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In vitro activity of ceftazidime/avibactam and comparators against Gram-negative bacterial isolates collected from Latin American centres between 2015 and 2017

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Objectives: We report the *in vitro* activity of ceftazidime/avibactam and comparators against 7729 Enterobacterales isolates and 2053 *Pseudomonas aeruginosa* isolates collected from six Latin American countries between 2015 and 2017.

Methods: A central reference laboratory performed antimicrobial susceptibility testing using broth microdilution panels according to CLSI guidelines. The presence of β-lactamases was confirmed using multiplex PCR assays.

Results: Susceptibility rates among Enterobacterales were highest for ceftazidime/avibactam (99.3%, MIC_{90} = 0.5 mg/L), meropenem (95.4%, MIC_{90} = 0.12 mg/L) and amikacin (93.5%, MIC_{90} = 8 mg/L). High susceptibility rates were observed for ceftazidime/avibactam in all six countries. The majority of carbapenemase-positive isolates among Enterobacterales (*N* = 366, 4.7%) were susceptible to ceftazidime/avibactam (86.9%), colistin (76.8%) and amikacin (60.9%); MBL-positive isolates (*N* = 49, 0.6%) were susceptible only to colistin (79.6%), with a minority susceptible to amikacin (49.0%), aztreonam and levofloxacin (both 30.6%). Highest rates of susceptibility among *P. aeruginosa* isolates were for colistin (99.2%) and ceftazidime/avibactam (86.6%), with rates of susceptibility to all other agents being <80.0%. MDR *P. aeruginosa* isolates (*N* = 712, 34.7%) had a high rate of susceptibility to colistin (98.9%); the rate of susceptibility to ceftazidime/avibactam was 61.4% and <50.0% to all other comparator agents. A total of 235 (11.4%) isolates of *P. aeruginosa* were carbapenemase positive and 148 (7.2%) were MBL positive; both subsets had high rates of susceptibility to colistin (98.3% and 100%, respectively).

Conclusions: Ceftazidime/avibactam susceptibility rates in Latin American countries are stable and high; ceftazidime/avibactam can be an appropriate treatment for patients with infections caused by Enterobacterales or *P. aeruginosa* and for whom treatment options may be limited.

Introduction

Infections caused by pathogens with resistance to β-lactam agents amongst Enterobacterales and *Pseudomonas aeruginosa* are associated with increased morbidity and mortality, and are of increasing concern globally and in Latin America.[1,2] Carbapenem-resistant Enterobacterales have been categorized in the critical and highest priority group of pathogens by the WHO and are listed as an urgent threat by the CDC.[3,4] *P. aeruginosa* is a major cause of healthcare-associated infections that include urinary tract, surgical site, bloodstream, abdominal and skin and soft tissue infections and nosocomial pneumonia.[4–7]

Acquisition of plasmid-mediated carbapenemase genes is a frequent mechanism of resistance among Enterobacterales and is often attributable to expression of serine proteases, such as KPC and OXA-48-like enzymes, or MBLs, which include NDM-, IMP-, SPM- and VIM-like enzymes. Other important mechanisms include the production of ESBLs or Ambler class C β-lactamases, expression of efflux pumps, or loss of function of outer-membrane pore-forming proteins.[8,9] Resistance to penicillins and cephalosporins amongst *P. aeruginosa* is frequently inferred to be caused by stable derepression of the intrinsic, chromosomally encoded AmpC cephalosporinase, whilst resistance to carbapenems can be mediated by additional up-regulation of efflux transporters or decrease or loss of the OprD porin.[10–12] Transmission of β-lactamases and carbapenemases is a further cause of resistance, although less common than mutational resistance.[10,12,13]

Avibactam is a first-in-class diazabicyclooctanone non-β-lactam β-lactamase inhibitor and the combination of ceftazidime

with avibactam possesses *in vitro* activity against Enterobacterales and *P. aeruginosa* carrying β-lactamases of Ambler class A (ESBLs and KPCs), class C (AmpC cephalosporinases) and some of class D (e.g. OXA-48-type, many carriers of which co-carry ESBLs).[14–21] Ceftazidime/avibactam does not possess *in vitro* activity against MBL producers, or Enterobacterales or *P. aeruginosa* that encode sequence alterations in target proteins (AmpC, KPC and PBP3).[22,23]

The combination of ceftazidime with avibactam has been approved by the FDA for the treatment of adult patients with complicated intra-abdominal infections, complicated urinary tract infections (including pyelonephritis) and hospital-acquired pneumonia (including ventilator-associated pneumonia).[24] The *in vitro* activity of ceftazidime/avibactam and a panel of comparator agents against isolates of Enterobacterales and *P. aeruginosa* has been tracked via the International Network for Optimal Resistance Monitoring (INFORM) global surveillance programme, which was established in 2012 and was succeeded by the Antimicrobial Testing Leadership and Surveillance (ATLAS) study in 2018. The data presented here are an update to surveillance data from isolates collected from 2012 to 2015 in Latin America and reported by Karlowsky *et al.*[25]

Materials and methods

A total of 9782 non-duplicate clinical isolates of Enterobacterales and *P. aeruginosa* were collected from 28 centres in six Latin American countries (Argentina, Brazil, Chile, Colombia, Mexico and Venezuela) between 2015 and 2017 as part of the INFORM surveillance study. A predefined number of selected bacterial species were collected by each site from patients with bloodstream infections, intra-abdominal infections, lower respiratory tract infections, skin and soft tissue infections and urinary tract infections. Isolates were accepted into the study regardless of antimicrobial susceptibility. Following shipment to the central reference laboratory [International Health Management Associates, Inc. (IHMA), Schaumburg, IL, USA], identification of samples was performed using MALDI-TOF (Bruker Biotyper MALDI-TOF, Bruker Daltonics, Billerica, MA, USA).

Susceptibility testing was performed with frozen broth microdilution panels manufactured by IHMA, for isolates collected in 2015 and 2016, and by TREK (TREK Diagnostic Systems, Thermo Fisher Scientific, Oakwood Village, OH, USA), for isolates collected in 2017, according to CLSI guidelines.[26] Avibactam was tested at a fixed concentration of 4 mg/L in combination with doubling dilutions of ceftazidime (range from ≤0.015 mg/L to 128 mg/L) against all isolates. MICs were interpreted using EUCAST 2019 breakpoints, version 9.0.[27] Definition of an MDR phenotype was resistance, according to EUCAST 2019 breakpoints, to at least one agent in three or more drug classes [aminoglycosides (amikacin); β-lactam/β-lactamase inhibitor combinations (piperacillin/tazobactam); monobactams (aztreonam); cephalosporins (cefepime or ceftazidime); carbapenems (imipenem or meropenem); fluoroquinolones (levofloxacin); and polymyxins (colistin)] following published recommendations.[28] Isolates of *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca* and *Proteus mirabilis* with MICs of ≥2 mg/L to ceftazidime or aztreonam determined by broth microdilution, collected in 2015, were tested for ESBL activity by determining susceptibility to cefotaxime, cefotaxime/clavulanate, ceftazidime and ceftazidime/clavulanate as recommended by CLSI guidelines.[29] Isolates that tested as phenotypically positive for ESBL activity, or that were negative but with a ceftazidime MIC ≥16 mg/L, were screened for the presence of genes encoding SHV, TEM, CTX-M, VEB, PER, GES, plasmid-encoded AmpC, KPC, OXA-48-like, NDM, IMP, VIM, SPM and GIM using published multiplex PCR assays.[30] Isolates of *E. coli*, *K. pneumoniae*, *K. oxytoca* and *P. mirabilis* with meropenem, ceftazidime or aztreonam MICs ≥2 mg/L, collected during 2016 and 2017, were also screened for β-lactamase genes using multiplex PCR. Additionally, all other Enterobacterales isolates with meropenem MIC ≥2 mg/L, collected between 2015 and 2017, were also screened for β-lactamases using published multiplex PCR assays.[30] All *P. aeruginosa* isolates with meropenem MIC ≥4 mg/L, collected between 2015 and 2017, were screened for β-lactamases to determine the presence of genes encoding IMP, VIM, OXA-24, NDM, KPC, SPM, GIM, TEM, SHV, VEB, PER and GES.[31] All detected β-lactamase genes, excluding original spectrum β-lactamases (TEM-type β-lactamases that do not possess substitutions at amino acid positions 104, 164 or 238 and SHV-type β-lactamases that do not possess substitutions at amino acid positions 146, 238 or 240) were amplified using flanking primers and sequenced. Sequences were compared against databases maintained by the National Center for Biotechnology Information (www.ncbi.nlm.nih.gov) and the Lahey Clinic (www.lahey.org/studies).

Results

A total of 9782 isolates were collected from six Latin American countries between 2015 and 2017 (Table S1, available as Supplementary data at *JAC* Online). The highest proportion of isolates was collected from centres in Mexico (24.3%) and the lowest from Colombia (12.4%). The majority of isolates were collected from patients located in non-ICUs (71.4%) and just over half of isolates were collected from male patients (50.8%). Most isolates were collected from adult patients (89.9%) and the most common sources were genitourinary (28.1%) and integumentary (21.4%).

Susceptibility to ceftazidime/avibactam and comparator agents

Enterobacterales

Susceptibility rates among all Enterobacterales isolates pooled ($N = 7729$, Table 1) were highest to ceftazidime/avibactam (99.3%, $MIC_{90} = 0.5$ mg/L), showing restoration of *in vitro* activity when compared with ceftazidime alone (susceptibility 66.3%, $MIC_{90} = 64$ mg/L). Susceptibility rates among the Enterobacterales were also high for meropenem (95.4%, $MIC_{90} = 0.12$ mg/L) and amikacin (93.5%, $MIC_{90} = 8$ mg/L). The rate of susceptibility to colistin among *Enterobacter cloacae*, *E. coli*, *Klebsiella aerogenes*, *K. oxytoca* and *K. pneumoniae* isolates was ≥94.4%.

Ceftazidime/avibactam showed consistent *in vitro* activity against all species of Enterobacterales isolates (Table 1), with susceptibility rates ranging from 98.2% (*E. cloacae*) to 100% (*K. aerogenes*, *P. mirabilis* and *Serratia marcescens*). Rates of susceptibility to most agents were reduced among the *K. pneumoniae* isolates when compared with rates for all Enterobacterales isolates pooled, with reductions observed for piperacillin/tazobactam (−19.4%), cefepime (−17.2%), ceftazidime (−16.1%) and aztreonam (−14.8%). The ceftazidime/avibactam susceptibility rate among *K. pneumoniae* isolates (98.8%) was similar to that of all Enterobacterales (99.3%); colistin (95.1%) and amikacin (89.4%) susceptibility rates were also high.

Resistance phenotypes among Enterobacterales

A total of 1860 (24.1%) Enterobacterales isolates were identified as ESBL positive (Table 2) and susceptibility to ceftazidime alone was 3.4% compared with 98.2% to ceftazidime/avibactam, a rate that was similar to the value observed among the overall set of Enterobacterales isolates (99.3%). The highest number of

Table 1. MIC_{50}, MIC_{90} and MIC range (mg/L) of, and antimicrobial susceptibility and resistance to, ceftazidime/avibactam and comparator agents for Enterobacterales and *P. aeruginosa* isolates collected in Latin America as part of the INFORM study[a], 2015–17

Organism/antimicrobial	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	S (%)	R (%)
All Enterobacterales (*N* = 7729)[b,c]					
ceftazidime/avibactam	0.12	0.5	≤0.015 to ≥256	99.3	0.7
ceftazidime	0.25	64	≤0.015 to ≥256	66.3	29.2
cefepime	≤0.12	≥32	≤0.12 to ≥32	69.2	26.9
amoxicillin/clavulanate	16	≥64	≤0.12 to ≥64	45.7	54.3
piperacillin/tazobactam	4	128	≤0.25 to ≥256	77.8	17.8
aztreonam	0.12	128	≤0.015 to ≥256	66.5	30.8
meropenem	0.03	0.12	≤0.004 to ≥16	95.4	3.2
amikacin	2	8	≤0.25 to ≥64	93.5	3.5
levofloxacin	0.25	≥16	≤0.004 to ≥16	61.1	33.4
tigecycline	0.5	1	≤0.015 to ≥16	—	—
E. cloacae (*N* = 504)					
ceftazidime/avibactam	0.25	1	≤0.015 to ≥256	98.2	1.8
ceftazidime	0.5	128	0.06 to ≥256	58.9	37.3
cefepime	≤0.12	≥32	≤0.12 to ≥32	66.9	23.4
amoxicillin/clavulanate	≥64	≥64	1 to ≥64	2.6	97.4
piperacillin/tazobactam	4	≥256	≤0.25 to ≥256	69.0	26.6
aztreonam	0.25	128	≤0.015 to ≥256	61.9	36.3
imipenem	0.5	1	≤0.03 to ≥16	94.4	4.2
meropenem	0.06	0.25	≤0.004 to ≥16	95.4	2.8
colistin	0.25	1	0.12 to ≥16	94.4	5.6
amikacin	1	8	0.5 to ≥64	93.8	3.8
levofloxacin	0.06	8	0.008 to ≥16	74.2	17.7
tigecycline	0.5	1	0.12 to 8	—	—
E. coli (*N* = 2625)					
ceftazidime/avibactam	0.12	0.25	≤0.015 to ≥256	99.9	0.1
ceftazidime	0.25	32	≤0.015 to ≥256	66.1	28.2
cefepime	≤0.12	≥32	≤0.12 to ≥32	66.0	30.4
amoxicillin/clavulanate	8	32	≤0.12 to ≥64	55.5	44.5
piperacillin/tazobactam	2	16	≤0.25 to ≥256	85.6	9.5
aztreonam	0.12	64	≤0.015 to ≥256	64.0	32.6
imipenem	0.12	0.25	≤0.03 to ≥16	99.4	0.3
meropenem	0.03	0.06	0.008 to ≥16	99.4	0.1
colistin	0.25	0.5	≤0.06 to ≥16	99.2	0.8
amikacin	2	8	≤0.25 to ≥64	94.4	1.7
levofloxacin	1	≥16	≤0.004 to ≥16	48.3	49.1
tigecycline	0.25	0.5	≤0.015 to 4	97.8	2.2
K. aerogenes (*N* = 276)					
ceftazidime/avibactam	0.12	0.5	≤0.015 to 2	100	0.0
ceftazidime	0.25	64	≤0.015 to ≥256	70.3	26.8
cefepime	≤0.12	1	≤0.12 to ≥32	92.4	6.5
amoxicillin/clavulanate	≥64	≥64	2 to ≥64	2.2	97.8
piperacillin/tazobactam	4	64	≤0.25 to ≥256	73.6	23.6
aztreonam	0.12	32	≤0.015 to ≥256	71.7	25.7
imipenem	1	2	0.12 to ≥16	95.7	2.9
meropenem	0.06	0.12	0.015 to ≥16	97.1	2.2
colistin	0.25	0.5	0.12 to ≥16	98.6	1.4
amikacin	1	2	≤0.25 to ≥64	99.3	0.7
levofloxacin	0.06	0.5	≤0.03 to ≥16	90.9	4.7
tigecycline	0.5	0.5	0.06 to 4	—	—
K. oxytoca (*N* = 341)					
ceftazidime/avibactam	0.12	0.25	≤0.015 to ≥256	98.5	1.5

Continued

Table 1. *Continued*

Organism/antimicrobial	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	S (%)	R (%)
ceftazidime	0.12	4	0.03 to ≥256	88.6	9.1
cefepime	≤0.12	2	≤0.12 to ≥32	88.6	5.9
amoxicillin/clavulanate	4	32	≤0.12 to ≥64	81.5	18.5
piperacillin/tazobactam	2	64	≤0.25 to ≥256	87.4	12.3
aztreonam	0.12	32	≤0.015 to ≥256	83.0	14.7
imipenem	0.25	0.5	0.06 to ≥16	97.1	1.5
meropenem	0.03	0.06	0.015 to ≥16	97.9	1.2
colistin	0.25	1	0.12 to ≥16	99.1	0.9
amikacin	1	4	0.5 to ≥64	97.4	1.5
levofloxacin	0.06	1	0.008 to ≥16	86.5	9.1
tigecycline	0.25	0.5	0.12 to 2	—	—
K. pneumoniae (*N* = 2203)					
ceftazidime/avibactam	0.12	1	≤0.015 to ≥256	98.8	1.2
ceftazidime	1	128	0.03 to ≥256	50.2	45.8
cefepime	0.5	≥32	≤0.12 to ≥32	52.0	43.8
amoxicillin/clavulanate	16	≥64	≤0.12 to ≥64	47.3	52.7
aztreonam	0.5	≥256	≤0.015 to ≥256	51.7	46.8
imipenem	0.25	8	0.06 to ≥16	87.3	11.0
meropenem	0.06	8	0.015 to ≥16	87.5	9.5
colistin	0.25	1	0.12 to ≥16	95.1	4.9
amikacin	2	16	≤0.25 to ≥64	89.4	7.1
levofloxacin	0.5	≥16	≤0.004 to ≥16	54.6	36.5
piperacillin/tazobactam	8	≥256	≤0.25 to ≥256	58.4	35.3
tigecycline	0.5	1	0.06 to ≥16	—	—
P. mirabilis (*N* = 430)					
ceftazidime/avibactam	0.03	0.06	≤0.015 to 0.5	100	0.0
ceftazidime	0.06	0.5	≤0.015 to 32	93.7	2.3
cefepime	≤0.12	8	≤0.12 to ≥32	86.3	11.4
amoxicillin/clavulanate	2	16	≤0.5 to ≥64	82.8	17.2
piperacillin/tazobactam	≤0.25	1	≤0.25 to 64	98.8	0.5
aztreonam	≤0.015	0.5	≤0.015 to ≥256	93.7	3.5
imipenem	2	4	0.06 to 8	1.2	2.1
meropenem	0.06	0.12	0.015 to 1	100	0.0
colistin	≥16	≥16	0.25 to ≥16	0.5	99.5
amikacin	4	8	0.5 to ≥64	93.7	2.8
levofloxacin	0.12	≥16	≤0.03 to ≥16	69.1	27.7
tigecycline	2	4	0.12 to 8	—	—
S. marcescens (*N* = 247)					
ceftazidime/avibactam	0.12	0.5	0.03 to 4	100	0.0
ceftazidime	0.25	4	0.06 to ≥256	86.6	9.3
cefepime	≤0.12	8	≤0.12 to ≥32	87.0	11.3
amoxicillin/clavulanate	≥64	≥64	2 to ≥64	3.6	96.4
piperacillin/tazobactam	2	8	≤0.25 to ≥256	91.1	7.7
aztreonam	0.12	64	≤0.015 to ≥256	85.4	13.4
imipenem	0.5	2	0.25 to ≥16	94.7	4.9
meropenem	0.06	0.12	0.03 to ≥16	96.4	3.2
colistin	≥16	≥16	0.25 to ≥16	1.6	98.4
amikacin	2	8	0.5 to ≥64	91.9	5.7
levofloxacin	0.25	1	0.03 to ≥16	85.8	8.9
tigecycline	1	2	0.25 to 4	—	—
P. aeruginosa (*N* = 2053)					
ceftazidime/avibactam	2	32	0.03 to ≥256	86.6	13.4
ceftazidime	4	128	0.06 to ≥256	69.2	30.8

Continued

Table 1. *Continued*

Organism/antimicrobial	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	S (%)	R (%)
cefepime	4	≥32	≤0.12 to ≥32	72.5	27.5
amoxicillin/clavulanate	≥64	≥64	1 to ≥64	—	—
piperacillin/tazobactam	8	≥256	≤0.25 to ≥256	66.1	33.9
aztreonam	8	64	0.06 to ≥256	72.8	27.2
imipenem	2	≥16	0.12 to ≥16	65.8	34.2
meropenem	1	≥16	≤0.004 to ≥16	65.0	22.8
colistin	1	2	≤0.06 to ≥16	99.2	0.8
amikacin	4	≥64	≤0.25 to ≥64	77.7	18.0
levofloxacin	1	≥16	0.015 to ≥16	58.9	41.1
tigecycline	8	≥16	≤0.015 to ≥16	—	—

A dash indicates that breakpoints were unavailable for calculation of percentage susceptibility or resistance. R, resistant; S, susceptible.
[a]INFORM was succeeded by ATLAS in 2018.
[b]Includes Enterobacterales spp. in addition to those listed.
[c]Imipenem data not presented against all Enterobacterales due to intrinsic resistance among *Proteus* spp.; colistin data not presented due to intrinsic resistance among *Morganella* spp., *Proteus* spp., *Providencia* spp. and *Serratia* spp.

ESBL-positive isolates resistant to ceftazidime/avibactam were among *K. pneumoniae* (20/909, 2.2%) and *E. cloacae* (6/10, 60.0%). High overall rates of susceptibility were observed to colistin (94.5%), imipenem (88.7%) and tigecycline (97.7%) among *E. coli*, the only species with breakpoints for tigecycline (data not shown). Among the ESBL-positive isolates, there were reductions in the rates of susceptibility to meropenem (−5.6%) and amikacin (−10.4%), with susceptibility rates to all other agents reduced by 27% or more compared with corresponding values for the overall set of Enterobacterales (Table 2).

Among the 366 carbapenemase-positive Enterobacterales isolates (Table 2), susceptibility rates were highest for ceftazidime/avibactam (86.9%, a reduction of 13.0% compared with carbapenemase-negative isolates), colistin (76.8%, a reduction of 19.0%) and amikacin (60.9%, a reduction of 25.9%). Species with the highest proportion of carbapenemase-positive isolates that were resistant to ceftazidime/avibactam ($N = 48$) were *K. pneumoniae* (27/286, 9.4%) and *E. cloacae* (9/22, 40.9%). The *in vitro* activity of tigecycline against carbapenemase-positive isolates ($MIC_{50} = 0.5$ mg/L, $MIC_{90} = 2$ mg/L) was consistent with that against carbapenemase-negative isolates ($MIC_{50} = 0.25$ mg/L, $MIC_{90} = 1$ mg/L). A total of 49 isolates among the Enterobacterales collection were MBL positive and only colistin was active against most of these isolates (79.6% susceptibility). Limited susceptibility of MBL-positive isolates to aztreonam (49.0%), levofloxacin and aztreonam (both 30.6%) was observed. The tigecycline MIC_{90} value was reduced by two dilutions to 4 mg/L compared with 1 mg/L among the 2157 MBL-negative isolates. Among the MBL-negative subset, 99.9% of isolates were susceptible to ceftazidime/avibactam and 93.0% to colistin, whilst high susceptibility rates were also observed for meropenem (85.7%), imipenem (83.7%) and amikacin (83.3%).

P. aeruginosa

The highest rates of susceptibility among the 2053 *P. aeruginosa* isolates (Table 1) were for colistin (99.2%) and ceftazidime/avibactam (86.6%). Moderate susceptibility rates were also observed for amikacin (77.7%), aztreonam (72.8%) and cefepime (72.5%).

P. aeruginosa resistance phenotypes

A total of 712 (34.7%) *P. aeruginosa* isolates were defined as MDR (Table 3) and susceptibility rates were lower for all agents when compared with the overall *P. aeruginosa* collection, with the highest susceptibility rate being for colistin (98.9%). The only other agent with a susceptibility rate of >50% was ceftazidime/avibactam (61.4%). Low rates of susceptibility (≤41.7%) were observed among carbapenemase-positive isolates ($N = 235$) for all agents apart from colistin (98.3% susceptibility). A high percentage of isolates that were screened for β-lactamases and defined as carbapenemase negative ($N = 483$) were susceptible to colistin (99.6%) and the majority of isolates were also susceptible to ceftazidime/avibactam (83.4%) and amikacin (60.9%); susceptibility to all other comparator agents was <50%. The 148 MBL-positive isolates were all susceptible to colistin and 64.2% were susceptible to aztreonam; rates of susceptibility to all other agents were <10%. Among isolates that were screened for β-lactamases and that did not carry an MBL gene (MBL negative, $N = 570$), the highest susceptibility rates were for colistin (98.9%), ceftazidime/avibactam (78.2%) and amikacin (57.5%), with rates of susceptibility to all other comparator agents being <50%.

Susceptibility by country

Enterobacterales

There was little variation in susceptibility rates for all agents among Enterobacterales across countries (Table 4 and Table S2). Among ESBL-positive isolates, susceptibility rates to ceftazidime/avibactam were high, ranging from 97.3% in Mexico to 99.5% in Argentina, whilst the colistin susceptibility rate was highest in Mexico (98.5%) and lowest in Brazil (88.9%). Among carbapenemase-positive isolates, *in vitro* activity of ceftazidime/avibactam was consistently found among isolates collected from Argentina (97.6%) and Brazil (97.7%) (Table S3). There was a

Table 2. MIC_{50}, MIC_{90} and MIC range (mg/L) of, and antimicrobial susceptibility and resistance to, ceftazidime/avibactam and comparator agents for Enterobacterales resistance phenotypes collected in Latin America as part of the INFORM study[a], 2015–17

Phenotype/antimicrobial	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	S (%)	R (%)
ESBL positive (*N* = 1860)					
ceftazidime/avibactam	0.25	1	≤0.015 to ≥256	98.2	1.8
ceftazidime	32	≥256	0.25 to ≥256	3.4	86.3
cefepime	≥32	≥32	≤0.12 to ≥32	2.6	91.1
amoxicillin/clavulanate	16	≥64	≤0.12 to ≥64	17.0	83.0
piperacillin/tazobactam	16	≥256	≤0.25 to ≥256	49.2	39.5
aztreonam	64	≥256	0.12 to ≥256	0.5	94.2
imipenem	0.25	4	≤0.03 to ≥16	88.7	8.4
meropenem	0.06	4	0.008 to ≥16	89.8	7.3
colistin	0.25	1	≤0.06 to ≥16	94.5	5.5
amikacin	4	16	≤0.25 to ≥64	83.1	9.0
levofloxacin	≥16	≥16	0.03 to ≥16	15.4	76.1
tigecycline	0.5	1	≤0.015 to ≥16	—	—
CBPM positive (*N* = 366)					
ceftazidime/avibactam	1	64	≤0.015 to ≥256	86.9	13.1
ceftazidime	64	≥256	0.5 to ≥256	1.6	92.1
cefepime	≥32	≥32	≤0.12 to ≥32	4.1	86.3
amoxicillin/clavulanate	≥64	≥64	16 to ≥64	0.0	100
piperacillin/tazobactam	≥256	≥256	8 to ≥256	0.3	99.2
aztreonam	≥256	≥256	≤0.015 to ≥256	4.6	93.4
imipenem	≥16	≥16	0.25 to ≥16	5.2	80.9
meropenem	≥16	≥16	0.12 to ≥16	12.0	66.7
colistin	0.5	≥16	0.12 to ≥16	76.8	23.2
amikacin	4	≥64	≤0.25 to ≥64	60.9	26.5
levofloxacin	≥16	≥16	0.03 to ≥16	20.2	73.8
tigecycline	0.5	2	0.12 to 8	—	—
CBPM negative (*N* = 1840)					
ceftazidime/avibactam	0.25	1	≤0.015 to ≥256	99.9	0.1
ceftazidime	32	128	0.12 to ≥256	5.2	81.8
cefepime	≥32	≥32	≤0.12 to ≥32	8.0	83.4
amoxicillin/clavulanate	16	≥64	≤0.12 to ≥64	18.3	81.7
piperacillin/tazobactam	8	≥256	≤0.25 to ≥256	53.7	34.7
aztreonam	32	≥256	≤0.015 to ≥256	2.9	89.8
imipenem	0.25	0.5	≤0.03 to ≥16	97.2	0.4
meropenem	0.06	0.12	0.008 to ≥16	98.3	0.4
colistin	0.25	1	≤0.06 to ≥16	95.8	4.2
amikacin	4	16	≤0.25 to ≥64	86.8	6.5
levofloxacin	≥16	≥16	0.03 to ≥16	19.2	72
tigecycline	0.25	1	≤0.015 to ≥16	—	—
MBL positive (*N* = 49)					
ceftazidime/avibactam	≥256	≥256	8 to ≥256	2.0	98.0
ceftazidime	≥256	≥256	16 to ≥256	0.0	100
cefepime	≥32	≥32	1 to ≥32	2.0	95.9
amoxicillin/clavulanate	≥64	≥64	32 to ≥64	0.0	100
piperacillin/tazobactam	≥256	≥256	8 to ≥256	2.0	98.0
aztreonam	64	≥256	≤0.015 to ≥256	30.6	63.3
imipenem	≥16	≥16	2 to ≥16	4.1	77.6
meropenem	≥16	≥16	0.25 to ≥16	10.2	63.3
colistin	0.5	≥16	0.12 to ≥16	79.6	20.4
amikacin	16	≥64	1 to ≥64	49.0	38.8
levofloxacin	8	≥16	0.03 to ≥16	30.6	63.3
tigecycline	1	4	0.12 to 4	—	—

Continued

Table 2. *Continued*

Phenotype/antimicrobial	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	S (%)	R (%)
MBL negative (*N* = 2157)					
ceftazidime/avibactam	0.25	1	≤0.015 to ≥256	99.9	0.1
ceftazidime	32	≥256	0.12 to ≥256	4.7	83.1
cefepime	≥32	≥32	≤0.12 to ≥32	7.5	83.6
amoxicillin/clavulanate	16	≥64	≤0.12 to ≥64	15.6	84.4
piperacillin/tazobactam	16	≥256	≤0.25 to ≥256	45.8	44.2
aztreonam	64	≥256	≤0.015 to ≥256	2.5	91.0
imipenem	0.25	8	≤0.03 to ≥16	83.7	12.3
meropenem	0.06	≥16	0.008 to ≥16	85.7	10.2
colistin	0.25	1	≤0.06 to ≥16	93.0	7.0
amikacin	4	16	≤0.25 to ≥64	83.3	9.1
levofloxacin	≥16	≥16	0.03 to ≥16	19.1	72.5
tigecycline	0.5	1	≤0.015 to ≥16	—	—

A dash indicates that breakpoints were unavailable for calculation of percentage susceptibility or resistance. CBPM, carbapenemase; R, resistant; S, susceptible.
[a]INFORM was succeeded by ATLAS in 2018.

reduction of 79.8% in the rate of susceptibility to ceftazidime/avibactam in Mexico (Table 4) from 98.6% among all Enterobacterales isolates (*N* = 1855) to 18.8% among carbapenemase-positive isolates (*N* = 32). Smaller reductions in susceptibility rate were observed in Venezuela (from 99.2% to 70.8%) and Colombia (from 99.2% to 91.8%). All of the carbapenemase-positive isolates from Mexico that were resistant to ceftazidime/avibactam were MBL positive (*N* = 26/32, 81.2%), with most of these enzymes being carried by *K. pneumoniae* (*N* = 17) and *E. cloacae* (*N* = 5). Mexico had the highest number of MBL-positive isolates from the region (26/49, 53.1%); Colombia and Venezuela were the next highest, with 8/49 (16.3%) MBL-positive isolates from each country. The *in vitro* activity of colistin among carbapenemase-positive isolates collected in Colombia, Mexico and Venezuela was similar to or higher than that for all Enterobacterales isolates and rates were reduced among carbapenemase-positive isolates collected in Argentina (from 80.8% to 58.5%) and Brazil (from 82.1% to 77.5%). Reductions in amikacin susceptibility rate among carbapenemase-positive isolates compared with all Enterobacterales collected in individual countries were observed across the region, with the largest reductions observed in Venezuela (−51.3%), Mexico (−50.8%) and Argentina (−43.6%).

P. aeruginosa

Compared with the whole of Latin America, rates of susceptibility among *P. aeruginosa* collected in Colombia, Mexico and Venezuela were similar for ceftazidime/avibactam and comparator agents (Table S4) and the colistin susceptibility rate was consistently high (≥98.1%) among isolates from all countries (Table 5). Isolates collected from Argentina showed the highest rates of colistin (99.7%) and ceftazidime/avibactam (94.5%) susceptibility; this was also observed among isolates collected in Brazil (susceptibility rates of 99.4% and 93.9%, respectively). With the exception of colistin (99.7%), rates of susceptibility to all agents were lower among isolates from Chile, with 75.0% of isolates susceptible to ceftazidime/avibactam and 68.4% susceptible to amikacin. The proportion of MBL-positive isolates among *P. aeruginosa* isolates was highest in Chile (53/304, 17.4%), then Venezuela (49/309, 15.9%), was similar in Mexico and Colombia (25/524, 4.8% and 11/225, 4.9%, respectively) and was low (<2.0%) in Argentina and Brazil.

Rates of susceptibility to colistin among isolates of MDR *P. aeruginosa* (Table S5) were consistently high across all countries (≥96.4%), whilst the rate of susceptibility to ceftazidime/avibactam was reduced in all countries compared with overall *P. aeruginosa* rates. The largest reduction (−40.3%) was observed among isolates from Venezuela, which had the lowest ceftazidime/avibactam susceptibility rate of 42.9%, and the second largest reduction (−30.7%) was observed in Mexico, which had a susceptibility rate of 54.4%. Collections of MDR isolates from Venezuela and Mexico also showed rates of susceptibility to amikacin (19.8% and 39.1%, respectively) that were lower than values for the other Latin American countries.

Discussion

The ceftazidime/avibactam susceptibility rate among Enterobacterales isolates was consistently high across all Latin American countries included in this analysis of isolates from 2015 to 2017. Susceptibility rates of the overall set of Enterobacterales isolates were also high for meropenem and amikacin, and *in vitro* activity of tigecycline was demonstrated by low MIC_{90} values. The rate of susceptibility to colistin was high (≥94.4%) among Enterobacterales isolates, excluding *P. mirabilis* and *S. marcescens*, which possess intrinsic resistance to this agent. A previous analysis of isolates collected from Latin America between 2012 and 2015, as part of the INFORM study, reported 99.7% susceptibility to ceftazidime/avibactam[25] and a single-centre study at a teaching hospital in Brazil reported 99.4% susceptibility to ceftazidime/avibactam among 312 Enterobacterales isolates collected between 2014 and 2015, with 96.7% susceptibility to

Table 3. MIC_{50}, MIC_{90} and MIC range (mg/L) of, and antimicrobial susceptibility and resistance to, ceftazidime/avibactam and comparator agents for *P. aeruginosa* resistance phenotypes collected in Latin America as part of the INFORM study[a], 2015–17

Phenotype/antimicrobial	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	S (%)	R (%)
MDR (*N* = 712)					
ceftazidime/avibactam	8	64	0.12 to ≥256	61.4	38.6
ceftazidime	64	≥256	0.06 to ≥256	19.0	81.0
cefepime	16	≥32	0.5 to ≥32	23.2	76.8
piperacillin/tazobactam	128	≥256	4 to ≥256	10.3	89.7
aztreonam	32	≥256	0.12 to ≥256	27.0	73.0
imipenem	≥16	≥16	0.12 to ≥16	23.0	77.0
meropenem	≥16	≥16	0.03 to ≥16	19.0	63.3
colistin	1	2	≤0.06 to 8	98.9	1.1
amikacin	16	≥64	0.5 to ≥64	45.5	46.9
levofloxacin	≥16	≥16	0.03 to ≥16	16.4	83.6
tigecycline	≥16	≥16	0.25 to ≥16	—	—
CBPM positive (*N* = 235)					
ceftazidime/avibactam	32	≥256	1 to ≥256	21.3	78.7
ceftazidime	64	≥256	4 to ≥256	2.6	97.4
cefepime	≥32	≥32	2 to ≥32	5.1	94.9
piperacillin/tazobactam	128	≥256	8 to ≥256	3.4	96.6
aztreonam	32	≥256	2 to ≥256	41.7	58.3
imipenem	≥16	≥16	2 to ≥16	0.4	99.6
meropenem	≥16	≥16	4 to ≥16	0.0	95.3
colistin	1	2	0.12 to 4	98.3	1.7
amikacin	≥64	≥64	1 to ≥64	20.4	74.5
levofloxacin	≥16	≥16	0.25 to ≥16	4.3	95.7
tigecycline	≥16	≥16	1 to ≥16	—	—
CBPM negative (*N* = 483)					
ceftazidime/avibactam	4	32	0.25 to ≥256	83.4	16.6
ceftazidime	16	≥256	0.25 to ≥256	49.3	50.7
cefepime	16	≥32	0.5 to ≥32	49.7	50.3
piperacillin/tazobactam	32	≥256	≤0.25 to ≥256	38.7	61.3
aztreonam	32	128	0.25 to ≥256	42.7	57.3
imipenem	≥16	≥16	0.12 to ≥16	12.2	87.8
meropenem	≥16	≥16	4 to ≥16	0.0	50.7
colistin	1	2	0.25 to 8	99.6	0.4
amikacin	8	≥64	0.5 to ≥64	60.9	29.6
levofloxacin	4	≥16	0.25 to ≥16	28.4	71.6
tigecycline	≥16	≥16	0.25 to ≥16	—	—
MBL positive (*N* = 148)					
ceftazidime/avibactam	32	≥256	2 to ≥256	4.7	95.3
ceftazidime	64	≥256	4 to ≥256	2.7	97.3
cefepime	≥32	≥32	2 to ≥32	8.1	91.9
piperacillin/tazobactam	64	≥256	8 to ≥256	5.4	94.6
aztreonam	16	128	2 to ≥256	64.2	35.8
imipenem	≥16	≥16	8 to ≥16	0.0	100
meropenem	≥16	≥16	4 to ≥16	0.0	93.9
colistin	1	2	0.5 to 2	100	0.0
amikacin	≥64	≥64	2 to ≥64	9.5	85.8
levofloxacin	≥16	≥16	0.25 to ≥16	4.1	95.9
tigecycline	≥16	≥16	1 to ≥16	—	—
MBL negative (*N* = 570)					
ceftazidime/avibactam	4	32	0.25 to ≥256	78.2	21.8
ceftazidime	32	≥256	0.25 to ≥256	42.1	57.9
cefepime	16	≥32	0.5 to ≥32	42.1	57.9

Continued

Table 3. *Continued*

Phenotype/antimicrobial	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	S (%)	R (%)
piperacillin/tazobactam	64	≥256	≤0.25 to ≥256	32.8	67.2
aztreonam	≥64	≥256	0.25 to ≥256	36.7	63.3
imipenem	≥16	≥16	0.12 to ≥16	10.5	89.5
meropenem	≥16	≥16	4 to ≥16	0.0	57.9
colistin	1	2	0.12 to 8	98.9	1.1
amikacin	8	≥64	0.5 to ≥64	57.5	33.5
levofloxacin	8	≥16	0.25 to ≥16	24.7	75.3
tigecycline	≥16	≥16	0.25 to ≥16	—	—

A dash indicates that breakpoints were unavailable for calculation of percentage susceptibility or resistance. CBPM, carbapenemase; R, resistant; S, susceptible.
[a]INFORM was succeeded by ATLAS in 2018.

ceftazidime/avibactam observed among a separate population of 30 KPC-positive isolates.[3]

During the years of our analysis of INFORM, 2015–17, the rate of susceptibility to ceftazidime/avibactam was consistently high against isolates from the range of species belonging to Enterobacterales, including *K. pneumoniae*, which was generally less susceptible to most of the comparator agents. The susceptibility rates we observed for comparator agents such as amikacin, cefepime, ceftazidime and imipenem are similar to those reported among *K. pneumoniae* isolates collected from hospitalized patients with intra-abdominal and urinary tract infections in Latin America as part of the SMART study (2013 to 2015),[33] suggesting that susceptibility rates among *K. pneumoniae* in the region are not declining.

Among ESBL-positive Enterobacterales isolates collected for the current analysis, the highest rate of susceptibility was for ceftazidime/avibactam (98.2%), which restored susceptibility among this subset of isolates that had a susceptibility rate of just 3.4% for ceftazidime alone. Susceptibility to all agents was reduced among carbapenemase-positive isolates, including a reduction in ceftazidime/avibactam susceptibility rate from 99.3% to 86.6%. Among MBL-positive isolates, which are not susceptible to ceftazidime/avibactam, colistin was the only agent that showed meaningful *in vitro* activity.

Among the isolates collected for the current analysis, the rate of colistin susceptibility of *P. aeruginosa* was consistently high and this was observed among MDR, carbapenemase-positive and MBL-positive subsets. The rate of susceptibility to ceftazidime/avibactam among all *P. aeruginosa* was 86.6%, which is similar to the susceptibility reported by Karlowsky *et al.*[25] (87.4%) for the 2012–15 period of INFORM in Latin America; they too reported high rates of susceptibility to colistin (94.9%). The susceptibility rates we observed to comparator agents among isolates collected during 2015–17 were lower compared with ceftazidime/avibactam and colistin in the same period, but were similar or higher than rates for the same comparator agents as those reported by Karlowsky *et al.*[25] for the 2012–15 period of INFORM and were also similar to or higher than reported susceptibility rates from the SMART study during a longer period (2009–15) in Mexico, suggesting that susceptibility rates among *P. aeruginosa* are at least stable and could be increasing.[34]

For the period of the current study (2015–17), ceftazidime/avibactam and colistin were the only two agents to which the majority of MDR *P. aeruginosa* were susceptible; *in vitro* activity of all agents, except colistin, against carbapenemase-positive *P. aeruginosa* was generally low, demonstrated by susceptibility rates of <50% (apart from colistin). It is notable that among isolates screened for β-lactamases, but for which no carbapenemase was detected (and that would therefore possess MIC values of >16 mg/L to ceftazidime), the rate of susceptibility to ceftazidime/avibactam was similar to that to colistin.

The proportion of MDR *P. aeruginosa* isolates (34.7%) in the current analysis (2015–17) was higher than that reported by Karlowsky *et al.*[25] (25.3%). The INFORM study is not an epidemiological study and so the frequency of resistance phenotypes needs to be treated with caution. Fluctuating rates of MDR isolates among *P. aeruginosa* have been observed in the SENTRY study.[35] In an analysis of MDR rates from 1997 to 2016, the overall rate of *P. aeruginosa* isolates collected from Latin America being identified as MDR was 41.1% and was >40% for each of the periods 1997–2000, 2001–04, 2005–08 and 2009–12, followed by a decrease to <30% for the period 2013–16, suggesting that the frequency of MDR isolates among *P. aeruginosa* in Latin America is not increasing.

Ceftazidime/avibactam susceptibility rates in the current study were consistent across the collections of Enterobacterales isolates for individual countries, but were reduced among carbapenemase-positive Enterobacterales isolates in Colombia and Venezuela, and a substantial reduction was observed in Mexico. Reduced susceptibility rates were also observed among *P. aeruginosa* isolates from Chile and MDR *P. aeruginosa* isolates that were collected in Venezuela and Mexico. The proportion of MBL-positive isolates among Enterobacterales collected in Mexico, and among *P. aeruginosa* isolates from Chile, appear to have impacted upon overall susceptibility rates to almost all agents and susceptibility among resistance phenotypes in Colombia and Venezuela is also likely to have been reduced by the presence of MBL-positive isolates. The lower rates of susceptibility to many of the comparator agents on the INFORM panel among the isolates with resistance phenotypes are consistent with a previous surveillance study that reported high rates of resistance to third- and fourth-generation cephalosporins and piperacillin/tazobactam

Table 4. MIC_{50}, MIC_{90} and MIC range (mg/L) of, and antimicrobial susceptibility and resistance to, ceftazidime/avibactam and selected comparator agents for Enterobacterales, plus ESBL-positive and CBPM-positive phenotypes, collected in individual Latin America countries as part of the INFORM study[a], 2015–17

Country/antimicrobial	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	S (%)	R (%)
Argentina (*N* = 1191)					
All Enterobacterales					
ceftazidime/avibactam	0.12	5	≤0.015 to ≥256	99.7	0.3
imipenem	0.25	2	≤0.03 to ≥16	79.4	6.1
meropenem	0.03	0.12	0.008 to ≥16	93.5	4.6
colistin	0.25	≥16	≤0.06 to ≥16	80.8	19.2
amikacin	2	8	≤0.25 to ≥64	92.4	4.0
ESBL positive (*N* = 191)					
ceftazidime/avibactam	0.5	1	≤0.015 to 16	99.5	0.5
imipenem	0.25	≥16	0.06 to ≥16	84.8	12.6
meropenem	0.06	8	0.015 to ≥16	86.4	8.9
colistin	0.25	2	0.12 to ≥16	91.6	8.4
amikacin	4	32	≤0.25 to ≥64	77.5	11
CBPM positive (*N* = 82)					
ceftazidime/avibactam	0.5	2	0.12 to ≥256	97.6	2.4
imipenem	≥16	≥16	0.25 to ≥16	2.4	86.6
meropenem	≥16	≥16	0.12 to ≥16	7.3	65.9
colistin	1	≥16	0.25 to ≥16	58.5	41.5
amikacin	16	32	≤0.25 to ≥64	48.8	36.6
Brazil (*N* = 1469)					
All Enterobacterales					
ceftazidime/avibactam	0.12	0.5	≤0.015 to ≥256	99.8	0.2
imipenem	0.25	4	0.06 to ≥16	79.8	8.4
meropenem	0.03	1	0.008 to ≥16	91.4	7.1
colistin	0.5	≥16	≤0.06 to ≥16	82.1	17.9
amikacin	2	8	≤0.25 to ≥64	94.9	3.3
ESBL positive (*N* = 323)					
ceftazidime/avibactam	0.25	2	≤0.015 to ≥256	99.1	0.9
imipenem	0.25	≥16	0.06 to ≥16	73.7	21.7
meropenem	0.06	≥16	0.015 to ≥16	76.2	19.5
colistin	0.5	4	0.12 to ≥16	88.9	11.1
amikacin	4	32	≤0.25 to ≥64	85.8	10.2
CBPM positive (*N* = 129)					
ceftazidime/avibactam	1	2	≤0.015 to ≥256	97.7	2.3
imipenem	≥16	≥16	4 to ≥16	0	87.6
meropenem	≥16	≥16	1 to ≥16	6.2	79.8
colistin	0.5	≥16	0.12 to ≥16	77.5	22.5
amikacin	4	≥64	0.5 to ≥64	76	20.2
Chile[b] (*N* = 1032)					
All Enterobacterales					
ceftazidime/avibactam	0.12	0.5	≤0.015 to ≥256	99.8	0.2
imipenem	0.25	2	0.06 to ≥16	87.9	0.3
meropenem	0.06	0.12	0.008 to 8	98.7	0.0
colistin	0.25	≥16	≤0.06 to ≥16	83.9	16.1
amikacin	2	8	≤0.25 to ≥64	92.7	4.4
ESBL positive (*N* = 260)					
ceftazidime/avibactam	0.25	2	≤0.015 to ≥256	99.2	0.8
imipenem	0.25	1	0.12 to ≥16	93.1	0.8
meropenem	0.06	2	0.015 to 8	95.0	0.0
colistin	0.5	8	0.12 to ≥16	89.2	10.8
amikacin	4	32	0.5 to ≥64	81.9	11.9

Continued

Table 4. *Continued*

Country/antimicrobial	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	S (%)	R (%)
Colombia (*N* = 992)					
All Enterobacterales					
ceftazidime/avibactam	0.12	0.5	≤0.015 to ≥256	99.2	0.8
imipenem	0.25	4	≤0.03 to ≥16	80.4	8.1
meropenem	0.06	0.5	≤0.004 to ≥16	92.2	5.2
colistin	0.5	≥16	0.12 to ≥16	82.8	17.2
amikacin	2	8	≤0.25 to ≥64	92.3	2.8
ESBL positive (*N* = 204)					
ceftazidime/avibactam	0.25	1	≤0.015 to ≥256	97.5	2.5
imipenem	0.25	≥16	0.06 to ≥16	80.9	15.7
meropenem	0.06	≥16	0.015 to ≥16	83.8	14.7
colistin	0.5	1	0.12 to ≥16	96.1	3.9
amikacin	4	16	0.5 to ≥64	79.4	5.9
CBPM positive (*N* = 97)					
ceftazidime/avibactam	1	4	0.03 to ≥256	91.8	8.2
imipenem	≥16	≥16	0.5 to ≥16	12.4	72.2
meropenem	≥16	≥16	0.12 to ≥16	21.6	52.6
colistin	0.5	≥16	0.12 to ≥16	85.6	14.4
amikacin	4	32	0.5 to ≥64	60.8	17.5
Mexico (*N* = 1855)					
All Enterobacterales					
ceftazidime/avibactam	0.12	0.5	≤0.015 to ≥256	98.6	1.4
imipenem	0.25	2	≤0.03 to ≥16	87.4	1.5
meropenem	0.03	0.12	0.008 to ≥16	98.2	1.2
colistin	0.25	≥16	≤0.06 to ≥16	83.8	16.2
amikacin	2	8	≤0.25 to ≥64	94.6	2.6
ESBL positive (*N* = 603)					
ceftazidime/avibactam	0.25	0.5	≤0.015 to ≥256	97.3	2.7
imipenem	0.25	0.5	≤0.03 to ≥16	97	2.5
meropenem	0.03	0.06	0.008 to ≥16	96.5	2.3
colistin	0.25	1	0.12 to ≥16	98.5	1.5
amikacin	4	16	0.5 to ≥64	88.6	4.5
CBPM positive (*N* = 32)					
ceftazidime/avibactam	≥256	≥256	0.06 to ≥256	18.8	81.3
imipenem	≥16	≥16	0.5 to ≥16	12.5	71.9
meropenem	≥16	≥16	0.25 to ≥16	15.6	65.6
colistin	0.25	≥16	0.12 to ≥16	81.3	18.8
amikacin	16	≥64	0.5 to ≥64	43.8	46.9
Venezuela (*N* = 1190)					
All Enterobacterales					
ceftazidime/avibactam	0.12	0.25	≤0.015 to ≥256	99.2	0.8
imipenem	0.25	2	≤0.03 to ≥16	87.8	1.9
meropenem	0.03	0.12	0.008 to ≥16	97.9	1.3
colistin	0.25	≥16	≤0.06 to ≥16	84.7	15.3
amikacin	2	8	≤0.25 to ≥64	93.0	4.2
ESBL positive (*N* = 279)					
ceftazidime/avibactam	0.12	1	≤0.015 to ≥256	97.8	2.2
imipenem	0.25	1	0.06 to ≥16	92.5	4.7
meropenem	0.03	0.25	0.015 to ≥16	93.2	3.9
colistin	0.25	0.5	≤0.06 to ≥16	98.2	1.8
amikacin	4	≥64	≤0.25 to ≥64	75.6	15.8
CBPM positive (*N* = 24)					
ceftazidime/avibactam	1	≥256	0.5 to ≥256	70.8	29.2

Continued

Table 4. *Continued*

Country/antimicrobial	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	S (%)	R (%)
imipenem	8	≥16	2 to ≥16	4.2	70.8
meropenem	≥16	≥16	0.25 to ≥16	16.7	62.5
colistin	0.25	2	0.12 to ≥16	91.7	8.3
amikacin	16	≥64	1 to ≥64	41.7	37.5

CBPM, carbapenemase; R, resistant; S, susceptible.
[a]INFORM was succeeded by ATLAS in 2018.
[b]CBPM-positive data not presented for Chile due to the low number of isolates (*N* = 2).

Table 5. MIC_{50}, MIC_{90} and MIC range (mg/L) of, and antimicrobial susceptibility and resistance to, ceftazidime/avibactam and selected comparator agents for *P. aeruginosa* and MDR *P. aeruginosa*, collected in individual Latin America countries as part of the INFORM study[a], 2015–17

Country/antimicrobial	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	S (%)	R (%)
Argentina (*N* = 345)					
All *P. aeruginosa*					
ceftazidime/avibactam	2	8	0.25 to ≥256	94.5	5.5
imipenem	2	≥16	0.25 to ≥16	75.7	24.3
meropenem	0.5	≥16	0.03 to ≥16	70.1	15.4
colistin	1	1	≤0.06 to 8	99.7	0.3
amikacin	4	≥64	1 to ≥64	82.3	13.3
MDR (*N* = 101)					
ceftazidime/avibactam	8	16	0.5 to ≥256	81.2	18.8
imipenem	≥16	≥16	0.25 to ≥16	37.6	62.4
meropenem	8	≥16	0.25 to ≥16	17.8	49.5
colistin	1	2	≤0.06 to 8	99.0	1.0
amikacin	16	≥64	1 to ≥64	49.5	41.6
Brazil (*N* = 346)					
All *P. aeruginosa*					
ceftazidime/avibactam	2	8	0.03 to ≥256	93.9	6.1
imipenem	2	≥16	0.25 to ≥16	68.8	31.2
meropenem	0.5	≥16	0.03 to ≥16	70.2	19.9
colistin	1	2	≤0.06 to ≥16	99.4	0.6
amikacin	4	32	0.5 to ≥64	86.4	10.1
MDR (*N* = 110)					
ceftazidime/avibactam	8	32	0.25 to ≥256	80.9	19.1
imipenem	≥16	≥16	0.5 to ≥16	28.2	71.8
meropenem	≥16	≥16	0.06 to ≥16	30.0	57.3
colistin	1	2	≤0.06 to 2	100	0.0
amikacin	8	≥64	0.5 to ≥64	65.5	30.9
Chile (*N* = 304)					
All *P. aeruginosa*					
ceftazidime/avibactam	4	32	0.25 to ≥256	75.0	25.0
imipenem	4	≥16	0.5 to ≥16	50.0	50.0
meropenem	2	≥16	0.06 to ≥16	52.0	33.2
colistin	1	2	0.25 to 4	99.7	0.3
amikacin	8	≥64	≤0.25 to ≥64	68.4	26.3
MDR (*N* = 162)					
ceftazidime/avibactam	8	64	1 to ≥256	53.1	46.9
imipenem	≥16	≥16	1 to ≥16	14.2	85.8
meropenem	≥16	≥16	0.12 to ≥16	17.3	62.3
colistin	1	2	0.25 to 4	99.4	0.6

Continued

Table 5. *Continued*

Country/antimicrobial	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	S (%)	R (%)
amikacin	16	≥64	2 to ≥64	46.3	45.7
Colombia (*N* = 225)					
All *P. aeruginosa*					
ceftazidime/avibactam	2	16	0.12 to 128	86.7	13.3
imipenem	2	≥16	0.25 to ≥16	68.4	31.6
meropenem	0.5	≥16	0.03 to ≥16	68.4	23.6
colistin	1	1	≤0.06 to ≥16	99.6	0.4
amikacin	4	≥64	≤0.25 to ≥64	82.2	14.7
MDR (*N* = 79)					
ceftazidime/avibactam	8	64	0.12 to 128	62.0	38.0
imipenem	≥16	≥16	0.25 to ≥16	29.1	70.9
meropenem	≥16	≥16	0.03 to ≥16	29.1	63.3
colistin	1	2	0.12 to 2	100	0.0
amikacin	8	≥64	1 to ≥64	54.4	40.5
Mexico (*N* = 524)					
All *P. aeruginosa*					
ceftazidime/avibactam	2	64	0.03 to ≥256	85.1	14.9
imipenem	2	≥16	0.12 to ≥16	62.2	37.8
meropenem	1	≥16	≤0.004 to ≥16	62.2	23.1
colistin	1	2	0.12 to 8	98.1	1.9
amikacin	4	≥64	≤0.25 to ≥64	74.2	20.8
MDR (*N* = 169)					
ceftazidime/avibactam	8	≥256	1 to ≥256	54.4	45.6
imipenem	≥16	≥16	0.12 to ≥16	18.9	81.1
meropenem	≥16	≥16	0.12 to ≥16	14.2	69.2
colistin	1	2	0.12 to 4	96.4	3.6
amikacin	32	≥64	0.5 to ≥64	39.1	52.7
Venezuela (*N* = 309)					
All *P. aeruginosa*					
ceftazidime/avibactam	2	32	0.12 to ≥256	83.2	16.8
imipenem	2	≥16	0.25 to ≥16	70.9	29.1
meropenem	0.5	≥16	0.03 to ≥16	68.6	23.3
colistin	1	1	0.25 to 4	99.7	0.3
amikacin	4	≥64	1 to ≥64	74.4	21.4
MDR (*N* = 91)					
ceftazidime/avibactam	32	64	0.5 to ≥256	42.9	57.1
imipenem	≥16	≥16	1 to ≥16	18.7	81.3
meropenem	≥16	≥16	0.12 to ≥16	9.9	76.9
colistin	1	1	0.5 to 2	100	0.0
amikacin	≥64	≥64	1 to ≥64	19.8	69.2

R, resistant; S, susceptible.
[a]INFORM was succeeded by ATLAS in 2018.

among Enterobacterales and *P. aeruginosa* isolates in this country.[36] The continued low rates of susceptibility to established broad-spectrum agents and the emergence of infections caused by carbapenemase-positive Enterobacterales and/or MDR *P. aeruginosa* narrow the range of treatment options for physicians and mean that continued surveillance is vital.[1,2,7,37] Susceptibility to ceftazidime/avibactam in the Latin American region is stable, and at high rates; when the frequency of local MBL-mediated resistance is considered, ceftazidime/avibactam can be an appropriate agent for patients with infections caused by Enterobacterales or *P. aeruginosa* and for whom treatment options may be limited.

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Author contributions

A. Ponce-de-Leon participated in data collection and interpretation as well as drafting and reviewing the manuscript. G. G. Stone was involved in the study design and participated in data interpretation and drafting and review of the manuscript. All authors read and approved the final manuscript.

Supplementary data

Tables S1 to S5 are available as Supplementary data at *JAC* Online

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