



A Comparison Of Doripenem And Meropenem MICs by European Methods Against 109 Gram-positive And Gram-negative Organisms

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Abstract (Revised)

Background: Doripenem is a 1-β-methyl carbapenem with broad-spectrum activity against Gram-negative (GN) and Gram-positive (GP) pathogens. This 4-site study was done to compare doripenem and meropenem MIC methods with the CLSI broth microdilution method (BMD) against a selection of GP and GN strains. **Methods:** Each of the sites tested their MIC method (France (SFM), Sweden (SRGA), United Kingdom (BSAC), and Germany (DIN)) and the CLSI method against the same set of 109 strains (*S. aureus*, *S. saprophyticus*, *E. faecalis*, *S. pneumoniae*, viridans strep., *E. coli*, *S. marcescens*, *P. mirabilis*, *C. freundii*, *E. aerogenes*, *E. cloacae*, *K. pneumoniae*, *P. aeruginosa*, *H. influenzae*). Standard QC strains were also tested. **Results:** The geometric mean MICs for all strains for doripenem and meropenem were within 1/2 dilution for all methods. In comparison to CLSI doripenem MICs, with the exception of doripenem by BSAC against *S. aureus*, the overall essential agreements % (EA) were: SFM 100, SRGA 71.0 and BSAC 68.5. EA based on same method comparison at the German site (CLSI/DIN) was 98.1. With the exception of *H. influenzae*, doripenem BSAC and SRGA modal MICs are 1 dilution lower than CLSI. The geometric mean MICs (mg/L) for all strains tested were:

Testing Site/Method	n	Doripenem n	Meropenem n
France/SFM	107	0.11	0.12
France/CLSI	107	0.16	0.15
Sweden/SRGA	107	0.12	0.19
Sweden/CLSI	107	0.20	0.20
UK/BSAC	108	0.08	0.11
UK/CLSI	108	0.15	0.20
Germany/DIN/CLSI #1	107	0.12	0.13
Germany/CLSI/DIN #2	107	0.13	0.13

Conclusions: Doripenem MICs, by all European methods, correlated well with the CLSI BMD method with the same selected set of strains.

Introduction

- This study was performed to compare doripenem MIC results for a selection of Gram-positive and Gram-negative isolates as determined by Société Française de Microbiologie (SFM), Swedish Reference Group for Antibiotics (SRGA), British Society for Antimicrobial Chemotherapy (BSAC) and Deutsches Institut für Normung (DIN) and Clinical and Laboratory Standards Institute (CLSI) methods.
- Each study site tested the same set of strains using their country MIC method and the CLSI MIC method. Overall, there was good correlation of doripenem MICs by SFM, SRGA, BSAC agar dilution and CLSI/DIN broth microdilution methodologies.
- The geometric mean doripenem and meropenem MICs of all strains were within 1 and a 1/2 doubling dilution, respectively, for all methods.

Methods

Antimicrobial Agents

Doripenem – 0.002-64 µg/mL
Comparator Agent – Meropenem – 0.002-64 µg/mL

Testing Sites and Specific Method Tested

SFM – Claude-James Soussy, C.H.U. Henri Mondor, Créteil Cedex, France
SRGA – Gunnar Kahlmeter, Klinisk Mikrobiologi, Växjö, Sweden
BSAC – David Livermore, Central Public Health Laboratory, London, UK
DIN – Arne Rodloff, Universität Leipzig, Leipzig, Germany

Microorganisms

The same set of 109 strains were tested by all sites and included: 19 Staphylococci, 10 *E. faecalis*, 23 Streptococci, 37 Enterobacteriaceae, 10 *P. aeruginosa*, and 10 *H. influenzae*

Methods

SFM MIC Method

Agar dilution using Mueller Hinton Agar (MHA) for staphylococci and gram negative bacilli. MHA + 5% defibrinated sheep blood (SB) for streptococci and Haemophilus Test Media agar (HTMA) for *H. influenzae*. (2)

SRGA MIC Method

Agar dilutions using IsoSensitest (ISA) for staphylococci and gram negative bacilli and ISA + 5% defibrinated horse blood (HB) and 20 mg/L NAD for streptococci and *H. influenzae*. (3)

BSAC MIC Method

Agar dilution using IsoSensitest Agar (ISA) for staphylococci and gram negative bacilli and ISA+ 5% defibrinated horse blood (dHB) for streptococci and ISA+5% whole horse blood + 20 mg/L NAD for *H. influenzae*. (4)

DIN & CLSI MIC Method (All sites tested CLSI as common, comparative method)

Broth microdilution using Sensititre MIC panels (Trek, U.K.) with cation adjusted Mueller Hinton Broth (CAMHB) for staphylococci and gram negative bacilli and CAMHB + 5% Lysed Horse Blood (LHB) for streptococci and Haemophilus Test Media (HTM) for *H. influenzae*. (1,5)

Results

- The geometric mean doripenem MICs of all strains by all methods ranged from 0.08-0.2 µg/mL.
- The geometric mean meropenem MICs of all strains by all methods ranged from 0.11-0.2 µg/mL.

- Comparisons of Doripenem MICs to CLSI MICs in each country by organism group were:

SFM: Gram-positive and Enterobacteriaceae doripenem MICs averaged 1/2 dilution lower. *P. aeruginosa* MICs were similar and *H. influenzae* MICs were similar or one dilution higher.

SRGA: Doripenem MICs averaged 1 dilution lower with exception of *H. influenzae* and MRSA. SRGA MICs were 3 dilutions lower for 4 of the 7 MRSA tested. Although 5 of the 10 *H. influenzae* MICs were similar by both methods, 5 were 1-5 dilutions higher by SRGA.

BSAC: Doripenem MICs averaged 1 dilution lower for enterococci, streptococci and majority of the Enterobacteriaceae. BSAC doripenem MICs for *S. marcescens* and *P. mirabilis* were 2-3 dilutions lower. BSAC doripenem MICs were 2-4 dilutions lower than CLSI for 7 of the 14 *S. aureus* tested. The difference in BSAC and CLSI *P. aeruginosa* MICs varied, but BSAC MICs tended to be lower by 1-4 dilutions. *H. influenzae* doripenem MICs were 2-3 dilutions higher by BSAC.

DIN/CLSI: Doripenem MICs were very reproducible; all MICs except two results were within +/- one doubling dilution.

- Essential agreement compared to CLSI for doripenem were: SFM - 100%, SRGA – 71.0%, BSAC – 68.5%, DIN – 98.1%.

- Essential agreement compared to CLSI for meropenem were: SFM - 100%, SRGA – 83.2%, BSAC – 75.0%, DIN – 99.1%.

- Most strains were susceptible by all methods. One *E. cloacae* tested resistant by both methods in France and by CLSI at the Swedish site, and susceptible by both methods in the UK and Germany. The number of very major/minor errors in comparison to the CLSI MICs at each site among the 10 *P. aeruginosa* were DIN (0/0), SFM (0/0), SRGA (0/1) and BSAC (1/1).

- Doripenem staphylococci and *E. faecalis* MICs averaged 2 fold and 1.5 fold lower than meropenem MICs by all methods. Doripenem and meropenem MICs were similar for the other species tested.

References

- Clinical and Laboratory Standards Institute M7-A7. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 7th ed., CLSI, Wayne, PA; 2006.
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- British Society for Antimicrobial Chemotherapy. Determination of Minimum Inhibitory Concentrations. March 2006. www.bsac.org.uk
- NormenausschB Medizin im DIN Deutsches Institut für Normung e.V. Susceptibility testing of infectious agents and evaluation of performance of antimicrobial susceptibility test devices – Part 1: Reference method for testing the in vitro activity of antimicrobial agents against rapidly growing aerobic bacteria involved in infectious diseases (ISO 20776-1:2006). Berlin, Germany: DIN EN ISO 20776-1; 2007-02.

Figure 1: Geometric mean doripenem MICs (µg/mL) by method of staphylococci and *E. faecalis*

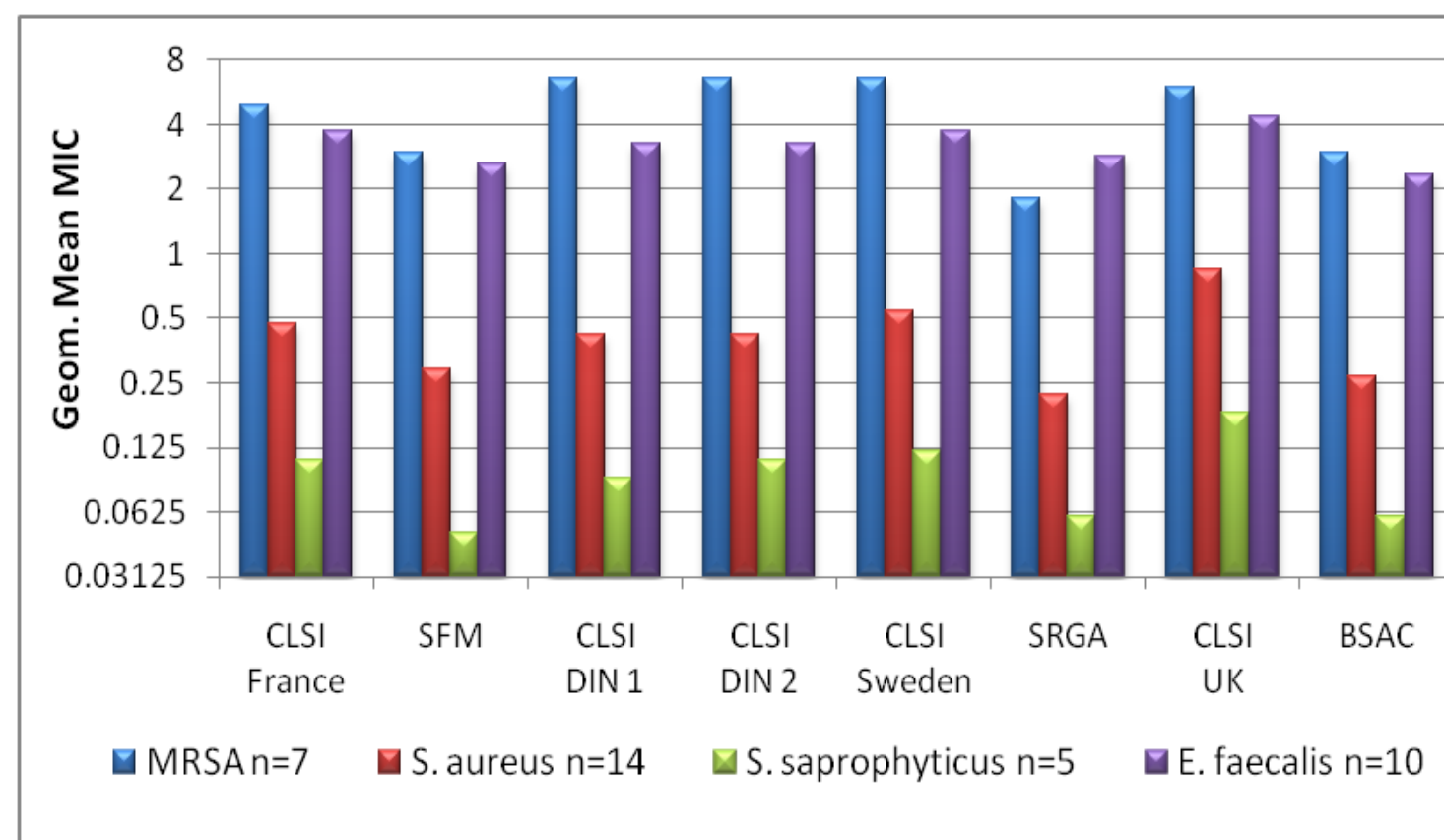


Figure 2: Geometric mean doripenem MICs (µg/mL) by method of streptococci

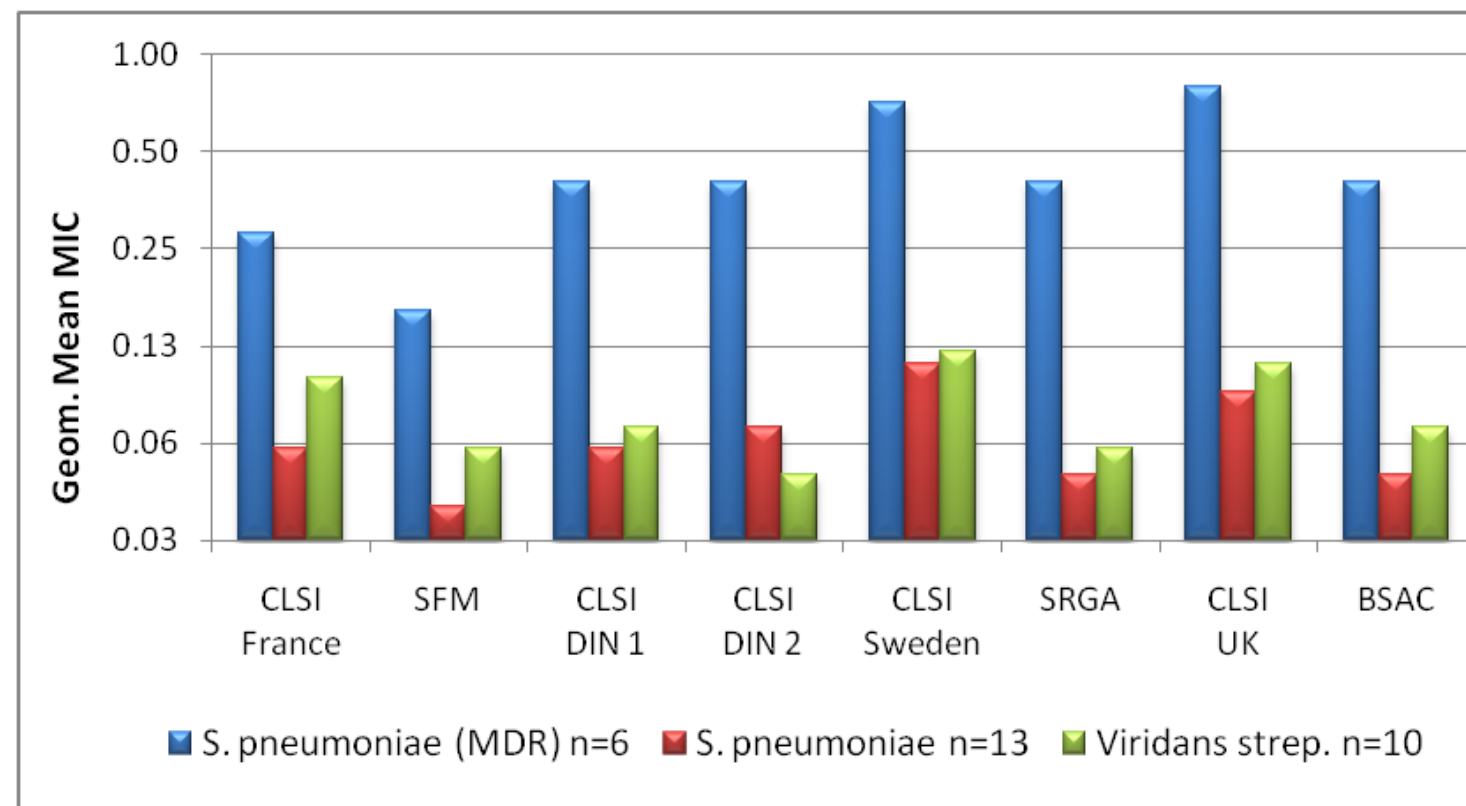


Figure 3: Geometric mean doripenem MICs (µg/mL) by method of Enterobacteriaceae, Pseudomonas aeruginosa and H. influenzae

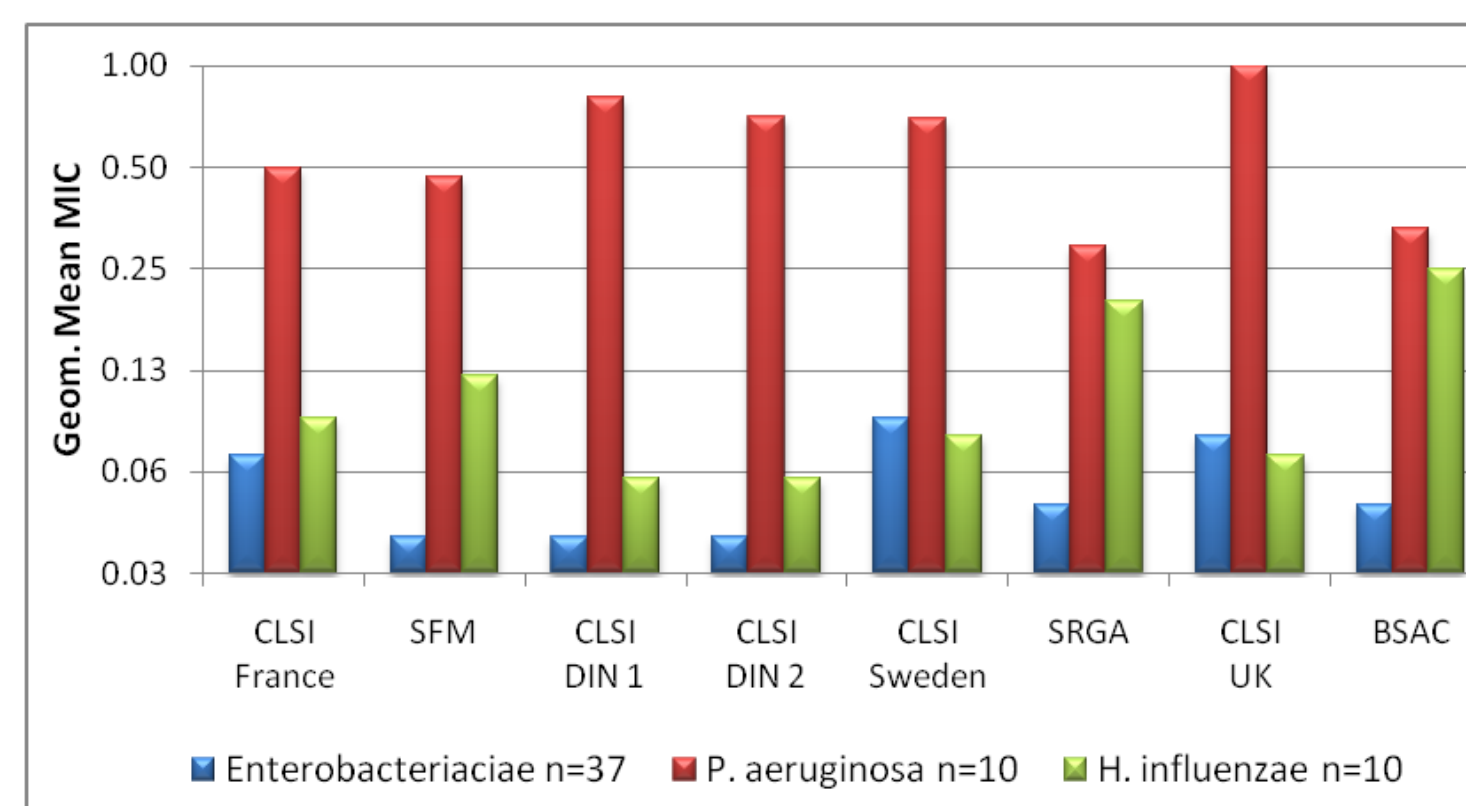


Table 1: Geometric mean doripenem and meropenem MICs (µg/mL) by method and organism

Microorganisms	(n)	France		Germany		Sweden		United Kingdom	
		CLSI BMD	SFM Agar	CLSI/DIN BMD	CLSI/DIN BMD	CLSI BMD	SRGA Agar	CLSI BMD	BSAC Agar
Doripenem									
MRSA	7	4.88	2.97	6.52	6.52	6.56	1.81	5.94	2.97
All <i>S. aureus</i>	14	0.47	0.29	0.42	0.42	0.54	0.22	0.85	0.27
<i>S. saprophyticus</i>	5	0.11	0.05	0.09	0.11	0.12	0.06	0.18	0.06
<i>E. faecalis</i>	10	3.73	2.64	3.25	3.25	3.73	2.83	4.32 ^d	2.33 ^d
<i>S. pneumoniae</i> (MDR)	6	0.28	0.16	0.4	0.4	0.71	0.4 ^b	0.79	0.4
All <i>S. pneumoniae</i>	13	0.06	0.04 ^b	0.06	0.07	0.11	0.05 ^b	0.09	0.05
Viridans streptococci	10	0.10	0.06	0.07	0.05	0.12 ^d	0.06 ^d	0.11	0.07
All Enterobacteriaceae	37	0.07	0.04	0.04	0.04	0.09 ^e	0.05 ^e	0.08	0.05
<i>P. aeruginosa</i>	10	0.50	0.47	0.81	0.71	0.7	0.29	1	0.33
<i>H. influenzae</i>	10	0.09 ^c	0.12 ^c	0.06 ^c	0.06 ^c	0.08	0.2	0.07	0.25
All Strains	109	0.16	0.11	0.13	0.12	0.2	0.12	0.15	0.08
Meropenem									
MRSA	7	7.25	5.38	11.89	16	16	4.42	32 ^a	4.42
All <i>S. aureus</i>	14	0.80	0.54	0.76	0.89	1.4	0.64	2.29 ^a	0.44
<i>S. saprophyticus</i>	5	0.19	0.14	0.14	0.16	0.22	0.22	0.33	0.22
<i>E. faecalis</i>	10	5.66	3.48	5.66	6.06	6.06	3.48	6.35 ^d	2.72 ^d
<i>S. pneumoniae</i> (MDR)	6	0.35	0.22	0.45	0.56	0.71	1	0.89	0.5
All <i>S. pneumoniae</i>	13	0.08	0.06	0.08	0.09	0.12	0.15	0.11	0.06
Viridans streptococci	10	0.14	0.08	0.08	0.06	0.17 ^d	0.16 ^d	0.12	0.09
All Enterobacteriaceae	37	0.04	0.02 ^b	0.03	0.02	0.05 ^e	0.05 ^e	0.05	0.03
<i>P. aeruginosa</i>	10	0.50	0.47	0.71	0.71	0.75	0.62	0.76	0.5
<i>H. influenzae</i>	10	0.04 ^c	0.07 ^c	0.04 ^c	0.06 ^c	0.05	0.12	0.05	0.05
All Strains	109	0.15	0.11	0.13	0.13	0.2	0.19	0.2	0.11

^a Some offscale (>) MICs included as one doubling dilution above the highest concentration tested
^b Some offscale (<) MICs included as the lowest concentration tested
^c 2 strains not tested, n=8
^d 1 strain not tested, n=9
^e 1 strain not tested, n=36

Table 2: Dilution difference of doripenem MICs (µg/mL) by method and organism

Microorganisms	SFM			SRGA					BSAC					CLSI/DIN									
	-1	0	+1	-3	-2	-1	0	1	2	3	-3	-2	-1	0	1	2	3	-2	-1	0	+1	+2	
<i>S. aureus</i> (MRSA)	5	2			4		2	1			1*		2	1	2					7			
<i>S. aureus</i> (MSSA)	5	2					3	2	1		3*	1	1	1						1	5	1	
<i>S. saprophyticus</i>	5			1		3	1				1*		4							1	3	1	
<i>E. faecalis</i>	5	5		1		3	5		1		1		6	2						10			
<i>S. pneumoniae</i>	4	2	1			5	2						6	1						6		1	
<i>S. pneumoniae</i> (MDR)	5	1		1		3	2				2		2	2						1	4	1	
Viridans streptococci	8	1	1	1		8					2		6	1						2	6	1	
<i>E. coli</i>	9	1				6	3	1			1		3	6						3	6	1	
<i>S. marcescens</i>	1	3				3	1				3	1									3	1	
<i>P. mirabilis</i>	4	1				3	1	1			1	3		1						1	3	1	
<i>C. freundii</i>	2	1	1					3						3	1							4	
<i>E. aerogenes</i>	3	1				1	2	1					3	1								4	
<i>E. cloacae</i>	1	3				1	1	2					4							1	3		
<i>K. pneumoniae</i>	4	2		1	1	3	1						3	2	1						5	1	
<i>P. aeruginosa</i>	2	7	1	2	1	5	2				2*	2	2	3						2	8		
<i>H. influenzae</i>	5	3					5	2	3*			1	2	1	1	5				1	7	1	
All Strains	63	34	10	9	18	43	27	6	1	3	14	13	43	26	5	1	6			13	84	8	2
Essential Agreement	100%			71.0%					68.5%					98.1%									

Conclusions

- The geometric mean doripenem MICs for all strains were within one doubling dilutions, with the exception of a slightly higher geometric mean for CLSI Sweden and a slightly lower geometric mean for BSAC.
- The geometric mean meropenem MICs for all strains were within one doubling dilution.
- There was very good intra- and inter-laboratory reproducibility of the CLSI method.
- Although there was a bias toward lower SRGA and BSAC MICs, the categorical agreement was high with this subset of primarily susceptible strains.
- Overall, there was good correlation of doripenem MICs by SFM, SRGA, BSAC agar dilution and CLSI/DIN broth microdilution methodologies.