781 *In Vitro* Antibacterial Activity of Meropenem/RPX7009, (a Carbapenem/β-lactamase Inhibitor Combination) Against Contemporary Enterobacteriaceae Isolated from Intra-abdominal and Urinary Tract Infections in the United States

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Amended Abstract

Background: We evaluated the *in vitro* activity of meropenem (MER) ± RPX7009 (RPX), a serine-β-lactamase inhibitor against consecutive clinical isolates of ENT obtained from IAI and UTI during 2014 in the USA. MIC testing included susceptible, carbapenem-resistant ENT (CRE), ESBL phenotype, and MER non-susceptible (NS) *K. pneumoniae* (KPN) isolates.

Methods: 1755 ENT were tested for MICs against MER ± RPX (fixed 8 µg/mL) and comparators using CLSI broth microdilution methodology.

Results: Against 1273 ENT from UTI, MER and MER/RPX both displayed $MIC_{50/90}$ values of ≤0.015/0.06 µg/mL (MIC ranges were ≤0.015-32 and ≤0.015-0.5 µg/mL, respectively). 100/100% of ENT from UTI were inhibited at ≤1/≤2 µg/mL of MER (CLSI/EUCAST Susceptible [S] breakpoints) in the presence of 8 µg/mL of RPX. Similarly, 99.4/99.6% of ENT from IAI (482) were inhibited at ≤1/≤2 µg/mL of MER in combination with 8 µg/mL of RPX. Against 16 isolates of CRE and 13 isolates of MER-NS KPN from UTI (Table), RPX in combination with MER restored MER MICs to ≤0.5 µg/mL (MIC_{90} 0.5 µg/mL). Susceptibility rates for comparator compounds against CRE were 62.5, 0, 0, and 12.5% for minocycline (MIN), piperacillin/tazobactam (P/T), ceftazidime (CAZ), and levofloxacin (LVX), respectively. Susceptibility rates for comparator compounds against MER-NS KPN were 69.2, 0, 0, and 7.7% for MIN, P/T, CAZ, and LVX, respectively. Against ENT displaying an ESBL-phenotype, MER/RPX MIC_{90} values were 2-fold lower than MER and the highest MER/RPX MIC observed was 0.5 µg/mL.

Conclusions: MER/RPX shows high activity against clinical isolates from UTIs and IAIs including those caused by CRE, MER-NS KPN, and isolates demonstrating an ESBL-phenotype that are often resistant to multiple antimicrobial agents. Clinical trials are in progress.

Organism group, (Infection type, no. tested)	Antimicrobial agent	MIC (µg/mL) MIC range	MIC_{50}	MIC_{90}
CRE, (UTI, 16)	MER	4->32	16	>32
	MER/RPX	≤0.015-0.5	0.03	0.5
	MIN	1->8	4	>8
	P/T	>64	>64	>64
	CAZ	32->32	>32	>32
	LVX	0.25->4	>4	>4
ENT ESBL-phenotype (UTI, 86)	MER	≤0.015-8	≤0.015	0.06
	MER/RPX	≤0.015-0.5	≤0.015	0.03
	MIN	0.25->8	1	>8
	P/T	1->64	4	32
	CAZ	0.25-32	16	>32
	LVX	≤0.12->4	>4	>4
MER-NS KPN (UTI, 13)	MER	4->32	16	>32
	MER/RPX	≤0.015-0.5	0.03	0.5
	MIN	1->8	4	8
	P/T	>64	>64	>64
	CAZ	>32	>32	>32
	LVX	0.25->4	>4	>4

Background

Carbapenem-resistant Enterobacteriaceae (CRE) have been detected worldwide and their elevated prevalence is mainly due to the dissemination of isolates producing carbapenemases, such as *Klebsiella pneumoniae* carbapenemase (KPC) and metallo-β-lactamases, largely NDM. Carbapenemase-producing Enterobacteriaceae (CPE) causing infections became a serious concern among infectious disease and clinical microbiology professionals worldwide because these infections are difficult to manage. CPE isolates are resistant to all or almost all β-lactam agents, and these organisms are usually resistant to other antimicrobial classes, limiting the therapeutic options.

The use of β-lactamase inhibitors combined with a broad-spectrum β-lactam agent has been a successful strategy for overcoming β-lactamase-mediated resistance; however, older inhibitors such as tazobactam, sulbactam and clavulanate are generally not active against isolates producing various contemporary β-lactamases, including KPC serine-carbapenemases. The increasing prevalence of multidrug-resistant (MDR) organisms producing KPC enzymes and other β-lactamases that are poorly inhibited by clinically available inhibitors suggest the need for new treatment alternatives.

RPX7009 is a cyclic boronic acid β-lactamase inhibitor that has activity against Ambler class A and C enzymes, including KPC. This inhibitor has been paired with meropenem, and in this study we evaluated this combination against a collection of 1,755 contemporary Enterobacteriaceae isolates obtained from intra-abdominal (IAI) and urinary tract infections (UTI) in the United States (USA).

Methods

A total of 1,755 Enterobacteriaceae obtained from patients in the USA with documented IAI and UTI infections (only one isolate per patient infection episode) during 2014 from a global surveillance program were included in the study and tested for susceptibility using methods recommended by the Clinical and Laboratory Standards Institute (CLSI) (M07-A10, 2015). Minimum inhibitory concentration (MIC) testing for meropenem/RPX7009 using the inhibitor at a fixed 8 µg/mL concentration and comparator agents was performed using validated dry-form broth microdilution panels manufactured by ThermoFisher Scientific (formerly TREK Diagnostics Systems/Sensititre; Cleveland, Ohio, USA).

Validation of the MIC values was performed with CLSI recommended quality control (QC) strains. MICs for comparator compounds were evaluated using CLSI (M100-S25, 2015) and European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2015) breakpoint interpretive criteria, where available. USA-FDA approved breakpoints were applied for tigecycline.

Resistance phenotypes were determined as outlined below:

- Carbapenem-resistant Enterobacteriaceae (CRE) was defined as any isolate displaying imipenem (*Proteus mirabilis* and indole-positive *Proteae* were not included due to the intrinsically elevated MIC values) and/or meropenem MIC values at ≥2 µg/mL CLSI criteria (2015).
- ESBL-phenotype defined as a MIC at ≥2 µg/mL for ceftriaxone or ceftazidime or aztreonam (CLSI, 2015) for *Escherichia coli*, *Klebsiella* spp., *K. pneumoniae*, *K. oxytoca* and *P. mirabilis*.
- Meropenem-susceptible (MIC, ≤1 µg/mL) and meropenem-non-susceptible (MIC, ≥2 µg/mL).

RPX7009 was supplied by The Medicines Company/Rempex to ThermoFisher Scientific (a Good Manufacturing Practice [GMP] facility) for dry-form broth microdilution panel production. Comparator compounds (selected by the sponsor in consultation with JMI Laboratories) were acquired from their respective manufacturers or from Sigma-Aldrich (St. Louis, Missouri, USA) and used by ThermoFisher Scientific for dry-form panel production.

Results

- A summary of the MIC results for meropenem ± RPX7009 (fixed 8 µg/mL) and comparator antimicrobials including the number of isolates tested, MIC_{50}, MIC_{90}, and percent susceptible, intermediate, and resistant according to CLSI breakpoint interpretive criteria is presented for 1,273 Enterobacteriaceae from UTI in Table 1 and for 482 Enterobacteriaceae from IAI in Table 2. The data is further subdivided within each table for the most common species and resistance phenotypes and presented in tabular form as cumulative % inhibited at each MIC in Table 3.
- The combination of meropenem/RPX7009 (MIC_{50} and MIC_{90}, ≤0.015 and 0.06 µg/mL) reduced the highest MIC observed against 1,273 Enterobacteriaceae isolates from UTI over meropenem alone (MIC_{50}/MIC_{90} ≤0.015/0.06 µg/mL) from >32 to 0.5 µg/mL (Table 3).
- Meropenem/RPX7009 reduced the MIC_{90} against 16 carbapenem-resistant Enterobacteriaceae (CRE) including a subset of 13 meropenem non-susceptible *Klebsiella pneumoniae* from >32 to 0.5 µg/mL (Table 1, Table 3 and Figure 1). The *E. coli* isolates included in the CRE group had individual meropenem MICs of 2, 4 and 8 µg/mL and meropenem/RPX7009 MICs of ≤0.015, ≤0.015 and 0.5 µg/mL.
- The ability of RPX7009 in combination with meropenem to restore activity against β-lactamase producing Enterobacteriaceae over meropenem tested alone is demonstrated through cumulative % inhibition data (Table 3) for each of the organism groups tested.
- Applying CLSI breakpoint interpretative criteria for meropenem to the meropenem/RPX7009 combination (for comparison purposes only) resulted in 100% of the CRE isolates from UTI testing as meropenem/RPX7009 susceptible (meropenem MICs ≤1 µg/mL).
- Against 16 isolates of carbapenem-resistant Enterobacteriaceae from UTI (Table 1), the most active comparator antimicrobials tested according to CLSI breakpoint interpretive criteria were amikacin, colistin (EUCAST breakpoints), minocycline and tigecycline (56.2, 68.8, 62.5 and 100.0% susceptible, respectively). These antimicrobials were also the most active comparators against a subset of 13 meropenem non-susceptible *K. pneumoniae* (53.8, 61.5, 69.2, and 100.0% susceptible, respectively).
- Applying CLSI breakpoint interpretive criteria for minocycline, 80.1 and 82.4% of 2014 Enterobacteriaceae isolates obtained from UTI (Table 1) and IAI (Table 2) infections, respectively, were susceptible to minocycline and 13.7 and 9.8%, respectively, were considered resistant.
- Meropenem/RPX7009 inhibited 100% of ESBL-phenotype *E. coli* (n=86) and *K. pneumoniae* (n=172) isolates from UTI at ≤0.5 µg/mL (Table 3). Corresponding meropenem susceptibilities were 96.5 and 92.4% (Table 1).
- The combination of meropenem/RPX7009 reduced the highest MIC observed against 482 Enterobacteriaceae and 87 *K. pneumoniae* from IAI infections by 4-fold (Table 3) over meropenem tested alone. MIC_{90} values for meropenem/RPX7009 against these organism groups as well as 53 ESBL-phenotype *E. coli* were 0.03 µg/mL (Table 2 and Table 3). Meropenem alone was active against these groups with 98.1 to 98.9% susceptible (CLSI breakpoint interpretive criteria; Table 2).

Table 1. Activity of Meropenem/RPX7009 (fixed 8 µg/mL) and comparator antimicrobial agents when tested against isolates of Enterobacteriaceae from urinary tract infections in the United States.

Organism (no. tested)/ Antimicrobial Agent	MIC (µg/mL): 50%	90%	CLSI[a] %S	%I	%R
Enterobacteriaceae (n=1,273)					
Meropenem/RPX7009	≤0.015	0.06	-	-	-
Meropenem	≤0.015	0.06	98.7	0.1	1.3
Ceftazidime	0.12	8	88.2	1.9	9.9
Piperacillin/tazobactam	2	8	93.2	3.1	3.7
Amikacin	2	4	99.4	0.5	0.1
Colistin	≤0.5	>8	(83.9)[b]	-	-
Levofloxacin	≤0.12	>4	81.7	1.4	16.9
Minocycline	1	>8	80.1	6.2	13.7
Tigecycline	0.12	0.5	99.2	0.8	0.0[c]
Carbapenem-resistant Enterobacteriaceae (n=16)[d]					
Meropenem/RPX7009	0.03	0.5	-	-	-
Meropenem	16	>32	0.0	0.0	100.0
Ceftazidime	>32	>32	0.0	0.0	100.0
Piperacillin/tazobactam	>64	>64	0.0	0.0	100.0
Amikacin	16	32	56.2	37.5	6.2
Colistin	≤0.5	>8	(68.8)[b]	-	-
Levofloxacin	>4	>4	12.5	0.0	87.5
Minocycline	4	>8	62.5	18.8	18.8
Tigecycline	0.25	1	100.0	0.0	0.0[c]
ESBL-phenotype *Escherichia coli* (n=86)					
Meropenem/RPX7009	≤0.015	0.03	-	-	-
Meropenem	≤0.015	0.06	96.5	1.2	2.3
Ceftazidime	16	>32	19.8	19.8	60.5
Piperacillin/tazobactam	4	32	83.7	10.5	5.8
Amikacin	2	8	98.8	1.2	0.0
Colistin	≤0.5	≤0.5	(100.0)[b]	-	-
Levofloxacin	>4	>4	18.6	1.2	80.2
Minocycline	1	>8	80.2	8.1	11.6
Tigecycline	0.06	0.12	100.0	0.0	0.0[c]
Meropenem non-susceptible *E. coli* (n=3)					
Meropenem/RPX7009	≤0.015	-	-	-	-
Meropenem	4	-	0.0	33.3	66.7
Ceftazidime	>32	-	0.0	0.0	100.0
Piperacillin/tazobactam	>64	-	0.0	33.3	66.7
Amikacin	16	-	66.7	33.3	0.0
Colistin	≤0.5	-	(100.0)[b]	-	-
Levofloxacin	>4	-	0.0	0.0	100.0
Minocycline	8	-	33.3	33.3	33.4
Tigecycline	0.06	-	100.0	0.0	0.0[c]
***Klebsiella pneumoniae* (n=172)**					
Meropenem/RPX7009	0.03	0.03	-	-	-
Meropenem	0.03	0.12	92.4	0.0	7.6
Ceftazidime	0.12	>32	83.1	1.2	15.7
Piperacillin/tazobactam	4	>64	87.8	1.7	10.5
Amikacin	1	4	95.9	3.5	0.6
Colistin	≤0.5	1	(94.7)[b]	-	-
Levofloxacin	≤0.12	>4	84.9	2.3	12.8
Minocycline	2	8	84.9	5.2	9.9
Tigecycline	0.25	0.5	100.0	0.0	0.0[c]
Meropenem non-susceptible *K. pneumoniae* (n=13)					
Meropenem/RPX7009	0.03	0.5	-	-	-
Meropenem	16	>32	0.0	0.0	100.0
Ceftazidime	>32	>32	0.0	0.0	100.0
Piperacillin/tazobactam	>64	>64	0.0	0.0	100.0
Amikacin	16	32	53.8	38.5	7.7
Colistin	≤0.5	>8	(61.5)[b]	-	-
Levofloxacin	>4	>4	7.7	0.0	92.3
Minocycline	4	8	69.2	23.1	7.7
Tigecycline	0.25	0.5	100.0	0.0	0.0[c]

a. Criteria as published by CLSI [2015]
b. Criteria as published by EUCAST [2015]
c. Breakpoints from FDA Package Insert revised 12/2014
d. Includes 3 carbapenem-resistant *E. coli* and 13 meropenem non-susceptible *K. pneumoniae*

Table 2. Activity of Meropenem/RPX7009 (fixed 8 µg/mL) and comparator antimicrobial agents when tested against isolates of Enterobacteriaceae from intra-abdominal infections in the United States.

Organism (no. tested)/ Antimicrobial Agent	MIC (µg/mL): 50%	90%	CLSI[a] %S	%I	%R
Enterobacteriaceae (n=482)					
Meropenem/RPX7009	≤0.015	0.03	-	-	-
Meropenem	≤0.015	0.06	98.8	0.6	0.6
Ceftazidime	0.25	16	86.7	1.7	11.6
Piperacillin/tazobactam	2	16	91.1	3.1	5.8
Amikacin	1	4	99.6	0.2	0.2
Colistin	≤0.5	>8	(89.8)[b]	-	-
Levofloxacin	≤0.12	>4	84.2	0.4	15.4
Minocycline	2	8	82.4	7.9	9.8
Tigecycline	0.12	0.5	99.8	0.2	0.0[c]
Carbapenem-resistant Enterobacteriaceae (n=4)					
Meropenem/RPX7009	2	-	-	-	-
Meropenem	4	-	0.0	25.0	75.0
Ceftazidime	>32	-	0.0	0.0	100.0
Piperacillin/tazobactam	>64	-	0.0	25.0	75.0
Amikacin	2	-	75.0	25.0	0.0
Colistin	≤0.5	-	(100.0)[b]	-	-
Levofloxacin	0.25	-	25.0	25.0	50.0
Minocycline	8	-	25.0	25.0	50.0
Tigecycline	0.25	-	100.0	0.0	0.0[c]
ESBL-phenotype *Escherichia coli* (n=53)					
Meropenem/RPX7009	≤0.015	0.03	-	-	-
Meropenem	≤0.015	0.06	98.1	0.0	1.9
Ceftazidime	16	>32	35.8	9.4	54.7
Piperacillin/tazobactam	4	>64	81.1	3.8	15.1
Amikacin	2	8	96.2	1.9	1.9
Colistin	≤0.5	≤0.5	(100.0)[b]	-	-
Levofloxacin	>4	>4	26.4	0.0	73.6
Minocycline	2	>8	64.2	17.0	18.9
Tigecycline	0.12	0.25	100.0	0.0	0.0[c]
***Klebsiella pneumoniae* (n=87)**					
Meropenem/RPX7009	0.03	0.03	-	-	-
Meropenem	0.03	0.03	98.9	1.1	0.0
Ceftazidime	0.12	4	92.0	2.3	5.7
Piperacillin/tazobactam	2	8	95.4	0.0	4.6
Amikacin	1	2	100.0	0.0	0.0
Colistin	≤0.5	1	(97.7)[b]	-	-
Levofloxacin	≤0.12	0.5	92.0	0.0	8.0
Minocycline	2	8	89.7	4.6	5.7
Tigecycline	0.25	0.5	100.0	0.0	0.0[c]
ESBL-phenotype *K. pneumoniae* (n=9)					
Meropenem/RPX7009	0.03	-	-	-	-
Meropenem	0.03	-	88.9	11.1	0.0
Ceftazidime	16	-	22.2	22.2	55.6
Piperacillin/tazobactam	16	-	55.6	0.0	44.4
Amikacin	2	-	100.0	0.0	0.0
Colistin	≤0.5	-	(100.0)[b]	-	-
Levofloxacin	>4	-	22.2	0.0	77.8
Minocycline	8	-	44.4	33.3	22.2
Tigecycline	0.25	-	100.0	0.0	0.0[c]

a. Criteria as published by CLSI [2015]
b. Criteria as published by EUCAST [2015]
c. Breakpoints from FDA Package Insert revised 12/2014

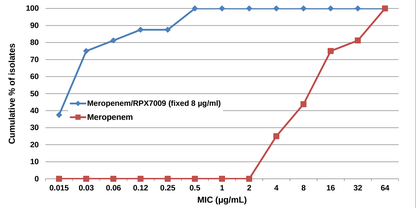
Table 3. Cumulative % inhibition for meropenem and meropenem/RPX7009 (fixed 8 µg/mL) against Enterobacteriaceae isolated from urinary tract and intra-abdominal infections in the United States.

Organism (no. tested) Antimicrobial Agent	Infection Type[a]	MIC_{50}	MIC_{90}	MIC Range	Cumulative % Inhibited at MIC (µg/mL) ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8
Enterobacteriaceae (1273)														
Meropenem	UTI	≤0.015	0.06	≤0.015->32	56.2	83.7	95	97.8	98.2	98.4	98.7	98.7	99.1	99.3
Meropenem/RPX7009	UTI	≤0.015	0.06	≤0.015-0.5	64.8	89.0	98.1	99.5	99.6	100.0				
Carbapenem-resistant Enterobacteriaceae (16)[b]														
Meropenem	UTI	16	>32	4->32	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	25.0	43.8
Meropenem/RPX7009	UTI	0.03	0.5	≤0.015-0.5	37.5	75.0	81.2	87.5	87.5	100.0				
ESBL-phenotype *E. coli* (86)														
Meropenem	UTI	≤0.015	0.06	≤0.015-8	52.3	86.0	91.9	96.5	96.5	96.5	97.7	98.8	100.0	
Meropenem/RPX7009	UTI	≤0.015	0.03	≤0.015-0.5	84.9	96.5	97.7	98.8	98.8	100.0				
Meropenem non-susceptible *E. coli* (3)														
Meropenem	UTI	4	--	2-8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	33.3	66.6	100.0
Meropenem/RPX7009	UTI	≤0.015	--	≤0.015-0.5	66.6	66.6	66.6	66.6	66.6	100.0				
***Klebsiella pneumoniae* (172)**														
Meropenem	UTI	0.03	0.12	≤0.015->32	29.7	86.0	89.0	91.3	91.3	91.3	92.4	92.4	94.2	95.3
Meropenem/RPX7009	UTI	0.03	0.03	≤0.015-0.5	37.8	95.9	97.7	98.8	98.8	100.0				
Meropenem non-susceptible *K. pneumoniae* (13)														
Meropenem	UTI	16	>32	4->32	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	23.1	38.5
Meropenem/RPX7009	UTI	0.03	0.5	≤0.015-0.5	23.1	69.2	76.9	84.6	84.6	100.0				

Organism (no. tested) Antimicrobial Agent	Infection Type[a]	MIC_{50}	MIC_{90}	MIC Range	Cumulative % Inhibited at MIC (µg/mL) ≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8
Enterobacteriaceae (482)														
Meropenem	IAI	≤0.015	0.06	≤0.015-16	53.1	89.0	97.1	98.3	98.9	98.8	98.8	99.4	99.8	99.8
Meropenem/RPX7009	IAI	≤0.015	0.03	≤0.015-4	65.6	94.0	97.5	98.8	99.0	99.4	99.4	99.6	100.0	
Carbapenem-resistant Enterobacteriaceae (4)														
Meropenem	IAI	4	--	2-8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	25.0	75.0	75.0
Meropenem/RPX7009	IAI	2	--	0.5-4	0.0	0.0	0.0	0.0	0.0	25.0	25.0	50.0	100.0	
ESBL-phenotype *E. coli* (53)														
Meropenem	IAI	≤0.015	0.06	≤0.015-4	54.7	88.7	98.1	98.1	98.1	98.1	98.1	98.1	100.0	
Meropenem/RPX7009	IAI	≤0.015	0.03	≤0.015-2	86.8	98.1	98.1	98.1	98.1	98.1	98.1	100.0		
***Klebsiella pneumoniae* (87)**														
Meropenem	IAI	0.03	0.03	≤0.015-2	31.0	95.4	97.7	97.7	98.9	98.9	98.9	100.0		
Meropenem/RPX7009	IAI	0.03	0.03	≤0.015-0.5	34.5	97.7	97.7	97.7	98.9	100.0				
ESBL-phenotype *K. pneumoniae* (9)														
Meropenem	IAI	0.03	--	≤0.015-2	11.1	66.7	77.8	77.8	88.9	88.9	88.9	100.0		
Meropenem/RPX7009	IAI	0.03	--	≤0.015-0.5	44.4	77.8	77.8	88.9	100.0					

a. UTI = Urinary tract infection, IAI = Intra-abdominal infection
b. Includes 3 meropenem non-susceptible *E. coli* and 13 meropenem non-susceptible *K. pneumoniae*

Figure 1: Meropenem and meropenem/RPX7009 cumulative % inhibition against 16 carbapenem-resistant Enterobacteriaceae from UTI.



Conclusions

- The combination of meropenem/RPX7009 demonstrated potent *in vitro* antibacterial activity against Enterobacteriaceae obtained from UTI and IAI in the USA (100% and 99.4% inhibited at ≤1 µg/mL, respectively) including isolates displaying carbapenem-resistance, an ESBL-phenotype or meropenem-non-susceptibility.
- The ability of RPX7009 to restore meropenem activity over meropenem alone was observed with each of the organism groups analyzed. Restoration of meropenem activity by RPX7009 was most apparent among the carbapenem-resistant Enterobacteriaceae and *E. coli* and *K. pneumoniae* isolates displaying meropenem-non-susceptibility.
- The potent *in vitro* activity of meropenem in combination with RPX7009 against Enterobacteriaceae, including activity against resistant organism groups warrants further investigation in difficult to treat serious infections where these resistant bacteria often occur. Clinical trials are in progress.

Disclosures

This project has been funded in whole or in part with federal funds from the Department of Health and Human Services; Office of the Assistant Secretary for Preparedness and Response; Biomedical Advanced Research and Development Authority (BARDA), under Contract No. HHSO100201400002 with Rempex Pharmaceuticals, a wholly-owned subsidiary of The Medicines Company. JMI Laboratories also received compensation fees for services with regards to the SENTRY Antimicrobial Surveillance Program platform and abstract/poster preparation and presentation.

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Presented at IDWeek 2015, October 7-11, 2015, San Diego, CA