13 – 0	7
2.	To accept the proposal to include oxacillin disk diffusion for *S. epidermidis* (S = ≥18 mm and R = ≤17 mm) in Table 2C.	13 – 0	9
3.	To accept the proposal that the CLSI and EUCAST media are equivalent with a follow-up on the Site 2 QC issue and draft text to add to the testing conditions box for the *S. pneumoniae* table.	11 – 1	10
4.	To retain the current DD breakpoints (no intermediate) and include a comment recommending that when DD results are in the 18 – 20 mm range, a confirmatory MIC test should be performed.	13 – 0	11
5.	To accept the AHWG breakpoint proposal for meropenem-vaborbactam and *Enterobacteriaceae* (MIC: S = ≤4/8; I = 8/8; R = 16/8 and DD: S = ≥18 mm; I = 15-17mm; R = ≤14mm).	12 – 0 - 1	15
6.	To place meropenem-vaborbactam in Table 1A for *Enterobacteriaceae* in Group B.	12 – 0 - 1	15
7.	To place meropenem-vaborbactam, ceftazidime-avibactam, and ceftolozane-tazobactam in three separate boxes in Table 1A, Group B and place the other three β-lactam combination agents together in the same box for *Enterobacteriaceae*.	13 – 0	15
8.	To accept the *P. aeruginosa* disk correlates for ciprofloxacin as proposed: >25 (S); 19-24 (I); <18 (R)	13 – 0	16
9.	A motion to accept the disk correlates for ciprofloxacin and levofloxacin with *Enterobacteriaceae* and *P. aeruginosa* with levofloxacin as shown was made and seconded. Vote: 13-0 (Pass).		17
10.	To accept the AHWG proposal to establish an "S" breakpoint for *Neisseria gonorrheoae* and azithromycin at ≤ 1, include the proposed comment in Table 2F, and to place azithromycin for *N. gonorrheoae* in Table 1B, Group A.	13 – 0	18
11.	To accept the S-I-R or S-SDD-R option for all newly approved drugs having 3 categories (none with only 2 categories but with an S-only would be acceptable) was made and seconded. The drugs currently in the document would stay the same.	9 - 4	24
12.	To approve the addition of the proposed footnote to the anaerobe antibiogram for *Cutibacterium* (*Propionibacterium*) *acnes* in Appendix D2	13 – 0	24
13.	To delete the ampicillin-sulbactam comment (Footnote a) from the *A. baumannii/calcoaceticus* complex row in the Intrinsic Resistance (IR) table.	13 – 0	25
14.	To delete the "R" in the B. cepacia row in the IR table for the designated drugs and include the proposed comment.	12 – 0 - 1	26
15.	To accept the revision of fosfomycin comments in M100 as presented with understanding that the numbering will be corrected.	11 – 0; 2 absent	27
16.	To accept the WG's proposed *Enterococcus* breakpoints for daptomycin (S: ≤1 µg/mL; SDD: 2-4 µg/mL; R: ≥ 8 µg/mL) with the inclusion of the proposed comments.	13 – 0	33
17.	To accept the revised ceftaroline MIC and DD breakpoints for *Staphylococcus aureus* (MIC: ≤1 [S]; 2-4 [SDD]; ≥8 [R]; DD: ≥25 [S]; 20-24 [SDD]; ≤19 [R])	10 - 3	34
18.	To approve the proposed MIC breakpoints for cefiderocol as provisional and place them in the appropriate Tables 2 only with a designation of investigational (INV) and continue to review data as it becomes available.	12 - 1	36
19.	To accept cefpodoxime-ETX1317 (1:2) MIC QC ranges as presented.	11 – 0 – 1;	37

Summary of Passing Votes			
#	**Motion Made and Seconded**	**Results***	**Page**
		1 absent	
20.	To accept cefpodoxime MIC QC ranges as presented.	13 - 0	38
21.	To accept the gepotidacin DD QC ranges as presented.	13 - 0	38
22.	To accept DD QC ranges for imipenem-relebactam and imipenem as presented.	13 - 0	39
23.	To accept DD QC ranges for tebipenem as presented.	13 - 0	40
24.	To accept the revisions to the troubleshooting guide (Table 5G) as proposed.	13 - 0	43
25.	To delete the 4 quinolones (Enofloxacin, Lomefloxacin, Ofloxacin, and Fleroxacin) from Table 2F and move them to the archive table on the website.	12 – 0; 1 absent	47
26.	To delete the 6 cephalosporins (Cefoxitin, Cefuroxime, Cefmetazole, Cefotetan, Ceftazidime, Cefetamet) from Table 2F and move them to the archive table on the website.	12 – 0; 1 absent	47

* Key for voting: X-X-X-X = For-against-abstention-absent

Respectfully submitted,

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