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SUSCEPTIBILITY

In Vitro Activity of Imipenem-Relebactam against Clinical Isolates of Gram-Negative Bacilli Isolated in Hospital Laboratories in the United States as Part of the SMART 2016 Program

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ABSTRACT Relebactam is a non-β-lactam, bicyclic diazabicyclooctane β-lactamase inhibitor of class A and class C β-lactamases, including *Klebsiella pneumoniae* carbapenemases (KPCs). It is in phase 3 clinical development in combination with imipenem/cilastatin. The *in vitro* activities of imipenem-relebactam, imipenem, and comparators were determined using the Clinical and Laboratory Standards Institute (CLSI) reference broth microdilution method for isolates of *Enterobacteriaceae* (n = 3,419) and *Pseudomonas aeruginosa* (n = 896) collected in 2016 by 21 U.S. hospital laboratories participating in the SMART (Study for Monitoring Antimicrobial Resistance Trends) global surveillance program. Relebactam was tested at a fixed concentration of 4 μg/ml. Imipenem-relebactam MICs were interpreted using CLSI breakpoints for imipenem. Rates of susceptibility to imipenem-relebactam and imipenem for non-*Proteeae Enterobacteriaceae* (n = 3,143) and *P. aeruginosa* were 99.1% (3,115/3,143) and 95.9% (3,013/3,143) and were 94.4% (846/896) and 74.7% (669/896), respectively. Relebactam restored imipenem susceptibility to 78.5% (102/130) of imipenem-nonsusceptible non-*Proteeae Enterobacteriaceae* and to 78.0% (177/227) of imipenem-nonsusceptible *P. aeruginosa* isolates. Susceptibility to imipenem-relebactam was 98.2% (444/452) and 82.2% (217/264) for multidrug-resistant (MDR) non-*Proteeae Enterobacteriaceae* and MDR *P. aeruginosa*, respectively. Given the ability of relebactam to restore susceptibility to imipenem in nonsusceptible isolates of both non-*Proteeae Enterobacteriaceae* and *P. aeruginosa* and to demonstrate potent activity against current MDR isolates of both non-*Proteeae Enterobacteriaceae* and *P. aeruginosa*, further development of imipenem-relebactam appears warranted.

KEYWORDS SMART, surveillance, imipenem, relebactam, Gram negative, United States

The emergence and spread of antimicrobial resistance in bacterial pathogens are an ongoing process fostered by selective antimicrobial pressure and imperfect infection control practice. They commonly result from horizontal acquisition of new resistance genes and/or the generation of DNA mutations in target site or regulatory genes which disseminate vertically via clonal expansion. Over time, the appearance of new multidrug-resistant (MDR) phenotypes is inevitable. In the United States, steady increases in rates of extended-spectrum β-lactamase (ESBL)-producing, carbapenem-resistant, and MDR *Enterobacteriaceae*; MDR *Pseudomonas aeruginosa*; and other highly resistant nonfermentative Gram-negative bacilli have been observed since 2000 (1–4). The unchecked spread of MDR, extensively drug-resistant, and pan-drug-resistant

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Gram-negative bacilli is particularly concerning as effective therapeutic choices for such isolates are currently limited and novel agents have been slow to appear (1, 5).

Carbapenems, such as imipenem, are broad-spectrum parenteral antibacterial agents that are generally reserved for use as agents of last resort in the treatment of serious nosocomial infections. Carbapenems are stable to the hydrolytic action of class A and class C (AmpC) β-lactamases. Mechanisms of resistance to carbapenems demonstrated by Gram-negative bacteria include one or more of carbapenemase production, impaired outer membrane permeability (due most commonly to reduced expression of certain outer membrane proteins) in combination with β-lactamase hyperproduction, and efflux across the outer membrane. Carbapenemases include class A β-lactamases such as *Klebsiella pneumoniae* carbapenemases (KPCs), class B metallo-β-lactamases (e.g., NDM, IMP, and VIM), and class D β-lactamases (e.g., OXA type). Carbapenem resistance in *P. aeruginosa* most commonly occurs as the result of downregulation of the porin protein OprD in combination with production of the intrinsic, chromosomally encoded AmpC β-lactamase (*Pseudomonas*-derived cephalosporinase [PDC]).

Relebactam, formerly MK-7655, is a novel piperidine analogue, non-β-lactam bicyclic diazabicyclooctane β-lactamase inhibitor that is active *in vitro* against class A β-lactamases, including KPC-type carbapenemases, and class C β-lactamases (6). Relebactam is structurally related to avibactam and is not an inducer of AmpC enzymes (7). Relebactam differs from avibactam in that it does not inhibit class D carbapenemases (e.g., OXA-48-like) but does possess inhibitory activity (in the combination imipenem-relebactam) against clinical isolates of *K. pneumoniae* carrying variant KPC-3 enzymes that are resistant to ceftazidime-avibactam (8, 9).

Relebactam has been combined with the carbapenem/renal dehydropeptidase I inhibitor imipenem/cilastatin, primarily to restore imipenem's clinical activity against KPC-producing *K. pneumoniae* as well as other carbapenem-resistant *Enterobacteriaceae* and against *P. aeruginosa* isolates that demonstrate carbapenem resistance via impermeability arising from porin loss in combination with AmpC expression (6, 9). Imipenem would appear to be an excellent partner for relebactam to treat pseudomonal infections because imipenem, unlike other β-lactams, evades upregulated efflux frequently present in *P. aeruginosa* (9). Relebactam has been shown to lower imipenem MICs by up to 64-fold for KPC-producing *K. pneumoniae* and to also demonstrate modest potentiation of imipenem activity against carbapenem-resistant *Enterobacteriaceae* (CRE) isolates carrying ESBL and AmpC enzymes (8, 10, 11). Imipenem-relebactam, like ceftazidime-avibactam, is inactive against metallo-β-lactamase-producing Gram-negative bacilli (5, 6, 8). The presence of some major OmpK36 mutations (an IS*5* promoter insertion or OmpK36 ins AA135–136 GD) has also been reported to be independently associated with higher imipenem-relebactam and imipenem MICs (8), while OmpK35 mutations were not associated with differences in MICs of either agent (8, 12).

The intent of the current study was to determine the *in vitro* activity of imipenem-relebactam against a current (2016) collection of non-*Proteeae Enterobacteriaceae* (NPE) and *P. aeruginosa* isolates from patients with intra-abdominal, lower respiratory tract, and urinary tract infections in the United States. Isolates tested in this study were collected as part of the Study for Monitoring Antimicrobial Resistance Trends (SMART) global surveillance program, which has monitored *in vitro* antimicrobial susceptibility profiles of clinical isolates of aerobic and facultative Gram-negative bacilli collected by laboratories worldwide from patients with intra-abdominal (since 2002), urinary tract (since 2009), and lower respiratory tract (since 2015) infections (13).

(The results of this report have been presented in part on 26 February 2018 at the 47th Critical Care Congress in San Antonio, TX.)

RESULTS

Of the 3,143 isolates of non-*Proteeae Enterobacteriaceae* tested, 99.1% (3,115/3,143) were susceptible to imipenem-relebactam, 95.9% (3,013/3,143) were susceptible to

TABLE 1 *In vitro* activity of imipenem-relebactam, imipenem, and ertapenem against the 12 most common species of *Enterobacteriaceae* collected as part of the SMART global surveillance program in the United States in 2016

Species of *Enterobacteriaceae*	*n*	% susceptible to drug:		
		Imipenem-relebactam	Imipenem	Ertapenem
Escherichia coli	1,321	100	99.6	98.8
Klebsiella pneumoniae	717	99.4	96.9	95.5
Enterobacter cloacae	276	100	96.7	85.9
Serratia marcescens	203	89.7	64.0	96.6
Proteus mirabilis	182	65.9	54.4	98.9
Klebsiella oxytoca	174	100	100	99.4
Klebsiella aerogenes	126	98.4	95.2	95.2
Citrobacter freundii	94	100	94.7	90.4
Morganella morganii	48	25.0	8.3	100
Enterobacter asburiae	44	100	88.6	77.3
Klebsiella variicola	42	100	100	100
Citrobacter koseri	38	100	97.4	100
All *Enterobacteriaceae* spp.	3,419	96.1	92.2	96.3
All non-*Proteeae Enterobacteriaceae* spp.[a]	3,143	99.1	95.9	96.1

[a]All non-*Proteeae Enterobacteriaceae* spp. exclude *Proteus* spp., *Providencia* spp., and *Morganella* spp.

imipenem, and 96.1% (3,019/3,143) were susceptible to ertapenem (Table 1). Imipenem-relebactam inhibited all isolates of the 10 most commonly collected species of non-*Proteeae Enterobacteriaceae* at the susceptible MIC breakpoint for imipenem (1 μg/ml) with three exceptions: *K. pneumoniae* (99.4% susceptible to imipenem-relebactam), *Klebsiella aerogenes* (98.4% susceptible), and *Serratia marcescens* (89.7% susceptible). *S. marcescens* accounted for only 6.5% (203/3,143) of all isolates of non-*Proteeae Enterobacteriaceae* tested but contributed the majority (56.2%; 73/130) of imipenem-nonsusceptible isolates (Fig. 1). More than 95% of isolates of non-*Proteeae Enterobacteriaceae* were susceptible to imipenem with three exceptions: *Citrobacter freundii* (94.7% susceptible), *Enterobacter asburiae* (88.6%), and *S. marcescens* (64.0%) (Table 1). As expected, imipenem showed weak activity against *Proteus mirabilis* (54.4% susceptible) and *Morganella morganii* (8.3%), with relebactam increasing percent susceptibility to imipenem by only 11.5 to 16.7%.

Table 2 depicts the *in vitro* activity of imipenem-relebactam, imipenem, and comparator antimicrobial agents against all isolates of non-*Proteeae Enterobacteriaceae* (n = 3,143) as well as against nonsusceptible and MDR-phenotype subsets of isolates.

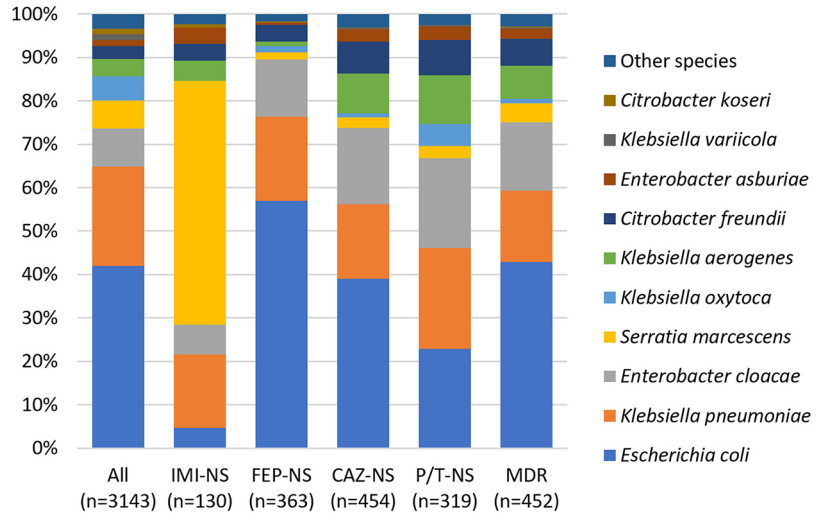

FIG 1 Species distribution among non-*Proteeae Enterobacteriaceae* and imipenem-nonsusceptible (IMI-NS), cefepime-nonsusceptible (FEP-NS), ceftazidime-nonsusceptible (CAZ-NS), piperacillin-tazobactam-nonsusceptible (P/T-NS), and MDR (multidrug-resistant) phenotypes.

TABLE 2 *In vitro* activity of imipenem-relebactam and comparative antimicrobial agents against non-*Proteeae Enterobacteriaceae* collected as part of the SMART global surveillance program in the United States in 2016

Phenotype (*n*)	Antimicrobial agent	MIC determination (μg/ml)			MIC interpretation		
		MIC_{50}	MIC_{90}	MIC range	% susceptible	% intermediate	% resistant
All (3,143)	Imipenem-relebactam[a]	0.12	0.5	≤0.06 to >32	99.1	0.5	0.4
	Imipenem	≤0.5	1	≤0.5 to >32	95.9	2.2	2.0
	Ertapenem	≤0.06	0.12	≤0.06 to >4	96.1	1.6	2.4
	Amikacin	≤4	≤4	≤4 to >32	99.6	0.3	0.2
	Aztreonam	≤1	>16	≤1 to >16	83.8	1.9	14.2
	Cefepime[b]	≤1	4	≤1 to >32	88.5	3.8	7.8
	Ceftazidime	≤1	16	≤1 to >32	85.6	2.3	12.2
	Ceftriaxone	≤1	>32	≤1 to >32	79.8	1.9	18.2
	Ciprofloxacin	≤0.25	>2	≤0.25 to >2	80.5	1.5	18.0
	Colistin[c]	≤1	≤1	≤1 to >4	91.3		8.7
	Piperacillin-tazobactam	≤2	32	≤2 to >64	89.9	4.6	5.5
Imipenem nonsusceptible (130)	Imipenem-relebactam[a]	0.5	2	≤0.06 to >32	78.5	12.3	9.2
	Imipenem	2	32	2 to >32	0	52.3	47.7
	Ertapenem	≤0.06	>4	≤0.06 to >4	66.9	1.5	31.5
	Amikacin	≤4	16	≤4 to >32	97.7	1.5	0.8
	Aztreonam	≤1	>16	≤1 to >16	64.6	1.5	33.9
	Cefepime[b]	≤1	>32	≤1 to >32	71.5	6.9	21.5
	Ceftazidime	≤1	>32	≤1 to >32	66.9	3.1	30.0
	Ceftriaxone	≤1	>32	≤1 to >32	60.8	3.9	35.4
	Ciprofloxacin	≤0.25	>2	≤0.25 to >2	76.2	5.4	18.5
	Colistin[c]	>4	>4	≤1 to >4	41.5		58.5
	Piperacillin-tazobactam	≤2	>64	≤2 to >64	67.7	5.4	26.9
Cefepime nonsusceptible (363)	Imipenem-relebactam[a]	0.12	0.25	≤0.06 to >32	98.4	0.8	0.8
	Imipenem	≤0.5	2	≤0.5 to >32	89.8	1.4	8.8
	Ertapenem	≤0.06	>4	≤0.06 to >4	76.9	8.3	14.9
	Amikacin	≤4	16	≤4 to >32	97.3	1.9	0.8
	Aztreonam	>16	>16	≤1 to >16	8.5	7.4	84.0
	Cefepime[b]	32	>32	4 to >32	0	32.8	67.2
	Ceftazidime	16	>32	≤1 to >32	17.6	14.6	67.8
	Ceftriaxone	>32	>32	≤1 to >32	1.7	0.3	98.1
	Ciprofloxacin	>2	>2	≤0.25 to >2	24.2	6.3	69.4
	Colistin[c]	≤1	≤1	≤1 to >4	96.1		3.9
	Piperacillin-tazobactam	16	>64	≤2 to >64	60.6	11.0	28.4
Ceftazidime nonsusceptible (454)	Imipenem-relebactam[a]	0.12	0.5	≤0.06 to >32	98.7	0.7	0.7
	Imipenem	≤0.5	1	≤0.5 to >32	90.5	1.8	7.7
	Ertapenem	0.12	4	≤0.06 to >4	78.0	7.9	14.1
	Amikacin	≤4	8	≤4 to >32	98.0	1.5	0.4
	Aztreonam	>16	>16	≤1 to >16	5.5	5.7	88.8
	Cefepime[b]	8	>32	≤1 to >32	34.1	17.4	48.5
	Ceftazidime	32	>32	8 to >32	0	15.9	84.1
	Ceftriaxone	>32	>32	≤1 to >32	1.5	1.3	97.1
	Ciprofloxacin	>2	>2	≤0.25 to >2	42.5	5.1	52.4
	Colistin[c]	≤1	≤1	≤1 to >4	93.4		6.6
	Piperacillin-tazobactam	32	>64	≤2 to >64	48.7	24.7	26.7
Piperacillin-tazobactam nonsusceptible (319)	Imipenem-relebactam[a]	0.12	0.5	≤0.06 to >32	98.1	0.9	0.9
	Imipenem	≤0.5	4	≤0.5 to >32	86.8	2.2	11.0
	Ertapenem	0.25	>4	≤0.06 to >4	69.9	11.0	19.1
	Amikacin	≤4	8	≤4 to >32	97.5	1.6	0.9
	Aztreonam	>16	>16	≤1 to >16	24.5	3.8	71.8
	Cefepime[b]	2	>32	≤1 to >32	55.2	18.2	26.7
	Ceftazidime	32	>32	≤1 to >32	27.0	4.4	68.7
	Ceftriaxone	32	>32	≤1 to >32	21.0	0.9	78.1
	Ciprofloxacin	≤0.25	>2	≤0.25 to >2	58.9	4.7	36.4
	Colistin[c]	≤1	≤1	≤1 to >4	91.9		8.2
	Piperacillin-tazobactam	>64	>64	32 to >64	0	45.5	54.6
MDR (452)	Imipenem-relebactam[a]	0.12	0.5	≤0.06 to >32	98.2	0.9	0.9
	Imipenem	≤0.5	2	≤0.5 to >32	88.9	2.4	8.6
	Ertapenem	0.12	4	≤0.06 to >4	77.9	8.0	14.2

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TABLE 2 (Continued)

Phenotype (*n*)	Antimicrobial agent	MIC determination (μg/ml)			MIC interpretation		
		MIC_{50}	MIC_{90}	MIC range	% susceptible	% intermediate	% resistant
	Amikacin	≤4	8	≤4 to >32	97.8	1.6	0.7
	Aztreonam	>16	>16	≤1 to >16	3.3	8.2	88.5
	Cefepime[b]	16	>32	≤1 to >32	26.3	20.6	53.1
	Ceftazidime	32	>32	≤1 to >32	10.0	13.3	76.8
	Ceftriaxone	>32	>32	≤1 to >32	2.7	0.4	96.9
	Ciprofloxacin	>2	>2	≤0.25 to >2	35.0	6.0	59.1
	Colistin[c]	≤1	≤1	≤1 to >4	91.2		8.9
	Piperacillin-tazobactam	32	>64	≤2 to >64	47.1	26.1	26.8

[a]Breakpoints for imipenem-relebactam have not been defined. For the purpose of comparison, MICs were interpreted using CLSI imipenem MIC breakpoints for *Enterobacteriaceae* (susceptible, ≤1 μg/ml; intermediate, 2 μg/ml; resistant, ≥4 μg/ml) (24).
[b]For cefepime, the intermediate category is replaced by the "susceptible-dose dependent" category (24).
[c]CLSI breakpoints for colistin have not been defined against *Enterobacteriaceae*, and MICs were interpreted using EUCAST breakpoints (26).

Figure 2 depicts the prevalence of imipenem-nonsusceptible (4.1%), cefepime-nonsusceptible (11.5%), ceftazidime-nonsusceptible (14.4%), piperacillin-tazobactam-nonsusceptible (10.1%), and MDR (14.4%) phenotypes for non-*Proteeae Enterobacteriaceae*. Imipenem-relebactam susceptibility was ≥98% for cefepime-nonsusceptible, ceftazidime-nonsusceptible, and piperacillin-tazobactam-nonsusceptible phenotype subsets as well as for MDR isolates (Table 2). Relebactam restored *in vitro* susceptibility to 78.5% (102/130) for imipenem-nonsusceptible isolates and lowered the imipenem MIC_{90} by 16-fold. Relebactam also increased percent susceptibility to imipenem by 8.2 to 11.3% for cefepime-nonsusceptible, ceftazidime-nonsusceptible, piperacillin-tazobactam-nonsusceptible, and MDR phenotypes. Of the comparator agents, only amikacin demonstrated *in vitro* activity comparable to imipenem-relebactam against all isolates of non-*Proteeae Enterobacteriaceae*. Imipenem-relebactam inhibited 98.2% of all MDR isolates and 100% of seven of the eight most common MDR phenotypes, the exception being the MDR phenotype that included nonsusceptibility to aztreonam, ceftazidime, cefepime, ciprofloxacin, imipenem, and piperacillin-tazobactam, which accounted for only 4.0% of MDR phenotypes and was 88.9% susceptible to imipenem-relebactam (Table 3).

Among all *P. aeruginosa* isolates tested, 94.4% (846/896) and 74.7% (669/896) of isolates were susceptible to imipenem-relebactam and imipenem, respectively (Table 4).

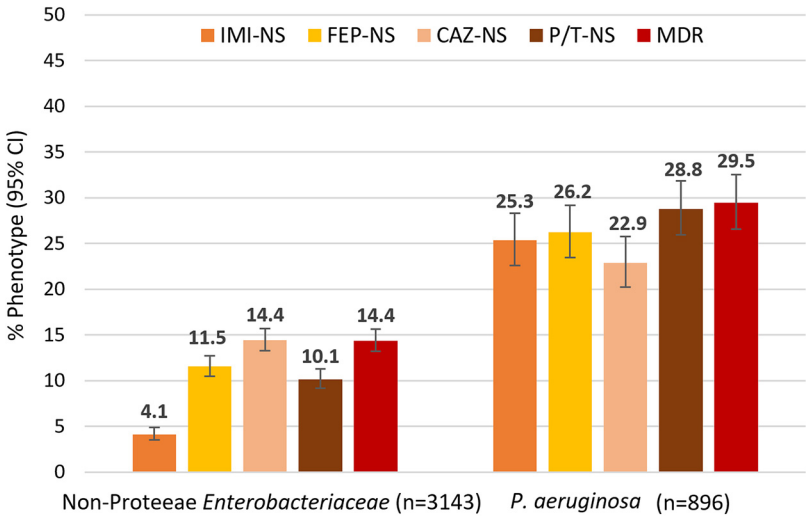

FIG 2 Prevalence of imipenem-nonsusceptible (IMI-NS), cefepime-nonsusceptible (FEP-NS), ceftazidime-nonsusceptible (CAZ-NS), piperacillin-tazobactam-nonsusceptible (P/T-NS), and MDR (multidrug-resistant) phenotypes among non-*Proteeae Enterobacteriaceae* and *P. aeruginosa* isolates. 95% CI, 95% confidence interval.

TABLE 3 *In vitro* activity of imipenem-relebactam against the most common MDR phenotypes of non-*Proteeae Enterobacteriaceae*

Phenotype[a]	*n* (% of all MDR isolates)	Imipenem-relebactam	
		MIC_{90} (μg/ml)	% susceptible
All non-*Proteeae Enterobacteriaceae*	3,143	0.25	99.1
All MDR	452[b]	0.5	98.2
ATM, CAZ, FEP, CIP	137 (30.3)	0.25	100
ATM, CAZ, P/T	69 (15.3)	0.25	100
ATM, CAZ, FEP, CIP, P/T	57 (12.6)	0.25	100
ATM, CAZ, FEP, P/T	31 (6.9)	0.25	100
ATM, FEP, CIP	28 (6.2)	0.25	100
ATM, CAZ, FEP	21 (4.6)	0.5	100
ATM, CAZ, FEP, CIP, IMI, P/T	18 (4.0)	4	88.9
ATM, CAZ, FEP, IMI, P/T	10 (2.2)	0.25	100

[a]Sentinel agents used for the definition of MDR included amikacin, aztreonam (ATM), cefepime (FEP), ceftazidime (CAZ), ciprofloxacin (CIP), colistin, imipenem (IMI), and piperacillin-tazobactam (P/T). The MDR phenotypes listed accounted for 82.1% (371/452) of all MDR phenotypes identified; amikacin or colistin resistance was not observed among the most common MDR phenotypes identified. Agents shown in the table tested as nonsusceptible; the other sentinel agents tested as susceptible. Agents tested but not included in the list of sentinel agents may have tested as susceptible or nonsusceptible.
[b]MDR isolates accounted for 14.4% (452/3,143) of all isolates of non-*Proteeae Enterobacteriaceae*.

Of the comparator agents, only the activities of amikacin and colistin approximated or exceeded that of imipenem-relebactam. Among imipenem-nonsusceptible *P. aeruginosa* isolates, 78.0% (177/227) of isolates were rendered susceptible by the addition of relebactam. The MIC_{90} for imipenem-relebactam was 4-fold lower than that for imipenem alone. Among cefepime-nonsusceptible, ceftazidime-nonsusceptible, piperacillin-tazobactam-nonsusceptible, and MDR subsets, imipenem-relebactam susceptibility was ≥82.1%.

Figure 2 shows that the prevalences of imipenem-nonsusceptible (25.3%), cefepime-nonsusceptible (26.2%), ceftazidime-nonsusceptible (22.9%), piperacillin-tazobactam-nonsusceptible (28.8%), and MDR (29.5%) phenotypes were relatively similar (maximum difference, 6.6%) among *P. aeruginosa* isolates. These rates were approximately 2 to 3 times higher than those among non-*Proteeae Enterobacteriaceae*, except for the imipenem-nonsusceptible phenotype, which was approximately 6 times (25.3% versus 4.1%) more common among *P. aeruginosa* isolates.

Imipenem-relebactam inhibited 82.2% of all isolates of *P. aeruginosa* with an MDR phenotype (Table 5). Imipenem-relebactam inhibited all isolates of three of the seven most common MDR phenotypes but <90% of the other four most common MDR phenotypes. The most common MDR phenotypes with susceptibility to imipenem-relebactam of <90% were all nonsusceptible to imipenem, while phenotypes with 100% susceptibility to imipenem-relebactam were all susceptible to imipenem. All seven of the most common MDR phenotypes were nonsusceptible to aztreonam and piperacillin-tazobactam, and six of seven were nonsusceptible to ceftazidime.

DISCUSSION

The current study determined that 99.1% of isolates of non-*Proteeae Enterobacteriaceae* and 94.4% of isolates of *P. aeruginosa* submitted to the SMART global surveillance program in 2016 from 21 hospital laboratories in the United States were susceptible to imipenem-relebactam. Imipenem-relebactam demonstrated potent *in vitro* activity against cefepime-, ceftazidime-, and piperacillin-nonsusceptible as well as MDR subsets of non-*Proteeae Enterobacteriaceae* (>98% susceptible to imipenem-relebactam) and of *P. aeruginosa* (>82% susceptible to imipenem-relebactam). Relebactam restored imipenem susceptibility to 78.5% of imipenem-nonsusceptible non-*Proteeae Enterobacteriaceae* and to 78.0% of imipenem-nonsusceptible *P. aeruginosa* isolates. The results of the current study are comparable to a previous 2015 study of Gram-negative bacilli from the United States, which was restricted to patients with lower respiratory tract infections. The 2015 study reported similar but slightly lower rates of susceptibility to imipenem-relebactam of 97.2% (829/853) for isolates of non-*Proteeae Enterobacteria-*

TABLE 4 *In vitro* activity of imipenem-relebactam and comparative antimicrobial agents against *P. aeruginosa*

Phenotype[a] (*n*)	Antimicrobial agent	MIC determination (μg/ml)			MIC interpretation		
		MIC_{50}	MIC_{90}	MIC range	% susceptible	% intermediate	% resistant
All (896)	Imipenem-relebactam[a]	0.5	2	≤0.06 to >32	94.4	2.8	2.8
	Imipenem	1	16	≤0.5 to >32	74.7	5.1	20.2
	Amikacin	≤4	8	≤4 to >32	95.2	2.0	2.8
	Aztreonam	8	>16	≤1 to >16	63.1	12.8	24.1
	Cefepime	4	32	≤1 to >32	73.8	13.4	12.8
	Ceftazidime	4	>32	≤1 to >32	77.1	5.4	17.5
	Ciprofloxacin	≤0.25	>2	≤0.25 to >2	72.9	5.4	21.8
	Colistin	≤1	≤1	≤1 to >4	99.7		0.3
	Piperacillin-tazobactam	8	>64	≤2 to >64	71.2	12.4	16.4
Imipenem nonsusceptible (227)	Imipenem-relebactam[a]	2	8	0.25 to >32	78.0	11.0	11.0
	Imipenem	16	32	4 to >32	0	20.3	79.7
	Amikacin	≤4	32	≤4 to >32	88.1	5.3	6.6
	Aztreonam	>16	>16	≤1 to >16	33.0	15.9	51.1
	Cefepime	16	>32	≤1 to >32	40.5	26.4	33.0
	Ceftazidime	8	>32	≤1 to >32	50.7	10.6	38.8
	Ciprofloxacin	>2	>2	≤0.25 to >2	42.7	7.1	50.2
	Colistin	≤1	≤1	≤1 to >4	99.1		0.9
	Piperacillin-tazobactam	32	>64	≤2 to >64	41.0	22.0	37.0
Cefepime nonsusceptible (235)	Imipenem-relebactam[a]	1	4	≤0.06 to >32	82.1	8.5	9.4
	Imipenem	8	32	≤0.5 to >32	42.6	6.4	51.1
	Amikacin	≤4	32	≤4 to >32	86.4	6.0	7.7
	Aztreonam	>16	>16	≤1 to >16	14.5	14.5	71.1
	Cefepime	16	>32	16 to >32	0	51.1	48.9
	Ceftazidime	32	>32	2 to >32	24.7	11.1	64.3
	Ciprofloxacin	2	>2	≤0.25 to >2	47.7	8.5	43.8
	Colistin	≤1	≤1	≤1 to >4	99.6		0.4
	Piperacillin-tazobactam	>64	>64	≤2 to >64	16.6	23.4	60.0
Ceftazidime nonsusceptible (205)	Imipenem-relebactam[a]	1	4	≤0.06 to >32	82.4	8.3	9.3
	Imipenem	4	32	≤0.5 to >32	45.4	5.4	49.3
	Amikacin	≤4	32	≤4 to >32	87.3	4.9	7.8
	Aztreonam	>16	>16	≤1 to >16	9.8	14.2	76.1
	Cefepime	16	>32	2 to >32	13.7	38.1	48.3
	Ceftazidime	32	>32	16 to >32	0	23.4	76.6
	Ciprofloxacin	2	>2	≤0.25 to >2	48.8	7.3	43.9
	Colistin	≤1	≤1	≤1 to >4	99.5		0.5
	Piperacillin-tazobactam	>64	>64	≤2 to >64	6.3	25.4	68.3
Piperacillin-tazobactam nonsusceptible (258)	Imipenem-relebactam[a]	1	4	≤0.06 to >32	83.7	7.8	8.5
	Imipenem	4	32	≤0.5 to >32	48.1	5.4	46.5
	Amikacin	≤4	16	≤4 to >32	90.3	2.7	7.0
	Aztreonam	>16	>16	≤1 to >16	10.1	16.7	73.3
	Cefepime	16	>32	≤1 to >32	24.0	35.3	40.7
	Ceftazidime	32	>32	2 to >32	25.6	15.1	59.3
	Ciprofloxacin	1	>2	≤0.25 to >2	50.4	6.6	43.0
	Colistin	≤1	≤1	≤1 to >4	99.6		0.4
	Piperacillin-tazobactam	>64	>64	32 to >64	0	43.0	57.0
MDR (264)	Imipenem-relebactam[a]	1	4	≤0.06 to >32	82.2	8.7	9.1
	Imipenem	8	32	≤0.5 to >32	40.2	6.1	53.8
	Amikacin	≤4	32	≤4 to >32	87.5	5.3	7.2
	Aztreonam	>16	>16	≤1 to >16	8.7	20.5	70.8
	Cefepime	16	>32	2 to >32	19.7	39.0	41.3
	Ceftazidime	32	>32	2 to >32	24.6	16.3	59.1
	Ciprofloxacin	2	>2	≤0.25 to >2	42.4	8.3	49.2
	Colistin	≤1	≤1	≤1 to >4	98.9		1.1
	Piperacillin-tazobactam	>64	>64	≤2 to >64	12.1	32.6	55.3

[a]Breakpoints for imipenem-relebactam have not been defined. For the purpose of comparison, MICs were interpreted using CLSI imipenem MIC breakpoints for *P. aeruginosa* (susceptible, ≤2 μg/ml; intermediate, 4 μg/ml; resistant, ≥8 μg/ml) (24).

ceae and 93.1% (557/598) for isolates of *P. aeruginosa* (using CLSI MIC interpretative criteria for imipenem); relebactam restored imipenem susceptibility to 66.7% (48/72) and 78.5% (150/191) of isolates of imipenem-nonsusceptible non-*Proteeae Enterobacteriaceae* and *P. aeruginosa*, respectively (10).

A limited number of previous studies have also reported that relebactam restored the *in vitro* activity of imipenem against Gram-negative pathogens nonsusceptible to carbapenems by mechanisms other than metallo-β-lactamases (8, 9, 11, 12). The greatest impact of the addition of relebactam to imipenem has been reported for

TABLE 5 *In vitro* activity of imipenem-relebactam against the most common MDR phenotypes of *P. aeruginosa*[a]

Phenotype[a]	*n* (% of all MDR)	Imipenem-relebactam	
		MIC_{90} (μg/ml)	% susceptible
All *P. aeruginosa*	896	2	94.4
All MDR	264[b]	4	82.2
ATM, CAZ, CIP, FEP, IMI, P/T	57 (21.6)	8	64.9
ATM, CAZ, FEP, P/T	53 (20.1)	0.5	100
ATM, CAZ, FEP, IMI, P/T	24 (9.1)	4	87.5
AMK, ATM, CAZ, CIP, FEP, IMI, P/T	13 (4.9)	32	53.8
ATM, CIP, FEP, IMI, P/T	12 (4.5)	8	58.3
ATM, CAZ, P/T	12 (4.5)	0.5	100
ATM, CAZ, CIP, FEP, P/T	10 (3.8)	0.5	100

[a]Sentinel agents used for the definition of MDR included amikacin (AMK), aztreonam (ATM), cefepime (FEP), ceftazidime (CAZ), ciprofloxacin (CIP), colistin, imipenem (IMI), and piperacillin-tazobactam (P/T). The MDR phenotypes listed accounted for 68.7% (181/264) of all MDR phenotypes identified; colistin resistance was not observed among the most common MDR phenotypes identified. Agents shown in the table tested as nonsusceptible; the other sentinel agents tested as susceptible. Agents tested but not included in the list of sentinel agents may have tested as susceptible or nonsusceptible.

[b]MDR isolates accounted for 29.5% (264/896) of all isolates of *P. aeruginosa*.

isolates of *K. pneumoniae* that harbor KPC-type carbapenemases and ESBLs, as well as for isolates of carbapenem-resistant *P. aeruginosa* that lack OprD and express AmpC β-lactamase (9, 12). Lob et al. also showed that imipenem-relebactam inhibited all (n = 21) KPC-producing *K. pneumoniae* and *Enterobacter* spp. collected in the United States in 2015 as part of the SMART program (11). Relebactam increased imipenem susceptibility from 8 to 88% in 100 isolates of carbapenem-resistant *Enterobacteriaceae* (8). Relebactam restored imipenem activity against CRE isolates regardless of KPC or ESBL type (8). The addition of relebactam at a fixed concentration of 4 μg/ml to imipenem has also been shown to lower imipenem MICs for 14 isolates of KPC-producing *K. pneumoniae* that also expressed *ramA* or *acrB* or were without frameshift mutations in *ompK35* or demonstrated reduced or elevated expression of *ompK36* (12). Livermore et al. indicated that both imipenem and relebactam were poor substrates for efflux in *P. aeruginosa* and speculated that relebactam potentiates the activity of imipenem against *P. aeruginosa* by inhibiting the imipenem-hydrolyzing AmpC ubiquitous in that species (9).

The 2015 U.S. study showed that 63.8% (83/130) and 85.4% (111/130) of *S. marcescens* isolates were susceptible to imipenem and imipenem-relebactam, respectively (10), consistent with the results of the current study. Lob et al. determined that imipenem nonsusceptibility in 91.5% (43/47) of imipenem-nonsusceptible *S. marcescens* isolates was not attributable to any of the screened acquired β-lactamases (10). Although the chromosomally encoded Ambler class A *Serratia marcescens* enzyme (SME) carbapenemase was not included in the testing algorithm, the antimicrobial susceptibility patterns of these isolates were not consistent with the susceptibilities displayed by the majority of SME producers (14–16). In the current study, the low susceptibility of *S. marcescens* to imipenem was increased by >25% to 89.7% by the addition of relebactam (Table 1). The findings that 96.9% of isolates of *S. marcescens* were susceptible to ertapenem and that susceptibility to imipenem increased by >25% when combined with relebactam suggest that the observed nonsusceptibility to imipenem for *S. marcescens* may be due, in part, to an undetected imipenem-hydrolyzing β-lactamase but that additional mechanisms conferring imipenem nonsusceptibility must also be present in some isolates. The resistance mechanisms among *Serratia* spp. are currently under further investigation.

In the literature, there is a lack of antimicrobial susceptibility data related to the activity of imipenem-relebactam against isolates resistant to commonly tested β-lactams and against MDR isolates. The current study found susceptibility rates of ~98% and ~82%, respectively, for NPE and *P. aeruginosa* isolates that were nonsusceptible to cephalosporins, nonsusceptible to piperacillin-tazobactam, or MDR. Surveil-

lance reports indicate that the prevalence of MDR infections caused by *Enterobacteriaceae* and *P. aeruginosa* among hospitalized patients is increasing in the United States and elsewhere (3, 4). The identification of MDR bacterial pathogens is commonly an actionable result for hospital infection prevention and control programs. Definitions of MDR vary (17, 18), but MDR pathogens are widely appreciated to be associated with significant morbidity and mortality, longer hospitalizations, and increased costs compared with infections caused by susceptible organisms (19–22). Pan-drug-resistant isolates of *K. pneumoniae* producing carbapenemases and *P. aeruginosa* have been reported (23). Sader and coworkers recently published a study of 94 U.S. hospital laboratories from 2013 to 2016 and reported the prevalence of carbapenem-resistant isolates (resistant to imipenem, meropenem, or doripenem) of *Enterobacteriaceae* to be 1.4% (2), similar to but slightly lower than our finding (2.0 to 2.4% carbapenem-resistant non-*Proteeae Enterobacteriaceae*), and an MDR rate of 8.1% (2,953/36,380) (2), approximately one-half the rate of MDR identified in the current study (14.4%; 452/3,143). The difference in MDR rates may be attributable to different definitions of MDR used in the two studies as well as to isolates tested from different infection sources. The same investigators also reported 18.7% of *P. aeruginosa* as carbapenem nonsusceptible and 19.9% (1,562/7,868) of isolates as MDR (2), lower than the 25.3% and 29.5% (264/896) of isolates identified as carbapenem-nonsusceptible and MDR, respectively, in the current study. These differences may again reflect the different definitions of MDR and the different infection sources used in the two studies.

A review of the data for imipenem-nonsusceptible isolates of *Enterobacteriaceae* (Table 2) and *P. aeruginosa* (Table 4) in the current study identified an unexpected finding. Of the 130 isolates of imipenem-nonsusceptible *Enterobacteriaceae*, percent susceptibilities to ertapenem, cephalosporins, piperacillin-tazobactam, and aztreonam all exceeded 60%. This observation appears to be largely the result of the application of CLSI MIC interpretative breakpoints for imipenem (susceptible, 1 μg/ml) (24) against a collection of isolates of *Enterobacteriaceae* where the upper limit of the wild-type population for some species of *Enterobacteriaceae* in the collection (specifically *Serratia* spp.) is 1 doubling-dilution above the CLSI susceptible breakpoint for imipenem (i.e., 2 μg/ml); imipenem MICs of 2 μg/ml account for >10% of wild-type isolates of *Serratia* spp. (25). The unexpectedly low percent susceptibility of *S. marcescens* isolates to imipenem in the current study (64.0% susceptible; 130/203 isolates) was due primarily to 47 isolates (23.2% of isolates of *S. marcescens*) with imipenem MICs of 2 μg/ml (data not shown); similarly, there were 13 isolates of *S. marcescens* (6.4% of isolates) with imipenem-relebactam MICs of 2 μg/ml (data not shown). If the imipenem MIC data in the current study were interpreted using EUCAST MIC breakpoints, 87.2% (177/203) of isolates of *S. marcescens* would be imipenem susceptible (MIC, $\leq$2 μg/ml), only 3.4% (7/203) of isolates would be imipenem resistant, 96.1% (195/203) of isolates of *S. marcescens* would be imipenem-relebactam susceptible (MIC, $\leq$2 μg/ml), and none of the isolates would be imipenem-relebactam resistant (26). Similarly, the upper limit of the wild-type population of *P. aeruginosa* is 1 doubling-dilution above the CLSI susceptible breakpoint for imipenem (i.e., 4 μg/ml) (25). If the imipenem MIC data in the current study were interpreted using EUCAST MIC breakpoints for *P. aeruginosa*, 79.8% (715/896) of isolates of *P. aeruginosa* would be imipenem susceptible (MIC, $\leq$4 μg/ml), 14.0% (125/896) of isolates would be imipenem resistant (MIC, >8 μg/ml), 97.2% (871/896) of isolates of *P. aeruginosa* would be imipenem-relebactam susceptible (MIC, $\leq$4 μg/ml), and 1.3% (12/896) of isolates would be imipenem-relebactam resistant (MIC, >8 μg/ml) (data not shown) (26).

We conclude that non-*Proteeae Enterobacteriaceae* and *P. aeruginosa* submitted to the SMART global surveillance program in 2016 from 21 hospital laboratories in the United States demonstrated reduced *in vitro* susceptibility to advanced-generation cephalosporins (cefepime, ceftazidime, and ceftriaxone), piperacillin-tazobactam, and fluoroquinolones (ciprofloxacin) and that relebactam demonstrated a strong propensity to restore the *in vitro* activity of imipenem against carbapenem-nonsusceptible and MDR isolates of non-*Proteeae Enterobacteriaceae* and *P. aeruginosa*. Imipenem-

relebactam also demonstrated potent *in vitro* activity against cefepime-, ceftazidime-, and piperacillin-nonsusceptible isolates of non-*Proteeae Enterobacteriaceae* and *P. aeruginosa*. Further development of imipenem-relebactam, which is currently in phase 3 development for the treatment of imipenem-resistant Gram-negative infections, including hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (see https://clinicaltrials.gov/ct2/results?term=MK-7655&Search=Search), appears warranted. Imipenem-relebactam would provide an additional option for treating patients with infections caused by antimicrobial-resistant non-*Proteeae Enterobacteriaceae* and *P. aeruginosa* beyond therapy with polymyxins, aminoglycosides, and tigecycline, which are associated with increasing resistance and significant morbidity (polymyxins and aminoglycosides), as well as intrinsic resistance of *P. aeruginosa* (tigecycline).

MATERIALS AND METHODS

Bacterial isolates. In 2016, 21 hospital laboratories in 15 U.S. states (California, Colorado, Florida, Georgia, Illinois, Indiana, Iowa, Kentucky, Michigan, New York, North Carolina, Ohio, Pennsylvania, Washington, and Wisconsin) participated in the SMART global surveillance program. Each hospital laboratory was asked to collect and transport consecutive aerobic and/or facultative Gram-negative pathogens cultured from lower respiratory tract ($n = 100$), intra-abdominal ($n = 100$), or urinary tract ($n = 50$) specimens of unique patients to International Health Management Associates, Inc. (IHMA; Schaumburg, IL), which acted as the central testing laboratory for the SMART global surveillance program. In total, the 21 participating hospital laboratories submitted 4,678 isolates of Gram-negative bacilli from lower respiratory tract ($n = 1,954$), intra-abdominal ($n = 1,633$), urinary tract ($n = 1,050$), and unspecified ($n = 41$) specimens. Of the 4,678 isolates, 3,419 were *Enterobacteriaceae* (3,143 non-*Proteeae Enterobacteriaceae* and 276 *Proteeae*), 896 were *P. aeruginosa*, and 363 were other Gram-negative bacilli. All isolates received by IHMA were reidentified using matrix-assisted laser desorption ionization–time of flight (MALDI-TOF) mass spectrometry (Bruker Daltonics, Billerica, MA, USA).

Antimicrobial susceptibility testing. Antimicrobial susceptibility testing was performed at IHMA using the Clinical and Laboratory Standards Institute (CLSI) reference broth microdilution method (24, 27) with custom-made dehydrated Trek Diagnostic Systems panels (Thermo Scientific, Independence, OH). Species within the tribe *Proteeae* were excluded from testing because they are intrinsically resistant to imipenem, by a mechanism independent of carbapenemase production (24, 28), and imipenem-relebactam is not anticipated to possess clinically useful activity against *Proteeae*. Non-*Enterobacteriaceae* Gram-negative bacilli other than *P. aeruginosa* were also excluded from testing because of their intrinsic resistance to imipenem (*Stenotrophomonas maltophilia* [$n = 145$] and *Burkholderia* spp. [$n = 20$]) (24), limited susceptibility to imipenem (*Acinetobacter baumannii* [$n = 72$]) (12, 29), or low numbers of isolates (126 isolates from 32 species). The concentration ranges for each of the antimicrobial agents tested in this study were as indicated: imipenem-relebactam, 0.06 to 32 μg/ml; imipenem, 0.5 to 32 μg/ml; ertapenem, 0.06 to 4 μg/ml; amikacin, 4 to 32 μg/ml; aztreonam, 1 to 16 μg/ml; cefepime, 1 to 32 μg/ml; ceftazidime, 1 to 32 μg/ml; ceftriaxone, 1 to 32 μg/ml; ciprofloxacin, 0.25 to 2 μg/ml; colistin, 1 to 4 μg/ml; and piperacillin-tazobactam, 2 to 64 μg/ml. Relebactam was tested at a fixed concentration of 4 μg/ml in combination with 2-fold dilutions of imipenem. MICs were interpreted as susceptible, intermediate, or resistant using CLSI breakpoints (24). For comparative purposes, MICs for imipenem-relebactam were interpreted using CLSI imipenem MIC breakpoints for *Enterobacteriaceae* (susceptible, 1 μg/ml; intermediate, 2 μg/ml; resistant, 4 μg/ml) and *P. aeruginosa* (susceptible, 2 μg/ml; intermediate, 4 μg/ml; resistant, 8 μg/ml). European Committee on Antimicrobial Susceptibility Testing (EUCAST) MIC breakpoints for colistin tested against *Enterobacteriaceae* were used (susceptible, $\leq$2 μg/ml; resistant, $\geq$4 μg/ml) (26) because CLSI or FDA colistin breakpoints have not been defined for *Enterobacteriaceae*. *Escherichia coli* ATCC 25922, *E. coli* ATCC 35218, and *P. aeruginosa* ATCC 27853 were used as quality control strains for testing (24).

For both *Enterobacteriaceae* and *P. aeruginosa*, MDR was defined as nonsusceptibility (intermediate or resistant) to any three or more of the following eight sentinel agents: amikacin, aztreonam, cefepime, ceftazidime, ciprofloxacin, colistin, imipenem, and piperacillin-tazobactam.

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