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In Vitro Activity of Ceftazidime-Avibactam against Clinical Isolates of *Enterobacteriaceae* and *Pseudomonas aeruginosa* Collected in Asia-Pacific Countries: Results from the INFORM Global Surveillance Program, 2012 to 2015

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ABSTRACT The *in vitro* activities of ceftazidime-avibactam and comparators against 9,149 isolates of *Enterobacteriaceae* and 2,038 isolates of *Pseudomonas aeruginosa* collected by 42 medical centers in nine countries in the Asia-Pacific region from 2012 to 2015 were determined as part of the International Network for Optimal Resistance Monitoring (INFORM) global surveillance program. Antimicrobial susceptibility testing was conducted by Clinical and Laboratory Standards Institute (CLSI) broth microdilution, and isolate subset analysis was performed on the basis of the resistant phenotypes and β-lactamase content. Ceftazidime-avibactam demonstrated potent *in vitro* activity (MIC, ≤8 μg/ml) against all *Enterobacteriaceae* tested (99.0% susceptible) and was the most active against isolates that were metallo-β-lactamase (MBL) negative (99.8% susceptible). Against *P. aeruginosa*, 92.6% of all isolates and 96.1% of MBL-negative isolates were susceptible to ceftazidime-avibactam (MIC, ≤8 μg/ml). The rates of susceptibility to ceftazidime-avibactam ranged from 97.0% (Philippines) to 100% (Hong Kong, South Korea) for *Enterobacteriaceae* and from 83.1% (Thailand) to 100% (Hong Kong) among *P. aeruginosa* isolates, with lower susceptibilities being observed in countries where MBLs were more frequently encountered (Philippines, Thailand). Ceftazidime-avibactam inhibited 97.2 to 100% of *Enterobacteriaceae* isolates, per country, that carried serine β-lactamases, including extended-spectrum β-lactamases, AmpC cephalosporinases, and carbapenemases (KPC, GES, OXA-48-like). It also inhibited 91.3% of *P. aeruginosa* isolates that were carbapenem nonsusceptible in which no acquired β-lactamase was detected. Among MBL-negative *Enterobacteriaceae* isolates that were ceftazidime nonsusceptible, meropenem nonsusceptible, colistin resistant, and multidrug resistant, ceftazidime-avibactam inhibited 96.1, 87.7, 100, and 98.8% of isolates, respectively, and among MBL-negative *P. aeruginosa* isolates that were ceftazidime nonsusceptible, meropenem nonsusceptible, colistin resistant, and multidrug resistant, ceftazidime-avibactam inhibited 79.6, 83.6, 83.3, and 68.2% of isolates, respectively. Overall, clinical isolates of *Enterobacteriaceae* and *P. aeruginosa* collected in nine Asia-Pacific countries from 2012 to 2015 were highly susceptible to ceftazidime-avibactam.

KEYWORDS ceftazidime-avibactam, Asia-Pacific, surveillance, Gram negative, *Enterobacteriaceae*, *Pseudomonas aeruginosa*, INFORM

Avibactam (AVI) is a non-β-lactam β-lactamase inhibitor that inhibits the activity of Ambler class A β-lactamases, including extended-spectrum β-lactamases (ESBLs; e.g., TEM-type, SHV-type, and CTX-M-type β-lactamases); KPC carbapenemases; AmpC cephalosporinases (Ambler class C β-lactamases); and some Ambler class D

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β-lactamases (e.g., OXA-48) (1–3). Avibactam in combination with ceftazidime (CAZ) has previously demonstrated potent *in vitro* activity against KPC-producing clinical isolates of *Enterobacteriaceae*, including isolates that also carry AmpC and ESBL enzymes and/or that have impaired permeability, as well as *Pseudomonas aeruginosa* (1–7). Metallo-β-lactamase-(MBL)-producing *Enterobacteriaceae* and *Pseudomonas aeruginosa* are not susceptible to ceftazidime-avibactam (1, 6).

To date, only a limited number of surveillance studies have been conducted in which data for isolates from the Asia-Pacific region have been specifically analyzed (8–10) and not grouped with data from countries outside the region. Previous surveillance studies have reported that the prevalence of β-lactam-resistant and multidrug-resistant (MDR) *Enterobacteriaceae* and nonfermentative Gram-negative bacilli (GNB) is higher in certain countries within the Asia-Pacific region than in other nations in that region and in other geographic locations (2, 4, 5, 8–12). β-Lactam resistance rates have been observed to be lower in Australia, New Zealand, and Japan and higher in China, India, Indonesia, Philippines, Taiwan, and Thailand (2, 4, 5, 8–12). To date, the majority of published studies have not included molecular characterization of β-lactamases specifically from the Asia-Pacific region or provided ceftazidime-avibactam susceptibility data for Gram-negative bacilli isolated from patients in many Asia-Pacific countries (8–10). The intent of the current study was to augment currently published phenotypic data by determining the *in vitro* susceptibilities to ceftazidime-avibactam and comparators of clinical isolates of *Enterobacteriaceae* and *P. aeruginosa* collected from hospitalized patients in Asia-Pacific countries over a recent 4-year time period (2012 to 2015), as well as to analyze the activity of ceftazidime-avibactam against antimicrobial-resistant and molecularly characterized β-lactamase-producing subsets at both the regional and country levels. These data were collected as part of the International Network for Optimal Resistance Monitoring (INFORM) global surveillance program. The INFORM global surveillance program was established in 2012 to benchmark and track the *in vitro* activity of ceftazidime-avibactam and comparative agents against clinical isolates of β-lactamase-producing *Enterobacteriaceae* and nonfermentative Gram-negative bacilli, including *P. aeruginosa*.

RESULTS

Of the 9,149 isolates of *Enterobacteriaceae* tested, 99.0% were susceptible to ceftazidime-avibactam (MIC_{90}, 0.5 μg/ml); the percentages of susceptibility were lower for meropenem (98.4%), doripenem (98.3%), amikacin (97.5%), tigecycline (93.9%), piperacillin-tazobactam (86.9%), colistin (83.0%), and the other agents tested (<80%) (Table 1). Ceftazidime-avibactam MIC_{90} values for individual species or species groups within the *Enterobacteriaceae* family ranged from 0.12 μg/ml (*Proteeae*) to 1 μg/ml (*Enterobacter* spp.), with only minor variation (<2%) in the percent susceptibility to ceftazidime-avibactam, which ranged from 98.1% (*Enterobacter* spp.) to 99.9% (*Escherichia coli*), being observed (Table 1). Percent susceptibility to ceftazidime-avibactam was higher for *Enterobacteriaceae* isolates that did not carry MBLs (99.8% susceptible) than for MBL-positive isolates (1.4% susceptible) (Table 1). Accordingly, the percent susceptibilities to ceftazidime-avibactam for MBL-negative isolates of individual species or species groups of *Enterobacteriaceae* (99.5 to 100% susceptible) were marginally higher (<2%) than the percent susceptibilities for all isolates of individual species or species groups (98.1 to 99.9%) (Table 1). Percent susceptibility to ceftazidime-avibactam for *Enterobacteriaceae* isolates from each of the Asia-Pacific countries surveyed ranged from 99.1 to 100% (MIC_{90}, 0.25 to 0.5 μg/ml) for all countries except China (98.8% susceptible; MIC_{90}, 0.5 μg/ml), Thailand (98.7%; MIC_{90}, 0.5 μg/ml), and Philippines (97.0%; MIC_{90}, 0.5 μg/ml) (Fig. 1; see also Tables S2A to S10A in the supplemental material).

Table 2 depicts the *in vitro* activity of ceftazidime-avibactam and the comparator agents against subsets of *Enterobacteriaceae* isolates that were molecularly characterized for β-lactamase content. Ceftazidime-avibactam inhibited 99.6%, 99.3%, 98.9%, 97.7%, and 97.2% of ESBL-positive, AmpC-positive, ESBL-positive and AmpC-

TABLE 1 *In vitro* activities of ceftazidime-avibactam and comparator antimicrobial agents tested against 9,149 isolates of *Enterobacteriaceae* and 2,038 isolates of *P. aeruginosa* collected in the Asia-Pacific region as part of the INFORM global surveillance program from 2012 to 2015

Organism, phenotype/genotype (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b]			% susceptible[c]
		50%	90%	Range	
Enterobacteriaceae (9,149)	Ceftazidime-avibactam	0.12	0.5	≤0.015 to >128	99.0
	Ceftazidime	0.25	64	≤0.015 to >128	75.1
	Cefepime	≤0.12	>16	≤0.12 to >16	77.8
	Aztreonam	0.12	64	≤0.015 to >128	73.9
	Piperacillin-tazobactam	2	64	≤0.25 to >128	86.9
	Doripenem	0.06	0.25	≤0.008 to >4	98.3
	Imipenem	0.25	2	≤0.03 to >8	85.1
	Meropenem	0.03	0.12	≤0.004 to >8	98.4
	Amikacin	2	8	≤0.25 to >32	97.5
	Colistin (n = 4,140)[d]	0.5	>4	≤0.12 to >4	83.0
	Tigecycline	0.5	2	≤0.015 to >8	93.9
	Levofloxacin	0.12	>4	≤0.03 to >4	74.6
Enterobacteriaceae, MBL negative (9,075)	Ceftazidime-avibactam	0.12	0.5	≤0.015 to >128	99.8
	Ceftazidime	0.25	64	≤0.015 to >128	75.7
	Cefepime	≤0.12	>16	≤0.12 to >16	78.4
	Aztreonam	0.12	64	≤0.015 to >128	74.3
	Piperacillin-tazobactam	2	32	≤0.25 to >128	87.5
	Doripenem	0.06	0.25	≤0.008 to >4	99.1
	Imipenem	0.25	2	≤0.03 to >8	85.7
	Meropenem	0.03	0.12	≤0.004 to >8	99.1
	Amikacin	2	8	≤0.25 to >32	97.8
	Colistin (n = 4,103)[d]	0.5	>4	≤0.12 to >4	82.9
	Tigecycline	0.5	2	≤0.015 to >8	94.0
	Levofloxacin	0.12	>4	≤0.03 to >4	74.9
Escherichia coli (3,140)	Ceftazidime-avibactam	0.12	0.25	≤0.015 to >128	99.9
	Ceftazidime	0.25	32	≤0.015 to >128	72.6
	Cefepime	≤0.12	>16	≤0.12 to >16	69.4
	Aztreonam	0.12	64	≤0.015 to >128	68.5
	Piperacillin-tazobactam	2	16	≤0.25 to >128	92.1
	Doripenem	0.03	0.06	≤0.008 to >4	99.6
	Imipenem	0.25	0.25	≤0.03 to >8	99.1
	Meropenem	0.03	0.06	≤0.004 to >8	99.4
	Amikacin	2	8	≤0.25 to >32	98.2
	Colistin (n = 1,344)[d]	0.5	1	≤0.12 to >4	99.1
	Tigecycline	0.25	0.5	≤0.015 to 8	99.9
	Levofloxacin	0.5	>4	≤0.03 to >4	55.8
Escherichia coli, MBL negative (3,137)	Ceftazidime-avibactam	0.12	0.25	≤0.015 to >128	>99.9
	Ceftazidime	0.25	32	≤0.015 to >128	72.6
	Cefepime	≤0.12	>16	≤0.12 to >16	69.5
	Aztreonam	0.12	64	≤0.015 to >128	68.5
	Piperacillin-tazobactam	2	16	≤0.25 to >128	92.2
	Doripenem	0.03	0.06	≤0.008 to >4	99.7
	Imipenem	0.25	0.25	≤0.03 to >8	99.2
	Meropenem	0.03	0.06	≤0.004 to >8	99.5
	Amikacin	2	8	≤0.25 to >32	98.3
	Colistin (n = 1,343)[d]	0.5	1	≤0.12 to >4	99.1
	Tigecycline	0.25	0.5	≤0.015 to 8	99.9
	Levofloxacin	0.5	>4	≤0.03 to >4	55.8
Klebsiella pneumoniae (2,538)	Ceftazidime-avibactam	0.12	0.5	≤0.015 to >128	98.3
	Ceftazidime	0.25	128	≤0.015 to >128	69.4
	Cefepime	≤0.12	>16	≤0.12 to >16	71.7
	Aztreonam	0.12	128	≤0.015 to >128	69.6
	Piperacillin-tazobactam	4	>128	≤0.25 to >128	79.4
	Doripenem	0.06	0.12	0.015 to >4	96.8
	Imipenem	0.25	1	≤0.03 to >8	94.3
	Meropenem	0.03	0.12	≤0.004 to >8	96.7
	Amikacin	1	4	≤0.25 to >32	96.3

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TABLE 1 (Continued)

Organism, phenotype/genotype (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b]			% susceptible[c]
		50%	90%	Range	
	Colistin (n = 1,288)[d]	1	1	0.12 to >4	97.9
	Tigecycline	0.5	2	≤0.015 to >8	96.3
	Levofloxacin	0.12	>4	≤0.03 to >4	78.6
Klebsiella pneumoniae, MBL negative (2,501)	Ceftazidime-avibactam	0.12	0.5	≤0.015 to >128	99.7
	Ceftazidime	0.25	128	≤0.015 to >128	70.4
	Cefepime	≤0.12	>16	≤0.12 to >16	72.7
	Aztreonam	0.06	128	≤0.015 to >128	70.4
	Piperacillin-tazobactam	4	>128	≤0.25 to >128	80.5
	Doripenem	0.06	0.12	0.015 to >4	98.2
	Imipenem	0.25	1	≤0.03 to >8	95.5
	Meropenem	0.03	0.06	≤0.004 to >8	98.0
	Amikacin	1	4	≤0.25 to >32	96.8
	Colistin (n = 1,266)[d]	1	1	0.12 to >4	98.0
	Tigecycline	0.5	2	≤0.015 to >8	96.3
	Levofloxacin	0.12	>4	≤0.03 to >4	79.2
Klebsiella oxytoca (432)	Ceftazidime-avibactam	0.12	0.25	≤0.015 to 128	98.8
	Ceftazidime	0.12	8	≤0.015 to >128	89.8
	Cefepime	≤0.12	2	≤0.12 to >16	92.1
	Aztreonam	0.25	32	≤0.015 to >128	82.9
	Piperacillin-tazobactam	2	64	≤0.25 to >128	89.1
	Doripenem	0.06	0.12	0.015 to >4	98.8
	Imipenem	0.25	0.5	0.06 to >8	98.2
	Meropenem	0.03	0.06	0.015 to >8	98.8
	Amikacin	1	4	0.5 to >32	98.6
	Colistin (n = 187)[d]	0.5	1	0.25 to 4	98.9
	Tigecycline	0.25	1	0.06 to 4	99.5
	Levofloxacin	0.06	1	≤0.03 to >4	94.0
Klebsiella oxytoca, MBL negative (428)	Ceftazidime-avibactam	0.12	0.25	≤0.015 to 16	99.8
	Ceftazidime	0.12	4	≤0.015 to >128	90.7
	Cefepime	≤0.12	2	≤0.12 to >16	92.8
	Aztreonam	0.25	32	≤0.015 to >128	83.4
	Piperacillin-tazobactam	2	32	≤0.25 to >128	89.7
	Doripenem	0.06	0.06	0.015 to 2	99.8
	Imipenem	0.25	0.5	0.06 to 8	99.1
	Meropenem	0.03	0.06	0.015 to 8	99.8
	Amikacin	1	4	0.5 to >32	99.1
	Colistin (n = 186)[d]	0.5	1	0.25 to 4	98.9
	Tigecycline	0.25	1	0.06 to 4	99.5
	Levofloxacin	0.06	1	≤0.03 to >4	94.4
Enterobacter spp.[e] (1,088)	Ceftazidime-avibactam	0.25	1	≤0.015 to >128	98.1
	Ceftazidime	0.5	128	≤0.015 to >128	66.0
	Cefepime	≤0.12	8	≤0.12 to >16	84.8
	Aztreonam	0.12	64	≤0.015 to >128	67.6
	Piperacillin-tazobactam	4	128	≤0.25 to >128	76.3
	Doripenem	0.06	0.25	0.015 to >4	97.7
	Imipenem	1	2	≤0.03 to >8	80.7
	Meropenem	0.06	0.12	0.008 to >8	97.8
	Amikacin	1	4	≤0.25 to >32	98.2
	Colistin (n = 481)[d]	0.5	>4	≤0.12 to >4	86.7
	Tigecycline	0.5	1	0.06 to 8	97.2
	Levofloxacin	0.06	2	≤0.03 to >4	90.7
Enterobacter spp., MBL negative (1,069)	Ceftazidime-avibactam	0.25	1	≤0.015 to 64	99.7
	Ceftazidime	0.5	128	≤0.015 to >128	67.2
	Cefepime	≤0.12	8	≤0.12 to >16	86.3
	Aztreonam	0.12	64	≤0.015 to >128	68.2
	Piperacillin-tazobactam	4	128	≤0.25 to >128	77.3
	Doripenem	0.06	0.25	0.015 to >4	99.4
	Imipenem	1	2	≤0.03 to >8	82.1
	Meropenem	0.06	0.12	0.008 to >8	99.4

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TABLE 1 (Continued)

Organism, phenotype/genotype (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b] 50%	90%	Range	% susceptible[c]
	Amikacin	1	4	≤0.25 to >32	98.5
	Colistin (n = 471)[d]	0.5	>4	≤0.12 to >4	86.8
	Tigecycline	0.5	1	0.06 to 8	97.8
	Levofloxacin	0.06	2	≤0.03 to >4	91.9
Citrobacter spp.[f] (558)	Ceftazidime-avibactam	0.12	0.5	≤0.015 to >128	98.4
	Ceftazidime	0.5	128	0.06 to >128	73.5
	Cefepime	≤0.12	8	≤0.12 to >16	88.0
	Aztreonam	0.12	64	≤0.015 to >128	73.8
	Piperacillin-tazobactam	4	64	≤0.25 to >128	81.9
	Doripenem	0.06	0.12	≤0.008 to >4	98.4
	Imipenem	0.25	1	0.06 to >8	91.6
	Meropenem	0.03	0.06	0.008 to >8	98.6
	Amikacin	2	4	≤0.25 to >32	97.3
	Colistin (n = 229)[d]	0.5	1	≤0.12 to >4	99.6
	Tigecycline	0.5	1	0.06 to 4	99.6
	Levofloxacin	0.06	4	≤0.03 to >4	88.7
Citrobacter spp., MBL negative (552)	Ceftazidime-avibactam	0.12	0.5	≤0.015 to >128	99.5
	Ceftazidime	0.25	128	0.06 to >128	74.3
	Cefepime	≤0.12	4	≤0.12 to >16	89.0
	Aztreonam	0.12	64	≤0.015 to >128	74.3
	Piperacillin-tazobactam	4	64	≤0.25 to >128	82.6
	Doripenem	0.06	0.12	≤0.008 to >4	99.3
	Imipenem	0.25	1	0.06 to >8	92.4
	Meropenem	0.03	0.06	0.008 to >8	99.3
	Amikacin	2	4	≤0.25 to >32	97.5
	Colistin (n = 227)[d]	0.5	1	≤0.06 to >4	99.6
	Tigecycline	0.25	1	0.06 to 4	99.6
	Levofloxacin	0.06	4	≤0.03 to >4	89.1
Proteeae[g] (1,190)	Ceftazidime-avibactam	0.06	0.12	≤0.015 to 64	99.5
	Ceftazidime	0.06	1	≤0.015 to >128	94.8
	Cefepime	≤0.12	0.5	≤0.12 to >16	94.0
	Aztreonam	≤0.015	0.25	≤0.015 to 128	96.8
	Piperacillin-tazobactam	0.5	1	≤0.25 to >128	99.0
	Doripenem	0.25	0.5	0.03 to >4	98.5
	Imipenem	2	4	0.06 to >8	24.3
	Meropenem	0.06	0.12	≤0.004 to >8	99.5
	Amikacin	4	8	≤0.25 to >32	97.1
	Colistin (n = 521)[d]	>4	>4	0.25 to >4	0.4
	Tigecycline	2	4	0.03 to >8	65.0
	Levofloxacin	0.12	>4	≤0.03 to >4	83.8
Proteeae, MBL negative (1,186)	Ceftazidime-avibactam	0.06	0.12	≤0.015 to 32	99.8
	Ceftazidime	0.06	0.5	≤0.015 to >128	95.1
	Cefepime	≤0.12	0.5	≤0.12 to >16	94.3
	Aztreonam	≤0.12	0.25	≤0.015 to 128	96.9
	Piperacillin-tazobactam	0.5	1	≤0.25 to >128	99.2
	Doripenem	0.25	0.5	0.03 to >4	98.8
	Imipenem	2	4	0.06 to >8	24.4
	Meropenem	0.06	0.12	≤0.004 to >8	99.7
	Amikacin	4	8	≤0.25 to >32	97.2
	Colistin (n = 520)[d]	>4	>4	0.25 to >4	0.4
	Tigecycline	2	4	0.03 to >8	64.9
	Levofloxacin	0.12	>4	≤0.03 to >4	84.0
Other *Enterobacteriaceae*[h] (203)	Ceftazidime-avibactam	0.12	0.5	≤0.015 to >128	99.5
	Ceftazidime	0.25	1	≤0.015 to >128	93.6
	Cefepime	≤0.12	1	≤0.12 to >16	92.6
	Aztreonam	0.12	2	≤0.015 to >128	92.6
	Piperacillin-tazobactam	2	8	≤0.25 to >128	94.1
	Doripenem	0.12	0.25	0.015 to >4	99.0
	Imipenem	0.5	2	0.06 to >8	88.7

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TABLE 1 (Continued)

Organism, phenotype/genotype (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b]			% susceptible[c]
		50%	90%	Range	
	Meropenem	0.06	0.12	0.03 to >8	99.0
	Amikacin	2	4	≤0.25 to 32	99.5
	Colistin (n = 90)[d]	>4	>4	0.25 to >4	10.0
	Tigecycline	1	2	0.25 to >8	96.6
	Levofloxacin	0.12	2	≤0.03 to >4	93.1
Other *Enterobacteriaceae*, MBL negative (202)	Ceftazidime-avibactam	0.12	0.5	≤0.015 to 1	100
	Ceftazidime	0.25	1	≤0.015 to >128	94.1
	Cefepime	≤0.12	1	≤0.12 to >16	93.1
	Aztreonam	0.12	2	≤0.015 to >128	92.6
	Piperacillin-tazobactam	2	8	≤0.25 to >128	94.1
	Doripenem	0.12	0.25	0.015 to >4	99.5
	Imipenem	0.5	2	0.06 to >8	89.1
	Meropenem	0.06	0.12	0.03 to >8	99.5
	Amikacin	2	4	≤0.25 to 32	99.5
	Colistin (n = 90)[d]	>4	>4	0.25 to >4	10.0
	Tigecycline	1	2	0.25 to >8	96.5
	Levofloxacin	0.12	2	≤0.03 to 4	93.6
Pseudomonas aeruginosa (2,038)	Ceftazidime-avibactam	2	8	0.03 to >128	92.6
	Ceftazidime	2	64	0.12 to >128	77.9
	Cefepime	4	>16	≤0.12 to >16	80.6
	Aztreonam	8	32	0.06 to >128	64.5
	Piperacillin-tazobactam	8	>128	≤0.25 to >128	71.0
	Doripenem	0.5	>4	0.03 to >4	78.7
	Imipenem	2	>8	0.06 to >8	67.9
	Meropenem	0.5	>8	0.015 to >8	77.6
	Amikacin	4	8	≤0.25 to >32	94.4
	Colistin (n = 1,278)[d]	2	2	≤0.12 to >8	93.5
	Levofloxacin	0.5	>4	≤0.03 to >4	77.1
Pseudomonas aeruginosa, MBL negative (1,964)	Ceftazidime-avibactam	2	8	0.03 to >128	96.1
	Ceftazidime	2	64	0.12 to >128	80.8
	Cefepime	4	16	≤0.12 to >16	83.5
	Aztreonam	8	32	0.06 to >128	65.8
	Piperacillin-tazobactam	8	>128	≤0.25 to >128	73.4
	Doripenem	0.5	>4	0.03 to >4	81.7
	Imipenem	2	>8	0.06 to >8	70.4
	Meropenem	0.5	8	0.015 to >8	80.5
	Amikacin	4	8	≤0.25 to >32	96.8
	Colistin (n = 1,225)[d]	2	2	≤0.12 to >8	93.5
	Levofloxacin	0.5	>4	≤0.03 to >4	79.9

[a]MBL negative, no gene encoding a metallo-β-lactamase was detected by PCR.
[b]MIC_{50} and MIC_{90} were not calculated for <10 isolates.
[c]Percent susceptibility was determined according to CLSI 2016 breakpoints, with the exception of that to ceftazidime-avibactam and tigecycline, where U.S. FDA breakpoints were applied. Because CLSI colistin breakpoints are not available for the *Enterobacteriaceae*, susceptibility for this organism group was determined using the EUCAST 2016 breakpoints for colistin.
[d]Values are for colistin tested without 0.002% polysorbate 80; data are for isolates collected in 2014 and 2015 only.
[e]The *Enterobacter* spp. included *Enterobacter aerogenes* (n = 439), *Enterobacter asburiae* (n = 89), *Enterobacter cloacae* (n = 525), *Enterobacter kobei* (n = 29), and *Enterobacter ludwigii* (n = 6).
[f]The *Citrobacter* spp. included *Citrobacter amalonaticus* (n = 10), *Citrobacter braakii* (n = 23), *Citrobacter farmeri* (n = 3), *Citrobacter freundii* (n = 274), *Citrobacter koseri* (n = 246), *Citrobacter sedlakii* (n = 1), and a *Citrobacter* isolate whose species was not determined (n = 1).
[g]The *Proteeae* included *Morganella morganii* (n = 253), *Proteus mirabilis* (n = 566), *Proteus penneri* (n = 14), *Proteus vulgaris* (n = 274), *Providencia alcalifaciens* (n = 2), *Providencia rettgeri* (n = 50), and *Providencia stuartii* (n = 31).
[h]Other *Enterobacteriaceae* included *Klebsiella ozaenae* (n = 1), *Kluyvera ascorbata* (n = 1), *Raoultella ornithinolytica* (n = 12), *Raoultella planticola* (n = 2), *Serratia liquefaciens* (n = 5), *Serratia marcescens* (n = 181), and *Serratia rubidaea* (n = 1).

positive, original-spectrum β-lactamase (OSBL)-positive, and KPC-positive isolates, respectively, as well as all GES-positive (class A carbapenemase) and OXA-48-like-positive (class D carbapenemase) isolates. The MIC_{90} values for ceftazidime-avibactam against these subsets of β-lactamase-positive *Enterobacteriaceae* ranged from 0.5 μg/ml (OSBL-positive and ESBL-positive isolates) to 4 μg/ml (KPC-positive isolates). The percentages of isolates susceptible to doripenem (93.2 to 99.0%) and

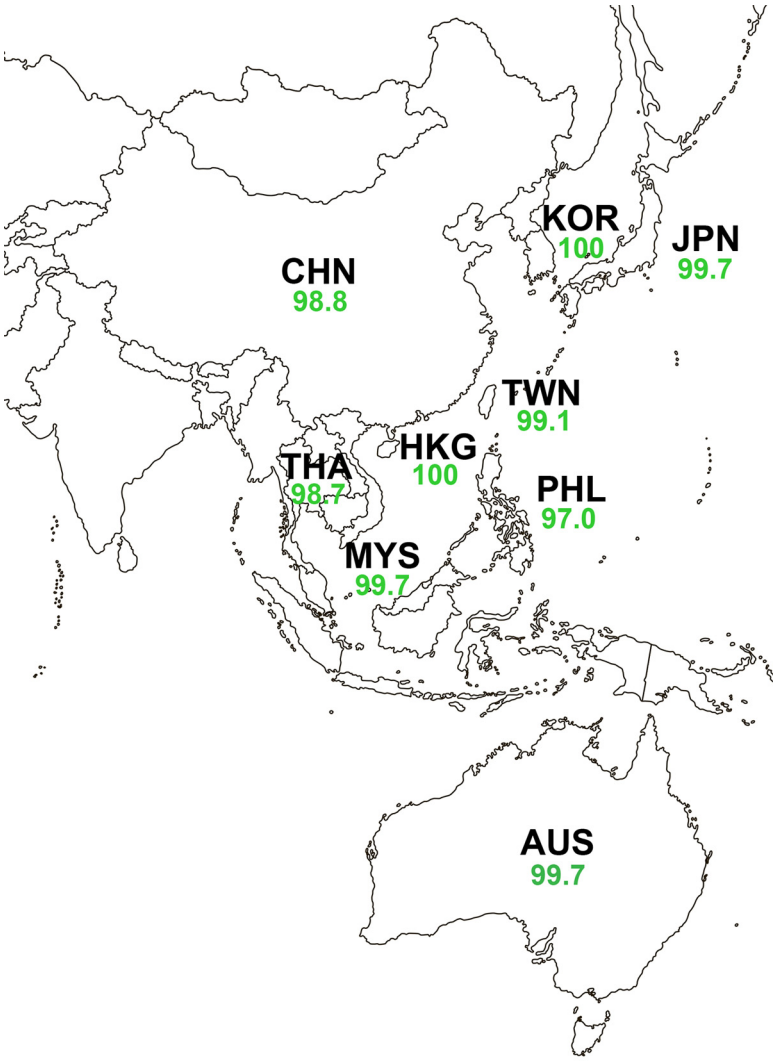

FIG 1 Percent susceptibility to ceftazidime-avibactam for isolates of *Enterobacteriaceae* collected from 2012 to 2015, by Asia-Pacific country. Ceftazidime-avibactam susceptible was defined as an MIC of ≤8 μg/ml; ceftazidime-avibactam resistant was defined as an MIC of ≥16 μg/ml. The green font indicates that >90% of isolates were ceftazidime-avibactam susceptible. Country abbreviations are as follows: AUS, Australia; CHN, China; HKG, Hong Kong; JPN, Japan; KOR, South Korea; MYS, Malaysia; PHL, Philippines; TWN, Taiwan; THA, Thailand. No isolates were obtained from patients in mainland China in 2014 or 2015 or patients in Hong Kong in 2015 due to export restrictions.

meropenem (96.2 to 98.5%) were equivalent to or slightly lower than the percentages of isolates susceptible to ceftazidime-avibactam observed for ESBL-positive, AmpC-positive, ESBL-positive and AmpC-positive, and OSBL-positive isolates. As anticipated, ceftazidime-avibactam was poorly active against isolates carrying MBLs (MIC_{90}, >128 μg/ml; 1.4% susceptible); only tigecycline (MIC_{90}, 4 μg/ml; 89.2% susceptible) and colistin (MIC_{90}, >4 μg/ml; 86.5% susceptible) retained *in vitro* activity against the majority of MBL-positive isolates. The distribution of serine β-lactamases and MBLs among molecularly characterized isolates from each country in the Asia-Pacific region is summarized in the supplemental material (Tables S2B to S10B; Fig. S1A to D). CTX-M-type ESBLs accounted for 85.2% of all ESBLs, with CTX-M-15 (41.4%) being the most common ESBL identified (Fig. S1B). DHA-1 (55.3%) and CMY-2 (37.1%) accounted for the majority of all AmpC enzymes identified (Fig. S1C). ESBLs and AmpC β-lactamases were found in all countries in the region but differed in prevalence across the different countries (Fig. S1B and C). Carbapenemases were found in all countries in the Asia-Pacific region except Hong Kong.

TABLE 2 *In vitro* activities of ceftazidime-avibactam and comparator antimicrobial agents tested against 3,020 isolates of β-lactamase-positive *Enterobacteriaceae* ($n = 2,388$) and *P. aeruginosa* ($n = 632$) collected in the Asia-Pacific region as part of the INFORM global surveillance program from 2012 to 2015

Organism, genotype (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b] 50%	90%	Range	% susceptible[c]
Enterobacteriaceae (2,388)					
OSBL positive (44)	Ceftazidime-avibactam	0.25	0.5	0.03 to >128	97.7
	Ceftazidime	2	16	0.06 to >128	68.2
	Cefepime	0.5	8	≤0.12 to >16	81.8
	Aztreonam	1	64	≤0.015 to >128	75.0
	Piperacillin-tazobactam	4	>128	≤0.25 to >128	61.4
	Doripenem	0.06	0.25	0.015 to >4	93.2
	Imipenem	0.25	2	0.12 to 4	72.7
	Meropenem	0.03	0.25	0.015 to 8	97.7
	Amikacin	1	4	≤0.25 to >32	95.5
	Colistin ($n = 20$)[d]	1	1	0.25 to >4	95.0
	Tigecycline	0.5	1	0.06 to 4	97.7
	Levofloxacin	0.5	>4	0.06 to >4	56.8
SHV, spectrum undefined (1)[e]	Ceftazidime-avibactam	—	—	0.25	100
	Ceftazidime	—	—	128	0
	Cefepime	—	—	≤0.12	100
	Aztreonam	—	—	64	0
	Piperacillin-tazobactam	—	—	64	0
	Doripenem	—	—	0.12	100
	Imipenem	—	—	2	0
	Meropenem	—	—	0.12	100
	Amikacin	—	—	1	100
	Colistin ($n = 0$)[d]	—	—	ND[f]	ND
	Tigecycline	—	—	1	100
	Levofloxacin	—	—	1	100
ESBL positive (1,593)[g]	Ceftazidime-avibactam	0.25	0.5	≤0.015 to >128	99.6
	Ceftazidime	32	>128	0.03 to >128	24.7
	Cefepime	>16	>16	≤0.12 to >16	8.5
	Aztreonam	64	>128	≤0.015 to >128	11.5
	Piperacillin-tazobactam	8	>128	≤0.25 to >128	73.4
	Doripenem	0.06	0.12	0.015 to >4	99.0
	Imipenem	0.25	0.5	≤0.03 to >8	96.9
	Meropenem	0.03	0.06	0.008 to >8	98.5
	Amikacin	4	16	≤0.25 to >32	95.1
	Colistin ($n = 729$)[d]	0.5	1	≤0.12 to >4	96.2
	Tigecycline	0.5	2	0.06 to 8	96.2
	Levofloxacin	>4	>4	≤0.03 to >4	34.5
AmpC positive (446)[h]	Ceftazidime-avibactam	0.25	1	≤0.015 to 64	99.3
	Ceftazidime	32	>128	0.03 to >128	33.9
	Cefepime	0.25	4	≤0.12 to >16	87.0
	Aztreonam	8	64	≤0.015 to >128	46.0
	Piperacillin-tazobactam	8	>128	≤0.25 to >128	65.5
	Doripenem	0.12	0.5	0.015 to >4	97.5
	Imipenem	1	2	0.12 to >8	54.3
	Meropenem	0.06	0.25	≤0.004 to >8	98.4
	Amikacin	2	4	≤0.25 to >32	96.2
	Colistin ($n = 167$)[d]	0.5	>4	0.25 to >4	88.0
	Tigecycline	0.5	2	0.06 to 8	94.2
	Levofloxacin	0.5	>4	≤0.03 to >4	69.7
ESBL positive + AmpC positive (186)[i]	Ceftazidime-avibactam	0.5	2	≤0.015 to 128	98.9
	Ceftazidime	128	>128	0.12 to >128	3.8
	Cefepime	>16	>16	≤0.12 to >16	17.7
	Aztreonam	64	>128	0.03 to >128	3.8
	Piperacillin-tazobactam	32	>128	0.5 to >128	44.6
	Doripenem	0.12	0.5	0.03 to >4	97.3
	Imipenem	1	2	0.06 to >8	74.7
	Meropenem	0.06	0.25	0.015 to >8	96.2
	Amikacin	4	>32	≤0.25 to >32	77.4

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TABLE 2 (Continued)

Organism, genotype (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b] 50%	90%	Range	% susceptible[c]
	Colistin (n = 66)[d]	1	1	0.25 to 4	98.5
	Tigecycline	0.5	2	0.06 to 8	97.3
	Levofloxacin	>4	>4	≤0.03 to >4	28.5
KPC positive (36)[j]	Ceftazidime-avibactam	1	4	0.06 to 16	97.2
	Ceftazidime	128	>128	0.12 to >128	5.6
	Cefepime	>16	>16	≤0.12 to >16	2.8
	Aztreonam	>128	>128	0.06 to >128	2.8
	Piperacillin-tazobactam	>128	>128	0.5 to >128	2.8
	Doripenem	>4	>4	0.06 to >4	8.3
	Imipenem	>8	>8	2 to >8	0
	Meropenem	>8	>8	0.06 to >8	2.8
	Amikacin	4	>32	≤0.25 to >32	77.8
	Colistin (n = 9)[d]	—	—	0.25 to 1	100
	Tigecycline	1	2	0.06 to 4	91.7
	Levofloxacin	>4	>4	0.12 to >4	22.2
GES carbapenemase positive (2)[k]	Ceftazidime-avibactam	—	—	0.06 to 1	100
	Ceftazidime	—	—	4 to >128	50.0
	Cefepime	—	—	2 to 16	50.0
	Aztreonam	—	—	4 to >128	50.0
	Piperacillin-tazobactam	—	—	1 to >128	50.0
	Doripenem	—	—	0.06 to 4	50.0
	Imipenem	—	—	0.5 to 4	50.0
	Meropenem	—	—	0.06 to >8	50.0
	Amikacin	—	—	2 to 2	100
	Colistin (n = 2)[d]	—	—	0.5 to 0.5	100
	Tigecycline	—	—	0.05 to 1	100
	Levofloxacin	—	—	0.5 to 2	100
OXA-48-like positive (6)[l]	Ceftazidime-avibactam	—	—	0.25 to 2	100
	Ceftazidime	—	—	0.5 to >128	16.7
	Cefepime	—	—	≤0.12 to >16	16.7
	Aztreonam	—	—	0.12 to >128	16.7
	Piperacillin-tazobactam	—	—	128 to >128	0
	Doripenem	—	—	0.25 to >4	83.3
	Imipenem	—	—	1 to >8	33.3
	Meropenem	—	—	1 to >8	33.3
	Amikacin	—	—	1 to 8	100
	Colistin (n = 6)[d]	—	—	0.25 to >4	83.3
	Tigecycline	—	—	0.12 to 0.5	100
	Levofloxacin	—	—	>4 to >4	0
MBL positive (74)[m]	Ceftazidime-avibactam	>128	>128	2 to >128	1.4
	Ceftazidime	>128	>128	32 to >128	0
	Cefepime	>16	>16	1 to >16	2.7
	Aztreonam	64	>128	≤0.015 to >128	25.7
	Piperacillin-tazobactam	>128	>128	0.5 to >128	16.2
	Doripenem	>4	>4	1 to >4	4.1
	Imipenem	>8	>8	0.5 to >8	6.8
	Meropenem	>8	>8	0.5 to >8	8.1
	Amikacin	4	>32	0.5 to >32	66.2
	Colistin (n = 37)[d]	1	>4	0.25 to >4	86.5
	Tigecycline	1	4	0.06 to 8	89.2
	Levofloxacin	>4	>4	0.06 to >4	36.5
P. aeruginosa (632)					
OSBL positive (3)[n]	Ceftazidime-avibactam	—	—	8 to 32	66.7
	Ceftazidime	—	—	16 to >128	0
	Cefepime	—	—	16 to >16	0
	Aztreonam	—	—	16 to 128	0
	Piperacillin-tazobactam	—	—	>128 to >128	0
	Doripenem	—	—	>4 to >4	0
	Imipenem	—	—	>8 to >8	0

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TABLE 2 (Continued)

Organism, genotype (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b] 50%	90%	Range	% susceptible[c]
	Meropenem	—	—	>8 to >8	0
	Amikacin	—	—	>32 to >32	0
	Colistin (n = 1)[d]	—	—	1	100
	Levofloxacin	—	—	4 to >4	0
ESBL positive (19)[n,o]	Ceftazidime-avibactam	64	>128	4 to >128	21.1
	Ceftazidime	>128	>128	128 to >128	0
	Cefepime	>16	>16	>16 to >16	0
	Aztreonam	>128	>128	16 to >128	0
	Piperacillin-tazobactam	128	>128	16 to >128	5.3
	Doripenem	>4	>4	4 to >4	0
	Imipenem	>8	>8	4 to >8	0
	Meropenem	>8	>8	4 to >8	0
	Amikacin	32	>32	8 to >32	36.8
	Colistin (n = 13)[d]	2	2	1 to 2	100
	Levofloxacin	>4	>4	>4 to >4	0
GES carbapenemase positive (3)[n]	Ceftazidime-avibactam	—	—	4 to 8	100
	Ceftazidime	—	—	8 to >128	33.3
	Cefepime	—	—	16 to >16	0
	Aztreonam	—	—	8 to 128	33.3
	Piperacillin-tazobactam	—	—	64 to >128	0
	Doripenem	—	—	>4 to >4	0
	Imipenem	—	—	2 to >8	33.3
	Meropenem	—	—	4 to >8	0
	Amikacin	—	—	8 to >32	33.3
	Colistin (n = 2)[d]	—	—	2 to 2	100
	Levofloxacin	—	—	>4 to >4	0
GES, spectrum undefined (3)[n,p]	Ceftazidime-avibactam	—	—	8 to 128	33.3
	Ceftazidime	—	—	64 to >128	0
	Cefepime	—	—	16 to >16	0
	Aztreonam	—	—	16 to 32	0
	Piperacillin-tazobactam	—	—	16 to >128	33.3
	Doripenem	—	—	>4 to >4	0
	Imipenem	—	—	4 to >8	0
	Meropenem	—	—	8 to >8	0
	Amikacin	—	—	32 to >32	0
	Colistin (n = 3)[d]	—	—	1 to 2	100
	Levofloxacin	—	—	>4 to >4	0
KPC positive (1)[n]	Ceftazidime-avibactam	—	—	4	100
	Ceftazidime	—	—	64	0
	Cefepime	—	—	>16	0
	Aztreonam	—	—	>128	0
	Piperacillin-tazobactam	—	—	>128	0
	Doripenem	—	—	>4	0
	Imipenem	—	—	>8	0
	Meropenem	—	—	>8	0
	Amikacin	—	—	4	100
	Colistin (n = 0)[d]	—	—	ND[f]	ND
	Levofloxacin	—	—	0.12	100
MBL positive (74)[n,q]	Ceftazidime-avibactam	128	>128	8 to >128	1.4
	Ceftazidime	>128	>128	8 to >128	1.4
	Cefepime	>16	>16	8 to >16	2.7
	Aztreonam	16	>128	4 to >128	28.4
	Piperacillin-tazobactam	128	>128	8 to >128	6.8
	Doripenem	>4	>4	4 to >4	0
	Imipenem	>8	>8	4 to >8	0
	Meropenem	>8	>8	2 to >8	1.4
	Amikacin	32	>32	4 to >32	28.4
	Colistin (n = 53)[d]	2	2	0.5 to 4	94.3
	Levofloxacin	>4	>4	0.25 to >4	4.1

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TABLE 2 (Continued)

Organism, genotype (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b] 50%	90%	Range	% susceptible[c]
No acquired β-lactamase detected (529)[n]	Ceftazidime-avibactam	4	8	0.12 to >128	91.3
	Ceftazidime	4	64	0.25 to >128	66.2
	Cefepime	8	>16	≤0.12 to >16	66.5
	Aztreonam	16	64	0.25 to >128	45.4
	Piperacillin-tazobactam	16	>128	≤0.25 to >128	52.2
	Doripenem	4	>4	0.03 to >4	38.6
	Imipenem	>8	>8	0.5 to >8	6.6
	Meropenem	4	>8	≤0.06 to >8	32.9
	Amikacin	4	16	≤0.25 to >32	94.0
	Colistin (n = 299)[d]	2	2	0.12 to 8	94.0
	Levofloxacin	2	>4	≤0.03 to >4	58.4

[a]OSBL, original-spectrum β-lactamase (e.g., TEM-1, SHV-1, SHV-11); ESBL, extended-spectrum β-lactamase; MBL, metallo-β-lactamase.
[b]—, MIC_{50} and MIC_{90} were not calculated for <10 isolates.
[c]Percent susceptibility was determined according to CLSI 2016 breakpoints, with the exception of that to ceftazidime-avibactam and tigecycline, where U.S. FDA breakpoints were applied. Because CLSI colistin breakpoints are not available for the *Enterobacteriaceae*, susceptibility for this organism group was determined using the EUCAST 2016 breakpoints for colistin.
[d]Values are for colistin tested without 0.002% polysorbate 80; data are for isolates collected in 2014 and 2015 only.
[e]SHV, spectrum undefined, SHV-type β-lactamase for which the spectrum of activity (original spectrum or extended spectrum) has not been biochemically determined.
[f]ND, not determined; MIC range and percent susceptible were not calculated for 0 isolates.
[g]Includes isolates carrying the chromosomal ESBL common to *K. oxytoca*, inhibitor-resistant β-lactamases (SHV-type and/or TEM-type β-lactamases that are not inhibited by clavulanic acid), SHV-type and/or TEM-type β-lactamases with an undefined spectrum of activity, and/or OSBLs.
[h]Includes isolates carrying the chromosomal AmpC common to *Citrobacter* spp., *Enterobacter* spp., *Morganella morganii*, *Providencia* spp., and *Serratia* spp. and isolates cocarrying SHV-type and/or TEM-type β-lactamases with an undefined spectrum of activity and/or OSBLs.
[i]Includes isolates carrying the chromosomal β-lactamases common to *Citrobacter* spp., *Enterobacter* spp., and *K. oxytoca* and isolates cocarrying OSBLs.
[j]Includes isolates carrying ESBLs, plasmidic and chromosomal AmpC β-lactamases, and/or OSBLs.
[k]Isolates cocarry ESBLs.
[l]Includes isolates carrying ESBLs, plasmidic AmpC β-lactamases, and/or OSBLs.
[m]Includes isolates cocarrying ESBLs, plasmidic and chromosomal AmpC β-lactamases, OSBLs, and serine carbapenemases (IMP-4 and KPC-2, 2 isolates; NDM-1 and OXA-232, 5 isolates).
[n]Assumed to carry the chromosomal AmpC common to *P. aeruginosa*.
[o]Includes isolates carrying OSBLs.
[p]Includes isolates carrying GES-24 (1 isolate) and GES-29 (2 isolates) β-lactamases, for which the spectrum of activity (ESBL or carbapenemase) has not been biochemically determined.
[q]Includes isolates cocarrying ESBLs.

NDM (35.2%) and KPC (30.4%) were the most common carbapenemases identified in the region. The majority of KPCs were KPC-2 (97.4%), and NDM-1 (81.8%) was the most common NDM type. Considerable differences in the types and prevalence of individual carbapenemases were observed across the countries. The *in vitro* activity of ceftazidime-avibactam against *Enterobacteriaceae* in each country was related to the proportion of MBL-positive isolates (Tables S2A to S10A).

Table 3 shows the *in vitro* activity of ceftazidime-avibactam and the comparator agents against 2,277 ceftazidime-nonsusceptible isolates of *Enterobacteriaceae* (24.9% of all isolates). Overall, 96.1% of ceftazidime-nonsusceptible isolates were susceptible to ceftazidime-avibactam (MIC_{90}, 1 μg/ml), with the MIC_{90}s against individual species of *Enterobacteriaceae* ranging from 0.5 to 2 μg/ml (93.9 to 99.5% susceptible) for *E. coli*, *Klebsiella pneumoniae*, *Enterobacter* spp., and *Citrobacter* spp. Ceftazidime-nonsusceptible isolates of *Proteeae* (MIC_{90}, 8 μg/ml; 90.3% susceptible) and *Klebsiella oxytoca* (MIC_{90}, 16 μg/ml; 88.6% susceptible) were less susceptible to ceftazidime-avibactam. The percentage of isolates susceptible to ceftazidime-avibactam increased for all species when the activity against isolates that did not produce an MBL was evaluated. Across the Asia-Pacific region, the percentage of *Enterobacteriaceae* isolates that tested nonsusceptible to ceftazidime ranged from 9.0% (Australia) to 35.5% (Philippines) (Fig. S2). The percentage of ceftazidime-nonsusceptible isolates that were susceptible to ceftazidime-avibactam was >95% (MIC_{90}, 0.5 to 2 μg/ml) in all countries except Philippines (MIC_{90}, 2 μg/ml; 91.5% susceptible) (Tables S2A to S10A). The lower activity demonstrated by ceftazidime-avibactam in Philippines, as well as in Thailand and China, can be attributed to the greater numbers of isolates carrying MBLs, as 99.1%, 99.5%, and 98.4% of ceftazidime-nonsusceptible MBL-negative isolates from these

TABLE 3 *In vitro* activities of ceftazidime-avibactam and comparator antimicrobial agents tested against 2,277 isolates of ceftazidime-nonsusceptible *Enterobacteriaceae* and 451 isolates of ceftazidime-nonsusceptible *P. aeruginosa* collected in the Asia-Pacific region as part of the INFORM global surveillance program from 2012 to 2015

Organism, phenotype (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b]			% susceptible[c]
		50%	90%	Range	
Enterobacteriaceae (2,277)	Ceftazidime-avibactam	0.25	1	≤0.015 to >128	96.1
	Ceftazidime	64	>128	8 to >128	0
	Cefepime	16	>16	≤0.12 to >16	29.3
	Aztreonam	64	>128	≤0.015 to >128	8.0
	Piperacillin-tazobactam	16	>128	≤0.25 to >128	55.3
	Doripenem	0.06	0.25	0.015 to >4	93.9
	Imipenem	0.25	2	≤0.03 to >8	86.8
	Meropenem	0.06	0.25	≤0.004 to >8	93.6
	Amikacin	2	16	≤0.25 to >32	92.1
	Colistin (n = 1,037)[d]	0.5	1	≤0.12 to >4	92.4
	Tigecycline	0.5	2	0.06 to 8	95.2
	Levofloxacin	>4	>4	≤0.03 to >4	44.1
Enterobacteriaceae, MBL negative (2,203)	Ceftazidime-avibactam	0.25	1	≤0.015 to >128	99.2
	Ceftazidime	64	>128	8 to >128	0
	Cefepime	16	>16	≤0.12 to >16	30.1
	Aztreonam	64	>128	≤0.015 to >128	7.4
	Piperacillin-tazobactam	16	>128	≤0.25 to >128	56.6
	Doripenem	0.06	0.25	0.015 to >4	97.0
	Imipenem	0.25	2	≤0.03 to >8	89.5
	Meropenem	0.06	0.12	≤0.004 to >8	96.5
	Amikacin	2	16	≤0.25 to >32	92.9
	Colistin (n = 1,000)[d]	0.5	1	≤0.12 to >4	92.6
	Tigecycline	0.5	2	0.06 to 8	95.4
	Levofloxacin	>4	>4	≤0.03 to >4	44.4
Escherichia coli (862)	Ceftazidime-avibactam	0.12	0.5	≤0.015 to >128	99.5
	Ceftazidime	32	128	8 to >128	0
	Cefepime	>16	>16	≤0.12 to >16	18.8
	Aztreonam	64	128	0.5 to >128	6.0
	Piperacillin-tazobactam	4	128	0.5 to >128	81.2
	Doripenem	0.06	0.06	0.015 to >4	98.6
	Imipenem	0.25	0.5	≤0.03 to >8	96.9
	Meropenem	0.03	0.06	≤0.004 to >8	98.0
	Amikacin	4	16	0.5 to >32	95.1
	Colistin (n = 362)[d]	0.5	1	≤0.12 to 4	98.1
	Tigecycline	0.25	0.5	0.06 to 8	99.8
	Levofloxacin	>4	>4	≤0.03 to >4	22.7
Escherichia coli, MBL negative (859)	Ceftazidime-avibactam	0.12	0.5	≤0.015 to >128	99.9
	Ceftazidime	32	128	8 to >128	0
	Cefepime	>16	>16	≤0.12 to >16	18.9
	Aztreonam	64	128	0.5 to >128	6.1
	Piperacillin-tazobactam	4	128	0.5 to >128	81.5
	Doripenem	0.06	0.06	0.015 to >4	99.0
	Imipenem	0.25	0.5	≤0.03 to >8	97.2
	Meropenem	0.03	0.06	≤0.004 to >8	98.4
	Amikacin	4	16	0.5 to >32	95.2
	Colistin (n = 361)[d]	0.5	1	≤0.12 to 4	98.1
	Tigecycline	0.25	0.5	0.06 to 8	99.8
	Levofloxacin	>4	>4	≤0.03 to >4	22.8
Klebsiella pneumoniae (778)	Ceftazidime-avibactam	0.5	2	≤0.015 to >128	94.3
	Ceftazidime	128	>128	8 to >128	0
	Cefepime	>16	>16	≤0.12 to >16	15.9
	Aztreonam	64	>128	0.06 to >128	5.7
	Piperacillin-tazobactam	64	>128	0.5 to >128	39.2
	Doripenem	0.12	2	0.015 to >4	89.9
	Imipenem	0.25	2	≤0.03 to >8	84.6
	Meropenem	0.06	2	0.015 to >8	89.2
	Amikacin	2	32	≤0.25 to >32	88.4

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TABLE 3 (Continued)

Organism, phenotype (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b]			% susceptible[c]
		50%	90%	Range	
	Colistin (n = 407)[d]	1	1	0.25 to >4	95.1
	Tigecycline	1	2	0.06 to 8	93.6
	Levofloxacin	>4	>4	≤0.03 to >4	44.9
Klebsiella pneumoniae, MBL negative (741)	Ceftazidime-avibactam	0.5	1	≤0.015 to >128	99.1
	Ceftazidime	64	>128	8 to >128	0
	Cefepime	>16	>16	≤0.12 to >16	16.7
	Aztreonam	64	>128	0.5 to >128	5.1
	Piperacillin-tazobactam	32	>128	0.5 to >128	40.6
	Doripenem	0.06	0.25	0.015 to >4	94.2
	Imipenem	0.25	2	≤0.03 to >8	88.3
	Meropenem	0.06	0.25	0.015 to >8	93.5
	Amikacin	2	32	≤0.25 to >32	89.9
	Colistin (n = 385)[d]	1	1	0.25 to >4	95.3
	Tigecycline	1	2	0.06 to 8	93.4
	Levofloxacin	>4	>4	≤0.03 to >4	44.9
Klebsiella oxytoca (44)	Ceftazidime-avibactam	0.25	16	≤0.015 to 128	88.6
	Ceftazidime	64	>128	8 to >128	0
	Cefepime	2	>16	≤0.12 to >16	50.0
	Aztreonam	32	>128	1 to >128	2.3
	Piperacillin-tazobactam	4	>128	1 to >128	65.9
	Doripenem	0.06	2	0.03 to >4	88.6
	Imipenem	0.25	4	0.12 to >8	84.1
	Meropenem	0.06	4	0.03 to >8	88.6
	Amikacin	2	32	0.5 to >32	88.6
	Colistin (n = 22)[d]	0.5	1	0.25 to 1	100
	Tigecycline	0.5	1	0.06 to 2	100
	Levofloxacin	0.5	>4	≤0.03 to >4	70.5
Klebsiella oxytoca, MBL negative (40)	Ceftazidime-avibactam	0.25	1	≤0.015 to 16	97.5
	Ceftazidime	32	>128	8 to >128	0
	Cefepime	2	16	≤0.12 to >16	52.5
	Aztreonam	32	>128	8 to >128	0
	Piperacillin-tazobactam	4	>128	1 to >128	70.0
	Doripenem	0.06	0.12	0.03 to 2	97.5
	Imipenem	0.25	1	0.12 to 8	92.5
	Meropenem	0.06	0.12	0.03 to 8	97.5
	Amikacin	2	8	0.5 to >32	92.5
	Colistin (n = 21)[d]	0.5	1	0.25 to 1	100
	Tigecycline	0.25	1	0.06 to 2	100
	Levofloxacin	0.5	>4	≤0.03 to >4	72.5
Enterobacter spp.[e] (370)	Ceftazidime-avibactam	0.5	2	≤0.015 to >128	94.3
	Ceftazidime	64	>128	8 to >128	0
	Cefepime	1	>16	≤0.12 to >16	60.5
	Aztreonam	32	128	0.06 to >128	7.6
	Piperacillin-tazobactam	64	>128	0.5 to >128	31.1
	Doripenem	0.12	0.5	0.03 to >4	93.8
	Imipenem	1	2	≤0.03 to >8	82.7
	Meropenem	0.12	0.25	0.015 to >8	93.8
	Amikacin	2	8	0.5 to >32	95.1
	Colistin (n = 160)[d]	0.5	>4	0.25 to >4	87.5
	Tigecycline	0.5	2	0.06 to 8	93.8
	Levofloxacin	0.25	>4	≤0.03 to >4	79.2
Enterobacter spp., MBL negative (351)	Ceftazidime-avibactam	0.5	1	≤0.015 to 64	99.2
	Ceftazidime	64	>128	8 to >128	0
	Cefepime	1	>16	≤0.12 to >16	63.5
	Aztreonam	32	128	0.5 to >128	6.3
	Piperacillin-tazobactam	64	>128	0.5 to >128	31.6
	Doripenem	0.12	0.25	0.03 to >4	98.6
	Imipenem	1	2	≤0.03 to >8	87.2
	Meropenem	0.12	0.25	0.015 to >8	98.3

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TABLE 3 (Continued)

Organism, phenotype (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b] 50%	90%	Range	% susceptible[c]
	Amikacin	2	8	0.5 to >32	96.0
	Colistin (n = 150)[d]	0.5	4	0.25 to >4	88.0
	Tigecycline	0.5	2	0.06 to 8	95.2
	Levofloxacin	0.12	>4	≤0.03 to >4	82.1
Citrobacter spp.[f] (148)	Ceftazidime-avibactam	0.5	2	0.03 to >128	93.9
	Ceftazidime	128	>128	8 to >128	0
	Cefepime	1	>16	≤0.12 to >16	63.5
	Aztreonam	32	128	0.5 to >128	8.8
	Piperacillin-tazobactam	32	>128	0.5 to >128	34.5
	Doripenem	0.06	0.25	0.015 to >4	93.9
	Imipenem	0.5	2	0.12 to >8	85.8
	Meropenem	0.06	0.25	0.015 to >8	94.6
	Amikacin	2	16	0.5 to >32	90.5
	Colistin (n = 52)[d]	0.5	1	0.25 to 2	100
	Tigecycline	0.5	1	0.12 to 4	99.3
	Levofloxacin	1	>4	≤0.03 to >4	71.0
Citrobacter spp., MBL negative (142)	Ceftazidime-avibactam	0.5	1	0.03 to >128	97.9
	Ceftazidime	64	>128	8 to >128	0
	Cefepime	1	>16	≤0.12 to >16	66.2
	Aztreonam	32	128	0.5 to >128	7.8
	Piperacillin-tazobactam	32	>128	0.5 to >128	35.2
	Doripenem	0.06	0.12	0.015 to >4	97.2
	Imipenem	0.5	2	0.12 to >8	88.7
	Meropenem	0.06	0.12	0.015 to >8	97.2
	Amikacin	2	16	0.5 to >32	90.9
	Colistin (n = 50)[d]	0.5	1	0.25 to 2	100
	Tigecycline	0.5	1	0.12 to 4	99.3
	Levofloxacin	1	>4	≤0.03 to >4	71.8
Proteeae[g] (62)	Ceftazidime-avibactam	0.25	8	≤0.015 to 64	90.3
	Ceftazidime	32	>128	8 to >128	0
	Cefepime	1	>16	≤0.12 to >16	61.3
	Aztreonam	2	32	≤0.015 to 128	66.1
	Piperacillin-tazobactam	1	32	≤0.25 to >128	83.9
	Doripenem	0.25	2	0.06 to >4	87.1
	Imipenem	4	8	0.5 to >8	9.7
	Meropenem	0.12	1	0.03 to >8	90.3
	Amikacin	4	>32	0.5 to >32	82.3
	Colistin (n = 26)[d]	>4	>4	>4 to >4	0
	Tigecycline	2	4	0.12 to 8	50.0
	Levofloxacin	>4	>4	≤0.03 to >4	33.9
Proteeae, MBL negative (58)	Ceftazidime-avibactam	0.12	1	≤0.015 to 32	96.6
	Ceftazidime	32	>128	8 to >128	0
	Cefepime	1	>16	≤0.12 to >16	65.5
	Aztreonam	2	32	≤0.015 to 128	65.5
	Piperacillin-tazobactam	1	32	≤0.25 to >128	87.9
	Doripenem	0.25	1	0.06 to >4	93.1
	Imipenem	4	8	0.5 to >8	10.3
	Meropenem	0.12	0.25	0.03 to >8	94.8
	Amikacin	4	>32	0.5 to >32	84.5
	Colistin (n = 25)[d]	>4	>4	>4 to >4	0
	Tigecycline	4	4	0.12 to 8	48.3
	Levofloxacin	4	>4	≤0.03 to >4	34.5
Other *Enterobacteriaceae*[h] (13)	Ceftazidime-avibactam	0.5	1	0.12 to >128	92.3
	Ceftazidime	16	>128	8 to >128	0
	Cefepime	16	>16	2 to >16	15.4
	Aztreonam	64	>128	0.25 to >128	15.4
	Piperacillin-tazobactam	32	>128	2 to >128	46.2
	Doripenem	0.12	>4	0.06 to >4	84.6
	Imipenem	0.5	>8	0.25 to >8	61.5

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TABLE 3 (Continued)

Organism, phenotype (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b] 50%	90%	Range	% susceptible[c]
	Meropenem	0.06	8	0.06 to >8	84.6
	Amikacin	4	16	0.5 to 32	92.3
	Colistin (n = 8)[d]	—	—	0.25 to >4	25.0
	Tigecycline	1	4	0.25 to 8	84.6
	Levofloxacin	1	>4	0.12 to >4	69.2
Other *Enterobacteriaceae*, MBL negative (12)	Ceftazidime-avibactam	0.25	1	0.12 to 1	100
	Ceftazidime	16	128	8 to >128	0
	Cefepime	8	>16	2 to >16	16.7
	Aztreonam	128	>128	2 to >128	8.3
	Piperacillin-tazobactam	64	>128	2 to >128	41.7
	Doripenem	0.12	0.5	0.06 to >4	91.7
	Imipenem	0.5	2	0.25 to >8	66.7
	Meropenem	0.06	0.25	0.06 to >8	91.7
	Amikacin	4	16	0.5 to 32	91.7
	Colistin (n = 8)[d]	—	—	0.25 to >4	25.0
	Tigecycline	1	4	0.25 to 8	83.3
	Levofloxacin	1	>4	0.12 to >4	75.0
Pseudomonas aeruginosa (451)	Ceftazidime-avibactam	8	128	0.03 to >128	66.7
	Ceftazidime	64	>128	16 to >128	0.0
	Cefepime	16	>16	1 to >16	21.7
	Aztreonam	32	128	1 to >128	13.1
	Piperacillin-tazobactam	128	>128	2 to >128	7.1
	Doripenem	4	8	0.06 to >4	43.5
	Imipenem	8	>8	0.25 to >8	39.5
	Meropenem	4	>8	0.03 to >8	44.6
	Amikacin	4	>32	≤0.25 to >32	78.7
	Colistin (n = 301)[d]	2	2	0.25 to >8	92.4
	Levofloxacin	>4	>4	≤0.03 to >4	43.7
Pseudomonas aeruginosa, MBL negative (378)	Ceftazidime-avibactam	8	32	0.03 to >128	79.6
	Ceftazidime	64	>128	16 to >128	0
	Cefepime	16	>16	1 to >16	25.7
	Aztreonam	32	128	1 to >128	10.3
	Piperacillin-tazobactam	128	>128	2 to >128	7.4
	Doripenem	2	8	0.06 to >4	51.9
	Imipenem	4	>8	0.25 to >8	47.1
	Meropenem	2	>8	0.03 to >8	52.9
	Amikacin	4	32	≤0.25 to >32	88.4
	Colistin (n = 248)[d]	2	2	0.25 to >8	91.9
	Levofloxacin	2	>4	≤0.03 to >4	51.3

[a]MBL negative, no gene encoding a metallo-β-lactamase was detected by PCR.
[b]—, MIC_{50} and MIC_{90} were not calculated for <10 isolates.
[c]Percent susceptibility was determined according to CLSI 2016 breakpoints, with the exception of that to ceftazidime-avibactam and tigecycline, where U.S. FDA breakpoints were applied. Because CLSI colistin breakpoints are not available for the *Enterobacteriaceae*, susceptibility for this organism group was determined using the EUCAST 2016 breakpoints for colistin.
[d]Values are for colistin tested without 0.002% polysorbate 80; data are for isolates collected in 2014 and 2015 only.
[e]The *Enterobacter* spp. included *Enterobacter aerogenes* (n = 147), *Enterobacter asburiae* (n = 26), *Enterobacter cloacae* (n = 185), *Enterobacter kobei* (n = 10), and *Enterobacter ludwigii* (n = 2).
[f]The *Citrobacter* spp. included *Citrobacter amalonaticus* (n = 1), *Citrobacter braakii* (n = 10), *Citrobacter freundii* (n = 115), *Citrobacter koseri* (n = 21), and *Citrobacter sedlakii* (n = 1).
[g]The *Proteeae* included *Morganella morganii* (n = 27), *Proteus mirabilis* (n = 22), *Proteus vulgaris* (n = 3), *Providencia rettgeri* (n = 6), and *Providencia stuartii* (n = 4).
[h]Other *Enterobacteriaceae* included *Raoultella ornithinolytica* (n = 2) and *Serratia marcescens* (n = 11).

countries, respectively, were susceptible to ceftazidime-avibactam (Tables S3A and B, S7A and B, and S10A and B; Fig. S1D).

Ceftazidime-avibactam displayed reduced activity (47.7% susceptible) against 149 isolates of meropenem-nonsusceptible *Enterobacteriaceae* (Table 4). This result is again largely explained by the observation that 45.6% of meropenem-nonsusceptible isolates were MBL positive; the activity against MBL-negative meropenem-nonsusceptible isolates was vastly improved (87.7% susceptible). The MIC_{90} values for ceftazidime-avibactam against all meropenem-nonsusceptible iso-

TABLE 4 *In vitro* activities of ceftazidime-avibactam and comparator antimicrobial agents tested against 149 isolates of meropenem-nonsusceptible *Enterobacteriaceae* and 457 isolates of meropenem-nonsusceptible *P. aeruginosa* collected in the Asia-Pacific region as part of the INFORM global surveillance program from 2012 to 2015

Organism, phenotype (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b]			% susceptible[c]
		50%	90%	Range	
Enterobacteriaceae (149)	Ceftazidime-avibactam	32	>128	0.06 to >128	47.7
	Ceftazidime	>128	>128	0.5 to >128	2.7
	Cefepime	>16	>16	≤0.12 to >16	3.4
	Aztreonam	128	>128	≤0.015 to >128	14.8
	Piperacillin-tazobactam	>128	>128	0.5 to >128	10.7
	Doripenem	>4	>4	0.03 to >4	10.1
	Imipenem	>8	>8	0.12 to >8	12.1
	Meropenem	>8	>8	2 to >8	0
	Amikacin	4	>32	≤0.25 to >32	69.8
	Colistin (n = 67)[d]	1	>4	0.25 to >4	85.1
	Tigecycline	1	4	0.06 to 8	85.9
	Levofloxacin	>4	>4	0.06 to >4	26.9
Enterobacteriaceae, MBL negative (81)	Ceftazidime-avibactam	1	16	0.06 to >128	87.7
	Ceftazidime	128	>128	0.5 to >128	4.9
	Cefepime	>16	>16	≤0.12 to >16	3.7
	Aztreonam	>128	>128	0.12 to >128	6.2
	Piperacillin-tazobactam	>128	>128	0.5 to >128	7.4
	Doripenem	>4	>4	0.03 to >4	18.5
	Imipenem	8	>8	0.12 to >8	18.5
	Meropenem	8	>8	2 to >8	0
	Amikacin	4	>32	≤0.25 to >32	75.3
	Colistin (n = 30)[d]	0.5	4	0.25 to >4	83.3
	Tigecycline	1	4	0.06 to 8	84.0
	Levofloxacin	>4	>4	0.25 to >4	19.8
Escherichia coli (19)	Ceftazidime-avibactam	1	>128	0.06 to >128	79.0
	Ceftazidime	128	>128	0.5 to >128	10.5
	Cefepime	>16	>16	2 to >16	5.3
	Aztreonam	128	>128	1 to >128	10.5
	Piperacillin-tazobactam	>128	>128	1 to >128	15.8
	Doripenem	2	>4	0.03 to >4	31.6
	Imipenem	4	>8	0.12 to >8	26.3
	Meropenem	8	>8	2 to >8	0
	Amikacin	4	>32	1 to >32	84.2
	Colistin (n = 3)[d]	—	—	0.25 to 1	100
	Tigecycline	0.25	1	0.06 to 2	100
	Levofloxacin	>4	>4	1 to >4	10.5
Escherichia coli, MBL negative (16)	Ceftazidime-avibactam	0.5	4	0.06 to >128	93.8
	Ceftazidime	128	>128	0.5 to >128	12.5
	Cefepime	>16	>16	2 to >16	6.3
	Aztreonam	128	>128	1 to >128	12.5
	Piperacillin-tazobactam	>128	>128	1 to >128	18.8
	Doripenem	2	>4	0.03 to >8	37.5
	Imipenem	4	>8	0.12 to >8	31.3
	Meropenem	4	>8	2 to >8	0
	Amikacin	4	>32	1 to >32	87.5
	Colistin (n = 2)[d]	0.25	0.25	0.25 to 0.25	100
	Tigecycline	0.25	1	0.06 to 2	100
	Levofloxacin	>4	8	1 to >8	12.5
Klebsiella pneumoniae (85)	Ceftazidime-avibactam	4	>128	0.12 to >128	51.8
	Ceftazidime	>128	>128	0.5 to >128	1.2
	Cefepime	>16	>16	≤0.12 to >16	2.4
	Aztreonam	128	>128	0.06 to >128	7.1
	Piperacillin-tazobactam	>128	>128	4 to >128	4.7
	Doripenem	>4	>4	0.12 to >4	8.2
	Imipenem	>8	>8	0.25 to >8	11.8
	Meropenem	>8	>8	2 to >8	0
	Amikacin	4	>32	≤0.25 to >32	67.1

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TABLE 4 (Continued)

Organism, phenotype (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b]			% susceptible[c]
		50%	90%	Range	
	Colistin (n = 49)[d]	1	4	0.25 to >4	87.8
	Tigecycline	1	4	0.06 to 8	89.4
	Levofloxacin	>4	>4	0.06 to >4	25.9
Klebsiella pneumoniae, MBL negative (49)	Ceftazidime-avibactam	1	16	0.12 to >128	89.8
	Ceftazidime	>128	>128	0.5 to >128	2.0
	Cefepime	>16	>16	≤0.12 to >16	4.1
	Aztreonam	>128	>128	0.12 to >128	2.0
	Piperacillin-tazobactam	>128	>128	16 to >128	2.0
	Doripenem	>4	>8	0.12 to >8	14.3
	Imipenem	>8	>8	0.25 to >8	14.3
	Meropenem	>8	>8	2 to >8	0
	Amikacin	4	>32	≤0.25 to >32	73.5
	Colistin (n = 27)[d]	0.5	4	0.25 to >8	85.2
	Tigecycline	1	4	0.06 to 8	83.7
	Levofloxacin	>4	>8	0.5 to >8	14.3
Klebsiella oxytoca (5)	Ceftazidime-avibactam	—	—	16 to 128	0
	Ceftazidime	—	—	64 to >128	0
	Cefepime	—	—	2 to >16	20.0
	Aztreonam	—	—	1 to >128	20.0
	Piperacillin-tazobactam	—	—	4 to >128	20.0
	Doripenem	—	—	2 to >4	0
	Imipenem	—	—	2 to >8	0
	Meropenem	—	—	4 to >8	0
	Amikacin	—	—	0.5 to >32	60.0
	Colistin (n = 1)[d]	—	—	1 to 1	100
	Tigecycline	—	—	0.5 to 1	100
	Levofloxacin	—	—	1 to 4	60.0
Klebsiella oxytoca, MBL negative (1)	Ceftazidime-avibactam	—	—	16	0
	Ceftazidime	—	—	128	0
	Cefepime	—	—	4	0
	Aztreonam	—	—	64	0
	Piperacillin-tazobactam	—	—	128	0
	Doripenem	—	—	2	0
	Imipenem	—	—	8	0
	Meropenem	—	—	8	0
	Amikacin	—	—	8	100
	Colistin (n = 0)[d]	—	—	ND[e]	ND
	Tigecycline	—	—	1	100
	Levofloxacin	—	—	2	100
Enterobacter spp.[f] (24)	Ceftazidime-avibactam	>128	>128	1 to >128	25.0
	Ceftazidime	>128	>128	2 to >128	4.2
	Cefepime	>16	>16	1 to >16	4.2
	Aztreonam	128	>128	0.06 to >128	25.0
	Piperacillin-tazobactam	>128	>128	4 to >128	12.5
	Doripenem	>4	>4	1 to >4	4.2
	Imipenem	>8	>8	0.5 to >8	4.2
	Meropenem	>8	>8	2 to >8	0
	Amikacin	4	>32	0.5 to >32	75.0
	Colistin (n = 10)[d]	0.5	>4	0.5 to >4	80.0
	Tigecycline	2	4	0.5 to 8	58.3
	Levofloxacin	>4	>4	0.06 to >4	25.0
Enterobacter spp., MBL negative (7)	Ceftazidime-avibactam	—	—	1 to 16	85.7
	Ceftazidime	—	—	2 to >128	14.3
	Cefepime	—	—	8 to >16	0
	Aztreonam	—	—	64 to >128	0
	Piperacillin-tazobactam	—	—	128 to >128	0
	Doripenem	—	—	1 to >4	14.3
	Imipenem	—	—	0.5 to >8	14.3
	Meropenem	—	—	2 to >8	0

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TABLE 4 (Continued)

Organism, phenotype (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b]			% susceptible[c]
		50%	90%	Range	
	Amikacin	—	—	0.5 to >32	71.4
	Colistin ($n = 0$)[d]	—	—	ND[e]	ND
	Tigecycline	—	—	0.5 to 4	42.9
	Levofloxacin	—	—	0.25 to >4	42.9
Citrobacter spp.[g] (8)	Ceftazidime-avibactam	—	—	0.25 to >128	37.5
	Ceftazidime	—	—	16 to >128	0
	Cefepime	—	—	>16 to >16	0
	Aztreonam	—	—	0.5 to >128	25.0
	Piperacillin-tazobactam	—	—	16 to >128	12.5
	Doripenem	—	—	2 to >4	0
	Imipenem	—	—	1 to >8	12.5
	Meropenem	—	—	2 to >8	0
	Amikacin	—	—	2 to >32	62.5
	Colistin ($n = 2$)[d]	—	—	1 to 1	100
	Tigecycline	—	—	0.5 to 1	100
	Levofloxacin	—	—	0.06 to >4	50.0
Citrobacter spp., MBL negative (4)	Ceftazidime-avibactam	—	—	0.25 to 128	75.0
	Ceftazidime	—	—	16 to >128	0
	Cefepime	—	—	>16 to >16	0
	Aztreonam	—	—	64 to >128	0
	Piperacillin-tazobactam	—	—	64 to >128	0
	Doripenem	—	—	2 to >4	0
	Imipenem	—	—	1 to >8	25.0
	Meropenem	—	—	4 to >8	0
	Amikacin	—	—	4 to >32	50.0
	Colistin ($n = 0$)[d]	—	—	ND	ND
	Tigecycline	—	—	0.5 to 1	100
	Levofloxacin	—	—	1 to >4	25.0
Proteeae[h] (6)	Ceftazidime-avibactam	—	—	0.06 to 64	33.3
	Ceftazidime	—	—	8 to >128	0
	Cefepime	—	—	4 to >16	0
	Aztreonam	—	—	≤0.015 to 32	66.7
	Piperacillin-tazobactam	—	—	0.5 to 128	50.0
	Doripenem	—	—	0.25 to >4	16.7
	Imipenem	—	—	1 to >8	16.7
	Meropenem	—	—	2 to >8	0
	Amikacin	—	—	1 to >32	50.0
	Colistin ($n = 2$)[d]	—	—	>4 to >4	0
	Tigecycline	—	—	0.5 to 8	66.7
	Levofloxacin	—	—	0.12 to >4	33.3
Proteeae, MBL negative (3)	Ceftazidime-avibactam	—	—	0.06 to 32	66.7
	Ceftazidime	—	—	8 to 128	0
	Cefepime	—	—	8 to >16	0
	Aztreonam	—	—	0.5 to 32	66.7
	Piperacillin-tazobactam	—	—	0.5 to 32	66.7
	Doripenem	—	—	0.25 to >4	33.3
	Imipenem	—	—	1 to >8	33.3
	Meropenem	—	—	2 to >8	0
	Amikacin	—	—	1 to >32	66.7
	Colistin ($n = 1$)[d]	—	—	>4	0
	Tigecycline	—	—	0.5 to 8	66.7
	Levofloxacin	—	—	2 to >4	33.3
Other *Enterobacteriaceae*[i] (2)	Ceftazidime-avibactam	—	—	1 to >128	50.0
	Ceftazidime	—	—	16 to >128	0
	Cefepime	—	—	>16 to >16	0
	Aztreonam	—	—	0.25 to >128	50.0
	Piperacillin-tazobactam	—	—	4 to >128	50.0
	Doripenem	—	—	>4 to >4	0
	Imipenem	—	—	>8 to >8	0

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TABLE 4 (Continued)

Organism, phenotype (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b]			% susceptible[c]
		50%	90%	Range	
	Meropenem	—	—	8 to >8	0
	Amikacin	—	—	0.5 to 1	100
	Colistin (n = 0)[d]	—	—	ND[e]	ND
	Tigecycline	—	—	0.5 to 1	100
	Levofloxacin	—	—	2 to >4	50.0
Other *Enterobacteriaceae*, MBL negative (1)	Ceftazidime-avibactam	—	—	1	100
	Ceftazidime	—	—	16	0
	Cefepime	—	—	>16	0
	Aztreonam	—	—	>128	0
	Piperacillin-tazobactam	—	—	>128	0
	Doripenem	—	—	>4	0
	Imipenem	—	—	>8	0
	Meropenem	—	—	>8	0
	Amikacin	—	—	0.5	100
	Colistin (n = 0)[d]	—	—	ND[e]	ND
	Tigecycline	—	—	1	100
	Levofloxacin	—	—	2	100
Pseudomonas aeruginosa (457)	Ceftazidime-avibactam	8	128	0.25 to >128	70.5
	Ceftazidime	16	>128	0.25 to >128	45.3
	Cefepime	16	>16	1 to >16	44.6
	Aztreonam	32	128	0.5 to >128	28.7
	Piperacillin-tazobactam	64	>128	1 to >128	31.1
	Doripenem	>4	>4	0.5 to >4	9.6
	Imipenem	>8	>8	0.5 to >8	5.5
	Meropenem	>8	>8	4 to >8	0
	Amikacin	8	>32	≤0.25 to >32	77.9
	Colistin (n = 286)[d]	2	2	0.25 to 8	96.2
	Levofloxacin	>4	>4	0.12 to >4	39.8
Pseudomonas aeruginosa, MBL negative (384)	Ceftazidime-avibactam	4	32	0.25 to >128	83.6
	Ceftazidime	8	128	0.25 to >128	53.7
	Cefepime	8	>16	1 to >16	52.6
	Aztreonam	32	128	0.5 to >128	28.9
	Piperacillin-tazobactam	32	>128	1 to >128	35.7
	Doripenem	>4	4	0.5 to >4	11.5
	Imipenem	>8	>8	0.5 to >8	6.5
	Meropenem	8	>8	4 to >8	0
	Amikacin	4	32	≤0.25 to >32	87.2
	Colistin (n = 233)[d]	2	2	0.25 to 8	96.6
	Levofloxacin	4	>4	0.12 to >4	46.6

[a]MBL negative, no gene encoding a metallo-β-lactamase was detected by PCR.
[b]—, MIC_{50} and MIC_{90} were not calculated for <10 isolates.
[c]Percent susceptibility was determined according to CLSI 2016 breakpoints, with the exception of that to ceftazidime-avibactam and tigecycline, where U.S. FDA breakpoints were applied. Because CLSI colistin breakpoints are not available for the *Enterobacteriaceae*, susceptibility for this organism group was determined using the EUCAST 2016 breakpoints for colistin.
[d]Values are for colistin tested without 0.002% polysorbate 80; data are for isolates collected in 2014 and 2015 only.
[e]ND, not determined; MIC range and percent susceptible were not calculated for 0 isolates.
[f]The *Enterobacter* spp. included *Enterobacter aerogenes* (n = 3), *Enterobacter asburiae* (n = 3), and *Enterobacter cloacae* (n = 18).
[g]The *Citrobacter* spp. included *Citrobacter braakii* (n = 1), *Citrobacter freundii* (n = 4), and *Citrobacter koseri* (n = 3).
[h]The *Proteeae* included *Proteus mirabilis* (n = 3), *Proteus vulgaris* (n = 1), *Providencia rettgeri* (n = 1), and *Providencia stuartii* (n = 1).
[i]Other *Enterobacteriaceae* included *Serratia marcescens* (n = 2).

lates and isolates of individual species or species groups of *Enterobacteriaceae* were >128 μg/ml. However, MIC_{90} values against subsets of MBL-negative meropenem-nonsusceptible isolates were significantly decreased, yielding susceptibility percentages of 85.7 to 93.8% for *E. coli*, *Enterobacter* spp., and *K. pneumoniae* (the only species with >10 isolates tested). Meropenem-nonsusceptible isolates were the most susceptible to tigecycline (85.9%), colistin (85.1%), and amikacin (69.8%), with the rates of susceptibility to β-lactams other than ceftazidime-avibactam being ≤15%. The percentage of isolates that tested nonsusceptible to meropenem was relatively low among the isolates from the Asia-Pacific countries, ranging from 0.3 to 4.2% (Fig. S2).

Ceftazidime-avibactam displayed high rates of activity (≥99%) against isolates collected in countries in which meropenem nonsusceptibility was conferred primarily by serine carbapenemases (KPC, OXA-48-like) or ESBL and/or AmpC β-lactamases presumably combined with additional resistance mechanisms (Tables S2A and B and S10A and B). In countries where MBLs were the major cause of nonsusceptibility to meropenem, the susceptibility of meropenem-nonsusceptible isolates to ceftazidime-avibactam was reduced.

Table 5 shows the *in vitro* activity of ceftazidime-avibactam and the comparator agents against 106 colistin-resistant isolates of *Enterobacteriaceae* (excluding data for the *Proteeae* and *Serratia* spp., which are intrinsically resistant to colistin). The percentage of isolates that were resistant to colistin ranged from <1% in Japan, South Korea, and Taiwan to 2.1% in Hong Kong and 2.3% in Philippines (Fig. S2). Ceftazidime-avibactam inhibited 96.2% of isolates at the MIC breakpoint (MIC_{90}, 1 μg/ml) and demonstrated activity similar to that of amikacin (96.2% susceptible) and tigecycline (98.1% susceptible). Ceftazidime-avibactam inhibited colistin-resistant isolates of *Enterobacteriaceae* from all countries (Tables S2A to S10A).

Table 6 depicts the *in vitro* activity of ceftazidime-avibactam and the comparator agents against 1,193 isolates of MDR *Enterobacteriaceae*. The rate of susceptibility to ceftazidime-avibactam was 93.8% (MIC_{90}, 2 μg/ml), which was similar to that for tigecycline (93.4% susceptible), and exceeded the rates of susceptibility to doripenem (89.4% susceptible), meropenem (88.8% susceptible), colistin (88.2% susceptible), amikacin (84.8% susceptible), imipenem (84.0% susceptible), and the other tested agents (<50% susceptible). The MIC_{90} values of ceftazidime-avibactam against MDR isolates varied from 0.5 to >128 μg/ml for different species of *Enterobacteriaceae*. Greater than 90% of *E. coli*, *K. pneumoniae*, and *Proteeae* isolates were susceptible to ceftazidime-avibactam (MIC_{90}, 0.5 to 4 μg/ml). The reduced activity of ceftazidime-avibactam against *K. oxytoca* (83.3% susceptible; MIC_{90}, 128 μg/ml), *Enterobacter* spp. (76.3% susceptible; MIC_{90}, >128 μg/ml), and *Citrobacter* spp. (81.8% susceptible; MIC_{90}, 128 μg/ml) could be attributed to the relatively high number of MBL-producing isolates among these species subsets. Again, the activity of ceftazidime-avibactam was much greater (as reflected by lower MIC values) against all and species-specific subsets of MDR MBL-negative isolates (98.8% susceptible; MIC_{90}, 1 μg/ml). The rate of susceptibility to ceftazidime-avibactam was greater than or comparable to that of colistin, tigecycline, and carbapenems among MDR isolates of all species of *Enterobacteriaceae*.

MDR rates ranged from 2.7% (Australia) to 19.4% (Thailand) across the nine Asia-Pacific countries (Fig. 2). In eight countries, ≥93.5% of MDR isolates of *Enterobacteriaceae* remained susceptible to ceftazidime-avibactam (Tables 7 and S2A to S10A). The activity of ceftazidime-avibactam was lowest against MDR isolates collected in Philippines (83.8% susceptible) (Table 7). The reduced activity observed can be explained by the relatively high number of MBL-producing isolates, as the activity of ceftazidime-avibactam against subsets of MBL-negative MDR isolates (98.0% susceptible) was restored (Tables 7 and S7A). Ceftazidime-avibactam demonstrated activity comparable or superior to that of all other agents tested against MDR isolates collected from individual countries (Tables S2A to S10A).

Of the 2,038 isolates of *P. aeruginosa* tested from 2012 to 2015, 92.6% were susceptible to ceftazidime-avibactam (MIC, ≤8 μg/ml); the MIC_{90} for ceftazidime-avibactam against all *P. aeruginosa* was 8 μg/ml (Table 1). Percent susceptibilities to the other agents tested were lower than those to ceftazidime-avibactam, with the exception of amikacin (94.4% susceptible) and colistin (93.5% susceptible). The percent susceptible rate for ceftazidime-avibactam increased to 96.1% when only MBL-negative isolates of *P. aeruginosa* were considered. There were 632 isolates of carbapenem-nonsusceptible *P. aeruginosa* that were screened for β-lactamase genes. Of these, 74 isolates (11.7%) were found to carry genes encoding an MBL with or without additional acquired serine β-lactamases. In the majority of isolates (83.7%), no acquired β-lactamase was identified (Tables 2 and S2A to S10A), and these isolates were inferred to harbor alterations in OprD or efflux pump expression, likely combined with the

TABLE 5 *In vitro* activities of ceftazidime-avibactam and comparator antimicrobial agents tested against 106 isolates of colistin-resistant *Enterobacteriaceae* and 6 isolates of colistin-resistant *P. aeruginosa* collected in the Asia-Pacific region as part of the INFORM global surveillance program from 2012 to 2015

Organism, phenotype (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b]			% susceptible[c]
		50%	90%	Range	
Enterobacteriaceae[d] (106)	Ceftazidime-avibactam	0.25	1	≤0.015 to >128	96.2
	Ceftazidime	2	>128	0.06 to >128	55.7
	Cefepime	≤0.12	>16	≤0.12 to >16	71.7
	Aztreonam	0.5	128	≤0.015 to >128	58.5
	Piperacillin-tazobactam	4	>128	0.5 to >128	74.5
	Doripenem	0.06	0.5	0.03 to >4	93.4
	Imipenem	0.5	4	0.06 to >8	80.2
	Meropenem	0.06	0.25	0.015 to >8	92.5
	Amikacin	2	8	1 to >32	96.2
	Colistin (n = 106)[e]	>4	>4	4 to >4	0
	Tigecycline	0.5	2	0.12 to 8	98.1
	Levofloxacin	0.12	>4	≤0.03 to >4	75.5
Enterobacteriaceae, MBL negative[d] (102)	Ceftazidime-avibactam	0.25	1	≤0.015 to 4	100
	Ceftazidime	1	128	0.06 to >128	57.8
	Cefepime	≤0.12	>16	≤0.12 to >16	73.5
	Aztreonam	0.5	128	≤0.015 to >128	58.8
	Piperacillin-tazobactam	4	>128	0.5 to >128	77.5
	Doripenem	0.06	0.25	0.03 to 4	97.1
	Imipenem	0.5	2	0.06 to 4	83.3
	Meropenem	0.06	0.25	0.015 to 8	96.1
	Amikacin	2	8	1 to >32	98.0
	Colistin (n = 102)[e]	>4	>4	4 to >4	0
	Tigecycline	0.5	1	0.12 to 8	98.0
	Levofloxacin	0.12	>4	≤0.03 to >4	77.5
Escherichia coli (12)	Ceftazidime-avibactam	0.12	0.25	0.03 to 0.5	100
	Ceftazidime	16	64	0.12 to >128	41.7
	Cefepime	4	>16	≤0.12 to >16	41.7
	Aztreonam	16	64	0.06 to 64	41.7
	Piperacillin-tazobactam	2	8	0.5 to >128	91.7
	Doripenem	0.06	0.12	0.03 to 0.12	100
	Imipenem	0.25	0.5	0.12 to 2	91.7
	Meropenem	0.03	0.06	0.03 to 0.12	100
	Amikacin	4	4	2 to 8	100
	Colistin (n = 12)[e]	4	4	4 to >4	0
	Tigecycline	0.25	1	0.12 to 2	100
	Levofloxacin	2	>4	≤0.03 to >4	58.3
Klebsiella pneumoniae (27)	Ceftazidime-avibactam	0.5	4	0.12 to >128	92.6
	Ceftazidime	128	>128	0.12 to >128	25.9
	Cefepime	>16	>16	≤0.12 to >16	33.3
	Aztreonam	128	>128	0.06 to >128	29.6
	Piperacillin-tazobactam	64	>128	0.5 to >128	44.4
	Doripenem	0.12	>4	0.03 to >4	81.5
	Imipenem	0.5	4	0.06 to >8	74.1
	Meropenem	0.06	8	0.03 to >8	77.8
	Amikacin	2	>32	1 to >32	85.2
	Colistin (n = 27)[e]	>4	>4	4 to >4	0
	Tigecycline	0.5	2	0.12 to 8	92.6
	Levofloxacin	>4	>4	0.06 to >4	37.0
Klebsiella pneumoniae, MBL negative (25)	Ceftazidime-avibactam	0.5	2	0.12 to 4	100
	Ceftazidime	128	>128	0.12 to >128	28.0
	Cefepime	>16	>16	≤0.12 to >16	36.0
	Aztreonam	128	>128	0.06 to >128	32.0
	Piperacillin-tazobactam	32	>128	0.5 to >128	48.0
	Doripenem	0.12	4	0.03 to >4	88.0
	Imipenem	0.5	4	0.06 to 4	80.0
	Meropenem	0.06	2	0.03 to 8	84.0
	Amikacin	2	16	1 to >32	92.0

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TABLE 5 (Continued)

Organism, phenotype (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b] 50%	90%	Range	% susceptible[c]
	Colistin (n = 25)[e]	>4	>4	4 to >4	0
	Tigecycline	0.5	2	0.12 to 8	92.0
	Levofloxacin	>4	>4	0.06 to >4	40.0
Klebsiella oxytoca (2)	Ceftazidime-avibactam	—	—	0.12 to 0.12	100
	Ceftazidime	—	—	0.12 to 0.12	100
	Cefepime	—	—	≤0.12 to ≤0.12	100
	Aztreonam	—	—	0.5 to 0.5	100
	Piperacillin-tazobactam	—	—	2 to 4	100
	Doripenem	—	—	0.06 to 0.06	100
	Imipenem	—	—	0.25 to 0.5	100
	Meropenem	—	—	0.06 to 0.06	100
	Amikacin	—	—	2 to 2	100
	Colistin (n = 2)[e]	—	—	4 to 4	0
	Tigecycline	—	—	0.5 to 0.5	100
	Levofloxacin	—	—	0.06 to 0.12	100
Enterobacter spp.[f] (64)	Ceftazidime-avibactam	0.25	1	0.03 to >128	96.9
	Ceftazidime	0.5	128	0.12 to >128	68.8
	Cefepime	≤0.12	2	≤0.12 to >16	92.2
	Aztreonam	0.12	32	≤0.015 to 64	71.9
	Piperacillin-tazobactam	4	64	0.5 to >128	82.8
	Doripenem	0.06	0.25	0.03 to >4	96.9
	Imipenem	1	4	0.25 to >8	81.3
	Meropenem	0.06	0.25	0.015 to >8	96.9
	Amikacin	2	2	1 to 16	100
	Colistin (n = 64)[e]	>4	>4	4 to >4	0
	Tigecycline	0.5	1	0.12 to 2	100
	Levofloxacin	0.06	1	≤0.03 to >4	93.8
Enterobacter spp., MBL negative (62)	Ceftazidime-avibactam	0.25	0.5	0.03 to 2	100
	Ceftazidime	0.5	128	0.12 to 128	71.0
	Cefepime	≤0.12	2	≤0.12 to >16	93.6
	Aztreonam	0.12	32	≤0.015 to 64	71.0
	Piperacillin-tazobactam	4	32	0.5 to >128	85.5
	Doripenem	0.06	0.25	0.03 to 0.5	100
	Imipenem	1	2	0.25 to 4	83.9
	Meropenem	0.06	0.12	0.015 to 0.5	100
	Amikacin	2	2	1 to 16	100
	Colistin (n = 62)[e]	>4	>4	4 to >4	0
	Tigecycline	0.5	1	0.12 to 2	100
	Levofloxacin	0.06	1	≤0.03 to >4	95.2
Citrobacter sp.[g] (1)	Ceftazidime-avibactam	—	—	≤0.015	100
	Ceftazidime	—	—	0.06	100
	Cefepime	—	—	≤0.12	100
	Aztreonam	—	—	≤0.015	100
	Piperacillin-tazobactam	—	—	0.5	100
	Doripenem	—	—	0.25	100
	Imipenem	—	—	4	0
	Meropenem	—	—	0.12	100
	Amikacin	—	—	2	100
	Colistin (n = 1)[e]	—	—	>4	0
	Tigecycline	—	—	1	100
	Levofloxacin	—	—	0.12	100
Pseudomonas aeruginosa (6)	Ceftazidime-avibactam	—	—	2 to 16	83.3
	Ceftazidime	—	—	1 to 128	66.7
	Cefepime	—	—	2 to >16	66.7
	Aztreonam	—	—	8 to 64	33.3
	Piperacillin-tazobactam	—	—	4 to >128	66.7
	Doripenem	—	—	0.25 to >4	83.3
	Imipenem	—	—	1 to >8	66.7

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TABLE 5 (Continued)

Organism, phenotype (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b] 50%	90%	Range	% susceptible[c]
	Meropenem	—	—	0.25 to 8	83.3
	Amikacin	—	—	2 to 16	100
	Colistin ($n = 6$)[e]	—	—	8 to >8	0
	Levofloxacin	—	—	0.5 to 4	83.3
Pseudomonas aeruginosa, MBL negative (6)	Ceftazidime-avibactam	—	—	2 to 16	83.3
	Ceftazidime	—	—	1 to 128	66.7
	Cefepime	—	—	2 to >16	66.7
	Aztreonam	—	—	8 to 64	33.3
	Piperacillin-tazobactam	—	—	4 to >128	66.7
	Doripenem	—	—	0.25 to >4	83.3
	Imipenem	—	—	1 to >8	66.7
	Meropenem	—	—	0.25 to 8	83.3
	Amikacin	—	—	2 to 16	100
	Colistin ($n = 6$)[e]	—	—	8 to >8	0
	Levofloxacin	—	—	0.5 to 4	83.3

[a]MBL negative, no gene encoding a metallo-β-lactamase was detected by PCR.
[b]—, MIC_{50} and MIC_{90} were not calculated for <10 isolates.
[c]Percent susceptibility was determined according to CLSI 2016 breakpoints, with the exception of that to ceftazidime-avibactam and tigecycline, where U.S. FDA breakpoints were applied. Because CLSI colistin breakpoints are not available for the *Enterobacteriaceae*, susceptibility for this organism group was determined using the EUCAST 2016 breakpoints for colistin.
[d]Excludes isolates of *Proteeae* and *Serratia* spp., which are intrinsically resistant to colistin.
[e]Values are for colistin tested without 0.002% polysorbate 80; data are for isolates collected in 2014 and 2015 only.
[f]The *Enterobacter* spp. included *Enterobacter asburiae* ($n = 28$), *Enterobacter cloacae* ($n = 33$), and *Enterobacter kobei* ($n = 3$).
[g]The *Citrobacter* sp. included *Citrobacter freundii* ($n = 1$).

hyperproduction of a chromosomal AmpC enzyme (13). VEB-type β-lactamases (80.6% of ESBLs) were the most common ESBLs identified and were found primarily in isolates from Thailand (Fig. S3A). VIM-type (58.0%) and IMP-type (35.8%) MBLs were the most common carbapenemases identified in the region. The majority of VIM-type enzymes detected were VIM-2 (80.9%), while the prevalence of the IMP-type enzymes was more varied, with IMP-26 (34.5%) and IMP-48 (20.7%) being the most common (Fig. S3B). In contrast to the *Enterobacteriaceae*, carbapenem nonsusceptibility in *P. aeruginosa* does not appear to be primarily mediated by the expression of carbapenemases (Fig. S3C). Ceftazidime-avibactam was not active against isolates carrying MBLs, as expected, but also demonstrated reduced activity against MBL-negative, ESBL-positive isolates (21.1% susceptible), while 91.3% of isolates with no acquired β-lactamase detected were susceptible to ceftazidime-avibactam (Table 2). The rate of susceptibility to ceftazidime-avibactam among all collected *P. aeruginosa* isolates ranged from 83.1% (Thailand) to 100% (Hong Kong) across the Asia-Pacific region, and the rate of susceptibility to ceftazidime-avibactam exceeded 90% for isolates from seven of the nine countries surveyed (Fig. 3).

Ceftazidime-nonsusceptible *P. aeruginosa* isolates were found across the region, with percentages varying from 12.0% (Australia) to 32.2% (Philippines) (Fig. S4). A total of 66.7% of ceftazidime-nonsusceptible *P. aeruginosa* isolates were susceptible to ceftazidime-avibactam, with the percent susceptibility ranging from 40.7% (Thailand) to 100% (Hong Kong) (Tables 3 and S2A to S10A). All comparator agents other than colistin (92.4% susceptible) and amikacin (78.7% susceptible) demonstrated lower activities than ceftazidime-avibactam against this subset of isolates. The activity of ceftazidime-avibactam against the MBL-negative ceftazidime-nonsusceptible subset (79.6% susceptible) was improved (Table 3).

The percentage of *P. aeruginosa* isolates that were meropenem nonsusceptible was 22.4% and ranged from 8.7% (Australia) to 31.5% (Thailand) (Tables 4 and S2A to S10A; Fig. S4). Overall, 70.5% of meropenem-nonsusceptible isolates collected in the region remained susceptible to ceftazidime-avibactam, which was a percent susceptibility higher than that observed for all other agents tested except colistin (96.2% susceptible) and amikacin (77.9% susceptible). The rate of susceptibility of meropenem-

TABLE 6 *In vitro* activities of ceftazidime-avibactam and comparator antimicrobial agents tested against 1,193 isolates of MDR *Enterobacteriaceae* and 301 isolates of MDR *P. aeruginosa* collected in the Asia-Pacific region as part of the INFORM global surveillance program from 2012 to 2015

Organism, genotype (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b]			% susceptible[c]
		50%	90%	Range	
Enterobacteriaceae (1,193)	Ceftazidime-avibactam	0.25	2	≤0.015 to >128	93.8
	Ceftazidime	64	>128	0.06 to >128	6.5
	Cefepime	>16	>16	≤0.12 to >16	5.1
	Aztreonam	64	>128	≤0.015 to >128	2.6
	Piperacillin-tazobactam	32	>128	≤0.25 to >128	46.9
	Doripenem	0.06	2	0.015 to >4	89.4
	Imipenem	0.25	4	0.06 to >8	84.0
	Meropenem	0.06	2	0.015 to >8	88.8
	Amikacin	4	>32	≤0.25 to >32	84.8
	Colistin (n = 509)[d]	0.5	4	0.25 to >4	88.2
	Tigecycline	0.5	2	0.06 to 8	93.4
	Levofloxacin	>4	>4	≤0.03 to >4	11.8
Enterobacteriaceae, MBL negative (1,133)	Ceftazidime-avibactam	0.25	1	≤0.015 to >128	98.8
	Ceftazidime	64	>128	0.06 to >128	6.8
	Cefepime	>16	>16	≤0.12 to >16	5.3
	Aztreonam	64	>128	≤0.015 to >128	1.8
	Piperacillin-tazobactam	32	>128	≤0.25 to >128	49.1
	Doripenem	0.06	0.5	0.015 to >4	94.1
	Imipenem	0.25	2	0.06 to >8	88.2
	Meropenem	0.06	0.25	0.015 to >8	93.3
	Amikacin	4	>32	≤0.25 to >32	86.2
	Colistin (n = 476)[d]	0.5	4	0.25 to >4	88.2
	Tigecycline	0.5	2	0.06 to 8	93.7
	Levofloxacin	>4	>4	≤0.03 to >4	10.9
Escherichia coli (569)	Ceftazidime-avibactam	0.25	0.5	≤0.015 to >128	99.3
	Ceftazidime	32	>128	0.5 to >128	7.0
	Cefepime	>16	>16	0.25 to >16	2.6
	Aztreonam	64	>128	8 to >128	0
	Piperacillin-tazobactam	8	>128	0.5 to >128	76.1
	Doripenem	0.06	0.12	0.015 to >4	97.9
	Imipenem	0.25	0.5	0.06 to >8	96.8
	Meropenem	0.03	0.12	0.015 to >8	97.2
	Amikacin	4	16	0.5 to >32	92.6
	Colistin (n = 205)[d]	0.5	1	0.25 to 4	97.6
	Tigecycline	0.25	0.5	0.06 to 4	99.8
	Levofloxacin	>4	>4	0.06 to >4	1.4
Escherichia coli, MBL negative (566)	Ceftazidime-avibactam	0.25	0.5	≤0.015 to >128	99.8
	Ceftazidime	32	>128	0.5 to >128	7.1
	Cefepime	>16	>16	0.25 to >16	2.7
	Aztreonam	64	>128	8 to >128	0
	Piperacillin-tazobactam	8	>128	0.5 to >128	76.5
	Doripenem	0.06	0.12	0.015 to >4	98.4
	Imipenem	0.25	0.5	0.06 to >8	97.4
	Meropenem	0.03	0.12	0.015 to >8	97.7
	Amikacin	4	16	0.5 to >32	92.8
	Colistin (n = 204)[d]	0.5	1	0.25 to 4	97.6
	Tigecycline	0.25	0.5	0.06 to 4	99.8
	Levofloxacin	>4	>4	0.06 to >4	1.4
Klebsiella pneumoniae (453)	Ceftazidime-avibactam	0.5	4	0.03 to >128	91.4
	Ceftazidime	128	>128	0.25 to >128	1.3
	Cefepime	>16	>16	≤0.12 to >16	3.8
	Aztreonam	128	>128	0.12 to >128	0.9
	Piperacillin-tazobactam	>128	>128	0.5 to >128	18.1
	Doripenem	0.12	>4	0.015 to >4	83.2
	Imipenem	0.5	>8	0.06 to >8	78.2
	Meropenem	0.06	>8	0.015 to >8	82.3
	Amikacin	4	>32	≤0.25 to >32	81.0

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TABLE 6 (Continued)

Organism, genotype (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b] 50%	90%	Range	% susceptible[c]
	Colistin (n = 234)[d]	1	2	0.25 to >4	91.5
	Tigecycline	1	2	0.06 to 8	91.4
	Levofloxacin	>4	>4	≤0.03 to >4	20.3
Klebsiella pneumoniae, MBL negative (421)	Ceftazidime-avibactam	0.5	2	0.03 to >128	98.3
	Ceftazidime	128	>128	0.25 to >128	1.4
	Cefepime	>16	>16	≤0.12 to >16	4.0
	Aztreonam	128	>128	0.12 to >128	0.5
	Piperacillin-tazobactam	>128	>128	0.5 to >128	19.2
	Doripenem	0.12	2	0.015 to >4	89.6
	Imipenem	0.25	2	0.06 to >8	83.6
	Meropenem	0.06	2	0.015 to >8	88.6
	Amikacin	4	>32	≤0.25 to >32	83.1
	Colistin (n = 214)[d]	0.5	2	0.25 to >4	91.6
	Tigecycline	1	2	0.06 to 8	91.0
	Levofloxacin	>4	>4	≤0.03 to >4	18.8
Klebsiella oxytoca (18)	Ceftazidime-avibactam	0.5	128	0.25 to 128	83.3
	Ceftazidime	64	>128	1 to >128	38.9
	Cefepime	16	>16	0.5 to >16	22.2
	Aztreonam	128	>128	32 to >128	0
	Piperacillin-tazobactam	>128	>128	16 to >128	5.6
	Doripenem	0.12	>4	0.03 to >4	83.3
	Imipenem	0.25	>8	0.12 to >8	83.3
	Meropenem	0.06	>8	0.03 to >8	83.3
	Amikacin	2	>32	1 to >32	77.8
	Colistin (n = 5)[d]	—	—	0.25 to 1	100
	Tigecycline	0.5	1	0.25 to 1	100
	Levofloxacin	4	>4	0.06 to >4	38.9
Klebsiella oxytoca, MBL negative (16)	Ceftazidime-avibactam	0.5	4	0.25 to 16	93.8
	Ceftazidime	16	>128	1 to >128	43.8
	Cefepime	8	>16	0.5 to >16	25.0
	Aztreonam	128	>128	32 to >128	0
	Piperacillin-tazobactam	>128	>128	16 to >128	6.3
	Doripenem	0.12	0.12	0.03 to 2	93.8
	Imipenem	0.25	0.5	0.12 to 8	93.8
	Meropenem	0.06	0.12	0.03 to 8	93.8
	Amikacin	2	>32	1 to >32	87.5
	Colistin (n = 5)[d]	0.25	1	0.25 to 1	100
	Tigecycline	0.5	1	0.25 to 1	100
	Levofloxacin	>4	>4	0.06 to >4	43.8
Enterobacter spp.[e] (76)	Ceftazidime-avibactam	1	>128	0.12 to >128	76.3
	Ceftazidime	>128	>128	2 to >128	4.0
	Cefepime	>16	>16	0.5 to >16	14.5
	Aztreonam	128	>128	0.06 to >128	6.6
	Piperacillin-tazobactam	>128	>128	4 to >128	13.2
	Doripenem	0.25	>4	0.03 to >4	72.4
	Imipenem	1	>8	0.25 to >8	64.5
	Meropenem	0.25	>8	0.03 to >8	71.1
	Amikacin	2	>32	0.5 to >32	81.6
	Colistin (n = 34)[d]	0.5	>4	0.25 to >4	70.6
	Tigecycline	1	4	0.25 to 8	79.0
	Levofloxacin	>4	>4	≤0.03 to >4	27.6
Enterobacter spp., MBL negative (61)	Ceftazidime-avibactam	1	8	0.12 to 64	95.1
	Ceftazidime	128	>128	2 to >128	4.9
	Cefepime	>16	>16	0.5 to >16	16.4
	Aztreonam	128	>128	16 to >128	0
	Piperacillin-tazobactam	>128	>128	4 to >128	14.8
	Doripenem	0.12	1	0.03 to >4	90.2
	Imipenem	1	2	0.25 to >8	80.3
	Meropenem	0.12	2	0.03 to >8	88.5

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TABLE 6 (Continued)

Organism, genotype (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b] 50%	90%	Range	% susceptible[c]
	Amikacin	2	>32	0.5 to >32	83.6
	Colistin (n = 24)[d]	1	>4	0.25 to >4	66.7
	Tigecycline	1	4	0.25 to 8	83.6
	Levofloxacin	>4	>4	≤0.03 to >4	31.2
Citrobacter spp.[f] (33)	Ceftazidime-avibactam	0.5	128	0.12 to >128	81.8
	Ceftazidime	128	>128	4 to >128	3.0
	Cefepime	>16	>16	≤0.12 to >16	15.2
	Aztreonam	64	>128	0.5 to >128	9.1
	Piperacillin-tazobactam	>128	>128	4 to >128	3.0
	Doripenem	0.12	>4	0.03 to >4	75.8
	Imipenem	1	>8	0.12 to >8	72.7
	Meropenem	0.12	>8	0.03 to >8	78.8
	Amikacin	8	>32	1 to >32	63.6
	Colistin (n = 6)[d]	—	—	0.25 to 1	100
	Tigecycline	0.5	1	0.12 to 2	100
	Levofloxacin	>4	>4	0.06 to >4	18.2
Citrobacter spp., MBL negative (28)	Ceftazidime-avibactam	0.5	4	0.12 to 128	96.4
	Ceftazidime	128	>128	4 to >128	3.6
	Cefepime	>16	>16	≤0.12 to >16	17.9
	Aztreonam	64	>128	4 to >128	3.6
	Piperacillin-tazobactam	>128	>128	4 to >128	3.6
	Doripenem	0.12	4	0.03 to >4	85.7
	Imipenem	1	4	0.12 to >8	82.1
	Meropenem	0.06	8	0.03 to >8	85.7
	Amikacin	8	>32	1 to >32	60.7
	Colistin (n = 4)[d]	0.25	0.5	0.25 to 0.5	100
	Tigecycline	0.5	2	0.12 to 2	100
	Levofloxacin	>4	>4	0.12 to >4	14.3
Proteeae[g] (35)	Ceftazidime-avibactam	0.12	4	≤0.015 to 64	91.4
	Ceftazidime	4	>128	0.06 to >128	54.3
	Cefepime	>16	>16	≤0.12 to >16	25.7
	Aztreonam	4	64	≤0.015 to 128	51.4
	Piperacillin-tazobactam	1	32	≤0.25 to 128	85.7
	Doripenem	0.25	2	0.06 to >4	88.6
	Imipenem	4	8	0.5 to >8	8.6
	Meropenem	0.12	2	0.03 to >8	88.6
	Amikacin	>32	>32	1 to >32	34.3
	Colistin (n = 19)[d]	>4	>4	>4 to >4	0
	Tigecycline	4	8	0.5 to 8	42.9
	Levofloxacin	>4	>4	0.12 to >4	5.7
Proteeae, MBL negative (33)	Ceftazidime-avibactam	0.12	1	≤0.015 to 32	97.0
	Ceftazidime	4	>128	0.06 to >128	57.6
	Cefepime	>16	>16	≤0.12 to >16	27.3
	Aztreonam	4	64	≤0.015 to 128	51.5
	Piperacillin-tazobactam	1	32	≤0.25 to 128	87.9
	Doripenem	0.25	0.5	0.06 to >4	93.9
	Imipenem	2	4	0.5 to >8	9.1
	Meropenem	0.12	0.25	0.03 to >8	93.9
	Amikacin	>32	>32	1 to >32	36.4
	Colistin (n = 19)[d]	>4	>4	>4 to >4	0
	Tigecycline	4	8	0.5 to 8	42.4
	Levofloxacin	>4	>4	0.12 to >4	6.1
Other *Enterobacteriaceae*[h] (9)	Ceftazidime-avibactam	—	—	0.12 to >128	88.9
	Ceftazidime	—	—	4 to >128	11.1
	Cefepime	—	—	4 to >16	0
	Aztreonam	—	—	0.25 to >128	11.1
	Piperacillin-tazobactam	—	—	4 to >128	33.3
	Doripenem	—	—	0.06 to >4	77.8
	Imipenem	—	—	0.25 to >8	66.7

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TABLE 6 (Continued)

Organism, genotype (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b] 50%	90%	Range	% susceptible[c]
	Meropenem	—	—	0.06 to >8	77.8
	Amikacin	—	—	0.5 to 16	100
	Colistin (n = 6)[d]	—	—	>4 to >4	0
	Tigecycline	—	—	0.5 to 8	66.7
	Levofloxacin	—	—	0.12 to >4	55.6
Other *Enterobacteriaceae*, MBL negative (8)	Ceftazidime-avibactam	—	—	0.12 to 1	100
	Ceftazidime	—	—	4 to >128	12.5
	Cefepime	—	—	4 to >16	0
	Aztreonam	—	—	16 to >128	0
	Piperacillin-tazobactam	—	—	4 to >128	25.0
	Doripenem	—	—	0.06 to >4	87.5
	Imipenem	—	—	0.25 to >8	75.0
	Meropenem	—	—	0.06 to >8	87.5
	Amikacin	—	—	0.5 to 16	100
	Colistin (n = 6)[d]	—	—	>4 to >4	0
	Tigecycline	—	—	0.5 to 8	62.5
	Levofloxacin	—	—	0.12 to >4	62.5
Pseudomonas aeruginosa (301)	Ceftazidime-avibactam	8	>128	1 to >128	52.8
	Ceftazidime	64	>128	1 to >128	8.3
	Cefepime	>16	>16	4 to >16	6.3
	Aztreonam	32	>128	4 to >128	9.3
	Piperacillin-tazobactam	>128	>128	4 to >128	4.0
	Doripenem	>4	>4	0.06 to >4	19.3
	Imipenem	>8	>8	0.5 to >8	18.9
	Meropenem	>8	>8	0.12 to >8	19.6
	Amikacin	8	>32	0.5 to >32	68.4
	Colistin (n = 193)[d]	2	2	0.25 to >8	94.8
	Levofloxacin	>4	>4	0.12 to >4	20.3
Pseudomonas aeruginosa, MBL negative (233)	Ceftazidime-avibactam	8	64	1 to >128	68.2
	Ceftazidime	64	>128	1 to >128	10.7
	Cefepime	>16	>16	4 to >16	8.2
	Aztreonam	64	>128	4 to >128	4.3
	Piperacillin-tazobactam	>128	>128	4 to >128	3.4
	Doripenem	>4	>4	0.06 to >4	24.9
	Imipenem	>8	>8	0.5 to >8	24.5
	Meropenem	>8	>8	0.12 to >8	25.3
	Amikacin	8	>32	0.5 to >32	80.3
	Colistin (n = 143)[d]	2	2	0.25 to >8	95.1
	Levofloxacin	>4	>4	0.12 to >4	25.8

[a]MBL negative, no gene encoding a metallo-β-lactamase was detected by PCR.
[b]—, MIC_{50} and MIC_{90} were not calculated for <10 isolates.
[c]Percent susceptibility was determined according to CLSI 2016 breakpoints, with the exception of that to ceftazidime-avibactam and tigecycline, where U.S. FDA breakpoints were applied. Because CLSI colistin breakpoints are not available for the *Enterobacteriaceae*, susceptibility for this organism group was determined using the EUCAST 2016 breakpoints for colistin.
[d]Values are for colistin tested without 0.002% polysorbate 80; data are for isolates collected in 2014 and 2015 only.
[e]The *Enterobacter* spp. included *Enterobacter aerogenes* (n = 11), *Enterobacter asburiae* (n = 5), *Enterobacter cloacae* (n = 59), and *Enterobacter kobei* (n = 1).
[f]The *Citrobacter* spp. included *Citrobacter braakii* (n = 2), *Citrobacter freundii* (n = 21), and *Citrobacter koseri* (n = 10).
[g]The *Proteeae* included *Morganella morganii* (n = 5), *Proteus mirabilis* (n = 26), *Proteus vulgaris* (n = 1), and *Providencia stuartii* (n = 3).
[h]Other *Enterobacteriaceae* included *Serratia marcescens* (n = 9).

nonsusceptible isolates to ceftazidime-avibactam was the lowest in Thailand (48.4% susceptible), Philippines (54.4% susceptible), and Malaysia (66.7% susceptible) and increased by 12.9 to 39.9% when isolates carrying MBLs were excluded (Tables S2A to S10A).

Only six isolates of *P. aeruginosa* collected in Asia-Pacific countries were resistant to colistin (0.3% of the total) (Table 5). No colistin-resistant isolates of *P. aeruginosa* that carried MBL genes were identified. Five of the six colistin-resistant isolates were susceptible to ceftazidime-avibactam. The single colistin- and ceftazidime-avibactam-resistant isolate was collected in Philippines (Table S7A).

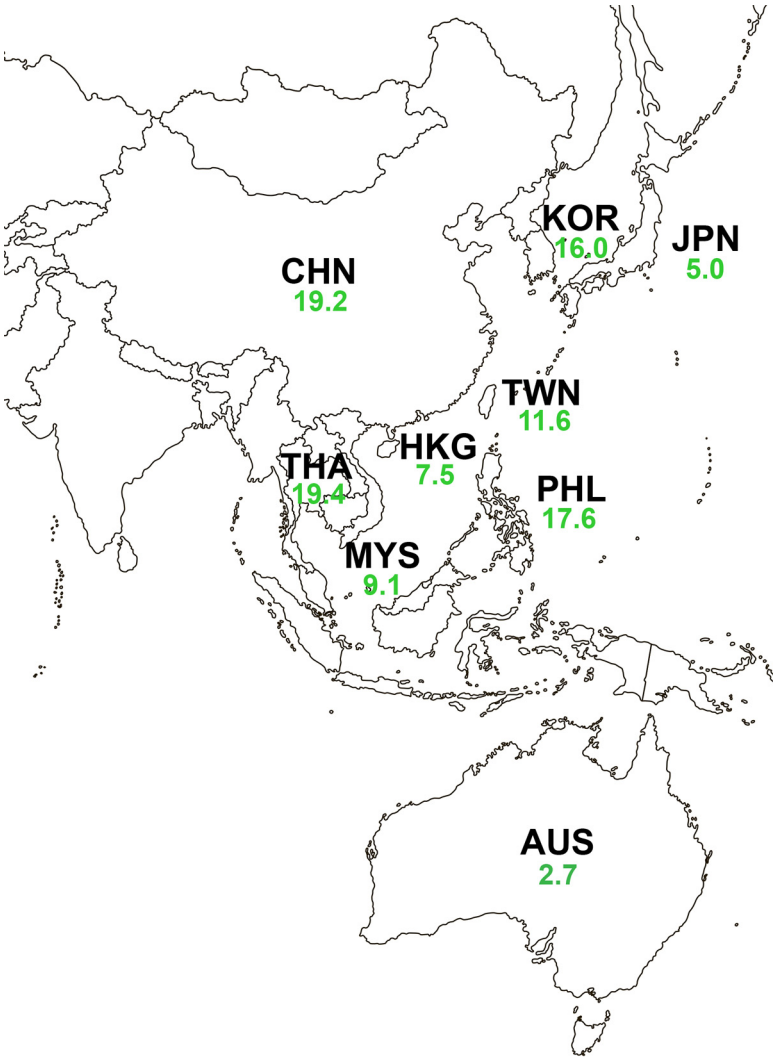

FIG 2 Percentage of isolates of *Enterobacteriaceae* collected from 2012 to 2015 that were multidrug resistant (MDR), by Asia-Pacific country. Multidrug resistance was defined as resistance by CLSI criteria to three or more sentinel antimicrobial agents from different chemical classes. The green font indicates that <20% of isolates were MDR. Country abbreviations are as follows: AUS, Australia; CHN, China; HKG, Hong Kong; JPN, Japan; KOR, South Korea; MYS, Malaysia; PHL, Philippines; TWN, Taiwan; THA, Thailand. No isolates were obtained from patients in mainland China in 2014 or 2015 or patients in Hong Kong in 2015 due to export restrictions.

A total of 301 MDR isolates of *P. aeruginosa* were identified (14.8% of all isolates), with the percentages of isolates testing as MDR varying from 5.7% (Australia) to 24.0% (Philippines) (Fig. 4). Of these, 52.8% remained susceptible to ceftazidime-avibactam; this percent susceptibility was higher than that observed to all other agents except colistin (94.8% susceptible) and amikacin (68.4% susceptible) (Table 6). Ceftazidime-avibactam was the least active against MDR isolates from Thailand (21.9% susceptible; MIC_{90}, >128 μg/ml), Philippines (37.0% susceptible; MIC_{90}, >128 μg/ml), and Malaysia (41.7% susceptible; MIC_{90}, >128 μg/ml) and was the most active against MDR isolates from China (83.3% susceptible; MIC_{90}, 64 μg/ml) and Australia (82.4% susceptible; MIC_{90}, 32 μg/ml) (Tables 7 and S2A to S10A). Although the activity of ceftazidime-avibactam against MBL-negative isolates improved, MIC_{90} values remained above the susceptibility breakpoint ($\leq$8 μg/ml) in all countries (Tables 7 and S2A to S10A). Nonetheless, ceftazidime-avibactam remained the second or third most active agent after colistin (and sometimes amikacin) against MDR isolates in each of the nine countries.

TABLE 7 *In vitro* activity of ceftazidime-avibactam tested against 1,193 isolates of MDR *Enterobacteriaceae* and 301 isolates of MDR *P. aeruginosa* stratified by Asia-Pacific region country of origin and collected as part of the INFORM global surveillance program from 2012 to 2015

Organism, genotype[a]	Country (no. of isolates)	Ceftazidime-avibactam MIC (μg/ml)[b]			% susceptible[c]
		50%	90%	Range	
Enterobacteriaceae	Australia (36)	0.25	1	0.06 to 32	97.2
	China (239)	0.25	4	≤0.015 to >128	94.1
	Hong Kong (11)[d]	0.12	0.5	0.06 to 0.5	100
	Japan (39)[d]	0.25	0.5	≤0.015 to 8	100
	Malaysia (59)	0.25	1	0.03 to >128	98.3
	Philippines (229)	0.5	>128	0.03 to >128	83.8
	South Korea (190)[d]	0.5	1	≤0.015 to 4	100
	Taiwan (145)	0.5	2	0.03 to >128	96.6
	Thailand (245)	0.25	2	≤0.015 to >128	93.5
Enterobacteriaceae, MBL negative	Australia (35)	0.25	1	0.06 to 4	100
	China (231)	0.25	4	≤0.015 to >128	97.4
	Hong Kong (11)	0.12	0.5	0.06 to 0.5	100
	Japan (39)	0.25	0.5	≤0.015 to 8	100
	Malaysia (58)	0.25	1	0.03 to 4	100
	Philippines (196)	0.25	1	0.03 to >128	98.0
	South Korea (190)	0.5	1	≤0.015 to 4	100
	Taiwan (142)	0.5	2	0.03 to 16	98.6
	Thailand (231)	0.25	1	≤0.015 to 64	99.1
Pseudomonas aeruginosa	Australia (17)[d]	8	32	1 to 128	82.4
	China (30)[d]	8	64	1 to 128	83.3
	Hong Kong (3)[d]	—	—	4 to 8	100
	Japan (23)	8	32	2 to >128	78.3
	Malaysia (12)	16	>128	4 to >128	41.7
	Philippines (73)	32	>128	2 to >128	37.0
	South Korea (44)	8	128	2 to >128	68.2
	Taiwan (35)[d]	8	32	2 to >128	65.7
	Thailand (64)	64	>128	2 to >128	21.9
Pseudomonas aeruginosa, MBL negative	Australia (17)	8	32	1 to 128	82.4
	China (30)	8	64	1 to 128	83.3
	Hong Kong (3)	—	—	4 to 8	100
	Japan (21)	8	16	2 to 32	85.7
	Malaysia (8)	—	—	4 to >128	62.5
	Philippines (36)	8	32	2 to 32	75.0
	South Korea (39)	8	128	2 to 128	76.9
	Taiwan (35)	8	32	2 to >128	65.7
	Thailand (44)	16	>128	2 to >128	31.8

[a]MBL negative, no gene encoding a metallo-β-lactamase was detected by PCR.
[b]—, MIC_{50} and MIC_{90} were not calculated for <10 isolates.
[c]Percent susceptibility for ceftazidime-avibactam was determined by applying U.S. FDA breakpoints.
[d]All isolates were MBL negative.

DISCUSSION

Only two previous studies have specifically described the *in vitro* activity of ceftazidime-avibactam against clinical isolates of *Enterobacteriaceae* and *P. aeruginosa* from the Asia-Pacific region (2, 14). In the first study, Flamm et al. tested 137 urinary isolates of *Enterobacteriaceae* collected in Australia, China, India, South Korea, Malaysia, Singapore, Thailand, and Hong Kong in 2011 (14). They reported the ceftazidime-avibactam MIC_{90} to be 1 μg/ml, slightly higher than the MIC_{90} values (0.25 to 0.5 μg/ml) for urinary isolates of *Enterobacteriaceae* from the United States, Europe, and Latin America (14). In the current study, we found that 99.0% of *Enterobacteriaceae* isolates were susceptible to ceftazidime-avibactam (MIC, ≤8 μg/ml) with a MIC_{90} of 0.5 μg/ml and that ceftazidime-avibactam MIC_{90} values for individual species or species groups within the family *Enterobacteriaceae* ranged from 0.12 μg/ml (*Proteeae*) to 1 μg/ml (*Enterobacter* spp.). We observed only a minor variation (<2%) in the percent susceptibility to ceftazidime-avibactam, which ranged from 98.1% (*Enterobacter* spp.) to 99.9% (*E. coli*) (Table 1). It was observed that country-specific variances in the incidence of

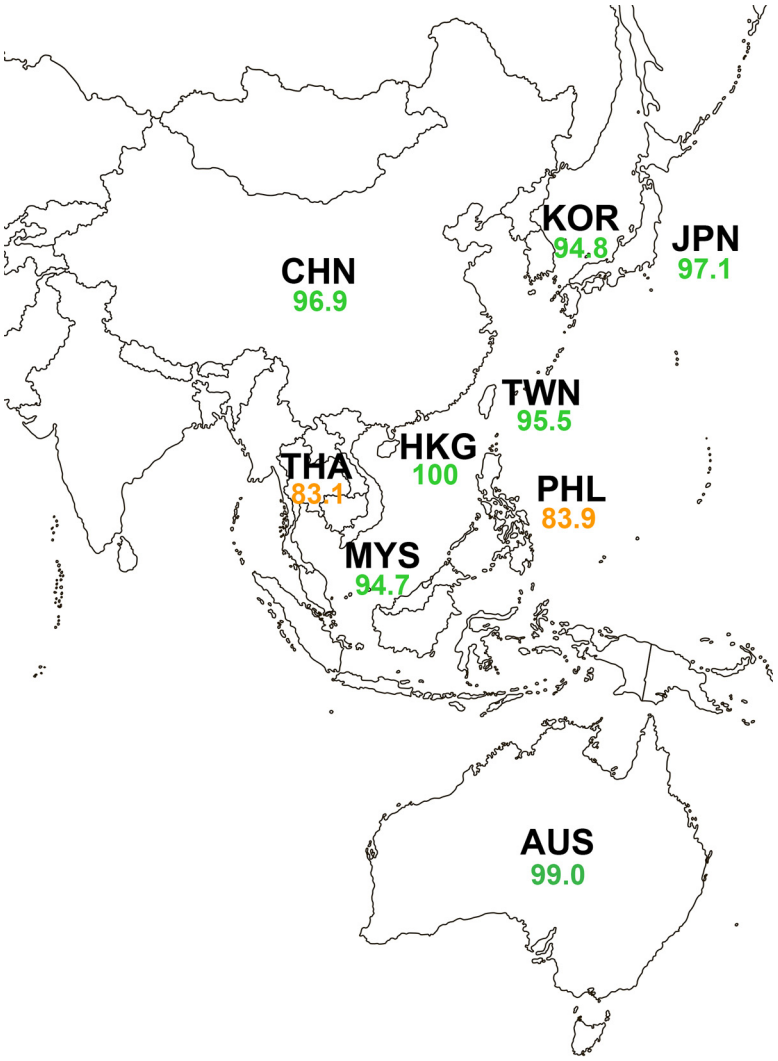

FIG 3 Percent susceptibility to ceftazidime-avibactam for isolates of *P. aeruginosa* collected from 2012 to 2015, by Asia-Pacific country. Ceftazidime-avibactam susceptible was defined as an MIC of ≤8 μg/ml; ceftazidime-avibactam resistant was defined as an MIC of ≥16 μg/ml. The green font indicates that >90% of isolates were ceftazidime-avibactam susceptible. The orange font indicates that 80 to 89.9% of isolates were ceftazidime-avibactam susceptible. Country abbreviations are as follows: AUS, Australia; CHN, China; HKG, Hong Kong; JPN, Japan; KOR, South Korea; MYS, Malaysia; PHL, Philippines; TWN, Taiwan; THA, Thailand. No isolates were obtained from patients in mainland China in 2014 or 2015 or patients in Hong Kong in 2015 due to export restrictions.

MBL-producing isolates must be considered when assessing the activity of ceftazidime-avibactam against clinical isolates of *Enterobacteriaceae* as well as *P. aeruginosa*. In the second study, Nichols et al. reported that 93.2% of *P. aeruginosa* isolates from nine Asia-Pacific countries (41 laboratories, 1,392 isolates) were susceptible to ceftazidime-avibactam and that nonsusceptibility to ceftazidime-avibactam could be explained by the possession of genes encoding MBLs in approximately one-half of the nonsusceptible isolates (2). Nichols et al. also found that 68.9% of ceftazidime-nonsusceptible isolates were susceptible to ceftazidime-avibactam, as were 71.7% of meropenem-nonsusceptible isolates (2). In the current study, which is an extension of the Nichols et al. study with one additional year of data, 92.6% of all *P. aeruginosa* isolates were susceptible to ceftazidime-avibactam with a MIC_{90} of 8 μg/ml (Table 1); 66.7% of ceftazidime-nonsusceptible isolates (range, 40.7% [Thailand] to 100% [Hong Kong]) and 70.5% of meropenem-nonsusceptible isolates (range, 48.4% [Thailand] to 100% [Hong Kong]) were also susceptible to ceftazidime-avibactam.

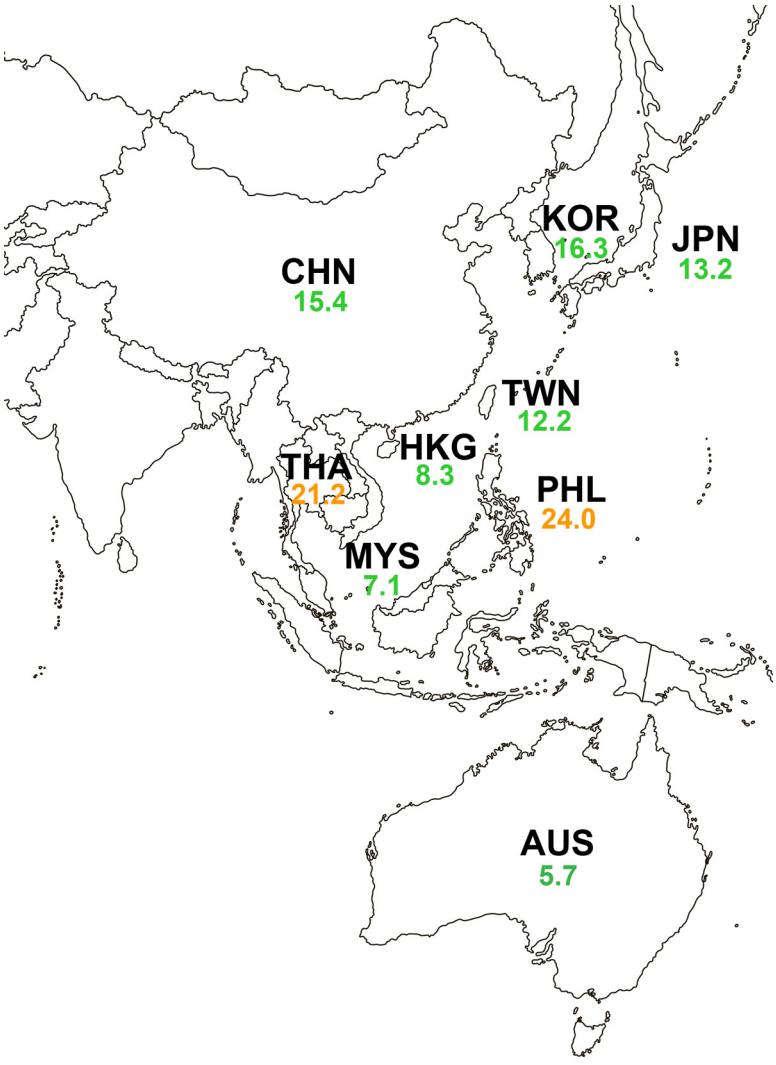

FIG 4 Percentage of isolates of *P. aeruginosa* collected from 2012 to 2015 that were multidrug resistant (MDR), by Asia-Pacific country. Multidrug resistance was defined as resistance by CLSI criteria to three or more sentinel antimicrobial agents from different chemical classes. The green font indicates that <20% of isolates were MDR. The orange font indicates that 20 to 29.9% of isolates were MDR. Country abbreviations are as follows: AUS, Australia; CHN, China; HKG, Hong Kong; JPN, Japan; KOR, South Korea; MYS, Malaysia; PHL, Philippines; TWN, Taiwan; THA, Thailand. No isolates were obtained from patients in mainland China in 2014 or 2015 or patients in Hong Kong in 2015 due to export restrictions.

In studies in which the prevalence of specific β-lactamases was assessed, Kiratisin et al. reported that among 500 *Enterobacteriaceae* isolates collected from 20 centers in five Asia-Pacific countries in 2010, ESBL-positive rates were the highest in Thailand (45.2%) and Vietnam (55.1%) and that 97.2% of *Enterobacteriaceae* were susceptible to all carbapenems tested (9). A total of 625 isolates of *P. aeruginosa* were also tested, and the investigators reported that between 10.3% (New Zealand) and 46.7% (Vietnam) (mean, 29.8%) of *P. aeruginosa* isolates were nonsusceptible to at least one carbapenem (9). Mendes et al. studied isolates from 12 Asia-Pacific countries and reported that ESBL-positive rates in *E. coli* and *K. pneumoniae* varied widely between countries (ranging from 10 to 15% in Australia and New Zealand to 47 to 91% in Taiwan, India, Indonesia, and Philippines) (10). *P. aeruginosa* isolates collected as part of the same study demonstrated rates of resistance of >20% to all antimicrobial agents tested, except for colistin (99% susceptible), amikacin (92% susceptible), gentamicin (85% susceptible), and tobramycin (85% susceptible) (10). Pfaller et al. studied isolates from 11 Asia-Pacific countries (29 laboratories) and reported the rates of the ESBL phenotype (MICs, ≥2

μg/ml for ceftazidime, ceftriaxone, or aztreonam), MDR, and carbapenem resistance among *E. coli* and *K. pneumoniae* isolates (8). For isolates from Australia and New Zealand combined, the rates of the ESBL and MDR phenotypes were 8.4% and 4.2%, respectively, among *E. coli* isolates and 8.5% and 2.4%, respectively, among *K. pneumoniae* isolates, with no carbapenem-resistant isolates being identified in either species (8). For isolates from China, the rates of the ESBL phenotype, MDR, and carbapenem resistance were 66.9%, 36.8%, and 1.1%, respectively, among *E. coli* isolates and 45.6%, 26.3%, and 12.9%, respectively, among *K. pneumoniae* isolates (8). For isolates from other Asian countries (Hong Kong, Indonesia, Malaysia, Philippines, Singapore, South Korea, Taiwan, and Thailand) combined, the rates of the ESBL and MDR phenotypes were 39.2% and 21.7%, respectively, for *E. coli* and 41.9% and 29.1%, respectively, for *K. pneumoniae*; no *E. coli* isolates and 4.2% of *K. pneumoniae* isolates were carbapenem resistant (8). Sheng et al. studied 699 genotypically characterized β-lactamase-positive isolates of *Enterobacteriaceae* collected in 2008 and 2009 from 11 countries (34 medical centers) in the Asia-Pacific region (15). They reported that CTX-M-type enzymes were the most common ESBLs found, comprising 90.3% of all ESBLs (CTX-M-15 accounted for 72.7% of CTX-M β-lactamases). CMY was the most frequently identified AmpC, accounting for 56.1% of detected AmpCs (CMY-2 was the most prevalent subtype), and NDM-type MBLs were the most common carbapenemases found, accounting for 82.3% of MBLs detected (15). Carbapenemases were almost exclusively found in *Enterobacteriaceae* from India, except for IMP-type carbapenemases, which were also detected in isolates from Philippines and Australia (15). IMP-positive isolates of *Enterobacteriaceae* and *P. aeruginosa* have previously been reported to be more common in the Asia-Pacific region than in other regions of the world (11, 16). Isolates containing plasmid-mediated AmpC β-lactamases, such as DHA and CMY, together with ESBLs or carbapenemases were also common in the Asia-Pacific region (15). Even though the INFORM study is not structured to determine the prevalence of β-lactamases causing specific resistance phenotypes, it is noteworthy that the current study observed β-lactamase distributions similar to those in the published reports described above.

In the current study, for the *Enterobacteriaceae*, generally only the presence of an MBL gene was associated with *in vitro* resistance to ceftazidime-avibactam (Table 2) (6, 7). Isolates of the *Enterobacteriaceae* nonsusceptible to carbapenems by other mechanisms, such as production of GES, KPC (3, 6, 7, 17), and OXA-48 (6, 17) carbapenemases (Table 2) or production of an ESBL or AmpC enzyme combined with reduced drug permeability (6), were susceptible to ceftazidime-avibactam. Intrinsic imipenem resistance among *Proteeae* species (18) also did not affect susceptibility to ceftazidime-avibactam (Table 1). The current study identified only a few isolates of *Enterobacteriaceae* (17 isolates; 0.2%) for which the reduced ceftazidime-avibactam susceptibility could not be explained by the presence of an MBL. The mechanism(s) of reduced susceptibility remains to be determined for those isolates but may be attributable to porin or penicillin-binding protein changes or the presence of avibactam-insensitive β-lactamases (e.g., other MBLs) that were not detected by the current molecular testing algorithm (16). None of the isolates with reduced susceptibility to ceftazidime-avibactam identified in this study carried KPC β-lactamases with amino acid substitutions in Ser130 or the Ω loop (Arg164 to Asp179), reported to confer resistance to ceftazidime-avibactam (19–22). Upregulated efflux of ceftazidime-avibactam is a less likely explanation, as efflux was not implicated in reduced susceptibility to ceftazidime-avibactam in a direct test of that mechanism (23).

We conclude that clinical isolates of *Enterobacteriaceae* (99.0% susceptible) and *P. aeruginosa* (92.6% susceptible) collected from nine Asia-Pacific countries from 2012 to 2015 were highly susceptible to ceftazidime-avibactam and that ceftazidime-avibactam was as active as and frequently more active than currently available antimicrobial agents of last resort (i.e., amikacin, colistin, and tigecycline). Ceftazidime-avibactam retained its potent *in vitro* activity against the majority of MBL-negative *Enterobacteriaceae* and *P. aeruginosa* isolates with ceftazidime-nonsusceptible, meropenem-nonsusceptible, colistin-resistant, and MDR phenotypes collected in the Asia-Pacific

region from 2012 to 2015. We observed that the percent susceptibility to ceftazidime-avibactam for *Enterobacteriaceae* isolates from six of the nine Asia-Pacific countries surveyed ranged from 99.1 to 100% (MIC_{90}, 0.25 to 0.5 μg/ml), while isolates from China (98.8% susceptible; MIC_{90}, 0.5 μg/ml), Thailand (98.7% susceptible; MIC_{90}, 0.5 μg/ml), and Philippines (97.0% susceptible; MIC_{90}, 0.5 μg/ml) were slightly less susceptible. This finding correlated with Philippines, Thailand, and China having the highest percentages of isolates carrying MBLs (2.7, 1.2, and 0.8%, respectively), while the percentages of MBL-positive isolates from the other six countries ranged from none (no isolates in Hong Kong and South Korea) to 0.6% (Taiwan). We also noted that the percent susceptibility to ceftazidime-avibactam for *P. aeruginosa* isolates was associated with the percentage of isolates carrying MBLs. For the seven countries with percent susceptibilities to ceftazidime-avibactam of >94%, the percentage of MBL-positive isolates ranged from none (no isolates in Australia and Hong Kong) to 3.0% (Malaysia), while Philippines (where 83.9% of isolates were susceptible to ceftazidime-avibactam) and Thailand (where 83.1% of isolates were susceptible to ceftazidime-avibactam) had 13.2 and 6.6% of isolates carrying an MBL, respectively. The differences in antimicrobial susceptibilities observed across countries in a specific geographic region, such as the Asia-Pacific region, demonstrate the importance of performing regional surveillance.

MATERIALS AND METHODS

Clinical isolates of *Enterobacteriaceae* and *P. aeruginosa*. The INFORM global surveillance program collected and confirmed the identities of 11,187 nonduplicate clinical isolates of Gram-negative bacilli (9,149 isolates of *Enterobacteriaceae*; 2,038 isolates of *P. aeruginosa*) from 42 medical center laboratories in nine Asia-Pacific countries from 2012 to 2015. Each participating medical center laboratory was requested to collect predefined numbers of selected bacterial pathogens isolated from patients with specific infection types on an annual basis (2, 5). Isolates were limited to one per patient, were determined by the participating laboratory algorithms to be clinically significant, and were collected irrespective of their antimicrobial susceptibility profile (2, 5). Isolates of the *Enterobacteriaceae* belonging to the tribe *Proteeae*, which includes the three genera *Proteus*, *Providencia*, and *Morganella*, were frequently analyzed together as a group. The demographic information associated with the 11,187 isolates is summarized in Table S1 in the supplemental material. Isolates were transported to International Health Management Associates, Inc. (IHMA; Schaumburg, IL, USA), which served as the central reference laboratory for the INFORM global surveillance study. At IHMA, the identity of each isolate was confirmed using a Bruker Biotyper matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry instrument (Bruker Daltonics, Billerica, MA, USA).

Antimicrobial susceptibility testing. Clinical and Laboratory Standards Institute (CLSI)-defined broth microdilution antimicrobial susceptibility testing was performed using in-house-prepared (at IHMA), 96-well broth microdilution panels (18, 24). Avibactam was tested at a fixed concentration of 4 μg/ml in combination with doubling dilutions of ceftazidime (18). MICs were interpreted using 2016 CLSI breakpoints (18), with the following exceptions. Ceftazidime-avibactam MICs were interpreted using U.S. FDA MIC breakpoints for *Enterobacteriaceae* and *P. aeruginosa* (susceptible, ≤8 μg/ml; resistant, ≥16 μg/ml) (25), as CLSI MIC breakpoints were not published at the time of the study. U.S. FDA MIC interpretative breakpoints were also used for tigecycline (26). EUCAST MIC interpretative breakpoints were used for colistin when it was tested against *Enterobacteriaceae* (27), as CLSI criteria for colistin are also not available.

Isolates of *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis* that tested with MICs of ≥2 μg/ml to ceftazidime or aztreonam were subjected to phenotypic combination testing with clavulanic acid to confirm the presence of an ESBL (18). An MDR phenotype was defined according to the criteria of Magiorakos et al. as resistance to sentinel agents from three or more antimicrobial agent classes (the sentinel agents are indicated in parentheses), including cephalosporins (cefepime), monobactams (aztreonam), β-lactam–β-lactamase inhibitor combinations (piperacillin-tazobactam), carbapenems (meropenem), fluoroquinolones (levofloxacin), aminoglycosides (amikacin), glycylcyclines (tigecycline), and polymyxins (colistin) (28).

Screening for β-lactamase genes. All *Enterobacteriaceae* isolates demonstrating a positive ESBL confirmatory test, MICs to ceftazidime of ≥16 μg/ml, or MICs to doripenem, imipenem, or meropenem of ≥2 μg/ml were screened for β-lactamase content using a combination of the microarray-based Check-MDR CT101 kit (Check-Points, Wageningen, Netherlands) and published multiplex PCR assays (29). These assays detected genes encoding carbapenemases (KPC, GES, NDM, IMP, VIM, SPM, GIM, OXA-48), ESBLs (TEM, SHV, CTX-M, VEB, PER, GES), original-spectrum β-lactamases (OSBLs; TEM and SHV enzymes that do not contain substitutions at amino acid position 104, 164, or 238 in TEM or 146, 238, or 240 in SHV, which are associated with ESBL activity, e.g., TEM-1, SHV-1, and SHV-11), and plasmid-mediated AmpC β-lactamases (ACC, ACT, CMY, DHA, FOX, MIR, MOX), as previously described (29). All *P. aeruginosa* isolates testing with MICs to doripenem, imipenem, or meropenem of ≥4 μg/ml were screened for genes encoding the carbapenemases, ESBLs, and OSBLs listed above, plus OXA-24, as described previously (2). Enzyme variants were identified by amplification of full-length β-lactamase genes, followed by DNA

sequencing and comparison of the sequences to those deposited in the National Center for Biotechnology Information database (www.ncbi.nlm.nih.gov) and on the Lahey Clinic website (www.lahey.org/studies).

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/AAC.02569-17.

SUPPLEMENTAL FILE 1, PDF file, 5.0 MB.

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