Summary Minutes
Subcommittee on Antimicrobial Susceptibility Testing
Buena Vista Palace
Lake Buena Vista, Florida
9-11 January 2011

A meeting of the CLSI Subcommittee on Antimicrobial Susceptibility Testing was held on 9-11 January 2011, at the Buena Vista Palace, Lake Buena Vista, Florida. The following were in attendance:

Franklin R. Cockerill, III, MD **Chairholder**	**Mayo Clinic**
Matthew A. Wikler, MD, MBA, FIDSA **Vice-Chairholder**	**IASO Pharma, Inc.**
John H. Rex **Area Committee on Microbiology** **Chairholder**	**AstraZeneca**
Mary Jane Ferraro, PhD, MPH **Area Committee on Microbiology** **Vice-Chairholder**	**Massachusetts General Hospital**

Members Present

Jeff Alder, PhD	Bayer Healthcare
Michael N. Dudley, PharmD, FIDSA	Mpex Pharmaceuticals
George M. Eliopoulos, MD	Beth Israel Deaconess Medical Center
Dwight J. Hardy, PhD	University of Rochester Medical Center
David W. Hecht, MD	Loyola University Medical Center
Janet F. Hindler, MCLS, MT(ASCP)	UCLA Medical Center
Jean B. Patel, PhD, D(ABMM)	Centers for Disease Control and Prevention
Mair Powell, MD, FRCP, FRCPath	MHRA
Richard B. Thomson, Jr., PhD	Evanston Hospital, NorthShore University HealthSystem
John D. Turnidge, II, MD	SA Pathology @ Women's and Children's Hospital
Melvin P. Weinstein, MD	Robert Wood Johnson University Hospital
Barbara L. Zimmer, PhD	Siemens Healthcare Diagnostics, Inc.

Advisors Present

Paul G. Ambrose, PharmD, FIDSA	ICPD/Ordway Research
Patricia A. Bradford, PhD	Novartis Institutes for Biomedical Research
Steven D. Brown, PhD	The Clinical Microbiology Institute
Karen Bush, PhD	Indiana University

William A. Craig, MD	University of Wisconsin School of Medicine
Cynthia L. Fowler, MD	bioMérieux, Inc.
Gunnar Kahlmeter, MD, PhD	ESCMID
James S. Lewis, II, PharmD	University of Texas Health Science Center
Frederic J. Marsik, PhD, ABMM	FDA Center for Drug Evaluation and Research
Linda A. Miller, PhD	GlaxoSmithKline
Harriette L. Nadler, PhD	EUSA USA Pharmaceuticals, Inc.
Freddie Mae Poole, BS, MT(ASCP, ISCLT)	FDA Center for Devices and Radiological Health
Flavia Rossi, MD	University of Sao Paulo
Dale A. Schwab, PhD, D(ABMM)	Quest Disagnostics, Nichols Institute
Jana M. Swenson, MMSc	Centers for Disease Control and Prevention
Joseph G. Toerner, MD, MPH	FDA CDER

Observers Present

Francis Arhin	The Medicines Company
Eliana S. Armstrong, PhD	Achaogen, Inc
Robert E. Badal	International Health Management Associates, Inc.
Dr. Susanne Berglund	Siemens Healthcare Diagnostics
Sujata Bhavnani, PharmD	Ordway Research Institute
Donald Biek, PhD	Cerexa, Inc.
Johanne Blais	Theravance
Lyn Boyer	Siemens Healthcare Diagnostics
Marissa Braff, PhD	Gilead Sciences, Inc.
William B. Brasso	BD Diagnostic Systems
Joyce R. Bray	Siemens Healthcare Diagnostics
Stephen M. Brecher, PhD	VA (West Roxbury) Boston Healthcare System
Dr. Derek Brown	PhD, D(ABMM), FCCM
Linda C. Bruno, MA, MT(ASCP)	University of Illinois Medical Center
Carey-Ann Burnham, PhD, D(ABMM)	Washington University School of Medicine
Kathy Burtner	Siemens Healthcare Diagnostics
Laurent Chesnel	Cubist Pharmaceuticals, Inc.
Ryan Cisz	Achaogen, Inc.
Diane M. Citron, M(ASCP)	R.M. Alden Research Laboratory
Christian Coogan	bioMérieux, Inc
Ian A. Critchley, PhD	Cerexa, Inc.
John A.Crump	CDC, Duke University Medical Center
Sharon K. Cullen, BS, RAC	Siemens Healthcare Disagnostics
Todd Davies, PhD	Johnson & Johnson Pharm Research & Develop.
Chris Doern	UT Southwestern Medical Center
Jennifer Dawson Driscoll	Siemens Healthcare Diagnostics
Lauarie DeBonnett,MD	Novartis Pharmaceuticals
Michael J. Dowzicky	Wyeth Pharmaceuticals.
Alan T. Evangelista, PhD, D(ABMM)	St. Christopher's Hospital for Children
Rob Eusebio, MSHA, MT(ASCP)	Siemens Healthcare Diagnostics
Gina Ewald, CLS(CA), MT(ASCP)	Siemens Healthcare Diagnostics
John Farley	U.S. Food and Drug Administration
David Farrell, PhD, D(ABMM), FCCM	JMI Laboratories
Steve Fitzsimmons,MS, MT(ASCP)	bioMérieux, Inc.

Robert K. Flamm, PhD.	Johnson & Johnson Pharm Research & Develop.
Lawrence V. Friedrich, PharmD	Cubist Pharmaceuticals, Inc.
Thomas R. Fritsche, PhD, MD	Marshfield Clinic
Evelyn Ellis-Grosse, PhD	E2g Consulting
Monica Giguere	BD Diagnostic Systems
Henry S. Heine, PhD	Ordway Research Institute, Inc.
Patriacia Hogan, MT(ASCP), MBA	Pfizer, Inc.
Denise Holliday	BD Diagnostics
Rebecca Horvat, PhD, D(ABMM)	University of Kansas Medical Center
Andre Hsiung, MS	Thermo Fisher Scientific
Michael D. Huband	Pfizer Global R&D
Jospeh P. Iaconis	AstraZeneca Pharmaceuticals
Stephen G. Jenkins, PhD, D(ABMM), F(AAM)	New York Prebysterian Hospital
Jack L. Johnson	International Health Management Associates, Inc
Judith Johnston, MS	Siemens Healthcare Diagnostics Inc.
James H. Jorgensen, PhD	University of Texas Health Science Center
Nachum Kaplan, PhD	Affinium Pharmaceuticals Inc.
Kevin Joyce	Centers for Disease Control and Prevention
Scott B. Killian	Trek Diangostic Systems
Cynthis C. Knapp, MS	Trek Diagnostic Systems
Laura M. Koeth, MT(ASCP)	Laboratory Specialists, Inc.
Melinda Lacy, PharmD	Ortho-McNeil
Katherine Laessig	DAIOP/FDA
S. Blaine Leppanen	Blaine Healthcare Associates, Inc.
Premavathy Levassuer, PhD	Parc Biocitech
Brandi Limbago, PhD	Centers for Disease Control and Prevention
Jim Lindsey	Mast International
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Yan B. Liu	BD Diagnostiac Systems
Jennifer Lorbach	Trek Diagnostic Systems
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Ann Macone	Paratek Pharmaceuticals, Inc.
Linda M. Mann, PhD, D(ABMM)	Siemens Medical Solutions Diagnostics
Maureen Mansfield	Trek Diagnostic Systems
Erika Matuschek, PhD	EUCAST
Christopher McCoy	Ortho McNeil
Dr. Greg Moeck	The Medicines Company
Lori Moon, MT(ASCP)	MSU Diagnostic Center for Population & Animal Health
Mary R.Motyl, PhD, D(ABMM)	Merck Sharp & Dohme Corp
Ross Mulder, MT(ASCP)	bioMérieux, Inc.
Susan D. Munro, MT(ASCP)	Stanford Hospital and Clinics
Kate Murfitt	Mount Auburn Hospital
Susan O'Rourke	BD Diagnostic System
Linda Otterson,MT(ASCP)	AstraZeneca Pharmaceuticals
Elizabeth Palavencino, MD	Wake Forest University Baptist Medical Center
Pritty Patel	Covance Central Lab Services
James A. Poupard, PhD	Pharma Institute of Philadelphia
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Jemes Ross	JMI Laboratories
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PLEASE NOTE: All slide presentations from the plenary session can be found on the CLSI website on the S/C for Antimicrobial Susceptibility Testing webpage under Microbiology by clicking the link provided below:

January 2011 AST Meeting Presentations

I. MEETING/OPENING REMARKS

Dr. Cockerill called the meeting to order at 8:00 a.m. on Monday, 10 January 2011. He thanked everyone for their participation in the Working Groups sessions held on Sunday, especially the Working Group chairholders, recording secretaries, and Working Group members for the significant work they do. He then noted 2 changes to the subcommittee roster - Dr. Karen Bush has stepped down from voting member to advisor and thanked her for her willingness to continue to work with the subcommittee. Dr. Jeff Alder has rotated from advisor to voting member.

Dr. Cockerill then thanked Dr. Mike Dudley for organizing the PK-PD Workshop that was held on Saturday. It was very informative and provided a better understanding on the use of PK-PD in setting breakpoints. He also thanked the speakers that presented during the workshop: Drs. Bill Craig, George Drusano, Paul Ambrose, and Sujata Bhavnani, for all the work in putting together this session.

Dr. Wikler reminded everyone the purpose of these meeting as stated in the subcommittee's mission statement that is provided in electronic tab B of the meeting CD. He emphasized the mission statement which is to "to provide useful information to enable laboratories to assist the clinician in the selection of appropriate antimicrobial therapy for patient care". He also emphasized that the values that guide this subcommittee are quality, accuracy, fairness, timeliness, teamwork, consensus, and trust. He asked that everyone keep these principles in mind during the course of these meetings. He then reminded meeting participants that the proceedings were being audiotaped per standard procedure for meetings of this subcommittee; therefore, should there be any questions on topics discussed the tapes could be reviewed.

Ms. Dooley provided a brief overview of the new CLSI streamlined document development process to improve the timeliness and quality of new and revised CLSI standards and guidelines including:

- Change of the Area Committee name to Consensus Committee
- Change of term limits for members of the Area Committee (now Consensus Committee) and Standing Subcommittee members from 6 to 4 consecutive years.
- Implementation of term limits to advisors
- Observers now called Reviewers with responsibilities for a more active role on committees.

Additional information is available on the CLSI website and free informational webinars are being held that will explain the changes in greater detail.

She then provided a brief update on recent and upcoming publications under the Microbiology Area Committee (now designated as the Consensus Committee).

Recently Published

M45-A2, *Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria* – August 2010

M53-P, *Laboratory Testing and Diagnosis of HIV Infections* - October 2010

M100-S21, *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-First Informational Supplement* – January 2011

Upcoming Publications

M24-A to A2, *Susceptibility Testing of Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes* –estimated for publication March 2011

X08-R, *Generation, Presentation and Application of AST Data for Bacteria of Animal Origin*; A Report – estimated for publication June 2011

II. CLSI UPDATE

Mr. Fine, Executive Vice President of CLSI thanked everyone for the tremendous work done by this subcommittee. The expertise of everyone present enables the development and revision of CLSI standards used by the healthcare community to better patient care.

He then provided an overview of the results of a survey designed and conducted by Franklin & Marshall College's Center for Opinion Research. The intent of the survey was to obtain input from the committee on how we can improve the CLSI and AST Subcommittee process.

The survey produced a wealth of actionable data both in the quantitative and qualitative sections and the results showed there is strong support for the CLSI processes overall but there are also a number of opportunities for improvements, mostly concerning process efficiencies, representativeness of stakeholders on specified activities, and disclosure of interests. CLSI's challenge will be to affect these processes without interfering with the quality and success of its current document creation.

Results of this survey are posted on the AST Subcommittee page of the CLSI website.

III. EUCAST UPDATE

Professor Kahlmeter provided an overview on what's new with EUCAST including:

- Currently developing a system to invite countries outside EU/Europe to be part of the EUCAST General Committee.

- Have worked over the past year to form National Antimicrobial Committees (NAC) with their tasks being to strategize at a national level to implement harmonized breakpoints and methods, educate through national workshops, serve as liaison and consult with EUCAST as well as groups involved in AMR-surveillance (ECDC, EARSS). These committees will then form as a whole, the European Network of Antimicrobial Committees which will be the EUCAST General Committee.

- Together with EMA have finalized daptomycin, tigecycline, and doripenem. Currently ongoing is glycopeptides.

- Expert Rules are coming out in the 2nd version.

- Currently have 39 Rationale Documents available on the website as well as various breakpoint tables. Also most of the material on the website has been translated into various languages including German, Spanish, and soon French.

IV. UPDATES TO THE CURRENT AST DISCLOSURE SUMMARY

Dr. Cockerill asked the members and advisors for any updates to the current disclosure summary provided on the CD of meeting materials. The below are the updates provided:

Dr. Ambrose: Recent consulting agreement with AstraZenica Pharmaceuticals

Ms. Hindler: Microbiology Advisory Board for Forrest Laboratories

V. REPORT OF THE FLUOROQUINOLONE BREAKPOINT WORKING GROUP *Minutes Submitted by Karen Bush* (Electronic Tab C in the Meeting Agenda)

Chairholder - Karen Bush

Working Group Members present - Sujata Bhavnani, George Eliopoulos, Robert Flamm, Cynthia Fowler, Mair Powell, Barth Reller, Helio Sader

Working Group Members absent - None

Items Proposed for Vote

1. **Eliminate the comment in Table 2A recommending use of Nalidixic Acid (NA) in any form (disk/MIC) to predict fluoroquinolone utility in treating extraintestinal infections caused by *Salmonella* sp**.

Initial Subcommittee vote – Not approved (3-7; 1 abstain; 1 absent). The decision was made that both the disk and MIC breakpoints should be addressed at the same time.

Final vote following discussions and approval of disk and MIC breakpoints (see item 2): Subcommittee Approved removing both current comment 29 and 31 in Table 2A (10-0; 1abstain [J. Alder]; 1 absent)

Those favoring the motion included four representatives outside CLSI who furnished letters requesting that the NA disk test be replaced by disk testing with the fluoroquinolone that is used

for therapy at that health center. Most of those in favor of the motion requested that both disk and MIC breakpoints should be changed.

Discussions from those in opposition to this motion cited the ease with which the NA screening test may be run, especially in areas where a disc diffusion test is inexpensive and simple to conduct. However, several voiced agreement that it would be more meaningful to test the agent that was actually going to be used for treatment. Much of the dissent was related to the fact that both disk and MIC breakpoints should be changed simultaneously.

2. **Breakpoints for ciprofloxacin against *Salmonella* sp**.

   a. MIC breakpoints for ciprofloxacin against *Salmonella* sp. were proposed as:

   S ≤ 0.06 µg/mL
   I 0.12 to 0.5 µg/mL
   R ≥1 µg/mL

   Approved, including an appropriate dosing comment about the I category shown below (11-0; 1 abstain [J. Alder])

The basis for these recommendations were PK/PD considerations, anecdotal reports of poor clinical responses for patients with *Salmonella* isolates exhibiting ciprofloxacin MICs >0. 25 µg/mL, and a bimodal distribution of MICs, with a wild type distribution of ciprofloxacin MICs ≤0.06 µg/mL in most studies. This susceptibility breakpoint would be in harmony with the EUCAST breakpoint, and would separate bacterial populations into those without resistance mechanisms from those with some form of resistance.

The broad intermediate category was proposed for several reasons, including the limited clinical data from two randomized, double-blind, comparative clinical trials of ciprofloxacin in patients infected with *Salmonella* sp. These trials reported both clinical cures and microbiological eradication in 13 of 13 *Salmonella*-infected patients with isolates that displayed ciprofloxacin MICs in the range of 0.12 (n= 4) to 1 µg/mL (n=1). PK/PD considerations also indicated that patients with isolates demonstrating ciprofloxacin MICs in this intermediate range might be successfully treated with high doses of ciprofloxacin (100% target attainment was reported at an MIC of 0.12 µg/mL). Further discussion centered on whether there was a need to include a comment about the possibility that clinicians could use maximal oral or IV doses if an isolate tested in the Intermediate category. The following dosing comment will be added as follows:

(X) Because of limited clinical experience, treatment of infections caused by organisms with ciprofloxacin MICs in the intermediate range, clinicians may wish to use maximal oral or parenteral dosage regimens.

   b. Disk diffusion breakpoints for ciprofloxacin against *Salmonella* sp. were proposed as:

   S ≥ 31 mm
   I 21 – 30 mm
   R ≤ 20 mm

Approved including an appropriate dosing comment about the I category: (10-0; 1 absent; 1 abstain [J. Alder])

These disk diffusion breakpoints were recommended based on two sets of scattergrams, one from JMI as presented by H. Sader, and one set from Parry et al. [AAC 54:5201 (Dec. 2010) – Agenda Book Tab C 8.2]. No major or very major errors were observed. The minor error rate was 8.5%.

Prior to publication of revised ciprofloxacin breakpoint changes, the intention is to reassess the MIC and disk diffusion breakpoints for other fluoroquinolones used to treat Salmonella infections, including levofloxacin, ofloxacin, and gatifloxacin.

3. **Enough evidence exists to support an M23 condition for reconsideration of breakpoints for fluoroquinolones and all Enterobacteriaceae**

   Subcommittee Approved (11-0; 1 absent)

The discussion centered upon information related to the same PK/PD considerations for *Salmonella* sp. and for the Enterobacteriaceae, and the increasing number of fluoroquinolone-resistant Enterobacteriaceae. No clinical data were brought forward in the agenda book to support an M23 condition. Limited data from controlled clinical trials were available from levofloxacin clinical trials to support the current breakpoints. Caution was urged about losing the fluoroquinolones as a class if the breakpoints were set too low. It was also noted that urinary tract infections might be susceptible to fluoroquinolones at higher MICs due to the high urinary concentrations achieved, so separate breakpoints might need to be considered for UTI. **Sponsors will be notified to provide data for the June 2011 meeting.**

Items for Information Only

In June, the Working Group will propose the re-evaluation of quinolone and fluoroquinolone groupings and their inclusion in Table 1 with a recommendation to Text and Tables for changes.

VI. REPORT OF THE QUALITY CONTROL WORKING GROUP

Minutes Submitted by Steve Brown **(Electronic Tab D in the Meeting Agenda)**

Co-Chairholder - Steven Brown

Co-chairholder - Sharon Cullen

Working Group Members present- Bill Brasso, Janet Hindler, Ann Macone, Ross Mulder, Susan Munro, Jean Patel, Bob Rennie

Working Group Members absent - Stephen Hawser, Michael Huband, Ron Jones, Paul Oefinger

Agenda:

Items Proposed for Vote based upon New M23 Studies:

AFN-1252 MIC QC Ranges
AZD9742 MIC QC Ranges
GSK2251052 MIC QC Ranges
GSK1322322 Disk QC Ranges
Doxycycline Disk QC Range
Omadacycline (PTK-0796) Disk QC Ranges
Ceftaroline/NXL104 Disk QC Ranges
Ceftazidime/NXL104 Disk QC Ranges

Items Proposed for Vote Based upon M23 Tier #3 Data:

Colistin vs. *E. Coli* ATCC 25922: 0.25-5 ug/mL
Cefepime vs. *P aeruginosa* ATCC 27853: 0.5-4 ug/mL

Items For Information Only (FYI) QC Monitoring:

Request for data on Teicoplanin MIC vs. *E. faecalis* ATCC 29212

Cefepime Disk Diffusion vs. *H. influenzae* ATCC 49247, *P. aeruginosa* ATCC 27853, & *S. pneumoniae* ATCC 49619

1. Quality Control Ranges

A. New QC Ranges Based upon M23 Studies

The Subcommittee Approved the new drugs as shown below (11-1; 1 absent):

Drug	Strain	Range (µg/ml or mm)	% Shoulder if present	%	Comment	WG Vote (Y/N/Abstain)
Ceftazidime/	*S. aureus* 25923	16-22		99.2%	RF 13-24, check RF. Rechecked as 16-21. , ceftaz 16-20	6-1-2 SB, JH
NXL104	*E. coli* 25922	27-35		97.9%	RF 26-35, ceftaz 25-32 Lab 4 outlier by one measure, Alternative 27-35	6-1-2 SB, JH
	E. coli 35218 in MHA	28-35		97.3%	RF 28-35, Alternative 28-35, Request 700603 study for future	6-1-2 SB, JH
	E. coli 35218 in HTM	27-34		97.3%	RF 27-34, Some media dif at low end. Need to assess abiltiy to detect NXL-104 deterioration and integrity of QC org (may need to use 700603)	6-0-2 SB, JH
	K. pneumoniae 700603	21-27		99.2%	RF 22-27, note: need recommendation for routine or supplemental QC in future	6-0-2 SB, JH
	P. aeruginosa 27853	25-31		99.4%	RF 25-30, ceftaz only 22-29	6-0-2 SB, JH
	H. influenzae 49247	25-31		99.4%	RF 28-34	6-0-2 SB, JH
Ceftaroline/	*S. aureus* 25923	25-34		99.4%	RF 19-34 (check RF, Rechecked	7-1-2 SB, JH
NXL104	*E. coli* 25922	27-34		98.5%	calculations rechecked & corrected	8-0-2 SB, JH
	E. coli 35218 in MHB	27-35		99.4%		7-0-2 SB, JH
	E. coli 35218 in HTM	26-34		98.5%		6-0-3 SB, JH, ??
	K. pneumoniae 700603	21-27		100.0%	Supplemental QC only RF 22-27, few orgs at extremes, narrower range suggested, alternative 21-27 calc %	7-0-2 SB, JH
	P. aeruginosa 27853	17-26		97.8%	Note correction in presentation disk variability, RF 17-26, alternative 17-26	7-0-2 SB, JH
	H. influenzae 49247	30-38		99.3%		7-0-2 SB, JH

Drug	Strain	Range (µg/ml or mm)	% Shoulder if present	%	Comment	WG Vote (Y/N/Abstain)
Omadacycline (PTK-0796)	*H. influenzae* 49247	21-29		100.0%	Note: correct conclusion slide (says 49619) Some media variability	6-0-1 (SB)-1 absent
AFN-1252	*S. aureus* 29213	0.002-0.015	70.6% @ 0.004 ug	99.7%	Fatty acid inhibitor - class? 43300 Staph had similar range. Not effective against Ec so 29212 wasn't evaluated (would be completely resistant)	9-0-0
Doxycycline	*S. pneumoniae* 49619	25-34		99.4%	Significant lab to lab variability, 1 lot media 2 dil higher	7-0-1 SB
AZD-9742	*S. areus* 29213	0.03-0.12	No	99.7%	Class? (4 amino pepperdine or quinolone like)	9-0-0
	E. faecaslis 29212	0.5-2	No	100.0%		
	S. pneumoniae 49619	0.06-0.25	No	100.0%		
GSK2251052	*E. coli* 25922	0.5-2	No	100.0%	Slight media variation-lot C lower	9-0-0
	P. aeruginosa 27853	2-8	No	98.8%	Slight media variation-lot C lower	
	H. influenzae 49247	0.25-1	No	100.0%	Slight media variation-lot D higher	
	S. pneumoniae 49619	0.25-1	No	99.1%	Slight media variation-1 lot higher,	
GSK1322322	*S. aureus* 25923	18-26		99.0%	Class? Pdf inhibitor	9-0-0
	H. influenzae 49247	20-28		99.0%	Some lab variability	
	S. pneumoniae 49619	22-30		98.8%	excluding lab "B"	

Add to GSK2250152 – New Class: Leucyl tRNA synthetase inhibitor

Reword Comment section for GSK1322322 – New Class: Peptide deformylase (pdf) inhibitor. *H. influenzae* – some lab variability; *S. pneumoniae* – some lab variability – accepted range excludes lab "B".

Drug	Strain	Range (µg/ml or mm)	% Shoulder if present	%	Comment	WG Vote (Y/N/Abstain)
Amoxicillin/clavu	*K. pneumoniae* 700603	15-19		calc	Supplemental QC only. (note: can replace with 700603 later when we have for all older b-lactam/b-lactamase combinations) Concerned about being confusing until all other combo drugs have ranges. Note: have only 1 disk control so doesn't meet M23 yet	Tabled
Teicoplanin	*E. faecaslis* 29212	0.12-1			Previously changed range from 0.06-0.25 to 0.25-1 in June 2009. Addn data suggests this is one well high and there is a difference in media lots. Proposed expanding to a 4 dilution range of 0.12 to 1.	No second so the motion dies. Additional data requested.

Revise amox/clav comment section to read: Supplemental QC only. (note: can include ~~replace with~~ ~~700603~~ later when we have ranges for all older b-lactam/b-lactamase combinations).Concerned about being confusing until all other combo drugs have ranges. Note: have only 1 disk lot ~~control~~ so doesn't meet M23 yet

B. Revised QC Ranges Based upon M23 Tier #3 Studies

Modified ranges for Cefepime/*P aeruginosa* ATCC 27853 on as shown below were approved by the subcommittee (11-0; 1 absent):

Colistin	*E. coli* 25922	0.25-2			Additional data with results at bottom end of range with some out low. Revised previously from 0.25-1 to 0.5-2. Expanded to include 0.25 which was prevously in range.	8-0-0 Motion passed by the QC WG but defeated by the AST Subcommittee. Additional data will be collected and submitted to the June 2011 mtg.
Cefepime	*P. aeruginosa 27853*	0.5-4		100% of on-scale values	Expanding existing range by 1 dilution.	6-1-2
Teicoplanin	*E. faecaslis* 29212	0.12-1			Previously changed range from 0.06-0.25 to 0.25-1 in June 2009. Addn data suggests this is one well high and there is a difference in media lots. Proposed expanding to a 4 dilution range of 0.12 to 1.	No second, request additional data

Notes:	

Additional info regarding NXL104 combinations
These compounds are active against TEM1 which is contained by E. coli 35218
Per GSK, Ceftazidime alone wouldh have similar range alone and with NXL104
Pg 49 has a range for Ceftazidime only with K. pneumoniae 700603 as 10-18mm
NXL-104 is active against K. pneumo 700603 so this should likely be routine QC instead of 35218. However, we don't have ranges for single drug only with 700603

Note: We need to add footnote c from Appendix C (pg 150) to the organism 35218 E. coli on Tables 3 and 4.
(It currently refers to the M7 and M2 text - this would link to info in supplement tables.

2. QC Monitoring—Requests for QC Data

- MIC QC Data for Teicoplanin vs. *E. faecalis* ATCC 29212
- Disk Diffusion Data for Cefepime vs.
  - *H. influenzae*ATCC 49247,
  - *P. aeruginosa* ATCC 27853
  - *S. pneumoniae* ATCC 49619

3. Quality Control: Tier 3 Monitoring

Antimicrobic/organism combinations monitoring/compiling data to re-evaluate the current QC range or have no QC ranges. M23 Tier 3 requirements: 3 labs, 2 media lots, 10 reps/lab and 50 reps per media, 2 disk lots for a total of 250 results with MIC and 500 with disk diffusion.

QC Strain	Antimicrobic	Method	Current Range	Observations	# Labs	# Reps	Orig M23	Comments
E.coli 25922	Ampicillin	Disk	16-22	6/06: Out low/double zones Remel: at low end, 18.5mm mean. M23 Study in June 2001 median at 19 and mode at 20. Oxoid zones low /HPLC data OK Double zone reported with multiple media lots, 15-16 mm. Addn report on double zones, outer zones on high end	Remel, UAH, Sweden	102, 54, 480, 12	N/A, May 2001	Is issue isolated or widespread? Request addn data?
H. influenzae 49247	Tigecycline	MIC	0.06-0.5	Mode at top of range, some out high. Variation in modes with media lots observed.	Trek, Wyeth (7), Wyeth (4)	21, 213, 481	June 2004	Monitor
P. aerug 27853	Etrapenem	MIC	2-8	Initial report out low. Addn data mode ranges from 2, 4 or 8. Discussed expanding to 4 dil but decided to monitor (2009-June)	CMI*, MS, BD, bioMerieux, MS	599,120, 195, 31, 102	Jan 2001	Monitor
S. aureus 29213	Quinupristin/ dalfopristin	MIC	0.25-1	Mode at low end with a few out low with one lab, mode in middle with other lab. Proposal to change range was defeated (2009-June)	MS, CDC	242, 246	June 1996	Monitor
P. aeruginosa 27853	Gentamicin	Disk	16-21	1-2 mm out high (Europe). Addn data received to support original complaint.	Sweden	12 (4 media mfg)	?	Request addn data?
P. aeruginosa 27853	Tobramycin	Disk	19-25	Data at high end or out high.	Sweden	12 (4 media mfg)	?	Request addn data?
E. coli 25922	Cefixime	Disk	23-27	Canadian lab reported 20-23mm with multiple lots disks and agar plates. No action taken (2009-June)	Canadian lab	35	NA, May 01 QC Study	Monitor
E. coli 25922	Meropenem	Disk	28-34	Data at high end or out high.	Sweden	12 (4 media mfg)	?	Request addn data?

QC Strain	Antimicrobic	Method	Current Range	Observations	# Labs	# Reps	Orig M23	Comments
E.coli 25922 P. aerug 27853	Colistin	MIC	~~0.25-1~~ ~~0.25-2~~ 0.5-2, 0.5-4	Mode at top of previous range & some out high with both organisms E. coli 0.5-2 & P. aerug 0.5-4 adjusted up 1 dil (2009-June) New data: 60 results, 3 lots mode at 0.5, 6 @ 0.25 with E. coli. Mode at @ 1, 1 result at 0.25 with P. aerug Verbal report Jan 2010 of lower MICs in plastic microbroth panel, but in range with macrotube.	MS, BD, BD, CDC. Trek,	28, 108, 201, 60	N/A	Monitor, QCWG approved refinement of range for E. coli 25922 to 0.25-2
E.faecalis 29212	Teicoplanin	MIC	0.06-0.25	Mode at top of range or out high Adjust to 0.25-1 2009-June with recommended actions (see comments) Additional data at bottom of revised range with significant number out of range	MS, CDC, MS	68, 246, 66 (2 lots media)		• Original data not available. • Surfactant lowers MIC by ½ to 1 dilution, but wouldn't affect range assigned. • Agar dilution data confirmed revised range. Proposed refinement of range to 0.12-1. Requested additional data
B. fragilis ATCC 25285	Pip/tazo	Agar MIC	0.12-1	Control drug (CXA-101/tazobactam study) had 12% out of range at 0.06.	1 of 7 labs in study	240	Jan 2010	Collect data and/or monitor
P. aeruginosa ATCC 27853	Cefepime	MIC		Results at bottom of range with some potentially out low	Orig data, JMI/Trek, MS	225, 72,131	1988-9	QCWG approved change to 0.5-4 by a vote of 6-1-2.
P. aeruginosa ATCC 27853, H. influenzae ATCC 49247, S. pneumoniae ATCC 49619	Cefepime	DD	24-30 25-31 28-35	Jones 2004 data includes the following 28-32 28-34 31-37	JMI,			Request data

*30 lab study coordinated by CMI

4. Glossary I and Glossare II Data

Name	GSK1322322
Previous identifier	
Abbreviation	
Solvent/Diluent	DMSO/water
Route of Administration	
Class/Subclass	New. Peptide deformylase inhibitor
Special instructions/troubleshooting	
Revision History	

Name	GSK2251052
Previous identifier	
Abbreviation	
Solvent/Diluent	DMSO/water
Route of Administration	
Class/Subclass	New. Leucyl t-RNA synthetase inhibitor
Special instructions/troubleshooting	
Revision History	

Name	AZD9742
Previous identifier	
Abbreviation	
Solvent/Diluent	DMSO/DMSO
Route of Administration	
Class/Subclass	4-amino-piperidine
Special instructions/troubleshooting	Quinolone “like” compound
Revision History	

Name	Ceftaroline/NXL104 (CPT104)
Previous identifier	
Abbreviation	CPT104 (All caps, no hyphen)
Solvent/Diluent	DMSO/water
Route of Administration	
Class/Subclass	
Special instructions/troubleshooting	
Revision History	

Name	Omadacycline (Formerly PTK796)
Previous identifier	PTK796
Abbreviation	OMC
Solvent/Diluent	Water/water
Route of Administration	PO and IV
Class/Subclass	Tetracycline/aminomethylcycline
Special instructions/troubleshooting	The compound is oxygen labile. Broth media must be less than 12 hours old at the time of MIC tray production.
Revision History	

VII. REPORT OF THE TEXT AND TABLES WORKING GROUP

Minutes Submitted by Jana Swenson **(Electronic Tab E in the Meeting Agenda)**

Chairholder – Jana Swenson

Recording Secretary – Susan Munro

Working Group Members present – David Farrell, Janet Hindler, Judy Johnston, Dyan Luper, Linda Mann, Flavia Rossi, Jeffrey Schapiro, Dale Schwab, Tom Thomson, and Mary York

Working Group Members absent – Fred Marsik, Al Sheldon, Mel Weinstein

1. Suggestion for slight revision of the dosage comment (Barth Reller)

(3) The dosage regimens shown in the comment column below are those ~~used to derive~~ plasma drug exposures (in adults with normal renal and hepatic functions) on which breakpoints were based. When implementing new breakpoints, it is strongly recommended that laboratories share this information with infectious disease practitioners, pharmacists, pharmacy and therapeutics committees, and infection control committees. ~~Prescribing information should be reviewed and institutional clinicians consulted for dosage regimens to treat infections in specific patients.~~

This is meant to be used for any table that has "dosage" comments like those added when cephalosporin breakpoints were changed for enteric organisms.

Working Group Vote: Passed (8 - 0; 4 absent).
Rationale: Improves the wording for clarity.

Approved by the Subcommittee: 11-0; 1 absent

2. Expand suggestions for testing/reporting of multi-drug resistant organisms (Janet Hindler)

Proposal for additional wording to be added to M100, D. Selective Reporting, pg. 22 shown underlined:

D. Selective Reporting

Each laboratory should decide which agents in the tables to report routinely (Group A) and which might be reported only selectively (from Group B), in consultation with the infectious disease practitioners and the pharmacy, as well as the pharmacy and the therapeutics and infection control committees of the medical staff of the hospital. Selective reporting should help improve the clinical relevance of test reports and help minimize the selection of multiresistant nosocomial strains by overuse of broad-spectrum agents. Results for Group B agents not reported routinely should be available on request, or they may be reported for selected specimens. Unexpected resistance, when confirmed, should be reported (eg, resistance to a secondary agent but susceptibility to a primary agent). **In addition, each laboratory should develop a protocol to address isolates that are confirmed as resistant to all agents on their routine test panel. This should include options for testing additional agents in house or sending the isolate to a reference laboratory.**

Working Group Vote: Passed unanimously.

Rationale: Provide instructions for labs on what to do with MDRO.

Approved by the Subcommittee: 12-0

3. Footnote similar to ESBL footnote (Table 1A, footnote i) needed for M100 to explain carbapenem breakpoints? (Janet Hindler).

Proposal was made to either add a footnote to Table 1A to explain carbapenem breakpoint changes or to delete the current footnote i for ESBLs.

Current footnote i for ESBLS:

i. Following evaluation of PK-PD properties and limited clinical data, new (revised) interpretive criteria for cephalosporins (cefazolin, cefotaxime, ceftazidime, ceftizoxime, and ceftriaxone) and aztreonam were established, and are listed in Table 2A. Cefepime and cefuroxime (parenteral) were also evaluated; however, no change in interpretive criteria was required for the dosages indicated in Table 2A. When using the new interpretive criteria, routine ESBL testing is no longer necessary before reporting results (ie, it is no longer necessary to edit results for cephalosporins, aztreonam, or penicillins from susceptible to resistant). However, until laboratories implement the new interpretive criteria, ESBL testing should be performed as described in Supplemental Table 2A-S1. ESBL testing may still be useful for epidemiological or infection control purposes.

Note that interpretive criteria for drugs with limited availability in many countries (eg, moxalactam, cefonicid, cefamandole, and cefoperazone) were not evaluated. If considering use of these drugs for E. coli, Klebsiella, or Proteus spp., ESBL testing should be performed (see

Supplemental Table 2A-S1). If isolates test ESBL positive, the results for moxalactam, cefonicid, cefamandole, and cefoperazone should be reported as resistant.

Discussion: the comment is not necessary. Information is found in Table 2A (dosage regimens) and Supplemental Tables 2A-S1 and -S2 and -S3 (testing and reporting instructions).

Working group: Remove footnote i, Table 1A. Passed (unanimous)

Rationale: Eliminate unnecessary verbiage.

Approved (12-0) by the Subcommittee to remove current footnote i shown above from Table 1A.

4. Suggestion to review selective reporting for certain species within an organism group since we are not consistent with FDA guidelines (Janet Hindler).

This suggestion was raised because we are inconsistent with the addition of selective reporting precautions in M100. During the Working Group meeting, discussion was centered specifically on footnotes m (for staphylococci) and p (for enterococci) in Table 1A, regarding quinupristin-dalfopristin: "For reporting against methicillin-susceptible *S. aureus* [or vancomycin-resistant *Enterococcus faecium*]"

Enterococci:

Background: In the process of discussion it was pointed out that FDA indications for Quinupristin-dalfopristin have changed and that it is no longer FDA approved for *Enterococcus* spp.

- Because of this there was a proposal to **remove quinupristin-dalfopristin from Table 1A, remove footnote p, and change Table 2D report group to "O".**

Working Group: passed unanimously
Approved by the Subcommittee 11-0; 1 absent

Rationale: change in FDA status for this organism/drug.

- The question of whether quinupristin-dalfopristin interpretive criteria and current comment 19 should remain in Table 2D?

Working Group: ask Subcommittee for guidance.

Approved by the Subcommittee to retain current comment 19 for quinupristin-dalfopristin in Table 2D (11-0; 1 absent)

Staphylococci:

- Proposal to remove Table 1A footnote m, and Table 2C comment 34.

Working Group: Passed (7 in favor, 3 opposed, 1 absent)

Rationale: As part of the process to begin removing selective reporting recommendations.

Subcommittee- Tabled for now.

Rationale: Subcommittee felt that removal of these comments should wait until rules can be established that would allow consistent application.

- Working group will make a list and review M100 document for similar footnotes and comments and discuss in June 2011.

VIII. REPORT OF THE STAPHYLOCOCCAL AND STREPTOCOCCAL WORKING GROUP - *Minutes Submitted by Jean Patel* (Electronic Tab F in the Meeting Agenda)

Chairholder - Jean Patel

Acting Recording Secretary - Brandi Limbago

Working Group Members present - Bill Craig, Mel Weinstein, Jana Swenson, Patty Bradford, Maria Traczewski, Mike Dudley, George Eliopoulos, Dan Sahm

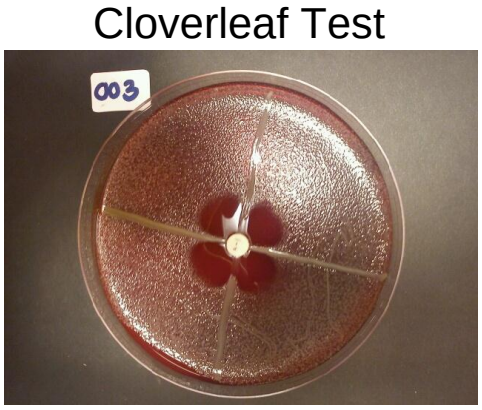
Working Group Members absent - Sandy Richter

Presenters: Robert Skov, Jim Jorgensen

β-Lactamase Detection in *S. aureus*

Robert Skov presented data from a multicenter study in which four methods for detection of β-lactamase production were evaluated. The study was conducted because previous studies have found that nitrocefin-based tests can fail to detect clinically relevant β-lactamase production. Currently, the test described in M100 is a nitrocefin-based test. The five methods evaluated were (1) Broth microdilution, (2) the cefinase test, (3) the Dryslide test, (4) the cloverleaf test, and (5) evaluating the zone edge of a penicillin disk diffusion test. These tests were compared to PCR for *bla*Z. A total of 348 isolates were tested and of these 303 isolates were negative for a functional *bla*Z (i.e., 300 isolates were *bla*Z negative by PCR and 3 isolates were *bla*Z PCR positive but significant mutations were identified in the sequence) and 45 isolates were PCR positive for *bla*Z and expression of *bla*Z could be detected by at least one phenotypic test. Of the 45 isolates that were *blaZ* positive, 23 isolates were penicillin susceptible by the broth microdilution method and 22 isolates were penicillin susceptible by disk diffusion.

A description of the cloverleaf test and a table showing test performance characteristic calculations from the study:



5% blood agar plate, 1U penicillin disk, *S. aureus* ATCC 25923 as the β-lactamase negative "lawn",

Test	Sensitivity	Specificity
Cefinase	77%	100%
Dryslide	88%	100%
Cloverleaf Test	100%	100%
Zone edge of penicillin disk test (fuzzy vs. sharp) *	96%	100%

*A fuzzy zone edge indicates no β-lactamase production and a sharp zone edge indicates β-lactamase production

The cloverleaf test and the penicillin disk tests demonstrated better performance than the nitrocefin-based tests (cefinase and Dryslide). Therefore, the working group favored replacing the CLSI recommendation to perform a nitrocefin-based test with a recommendation to evaluate the zone edge of a penicillin disk diffusion test and/or perform the cloverleaf test. Questions remained regarding how these tests would be implemented in the laboratory. Specific recommendations for implementation and placement in the document will be considered at the June, 2011 CLSI meeting.

A Screen Agar for the Detection of Vancomycin-Intermediate *S. aureus*

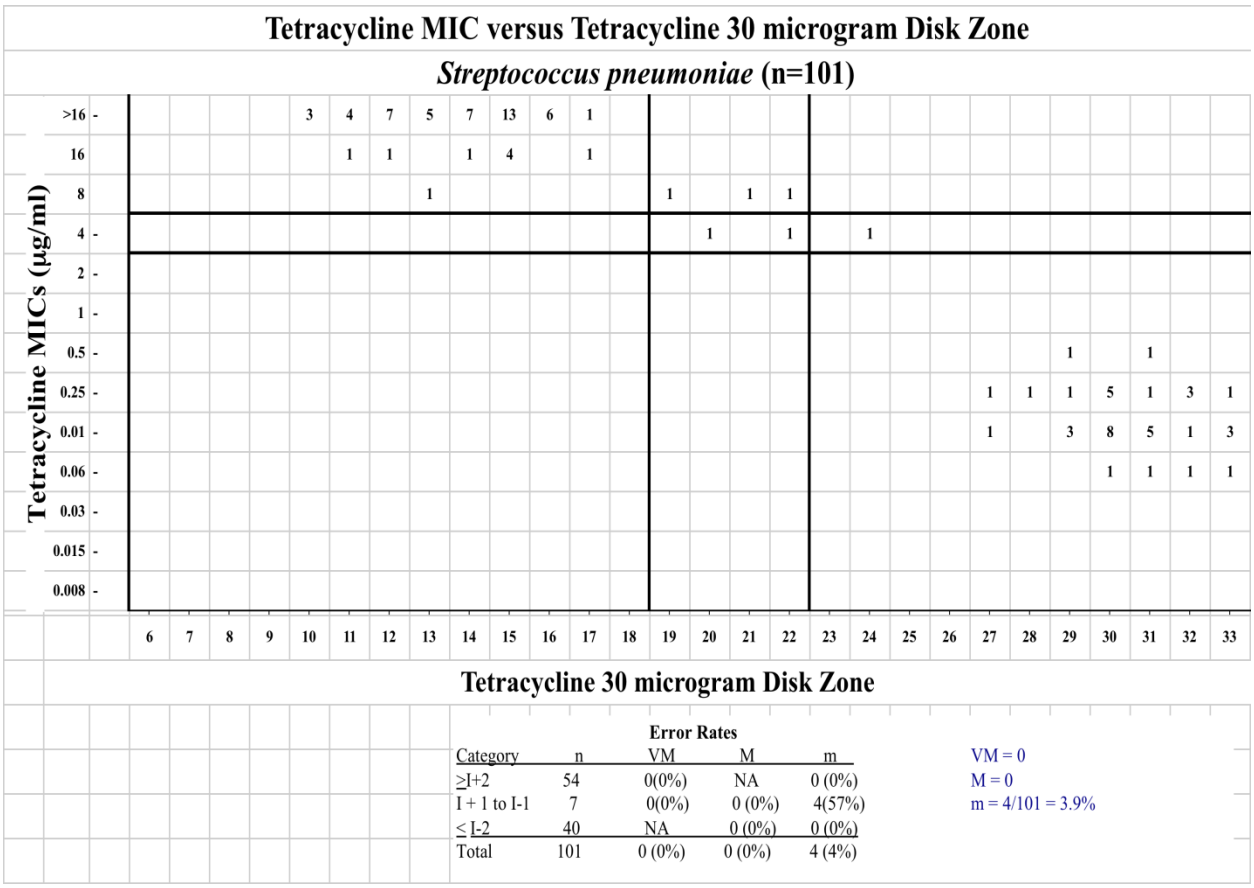
A study to identify a new screen agar for VISA detection will be lead by Robert Skov and Brandi Limbago. At the June, 2011 meeting the working group will review a proposed protocol for this study.

Doxycycline Breakpoints for *Streptococcus pneumoniae*

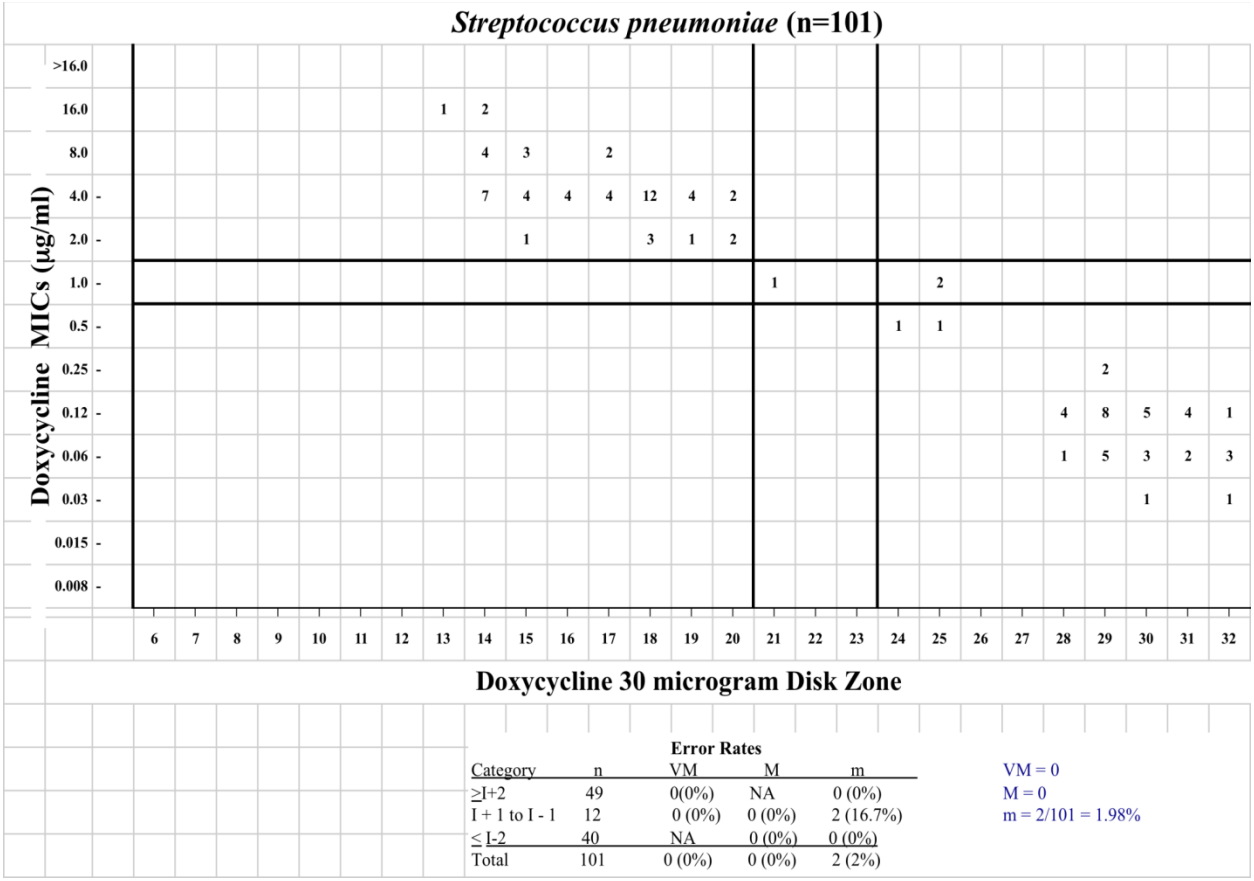
Currently there are no doxycycline breakpoints for *S. pneumoniae*, yet this drug is recommended for treatment of community acquired pneumonia caused by *S. pneumoniae*. Instead tetracycline susceptibility results are used to predict doxycycline susceptibility. Using tetracycline susceptibility to predict doxycycline susceptibility could result in the overestimation of resistance, especially if mechanisms of resistance other than *tetM* were to emerge in *S. pneumoniae*.

Jim Jorgensen presented data describing doxycycline and tetracycline susceptibility results by reference broth microdilution (BMD) and disk diffusion (DD). This was a single lab study of 101 *S. pneumoniae* isolates. Below are scattergrams comparing BMD results to DD results for each

drug. The tetracycline breakpoints are the current CLSI breakpoints and the doxycycline breakpoints shown are an example of possible breakpoints.



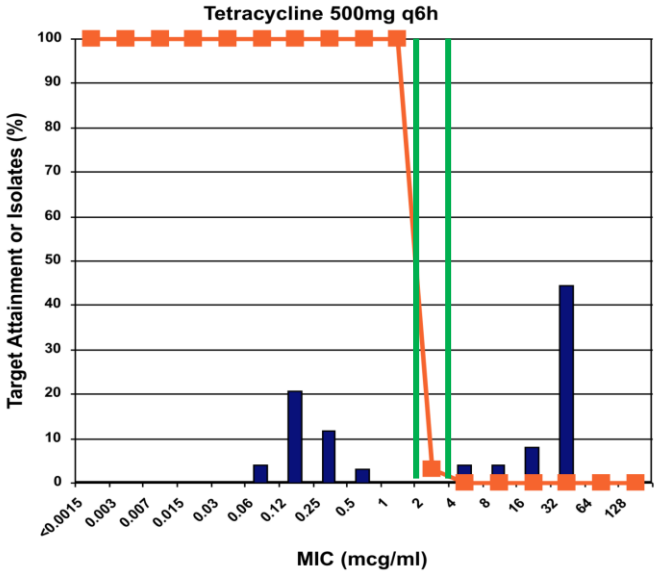
Doxycycline MIC versus Doxycycline 50µg Disk Zone



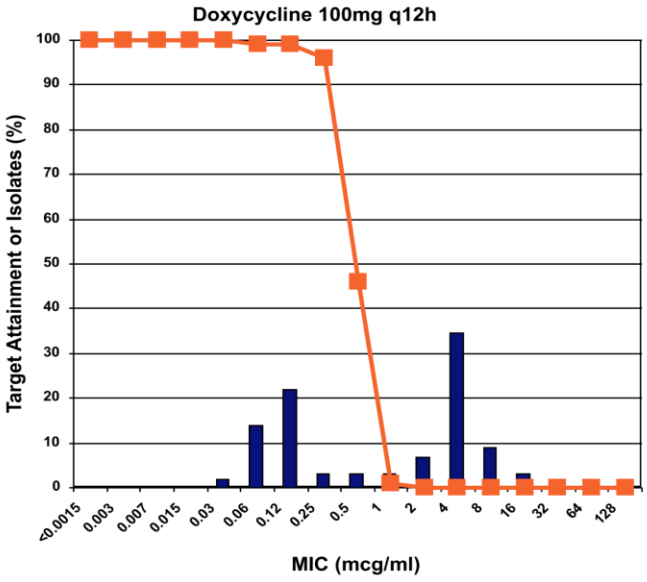
The correlation of tetracycline and doxycycline MICs with the presence of *tet*M

No. isolates	Tetracycline MIC	Doxycycline MIC	Presence of tetM
3	>16	16	2 of 3
2	>16	8	2 of 2
6	>16	4	5 of 6
6	>16 or 16	2	5 of 6
1	8	2	1 of 1
3	8	1	3 of 3
1	4	2	1 of 1
2	4	0.5	2 of 2
1	0.5	0.25	0 of 1
1	0.5	0.12	0 of 1
4	0.25	0.12	0 of 4
total of 30 isols			
24	≥ 4		21 of 24 or 88%
6	≤ 0.5		0 of 6
		≥ 0.5	21 of 24 or 88%
		≤ 0.25	0 of 6

In addition to the antimicrobial susceptibility data, Dr. Jorgensen reviewed the PK/PD data available from the literature (Burgess, et al. CMI, 2006). The data were very limited. A Monte Carlo simulation using drug levels collected from 6 male subjects were used with a PK/PD target of AUC/MIC ≥ 25.



Burgess, et al, 2006



Burgess, et al, 2006

The working group and subcommittee were generally in favor of setting doxycycline breakpoints. In addition, it was decided that the tetracycline breakpoints would be re-evaluated at the same time. It was requested that additional antimicrobial susceptibility data be collected from another laboratory and using a different lot of media. There was also a request for more PK/PD data, but it is likely that the only additional data will be from animal studies.

Tests for Inducible Clindamycin-Resistance in *S. pneumoniae*

At the June 2010 meeting, data supporting a single well broth-based test and a disk test to detect inducible clindamycin resistance in *Streptococcus pneumoniae* were considered. The working group asked for data on additional isolates and for more information to support a rationale or clinical context for doing this testing.

Rationale:

- Data from the CDC ABCs pneumococcal isolate surveillance showed that the percent of isolates resistant to erythromycin and expressing constitutive clindamycin resistance were increasing with each year. Although these isolates were not tested for inducible clindamycin resistance, the increase in constitutive resistance suggests that mechanisms of inducible resistance are circulating in these isolates.
- Data from the PROTEKT US study indicate an increase in *ermB*-mediated resistance among *S. pneumoniae* isolates.
- Clindamycin has been identified as an alternative agent for treatment of infections caused by *S. pneumoniae* in the following settings:
  - an alternative agent for treatment of otitis media in children
  - an alternative agent for treatment of sinusitis in adults and children
  - a 3rd line agent for treatment of bone and joint infections
  - combined with rifampin for prophylaxis of pneumococcal meningitis contacts

Results from microbiological studies:

- 102 isolates were tested, 66 isolates were positive for inducible resistance by the disk test, 65 isolates were positive by the broth test, and 37 isolates were negative by both the disk test and the broth test. Compared to *ermB* PCR, the disk test sensitivity was 98.5% and the broth test sensitivity was 97% sensitive.

The working group and subcommittee agreed that these tests were accurate for the detection of inducible resistance. However, the clinical significance of detecting inducible clindamycin resistance in *S. pneumoniae* is unknown just as it is unknown for beta-hemolytic streptococci. For this reason, concern was expressed that isolates testing positive for inducible clindamycin resistance should not be reported as resistant to clindamycin. Also, it was recommended that the document state that decisions on whether or not to perform this testing should be made at the institution level. Currently the recommendations for reporting beta-hemolytic streptococcal isolate results indicate that positive isolates be reported as resistant.

The subcommittee voted to include the clindamycin test in M100 but deferred a decision on how results should be reported until the June 2011 meeting. It was also decided that the reporting recommendations for beta-hemolytic streptococci be revisited in June as well. (**Approved 8-0; 1 oppose [J. Turnidge]; 3 absent**).

IX. REPORT OF *ENTEROBACTERICEAE* WORKING GROUP

Minutes Submitted by Patricia Bradford **(Electronic Tab G in the Meeting Agenda)**

Chairholder – Mike Dudley

Recording Secretary – *Enterobacteriaceae* – Patricia Bradford
Recording Secretary – *Pseudomonas* - Dwight Hardy

Working Group Members present - Paul Ambrose, Bill Craig, Steve Jenkins, Jim Lewis, Paul Schreckenberger, Lauri Thrupp, Mel Weinstein, Barb Zimmer

Working Group Members absent - Ron Jones

Items for Vote

A. Breakpoints for *P. aeruginosa* with Piperacillin (PIP) +/- tazobactam (PTZ) and Ticarcillin (TIC)+/- clavulanate (TIM) breakpoints for *P. aeruginosa*

Current breakpoints: S ≤64, R ≥ 128 µg/mL
Proposed: S ≤16, I= 32-64, R ≥ 128 µg/mL

1. A history of need for changing breakpoints for *P. aeruginosa* with PIP and PTZ was presented and additional data from the recent literature was reviewed.

2. A lengthy discussion was held regarding the isolates that test with MICs of 32 and 64 µg/mL and the role of the interpretation of "I." The issues included the need for combination therapy, or the need for use of high dose therapy.

3. A motion was made to accept the proposal that the MIC breakpoints for *P. aeruginosa* be changed for PIP, PTZ, TIC, and TIM as proposed (S ≤16, I= 32-64, R ≥ 128 µg/mL). Approved 11-0; 1opposed (M. Weinstein)

Action item: Disk correlates for *P. aeruginosa* will be presented for these agents at the June meeting (R. Jones).

A discussion was held regarding the Rx comment 5 (Table 2B-1, M100-S21) regarding the need for high dose therapy. A recommendation regarding this comment will be made at the June meeting.

B. Placement of anti-pseudomonal penicillins (carbenicillin, mezlocillin, azlocillin) in MIC tables

1. A discussion was held regarding the other anti-pseudomonal penicillins (carbenicillin, mezlocillin, azlocillin).

These drugs are no longer available in the US. This information will be confirmed in June.

2. A motion was made to remove carbenicillin, mezlocillin and azlocillin from the breakpoint tables for both Enterobacteriaceae and *Pseudomonas*. **Approved 11-0; 1 abstain (J. Alder)**

Items for Discussion

A. Review of Carbapenem breakpoints

1. Ertapenem breakpoints- Jim Lewis

A presentation was made with a request to change the recently modified MIC breakpoint of ertapenem from (≤0.25) to one dilution higher at ≤0.5 µg/mL. The main rationale for this proposal is that a susceptible breakpoint of ≤0.25 bisects the distribution of Enterobacteriaceae that do not express KPC or any other carbapenemase.

The presentation included the following discussion points:

a) Monte Carlo simulation data from the original ertapenem breakpoint discussion as well as the EUCAST rationale document suggested >80% and >90% target attainment at an MIC of 0.5 respectively.
b) MIC data from a recently published series from Cleveland (JCM 2010;48:4417), were reviewed. In this data set, a number of isolates that test with an MIC of 0.5 µg/mL expressed only an ESBL; these isolates should be susceptible to ertapenem. Similar data was presented from the University of Texas, San Antonio which showed that 17% of ESBL E. coli isolates had an MIC of 0.5 and were considered intermediate with the new breakpoints
c) At present only one commercial manufacturer can screen for breakpoints at ≤0.25 ug/mL

The following additional data will be provided at the next Working Group meeting in June 2011 before any changes in breakpoints are considered:

a) Surveillance data from other institutions for isolates that fall at MICs 0.25 and 0.5 µg/mL. (M. Ferraro and others)
b) For the patients from University of Texas, San Antonio presented here- additional information will be provided on creatinine clearance, body weights, etc to give an estimation of the exposure (J. Lewis)
c) Merck will present surveillance data generated by IHMA from SMART that are molecularly characterized. (M. Motyl). Post meeting note: Merck has asked for clarification on this request. M. Dudley will draft a response to Merck and circulate to the WG.
d) Population-PK models will be reviewed (S. Bhavnani)

2. Imipenem and Meropenem breakpoints- John Esterly

An informational presentation was made regarding clinical outcomes in Gram-negative bloodstream infections treated with carbapenems. A retrospective study evaluated patients with bloodstream infections with Gram-negative bacteria who were treated with carbapenems (imipenem or meropenem), who also had MIC data for the drug used in treatment. A strong correlation was found between mortality of these patients and MIC values of ≥4 mg/mL.

3. Update on MBL detection methods- Brandi Limbago

Although rare, MBLs have been detected in isolates in the US. MBLs can be detected using broth-microdilution MICs, MBL Etest, modified Hodge test (MHT), MIC +/- EDTA and phenanthroline, or the direct TE test. MIC based tests did not detect isolates producing IMP consistently. The MHT test did detect all of them, but was only subtly positive with NDM. The MHT can be done as a true cloverleaf test with streaks of test organism in all four directions to aid in the reading of the MHT with NDM.

4. Draft rationale document- Jim Lewis

A draft rationale document for the changes made to the carbapenem breakpoints for Enterobacteriaceae was presented to the working group and discussed. The working group will review it further and submit comments. M. Dudley will distribute a word document to aid in the editing process.

X. REPORT OF THE TOPICAL AGENTS WORKING GROUP

Minutes Submitted by Mair Powell **(Electronic Tab H in the Meeting Agenda)**

Chairholder – Mair Powell

Recording Secretary – Fred Marsik

Working Group Members present - Jeff Alder, Farah Babakhani, Ian Morrissey, Harriet Nadler, Robert Rennie, Jeffrey Shapiro, Lauri Thrupp

Working Group Members absent **–** Karen Carroll

The revised list of working group members was presented. This third meeting aimed to discuss three types of topical antibacterial drug usages of the five initially identified for use as examples for consideration by the working group. The other two types of use had been covered at the second meeting. There were four presentations, each followed by discussion, including:

1. Inhaled antibacterial agents in CF (M. Braff, Gilead Sciences)

Gilead Sciences had presented a poster at the 24th North American Cystic Fibrosis Conference in October 2010. They had conducted a retrospective analysis of data from the pre-registration Cayston (inhaled aztreonam) clinical studies to evaluate whether any relationship could be detected between MIC of aztreonam for *P. aeruginosa* isolated from chronically colonized patients and various outcome measures (RSS, FEV1 and sputum organism density). The analysis included data from aztreonam, placebo and comparator (TOBI) periods of administration. Criteria were applied to the outcome measures to classify patients as improved or worsened from pre-treatment. The Company was unable to identify a possible MIC breakpoint from these analyses. There are ongoing post-marketing studies and the Company plans further investigations along these same lines.

In the discussion, the criteria used to assign patients to improved or worsened categories were questioned. Similar data from studies in newly colonized CF patients (in which treatment aims to eradicate *P. aeruginosa* in an attempt to delay the onset of chronic colonization) are not yet available but are expected to emerge shortly and could be more informative. However, if breakpoints could be derived from such datasets they would be strictly applicable to this mode of use and patient population.

There are particular microbiological methodology issues surrounding attempts to document organism load and "eradication" from respiratory tract specimens. Some workers have attempted to describe drug concentrations in epithelial lining fluid but there remains uncertainty regarding the reliability of these data because of methodological issues of sampling.

As a post-meeting note, Novartis offered to present their data on use of TOBI in patients with first colonization events at the June 2011 meeting. The working group chair will follow-up on this offer.

2. Topical agents for skin (I. Morrissey)

The presentation summarized the microbiological investigations that are usually carried out for new agents intended for topical application to skin for various indications. For these types of agents (regardless of whether or not they are also used or being developed for systemic administration) particular attention may be paid to assessing effects of factors such as inoculum, temperature and pH on in-vitro activity.

It was discussed that the solubility of such compounds may limit the concentration used in clinical formulations and also impair the *in-vitro* assessment of activity against organisms since it may not be possible to determine actual MICs for some organisms. This fact, in turn, limits the potential for testing activity of the agent in animal models in which the deliberate selection of organisms with very high MICs could help to determine the highest MIC at which efficacy is still observed.

Obtaining PK data is fraught with difficulties and uncertainties. Data obtained from cadaveric skin preparations are of unknown relevance while data obtaining from biopsy of living treated skin are subject to the uncertainties posed by blood contamination and inability to differentiate concentrations in various skin layers. Hence PK/PD is not possible.

3. Oral agents intended for action within gut lumen (F. Babakhani)

The focus of this presentation was on agents developed for *C. difficile* since this is the area where most recent work has been conducted, including effectively non-absorbed antibacterial agents. The *in-vitro* data generated have included evaluations of effects on sporulation and germination.

The available clinical data, including those obtained from recently completed clinical studies with fidaxomicin, have not demonstrated any relationship between MICs measured for the *C. difficile* isolated from patients and clinical response parameters. Since this is a toxin-mediated clinical picture and the content of the gut flora is thought to be important for susceptibility to developing clinical symptoms and for recovery and relapses it seems unlikely that there is a simple relationship between in-vitro susceptibility and outcome. Work is in progress to try to develop newer animal models that might assist in these investigations.

Fecal levels can be measured and followed during treatment but concentrations in expelled fecal matter are of unknown relevance to concentrations achieved and maintained in the local environment of the organisms at the gut mucosa.

4. Consideration of role of biofilms specifically with respect to setting breakpoints for topical application of antibacterial agents (R. Rennie)

The presentation described recent developments towards attempting to identify standardized methodologies for assessing drug penetration into biofilms.

It was discussed that active workers in the field who have data of potential relevance to the topical application of antibacterial agents to infection have been identified and it was agreed that some of these investigators would be invited to present at the fourth meeting, at which considerable time would be devoted to further consider this issue.

5. Proposals for proceeding with the assessment of the potential for setting breakpoints for any mode of topical application of antibacterial agents

The working group and attendees acknowledged the potential difficulties raised in the presentations for setting interpretative criteria. Based on investigations and experience of working group members thus far it does not appear that there is any type of topical application of antibacterial agents for which there are sufficient and reliable data available to set either PK/PD or clinical breakpoints.

Conclusions

The MIC distributions can be documented but with no evidence of a strong relationship between in-vitro susceptibility testing and clinical outcome it is only possible to identify epidemiological cut-off values and, in some cases, limited solubility of test agents limits even this approach.

Overall, until such time as there are further developments in the field it was considered that the WG should likely cease regular meetings after the fourth (June 2011). This matter will be revisited at the June meeting in case of further information in the meantime that might influence the decision.

Action Items

The working group discussed that the feedback to the subcommittee should propose that the next meeting should likely be the last face to face meeting planned and that it should be devoted to further evaluation of the biofilm issue. The Chair will also arrange to invite Novartis to present on their data from CF patients with initial colonization.

It was also discussed that the working group would likely propose to the subcommittee that after the June 2011 meeting it should become a "virtual" group charged with monitoring any important scientific developments that might trigger further meetings on an *ad hoc* basis.

The output of the WGH deliberations thus far was discussed. During and possibly after the interval between the 3rd and 4th meetings the leads in each area will develop a short (few pages) summary of what is known, not known, and what might be done scientifically to address the gaps in knowledge. It will have to be discussed by the subcommittee and CLSI what is done with this report once ready and reviewed. A draft template for these reports on each area had already been circulated and will be used as a basis (with modification as needed) for the report sections.

XI. REPORT OF THE M39 WORKING GROUP

Minutes Submitted by Janet Hindler

Chairholder – Janet Hindler

Working Group Members present - Sharon Erdman, Alan Evangelista, Steve Jenkins, Judy Johnston, Jim Lewis, Dyan Luper

Working Group Members absent - Michael Barton, Ron Master, Graeme Nimmo

M39-A3 will be updated with the goal of publishing M39-A4 in 2012. A draft of M39-A4 will be included in the June 2011 agenda book. New information discussed at the January 2011 Working Group meeting to be added to M39-A4 includes:

1. Revision to Forward

   "The primary aim of this document is to guide the preparation of cumulative antimicrobial susceptibility test data reports that will prove useful to clinicians in the selection of the most appropriate agents for initial empirical antimicrobial therapy. Other analyses of antimicrobial susceptibility test data may also be of significant value to clinicians, infection control personnel, epidemiologists, pharmacists, and others ~~but lie outside the scope of this document.~~ **Several examples are included in M39."**

2. Addition of two new definitions:

   Multidrug-resistant organism (MDRO) – an organism resistant to multiple classes of antimicrobial agents. The definition can be based on recommendations provided by the US Centers for Disease Control and Prevention, recently published global recommendations (ref) or defined by a particular facility.

   Electronic medical record (EMR) - an electronic record of health-related information on an individual that can be created, gathered, managed and consulted by authorized clinicians and staff within one healthcare organization.

3. Modification of recommendations for presenting % ESBL and %KPCs when revised cephalosporin, aztreonam, and carbapenem breakpoints are used and phenotypic tests for detecting resistance mechanisms are not routinely performed.
   - %ESBL-producing isolates will be reported as % 3rd generation cephalosporin resistant
   - %KPC-producing isolates will be reported as % carbapenem resistant

4. Addition of suggestion for considering sharing external cumulative susceptibility data in select situations by including the following comment: "When data from an individual facility are not available (ie, internal data), data from external sources may be valuable to share with stakeholders, particularly for antimicrobial agent / organism combinations where resistance has not been reported or has rarely been reported to date. Sources of such data might be controlled surveillance studies performed by researchers, industry or public health organizations."

5. Addition of suggestion for considering reporting the number and percent of isolates that have specific resistance profiles in select situations. (eg, *E. coli* urine isolates susceptible to all drugs, resistant to ampicillin only, resistant to ampicillin plus ciprofloxacin, resistant to ampicillin plus ciprofloxacin plus trimethoprim-sulfa, etc.). Examples will be provided in M39-A4 and organisms listed that might be examined will include *Acinetobacter baumannii, E. coli* (urine), *Pseudomonas aeruginosa, Streptococcus pneumoniae*

6. Addition of suggestion for considering reporting % susceptible data for all organisms within a group from a specific source irrespective of species identification. An example will be provided in M39-A4 that focuses on % susceptible data for all GNR isolated from blood.

XII. AGENDA BOOK SUBMISSIONS FOR 12-14 JUNE 2011 MEETING

Materials for the June meeting will be distributed to the subcommittee on a CD prior to the meeting. The meeting rooms will be equipped with power strips for those who prefer to view the material on their computer instead of printing the material.

To meet the schedule for completing and shipping the CDs, submission due dates and requirements must be met. In order to present at the 12-14 June 2011 meeting please:

1) Submit agenda materials electronically as a PDF file **on or before Wednesday 4, May 2011.**

2) E-mail proposed agenda topics to Franklin R. Cockerill, III, MD (cockerill.franklin@mayo.edu) please copy his Administrative Assistant JoAnn Brunette (Brunette.Joann@mayo.edu) and also to Tracy Dooley (tdooley@clsi.org) for review.

XIII. ADJOURNMENT – The meeting adjourned at 11:15 a.m. on Tuesday, 11 January 2011.

Respectfully submitted,

Tracy A. Dooley, BS, MLT (ASCP), Standards Administrator