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

James A. Karlowsky,[a] Krystyna M. Kazmierczak,[a] Samuel K. Bouchillon,[a] Boudewijn L. M. de Jonge,[b*] Gregory G. Stone,[b*] Daniel F. Sahm[a]

[a]International Health Management Associates, Inc., Schaumburg, Illinois, USA
[b]AstraZeneca Pharmaceuticals, Waltham, Massachusetts, USA

ABSTRACT The International Network for Optimal Resistance Monitoring (INFORM) global surveillance program collected clinical isolates of *Enterobacteriaceae* ($n = 7,665$) and *Pseudomonas aeruginosa* ($n = 1,794$) from 26 medical centers in six Latin American countries from 2012 to 2015. The *in vitro* activity of ceftazidime-avibactam and comparators was determined for the isolates using the Clinical and Laboratory Standards Institute (CLSI) reference broth microdilution method. *Enterobacteriaceae* were highly susceptible (99.7%) to ceftazidime-avibactam, including 99.9% of metallo-β-lactamase (MBL)-negative isolates; 87.4% of all *P. aeruginosa* isolates and 92.8% of MBL-negative isolates were susceptible to ceftazidime-avibactam. Susceptibility to ceftazidime-avibactam ranged from 99.4% to 100% for *Enterobacteriaceae* and from 79.1% to 94.7% for *P. aeruginosa* when isolates were analyzed by country of origin. Ceftazidime-avibactam inhibited 99.6% to 100% of *Enterobacteriaceae* isolates that carried serine β-lactamases, including extended-spectrum β-lactamases (ESBLs), AmpC cephalosporinases, and carbapenemases (KPC and OXA-48-like) as well as 99.7%, 99.6%, 99.5%, and 99.2% of MBL-negative isolates demonstrating ceftazidime-nonsusceptible, multidrug-resistant (MDR), meropenem-nonsusceptible, and colistin-resistant phenotypes, respectively. Among carbapenem-nonsusceptible isolates of *P. aeruginosa* ($n = 750$), 14.7% carried MBLs with or without additional acquired serine β-lactamases, while in the majority of isolates (70.0%), no acquired β-lactamase was identified. Ceftazidime-avibactam inhibited 89.5% of carbapenem-nonsusceptible *P. aeruginosa* isolates in which no acquired β-lactamase was detected. Overall, clinical isolates of *Enterobacteriaceae* collected in Latin America from 2012 to 2015 were highly susceptible to ceftazidime-avibactam, including isolates that exhibited resistance to ceftazidime, meropenem, colistin, or an MDR phenotype. Country-specific variations were noted in the susceptibility of *P. aeruginosa* isolates to ceftazidime-avibactam.

KEYWORDS *Enterobacteriaceae*, Gram negative, Latin America, *Pseudomonas aeruginosa*, ceftazidime-avibactam, surveillance

Address correspondence to Krystyna M. Kazmierczak, kkazmierczak@ihmainc.com.

* Present address: Boudewijn L. M. de Jonge, Pfizer, Cambridge, Massachusetts, USA; Gregory G. Stone, Pfizer, Groton, Connecticut, USA.

The threat of increasing resistance to β-lactams (penicillins, cephalosporins, β-lactam/β-lactamase inhibitor combinations, carbapenems, and monobactams) among clinical isolates of *Enterobacteriaceae* and *Pseudomonas aeruginosa* in Latin American countries and elsewhere is of great concern because agents in this antimicrobial class reliably demonstrate both efficacy and safety and are widely used (1–9). β-Lactam resistance mechanisms include β-lactamase production, porin mutation or porin loss, membrane-associated efflux pumps, and structural alterations in penicillin-binding proteins. Resistance determinants may occur individually or in combination

and can confer a multitude of phenotypes upon *in vitro* testing. Among the mechanisms of β-lactam resistance identified to date, β-lactamase production is the most common in Gram-negative bacilli. The Ambler molecular classification system divides β-lactamases into four classes, A through D. The emergence and spread of carbapenemases, which are included among class A (e.g., KPC), class B (e.g., NDM, IMP, VIM, and SPM), and class D (e.g., OXA) β-lactamases, are of greatest concern because these enzymes frequently generate resistance to all β-lactams, and because isolates carrying carbapenemases often demonstrate multidrug-resistant (MDR) phenotypes that limit therapeutic options and are associated with increased risk of morbidity and mortality for patients (1, 3, 6, 10).

Avibactam is a newer non-β-lactam β-lactamase inhibitor that has been paired with ceftazidime to restore its activity and/or to improve its potency against isolates of Gram-negative bacilli carrying Ambler class A β-lactamases, including extended spectrum β-lactamases (ESBLs) (e.g., TEM-type, SHV-type, and CTX-M-type) and KPC carbapenemases, AmpC cephalosporinases (Ambler class C β-lactamases), and some class D β-lactamases (e.g., OXA-48), including isolates carrying ESBL and AmpC enzymes in combination with impaired permeability (1, 6, 10–14). Ceftazidime-avibactam is not active against *Enterobacteriaceae* and *P. aeruginosa* isolates producing class B metallo-β-lactamases (MBLs) (6, 13).

To date, only a limited number of surveillance studies to determine rates of antimicrobial resistance in clinical isolates from patients in Latin America has been conducted (2, 4–9, 15). Previous surveillance studies have reported that the prevalence of β-lactam-resistant and MDR *Enterobacteriaceae* and nonfermentative Gram-negative bacilli varies within Latin America. The data are diverse, study dependent and difficult to compare (1–9, 15). To date, the majority of published studies have neither included molecular characterization of β-lactamases specifically from the Latin American region nor provided ceftazidime-avibactam susceptibility data for Gram-negative bacilli isolated from patients in many Latin American countries (2–9, 15). The intent of the current study is to augment currently published phenotypic data by determining *in vitro* susceptibilities to ceftazidime-avibactam and comparators for clinical isolates of *Enterobacteriaceae* and *P. aeruginosa* specifically collected from hospitalized patients in six Latin American 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. 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 7,665 isolates of *Enterobacteriaceae* tested, 99.7% were susceptible to ceftazidime-avibactam (MIC_{90}, 0.5 μg/ml). Percentages of susceptibility to all other antimicrobial agents tested, including doripenem (95.5%), meropenem (94.9%), amikacin (94.9%), tigecycline (93.7%), imipenem (83.9%), colistin (83.0%), and piperacillin-tazobactam (81.1%), were lower than for ceftazidime-avibactam (Table 1). Ceftazidime-avibactam MIC_{90} values for individual species or species groups within the *Enterobacteriaceae* family ranged from 0.12 μg/ml (tribe Proteeae) to 1 μg/ml (*Enterobacter* spp. and *Klebsiella pneumoniae*), with percent susceptibility to ceftazidime-avibactam varying by only 0.7%, from 99.2% susceptible for *Enterobacter* spp. to 99.9% susceptible for *E. coli* and Proteeae isolates (Table 1). Percent susceptibility to ceftazidime-avibactam was higher for isolates of *Enterobacteriaceae* that did not carry MBLs (99.9% susceptible) (Table 1) than for MBL-positive isolates (5.9% susceptible; 1/17 isolates) (Table 2). Due to the low percentage of MBL-positive isolates collected in this region, percent susceptibilities to ceftazidime-avibactam were only marginally higher (≤0.5%) for MBL-negative isolates of individual species or species groups of *Enterobacteriaceae*

TABLE 1 *In vitro* activities of ceftazidime-avibactam and comparator antimicrobial agents tested against *Enterobacteriaceae* and *P. aeruginosa* isolates[a]

Organism, phenotype/genotype (no. of isolates)[b]	Antimicrobial agent	MIC (μg/ml)			% Susceptible[c]
		MIC$_{50}$	MIC$_{90}$	Range	
Enterobacteriaceae (7,665)	Ceftazidime-avibactam	0.12	0.5	≤0.015 to >128	99.7
	Ceftazidime	0.25	64	≤0.015 to >128	69.9
	Cefepime	≤0.12	>16	≤0.12 to >16	70.4
	Aztreonam	0.12	128	≤0.015 to >128	68.0
	Piperacillin-tazobactam	4	>128	≤0.25 to >128	81.1
	Doripenem	0.06	0.25	≤0.008 to >4	95.5
	Imipenem	0.25	2	≤0.03 to >8	83.9
	Meropenem	0.03	0.12	≤0.004 to >8	94.9
	Amikacin	2	8	≤0.25 to >32	94.9
	Colistin ($n = 4{,}516$)[d]	0.5	>4	≤0.12 to >4	83.0
	Tigecycline	0.5	2	≤0.015 to >8	93.7
	Levofloxacin	0.25	>4	≤0.03 to >4	67.5
Enterobacteriaceae, MBL negative (7,648)	Ceftazidime-avibactam	0.12	0.5	≤0.015 to >128	99.9
	Ceftazidime	0.25	64	≤0.015 to >128	70.0
	Cefepime	≤0.12	>16	≤0.12 to >16	70.5
	Aztreonam	0.12	128	≤0.015 to >128	68.0
	Piperacillin-tazobactam	4	128	≤0.25 to >128	81.3
	Doripenem	0.06	0.25	≤0.008 to >4	95.7
	Imipenem	0.25	2	≤0.03 to >8	84.1
	Meropenem	0.03	0.12	≤0.004 to >8	95.1
	Amikacin	2	8	≤0.25 to >32	95.0
	Colistin ($n = 4{,}500$)[d]	0.5	>4	≤0.12 to >4	83.1
	Tigecycline	0.5	2	≤0.015 to >8	93.8
	Levofloxacin	0.25	>4	≤0.03 to >4	67.6
Escherichia coli (2,705)	Ceftazidime-avibactam	0.12	0.25	≤0.015 to 32	99.9
	Ceftazidime	0.25	64	≤0.015 to >128	70.9
	Cefepime	≤0.12	>16	≤0.12 to >16	67.7
	Aztreonam	0.12	64	≤0.015 to >128	67.7
	Piperacillin-tazobactam	2	32	≤0.25 to >128	88.9
	Doripenem	0.03	0.06	≤0.008 to >4	99.5
	Imipenem	0.12	0.25	≤0.03 to >8	99.2
	Meropenem	0.03	0.06	≤0.004 to >8	99.4
	Amikacin	4	8	0.5 to >32	97.1
	Colistin ($n = 1{,}515$)[d]	0.5	1	≤0.12 to >4	99.5
	Tigecycline	0.25	0.5	≤0.015 to 4	99.9
	Levofloxacin	1	>4	≤0.03 to >4	51.9
Escherichia coli, MBL negative (2,703)	Ceftazidime-avibactam	0.12	0.25	≤0.015 to 8	100
	Ceftazidime	0.25	64	≤0.015 to >128	71.0
	Cefepime	≤0.12	>16	≤0.12 to >16	67.8
	Aztreonam	0.12	64	≤0.015 to >128	67.7
	Piperacillin-tazobactam	2	32	≤0.25 to >128	89.0
	Doripenem	0.03	0.06	≤0.008 to >4	99.6
	Imipenem	0.12	0.25	≤0.03 to >8	99.2
	Meropenem	0.03	0.06	≤0.004 to >8	99.5
	Amikacin	4	8	0.5 to >32	97.1
	Colistin ($n = 1{,}513$)[d]	0.5	1	≤0.12 to >4	99.5
	Tigecycline	0.25	0.5	≤0.015 to 4	99.9
	Levofloxacin	1	>4	≤0.03 to >4	51.9
Klebsiella pneumoniae (2,128)	Ceftazidime-avibactam	0.25	1	≤0.015 to >128	99.5
	Ceftazidime	2	128	≤0.015 to >128	52.9
	Cefepime	1	>16	≤0.12 to >16	54.5
	Aztreonam	1	>128	≤0.015 to >128	51.9
	Piperacillin-tazobactam	8	>128	≤0.25 to >128	63.3
	Doripenem	0.06	2	≤0.008 to >4	86.7
	Imipenem	0.25	4	0.06 to >8	87.8
	Meropenem	0.06	4	0.008 to >8	84.7
	Amikacin	2	16	≤0.25 to >32	90.7
	Colistin ($n = 1{,}347$)[d]	1	1	0.25 to >4	93.9
	Tigecycline	0.5	2	0.06 to >8	96.4
	Levofloxacin	0.5	>4	≤0.03 to >4	64.9

TABLE 1 (Continued)

Organism, phenotype/genotype (no. of isolates)[b]	Antimicrobial agent	MIC (µg/ml)			% Susceptible[c]
		MIC$_{50}$	MIC$_{90}$	Range	
Klebsiella pneumoniae, MBL negative (2,119)	Ceftazidime-avibactam	0.12	1	≤0.015 to >128	100
	Ceftazidime	1	128	≤0.015 to >128	53.1
	Cefepime	0.5	>16	≤0.12 to >16	54.7
	Aztreonam	1	>128	≤0.015 to >128	52.0
	Piperacillin-tazobactam	8	>128	≤0.25 to >128	63.5
	Doripenem	0.06	2	≤0.008 to >4	87.0
	Imipenem	0.25	4	0.06 to >8	88.2
	Meropenem	0.06	4	0.008 to >8	85.0
	Amikacin	2	16	≤0.25 to >32	90.9
	Colistin (n = 1,338)[d]	1	1	0.25 to 4	94.2
	Tigecycline	0.5	2	0.06 to >8	96.5
	Levofloxacin	0.5	>4	≤0.03 to >4	64.9
Klebsiella oxytoca (393)[e]	Ceftazidime-avibactam	0.12	0.25	≤0.015 to 16	99.8
	Ceftazidime	0.12	8	0.03 to >128	89.6
	Cefepime	≤0.12	4	≤0.12 to >16	88.0
	Aztreonam	0.12	64	≤0.015 to >128	81.9
	Piperacillin-tazobactam	2	128	≤0.25 to >128	86.5
	Doripenem	0.06	0.12	0.03 to >4	98.5
	Imipenem	0.25	0.5	0.06 to >8	96.7
	Meropenem	0.03	0.06	0.015 to >8	98.0
	Amikacin	2	4	0.5 to >32	98.2
	Colistin (n = 239)[d]	0.5	1	≤0.12 to 4	99.2
	Tigecycline	0.25	1	0.06 to 4	99.8
	Levofloxacin	0.06	1	≤0.03 to >4	93.4
Enterobacter spp. (855)[f]	Ceftazidime-avibactam	0.25	1	≤0.015 to 128	99.2
	Ceftazidime	0.5	128	0.03 to >128	66.7
	Cefepime	≤0.12	>16	≤0.12 to >16	78.2
	Aztreonam	0.12	128	≤0.015 to >128	66.2
	Piperacillin-tazobactam	4	>128	≤0.25 to >128	75.6
	Doripenem	0.06	0.25	≤0.008 to >4	97.3
	Imipenem	0.5	2	≤0.03 to >8	83.4
	Meropenem	0.06	0.12	0.008 to >8	97.3
	Amikacin	2	8	≤0.25 to >32	96.1
	Colistin (n = 496)[d]	0.5	1	≤0.12 to >4	93.5
	Tigecycline	0.5	1	0.06 to 8	97.8
	Levofloxacin	0.06	>4	≤0.03 to >4	86.4
Enterobacter spp., MBL negative (851)	Ceftazidime-avibactam	0.25	1	≤0.015 to 32	99.5
	Ceftazidime	0.5	128	0.03 to >128	66.9
	Cefepime	≤0.12	>16	≤0.12 to >16	78.5
	Aztreonam	0.12	128	≤0.015 to >128	66.0
	Piperacillin-tazobactam	4	>128	≤0.25 to >128	75.8
	Doripenem	0.06	0.25	≤0.008 to >4	97.8
	Imipenem	0.5	2	≤0.03 to >8	83.8
	Meropenem	0.06	0.12	0.008 to >8	97.6
	Amikacin	2	8	≤0.25 to >32	96.2
	Colistin (n = 493)[d]	0.5	1	≤0.12 to >4	93.5
	Tigecycline	0.5	1	0.06 to 8	97.8
	Levofloxacin	0.06	>4	≤0.03 to >4	86.4
Citrobacter spp. (394)[g]	Ceftazidime-avibactam	0.12	0.5	≤0.015 to 128	99.5
	Ceftazidime	0.5	128	≤0.015 to >128	74.6
	Cefepime	≤0.12	8	≤0.12 to >16	86.3
	Aztreonam	0.12	64	≤0.015 to >128	72.3
	Piperacillin-tazobactam	4	64	0.5 to >128	81.5
	Doripenem	0.06	0.12	0.015 to >4	98.7
	Imipenem	0.5	2	0.06 to >8	88.1
	Meropenem	0.03	0.06	≤0.004 to >8	98.0
	Amikacin	2	4	≤0.25 to >32	94.9
	Colistin (n = 237)[d]	0.5	1	≤0.12 to 2	100
	Tigecycline	0.25	1	0.06 to 4	99.5
	Levofloxacin	0.06	>4	≤0.03 to >4	86.8

TABLE 1 (Continued)

Organism, phenotype/genotype (no. of isolates)[b]	Antimicrobial agent	MIC (µg/ml)			% Susceptible[c]
		MIC$_{50}$	MIC$_{90}$	Range	
Citrobacter spp., MBL negative (393)	Ceftazidime-avibactam	0.12	0.5	≤0.015 to 128	99.8
	Ceftazidime	0.5	128	≤0.015 to >128	74.8
	Cefepime	≤0.12	8	≤0.12 to >16	86.5
	Aztreonam	0.12	64	≤0.015 to >128	72.5
	Piperacillin-tazobactam	4	64	0.5 to >128	81.7
	Doripenem	0.06	0.12	0.015 to >4	99.0
	Imipenem	0.5	2	0.06 to >8	88.3
	Meropenem	0.03	0.06	≤0.004 to >8	98.2
	Amikacin	2	4	≤0.25 to >32	94.9
	Colistin (n = 236)[d]	0.5	1	≤0.12 to 2	100
	Tigecycline	0.25	1	0.06 to 4	99.5
	Levofloxacin	0.06	>4	≤0.03 to >4	87.0
Proteeae (939)[h]	Ceftazidime-avibactam	0.06	0.12	≤0.015 to 64	99.9
	Ceftazidime	0.06	4	≤0.015 to >128	93.6
	Cefepime	≤0.12	8	≤0.12 to >16	88.2
	Aztreonam	≤0.015	1	≤0.015 to >128	95.0
	Piperacillin-tazobactam	0.5	2	≤0.25 to >128	98.5
	Doripenem	0.25	0.5	0.015 to >4	98.8
	Imipenem	2	4	0.06 to >8	23.2
	Meropenem	0.12	0.25	0.03 to 8	99.8
	Amikacin	4	8	≤0.25 to >32	96.3
	Colistin (n = 532)[d]	>4	>4	0.5 to >4	0.8
	Tigecycline	2	4	≤0.015 to >8	60.9
	Levofloxacin	0.12	>4	≤0.03 to >4	75.4
Proteeae, MBL negative (938)	Ceftazidime-avibactam	0.06	0.12	≤0.015 to 8	100
	Ceftazidime	0.06	2	≤0.015 to >128	93.7
	Cefepime	≤0.12	4	≤0.12 to >16	88.3
	Aztreonam	≤0.015	1	≤0.015 to >128	95.0
	Piperacillin-tazobactam	0.5	2	≤0.25 to >128	98.6
	Doripenem	0.25	0.5	0.015 to 4	98.9
	Imipenem	2	4	0.06 to >8	23.2
	Meropenem	0.12	0.12	0.03 to 2	99.9
	Amikacin	4	8	≤0.25 to >32	96.3
	Colistin (n = 531)[d]	>4	>4	0.5 to >4	0.8
	Tigecycline	2	4	≤0.015 to >8	61.0
	Levofloxacin	0.12	>4	≤0.03 to >4	75.4
Other Enterobacteriaceae (251)[e,i]	Ceftazidime-avibactam	0.25	0.5	≤0.015 to >128	99.6
	Ceftazidime	0.25	16	0.03 to >128	86.0
	Cefepime	≤0.12	16	≤0.12 to >16	87.2
	Aztreonam	0.12	64	0.03 to >128	84.0
	Piperacillin-tazobactam	2	16	≤0.25 to >128	92.8
	Doripenem	0.12	0.25	0.03 to >4	98.0
	Imipenem	0.5	1	0.06 to >8	90.0
	Meropenem	0.06	0.12	0.03 to >8	98.0
	Amikacin	2	8	≤0.25 to >32	92.4
	Colistin (n = 150)[d]	>4	>4	≤0.12 to >4	23.3
	Tigecycline	1	2	0.06 to 8	95.2
	Levofloxacin	0.12	2	≤0.03 to >4	93.6
Pseudomonas aeruginosa (1,794)	Ceftazidime-avibactam	2	16	0.12 to >128	87.4
	Ceftazidime	4	64	0.25 to >128	70.0
	Cefepime	4	>16	≤0.12 to >16	73.0
	Aztreonam	8	64	0.12 to >128	55.9
	Piperacillin-tazobactam	8	>128	≤0.25 to >128	62.5
	Doripenem	1	>4	≤0.015 to >4	66.0
	Imipenem	2	>8	0.12 to >8	56.9
	Meropenem	1	>8	0.03 to >8	64.2
	Amikacin	4	>32	≤0.25 to >32	81.6
	Colistin (n = 1,301)[d]	2	2	0.25 to >8	94.9
	Levofloxacin	1	>4	≤0.03 to >4	65.7

(Continued on next page)

TABLE 1 (Continued)

Organism, phenotype/genotype (no. of isolates)[b]	Antimicrobial agent	MIC (μg/ml)			% Susceptible[c]
		MIC_{50}	MIC_{90}	Range	
Pseudomonas aeruginosa, MBL negative (1,684)	Ceftazidime-avibactam	2	8	0.12 to >128	92.8
	Ceftazidime	4	64	0.25 to >128	74.4
	Cefepime	4	>16	≤0.12 to >16	77.1
	Aztreonam	8	64	0.12 to >128	58.1
	Piperacillin-tazobactam	8	>128	≤0.25 to >128	66.1
	Doripenem	1	>4	≤0.015 to >4	70.1
	Imipenem	2	>8	0.12 to >8	60.6
	Meropenem	1	>8	0.03 to >8	68.1
	Amikacin	4	>32	≤0.25 to >32	86.1
	Colistin ($n = 1,213$)[d]	2	2	0.25 to 8	94.8
	Levofloxacin	1	>4	≤0.03 to >4	69.1

[a]Isolates of *Enterobacteriaceae* ($n = 7,665$) and *P. aeruginosa* ($n = 1,794$) were collected in the Latin American region as part of the INFORM global surveillance program in 2012 to 2015.

[b]MBL negative; no gene encoding a metallo-β-lactamase was detected by PCR assay.

[c]Percent susceptibility was determined according to CLSI 2016 breakpoints, with the exception of those for ceftazidime-avibactam and tigecycline, where U.S. FDA breakpoints were applied, and for colistin, where EUCAST breakpoints were applied.

[d]Values are for colistin tested without 0.002% polysorbate-80; isolates collected in 2014 to 2015 only.

[e]All isolates were MBL negative.

[f]*Enterobacter* spp. included *Enterobacter aerogenes* ($n = 272$), *Enterobacter amnigenus* ($n = 1$), *Enterobacter asburiae* ($n = 48$), *Enterobacter cloacae* ($n = 512$), *Enterobacter kobei* ($n = 18$), and *Enterobacter ludwigii* ($n = 4$).

[g]*Citrobacter* spp. included *Citrobacter amalonaticus* ($n = 5$), *Citrobacter braakii* ($n = 19$), *Citrobacter farmeri* ($n = 1$), *Citrobacter freundii* ($n = 274$), and *Citrobacter koseri* ($n = 95$).

[h]Proteeae included *Morganella morganii* ($n = 213$), *Proteus mirabilis* ($n = 496$), *Proteus penneri* ($n = 13$), *Proteus vulgaris* ($n = 152$), *Providencia alcalifaciens* ($n = 2$), *Providencia rettgeri* ($n = 29$), and *Providencia stuartii* ($n = 34$).

[i]Other *Enterobacteriaceae* included *Escherichia vulneris* ($n = 1$), *Klebsiella variicola* ($n = 1$), *Kluyvera ascorbata* ($n = 1$), *Pantoea agglomerans* ($n = 1$), *Pluralibacter gergoviae* ($n = 2$), *Raoultella ornithinolytica* ($n = 33$), *Raoultella planticola* ($n = 1$), *Serratia liquefaciens* ($n = 2$), *Serratia marcescens* ($n = 206$), and *Serratia ureilytica* ($n = 3$).

(99.5% to 100% susceptible) than for data sets of individual species or species groups that included all isolates (99.2% to 99.9%) (Table 1). The lower susceptibility of *Enterobacteriaceae* isolates to imipenem (83.9%) compared to doripenem (95.5%) and meropenem (94.9%) was attributable to the presence of 939 isolates of Proteeae (12.3% of all *Enterobacteriaceae* tested), as species within the tribe Proteeae intrinsically demonstrate elevated MICs for imipenem (16). Percent susceptibility to ceftazidime-avibactam for all isolates of *Enterobacteriaceae* from each of the six countries in Latin America surveyed ranged from 99.4% to 100% (MIC_{90}, 0.25-1 μg/ml) (Fig. 1; Tables S2A to S7A).

Table 2 depicts the *in vitro* activity of ceftazidime-avibactam and comparator agents against isolates of *Enterobacteriaceae* molecularly characterized for β-lactamase content. Ceftazidime-avibactam inhibited 99.9%, 99.6%, and 99.0% of ESBL-positive, KPC-positive, and AmpC-positive isolates, respectively, as well as all isolates that carried both ESBL and AmpC enzymes, isolates carrying only original-spectrum β-lactamases (OSBLs; e.g., TEM-1, SHV-1, and SHV-11), and those carrying OXA-48-like class D carbapenemases. The MIC_{90} values for ceftazidime-avibactam against these subsets of β-lactamase-producing isolates ranged from 0.5 μg/ml for OSBL-positive isolates to 2 μg/ml for ESBL-positive and AmpC-positive, KPC-positive, and OXA-48-like-positive isolates. The percentages of susceptibility to doripenem (90.6% to 96.5%) and meropenem (90.6% to 96.4%) were 2.5% to 9.4% lower than observed for ceftazidime-avibactam among ESBL-positive, AmpC-positive, ESBL-positive and AmpC-positive, and OSBL-positive isolates. The activities of all β-lactams tested (0% to 10.8% susceptible) were significantly reduced compared to that of ceftazidime-avibactam against KPC-positive and OXA-48-like-positive isolates, with the notable exception of the activities of doripenem, imipenem, and meropenem against OXA-48-like-positive isolates (85.7% susceptible). As anticipated, ceftazidime-avibactam, similarly to all other β-lactams, was poorly active against isolates carrying MBLs (MIC_{90}, >128 μg/ml; 5.9% susceptible); only tigecycline (MIC_{90}, 4 μg/ml; 82.4% susceptible) retained *in vitro* activity against >80% of MBL-positive isolates.

TABLE 2 *In vitro* activities of ceftazidime-avibactam and comparator antimicrobial agents tested against β-lactamase-positive *Enterobacteriaceae* and *P. aeruginosa* isolates[a]

Organism or genotype (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b]			% Susceptible[c]
		MIC$_{50}$	MIC$_{90}$	Range	
Enterobacteriaceae (2,321)					
OSBL positive (55)	Ceftazidime-avibactam	0.25	0.5	≤0.03 to 2	100
	Ceftazidime	4	32	≤0.015 to >128	58.2
	Cefepime	1	16	≤0.12 to >16	80.0
	Aztreonam	1	64	≤0.015 to 128	72.7
	Piperacillin-tazobactam	128	>128	≤0.25 to >128	43.6
	Doripenem	0.06	0.5	0.03 to 2	96.4
	Imipenem	0.25	4	0.06 to 8	80.0
	Meropenem	0.06	0.12	0.03 to 2	96.4
	Amikacin	2	16	≤0.25 to >32	90.9
	Colistin ($n = 24$)[d]	1	>4	0.25 to 4	83.3
	Tigecycline	0.5	2	0.25 to 4	92.7
	Levofloxacin	0.5	>4	≤0.03 to >4	63.6
Spectrum undefined (2)[e]	Ceftazidime-avibactam	—[b]	—	0.12 to 1	100
	Ceftazidime	—	—	16 to 32	0
	Cefepime	—	—	≤0.12 to 16	50.0
	Aztreonam	—	—	4 to 32	50.0
	Piperacillin-tazobactam	—	—	4 to 64	50.0
	Doripenem	—	—	0.03 to 0.06	100
	Imipenem	—	—	0.25 to 0.25	100
	Meropenem	—	—	0.03 to 0.06	100
	Amikacin	—	—	0.5 to 1	100
	Colistin ($n = 0$)[d]	—	—	ND[d]	ND
	Tigecycline	—	—	0.5 to 2	100
	Levofloxacin	—	—	0.5 to >4	50.0
ESBL positive (1,701)[f]	Ceftazidime-avibactam	0.25	1	≤0.015 to 128	99.9
	Ceftazidime	32	>128	0.25 to >128	14.8
	Cefepime	>16	>16	≤0.12 to >16	5.9
	Aztreonam	64	>128	≤0.25 to >128	5.9
	Piperacillin-tazobactam	16	>128	≤0.25 to >128	62.4
	Doripenem	0.06	0.25	≤0.008 to >4	96.4
	Imipenem	0.25	0.5	0.06 to >8	96.8
	Meropenem	0.06	0.12	≤0.004 to >8	94.2
	Amikacin	4	32	≤0.25 to >32	89.8
	Colistin ($n = 988$)[d]	0.5	1	0.12 to >4	94.5
	Tigecycline	0.5	2	≤0.015 to >8	95.4
	Levofloxacin	>4	>4	≤0.03 to >4	27.9
AmpC positive (199)[g]	Ceftazidime-avibactam	0.25	1	0.03 to 32	99.0
	Ceftazidime	16	>128	0.03 to >128	45.7
	Cefepime	0.25	8	≤0.12 to >16	81.4
	Aztreonam	4	64	≤0.015 to >128	52.3
	Piperacillin-tazobactam	4	>128	≤0.25 to >128	70.4
	Doripenem	0.12	0.5	≤0.008 to >4	96.5
	Imipenem	2	4	0.12 to >8	45.7
	Meropenem	0.06	0.25	0.015 to >8	95.5
	Amikacin	2	8	≤0.25 to >32	96.5
	Colistin ($n = 94$)[d]	1	>4	0.25 to >4	86.2
	Tigecycline	0.5	2	0.06 to 4	95.5
	Levofloxacin	0.12	>4	≤0.03 to >4	72.4
ESBL positive + AmpC positive (64)[h]	Ceftazidime-avibactam	0.5	2	0.03 to 2	100
	Ceftazidime	128	>128	0.12 to >128	6.3
	Cefepime	>16	>16	≤0.12 to >16	12.5
	Aztreonam	128	>128	0.25 to >128	4.7
	Piperacillin-tazobactam	128	>128	2 to >128	31.3
	Doripenem	0.12	1	0.03 to >4	90.6
	Imipenem	0.5	4	0.06 to >8	78.1
	Meropenem	0.06	1	0.03 to >8	90.6
	Amikacin	4	32	0.5 to >32	76.6
	Colistin ($n = 26$)[d]	0.5	4	0.25 to >4	88.5
	Tigecycline	1	2	0.12 to 4	90.6
	Levofloxacin	>4	>4	0.06 to >4	17.2

TABLE 2 (Continued)

Organism or genotype (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b]			% Susceptible[c]
		MIC$_{50}$	MIC$_{90}$	Range	
KPC positive (269)[i]	Ceftazidime-avibactam	0.5	2	0.03 to 16	99.6
	Ceftazidime	64	>128	0.5 to >128	8.2
	Cefepime	>16	>16	≤0.12 to >16	10.8
	Aztreonam	>128	>128	4 to >128	1.5
	Piperacillin-tazobactam	>128	>128	8 to >128	0.7
	Doripenem	>4	>4	0.06 to >4	10.4
	Imipenem	>8	>8	0.12 to >8	1.5
	Meropenem	>8	>8	0.03 to >8	5.9
	Amikacin	8	>32	0.5 to >32	68.4
	Colistin ($n = 181$)[d]	1	>4	0.25 to >4	79.0
	Tigecycline	1	2	0.12 to 8	94.8
	Levofloxacin	>4	>4	≤0.03 to >4	25.3
OXA-48-like positive (14)[j]	Ceftazidime-avibactam	1	2	0.06 to 8	100
	Ceftazidime	128	>128	16 to >128	0
	Cefepime	>16	>16	2 to >16	7.1
	Aztreonam	64	128	1 to >128	7.1
	Piperacillin-tazobactam	>128	>128	4 to >128	7.1
	Doripenem	0.12	>4	0.03 to >4	85.7
	Imipenem	0.5	2	0.12 to 2	85.7
	Meropenem	0.12	>8	0.015 to >8	85.7
	Amikacin	8	32	1 to >32	78.6
	Colistin ($n = 10$)[d]	1	1	0.5 to 1	100
	Tigecycline	0.5	2	0.12 to 2	100
	Levofloxacin	>4	>4	0.06 to >4	21.4
MBL positive (17)[k]	Ceftazidime-avibactam	64	>128	0.12 to >128	5.9
	Ceftazidime	>128	>128	0.25 to >128	5.9
	Cefepime	>16	>16	1 to >16	5.9
	Aztreonam	16	128	0.03 to >128	47.1
	Piperacillin-tazobactam	>128	>128	1 to >128	5.9
	Doripenem	>4	>4	2 to >4	0
	Imipenem	8	>8	4 to >8	0
	Meropenem	8	>8	1 to >8	5.9
	Amikacin	16	>32	2 to >32	64.7
	Colistin ($n = 93$)[d]	1	>4	0.25 to >4	68.8
	Tigecycline	1	4	0.5 to 4	82.4
	Levofloxacin	1	>4	0.25 to >4	58.8
P. aeruginosa (750)					
OSBL positive (4)[l]	Ceftazidime-avibactam	—[b]	—	4 to 16	75.0
	Ceftazidime	—	—	4 to 64	50.0
	Cefepime	—	—	8 to >16	25.0
	Aztreonam	—	—	16 to 64	0
	Piperacillin-tazobactam	—	—	64 to >128	0
	Doripenem	—	—	1 to >4	50.0
	Imipenem	—	—	2 to >8	25.0
	Meropenem	—	—	2 to >8	25.0
	Amikacin	—	—	>32 to >32	0
	Colistin ($n = 1$)[d]	—	—	1	100
	Levofloxacin	—	—	>4 to >4	0
ESBL positive (29)[l,m]	Ceftazidime-avibactam	16	64	4 to >128	31.0
	Ceftazidime	>128	>128	8 to >128	3.4
	Cefepime	>16	>16	0.25 to >16	3.4
	Aztreonam	>128	>128	8 to >128	3.4
	Piperacillin-tazobactam	64	>128	8 to >128	20.7
	Doripenem	>4	>4	2 to >4	13.8
	Imipenem	>8	>8	>8 to >8	0
	Meropenem	>8	>8	4 to >8	0
	Amikacin	>32	>32	8 to >32	27.6
	Colistin ($n = 19$)[d]	1	4	0.5 to >4	89.5
	Levofloxacin	>4	>4	1 to >4	24.1

(Continued on next page)

TABLE 2 (Continued)

Organism or genotype (no. of isolates)[a]	Antimicrobial agent	MIC (μg/ml)[b]			% Susceptible[c]
		MIC$_{50}$	MIC$_{90}$	Range	
KPC positive (48)[l]	Ceftazidime-avibactam	8	32	1 to 128	77.1
	Ceftazidime	64	128	8 to >128	2.1
	Cefepime	>16	>16	0.5 to >16	2.1
	Aztreonam	>128	>128	64 to >128	0
	Piperacillin-tazobactam	>128	>128	32 to >128	0
	Doripenem	>4	>4	>4 to >4	0
	Imipenem	>8	>8	>8 to >8	0
	Meropenem	>8	>8	>8 to >8	0
	Amikacin	8	>32	1 to >32	77.1
	Colistin (n = 31)[d]	2	2	0.5 to 4	93.5
	Levofloxacin	>4	>4	0.25 to >4	8.3
GES carbapenemase positive (33)[l,n]	Ceftazidime-avibactam	32	128	0.12 to >128	27.3
	Ceftazidime	>128	>128	0.25 to >128	0
	Cefepime	>16	>16	1 to >16	0
	Aztreonam	128	>128	0.03 to >128	9.1
	Piperacillin-tazobactam	>128	>128	1 to >128	0
	Doripenem	>4	>4	2 to >4	0
	Imipenem	>8	>8	4 to >8	15.2
	Meropenem	>8	>8	1 to >8	0
	Amikacin	>32	>32	2 to >32	15.2
	Colistin (n = 27)[d]	2	2	0.25 to >4	92.6
	Levofloxacin	>4	>4	0.25 to >4	0
GES, spectrum-undefined positive (1)[l]	Ceftazidime-avibactam	—[b]	—	>128	0
	Ceftazidime	—	—	>128	0
	Cefepime	—	—	>16	0
	Aztreonam	—	—	>128	0
	Piperacillin-tazobactam	—	—	>128	0
	Doripenem	—	—	>4	0
	Imipenem	—	—	>8	0
	Meropenem	—	—	>8	0
	Amikacin	—	—	>32	0
	Colistin (n = 1)[d]	—	—	1	100
	Levofloxacin	—	—	>4	0
MBL-positive (110)[l,o]	Ceftazidime-avibactam	32	>128	2 to >128	5.5
	Ceftazidime	32	>128	4 to >128	2.7
	Cefepime	16	>16	4 to >16	10.0
	Aztreonam	16	64	2 to >128	21.8
	Piperacillin-tazobactam	64	>128	4 to >128	7.3
	Doripenem	>4	>4	1 to >4	2.7
	Imipenem	>8	>8	4 to >8	0
	Meropenem	>8	>8	1 to >8	3.6
	Amikacin	>32	>32	2 to >32	13.6
	Colistin (n = 88)[d]	2	2	0.5 to 4	95.5
	Levofloxacin	>4	>4	0.25 to >4	13.6
No acquired β-lactamase detected (525)[l]	Ceftazidime-avibactam	4	16	0.5 to >128	89.5
	Ceftazidime	8	64	1 to >128	61.1
	Cefepime	8	>16	0.25 to >16	61.5
	Aztreonam	16	64	0.25 to >128	33.9
	Piperacillin-tazobactam	32	>128	≤0.25 to >128	45.7
	Doripenem	4	>4	0.12 to >4	25.5
	Imipenem	>8	>8	1 to >8	6.9
	Meropenem	8	>8	≤0.06 to >8	19.4
	Amikacin	8	>32	0.5 to >32	74.9
	Colistin (n = 369)[d]	2	2	0.25 to 8	95.1
	Levofloxacin	4	>4	≤0.03 to >4	45.9

The distributions of serine-based β-lactamases and MBLs among molecularly characterized *Enterobacteriaceae* isolates from each of the six countries surveyed in Latin America are summarized in the supplemental material (Tables S2B to S7B; Fig. S1A to D). CTX-M-type ESBLs accounted for 88.7% (1,797/2,025) of all ESBLs identified in the region, with CTX-M-15 being the most common ESBL identified, accounting for 60.1%

(1,217/2,025) of all ESBLs found. However, the prevalence of ESBL types and individual enzyme variants differed across countries (Fig. S1B). CMY-2 (77.1% [74/96]) and DHA-1 (17.7% [17/96]) comprised the majority of AmpC enzymes identified, with differences in the prevalence of these and other variants observed among countries (Fig. S1C). ESBLs and AmpC β-lactamases were identified in isolates from all six countries as were KPC carbapenemases, which comprised 89.1% of detected carbapenemases. MBLs were only identified in isolates from Colombia (NDM-1), Mexico (NDM-1, VIM-23), and Venezuela (NDM-1), while OXA-48-like β-lactamases were found only in Argentina (OXA-163, OXA-439), Mexico (OXA-163, OXA-232), and Brazil (OXA-48, OXA-370) (Fig. S1D). KPC-2 (80.5% [243/302]), KPC-3 (8.6% [26/302]), and NDM-1 (3.3% [10/302]) were the most common carbapenemases identified, and OXA-163 (68.8% [11/16]), a variant with attenuated carbapenemase activity, was the most common OXA-48-like β-lactamase (17, 18). The types and relative prevalence of carbapenemases differed among the surveyed countries, with both the greatest variety of carbapenemases and the majority of MBL-positive isolates (64.7%; 11/17) collected in Mexico (Fig. S1D). The *in vitro* activity of ceftazidime-avibactam against *Enterobacteriaceae* isolates in each country was affected by the proportion of isolates carrying an MBL.

Table S8 describes the *in vitro* activity of ceftazidime-avibactam and comparator agents against the 2,310 isolates of *Enterobacteriaceae* identified with a ceftazidime-nonsusceptible phenotype (30.1% of all isolates). Overall, 99.0% of ceftazidime-nonsusceptible isolates were susceptible to ceftazidime-avibactam (MIC$_{90}$, 2 μg/ml), with MIC$_{90}$ values against individual species of *Enterobacteriaceae* ranging from 0.5 to 2 μg/ml (97.1% to 99.8% susceptible). Across the Latin American region, the percentage of *Enterobacteriaceae* isolates that tested as nonsusceptible to ceftazidime ranged from 23.6% in Venezuela to 38.6% in Mexico (Fig. S2), while the percentage of ceftazidime-nonsusceptible isolates that tested as susceptible to ceftazidime-avibactam was >98% (MIC$_{90}$, 1 to 2 μg/ml) in all six countries (Tables S2A to S7A).

Table S9 depicts the *in vitro* activity of ceftazidime-avibactam and comparator agents against the 389 isolates of *Enterobacteriaceae* identified with a meropenem-nonsusceptible phenotype (5.1% of all isolates); 95.4% of all meropenem-nonsusceptible isolates of *Enterobacteriaceae* were susceptible to ceftazidime-avibactam. MIC$_{90}$ values for ceftazidime-avibactam were 4 to 32 μg/ml for all meropenem-nonsusceptible isolates and isolates of individual species or species groups of *Enterobacteriaceae*. However, MIC$_{90}$ values decreased by up to 16-fold and susceptibilities increased to 99.7% to 100% for *Escherichia coli*, *Enterobacter* spp., and *K. pneumoniae* (the species with data for >10

TABLE 2 (Continued)

[a]Isolates (*n* = 3,071) of β-lactamase-positive *Enterobacteriaceae* and *P. aeruginosa* were collected in the Latin American region as part of the INFORM global surveillance program in 2012 to 2015. 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 *n* <10 isolates.
[c]Percent susceptibility was determined according to CLSI 2016 breakpoints, with the exception of those for ceftazidime-avibactam and tigecycline, where U.S. FDA breakpoints were applied, and for colistin, where EUCAST breakpoints were applied.
[d]Values are for colistin tested without 0.002% polysorbate-80; isolates collected in 2014 to 2015 only. ND, not determined; MIC range and % susceptible were not determined for *n* = 0 isolates.
[e]"Spectrum undefined" refers to SHV-type and/or TEM-type β-lactamases with undefined spectrum of activity.
[f]Included isolates carrying the chromosomal ESBL common to *K. oxytoca*, SHV-type and/or TEM-type β-lactamases with undefined spectrum of activity, and/or OSBLs.
[g]Included isolates carrying the chromosomal AmpCs common to *Citrobacter* spp., *Enterobacter* spp., *M. morganii*, and *Serratia* spp.; plasmid-mediated AmpCs; and isolates cocarrying OSBLs.
[h]Included isolates carrying the chromosomal β-lactamases common to *Citrobacter* spp., *Enterobacter* spp., *Providencia* spp., *Serratia* spp., and *K. oxytoca*, and isolates cocarrying OSBLs.
[i]Included isolates carrying ESBLs, plasmidic and chromosomal AmpC β-lactamases, β-lactamases with unknown spectrum of activity, OSBLs, and OXA-48-like β-lactamases (KPC-2 and OXA-163, 1 isolate; KPC-2 and OXA-370, 1 isolate).
[j]Included isolates carrying OXA-163 (10 isolates), OXA-48 (1 isolate), OXA-232 (1 isolate), OXA-370 (1 isolate), OXA-439 (1 isolate), and ESBLs, AmpC, and/or OSBLs. OXA-163 possesses weak carbapenemase activity that impacts the activity of carbapenems when combined with additional mechanisms of resistance, such as porin deficiencies. OXA-439 has not been confirmed to possess carbapenemase activity.
[k]Included isolates cocarrying ESBLs, chromosomal AmpC β-lactamases, and/or OSBLs.
[l]Assumed to carry the chromosomal AmpC common to *P. aeruginosa*.
[m]Included one isolate carrying a GES β-lactamase with an undefined spectrum of activity.
[n]Included isolates carrying GES β-lactamases with ESBL activity (GES-19 and GES-1).
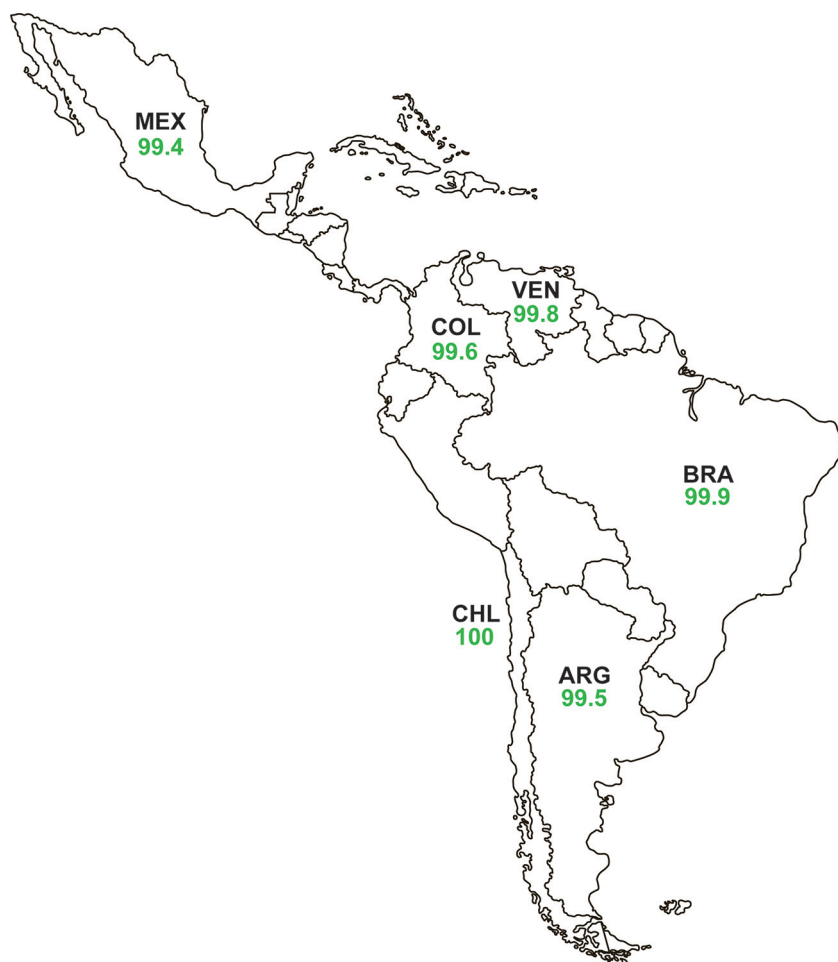[o]Included 1 isolate cocarrying an OSBL and 5 isolates cocarrying VIM-2 and KPC-2.

FIG 1 Percent susceptibility to ceftazidime-avibactam for isolates of *Enterobacteriaceae* collected in 2012 to 2015, by Latin American country. Ceftazidime-avibactam-susceptible, $\leq 8\ \mu$g/ml; ceftazidime-avibactam-resistant, $\geq 16\ \mu$g/ml, by U.S. FDA criteria. The green font indicates that >90% of isolates were ceftazidime-avibactam-susceptible. ARG, Argentina; BRA, Brazil; CHL, Chile; COL, Colombia; MEX, Mexico; VEN, Venezuela.

isolates tested) when only MBL-negative, meropenem-nonsusceptible isolates were considered. The percentages of isolates that tested as nonsusceptible to meropenem differed by <10% among the six Latin American countries, ranging from 1.2% in Mexico to 10.2% in Brazil (Fig. S3).

Table S10 shows the *in vitro* activity of ceftazidime-avibactam and comparator agents against 124 colistin-resistant isolates of *Enterobacteriaceae* (excluding isolates of Proteeae and *Serratia* spp., which are intrinsically resistant to colistin). The percentage of isolates per country that were resistant to colistin ranged from 1.1% in Venezuela to 2.3% in Chile (Fig. S4). Ceftazidime-avibactam inhibited 96.0% of colistin-resistant *Enterobacteriaceae* isolates (MIC_{90}, 2 μg/ml) and 99.2% of MBL-negative colistin-resistant isolates (MIC_{90}, 2 μg/ml). Percentages of susceptibility to ceftazidime-avibactam against colistin-resistant isolates were higher than those for all other agents tested.

Table S11 describes the *in vitro* activity of ceftazidime-avibactam and comparator agents against 1,596 isolates of MDR *Enterobacteriaceae*. Susceptibility to ceftazidime-avibactam was 98.8% (MIC_{90}, 2 μg/ml), exceeding susceptibility to all other agents tested. The MIC_{90} values of ceftazidime-avibactam against MDR isolates varied from 0.25 to 4 μg/ml for different species of *Enterobacteriaceae*, and $\geq 95\%$ of MDR isolates of each species were susceptible to ceftazidime-avibactam. Susceptibility to ceftazidime-avibactam was greater than that to tigecycline (92.9%), colistin (85.7%), and carbap-

FIG 2 Percentage of isolates of *Enterobacteriaceae* collected in 2012 to 2015 that were multidrug-resistant, by Latin American country. "Multidrug resistant" (MDR) isolates were defined as resistant, according to 2016 CLSI criteria, to three or more sentinel antimicrobial agents from different classes. The green font indicates that <20% of isolates were MDR, the orange font indicates that 20% to 29.9% of isolates were MDR, and the red font indicates that ≥30% of isolates were MDR. ARG, Argentina; BRA, Brazil; CHL, Chile; COL, Colombia; MEX, Mexico; VEN, Venezuela.

enems (77.1% to 79.7%) for the overall set of MDR *Enterobacteriaceae* isolates. MDR rates ranged across the region from 16.3% (Venezuela) to 24.2% (Chile) (Fig. 2), with ≥97.7% of MDR isolates collected in each country testing as susceptible to ceftazidime-avibactam. Ceftazidime-avibactam demonstrated the highest activity compared to those of all other agents tested against MDR isolates collected in all six individual countries (Tables S2A to S7A).

Of the 1,794 *P. aeruginosa* isolates collected from 2012 to 2015, 87.4% were susceptible to ceftazidime-avibactam (MIC$_{90}$, 16 μg/ml) (Table 1). Percent susceptibilities to other agents tested were lower than those for ceftazidime-avibactam, with the exception of that of colistin (94.9% susceptible). The percent susceptibility to ceftazidime-avibactam increased to 92.8% when only MBL-negative isolates of *P. aeruginosa* were considered.

There were 750 isolates of *P. aeruginosa* testing with a doripenem, imipenem, or meropenem MIC of ≥4 μg/ml that were screened for β-lactamase genes. Of these 750 isolates, 110 isolates (14.7%) carried MBLs with or without additional acquired serine β-lactamases (Table 2). No acquired β-lactamase was identified in the majority of screened isolates (70.0% [525/750]) (Table 2; Fig. S5A), which were assumed to possess alterations in OprD or efflux pump expression, likely combined with hyperproduction of the intrinsic chromosomal AmpC β-lactamase (19). ESBLs were found primarily in

isolates from Mexico (65.5% [36/55]) and differed in their distribution across Latin America, with PER-type enzymes found in isolates from Brazil, Chile, and Venezuela, and GES-type enzymes, comprising 67.3% ([37/55]) of ESBLs identified in *P. aeruginosa* isolates collected in the region, found in isolates from Argentina and Mexico (Fig. S5B). Considerable differences in the distribution of carbapenemases were also observed. VIM-2 (49.5% [97/196]), KPC-2 (27.0% [53/196]), and GES-20 (12.8% [25/196]) were the most common carbapenemases identified (Fig. S5C). VIM-2 was found in isolates from all six countries surveyed, while other MBLs were identified in Argentina, Brazil, and Mexico (IMP-type), Brazil (SPM-1), and Venezuela (VIM-50). KPC-2, which is rarely found in *P. aeruginosa* isolates collected outside Latin America, was identified in isolates from Argentina, Chile, and Colombia; all GES-type carbapenemases were identified in isolates collected in Mexico (Fig. S5C). In contrast to the *Enterobacteriaceae*, carbapenem nonsusceptibility in *P. aeruginosa* was not as reliant on the presence of carbapenemase genes (Fig. S5A). Ceftazidime-avibactam was not active against isolates carrying MBLs (5.5% susceptible), as expected, but it also demonstrated reduced activity against MBL-negative, ESBL-positive isolates (31.0% susceptible; composed of PER- and GES-type enzymes) and GES carbapenemase-positive isolates (27.3%) (Table 2). All of these isolates may have carried additional β-lactamases that were not included in the molecular testing algorithm and that were not inhibited by avibactam, or may have contained nonenzymatic resistance mechanisms. In contrast, 77.1% of KPC-positive isolates (MIC_{90}, 32 µg/ml) and 89.5% of carbapenem-nonsusceptible isolates with no acquired β-lactamase detected were susceptible to ceftazidime-avibactam (MIC_{90}, 16 µg/ml) (Table 2). Susceptibility to ceftazidime-avibactam among isolates of *P. aeruginosa* ranged from 79.1% (Chile) to 94.7% (Argentina) across the six countries of the Latin American region (Fig. 3).

Among ceftazidime-nonsusceptible *P. aeruginosa* isolates ($n = 538$), 58.0% of isolates were susceptible to ceftazidime-avibactam (Table S8); the percent susceptibility to ceftazidime-avibactam ranged from 34.3% (Venezuela) to 77.6% (Argentina) across the countries surveyed (Tables S2A to S7A). Percentages of susceptibility to comparator agents other than colistin (95.0% susceptible) were lower than susceptibility to ceftazidime-avibactam among this subset of isolates. The activity of ceftazidime-avibactam was improved against the subsets of ceftazidime-nonsusceptible, MBL-negative isolates collected in the overall region (71.7% susceptible; Table S8) and in the individual countries (56.6% to 92.0% susceptible; Tables S2A to S7A).

The percentage of isolates of *P. aeruginosa* that were meropenem-nonsusceptible in Latin American countries was 35.8% (Table 1, Table S9) and ranged from 32.3% (Venezuela) to 46.8% (Chile) (Fig. S7, Tables S2A–S7A). Overall, 67.5% of meropenem-nonsusceptible isolates collected in the Latin American region remained susceptible to ceftazidime-avibactam, which was higher than the susceptibilities observed to all other agents tested except colistin (95.1% susceptible) (Table S9). Susceptibility of meropenem-nonsusceptible isolates to ceftazidime-avibactam was lowest in Venezuela (50.0% susceptible) and highest in Argentina (84.7% susceptible); percentages of susceptibility increased 1.8% to 45.8%, to 71.1% to 95.8% susceptible across the 6 countries and to 79.7% for the overall region, when isolates carrying MBLs were excluded (Table S9, Tables S2A–S7A).

Only two *P. aeruginosa* isolates collected in Latin America in 2012 to 2015 tested as resistant to colistin (MIC ≥8 µg/ml, Fig. S8) (16). These isolates were collected in Argentina and Mexico and were susceptible to ceftazidime-avibactam (Tables S2A, S6A, and S10).

An MDR phenotype was present in 454 isolates of *P. aeruginosa* (25.3% of all isolates), with percentages of isolates testing as MDR varying from 20.4% (Mexico) to 34.0% (Chile) (Fig. 4). Of these MDR isolates, 57.1% were susceptible to ceftazidime-avibactam, a higher percent susceptibility than that observed for all other agents tested except colistin (94.9% susceptible) (Table S11). Ceftazidime-avibactam was least active against MDR isolates from Venezuela (37.3% susceptible; MIC_{90}, 32 µg/ml) and Mexico (45.2% susceptible, MIC_{90}, >128 µg/ml), and it was most active against MDR isolates from Argentina (77.6% suscep-
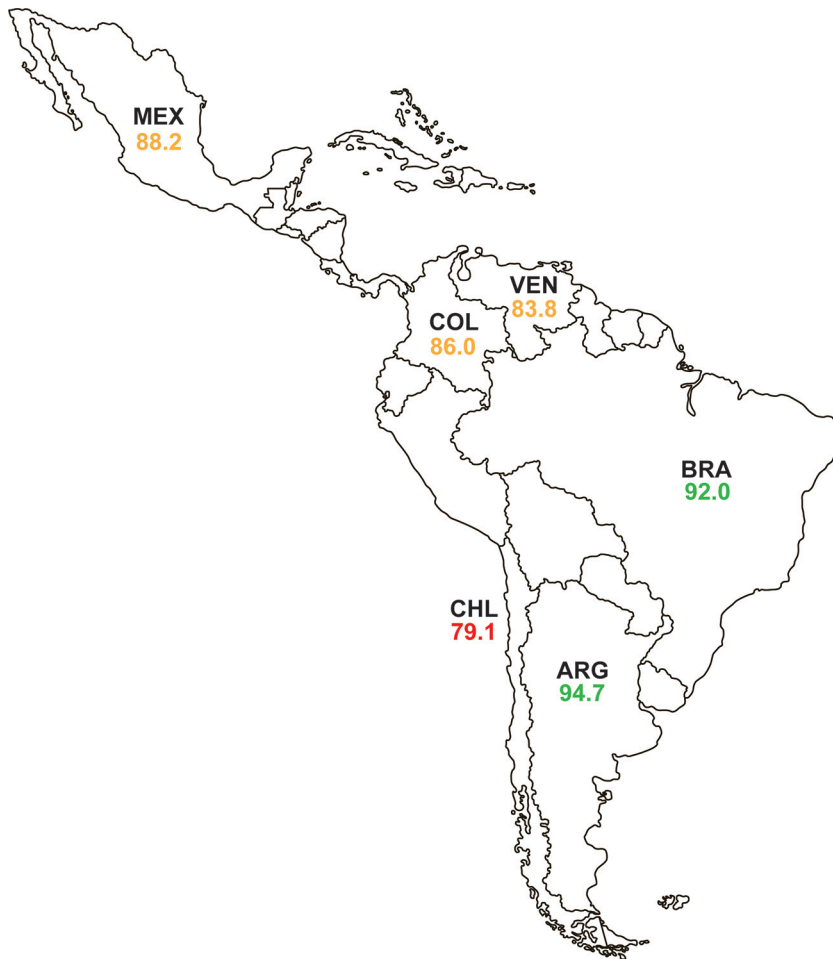
FIG 3 Percent susceptibility to ceftazidime-avibactam for isolates of *P. aeruginosa* collected in 2012 to 2015, by Latin American country. Ceftazidime-avibactam-susceptible, ≤8 μg/ml; ceftazidime-avibactam-resistant, ≥16 μg/ml by U.S. FDA criteria. The green font indicates that >90% of isolates were ceftazidime-avibactam susceptible. The orange font indicates that 80% to 89.9% of isolates were ceftazidime-avibactam susceptible. The red font indicates that <80% of isolates were ceftazidime-avibactam susceptible ARG, Argentina; BRA, Brazil; CHL, Chile; COL, Colombia; MEX, Mexico; VEN, Venezuela.

tible; MIC$_{90}$, 16 μg/ml) and Brazil (72.4% susceptible; MIC$_{90}$, 32 μg/ml) (Tables S2A to S7A). Activity was improved 2.4% to 55.8% against subsets of MBL-negative, MDR isolates, but the associated MIC$_{90}$ value decreased into the susceptible range only for isolates collected in Venezuela (MIC$_{90}$, 8 μg/ml) (Tables S2A to S7A). Ceftazidime-avibactam remained the second most active agent after colistin, and in one case was the third most active agent (after amikacin and colistin) against all MDR and MBL-negative MDR isolates in each of the six countries and in the region as a whole (Table S11).

DISCUSSION

In the current study, we found that 99.7% of isolates of *Enterobacteriaceae* were susceptible to ceftazidime-avibactam, 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. and *K. pneumoniae*), with only minor variation (0.7%) observed in the percent susceptibility to ceftazidime-avibactam, from 99.2% (*Enterobacter* spp.) to 99.9% (*E. coli* and Proteeae) (Table 1). Our results are in agreement with those of earlier studies by Rossi et al., who reported that 99.1% (339/342) of clinical isolates of *Enterobacteriaceae* collected at a teaching hospital in São Paulo, Brazil in 2014 to 2015 were susceptible to ceftazidime-avibactam (2), and by Flamm et al., who observed an MIC$_{90}$ of 0.25 μg/ml

FIG 4 Percentage of isolates of *P. aeruginosa* collected in 2012 to 2015 that were multidrug-resistant, by Latin American country. "Multidrug resistant" (MDR) isolates were defined as resistant, according to 2016 CLSI criteria, to three or more sentinel antimicrobial agents from different classes. The green font indicates that <20% of isolates were MDR. The orange font indicates that 20% to 29.9% of isolates were MDR. The red font indicates that ≥30% of isolates were MDR. ARG, Argentina; BRA, Brazil; CHL, Chile; COL, Colombia; MEX, Mexico; VEN, Venezuela.

for ceftazidime-avibactam tested against 130 urinary isolates of *Enterobacteriaceae* collected in seven Latin American countries in 2011 (4).

In the current study, we also noted that 87.4% of all isolates of *P. aeruginosa* tested were susceptible to ceftazidime-avibactam, with an MIC_{90} of 16 μg/ml (Table 1). Our results confirm earlier observations made regarding clinical isolates of *P. aeruginosa* from Latin American laboratories (2, 4, 6). Rossi et al. reported 84.0% (21/25) of *P. aeruginosa* isolates to be susceptible to ceftazidime-avibactam (2), Flamm et al. reported a ceftazidime-avibactam MIC_{90} of 16 μg/ml for 13 isolates of *P. aeruginosa* (4), and Nichols et al. reported 88.7% of 1,088 isolates of *P. aeruginosa* collected in six Latin American countries to be susceptible to ceftazidime-avibactam (MIC_{90}, 16 μg/ml) (6). In isolate subset analysis, Nichols et al. reported that 60.3% of ceftazidime-nonsusceptible ($n = 310$) and 70.2% of meropenem-nonsusceptible ($n = 382$) isolates of *P. aeruginosa* were susceptible to ceftazidime-avibactam (6).

ESBL production and carbapenem resistance among *Enterobacteriaceae* isolates are important concerns across all Latin American countries. Previous surveillance studies testing clinical isolates of *Enterobacteriaceae* have consistently reported ESBL rates in many Latin American countries to be 20% to >40% for both *E. coli* and *K. pneumoniae*, and have also reported rates of carbapenem-resistant *Enterobacteriaceae* that approach and often exceed 10%, particularly for *K. pneumoniae* and *Enterobacter* spp. (5, 7–9). The

distribution of ESBL and carbapenemase types observed in the current study was in general agreement with previous reports for Latin America (3, 15, 20). In the current study, we found that ceftazidime-avibactam inhibited 99.9% of ESBL-positive isolates, 99.7% of ceftazidime-nonsusceptible isolates, 99.5% of meropenem-nonsusceptible isolates, 99.0% of AmpC-positive isolates, 99.6% of MDR isolates, and 99.2% of colistin-resistant isolates of *Enterobacteriaceae* that were concurrently MBL-negative. Among clinical isolates of *P. aeruginosa* from Latin American countries, other investigators have reported country-specific percentages of susceptibility to ceftazidime that ranged from 50% to 80%, while 60% to 70% of isolates were carbapenem susceptible (7, 9), similar to our findings in the current study.

The current study identified only 24 isolates of *Enterobacteriaceae* (0.3% of all isolates) that were resistant to ceftazidime-avibactam; 16 (66.7%) of these 24 isolates were MBL positive (Table 2). For eight isolates (four *Enterobacter cloacae* and one each of *Citrobacter freundii*, *Klebsiella oxytoca*, *K. pneumoniae*, and *Raoultella ornithinolytica*), reduced ceftazidime-avibactam susceptibility could not be attributed to MBL production. These eight isolates were comprised of one CTX-M-2-positive isolate, one KPC-2-positive isolate, and six isolates that did not meet the criteria for molecular characterization or in which no acquired β-lactamase or only an OSBL was identified. Of these, two isolates were resistant to carbapenems, all were nonsusceptible or resistant to aztreonam, ceftazidime, and cefepime, and all displayed elevated MICs to another tested avibactam-cephalosporin combination. The mechanism(s) of reduced susceptibility remain to be determined for these isolates but may reflect the presence of an avibactam-insensitive β-lactamase that was not detected using the current molecular algorithm (20, 21) or a combination of mechanisms, such as increased KPC production with porin deficiency and altered efflux (22–24). Sequence insertions in penicillin-binding protein 3 have also been reported to result in reduced susceptibility to avibactam-cephalosporin combinations, although ceftazidime-avibactam remained active (MIC ≤8 μg/ml) against the isolates reported to date (25, 26). Upregulation of efflux transport systems or porin loss alone were not implicated in reduced susceptibility to ceftazidime-avibactam in a previous direct test of those mechanisms (27). Recently, isolated clinical cases in which ceftazidime-avibactam was prescribed to treat patients infected with KPC-producing *K. pneumoniae* have resulted in the emergence of resistance to ceftazidime-avibactam during treatment (23, 28–31). In each case, resistance to ceftazidime-avibactam was reported to be the result of mutations within a plasmid-borne bla_{KPC-3}, which was associated with a porin OmpK35 deficiency in one instance (23) and which coincidently restored carbapenem susceptibility in some isolates (28).

In general, the presence of an MBL gene was associated with *in vitro* resistance to ceftazidime-avibactam among isolates of *Enterobacteriaceae* (Table 2) (13, 14). Carbapenem-nonsusceptible isolates without MBLs, such as those carrying KPC (12–14, 32) or OXA-48-like (13, 32) carbapenemases, were generally susceptible to ceftazidime-avibactam (Table 2). Intrinsic imipenem resistance among Proteeae species (16) did not affect susceptibility to ceftazidime-avibactam (Table 1).

Among isolates of *P. aeruginosa* tested in the current study, we observed that 58.0% of ceftazidime-nonsusceptible isolates (range, 34.3% [Venezuela] to 77.6% [Argentina]) and 67.5% of meropenem-nonsusceptible isolates (range, 50.0% [Venezuela] to 84.7% [Argentina]) were susceptible to ceftazidime-avibactam. If only MBL-negative isolates of *P. aeruginosa* were considered, 71.7% of ceftazidime-nonsusceptible isolates (range, 56.6% [Mexico] to 92.0% [Venezuela]) and 79.7% of meropenem-nonsusceptible isolates (range, 71.1% [Mexico] to 95.8% [Venezuela]) were susceptible to ceftazidime-avibactam. Only 110 isolates (14.7% of molecularly characterized isolates; 6.1% of all isolates tested) were found to carry genes encoding an MBL, and the majority of MBLs identified were VIM-type (90.0% [99/110]) and IMP-type (9.1% [10/110]) enzymes (Fig. S5C). Previous studies also identified VIM-type MBLs among isolates of *P. aeruginosa* from Argentina, Chile, Colombia, Mexico, and Venezuela, and IMP-type MBLs among isolates of *P. aeruginosa* from Brazil and Mexico (33, 34). Isolates carrying bla_{SPM} have been reported to be endemic among clinical isolates of *P. aeruginosa* in Brazil (35);

however, we identified only one isolate carrying bla_{SPM}, collected in Brazil, in the current study. PER- and GES-type β-lactamases were heavily represented in *P. aeruginosa* isolates collected in Latin America, especially in isolates from Mexico (as reported previously [36]). Although MBL-negative subsets of ESBL- and GES-producing isolates showed reduced susceptibility to ceftazidime-avibactam, the enzyme variants found in these isolates are expected to be susceptible to inhibition by avibactam (37), suggesting the presence of additional undetermined resistance mechanisms.

We conclude that clinical isolates of *Enterobacteriaceae* from six Latin American countries in 2012 to 2015 were highly susceptible to ceftazidime-avibactam (99.0% susceptible) and that ceftazidime-avibactam was more active than currently available antimicrobial agents of last resort (e.g., amikacin, colistin, and tigecycline). Only 17 isolates of *Enterobacteriaceae* (0.2% of all isolates tested) carried an MBL. The current study demonstrated ceftazidime-avibactam to be a potent agent against ceftazidime-nonsusceptible, meropenem-nonsusceptible, colistin-resistant, and MDR isolates of *Enterobacteriaceae*. Ceftazidime-avibactam (87.4% susceptible) was the second most potent agent tested against isolates of *P. aeruginosa* from six Latin American countries in 2012 to 2015, after colistin (94.9% susceptible). Based on the *in vitro* susceptibilities and proven clinical efficacy (30, 31, 38–41), ceftazidime-avibactam should be considered in the treatment of indicated infections caused by susceptible *Enterobacteriaceae* and *P. aeruginosa* strains.

MATERIALS AND METHODS

Clinical isolates of *Enterobacteriaceae* and *P. aeruginosa*. The INFORM global surveillance program collected and confirmed the identities of 9,459 nonduplicate clinical isolates of Gram-negative bacilli (7,665 isolates of *Enterobacteriaceae* and 1,794 isolates of *P. aeruginosa*) from 26 medical center laboratories in six countries in Latin America from 2012 to 2015. The INFORM global surveillance program annually requested that each participating medical center laboratory collect predefined quotas of selected bacterial pathogens isolated from patients with specific types of infection (6, 10). Collection was limited to one isolate per patient. All isolates were determined to be clinically significant by algorithms used by the participating laboratories and were collected irrespective of antimicrobial susceptibility profile (6, 10). The demographic information associated with the 9,459 isolates is summarized in Table S1 in the supplemental material. All isolates were transported to International Health Management Associates, Inc. (IHMA; Schaumburg, IL) 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 mass spectrometry (MALDI-TOF) instrument (Bruker Daltonics, Billerica, MA).

Antimicrobial susceptibility testing. The Clinical and Laboratory Standards Institute (CLSI)-defined broth microdilution antimicrobial susceptibility testing was performed using 96-well broth microdilution panels prepared in-house at IHMA (16, 42). Avibactam was tested at a fixed concentration of 4 μg/ml in combination with doubling dilutions of ceftazidime (16). MICs were interpreted using 2016 CLSI breakpoints (16) 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) (38), as CLSI MIC interpretative breakpoints were not published at that time. U.S. FDA MIC interpretative breakpoints were also used for tigecycline (43). EUCAST MIC interpretative breakpoints were used for colistin tested against *Enterobacteriaceae* (44), as CLSI criteria are 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 (16). 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, including cephalosporins (sentinel agent cefepime), monobactams (aztreonam), β-lactam–β-lactamase inhibitor combinations (piperacillin-tazobactam), carbapenems (meropenem), fluoroquinolones (levofloxacin), aminoglycosides (amikacin), glycylcyclines (tigecycline), and polymyxins (colistin) (45).

Screening of clinical isolates of *Enterobacteriaceae* and *P. aeruginosa* for β-lactamase genes. All isolates of *Enterobacteriaceae* with MICs of ≥2 μg/ml to doripenem, imipenem, or meropenem and all isolates of *E. coli*, *K. pneumoniae*, *K. oxytoca* and *P. mirabilis* demonstrating a positive ESBL confirmatory test or MICs of ≥16 μg/ml to ceftazidime 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 (46). These assays were intended to detect genes encoding carbapenemases (KPC, GES, NDM, IMP, VIM, SPM, GIM, and OXA-48-like), ESBLs (TEM, SHV, CTX-M, VEB, PER, and GES), original-spectrum β-lactamases (OSBLs; TEM and SHV enzymes that do not contain substitutions at amino acid positions 104, 164, or 238 in TEM or at 146, 238, or 240 in SHV, which are associated with ESBL activity) (47), and plasmid-mediated AmpC β-lactamases (ACC, ACT, CMY, DHA, FOX, MIR, and MOX) as previously described (46). All isolates of *P. aeruginosa* testing with MICs of ≥4 μg/ml to doripenem, imipenem, or meropenem were screened for the genes encoding carbapenemases, ESBLs, and OSBLs listed above, plus OXA-24/40-like β-lactamases, as described previously (6). Enzyme variants were identified by amplification of full-length β-lactamase genes followed by DNA sequencing, and compar-

ison of the sequences generated to the National Center for Biotechnology Information database (www.ncbi.nlm.nih.gov) and the Lahey Clinic website (www.lahey.org/studies).

Data availability. The sequences of two new β-lactamase variants identified during this study were deposited in GenBank under accession no. KP727573 (OXA-439) and KU663375 (VIM-50).

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/AAC .01814-18.

SUPPLEMENTAL FILE 1, PDF file, 3.9 MB.

ACKNOWLEDGMENTS

REFERENCES

1. de Jonge BLM, Karlowsky JA, Kazmierczak KM, Biedenbach DJ, Sahm DF, Nichols WW. 2016. *In vitro* susceptibility to ceftazidime-avibactam of carbapenem-nonsusceptible *Enterobacteriaceae* isolates collected during the INFORM global surveillance study (2012 to 2014). Antimicrob Agents Chemother 60:3163–3169. https://doi.org/10.1128/AAC.03042-15.

2. Rossi F, Cury AP, Franco MRG, Testa R, Nichols WW. 2017. The *in vitro* activity of ceftazidime-avibactam against 417 gram-negative bacilli collected in 2014 and 2015 at a teaching hospital in São Paulo, Brazil. Braz J Infect Dis 21:569–573. https://doi.org/10.1016/j.bjid.2017.03.008.

3. Karlowsky JA, Lob SH, Kazmierczak KM, Badal RE, Young K, Motyl MR, Sahm DF. 2017. *In vitro* activity of imipenem against carbapenemase-positive *Enterobacteriaceae* isolates collected by the SMART global surveillance program from 2008 to 2014. J Clin Microbiol 55:1638–1649. https://doi.org/10.1128/JCM.02316-16.

4. Flamm RK, Sader HS, Farrell DJ, Jones RN. 2014. Ceftazidime-avibactam and comparator agents tested against urinary tract isolates from a global surveillance program (2011). Diagn Microbiol Infect Dis 80:233–238. https://doi.org/10.1016/j.diagmicrobio.2014.07.005.

5. Jones RN, Guzman-Blanco M, Gales AC, Gallegos B, Castro ALL, Martino MDV, Vega S, Zurita J, Cepparulo M, Castanheira M. 2013. Susceptibility rates in Latin American nations: report from a regional resistance surveillance program (2011). Braz J Infect Dis 17:672–681. https://doi.org/10.1016/j.bjid.2013.07.002.

6. Nichols WW, de Jonge BLM, Kazmierczak KM, Karlowsky JA, Sahm DF. 2016. *In vitro* susceptibility of global surveillance isolates of *Pseudomonas aeruginosa* to ceftazidime-avibactam (INFORM 2012 to 2014). Antimicrob Agents Chemother 60:4743–4749. https://doi.org/10.1128/AAC.00220-16.

7. Karlowsky JA, Hoban DJ, Hackel MA, Lob SH, Sahm DF. 2017. Resistance among gram-negative ESKAPE pathogens isolated from hospitalized patients with intra-abdominal and urinary tract infections in Latin American countries: SMART 2013–2015. Braz J Infect Dis 21:343–348. https://doi.org/10.1016/j.bjid.2017.03.006.

8. Sader HS, Castanheira M, Farrell DJ, Flamm RK, Mendes RE, Jones RN. 2016. Tigecycline antimicrobial activity tested against clinical bacteria from Latin American medical centres: results from SENTRY antimicrobial surveillance program (2011-2014). Int J Antimicrob Agents 48:144–150. https://doi.org/10.1016/j.ijantimicag.2016.04.021.

9. Fernández-Canigia L, Dowzicky MJ. 2012. Susceptibility of important gram-negative pathogens to tigecycline and other antibiotics in Latin America between 2004 and 2010. Ann Clin Microbiol Antimicrob 11:29. https://doi.org/10.1186/1476-0711-11-29.

10. Karlowsky JA, Biedenbach DJ, Kazmierczak KM, Stone GG, Sahm DF.

2016. Activity of ceftazidime-avibactam against extended-spectrum- and AmpC β-lactamase-producing *Enterobacteriaceae* collected in the INFORM global surveillance study from 2012 to 2014. Antimicrob Agents Chemother 60:2849–2857. https://doi.org/10.1128/AAC.02286-15.

11. Kazmierczak KM, Biedenbach DJ, Hackel M, Rabine S, de Jonge BLM, Bouchillon SK, Sahm DF, Bradford PA. 2016. Global dissemination of bla_{KPC} into bacterial species beyond *Klebsiella pneumoniae* and *in vitro* susceptibility to ceftazidime-avibactam and aztreonam-avibactam. Antimicrob Agents Chemother 60:4490–4500. https://doi.org/10.1128/AAC.00107-16.

12. Papp-Wallace KM, Bajaksouzian S, Abdelhamed AM, Foster AN, Winkler ML, Gatta JA, Nichols WW, Testa R, Bonomo R, Jacobs MR. 2015. Activities of ceftazidime, ceftaroline and aztreonam alone and combined with avibactam against isogenic *Escherichia coli* strains expressing selected single β-lactamases. Diagn Microbiol Infect Dis 82:65–69. https://doi.org/10.1016/j.diagmicrobio.2015.02.003.

13. Livermore DM, Mushtaq S, Warner M, Zhang J, Maharjan S, Doumith M, Woodford N. 2011. Activities of NXL104 combinations with ceftazidime and aztreonam against carbapenemase-producing *Enterobacteriaceae*. Antimicrob Agents Chemother 55:390–394. https://doi.org/10.1128/AAC.00756-10.

14. Li H, Estabrook M, Jacoby GA, Nichols WW, Testa RT, Bush K. 2015. *In vitro* susceptibility of characterized β-lactamase-producing strains tested with avibactam combinations. Antimicrob Agents Chemother 59:1789–1793. https://doi.org/10.1128/AAC.04191-14.

15. Kazmierczak KM, Lob SH, Hoban DJ, Hackel MA, Badal RE, Bouchillon SK. 2015. Characterizaton of extended-spectrum beta-lactamases and antimicrobial resistance of *Klebsiella pneumoniae* in intra-abdominal infection isolates in Latin America, 2008–2012. Results of the Study for Monitoring Antimicrobial Resistance Trends. Diagn Microbiol Infect Dis 82:209–214. https://doi.org/10.1016/j.diagmicrobio.2015.03.025.

16. Clinical and Laboratory Standards Institute. 2016. Performance standards for antimicrobial susceptibility testing, 26th informational supplement. CLSI document M100-S26. Clinical and Laboratory Standards Institute, Wayne, PA.

17. Oueslati S, Nordmann P, Poirel L. 2015. Heterogeneous hydrolytic features for OXA-48-like β-lactamases. J Antimicrob Chemother 70:1059–1063. https://doi.org/10.1093/jac/dku524.

18. Stojanoski V, Adamski CJ, Hu L, Mehta SC, Sankaran B, Zwart P, Prasad BV, Palzkill T. 2016. Removal of the side chain at the active-site serine by a glycine substitution increases the stability of a wide range of serine

β-lactamases by relieving steric strain. Biochemistry 55:2479–2490. https://doi.org/10.1021/acs.biochem.6b00056.

19. Lister PD, Wolter DJ, Hanson ND. 2009. Antibacterial-resistant *Pseudomonas aeruginosa*: clinical impact and complex regulation of chromosomally encoded resistance mechanisms. Clin Microbiol Rev 22:582–610. https://doi.org/10.1128/CMR.00040-09.

20. Logan LK, Weinstein RA. 2017. The epidemiology of carbapenem-resistant *Enterobacteriaceae*: the impact and evolution of a global menace. J Infect Dis 215:S28–S36. https://doi.org/10.1093/infdis/jiw282.

21. Lahiri SD, Giacobbe RA, Johnstone MR, Alm RA. 2014. Activity of avibactam against *Enterobacter cloacae* producing an extended spectrum class C β-lactamase enzyme. J Antimicrob Chemother 69:2942–2946. https://doi.org/10.1093/jac/dku237.

22. Nelson K, Hemarajata P, Sun D, Rubio-Aparicio D, Tsivkovski R, Yang S, Sebra R, Kasarskis A, Nguyen H, Hanson BM, Leopold S, Weinstock G, Lomovskaya O, Humphries RM. 2017. Resistance to ceftazidime-avibactam is due to transposition of KPC in a porin-deficient strain of *Klebsiella pneumoniae* with increased efflux activity. Antimicrob Agents Chemother 61:e0098917. https://doi.org/10.1128/AAC.00989-17.

23. Shen Z, Ding B, Ye M, Wang P, Bi Y, Wu S, Xu X, Guo Q, Wang M. 2017. High ceftazidime hydrolysis activity and porin OmpK35 deficiency contribute to the decreased susceptibility to ceftazidime/avibactam in KPC-producing *Klebsiella pneumoniae*. J Antimicrob Chemother 72:1930–1936. https://doi.org/10.1093/jac/dkx066.

24. Castanheira M, Mendes RE, Sader HS. 2017. Low frequency of ceftazidime-avibactam resistance among *Enterobacteriaceae* isolates carrying bla_{KPC} collected in hospitals from the United States from 2012 to 2015. Antimicrob Agents Chemother 61:e02369-16. https://doi.org/10.1128/AAC.02369-16.

25. Alm RA, Johnstone MR, Lahiri SD. 2015. Characterization of *Escherichia coli* NDM isolates with decreased susceptibility to aztreonam/avibactam: role of a novel insertion in PBP3. J Antimicrob Chemother 70:1420–1428. https://doi.org/10.1093/jac/dku568.

26. Zhang Y, Kashikar A, Brown CA, Denys G, Bush K. 2017. Unusual *Escherichia coli* PBP 3 insertion sequence identified from a collection of carbapenem-resistant *Enterobacteriaceae* tested *in vitro* with a combination of ceftazidime-, ceftaroline-, or aztreonam-avibactam. Antimicrob Agents Chemother 61:e00389-17. https://doi.org/10.1128/AAC.00389-17.

27. Pagès J-M, Peslier S, Keating TA, Lavigne J-P, Nichols WW. 2016. The role of the outer membrane and porins in the susceptibility of β-lactamase-producing *Enterobacteriaceae* to ceftazidime-avibactam. Antimicrob Agents Chemother 60:1349–1359. https://doi.org/10.1128/AAC.01585-15.

28. Shields RK, Chen L, Cheng S, Chavada KD, Press EG, Synder A, Pandey R, Doi Y, Kreiswirth BN, Nguyen MH, Clancy CJ. 2017. Emergence of ceftazidime-avibactam resistance due to plasmid-borne blaKPC-3 mutations during treatment of carbapenem-resistant *Klebsiella pneumoniae* infections. Antimicrob Agents Chemother 61:e02097-16. https://doi.org/10.1128/AAC.02097-16.

29. Shields RK, Nguyen MH, Press EG, Chen L, Kreiswirth BN, Clancy CJ. 2017. *In vitro* selection of meropenem resistance among ceftazidime-avibactam-resistant, meropenem-susceptible *Klebsiella pneumoniae* isolates with variant KPC-3 carbapenemases. Antimicrob Agents Chemother 61:e00079-17. https://doi.org/10.1128/AAC.00079-17.

30. Shields RK, Potoski BA, Haidar G, Hao B, Doi Y, Chen L, Press EG, Kreiswirth BN, Clancy CJ, Nguyen MH. 2016. Clinical outcomes, drug toxicity, and emergence of ceftazidime-avibactam resistance among patients treated for carbapenem-resistant *Enterobacteriaceae* infections. Clin Infect Dis 63:1615–1618. https://doi.org/10.1093/cid/ciw636.

31. Krapp F, Grant JL, Sutton SH, Ozer EA, Barr VO. 2017. Treating complicated carbapenem-resistant *Enterobacteriaceae* infections with ceftazidime/avibactam: a retrospective study with molecular strain characterization. Int J Antimicrob Agents 49:770–773. https://doi.org/10.1016/j.ijantimicag.2017.01.018.

32. Castanheira M, Mills JC, Costello SE, Jones RN, Sader HS. 2015. Ceftazidime-avibactam activity tested against *Enterobacteriaceae* isolates from U.S. hospitals (2011 to 2013) and characterization of β-lactamase-producing strains. Antimicrob Agents Chemother 59:3509–3517. https://doi.org/10.1128/AAC.00163-15.

33. Sader HS, Castanheira M, Mendes RE, Toleman M, Walsh TR, Jones RN. 2005. Dissemination and diversity of metallo-β-lactamases in Latin America: report from the SENTRY Antimicrobial Surveillance Program. Int J Antimicrob Agents 25:57–61. https://doi.org/10.1016/j.ijantimicag.2004.08.013.

34. Hong DJ, Bae IK, Jang IH, Jeong SH, Kang HK, Lee K. 2015. Epidemiology and characteristics of metallo-β-lactamase-producing *Pseudomonas aeruginosa*. Infect Chemother 47:81–97. https://doi.org/10.3947/ic.2015.47.2.81.

35. Silveira MC, Albano RM, Asensi MD, Carvalho-Assef AP. 2016. Description of genomic islands associated to the multidrug-resistant *Pseudomonas aeruginosa* clone ST227. Infect Genet Evol 42:60–65. https://doi.org/10.1016/j.meegid.2016.04.024.

36. Garza-Ramos U, Barrios H, Reyna-Flores F, Tamayo-Legorreta E, Catalan-Najera JC, Morfin-Otero R, Rodríguez-Noriega E, Volkow P, Cornejo-Juarez P, González A, Gaytan-Martinez J, Del Rocío Gónzalez-Martínez M, Vazquez-Farias M, Silva-Sanchez J. 2015. Widespread of ESBL- and carbapenemase GES-type genes on carbapenem-resistant *Pseudomonas aeruginosa* clinical isolates: a multicenter study in Mexican hospitals. Diagn Microbiol Infect Dis 81:135–137. https://doi.org/10.1016/j.diagmicrobio.2014.09.029.

37. Lahiri SD, Bradford PA, Nichols WW, Alm RA. 2016. Structural and sequence analysis of class A β-lactamases with respect to avibactam inhibition: impact of Ω-loop variations. J Antimicrob Chemother 71:2848–2855. https://doi.org/10.1093/jac/dkw248.

38. Allergan. 2017. Avycaz® (ceftazidime and avibactam) for injection, for intravenous use, prescribing information. Allergan USA, Inc., Irvine, CA.

39. Shields RK, Nguyen MH, Chen L, Press EG, Potoski BA, Marini RV, Doi Y, Kreiswirth BN, Clancy CJ. 2017. Ceftazidime-avibactam is superior to other treatment regimens against carbapenem-resistant *Klebsiella pneumoniae* bacteremia. Antimicrob Agents Chemother 61:e00883-17. https://doi.org/10.1128/AAC.00883-17.

40. Mazuski JE, Gasink LB, Armstrong J, Broadhurst H, Stone GG, Rank D, Llorens L, Newell P, Pachl J. 2016. Efficacy and safety of ceftazidime-avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infection: results from a randomized, controlled, double-blind, Phase 3 program. Clin Infect Dis 62:1380–1389. https://doi.org/10.1093/cid/ciw133.

41. Stone GG, Bradford PA, Newell P, Wardman A. 2017. *In vitro* activity of ceftazidime-avibactam against isolates in a Phase 3 open-label clinical trial for complicated intra-abdominal and urinary tract infections caused by ceftazidime-nonsusceptible Gram-negative pathogens. Antimicrob Agents Chemother 61:e01820-16. https://doi.org/10.1128/AAC.01820-16.

42. Clinical and Laboratory Standards Institute. 2015. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard, 10th ed. CLSI document M07-A10. Clinical and Laboratory Standards Institute, Wayne, PA.

43. Pfizer. 2016. Tygacil® (tigecycline) injection, powder, lyophilized, for solution, prescribing information. Pfizer, Inc., Philadelphia, PA.

44. The European Committee on Antimicrobial Susceptibility Testing. 2016. Breakpoint tables for interpretation of MICs and zone diameters, version 6.0. http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_6.0_Breakpoint_table.pdf.

45. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B, Paterson DL, Rice LB, Stelling J, Struelens MJ, Vatopoulos A, Weber JT, Monnet DL. 2012. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microb Infect 18:268–281. https://doi.org/10.1111/j.1469-0691.2011.03570.x.

46. Lob SH, Kazmierczak KM, Badal RE, Hackel MA, Bouchillon SK, Biedenbach DJ, Sahm DF. 2015. Trends in susceptibility of *Escherichia coli* from intra-abdominal infections to ertapenem and comparators in the United States according to data from the SMART Program, 2009 to 2013. Antimicrob Agents Chemother 59:3606–3610. https://doi.org/10.1128/AAC.05186-14.

47. Bradford PA. 2001. Extended-spectrum β-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. Clin Microbiol Rev 14:933–951. https://doi.org/10.1128/CMR.14.4.933-951.2001.