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Longitudinal analysis of the in vitro activity of ceftazidime/avibactam versus Enterobacteriaceae, 2012–2016

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ABSTRACT

Objectives: The in vitro activities of ceftazidime/avibactam and comparator antimicrobial agents were analysed against 59 828 Enterobacteriaceae isolates collected by 190 centres from all global regions except North America from 2012–2016 as part of the International Network for Optimal Resistance Monitoring (INFORM) global surveillance programme.
Methods: Antimicrobial susceptibility testing was performed using Clinical and Laboratory Standards Institute broth microdilution panels at a central reference laboratory, except for isolates collected in China that were tested using frozen, dehydrated broth microdilution panels at a central laboratory in China. The presence of extended-spectrum β-lactamases (ESBLs) was confirmed by multiplex PCR assays.
Results: Ceftazidime/avibactam was the most active agent against all Enterobacteriaceae (MIC_{90}, ≤1 mg/L, ≥98.4% susceptibility). High rates of susceptibility (>88%) were observed amongst *Citrobacter freundii*, *Citrobacter* spp., *Enterobacter* spp., *Escherichia coli*, *Klebsiella pneumoniae* and *Klebsiella oxytoca* to colistin, meropenem, amikacin and tigecycline. Ceftazidime/avibactam showed consistent in vitro activity against ESBL-positive isolates of *E. coli* ($n = 5674$; MIC_{90}, 0.5 mg/L, 99.5% susceptible), *K. pneumoniae* ($n = 7097$; MIC_{90}, 2 mg/L, 97.0% susceptible) and *K. oxytoca* ($n = 565$; MIC_{90}, 1 mg/L, 96.8% susceptible). Isolates identified as metallo-β-lactamase-positive ($n = 242$) were not susceptible to ceftazidime/avibactam but were susceptible to tigecycline (76.9%) and colistin ($n = 194$ isolates tested; 92.8%).
Conclusions: Clinical Enterobacteriaceae isolates, including ESBL-positive phenotypes, collected globally (excluding North America) from 2012–2016 were highly susceptible to ceftazidime/avibactam, suggesting it is a useful agent for serious infections caused by multidrug-resistant organisms belonging to the family Enterobacteriaceae when therapeutic options are limited.

1. Introduction

Serious infections caused by Gram-negative bacilli have been reported to have mortality rates of between 30% and 70% [1], and in recent years organisms belonging to the family Enterobacteriaceae[1] have been associated with increasing morbidity and mortality due to the increasing prevalence of multidrug-resistant phenotypes [2–5]. Treatment options for these infections, of which the mainstay has been β-lactams and carbapenems, have become increasingly limited due to rising rates of antimicrobial resistance to these agents in regions across the globe [6,7]. Antimicrobial resistance frequently arises due to acquisition of plasmid-mediated carbapenemase genes, production of extended-spectrum β-lactamases (ESBLs) or Ambler class C β-lactamases, expression of efflux pumps or loss of function of outer membrane pore-forming proteins [8,9]. Antimicrobial resistance among carbapenemase-producing Enterobacteriaceae is most frequently attributable to two types of carbapenemases: serine enzymes, which include *Klebsiella pneumoniae* carbapenemases (KPCs) and OXA-48-type enzymes; and metallo-β-lactamases (MBLs), which include IMP-, NDM- and VIM-type enzymes [8–10].

Avibactam is a first-in-class diazabicyclooctanone non-β-lactam β-lactamase inhibitor that restores the in vitro activity of ceftazidime against resistant phenotypes of Gram-negative bacteria, including KPC-producing Enterobacteriaceae, ESBL-positive and AmpC-positive isolates, and carbapenemase-negative

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[1] The definition of Enterobacteriaceae has been narrowed, and European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoint tables v.8.1 refer to the new taxonomy of Enterobacterales (see http://www.eucast.org/).

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carbapenem-not susceptible isolates with altered outer membrane permeability [11,12]. Enterobacteriaceae that produce MBLs or that harbour sequence alterations in target proteins (AmpC, KPC and penicillin-binding protein 3) are not susceptible to ceftazidime/avibactam [13,14].

Ceftazidime/avibactam was recently approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of adult patients with complicated intra-abdominal infection, complicated urinary tract infection (including pyelonephritis), hospital-acquired pneumonia (including ventilator-associated pneumonia), and infections caused by aerobic Gram-negative bacteria in adults with limited treatment options [15,16]. The in vitro activities of ceftazidime/avibactam and a panel of comparator agents against isolates of Enterobacteriaceae have been reported previously as part of the International Network for Optimal Resistance Monitoring (INFORM) global surveillance programme [13,17–20]. The current study analysed the antimicrobial activity against a global population of Enterobacteriaceae isolates collected between 2012 and 2016 as well as ESBL and MBL subsets and by region; some data have been previously reported by Estabrook et al. at the 28th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) [21].

2. Materials and methods

A total of 190 centres collected 59 828 non-duplicate clinical isolates of Enterobacteriaceae from patients with bloodstream infections, intra-abdominal infections, lower respiratory tract infections, skin and soft-tissue infections and urinary tract infections. Sites were medical centre laboratories located in Europe (102 laboratories), Asia-Pacific (35 laboratories), Latin America (26 laboratories), Africa/Middle East (17 laboratories) and Oceania (10 laboratories). Each site collected a predefined number of selected Enterobacteriaceae regardless of antimicrobial susceptibility during a 5-year time period (2012–2016) as part of the INFORM surveillance study. The identity of samples was determined following shipment to a central reference laboratory (International Health Management Associates, Inc., Schaumburg, IL, USA) using matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF/MS) (Bruker Biotyper MALDI-TOF; Bruker Daltonics, Billerica, MA, USA). Isolates from China were tested at a central laboratory in China.

Antimicrobial susceptibility testing was performed using frozen broth microdilution panels, except for isolates collected in China that were tested at a central laboratory in China using frozen, dehydrated broth microdilution panels manufactured by Thermo Fisher [22]. Avibactam was tested at a fixed concentration of 4 mg/L in combination with doubling dilutions of ceftazidime (range, ≤0.015 mg/L to ≥128 mg/L) against all isolates. Colistin (in the absence of added surfactant) was tested only in the years 2014–2016. Minimum inhibitory concentrations (MICs) were interpreted using European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2018 breakpoints [23]. Isolates of *Escherichia coli*, *K. pneumoniae*, *Klebsiella oxytoca* and *Proteus mirabilis* with MICs > 1 mg/L to ceftazidime or aztreonam were confirmed for ESBL activity by phenotypic combination testing with clavulanic acid [24]. Any isolates testing phenotypically positive for ESBL activity or with MIC ≥ 16 mg/L to ceftazidime as well as any Enterobacteriaceae with MICs > 1 mg/L to doripenem, meropenem or imipenem were screened for the presence of clinically relevant β-lactamases using a combination of the microarray-based Check-MDR CT101 Kit (Check-Points, Wageningen, the Netherlands) and previously described multiplex PCR assays [25]. All detected β-lactamase genes, excluding original-spectrum β-lactamases, were amplified using flanking primers and were sequenced. Sequences were compared against databases maintained by the National Center for Biotechnology Information (NCBI) (www.ncbi.nlm.nih.gov) and the Lahey Clinic (www.lahey.org/studies).

3. Results

A total of 59 828 Enterobacteriaceae isolates were collected from global regions as part of the INFORM study between 2012 and 2016. Approximately one-half of these isolates (54.1%) were collected from European centres (Table 1) and 75.2% were from patients located in wards that were not classified as intensive care units. A slightly larger proportion of isolates was collected from male patients (53.5%) compared with female patients (45.7%), and >90% were from adult patients. The predominant isolate sources were genitourinary (28.1%), skin and skin structure (24.6%) and respiratory (21.6%).

3.1. Susceptibility to ceftazidime/avibactam and comparator agents

3.1.1. *Citrobacter freundii*

Susceptibility of *C. freundii* ($n = 2076$) isolates was highest to colistin (99.6%), ceftazidime/avibactam (98.4%) and carbapenems (≥97.5%) (Table 2). The majority of isolates were also susceptible to amikacin (96.9%) and tigecycline (95.1%).

3.1.2. Citrobacter *spp*

The susceptibility pattern of *Citrobacter* spp. ($n = 3777$, including *C. freundii*) was similar to that observed for the *C. freundii* subset and was highest to colistin (99.7%), ceftazidime/avibactam (99.0%), carbapenems (≥98.3%), amikacin (97.7%) and tigecycline (97.0%) (Table 2).

Table 1
Patient demographics and culture source for isolates collected globally (excluding North America) as part of the INFORM surveillance study, 2012–2016.

Parameter	% of patients (N = 59,828)
Region	
Africa/Middle East	9.2
Asia	16.3
Europe	54.1
Oceania	3.1
Latin America	17.3
Patient location	
ICU	20.3
Non-ICU	75.2
Unknown	4.5
Inpatient	86.4
Outpatient	9.2
Unknown	4.5
Sex	
Male	53.5
Female	45.7
Unknown	0.8
Age	
0–17 years	8.3
18–64 years	45.8
≥65 years	45.0
Unknown	0.9
Culture source	
Bodily fluid	7.2
Cardiovascular	6.0
Gastrointestinal	12.2
Genitourinary	28.1
Skin and skin structure	24.6
Respiratory	21.6
Other[a]	0.1
Unknown	0.2

ICU, intensive care unit.
[a] Head, eyes, ears, nose and throat, and reproductive culture sources.

Table 2
Minimum inhibitory concentrations (MICs) and percentage antimicrobial susceptibility of Enterobacteriaceae isolates collected as part of the INFORM study, 2012–2016, to ceftazidime/avibactam and comparator agents.

Organism/antimicrobial agent	MIC (mg/L)			Susceptibility	
	MIC_{50}	MIC_{90}	Range	%S	%R
Citrobacter freundii (*n* = 2076)					
Amikacin	2	4	≤0.25 to ≥64	96.9	1.8
Levofloxacin	0.12	4	0.008 to ≥16	76.6	17.3
Aztreonam	0.25	64	≤0.015 to ≥256	64.8	32.1
Ceftazidime	0.5	128	≤0.015 to ≥256	63.2	33.2
Cefepime	≤0.12	4	≤0.12 to ≥32	83.6	9.0
Doripenem	0.06	0.12	≤0.008 to ≥16	98.0	1.8
Imipenem	0.5	2	≤0.03 to ≥16	97.5	0.3
Meropenem	0.03	0.12	≤0.004 to ≥16	98.3	0.5
Tigecycline	0.5	1	≤0.015 to 4	95.1	1.2
AMC	32	≥64	≤0.12 to ≥64	9.6	90.4
TZP	4	128	≤0.25 to ≥256	69.7	23.5
Ceftazidime/avibactam	0.12	0.5	≤0.015 to ≥256	98.4	1.6
Colistin (*n* = 1406)[a]	0.5	1	≤0.06 to ≥16	99.6	0.4
Citrobacter spp. (n = 3777)[b]					
Amikacin	2	4	≤0.25 to ≥64	97.7	1.4
Levofloxacin	0.06	2	≤0.004 to ≥16	84.8	11.1
Aztreonam	0.12	32	≤0.015 to ≥256	75.7	21.6
Ceftazidime	0.25	128	≤0.015 to ≥256	75.7	21.6
Cefepime	≤0.12	2	≤0.12 to ≥32	88.3	6.6
Doripenem	0.06	0.12	≤0.008 to ≥16	98.6	1.2
Imipenem	0.5	1	≤0.03 to ≥16	98.3	0.3
Meropenem	0.03	0.06	≤0.004 to ≥16	98.8	0.3
Tigecycline	0.25	1	≤0.015 to 4	97.0	0.6
AMC	16	≥64	≤0.12 to ≥64	41.8	58.2
TZP	4	64	≤0.25 to ≥256	78.7	15.3
Ceftazidime/avibactam	0.12	0.5	≤0.015 to ≥256	99.0	1.0
Colistin (*n* = 2569)[a]	0.5	1	≤0.06 to ≥16	99.7	0.3
Enterobacter spp. (n = 6892)					
Amikacin	2	4	≤0.25 to ≥64	96.7	2.1
Levofloxacin	0.06	2	≤0.004 to ≥16	84.0	11.0
Aztreonam	0.12	64	≤0.015 to ≥256	66.0	31.0
Ceftazidime	0.5	128	≤0.015 to ≥256	64.4	32.6
Cefepime	≤0.12	8	≤0.12 to ≥32	80.8	11.9
Doripenem	0.06	0.25	≤0.008 to ≥16	97.4	2.2
Imipenem	0.5	2	≤0.03 to ≥16	96.6	1.2
Meropenem	0.06	0.12	≤0.004 to ≥16	97.9	1.0
Tigecycline	0.5	1	≤0.015 to ≥16	91.9	2.9
AMC	32	≥64	≤0.12 to ≥64	4.1	95.9
TZP	4	128	≤0.25 to ≥256	69.1	24.9
Ceftazidime/avibactam	0.25	1	≤0.015 to ≥256	98.5	1.5
Colistin (*n* = 4405)[a]	0.5	1	≤0.06 to ≥16	93.1	6.9
Escherichia coli (n = 19 879)					
Amikacin	2	8	≤0.25 to ≥64	94.2	1.9
Levofloxacin	0.25	≥16	≤0.004 to ≥16	59.2	37.8
Aztreonam	0.12	64	≤0.015 to ≥256	72.2	24.3
Ceftazidime	0.25	32	≤0.015 to ≥256	73.8	21.1
Cefepime	≤0.12	≥32	≤0.12 to ≥32	74.3	22.1
Doripenem	0.03	0.06	≤0.008 to ≥16	99.6	0.3
Imipenem	0.25	0.25	≤0.03 to ≥16	99.5	0.2
Meropenem	0.03	0.06	≤0.004 to ≥16	99.6	0.1
Tigecycline	0.25	0.5	≤0.015 to ≥16	99.2	0.2
AMC	8	32	≤0.12 to ≥64	64.9	35.1
TZP	2	16	≤0.25 to ≥256	84.2	10.0
Ceftazidime/avibactam	0.12	0.25	≤0.015 to ≥256	99.9	0.1
Colistin (*n* = 12 374)[a]	0.5	1	≤0.06 to ≥16	99.5	0.5
E. coli, ESBL-positive (*n* = 5674)					
Amikacin	4	16	≤0.25 to ≥64	84.2	5.6
Levofloxacin	8	≥16	≤0.004 to ≥16	19.9	77.2
Aztreonam	32	128	≤0.015 to ≥256	2.7	84.9
Ceftazidime	16	128	≤0.015 to ≥256	8.4	73.8
Cefepime	≥32	≥32	≤0.12 to ≥32	13.4	76.3
Doripenem	0.03	0.06	≤0.008 to ≥16	98.7	0.9
Imipenem	0.25	0.5	≤0.03 to ≥16	98.5	0.5
Meropenem	0.03	0.06	≤0.004 to ≥16	98.7	0.4
Tigecycline	0.25	0.5	≤0.015 to ≥16	98.9	0.2
AMC	16	32	≤0.12 to ≥64	33.3	66.7
TZP	8	128	≤0.25 to ≥256	63.6	21.5
Ceftazidime/avibactam	0.12	0.5	≤0.015 to ≥256	99.5	0.5
Colistin (*n* = 3535)[a]	0.5	1	≤0.06 to ≥16	99.2	0.8

Table 2 (*Continued*)

Organism/antimicrobial agent	MIC (mg/L)			Susceptibility	
	MIC_{50}	MIC_{90}	Range	%S	%R
Klebsiella pneumoniae (*n* = 16 563)					
Amikacin	1	8	≤0.25 to ≥64	90.5	6.6
Levofloxacin	0.12	8	≤0.004 to ≥16	59.1	31.0
Aztreonam	0.12	≥256	≤0.015 to ≥256	59.0	39.2
Ceftazidime	0.5	128	≤0.015 to ≥256	58.1	39.2
Cefepime	≤0.12	≥32	≤0.12 to ≥32	60.4	36.4
Doripenem	0.06	0.5	≤0.008 to ≥16	91.5	7.4
Imipenem	0.25	1	≤0.03 to ≥16	92.2	5.3
Meropenem	0.06	0.5	≤0.004 to ≥16	92.1	5.9
Tigecycline	0.5	2	≤0.015 to ≥16	88.3	3.3
AMC	8	32	≤0.12 to ≥64	56.8	43.2
TZP	4	≥256	≤0.25 to ≥256	61.7	29.1
Ceftazidime/avibactam	0.12	1	≤0.015 to ≥256	98.7	1.3
Colistin (*n* = 11 529)[a]	0.5	1	≤0.06 to ≥16	96.0	4.0
K. pneumoniae, ESBL-positive (*n* = 7097)					
Amikacin	4	32	≤0.25 to ≥64	78.9	14.8
Levofloxacin	8	≥16	0.03 to ≥16	19.7	63.3
Aztreonam	64	≥256	≤0.015 to ≥256	4.3	91.5
Ceftazidime	64	≥256	0.03 to ≥256	2.2	91.5
Cefepime	≥32	≥32	≤0.12 to ≥32	8.6	84.6
Doripenem	0.06	8	0.015 to ≥16	80.6	17.0
Imipenem	0.25	≥16	≤0.03 to ≥16	82.1	12.4
Meropenem	0.06	≥16	≤0.004 to ≥16	81.8	13.6
Tigecycline	1	2	≤0.015 to ≥16	81.0	5.3
AMC	32	≥64	0.5 to ≥64	11.5	88.5
TZP	64	≥256	≤0.25 to ≥256	22.6	61.5
Ceftazidime/avibactam	0.5	2	≤0.015 to ≥256	97.0	3.0
Colistin (*n* = 4908)[a]	0.5	2	≤0.06 to ≥16	92.1	7.9
Klebsiella oxytoca (*n* = 3266)					
Amikacin	1	4	≤0.25 to ≥64	98.0	0.9
Levofloxacin	0.06	0.5	0.008 to ≥16	91.2	6.4
Aztreonam	0.12	32	≤0.015 to ≥256	83.2	13.9
Ceftazidime	0.12	1	≤0.015 to ≥256	90.6	6.4
Cefepime	≤0.12	2	≤0.12 to ≥32	89.6	5.0
Doripenem	0.06	0.12	≤0.008 to ≥16	98.9	0.8
Imipenem	0.25	0.5	≤0.03 to ≥16	98.7	0.3
Meropenem	0.03	0.06	≤0.004 to ≥16	99.0	0.4
Tigecycline	0.25	0.5	≤0.015 to 4	97.6	0.5
AMC	4	16	≤0.12 to ≥64	84.2	15.8
TZP	2	128	≤0.25 to ≥256	86.5	12.0
Ceftazidime/avibactam	0.12	0.25	≤0.015 to ≥256	99.4	0.6
Colistin (*n* = 2072)[a]	0.5	1	≤0.12 to ≥16	99.4	0.6
K. oxytoca, ESBL-positive (*n* = 565)					
Amikacin	2	8	≤0.25 to ≥64	90.3	4.8
Levofloxacin	0.25	8	0.015 to ≥16	64.2	28.1
Aztreonam	32	≥256	0.06 to ≥256	2.8	80.4
Ceftazidime	2	128	≤0.015 to ≥256	45.5	37.0
Cefepime	2	16	≤0.12 to ≥32	41.9	28.5
Doripenem	0.06	0.25	0.015 to ≥16	93.8	4.8
Imipenem	0.25	1	≤0.03 to ≥16	92.7	1.6
Meropenem	0.06	0.25	≤0.004 to ≥16	94.3	2.5
Tigecycline	0.5	1	≤0.015 to 4	92.7	1.6
AMC	16	32	≤0.12 to ≥64	21.1	78.9
TZP	≥256	≥256	0.5 to ≥256	28.3	65.8
Ceftazidime/avibactam	0.25	1	≤0.015 to ≥256	96.8	3.2
Colistin (*n* = 359)[a]	0.5	1	≤0.12 to ≥16	99.2	0.8
Serratia marcescens (*n* = 1363)					
Amikacin	2	8	≤0.25 to ≥64	94.0	4.3
Levofloxacin	0.25	1	≤0.03 to ≥16	85.0	9.3
Aztreonam	0.12	8	≤0.015 to ≥256	87.4	10.3
Ceftazidime	0.25	2	0.03 to ≥256	89.0	7.9
Cefepime	≤0.12	1	≤0.12 to ≥32	90.1	7.6
Doripenem	0.12	0.25	0.015 to ≥16	98.3	1.5
Imipenem	0.5	2	≤0.06 to ≥16	97.2	1.8
Meropenem	0.06	0.12	0.008 to ≥16	98.5	1.2
Tigecycline	1	2	0.06 to ≥16	73.4	4.6
AMC	32	≥64	0.25 to ≥64	4.6	95.4
TZP	2	8	≤0.25 to ≥256	90.1	6.3
Ceftazidime/avibactam	0.12	0.5	≤0.015 to ≥256	99.3	0.7
Colistin (*n* = 875)[a]	≥16	≥16	0.25 to ≥16	4.6	95.4

Table 2 (*Continued*)

Organism/antimicrobial agent	MIC (mg/L)			Susceptibility	
	MIC_{50}	MIC_{90}	Range	%S	%R
Other Enterobacteriaceae (n = 8088)[c]					
Amikacin	4	8	≤0.25 to ≥64	94.5	3.0
Levofloxacin	0.12	8	0.008 to ≥16	70.7	24.3
Aztreonam	≤0.015	1	≤0.015 to ≥256	92.6	4.1
Ceftazidime	0.06	2	≤0.015 to ≥256	89.1	6.9
Cefepime	≤0.12	1	≤0.12 to ≥32	91.0	6.7
Doripenem	0.25	0.5	≤0.008 to ≥16	98.6	0.7
Imipenem	2	4	≤0.03 to ≥16	68.1	0.6
Meropenem	0.12	0.12	≤0.004 to ≥16	99.6	0.2
Tigecycline	2	4	≤0.015 to ≥16	35.7	30.3
AMC	8	≥64	≤0.12 to ≥64	61.9	38.1
TZP	0.5	2	≤0.25 to ≥256	97.5	1.7
Ceftazidime/avibactam	0.06	0.12	≤0.015 to ≥256	99.5	0.5
Colistin (n = 5120)	≥16	≥16	0.12 to ≥16	5.5	94.5

$MIC_{50/90}$, MIC required to inhibit growth of 50% and 90% of isolates, respectively; %S, percentage susceptible; %R, percentage resistant; AMC, amoxicillin/clavulanic acid; TZP, piperacillin/tazobactam; ESBL, extended-spectrum β-lactamase.

[a] Colistin was tested against isolates collected from 2014–2016 only.

[b] *Citrobacter* spp. isolates comprised *C. amalonaticus*, *C. braakii*, *C. farmeri*, *C. freundii*, *C. gillenii*, *C. koseri*, *C. murliniae*, *C. sedlakii*, *C. youngae* and *Citrobacter* non-speciated.

[c] Other Enterobacteriaceae comprised *Cronobacter sakazakii* (n = 1), *Escherichia fergusonii* (n = 1), *Escherichia hermannii* (n = 2), *Escherichia vulneris* (n = 1), *Hafnia alvei* (n = 4), *Klebsiella ozaenae* (n = 1), *Klebsiella variicola* (n = 147), *Kluyvera ascorbata* (n = 3), *Lelliottia amnigenus* (n = 1), *Morganella morganii* (n = 1638), *Pantoea agglomerans* (n = 2), *Pantoea septica* (n = 2), *Pluralibacter gergoviae* (n = 5), *Proteus hauseri* (n = 75), *Proteus mirabilis* (n = 3613), *Proteus penneri* (n = 71), *Proteus rettgeri* (n = 2), *Proteus vulgaris* (n = 1635), *Providencia alcalifaciens* (n = 24), *Providencia rettgeri* (n = 302), *Providencia stuartii* (n = 388), *Raoultella ornithinolytica* (n = 110), *Raoultella planticola* (n = 28), *Raoultella terrigena* (n = 2), *Serratia liquefaciens* (n = 20), *Serratia odorifera* (n = 1), *Serratia rubidaea* (n = 2) and *Serratia ureilytica* (n = 7).

3.1.3. Enterobacter *spp*

The *Enterobacter* spp. isolates (n = 6892) were susceptible to ceftazidime/avibactam (98.5%), carbapenems (≥96.6%), amikacin (96.7%), colistin (93.1%) and tigecycline (91.9%) (Table 2).

3.1.4. *E. coli*

E. coli isolates (n = 19 879) were the most commonly collected of all the organisms in this study, and >99% in vitro susceptibility was observed to ceftazidime/avibactam, colistin, carbapenems and tigecycline, whilst there were slightly lower rates of susceptibility to amikacin (94.2%) and piperacillin/tazobactam (TZP) (84.2%) (Table 2). Isolates identified as ESBL-positive (n = 5674; 28.5%) showed similar susceptibility compared with all *E. coli* isolates to ceftazidime/avibactam (99.5%), colistin (99.2%), carbapenems (≥98.5%) and tigecycline (98.9%) but was reduced compared with all *E. coli* isolates both for amikacin (84.2%) and TZP (63.6%). The MIC_{50} and MIC_{90} values (MICs required to inhibit the growth of 50% and 90% of isolates, respectively) for agents that retained activity against ESBL-positive isolates were similar compared with all *E. coli* isolates; however values for ESBL-positive isolates increased for amikacin (MIC_{50}, 2 mg/L to 4 mg/L; MIC_{90}, 8 mg/L to 16 mg/L) and TZP (MIC_{50}, 2 mg/L to 8 mg/L; MIC_{90}, 16 mg/L to 128 mg/L).

The small number of MBL-positive *E. coli* isolates (n = 24; 0.1%) collected in this study showed greatly reduced susceptibility to all

Table 3
Minimum inhibitory concentrations (MICs) and percentage antimicrobial susceptibility of metallo-β-lactamase (MBL)-negative and -positive Enterobacteriaceae isolates collected as part of the INFORM study, 2012–2016, to ceftazidime/avibactam and comparator agents.

Organism/antimicrobial agent	MBL-negative isolates					MBL-positive isolates				
	MIC (mg/L)			Susceptibility		MIC (mg/L)			Susceptibility	
	MIC_{50}	MIC_{90}	Range	%S	%R	MIC_{50}	MIC_{90}	Range	%S	%R
Escherichia coli	n = 19 855					n = 24				
Amikacin	2	8	≤0.25 to ≥64	94.2	1.9	8	≥64	1 to ≥64	50.0	41.7
Ceftazidime/avibactam	0.12	0.25	≤0.015 to ≥256	>99.9	<0.1	≥256	≥256	32 to ≥256	0.0	100
Meropenem	0.03	0.06	≤0.004 to ≥16	99.7	0.1	≥16	≥16	0.5 to ≥16	4.2	75.0
Tigecycline	0.25	0.5	≤0.015 to ≥16	99.2	0.2	0.25	1	0.06–2	95.8	0.0
Colistin[a]	[n = 12 355]					[n = 19]				
	0.5	1	≤0.06 to ≥16	99.5	0.5	0.25	1	0.12–1	100	0.0
Klebsiella pneumoniae	n = 16 360					n = 203				
Amikacin	1	8	≤0.25 to ≥64	91.1	6.1	16	≥64	1 to ≥64	36.0	47.3
Ceftazidime/avibactam	0.12	0.5	≤0.015 to ≥256	99.9	0.1	≥256	≥256	2 to ≥256	2.5	97.5
Meropenem	0.06	0.25	≤0.004 to ≥16	93.2	4.9	≥16	≥16	0.25 to ≥16	6.9	79.8
Tigecycline	0.5	2	≤0.015 to ≥16	88.5	3.3	1	2	0.12–8	73.4	5.9
Colistin[a]	[n = 11 362]					[n = 167]				
	0.5	1	≤0.06 to ≥16	96.0	4.0	0.5	2	0.25 to ≥16	91.6	8.4
Klebsiella oxytoca	n = 3251					n = 15				
Amikacin	1	4	≤0.25 to ≥64	98.2	0.8	2	≥64	0.5 to ≥64	66.7	20.0
Ceftazidime/avibactam	0.12	0.25	≤0.015 to 16	99.9	0.1	≥256	≥256	32 to ≥256	0.0	100
Meropenem	0.03	0.06	≤0.004 to ≥16	99.4	0.2	4	≥16	0.25 to ≥16	20.0	40.0
Tigecycline	0.25	0.5	≤0.015 to 4	97.6	0.5	0.5	1	0.12–2	93.3	0.0
Colistin[a]	[n = 2064]					[n = 8]				
	0.5	1	≤0.12 to ≥16	99.4	0.6	0.5	1	0.25–1	100	0.0

$MIC_{50/90}$, MIC required to inhibit the growth of 50% and 90% of isolates, respectively; %S, percentage susceptible; %R, percentage resistant.

[a] Colistin was tested against isolates collected from 2014–2016 only.

agents except colistin and tigecycline compared with non-MBL-positive *E. coli* isolates (Table 3), with only 50.0% of isolates susceptible to amikacin, 4.2% susceptible to meropenem and all 24 (100%) isolates resistant to ceftazidime/avibactam. A high proportion of MBL-positive *E. coli* isolates were susceptible to tigecycline (95.8%) and all 19 MBL-positive *E. coli* collected from 2014–2016 were susceptible to colistin.

3.1.5. Klebsiella *spp*

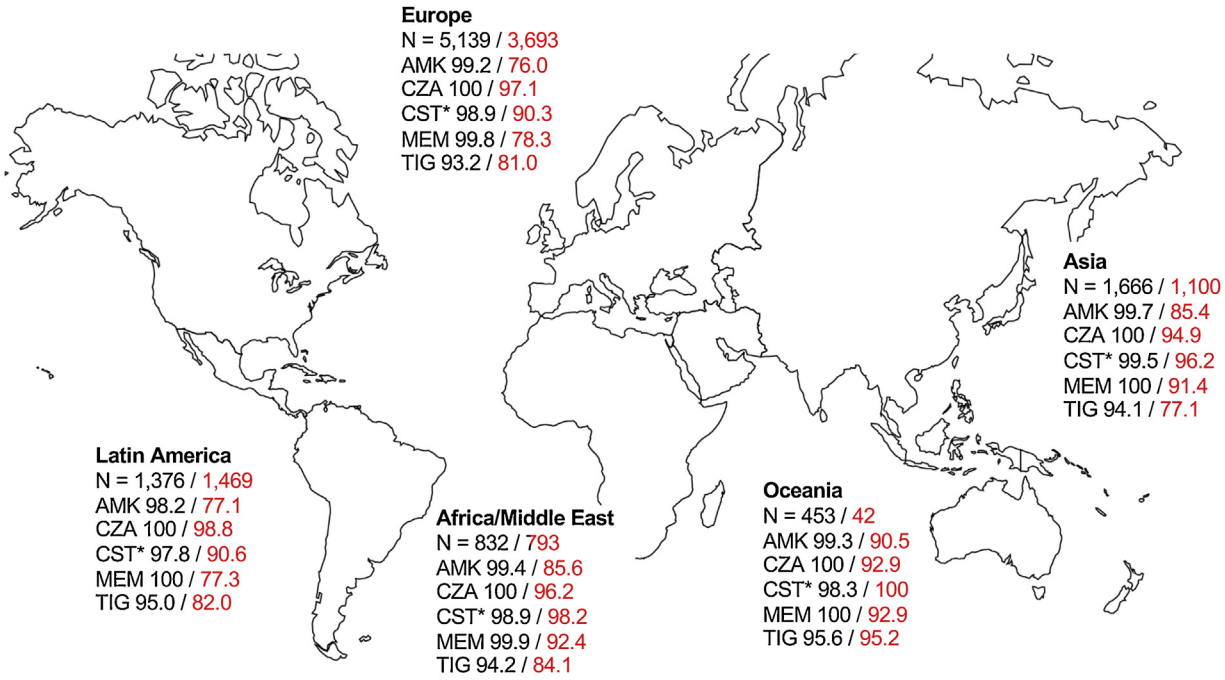
High proportions of the *K. pneumoniae* isolates (n = 16 563) collected in the study were susceptible to ceftazidime/avibactam (98.7%) and colistin (n = 11 529 isolates tested; 96.0%). More than 90% of isolates were susceptible to the carbapenems and amikacin, and 88.3% were susceptible to tigecycline. Susceptibility to TZP was 61.7% and was less than this to all other comparator agents. A large proportion of *K. pneumoniae* isolates were identified as ESBL-positive (n = 7097; 42.8%), and susceptibility to ceftazidime/avibactam (97.0%) and colistin (n = 4908 isolates tested; 92.1%) was similar compared with all *K. pneumoniae* isolates. Among the ESBL-positive isolates, there were reductions in susceptibility to amikacin (78.9%), carbapenems (80.6–82.1%) and tigecycline (81.0%) compared with all *K. pneumoniae* isolates. The MIC_{90} value for tigecycline was 2 mg/L for both sets of isolates, however for amikacin the MIC_{50} increased from 1 mg/L to 4 mg/L and the MIC_{90} increased from 8 mg/L to 32 mg/L for ESBL-positive isolates. The MIC_{50} values for carbapenems were similar for all *K. pneumoniae* isolates and ESBL-positive *K. pneumoniae* isolates, however there was at least a four doubling dilution rise in MIC_{90} values.

Regional susceptibilities of ESBL-positive *K. pneumoniae* and non-ESBL *K. pneumoniae* isolates to amikacin, ceftazidime/avibactam, colistin, meropenem and tigecycline are compared in Fig. 1. In the absence of ESBLs, *K. pneumoniae* isolates showed little regional variation in susceptibility to ceftazidime/avibactam, amikacin, colistin, meropenem and tigecycline. The reduction in susceptibility of ESBL-positive *K. pneumoniae* isolates was most marked in Europe and Latin America, for which there were falls of approximately 20% in susceptibility to amikacin and meropenem and approximately 10% to tigecycline. Rates of susceptibility of ESBL-positive *K. pneumoniae* isolates to ceftazidime/avibactam and colistin were similar across all regions. The decrease in susceptibility to ceftazidime/avibactam and colistin was <10% when comparing susceptibility rates of all *K. pneumoniae* isolates with ESBL-positive isolates, and decreases in susceptibility of 5–10% were observed to colistin in Europe (–8.6%) and Latin America (–7.2%), and susceptibility to ceftazidime/avibactam was reduced in Oceania (–7.1%) and Asia (–5.1%).

A small proportion of *K. pneumoniae* isolates were identified as MBL-positive (n = 203; 1.2%), and the in vitro activity of most agents was reduced compared with their respective activity against non-MBL-positive isolates (Table 3), with MIC_{90} values that were three doubling dilutions or more higher for amikacin, ceftazidime/avibactam and meropenem. The MIC_{90} value for tigecycline was the same against MBL-positive and MBL-negative isolates, however susceptibility was lower against MBL-positive isolates (73.4% vs. 88.5% for MBL-negative isolates). Colistin was the only agent to demonstrate good in vitro activity against MBL-positive *K. pneumoniae*, with 91.6% (n = 167 isolates tested) of isolates susceptible.

A total of 3266 *K. oxytoca* isolates were collected in the study and the majority were susceptible to most agents (Table 2). The highest rates of susceptibility were to ceftazidime/avibactam and colistin (both 99.4%), carbapenems (≥98.7%), amikacin (98.0%) and tigecycline (97.6%). At least 80% of isolates were susceptible to all other agents.

Seven agents retained in vitro activity against *K. oxytoca* isolates that were identified as ESBL-positive (n = 565; 17.3%), which were most susceptible to colistin (n = 359 isolates tested; 99.2%) and ceftazidime/avibactam (96.8%). More than 90% of ESBL-positive



AMK, amikacin; CZA, ceftazidime-avibactam; CST, colistin; MEM, meropenem; TIG, tigecycline.
Values for non-ESBL isolates are in black / values for ESBL isolates are in red
*CST N values: Africa/ Middle East 609 / 546; Asia 1,014 / 676; Europe 3,699 / 2,600; Oceania 292 / 29; Latin America 1,007 / 1,057.

Fig. 1. Comparison of the regional susceptibilities of non-ESBL-positive and ESBL-positive *Klebsiella pneumoniae* isolates collected as part of the INFORM surveillance study, 2012–2016, to ceftazidime/avibactam and selected comparator agents. ESBL, extended-spectrum β-lactamase.

isolates also were susceptible to amikacin, carbapenems and tigecycline, whilst susceptibility to other agents did not exceed 65%.

Only 15 MBL-positive *K. oxytoca* isolates were collected during the study, and 66.7% of these were susceptible to amikacin (Table 3). Susceptibility to meropenem was greatly reduced compared with all *K. oxytoca* isolates with only 20.0% of isolates susceptible, and all MBL-positive isolates were resistant to ceftazidime/avibactam. All MBL-positive *K. oxytoca* isolates collected from 2014–2016 (n = 8 isolates tested) were susceptible to colistin.

3.1.6. Serratia marcescens

Almost all of the *S. marcescens* isolates collected in this study (n = 1363) were susceptible to ceftazidime/avibactam (99.3%), meropenem (98.5%), doripenem (98.3%) and imipenem (97.2%). Susceptibility was 94.0% to amikacin and 90.1% to cefepime and TZP.

3.1.7. Other Enterobacteriaceae

The collection of isolates belonging to other Enterobacteriaceae (n = 8088) (Table 2) were highly susceptible to meropenem (99.6%), ceftazidime/avibactam (99.5%), doripenem (98.6%) and TZP (97.5%). Susceptibility was >90% to three further agents (amikacin, aztreonam and cefepime) and were 89.1% to ceftazidime, whilst susceptibility was lower to imipenem (68.1%) compared with the two other carbapenems on the INFORM panel. The in vitro activity of colistin ($MIC_{50/90}$, ≥16 mg/L) was much reduced amongst this collection of other Enterobacteriaceae (n = 5120 isolates tested), which included species with intrinsic resistance to colistin, such as Morganella morganii and Proteus spp., and just 5.5% of isolates were susceptible.

3.2. Distribution of extended-spectrum β-lactamase and metallo-β-lactamase phenotypes

Isolates of three species (*E. coli*, *K. pneumoniae* and *K. oxytoca*; n = 39 708) were screened for ESBLs (n = 13 336; 33.6%) and MBLs (n = 242; 0.6%). Almost one-half of ESBL-positive isolates were collected from centres in Europe (47.2%), and regions with the highest proportion of ESBL-positive isolates were Latin America (41.8%) and Asia (40.2%) (Fig. 2). Centres from Europe also contributed almost one-half of MBL-positive isolates (49.2%) collected in the study (Fig. 3), followed by Asia (25.6%) and Africa/Middle East (14.5%), with the lowest proportion of MBL-positive isolates collected in Latin America (8.7%) and Oceania (2.1%).

4. Discussion

In this study, Enterobacteriaceae collected from centres based in all reported regions were highly susceptible to ceftazidime/avibactam across all species (≥98.4% susceptible, MIC_{90} ≤1 mg/L). The only other agent on the panel of comparators to offer similar activity was colistin (although it should be noted that this agent is not active against intrinsically resistant organisms such as *S. marcescens*), whilst carbapenems such as meropenem demonstrated consistent in vitro activity, with the majority (>90%) of

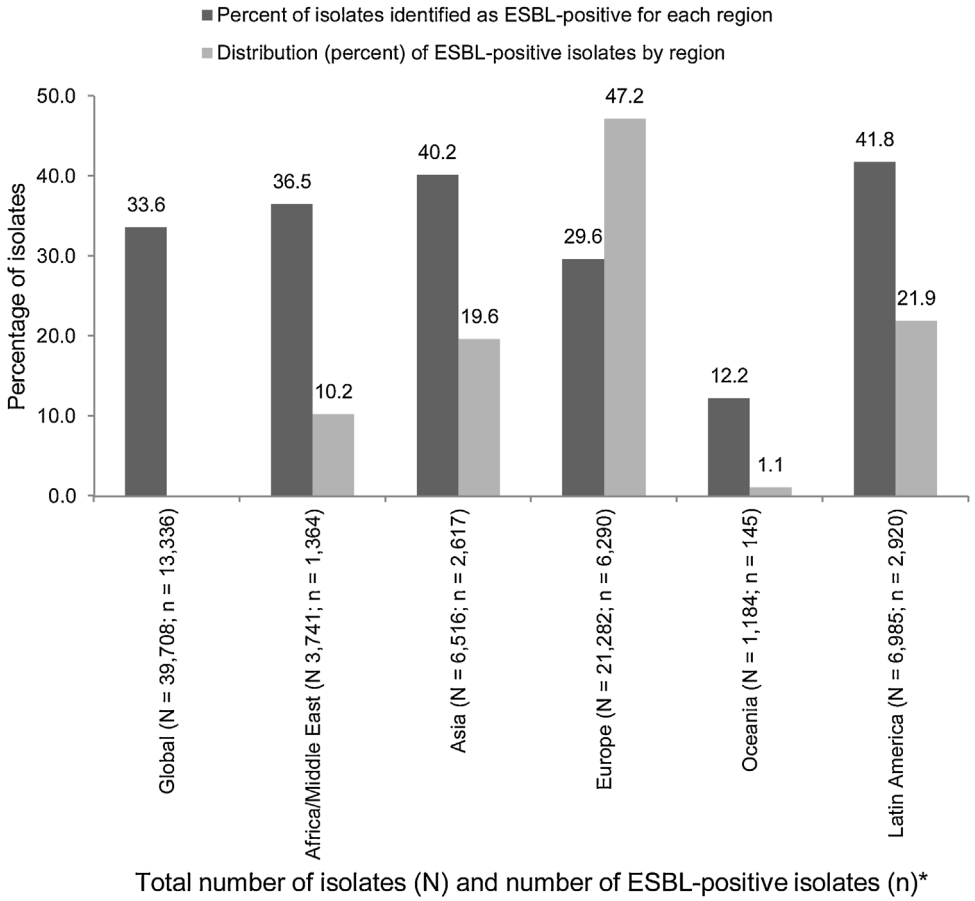


Fig. 2. Percent and regional distribution of *Escherichia coli*, *Klebsiella pneumoniae* and *Klebsiella oxytoca* isolates collected as part of the INFORM surveillance study, 2012–2016, that were identified as extended-spectrum β-lactamase (ESBL)-positive.
*Excludes colistin, which was tested against isolates from 2014 and 2016 only.

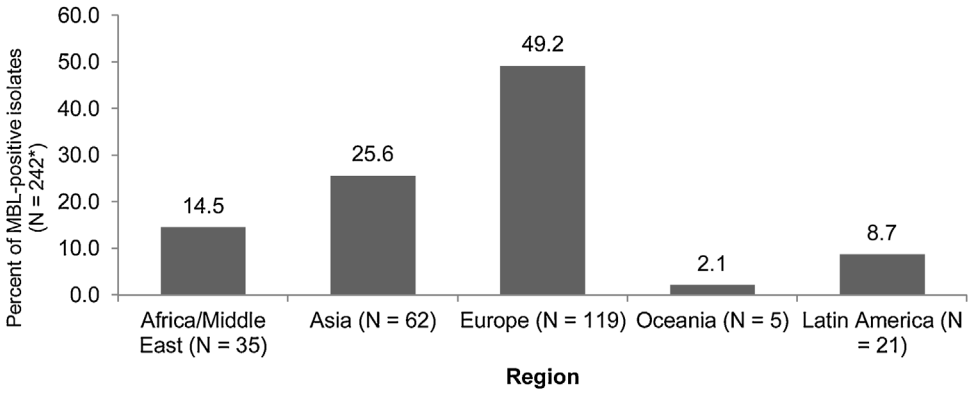


Fig. 3. Number (%) of metallo-β-lactamase (MBL)-positive isolates collected from regions participating in the INFORM study, 2012–2016.
*Excludes colistin, which was tested against isolates collected from 2014 to 2016 only.

isolates being susceptible. Amikacin and tigecycline were also active against the majority of isolates collected in this study.

Surveillance data of ceftazidime/avibactam from this study are consistent with two previous INFORM studies that collected Enterobacteriaceae isolates between 2012 and 2015 from centres in the Asia-Pacific [18] and Europe [20], both of which observed >99% susceptibility to ceftazidime/avibactam using the FDA breakpoint of ≤8 mg/L. Consistent in vitro activity against Enterobacteriaceae isolates has also been reported from microbiological analysis of ceftazidime/avibactam from Phase 3 clinical trials [26–28]. The REPRISE study enrolled patients with complicated urinary tract infections (cUTIs) or complicated intra-abdominal infections caused by ceftazidime-not susceptible Gram-negative pathogens, and the MIC_{90} value of 1 mg/L for ceftazidime/avibactam against 341 Enterobacteriaceae isolates [26] is consistent with findings from the current INFORM surveillance study. A further two Phase 3 studies (RECAPTURE 1 & 2) enrolled patients with cUTIs due to Gram-negative organisms, and ceftazidime/avibactam was highly active against the 799 isolates of Enterobacteriaceae, including 154 ceftazidime-not susceptible isolates, with an MIC_{90} value of 0.5 mg/L [27]. Microbiological analysis of 317 Enterobacteriaceae isolates collected from patients with nosocomial pneumonia enrolled into the Phase 3 REPROVE study also found a ceftazidime/avibactam MIC_{90} of 0.5 mg/L [28], similar to the MIC_{90} values observed in the current INFORM study.

With the exception of colistin, comparator agents in the current INFORM study did not demonstrate the same level of consistent in vitro activity against Enterobacteriaceae, underlining the difficulty that physicians can face in selecting appropriate antimicrobial treatment for patients. The in vitro activity of another cephalosporin/inhibitor combination (ceftolozane/tazobactam) has been compared with ceftazidime/avibactam in the SMART surveillance study in Taiwan [29], in which almost all isolates (≥99.1%) were susceptible to ceftazidime/avibactam whilst fewer were susceptible to ceftolozane/tazobactam (*E. coli* 94.3%; *K. pneumoniae* 84.1%). Potent in vitro activity of ceftazidime/avibactam was also reported by Yin et al. in a multicentre study in China [30], in which 94.6% of 1774 Enterobacteriaceae isolates were susceptible to ceftazidime/avibactam and 90.5% of *E. coli* and 93.8% of *P. mirabilis* isolates were susceptible to ceftolozane/tazobactam. A further surveillance study of the in vitro activity of ceftolozane/tazobactam amongst 8341 Enterobacteriaceae collected from European hospitals during 2011 and 2012 reported inhibition of 95.2% of isolates at ≤8 mg/L [31].

Infections caused by ESBL-positive phenotypes pose a serious threat to the health of patients, and agents that inhibit β-lactamases offer improved treatment options for resistant strains of Enterobacteriaceae [1,3,5–10,32]. In the current INFORM study, the in vitro activity of ceftazidime/avibactam was retained against ESBL-positive isolates, demonstrated by MIC_{90} values against ESBL-positive *E. coli*, *K. oxytoca* and *K. pneumoniae* of 0.5, 1 and 2 mg/L, respectively, values that were at least two doubling dilutions below the EUCAST breakpoint of 8 mg/L. The SMART study in Taiwan reported by Jean et al. revealed a notable difference in non-susceptibility of ESBL-positive isolates of *E. coli* and *K. pneumoniae* to ceftazidime/avibactam (0% and 3.3%, respectively) and ceftolozane/tazobactam (27.7% and 80.4%, respectively) [29]. A difference in susceptibility rates was also reported by Yin et al. in their multicentre study in China, which observed that amongst carbapenem-resistant Enterobacteriaceae (CRE) strains, 28.6% of *E. coli* isolates were susceptible to ceftazidime/avibactam and 7.1% to ceftolozane/tazobactam versus 85.5% and 1.9% of CRE strains of *K. pneumoniae* [30]. Further data from the surveillance study of isolates collected in Europe by Sader et al. [31] showed good in vitro activity of ceftolozane/tazobactam (MIC_{90}, >32 mg/L, 73.6% inhibition) against ESBL-positive *K. pneumoniae* isolates that were susceptible to meropenem, and inhibition of 93.1% of ESBL-positive *E. coli* isolates. However, this combination was inactive against meropenem-not susceptible *K. pneumoniae* isolates, suggesting reduced potency of ceftolozane/tazobactam against carbapenemases [31]. A recent study of ceftolozane/tazobactam against 2647 Enterobacteriaceae from hospitalised patients with bloodstream infections in the USA from 2013–2015 noted that 95.5% of isolates were susceptible, and whilst most ESBL-positive non-CRE phenotype isolates were susceptible to ceftolozane/tazobactam (87.1%), the authors noted that no useful antimicrobial activity was observed against CRE strains [33]. A small study comparing the in vitro activities of ceftolozane/tazobactam and ceftazidime/avibactam against 120 multidrug-resistant *E. coli* and *K. pneumoniae* isolates collected from patients admitted to hospital in Abu Dhabi, United Arab Emirates, reported that 28 of 29 ESBL-positive isolates were susceptible to ceftolozane/tazobactam (MIC_{90}, 1 mg/L) and all to ceftazidime/avibactam (MIC_{90}, 0.38 mg/L) [34]. Against 60 carbapenem-resistant isolates, 45% were susceptible to ceftazidime/avibactam and 10% to ceftolozane/tazobactam; 55% of these isolates were identified as NDM-1-positive and would be expected to be resistant to ceftazidime/avibactam.

Recently published surveillance data suggest that innovative antibiotic/inhibitor combinations offer potent in vitro activity against Enterobacteriaceae. High rates of susceptibility to imipenem/relebactam (≥94.8%) amongst Enterobacteriaceae collected in Europe [19] and to meropenem/vaborbactam (99.6%) in a worldwide SENTRY study using a breakpoint of ≤8 mg/L have been observed [35]. The MIC_{90} of meropenem/vaborbactam against a panel of 991 KPC-positive Enterobacteriaceae clinical isolates collected globally during 2014–2015 was 1 mg/L (lowered from

>32 mg/L for meropenem alone), and 99.0% of isolates were susceptible [36]; 79.6% of 265 CRE isolates from the SENTRY study were inhibited by meropenem/vaborbactam at 8 mg/L [35].

The activity of ceftazidime/avibactam against Ambler class A and C β-lactamases as well as some class D β-lactamases is likely to account for the high susceptibility rates seen in the current study [11–13]. In addition to ceftazidime/avibactam, a high proportion of ESBL-positive isolates (95.2%) were susceptible to colistin, although a slightly lower proportion of ESBL-positive *K. pneumoniae* (92.1%) isolates were susceptible to colistin compared with ESBL-positive *E. coli* and *K. oxytoca* (both 99.2%). A pattern of reduced susceptibility of approximately 10% was observed to amikacin, carbapenems and tigecycline amongst ESBL-positive *K. pneumoniae* isolates compared with all *K. pneumoniae* isolates. Ceftazidime/avibactam is not active against MBLs [12,13] and this was confirmed in the current study by the finding of nearly all MBL-positive isolates (237/242) displaying resistance in vitro to ceftazidime/avibactam. Colistin was the sole agent to which MBL-positive isolates were highly susceptible (92.8%) and a majority of isolates were susceptible to tigecycline (76.9%).

The INFORM study is not prevalence-based and so the proportion of ESBL and MBL phenotype isolates amongst *E. coli* and *Klebsiella* cannot be viewed as an estimate of prevalence. However, we note that in the current INFORM study, *K. pneumoniae* isolates comprised the highest proportion of isolates identified as ESBL-positive. The ESBL-positive phenotype depressed susceptibility rates to amikacin, meropenem and tigecycline in Europe and Latin America compared with non-ESBL *K. pneumoniae* isolates (Fig. 1), whilst susceptibility to ceftazidime/avibactam and colistin was either similar between the two sets of isolates or was only slightly reduced amongst ESBL-positive *K. pneumoniae*. The relatively low proportion of MBL-positive isolates (<1%) identified amongst the large sample of Enterobacteriaceae in this study was similar to that reported by Castanheira et al. (0.4%; $n = 41$) in the SENTRY study [35]. The relatively low number of MBL-positive isolates in the INFORM study had a minimal impact on global susceptibility to ceftazidime/avibactam, and although in the SENTRY study the meropenem/vaborbactam combination showed no improved in vitro activity against MBL-positive isolates compared with meropenem ($MIC_{50/90}$, 32/>32 mg/L) this did not severely affect the overall susceptibility rate of Enterobacteriaceae to meropenem/vaborbactam [35].

In the current INFORM study, ESBL-positive isolates were highly susceptible to ceftazidime/avibactam and colistin, however they were also associated with reduced susceptibility to other key agents on the panel. Despite this, it is important to note that this may not necessarily directly correlate with increased risk of clinical failure, and local patterns of antimicrobial resistance regarding resistant phenotypes, corresponding resistance mechanisms and their impact on MICs should always be considered [37]. Based on data reported in the current study, both ceftazidime/avibactam and colistin are likely to be consistently effective treatment options for infections caused by organisms belonging to the family Enterobacteriaceae. Meropenem, tigecycline and amikacin also offered consistent in vitro activity against a large majority of isolates. Regular local monitoring of in vitro antibiotic activity is required to identify clinically important changes in resistance profiles amongst Enterobacteriaceae, with the aim of informing appropriate use of antibiotics.

5. Conclusions

Here we report that ceftazidime/avibactam showed potent in vitro activity against isolates of Enterobacteriaceae, including ESBL-positive phenotypes (but not MBL-positive isolates), collected globally from 2012–2016. Enterobacteriaceae isolates were also highly susceptible to the comparator agents colistin, meropenem, amikacin and meropenem, although MBL-positive isolates were only susceptible to colistin. The data presented in the current study should provide guidance to identifying appropriate treatment options for infections caused by Enterobacteriaceae, particularly resistant strains, when therapeutic options are limited.

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Competing interests

GGS is a shareholder and employee of Pfizer, Inc. ER declares no competing interests.

Ethical approval

Not required.

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