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Meropenem-Vaborbactam Tested against Contemporary Gram-Negative Isolates Collected Worldwide during 2014, Including Carbapenem-Resistant, KPC-Producing, Multidrug-Resistant, and Extensively Drug-Resistant *Enterobacteriaceae*

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ABSTRACT We evaluated the activity of meropenem-vaborbactam against contemporary nonfastidious Gram-negative clinical isolates, including *Enterobacteriaceae* isolates with resistance phenotypes and carbapenemase genotypes. Meropenem-vaborbactam (inhibitor at 8 μg/ml) and comparators were susceptibility tested by reference broth microdilution methods against 14,304 Gram-negative clinical isolates collected worldwide during 2014. Carbapenemase-encoding genes were screened by PCR and sequencing. Meropenem-vaborbactam ($MIC_{50/90}$, $\leq$0.015/0.06 μg/ml) inhibited 99.1 and 99.3% of the 10,426 *Enterobacteriaceae* isolates tested at $\leq$1 and $\leq$2 μg/ml, respectively. Meropenem inhibited 97.3 and 97.7% of these isolates at the same concentrations. Against *Enterobacteriaceae* isolates displaying carbapenem-resistant *Enterobacteriaceae* (CRE) (n = 265), multidrug-resistant (MDR) (n = 1,210), and extensively drug-resistant (XDR) (n = 161) phenotypes, meropenem-vaborbactam displayed $MIC_{50/90}$ values of 0.5/32, 0.03/1, and 0.5/32 μg/ml, respectively, whereas meropenem activities were 16/>32, 0.06/32, and 0.5/32 μg/ml, respectively. Among all geographic regions, the highest meropenem-vaborbactam activities were observed for CRE and MDR isolates from the United States ($MIC_{50/90}$, 0.03/1 and 0.03/0.12 μg/ml, respectively). Meropenem-vaborbactam was very active against 135 KPC producers, and all isolates were inhibited by concentrations of $\leq$8 μg/ml (133 isolates by concentrations of $\leq$2 μg/ml). This combination had limited activity against isolates producing metallo-β-lactamases (including 25 NDM-1 and 16 VIM producers) and/or oxacillinases (27 OXA-48/OXA-163 producers) that were detected mainly in Asia-Pacific and some European countries. The activity of meropenem-vaborbactam was similar to that of meropenem alone against *Pseudomonas aeruginosa*, *Acinetobacter* spp., and *Stenotrophomonas maltophilia*. Meropenem-vaborbactam was active against contemporary *Enterobacteriaceae* isolates collected worldwide, and this combination demonstrated enhanced activity compared to those of meropenem and most comparator agents against CRE isolates and KPC producers, the latter of which are often MDR.

KEYWORDS meropenem-vaborbactam, CRE, KPC producers

Serious infections caused by Gram-negative bacilli are increasingly reported worldwide, and these organisms contribute to infection mortality rates that range from 30 to 70% (1). Bacterial species within this group are among the pathogens that are most difficult to treat, due to either intrinsic or acquired resistance mechanisms. Among

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Gram-negative species, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp. have been identified as organisms that should be monitored due to limited treatment options and patient management challenges for infections caused by these pathogens (2).

Pseudomonas aeruginosa and *Acinetobacter* spp. are intrinsically less susceptible to many antimicrobial agents (3). Additionally, these organisms can acquire or develop resistance at high frequencies through mutations and acquisition of foreign DNA (4). *Enterobacteriaceae* species are usually more susceptible, but the rise of *K. pneumoniae* and other organisms displaying multidrug-, extensively drug-, and pandrug-resistant (MDR, XDR, and PDR, respectively) phenotypes are threatening the current treatment protocols for serious infections caused by these species (2, 3, 5).

Carbapenems were often considered the last resource for treating serious infections caused by MDR organisms or isolates producing β-lactamases, but these agents are now often hydrolyzed by carbapenemases, which include KPC serine carbapenemases, OXA-48, and class B metallo-β-lactamases (MBLs) that have become disseminated worldwide. Isolates producing KPC enzymes have been detected in all but two states in the United States according to the Centers for Disease Control and Prevention (CDC) (http://www.cdc.gov/hai/organisms/cre/TrackingCRE.html), and isolates producing these enzymes have high prevalences in the New York City area (6) and Texas (7). KPC-producing isolates have also been reported in Germany, Poland, Belgium, Hungary, Croatia, and the United Kingdom. The corresponding genes are considered endemic in Greece and Italy (http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-carbapenemase-producing-bacteria-europe.pdf), and these enzymes are also very prevalent in other countries, such as Israel, China, and Brazil (5). KPC enzymes hydrolyze virtually all β-lactams, and isolates producing these enzymes are often MDR, and in some instances can be XDR or PDR (resistant to all available classes of antimicrobial agents).

Vaborbactam (formerly named RPX7009) is a cyclic boronic acid β-lactamase inhibitor that has activity against Ambler class A (including KPC) and C enzymes (8). This inhibitor has been combined with meropenem, and vaborbactam enhances the activity of this carbapenem against KPC-producing isolates compared to that of the β-lactam tested alone (9, 10).

In this study, we evaluated the activities of meropenem-vaborbactam and comparator antimicrobial agents against 14,304 nonfastidious Gram-negative bacillus clinical isolates collected in 82 hospitals worldwide during 2014. We also analyzed *Enterobacteriaceae* isolates according to their resistance phenotypes and carbapenemase genotypes.

RESULTS

Overall activity of meropenem-vaborbactam against isolates. Among 14,304 Gram-negative nonfastidious clinical isolates collected worldwide, 897 isolates were from the Asia-Pacific region (6.3% overall), 7,033 from Europe (49.2%), 716 from Latin America (5.0%), and 5,658 from the United States (39.6%). These isolates were collected from the following specimen sources: bloodstream infections (3,299 [23.1%]), pneumonia in hospitalized patients (4,174 [29.2%]), skin and skin structure infections (2,880 [20.1%]), urinary tract infections (2,603 [18.2%]), intra-abdominal infections (1,086 [7.6%]), and other, less prevalent or undetermined clinical specimen types (262 [1.8%]). This collection comprised all Gram-negative isolates collected in 82 hospitals as part of the SENTRY Antimicrobial Surveillance Program.

Overall, meropenem-vaborbactam (vaborbactam at 8 μg/ml; MIC_{50} and MIC_{90}, $\leq$0.015 and 0.06 μg/ml, respectively) (Table 1) inhibited 99.3% of all *Enterobacteriaceae* isolates at $\leq$2 μg/ml and 99.1% of the isolates at $\leq$1 μg/ml (EUCAST and CLSI susceptibility breakpoints, respectively, for meropenem tested alone [used for comparison purposes only]) (Table 1). Using a tentative breakpoint of 8 μg/ml, based on the proposed dosing scheme and modeled attainment for meropenem-vaborbactam (11), this combination inhibited 99.6% of the *Enterobacteriaceae* isolates (Table 1). Mero-

TABLE 1 Antimicrobial activity of meropenem-vaborbactam (inhibitor at fixed concentration of 8 μg/ml) against clinical isolates belonging to common Gram-negative species collected worldwide during 2014

Group or organism name	No. of isolates tested	No. of isolates (cumulative %) at meropenem-vaborbactam MIC (μg/ml) of:													MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
		≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32		
Enterobacteriaceae	10,426	6,171 (59.2)	2,828 (86.3)	947 (95.4)	190 (97.2)	80 (98.0)	66 (98.6)	47 (99.1)	19 (99.3)	24 (99.5)	12 (99.6)	8 (99.7)	14 (99.8)	20 (100.0)	≤0.015	0.06
Escherichia coli	4,238	3,916 (92.4)	274 (98.9)	32 (99.6)	2 (99.7)	4 (99.8)	3 (99.8)	4 (99.9)	1 (>99.9)	1 (>99.9)	0 (>99.9)	0 (>99.9)	1 (100.0)		≤0.015	≤0.015
Klebsiella pneumoniae	2,010	819 (40.7)	928 (86.9)	32 (88.5)	41 (90.5)	50 (93.0)	47 (95.4)	28 (96.8)	9 (97.2)	12 (97.8)	6 (98.1)	7 (98.5)	12 (99.1)	19 (100.0)	0.03	0.12
Klebsiella oxytoca	429	210 (49.0)	214 (98.8)	1 (99.1)	0 (99.1)	0 (99.1)	1 (99.3)	1 (99.5)	0 (99.5)	0 (99.5)	1 (99.8)	1 (100.0)			0.03	0.03
Enterobacter cloacae species complex	950	626 (65.9)	281 (95.5)	13 (96.8)	9 (97.8)	4 (98.2)	4 (98.6)	4 (99.1)	2 (99.3)	6 (99.9)	1 (100.0)				≤0.015	0.03
Enterobacter aerogenes	355	145 (40.8)	195 (95.8)	7 (97.7)	1 (98.0)	2 (98.6)	2 (99.2)	2 (99.7)	1 (100.0)						0.03	0.03
Citrobacter freundii species complex	276	199 (72.1)	65 (95.7)	3 (96.7)	2 (97.5)	0 (97.5)	1 (97.8)	0 (97.8)	3 (98.9)	1 (99.3)	2 (100.0)				≤0.015	0.03
Citrobacter koseri	194	174 (89.7)	20 (100.0)												≤0.015	0.03
Proteus mirabilis	525	4 (0.8)	148 (29.0)	269 (80.2)	85 (96.4)	9 (98.1)	6 (99.2)	4 (100.0)							0.06	0.12
Indole-positive *Proteeae* spp.	585	2 (0.3)	176 (30.4)	358 (91.6)	37 (97.9)	8 (99.3)	0 (99.3)	2 (99.7)	1 (99.8)	0 (99.8)	0 (99.8)	0 (99.8)	0 (99.8)	1 (100.0)	0.06	0.06
Serratia marcescens	666	6 (0.9)	435 (66.2)	199 (96.1)	12 (97.9)	3 (98.3)	2 (98.6)	1 (98.8)	1 (98.9)	4 (99.5)	2 (99.8)	0 (99.8)	1 (100.0)		0.03	0.06
Pseudomonas aeruginosa	2,604	41 (1.6)	78 (4.6)	245 (14.0)	442 (31.0)	424 (47.2)	438 (64.1)	234 (73.0)	159 (79.1)	185 (86.3)	138 (91.6)	125 (96.4)	52 (98.3)	43 (100.0)	0.5	8
Acinetobacter spp.	708		6 (0.8)	16 (3.1)	64 (12.1)	65 (21.3)	57 (29.4)	37 (34.6)	12 (36.3)	9 (37.6)	15 (39.7)	47 (46.3)	124 (63.8)	256 (100.0)	32	>32
Stenotrophomonas maltophilia	353	1 (0.3)	2 (0.8)	1 (1.1)	2 (1.7)	3 (2.5)	1 (2.8)	0 (2.8)	0 (2.8)	2 (3.4)	1 (3.7)	15 (7.9)	40 (19.3)	285 (100.0)	>32	>32

penem alone (MIC_{50} and MIC_{90}, 0.03 and 0.06 μg/ml) inhibited 97.7 and 97.3% of the isolates at the current EUCAST and CLSI susceptibility breakpoints of ≤2 and ≤1 μg/ml, respectively (Table 2). Susceptibility rates for the comparator antimicrobial agents tested against *Enterobacteriaceae* isolates ranged from 79.7 to 99.5% and from 78.2 to 96.2% by applying the CLSI and EUCAST breakpoints, respectively (Table 2). The lowest susceptibility rates were noted for levofloxacin and the highest for tigecycline by applying the U.S. FDA breakpoint (Table 2).

Meropenem-vaborbactam (MIC_{50} and MIC_{90}, ≤0.015 and ≤0.015 μg/ml) (Table 1) inhibited all but one *Escherichia coli* isolate ($n = 4,238$) at ≤4 μg/ml, and ≥99.9% of the isolates were inhibited by this carbapenem–β-lactamase inhibitor combination at ≤2 or ≤1 μg/ml. Selected comparator agents displayed good activity against *E. coli* isolates, and meropenem (99.8% susceptible [CLSI interpretation]), amikacin (99.6% susceptible [CLSI]), imipenem (99.7% susceptible [CLSI]), colistin (99.5% susceptible [EUCAST]), and tigecycline (100.0% susceptible [U.S. FDA]) inhibited >90% of the isolates at current breakpoints (data not shown). A total of 96.8 and 97.2% of the *K. pneumoniae* isolates ($n = 2,010$) were inhibited by meropenem-vaborbactam (MIC_{50} and MIC_{90}, 0.03 and 0.12 μg/ml) at ≤1 and ≤2 μg/ml, respectively, and 98.1% of the isolates tested were inhibited by this combination at ≤8 μg/ml. Meropenem (MIC_{50} and MIC_{90}, 0.03 and 4 μg/ml [data not shown]) inhibited 89.0, 89.9, and 92.6% of these isolates at the same concentrations. Other comparator agents inhibiting >90.0% of isolates at current breakpoints were limited to amikacin (92.6% susceptible [CLSI criteria]), tigecycline (99.9% susceptible [U.S. FDA]), imipenem (90.3% susceptible [EUCAST]), and colistin (94.2% susceptible [EUCAST]) (data not shown).

The activity of meropenem-vaborbactam (MIC_{90} range, 0.03 to 0.12 μg/ml) (Table 1) was elevated against other *Enterobacteriaceae* species, and this combination inhibited 99.5% of *Klebsiella oxytoca* isolates ($n = 429$), 99.3% of *Enterobacter cloacae* isolates ($n = 950$), 98.9% of *Citrobacter freundii* isolates ($n = 276$), 99.8% of the indole-positive *Proteeae* sp. isolates ($n = 585$), and 98.9% of *Serratia marcescens* isolates ($n = 666$) at ≤2 μg/ml. Meropenem-vaborbactam inhibited 99.8 to 100% of the isolates belonging to these species at ≤8 μg/ml (Table 1). All *Enterobacter aerogenes* ($n = 355$), *Citrobacter koseri* ($n = 194$), and *Proteus mirabilis* ($n = 525$) isolates were inhibited by meropenem-vaborbactam at ≤2 μg/ml (Table 1).

The activity of meropenem-vaborbactam was similar to that of meropenem alone (MIC_{50} and MIC_{90}, 0.5 and 8 μg/ml, respectively, for both) (Tables 1 and 2) for 2,604 *P. aeruginosa* isolates tested. The presence of vaborbactam slightly enhanced the activity of meropenem: 78.4% of isolates were inhibited by meropenem alone at ≤2 μg/ml (CLSI/EUCAST susceptibility breakpoint), and 79.1% were inhibited by meropenem-vaborbactam at the same concentration (Tables 1 and 2). Additionally, this combination inhibited 91.6% of the *P. aeruginosa* isolates tested at ≤8 μg/ml.

As observed with meropenem alone (MIC_{50} and MIC_{90}, >8 and >8 μg/ml for both groups [data not shown]), meropenem-vaborbactam had limited activity against *Acinetobacter* spp. (MIC_{50} and MIC_{90}, 32 and >32 μg/ml) and *Stenotrophomonas maltophilia* (MIC_{50} and MIC_{90}, >32 and >32 μg/ml) (Table 1). These isolates were also resistant to other β-lactams tested (data not shown).

Meropenem-vaborbactam testing against CRE. A total of 265 carbapenem-resistant *Enterobacteriaceae* (CRE) isolates were observed in hospitals worldwide during 2014, including 167 in Europe (3.2% of isolates from this region), 65 (1.6%) in the United States, 24 (4.8%) in Latin America, and 9 (1.5%) in Asia-Pacific countries. These isolates were mostly *K. pneumoniae* (211/265 isolates [79.6%]), but there were also isolates of *Enterobacter cloacae* (18 isolates), *Serratia marcescens* (10), *E. coli* (9), *Citrobacter freundii* (7), *Enterobacter aerogenes* (3), *K. oxytoca* (4), *Enterobacter kobei* (1), *Hafnia alvei* (1), and *Providencia stuartii* (1).

Meropenem alone displayed very limited activity against CRE isolates (MIC_{50} and MIC_{90}, 16 and >32 μg/ml), and only 1.9 and 7.9% of these isolates were categorized as susceptible to this carbapenem by applying the CLSI and EUCAST criteria, respectively

TABLE 2 Activities of meropenem-vaborbactam (inhibitor at fixed concentration of 8 μg/ml) and comparator antimicrobial agents against Gram-negative isolates collected during 2014

Bacterial group (*n*) and antimicrobial agent	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	MIC range (μg/ml)	Susceptibility using CLSI breakpoint[a]			Susceptibility using EUCAST breakpoint[a]		
				% S	% I	% R	% S	% I	% R
Enterobacteriaceae (10,426)									
Meropenem-vaborbactam	≤0.015	0.06	≤0.015–>32						
Meropenem	0.03	0.06	≤0.015–>32	97.3	0.3	2.3	97.7	0.8	1.5
Aztreonam	≤0.12	>16	≤0.12–>16	81.6	1.9	16.5	78.9	2.7	18.4
Cefepime	≤0.5	16	≤0.5–>16	85.2	3.3[b]	11.5	83.2	3.6	13.2
Ceftazidime	0.25	>16	≤0.12–>16	83.1	2.7	14.3	79.2	3.9	16.9
Piperacillin-tazobactam	2	32	≤0.5–>64	88.1	4.6	7.3	84.2	3.8	11.9
Amikacin	2	4	≤0.25–>32	98.1	1.1	0.8	96.7	1.4	1.9
Colistin	≤0.5	>8	≤0.5–>8				79.4		20.6
Levofloxacin	≤0.12	>4	≤0.12–>4	79.7	1.9	18.4	78.2	1.5	20.3
Tigecycline[c]	0.12	0.5	≤0.015–4	99.5	0.5	0.0	96.2	3.2	0.5
CRE (265)									
Meropenem-vaborbactam	0.5	32	≤0.015–>32						
Meropenem	16	>32	0.25–>32	1.9	6.0	92.1	7.9	32.1	60.0
Aztreonam	>16	>16	≤0.12–>16	9.1	1.5	89.4	7.2	1.9	90.9
Cefepime	>16	>16	≤0.5–>16	7.2	5.3[b]	87.5	5.7	5.3	89.1
Ceftazidime	>16	>16	0.25–>16	6.4	1.5	92.1	5.7	0.8	93.6
Piperacillin-tazobactam	>64	>64	1–>64	3.0	2.3	94.7	2.6	0.4	97.0
Amikacin	16	>32	0.5–>32	56.2	29.8	14.0	40.8	15.5	43.8
Colistin	≤0.5	>8	≤0.5–>8				70.3		29.7
Levofloxacin	>4	>4	≤0.12–>4	18.9	1.9	79.2	15.9	3.0	81.1
Tigecycline[c]	0.25	1	0.06–4	99.2	0.8	0.0	92.5	6.8	0.8
KPC producers (135)									
Meropenem-vaborbactam	0.12	0.5	≤0.015–8						
Meropenem	>32	>32	1–>32	0.7	4.4	94.8	5.2	15.6	79.3
Aztreonam	>16	>16	2–>16	0.7	0.7	98.5	0.0	0.7	99.3
Cefepime	>16	>16	≤0.5–>16	1.5	3.0[b]	95.6	1.5	0.7	97.8
Ceftazidime	>16	>16	0.25–>16	1.5	0.7	97.8	0.7	0.7	98.5
Piperacillin-tazobactam	>64	>64	2–>64	0.7	0.7	98.5	0.7	0.0	99.3
Amikacin	32	>32	0.5–>32	39.3	48.9	11.9	26.7	12.6	60.7
Colistin	≤0.5	>8	≤0.5–>8				72.4		27.6
Levofloxacin	>4	>4	≤0.12–>4	10.4	1.5	88.1	7.5	3.0	89.6
Tigecycline[c]	0.25	1	0.06–2	100.0	0.0	0.0[b]	96.3	3.7	0.0
Non-KPC-producing CRE (129)									
Meropenem-vaborbactam	4	>32	≤0.015–>32						
Meropenem	8	>32	0.25–>32	3.1	7.0	89.9	10.1	49.6	40.3
Aztreonam	>16	>16	≤0.12–>16	17.8	2.3	79.8	14.7	3.1	82.2
Cefepime	>16	>16	≤0.5–>16	13.2	7.8[b]	79.1	10.1	10.1	79.8
Ceftazidime	>16	>16	0.25–>16	11.6	2.3	86.0	10.9	0.8	88.4
Piperacillin-tazobactam	>64	>64	1–>64	5.4	3.9	90.7	4.7	0.8	94.6
Amikacin	8	>32	0.5–>32	73.6	10.1	16.3	55.0	18.6	26.4
Colistin	1	>8	≤0.5–>8				68.0		32.0
Levofloxacin	>4	>4	≤0.12–>4	27.9	2.3	69.8	24.8	3.1	72.1
Tigecycline[c]	0.25	2	0.06–4	98.4	1.6	0.0[b]	88.4	10.1	1.6
Carbapenemase-negative isolates (63)									
Meropenem-vaborbactam	1	4	≤0.015–32						
Meropenem	4	16	0.25–>32	3.2	4.8	92.1	7.9	74.6	17.5
Aztreonam	>16	>16	≤0.12–>16	6.3	3.2	90.5	6.3	0.0	93.7
Cefepime	>16	>16	≤0.5–>16	12.7	6.3[b]	81.0	9.5	7.9	82.5
Ceftazidime	>16	>16	0.25–>16	7.9	0.0	92.1	7.9	0.0	92.1
Piperacillin-tazobactam	>64	>64	1–>64	9.5	6.3	84.1	7.9	1.6	90.5
Amikacin	8	32	1–>32	77.8	14.3	7.9	58.7	19.0	22.2
Colistin	1	>8	≤0.5–>8				67.7		32.3
Levofloxacin	>4	>4	≤0.12–>4	25.4	0.0	74.6	23.8	1.6	74.6
Tigecycline[c]	0.25	1	0.06–2	100.0	0.0	0.0	93.7	6.3	0.0

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TABLE 2 (Continued)

Bacterial group (*n*) and antimicrobial agent	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)	MIC range (μg/ml)	Susceptibility using CLSI breakpoint[a]			Susceptibility using EUCAST breakpoint[a]		
				% S	% I	% R	% S	% I	% R
MDR isolates (1,210)									
Meropenem-vaborbactam	0.03	1	≤0.015–>32						
Meropenem	0.06	32	≤0.015–>32	77.7	2.5	19.8	80.2	6.8	13.1
Aztreonam	>16	>16	≤0.12–>16	17.8	3.0	79.3	11.7	6.1	82.2
Cefepime	>16	>16	≤0.5–>16	21.6	9.7[b]	68.7	17.0	8.7	74.4
Ceftazidime	>16	>16	≤0.12–>16	18.3	8.9	72.8	11.7	6.5	81.7
Piperacillin-tazobactam	64	>64	≤0.5–>64	36.6	20.6	42.8	28.7	7.9	63.4
Amikacin	4	32	≤0.25–>32	84.2	8.5	7.3	75.5	8.7	15.8
Colistin	≤0.5	>8	≤0.5–>8				73.7		26.3
Levofloxacin	>4	>4	≤0.12–>4	14.6	7.5	77.9	12.1	2.5	85.4
Tigecycline[c]	0.25	1	0.03–4	97.9	2.1	0.0	90.6	7.3	2.1
XDR isolates (161)									
Meropenem-vaborbactam	0.5	32	≤0.015–>32						
Meropenem	16	>32	≤0.015–>32	13.0	6.8	80.1	19.9	28.6	51.6
Aztreonam	>16	>16	≤0.12–>16	7.5	1.2	91.3	5.6	1.9	92.5
Cefepime	>16	>16	≤0.5–>16	4.3	3.7[b]	91.9	3.1	3.7	93.2
Ceftazidime	>16	>16	0.25–>16	4.3	1.9	93.8	3.1	1.2	95.7
Ceftriaxone	>8	>8	2–>8	0.0	1.2	98.8	0.0	1.2	98.8
Piperacillin-tazobactam	>64	>64	≤0.5–>64	2.5	5.6	91.9	2.5	0.0	97.5
Amikacin	16	>32	0.5–>32	58.4	20.5	21.1	42.2	16.1	41.6
Colistin	4	>8	≤0.5–>8				45.3		54.7
Levofloxacin	>4	>4	0.25–>4	0.6	5.0	94.4	0.6	0.0	99.4
Tigecycline[c]	0.5	2	0.06–4	96.3	3.7	0.0	88.2	8.1	3.7
P. aeruginosa (2,604)									
Meropenem-vaborbactam	0.5	8	≤0.015–>32						
Meropenem	0.5	8	≤0.015–>32	78.4	7.0	14.6	78.4	12.9	8.7
Aztreonam	8	>16	≤0.12–>16	59.6	14.8	25.6	4.6	69.7	25.6
Cefepime	2	16	≤0.5–>16	83.7	9.1	7.2	83.7		16.3
Ceftazidime	2	>16	≤0.12–>16	79.0	5.6	15.4	79.0		21.0
Piperacillin-tazobactam	4	>64	≤0.5–>64	79.2	10.3	10.5	79.2		20.8
Amikacin	2	16	≤0.25–>32	94.0	2.2	3.8	89.6	4.5	6.0
Colistin	2	2	≤0.5–4	98.3	1.7	0.0	100.0		0.0
Levofloxacin	0.5	>4	≤0.12–>4	73.4	5.9	20.7	65.3	8.1	26.6
Tigecycline[c]	4	8	0.06–>16						

[a]As published by CLSI (13) and EUCAST (14). S, susceptible; I, intermediate; R, resistant.
[b]Intermediate was interpreted as susceptible but dose dependent.
[c]Breakpoints for the CLSI column were from the U.S. FDA package insert (December 2014 revision).

(Table 3). Meropenem-vaborbactam (MIC_{50} and MIC_{90}, 0.5 and 32 μg/ml) inhibited 65.3 and 70.9% of the CRE isolates at ≤1 and ≤2 μg/ml, respectively, and 84.2% of these isolates were inhibited at ≤8 μg/ml (Table 3). This combination was very active against U.S. (MIC_{50} and MIC_{90}, 0.03 and 1 μg/ml) and Latin American (MIC_{50} and MIC_{90}, 0.12 and 4 μg/ml) CRE isolates, but limited activity was noted against isolates from the Asia-Pacific region (MIC_{50}, 32 μg/ml) (Table 3).

CRE isolates were highly resistant to comparator agents, and the highest susceptibility rates were observed for amikacin (56.2 and 40.8% susceptible by CLSI and EUCAST criteria, respectively), colistin (70.3% susceptible by EUCAST criteria), and tigecycline (99.2 and 92.5% susceptible by U.S. FDA and EUCAST criteria) (Table 2). Meropenem-vaborbactam was the most active β-lactam agent tested against these isolates (Table 2).

Meropenem-vaborbactam testing against MDR and XDR *Enterobacteriaceae*. Meropenem-vaborbactam (MIC_{50} and MIC_{90}, 0.03 and 1 μg/ml) was very active against 1,210 *Enterobacteriaceae* isolates displaying an MDR phenotype (11.6% of all *Enterobacteriaceae* isolates), and the activity of this combination was higher than those of meropenem ($MIC_{50/90}$, 0.06/32 μg/ml) and other comparators (Table 2). Meropenem-vaborbactam inhibited 68.9 and 74.5% of the 161 XDR isolates (1.5% of all *Enterobacteriaceae* isolates) at ≤1 and ≤2 μg/ml, respectively, whereas meropenem inhibited

TABLE 3 Antimicrobial activity of meropenem with or without vaborbactam (at a fixed concentration of 8 μg/ml) against groups of clinical *Enterobacteriaceae* isolates with different resistance phenotypes and genotypes, collected worldwide during 2014

Organism group (no. of isolates tested) and antimicrobial agent	No. of isolates (cumulative %) from all regions at meropenem-vaborbactam MIC (μg/ml) of:													$MIC_{50/90}$ (μg/ml) by region, with no. (%) of isolates for each organism group[a]				
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32	Overall	Asia-Pacific	Europe	Latin America	United States
CRE (265)														265 (2.5)	9 (1.5)	167 (3.2)	24 (4.8)	65 (1.6)
Meropenem-vaborbactam	36 (13.6)	20 (21.1)	7 (23.8)	21 (31.7)	29 (42.6)	34 (55.5)	26 (65.3)	15 (70.9)	23 (79.6)	12 (84.2)	8 (87.2)	14 (92.5)	20 (100.0)	0.5/32	32/NA	1/32	0.12/4	0.03/1
Meropenem					1 (0.4)	1 (0.8)	3 (1.9)	16 (7.9)	48 (26.0)	37 (40.0)	34 (52.8)	29 (63.8)	96 (100.0)	16/>32	>32/NA	16/>32	32/>32	16/>32
Carbapenem-resistant *K. pneumoniae* (211)														211 (10.5)	9 (4.5)	132 (13.8)	24 (15.4)	46 (6.6)
Meropenem-vaborbactam	29 (13.7)	17 (21.8)	6 (24.6)	20 (34.1)	28 (47.4)	27 (60.2)	21 (70.1)	8 (73.9)	11 (79.1)	6 (82.0)	7 (85.3)	12 (91.0)	19 (100.0)	0.5/32	32/NA	0.5/>32	0.12/4	0.03/1
Meropenem								8 (3.8)	28 (17.1)	27 (29.9)	28 (43.1)	26 (55.5)	94 (100.0)	32/>32	>32/NA	32/>32	32/>32	16/>32
KPC producers (135)														135 (1.3)	0 (0)	63 (1.2)	21 (4.2)	51 (1.2)
Meropenem-vaborbactam	35 (25.9)	19 (40.0)	7 (45.2)	19 (59.3)	24 (77.0)	19 (91.1)	7 (96.3)	3 (98.5)	1 (99.3)	1 (100.0)				0.12/0.5	NA	0.25/0.5	0.12/2	0.03/0.5
Meropenem							1 (0.7)	6 (5.2)	11 (13.3)	10 (20.7)	21 (36.3)	16 (48.1)	70 (100.0)	>32/>32	NA	>32/>32	>32/>32	16/>32
OXA-48-like-producers (25)														25 (0.2)	0 (0)	23 (0.4)	1 (0.2)	1 (<0.1)
Meropenem-vaborbactam						2 (8.0)	0 (8.0)	0 (8.0)	3 (20.0)	5 (40.0)	5 (60.0)	5 (80.0)	5 (100.0)	16/>32	NA	16/>32	8[b]	0.5[b]
Meropenem						1 (4.0)	0 (4.0)	1 (8.0)	2 (16.0)	5 (36.0)	5 (56.0)	6 (80.0)	5 (100.0)	16/>32	NA	16/>32	8[b]	2[b]
MBL producers (41)														41 (0.4)	7 (1.2)	32 (0.6)	1 (0.2)	1 (<0.1)
Meropenem-vaborbactam							2 (4.9)	4 (14.6)	5 (26.8)	5 (39.0)	2 (43.9)	8 (63.4)	15 (100.0)	32/>32	32/NA	32/>32	4[b]	>32[b]
Meropenem							1 (2.4)	5 (14.6)	6 (29.3)	4 (39.0)	2 (43.9)	5 (56.1)	18 (100.0)	32/>32	>32/NA	16/>32	2[b]	>32[b]
Carbapenemase-negative isolates (63)														63 (0.6)	2 (0.3)	48 (0.9)	1 (0.2)	12 (0.3)
Meropenem-vaborbactam	1 (1.6)	1 (3.2)	0 (3.2)	2 (6.3)	5 (14.3)	13 (34.9)	17 (61.9)	7 (73.0)	14 (95.2)	1 (96.8)	1 (98.4)	1 (100.0)		1/4	16/NA	1/4	1[b]	0.5/4
Meropenem					1 (1.6)	0 (1.6)	1 (3.2)	3 (7.9)	29 (54.0)	18 (82.5)	6 (92.1)	2 (95.2)	3 (100.0)	4/16	8/NA	4/16	8[b]	4/32
MDR isolates (1,210)														1,210 (11.6)	65 (11.1)	714 (13.7)	116 (23.4)	315 (7.6)
Meropenem-vaborbactam	499 (41.2)	295 (65.6)	106 (74.4)	65 (79.8)	59 (84.6)	54 (89.1)	40 (92.4)	16 (93.7)	22 (95.5)	12 (96.5)	8 (97.2)	14 (98.3)	20 (100.0)	0.03/1	≤0.015/16	0.03/1	0.03/0.5	0.03/0.12
Meropenem	214 (17.7)	312 (43.5)	229 (62.4)	83 (69.3)	30 (71.7)	35 (74.6)	37 (77.7)	30 (80.2)	46 (84.0)	36 (86.9)	34 (89.8)	28 (92.1)	96 (100.0)	0.06/32	0.03/32	0.06/32	0.03/>32	0.06/16
XDR isolates (161)														161 (1.5)	9 (1.5)	94 (1.8)	22 (4.4)	36 (0.9)
Meropenem-vaborbactam	19 (11.8)	18 (23.0)	9 (28.6)	10 (34.8)	15 (44.1)	17 (54.7)	23 (68.9)	9 (74.5)	6 (78.3)	6 (82.0)	5 (85.1)	10 (91.3)	14 (100.0)	0.5/32	32/NA	1/>32	0.12/2	0.03/0.5
Meropenem	1 (0.6)	4 (3.1)	5 (6.2)	6 (9.9)	2 (11.2)	2 (12.4)	1 (13.0)	11 (19.9)	24 (34.8)	22 (48.4)	18 (59.6)	15 (68.9)	50 (100.0)	16/>32	>32/NA	8/>32	32/>32	16/>32

[a]Percentages of carbapenem-resistant *K. pneumoniae* were calculated using the number of *K. pneumoniae* isolates. The remaining percentages were calculated using the total number of *Enterobacteriaceae* isolates. NA, not applicable.

[b]The value displayed is the actual MIC for the isolate.

only 13.0 and 19.9% of these isolates at the same MIC values. Additionally, meropenem-vaborbactam inhibited 82.0% of the XDR *Enterobacteriaceae* isolates at ≤8 μg/ml (Table 3). The activity of meropenem-vaborbactam was elevated against XDR isolates from U.S. (MIC_{50} and MIC_{90}, 0.03 and 0.5 μg/ml) and Latin American (MIC_{50} and MIC_{90}, 0.12 and 2 μg/ml) hospitals, the latter of which displayed the highest XDR rate among the four continents (4.4% versus 0.9 to 1.8% for the others) (Table 3).

Only one *Enterobacteriaceae* isolate displayed a PDR phenotype (<0.1%), and this isolate had elevated MIC values for meropenem alone and meropenem-vaborbactam (MIC, >32 μg/ml). This isolate was a VIM-1-producing *Providencia stuartii* isolate recovered from the peritoneal fluid of a patient hospitalized in Greece.

Meropenem-vaborbactam testing against carbapenemase-producing *Enterobacteriaceae*. A total of 264 CRE isolates were screened for the presence of genes encoding carbapenemases, and 201 (75.8%) isolates carried these resistance genes. One isolate could not be recovered for further testing. A total of 135 (50.9% of the CRE isolates; 1.3% of the overall population) isolates carried bla_{KPC} genes, including 60 bla_{KPC-2}, 74 bla_{KPC-3}, and 1 bla_{KPC-4} gene (Table 4). KPC-producing isolates were detected in five European countries (63/166 CRE isolates), namely, Greece (16/21 CRE isolates), Italy (37/38 CRE isolates), Israel (4/4 CRE isolates), Poland (5/55 CRE isolates), and the United Kingdom (1/2 CRE isolates). These isolates were also found in the United States (51/65 CRE isolates), Brazil (15/15 CRE isolates), and Argentina (6/7 CRE isolates).

Genes encoding MBLs were detected among 41 isolates (15.5% of CRE isolates; 0.4% of the overall collection), with the gene encoding NDM-1 being the most common (25 isolates), followed by bla_{VIM-1} (11 isolates), bla_{VIM-4} (4 isolates), and bla_{VIM-2} (1 isolate). MBL-producing isolates belonged to the follow bacterial species: *C. freundii* (5 isolates), *E. cloacae* (7 isolates), *K. oxytoca* (2 isolates), *K. pneumoniae* (25 isolates), *P. stuartii* (1 isolate), and *S. marcescens* (1 isolate). These isolates were collected in hospitals located in Europe (32 isolates), Asia Pacific (7 isolates), Latin America (1 isolate), and the United States (1 isolate). NDM-1 was detected among isolates from Malaysia (5 isolates), Thailand (2 isolates), Poland (7 isolates), Romania (2 isolates), Russia (3 isolates), Turkey (2 isolates), Ukraine (2 isolates), Mexico (1 isolate), and the United States (1 isolate).

OXA-48-like genes were detected among 27 isolates (10.2% of CRE isolates; 0.3% of the overall collection), 2 of which also carried VIM-1. OXA-48 genes were detected mainly in *K. pneumoniae* isolates (17/27 isolates) and were isolated primarily from European countries (25/27 isolates [1 each from Germany, Ireland, Romania, Ukraine, and Sweden, 11 from Turkey, and 9 from Russia]). The two remaining isolates were observed in Argentina (OXA-163; *K. pneumoniae*) and the United States (*E. cloacae* isolate from Rochester, NY).

Meropenem-vaborbactam (MIC_{50} and MIC_{90}, 0.12 and 0.5 μg/ml) exhibited good activity against KPC-producing isolates. All other β-lactam agents displayed limited activity against KPC-producing isolates, and the most active non-β-lactam agents against these isolates were tigecycline (100.0 and 96.3% susceptible by applying U.S. FDA and EUCAST breakpoints, respectively) and colistin (72.4% susceptible by using EUCAST breakpoints) (Table 2).

All but two KPC-producing isolates were inhibited by meropenem-vaborbactam at ≤2 μg/ml. The other two isolates displayed MIC values of 4 and 8 μg/ml, were *K. pneumoniae* isolates from Brazil and Italy, and displayed resistant MIC values for meropenem (>32 μg/ml for both), imipenem (>8 μg/ml for both), doripenem (>4 μg/ml for both), levofloxacin (>4 μg/ml for both), and gentamicin (≥8 μg/ml). The isolate from Brazil was colistin resistant (MIC, >8 μg/ml [EUCAST breakpoint]) but was susceptible to amikacin (MIC, 8 μg/ml), whereas the isolate from Italy was susceptible to colistin (MIC, 0.5 μg/ml) and resistant to amikacin (MIC, >32 μg/ml). Both isolates displayed low tigecycline MIC results (0.5 and 1 μg/ml). These isolates were recovered from wound and blood specimens from 62- and 56-year-old male patients hospitalized in renal and hematology wards, respectively.

TABLE 4 Activity of meropenem with or without vaborbactam (at a fixed concentration of 8 μg/ml) against isolates carrying carbapenemases

Region (no. of isolates carrying carbapenemases)	Carbapenemase group (no. of isolates)	Meropenem-vaborbactam		Meropenem (μg/ml)		Carbapenemase(s) detected (no. of isolates)	Organism(s) (no. of isolates)	Country or countries (no. of isolates)
		MIC_{50} (μg/ml)[a]	MIC_{90} (μg/ml)[b]	MIC_{50} (μg/ml)[a]	MIC_{90} (μg/ml)[b]			
All regions (202)	KPC (135)	0.12	0.5	>32	>32	KPC-2 (60), KPC-3 (74), KPC-4 (1)	*Citrobacter freundii* (1), *Escherichia coli* (5), *Enterobacter cloacae* species complex (3), *Klebsiella oxytoca* (2), *K. pneumoniae* (123), *Serratia marcescens* (1)	Argentina (6), Brazil (15), Greece (16), Israel (4), Italy (37), Poland (5), United Kingdom (1), U.S. (51)
	OXA-48-like (25, plus 2 carrying bla_{VIM-1} that were not included in the MIC data)	16	>32	16	>32	OXA-48 (26 [2 carrying bla_{VIM-1}]), OXA-163 (1)	*Citrobacter freundii* (1), *Escherichia coli* (1), *Enterobacter cloacae* species complex (2), *Klebsiella oxytoca* (1), *K. pneumoniae* (17), *Serratia marcescens* (5)	Argentina (1), Germany (1), Ireland (1), Romania (1), Russia (9), Sweden (1), Turkey (11), Ukraine (1), U.S. (1)
	MBL (41)	32	>32	32	>32	NDM-1 (25), VIM-1 (11), VIM-2 (1), VIM-4 (4)	*Citrobacter freundii* (5), *Enterobacter cloacae* species complex (7), *Klebsiella oxytoca* (2), *K. pneumoniae* (25), *Providencia stuartii* (1), *Serratia marcescens* (1)	Greece (5), Malaysia (5), Mexico (1), Poland (13), Portugal (1), Romania (2), Russia (3), Spain (1), Thailand (2), Turkey (5), Ukraine (2), U.S. (1)
U.S. (53)	KPC (51)	0.03	0.5	16	>32	KPC-2 (19), KPC-3 (31), KPC-4 (1)	*Citrobacter freundii* (1), *Escherichia coli* (5), *Enterobacter cloacae* (1), *Klebsiella oxytoca* (2), *K. pneumoniae* (41), *Serratia marcescens* (1)	U.S. (51)
	OXA-48-like (1)	0.5	NA	2	NA	OXA-48 (1)	*Enterobacter cloacae* species complex (1)	U.S. (1)
	MBL (1)	>32	NA	>32	NA	NDM-1 (1)	*K. pneumoniae* (1)	U.S. (1)
Europe (118)	KPC (63)	0.25	0.5	>32	>32	KPC-2 (21), KPC-3 (42)	*Enterobacter cloacae* species complex (2), *Klebsiella pneumoniae* (61)	Greece (16), Israel (4), Italy (37), Poland (5), United Kingdom (1)
	OXA-48-like (23, plus 2 carrying bla_{VIM-1} that were not included in the MIC data)	16	>32	16	>32	OXA-48 (25 [2 carrying bla_{VIM-1}])	*Citrobacter freundii* species complex (1), *Escherichia coli* (1), *Enterobacter cloacae* species complex (1), *Klebsiella oxytoca* (1), *K. pneumoniae* (16), *Serratia marcescens* (5)	Germany (1), Ireland (1), Romania (1), Russia (9), Sweden (1), Turkey (11), Ukraine (1)
	MBL (32)	32	>32	16	>32	NDM-1 (16), VIM-1 (11), VIM-2 (1), VIM-4 (4)	*Citrobacter freundii* species complex (5), *Enterobacter cloacae* species complex (7), *Klebsiella oxytoca* (2), *K. pneumoniae* (16), *Providencia stuartii* (1), *Serratia marcescens* (1)	Greece (5), Poland (13), Portugal (1), Romania (2), Russia (3), Spain (1), Turkey (5), Ukraine (2)
Latin America (23)	KPC (21)	0.12	2	>32	>32	KPC-2 (20), KPC-3 (1)	*K. pneumoniae* (21)	Argentina (6), Brazil (15)
	OXA-48-like (1)	8	NA	8	NA	OXA-163 (1)	*K. pneumoniae* (1)	Argentina (1)
	MBL (1)	4	NA	2	NA	NDM-1 (1)	*K. pneumoniae* (1)	Mexico (1)
Asia-Pacific (7)	MBL (7)	32	NA	>32	NA	NDM-1 (7)	*K. pneumoniae* (7)	Malaysia (5), Thailand (2)

[a]If only 1 isolate was detected, the MIC value is displayed.
[b]NA, not available for groups with <10 isolates.

The activity of meropenem-vaborbactam against isolates harboring bla_{OXA-48}-like genes ($MIC_{50/90}$, 16/>32 μg/ml) and/or MBL-encoding genes ($MIC_{50/90}$, 32/>32 μg/ml) was similar to that of meropenem (Table 4).

A total of 63 isolates yielded negative results for the carbapenemase-encoding genes tested, including less frequent genes. These isolates were mainly *K. pneumoniae* isolates from Europe (48/63 isolates [76.2%]) (Table 3). Meropenem-vaborbactam ($MIC_{50/90}$, 1/4 μg/ml) was 4-fold more active than meropenem alone ($MIC_{50/90}$, 4/16 μg/ml) against these isolates (Table 3), which were also resistant to most comparator agents tested (Table 2).

DISCUSSION

In this study, we evaluated the activities of meropenem-vaborbactam and comparator antimicrobial agents against a large collection of clinical isolates including 10,426 *Enterobacteriaceae* isolates. These isolates represent all nonfastidious Gram-negative organisms collected during 2014 as part of a large surveillance network collecting consecutive isolates per infection type; thus, rates for different phenotypes and genotypes are likely representative of the overall prevalences.

Among *Enterobacteriaceae* isolates, the worldwide rates for CRE, MDR, and XDR isolates were 2.5, 11.6, and 1.5%, respectively. Although variations were observed in the geographic regions analyzed, these isolates were detected in all four regions, highlighting the importance of developing therapeutic options that are efficacious against these difficult-to-treat organisms.

KPC is still the most common carbapenemase (1.3% of the overall population; 50.9% of CRE isolates) detected worldwide, and in certain surveyed countries, such as the United States, Brazil, Italy, and Argentina, KPC producers are the dominant population among CRE isolates. Vaborbactam is a potent KPC inhibitor, and in previous studies, the combination of this inhibitor with various carbapenems reduced the MIC values 16- to >64-fold for tested KPC-producing isolates (8). When vaborbactam was tested in combination with biapenem against 300 *Enterobacteriaceae* isolates, this combination was very active against KPC-producing isolates, but the activity of this combination was variable against isolates with a combination of extended-spectrum β-lactamase (ESBL) or derepressed AmpC genes and intrinsic resistance mechanisms or against isolates producing Ambler class B or D enzymes (10). Against KPC-producing *K. pneumoniae*, *E. cloacae*, *P. aeruginosa*, and *Acinetobacter* sp. isolates from New York City, meropenem-vaborbactam enhanced the activity of carbapenems; however, decreased expression of *ompK36* reduced the effect of the β-lactamase inhibitor 8- to 16-fold compared to that against isolates producing the same β-lactamases (9).

In this study, 133 of the 135 KPC-producing isolates detected were inhibited by meropenem-vaborbactam at ≤2 μg/ml, and all isolates were inhibited by this combination at ≤8 μg/ml. These isolates are the main target for this combination, and simulated human exposures of meropenem-vaborbactam against CRE isolates by use of a hollow-fiber model demonstrated that a regimen of 2 g meropenem-2 g vaborbactam every 8 h by 3-h infusion was highly efficacious against isolates producing KPC with meropenem-vaborbactam MIC values of up to 8 μg/ml (11). Additionally, a phase 3 clinical trial for complicated urinary tract infection isolates was recently completed to support this dosing regimen, and another is ongoing for the treatment of CRE (https://clinicaltrials.gov/ct2/results?term=vaborbactam&Search=Search).

Meropenem-vaborbactam was active against contemporary *Enterobacteriaceae* isolates collected worldwide, and this combination displayed good activity against CRE, MDR, and XDR *Enterobacteriaceae* isolates with MIC_{50} and MIC_{90} values that were lower than those for comparator agents (except tigecycline). Additionally, and as reported by Lapuebla et al. (9), the activity of this combination was similar to that of meropenem alone against other Gram-negative nonfastidious species. As with other β-lactamase inhibitors that are clinically available or in late development stages (18), vaborbactam does not inhibit MBL-producing isolates, and the meropenem-vaborbactam combination displays limited activity against isolates

producing class D oxacillinases associated with resistance to carbapenems. Isolates producing MBLs and OXA-48-like enzymes were detected mainly in Asia-Pacific and some European countries, but the worldwide spread of these resistance determinants is a matter of great concern, and the development of treatment options for these organisms is warranted.

MATERIALS AND METHODS

Bacterial isolates. A total of 14,304 Gram-negative bacterial clinical isolates were collected consecutively during 2014 in 82 hospitals, located in 31 countries and grouped into four regions: United States (29 hospitals), Europe (35 hospitals), Latin America (8 hospitals), and Asia-Pacific (10 hospitals). Isolates were collected consecutively according to standardized protocols, and only clinically significant isolates were included in the study (1 per patient episode). Species identification was confirmed when necessary by matrix-assisted laser desorption ionization–time of flight mass spectrometry, using a Bruker Daltonics MALDI Biotyper (Billerica, Massachusetts, USA) following the manufacturer's instructions.

Antimicrobial susceptibility testing. All isolates were susceptibility tested using the reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI) (12), using validated panels produced by ThermoFisher Scientific (formerly TREK, Cleveland, OH). Meropenem was combined with vaborbactam at a fixed concentration of 8 μg/ml. Categorical interpretations for all comparator agents were those found in CLSI document M100-S26 (13), at the EUCAST website (14), or in U.S. Food and Drug Administration (FDA) package inserts. Quality control (QC) was performed using *Escherichia coli* ATCC 25922 and ATCC 35218, *K. pneumoniae* ATCC 700603 and BAA-1705, and *P. aeruginosa* ATCC 27853 as reference strains. All QC MIC results were within acceptable ranges as published in CLSI documents (13).

Definitions. Carbapenem-resistant *Enterobacteriaceae* (CRE) isolates were defined as any isolates exhibiting imipenem (*Proteus mirabilis* and indole-positive *Proteeae* were not included due to their intrinsically elevated MIC values) and/or meropenem MIC values of $\geq$4 μg/ml.

MDR and XDR *Enterobacteriaceae* isolates were classified as such per recently recommended guidelines (15) and as adapted by Farrell et al. (16), using the following antimicrobial class representative agents and CLSI interpretive criteria for *Enterobacteriaceae*: ceftriaxone ($\geq$2 μg/ml), meropenem ($\geq$2 μg/ml), piperacillin-tazobactam ($\geq$32 μg/ml-4 μg/ml), levofloxacin ($\geq$4 μg/ml), gentamicin ($\geq$8 μg/ml), tigecycline ($\geq$4 μg/ml), and colistin ($\geq$4 μg/ml). Classifications were based on the following recommended parameters: MDR if nonsusceptible to at least one agent in $\geq$3 antimicrobial classes and XDR if nonsusceptible to at least one agent in all but $\leq$2 antimicrobial classes. PDR isolates were resistant to all antimicrobial classes tested.

Carbapenemase screening. All CRE isolates were screened by PCR followed by DNA sequencing of bla_{KPC}, bla_{IMP}, bla_{VIM}, bla_{NDM}, bla_{OXA-48}, bla_{GES} (bla_{GES-2}, $_{-4}$, $_{-5}$, $_{-6}$, and $_{-8}$), bla_{NMC-A}, bla_{SME}, and bla_{IMI} amplicons as previously described (17). Isolates yielding negative results for these genes were tested for less common carbapenemases, including FRI-1, BKC-1, GIM-1/-2, SIM-1, SPM-1, KHM-1, AIM-1, BIC-1, and DIM-1.

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