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Activity of ceftolozane-tazobactam and comparators when tested against Gram-negative isolates collected from paediatric patients in the USA and Europe between 2012 and 2016 as part of a global surveillance programme

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ABSTRACT

Ceftolozane-tazobactam is a combination of an antipseudomonal cephalosporin and a β-lactamase inhibitor. Ceftolozane-tazobactam was approved by the US Food and Drug Administration in 2014 and by the European Medicines Agency in 2015 for use in adults to treat complicated urinary tract infections, acute pyelonephritis, and complicated intra-abdominal infections with metronidazole. Studies for paediatric indications are planned. The Programme to Assess Ceftolozane-Tazobactam Susceptibility monitors the resistance of ceftolozane-tazobactam to Gram-negative isolates worldwide. In total, 6240 Gram-negative isolates were collected between 2012 and 2016 from paediatric patients (<18 years old) in 31 US hospitals (4207 isolates) and 48 European hospitals (2033 isolates), and tested for susceptibility (S) to ceftolozane-tazobactam by broth microdilution. Other antibiotics tested included amikacin, colistin and meropenem. The most common infection type in hospitalized paediatric patients was pneumonia (n=2018), followed by urinary tract infection (n=1569) and bloodstream infection (n=1236). In total, 4316 Enterobacteriaceae and 1765 non-enterics were isolated. The most common species were *Escherichia coli* (n=1919), *Pseudomonas aeruginosa* (n=1236) and *Klebsiella pneumoniae* (n=709). In all regions, the three most active antimicrobials against paediatric Enterobacteriaceae isolates were amikacin (99.0%S), meropenem (98.9%S) and ceftolozane-tazobactam (94.6%S). For all *P. aeruginosa*, colistin (98.9%S) and ceftolozane-tazobactam (97.4%S) were the most active. In conclusion, for all Enterobacteriaceae, ceftolozane-tazobactam was the most potent cephalosporin tested, with only meropenem and colistin having higher susceptibility rates. For *P. aeruginosa*, ceftolozane-tazobactam was the most potent β-lactam and had a similar susceptibility rate to colistin.

1. Introduction

Antibiotic resistance is a continuing problem in the treatment of adult and paediatric infections. More recently, multi-drug-resistant (resistant to at least three classes of agents) Gram-negative bacilli have become increasingly prevalent in hospitals [1]. Furthermore, multi-drug-resistant pathogens such as *Pseudomonas aeruginosa*, carbapenem-resistant Enterobacteriaceae (CRE) and extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae are increasingly common in children as well as adults [1,2]. Due to the relative lack of new antimicrobials to treat these infections, particularly agents approved for use in children, empirical therapy is often ineffective and requires the use of combinations of antibacterial agents to achieve optimal coverage [3,4]. Differences between adult and paediatric isolate susceptibilities are not well described as all ages are typically grouped together in surveillance studies and hospital antibiograms [5].

Ceftolozane-tazobactam is a combination of an antipseudomonal cephalosporin and a β-lactamase inhibitor, with activity against antibiotic-resistant *P. aeruginosa* and other common Gram-negative bacilli, including most ESBL-producing Enterobacteriaceae strains [6,7]. Ceftolozane-tazobactam has limited activity against *Acinetobacter* spp., *Stenotrophomonas maltophilia*, Gram-positive cocci, organisms producing carbapenemases or metallo-β-lactamases, and de-repressed AmpC β-lactamases found in Enterobacteriaceae. Ceftolozane-tazobactam has been approved in over 60 countries to treat complicated intra-abdominal infections in combination with metronidazole, and complicated urinary tract infections in adults [8]. Ceftolozane-tazobactam paediatric

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Table 1
Antimicrobial activity of ceftolozane-tazobactam tested against the main organisms and organism groups of isolates from the USA.

Organism/organism group (no. of isolates)	No. and cumulative % of isolates at MIC (mg/L) of:													MIC_{50}	MIC_{90}
	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>[a]		
Enterobacteriaceae (2969)	0	1	34	1006	1126	510	120	**55**	41	45	16	6	9	0.25	0.5
	0.0	<0.1	1.2	35.1	73.0	90.2	94.2	**96.1**	97.4	99.0	99.5	99.7	100.0		
CRE (7)					0	1	0	**1**	0	3	1	0	1	8	N/A
					0.0	14.3	14.3	**28.6**	28.6	71.4	85.7	85.7	100.0		
ESBL, non-CRE (178)			0	13	50	63	19	**16**	9	4	2	0	2	0.5	2
			0.0	7.3	35.4	70.8	81.5	**90.4**	95.5	97.8	98.9	98.9	100.0		
Escherichia coli (1311)		0	28	665	505	87	11	**5**	4	3	1	0	2	0.12	0.25
		0.0	2.1	52.9	91.4	98.0	98.9	**99.2**	99.5	99.8	99.8	99.8	100.0		
ESBL, non-CRE (119)			0	12	39	45	10	**4**	4	2	1	0	2	0.5	2
			0.0	10.1	42.9	80.7	89.1	**92.4**	95.8	97.5	98.3	98.3	100.0		
Klebsiella pneumoniae (429)			0	117	188	79	26	**10**	3	3	2	0	1	0.25	1
			0.0	27.3	71.1	89.5	95.6	**97.9**	98.6	99.3	99.8	99.8	100.0		
ESBL, non-CRE (44)				0	10	14	5	**9**	3	2	1			0.5	4
				0.0	22.7	54.5	65.9	**86.4**	93.2	97.7	100.0				
Pseudomonas aeruginosa (823)		0	1	3	91	513	153	40	**18**	2	1	0	1	0.5	1
		0.0	0.1	0.5	11.5	73.9	92.5	97.3	**99.5**	99.8	99.9	99.9	100.0		
Ceftazidime-non-susceptible (MIC ≥16 mg/L) (60)					0	5	10	25	**16**	2	1	0	1	2	4
					0.0	8.3	25.0	66.7	**93.3**	96.7	98.3	98.3	100.0		
Meropenem-non-susceptible (MIC ≥4 mg/L) (64)				0	1	26	18	11	**5**	2	1			1	4
				0.0	1.6	42.2	70.3	87.5	**95.3**	98.4	100.0				
Cefepime-non-susceptible (MIC >2 mg/L) (48)					0	1	6	21	**16**	2	1	0	1	2	4
					0.0	2.1	14.6	58.3	**91.7**	95.8	97.9	97.9	100.0		
Piperacillin-tazobactam-non-susceptible (MIC >16 mg/L) (76)					0	10	23	24	**16**	2	0	0	1	2	4
					0.0	13.2	43.4	75.0	**96.1**	98.7	98.7	98.7	100.0		
β-lactam-non-susceptible (12)							0	5	**5**	2				4	8
							0.0	41.7	**83.3**	100.0					

CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase; MIC, minimal inhibitory concentration.
[a] Greater than the highest dilution tested.Food and Drug Administration/Clinical Laboratory Standards Institute susceptible breakpoint indicated in bold [13].

Table 2
Antimicrobial activity of ceftolozane-tazobactam tested against the main organisms and organism groups of isolates from Europe.

Organism/organism group (no. of isolates)	No. and cumulative % of isolates at MIC (mg/L) of:												MIC_{50}	MIC_{90}
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>[a]		
Enterobacteriaceae (1347)	0	15	340	492	256	**101**	27	30	25	14	10	37	0.25	2
	0.0	1.1	26.4	62.9	81.9	**89.4**	91.4	93.6	95.5	96.5	97.3	100.0		
CRE (35)					0	**2**	2	1	3	2	3	22	>32	>32
					0.0	**5.7**	11.4	14.3	22.9	28.6	37.1	100.0		
ESBL, non-CRE (257)		0	3	51	88	**55**	13	14	10	5	5	13	0.5	8
		0.0	1.2	21.0	55.3	**76.7**	81.7	87.2	91.1	93.0	94.9	100.0		
Escherichia coli (608)	0	6	236	256	62	**29**	4	5	2	1	1	6	0.25	0.5
	0.	1.0	39.8	81.9	92.1	**96.9**	97.5	98.4	98.7	98.8	99.0	100.0		
ESBL, non-CRE (131)		0	3	36	46	**29**	3	5	2	1	1	5	0.5	4
		0.0	2.3	29.8	64.9	**87.0**	89.3	93.1	94.7	95.4	96.2	100.0		
Klebsiella pneumoniae (280)	0	3	33	96	65	**27**	10	9	6	4	7	20	0.5	16
	0.0	1.1	12.9	47.1	70.4	**80.0**	83.6	86.8	88.9	90.4	92.9	100.0		
ESBL, non-CRE (113)			0	15	40	**21**	9	8	6	3	4	7	1	16
			0.0	13.3	48.7	**67.3**	75.2	82.3	87.6	90.3	93.8	100.0		
Pseudomonas aeruginosa (413)		0	2	23	229	91	21	**19**	7	5	3	13	0.5	4
		0.0	0.5	6.1	61.5	83.5	88.6	**93.2**	94.9	96.1	96.9	100.0		
Ceftazidime-non-susceptible (MIC ≥16 mg/L) (79)				0	1	18	15	**18**	6	5	3	13	4	>32
				0.0	1.3	24.1	43.0	**65.8**	73.4	79.7	83.5	100.0		
Meropenem-non-susceptible (MIC ≥4 mg/L) (95)				0	22	23	11	**13**	7	4	3	12	2	>32
				0.0	23.2	47.4	58.9	**72.6**	80.0	84.2	87.4	100.0		
Cefepime-non-susceptible (MIC >2 mg/L) (66)					0	8	13	**18**	7	5	3	12	4	>32
					0.0	12.1	31.8	**59.1**	69.7	77.3	81.8	100.0		
Piperacillin-tazobactam-non-susceptible (MIC >16 mg/L) (89)			0	1	5	22	16	**17**	7	5	3	13	4	>32
			0.0	1.1	6.7	31.5	49.4	**68.5**	76.4	82.0	85.4	100.0		
β-lactam-non-susceptible (43)					0	4	4	**11**	6	4	3	11	8	>32
					0.0	9.3	18.6	**44.2**	58.1	67.4	74.4	100.0		

CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase; MIC, minimal inhibitory concentration.
[a] Greater than the highest dilution tested.European Committee on Antimicrobial Susceptibility Testing 2017 susceptible breakpoint indicated in bold [14].

Table 3
Activity of ceftolozane-tazobactam and comparator antimicrobial agents tested against 3792 Enterobacteriaceae and *Pseudomonas aeruginosa* isolates from paediatric patients in the USA.

Organism/organism group Antimicrobial agent	MIC_{50}	MIC_{90}	CLSI[a]			EUCAST[a]		
	(mg/L)		%S	%I	%R	%S	%I	%R
Enterobacteriaceae (*n*=2969)								
Ceftolozane-tazobactam	0.25	0.5	96.1	1.4	2.6	94.2		5.8
Amikacin	2	4	99.8	0.1	0.1	99.4	0.4	0.2
Cefepime	≤0.5	≤0.5	95.2	1.7[b]	3.0	93.5	2.7	3.8
Ceftazidime	0.12	2	91.0	1.0	7.9	89.5	1.5	9.0
Ceftriaxone	≤0.06	8	87.8	1.0	11.2	87.8	1.0	11.2
Colistin	≤0.5	>8				81.9		18.1
Levofloxacin	≤0.12	0.5	92.9	0.6	6.5	90.5	1.7	7.8
Meropenem	≤0.06	≤0.06	99.7	0.2	0.2	99.8	0.1	0.1
Piperacillin-tazobactam	2	8	94.0	3.5	2.5	91.7	2.3	6.0
Escherichia coli (*n*=1311)								
Ceftolozane-tazobactam	0.12	0.25	99.2	0.3	0.5	98.9		1.1
Amikacin	2	4	99.7	0.2	0.1	99.1	0.6	0.3
Cefepime	≤0.5	≤0.5	94.0	1.2[b]	4.7	93.4	1.4	5.2
Ceftazidime	0.12	0.5	93.8	1.0	5.2	91.8	2.0	6.2
Ceftriaxone	≤0.06	0.25	91.2	0.2	8.6	91.2	0.2	8.6
Colistin	≤0.5	≤0.5				99.8		0.2
Levofloxacin	≤0.12	>4	86.2	0.7	13.1	84.7	1.2	14.1
Meropenem	≤0.06	≤0.06	99.8	0.2	0.0	100.0	0.0	0.0
Piperacillin-tazobactam	2	4	96.9	1.8	1.3	95.5	1.5	3.1
Klebsiella pneumoniae (*n*=429)								
Ceftolozane-tazobactam	0.25	1	97.9	0.7	1.4	95.6		4.4
Amikacin	1	2	99.8	0.2	0	99.5	0.2	0.2
Cefepime	≤0.5	≤0.5	92.3	3.0[b]	4.7	91.4	1.6	7
Ceftazidime	0.12	2	90.9	1.9	7.2	90	0.9	9.1
Ceftriaxone	≤0.06	1	90.4	0.5	9.1	90.4	0.5	9.1
Colistin	≤0.5	≤0.5				98.8		1.2
Levofloxacin	≤0.12	0.5	98.1	0.5	1.4	94.9	2.8	2.3
Meropenem	≤0.06	≤0.06	98.8	0.2	0.9	99.1	0.5	0.5
Piperacillin-tazobactam	4	16	95.3	2.1	2.6	89.7	5.6	4.7
Pseudomonas aeruginosa (*n*=823)								
Ceftolozane-tazobactam	0.5	1	99.5	0.2	0.2	99.5		0.5
Amikacin	4	8	97.1	1.3	1.6	93.7	3.4	2.9
Cefepime	2	8	94.2	4.4	1.5	94.2		5.8
Ceftazidime	2	8	92.7	2.6	4.7	92.7		7.3
Ceftriaxone	>8	>8						
Colistin	1	2	99.3		0.7	99.3		0.7
Levofloxacin	0.5	2	90.4	3.9	5.7	83		17
Meropenem	0.25	2	92.2	4.0	3.8	92.2	6.3	1.5
Piperacillin-tazobactam	4	16	90.8	4.4	4.9	90.8		9.2

MIC, minimal inhibitory concentration; CLSI, Clinical Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; S, susceptible; I, intermediate; R, resistant.

[a] Criteria as published by CLSI and EUCAST [13,14].

[b] Intermediate interpreted as susceptible-dose dependent.Organisms include: *Citrobacter amalonaticus* (3), *C. braakii* (10), *C. farmeri* (2), *C. freundii* (54), *C. freundii* species complex (12), *C. koseri* (24), *C. youngae* (4), *Enterobacter aerogenes* (88), *E. asburiae* (14), *E. cloacae* (259), *E. cloacae* species complex (101), *E. intermedius* (1), *Escherichia coli* (1,311), *E. hermannii* (1), *E. vulneris* (1), Gram-negative rods in the family Enterobacteriaceae (1), *Hafnia alvei* (1), *Klebsiella oxytoca* (178), *K. pneumoniae* (429), *K. variicola* (2), *Kluyvera ascorbata* (2), *Kosakonia cowanii* (2), *Leclercia adecarboxylata* (1), *Morganella morganii* (50), *Pantoea agglomerans* (5), *P. dispersa* (1), *Pluralibacter gergoviae* (3), *Proteus mirabilis* (98), *P. vulgaris* (11), *Providencia rettgeri* (13), *P. stuartii* (3), *Raoultella ornithinolytica* (3), *R. planticola* (1), *Serratia liquefaciens* (5), *S. marcescens* (264), *Shigella sonnei* (1), unspeciated *Citrobacter* spp. (1), unspeciated *Enterobacter* spp. (1), unspeciated *Pantoea* spp. (5), unspeciated *Raoultella* spp. (2) and unspeciated *Serratia* spp. (1).

trials for these indications are in progress (NCT03230838 and NCT03217136).

The Programme to Assess Ceftolozane-Tazobactam Susceptibility has monitored predominant pathogens and antimicrobial resistance patterns in hospitals as part of the global SENTRY Antimicrobial Surveillance Programme since 2011. The present study investigated the susceptibilities of ceftolozane-tazobactam and comparators when tested against isolates from paediatric patients. From 2012 to 2016, isolates were collected from paediatric patients (<18 years old) hospitalized with various types of infection in hospitals in the USA and Europe.

2. Materials and methods

2.1. Bacterial isolates

An analysis was performed on 6240 Gram-negative isolates collected from 2012 to 2016 prospectively from patients aged <18 years in 31 US (4207 isolates) and 48 European medical centres in 22 countries (2033 isolates) [9,10]. The number of participating centres in each country varied between one and eight. Participating centres submitted clinical bacterial isolates (one isolate per patient per infection episode) that were collected consecutively by infection type according to a common protocol that has been described previously [11]. Each institution contributed 250 isolates per year with approximately 50 consecutive isolates per target infection type (bloodstream infections, community-acquired respiratory tract infections, pneumonia in hospitalized patients, skin and skin structure infections, intra-abdominal infections and urinary tract infections). Only isolates which were determined to be significant by local criteria and reported as the probable cause of infection were submitted. Isolates included in this study were from all infection types. Isolates were identified at each medical centre and were confirmed by the central laboratory (JMI Laboratories, North Liberty, IA, USA) using matrix-assisted laser desorption ionization

Table 4
Activity of ceftolozane-tazobactam and comparator antimicrobial agents tested against 1760 Enterobacteriaceae and *Pseudomonas aeruginosa* isolates from paediatric patients in Europe.

Organism/organism group Antimicrobial agent	MIC_{50}	MIC_{90}	CLSI[a]			EUCAST[a]		
	(mg/L)		%S	%I	%R	%S	%I	%R
Enterobacteriaceae (*n*=1347)								
Ceftolozane-tazobactam	0.25	2	91.4	2.2	6.4	89.4		10.6
Amikacin	2	4	97.2	1.0	1.9	95.9	1.3	2.8
Cefepime	≤0.5	>16	79.0	3.8[b]	17.2	76.8	4.2	19
Ceftazidime	0.25	32	78.5	3.0	18.6	74.4	4.1	21.5
Ceftriaxone	≤0.06	>8	72.2	0.9	26.9	72.2	0.9	26.9
Colistin	≤0.5	>8				85.7		14.3
Levofloxacin	≤0.12	>4	88.0	1.7	10.3	83.0	3.9	13.1
Meropenem	≤0.06	≤0.06	97.3	0.7	2.0	98.0	0.9	1.1
Piperacillin-tazobactam	2	64	86.2	4.7	9.1	82.8	3.4	13.8
Escherichia coli (*n*=608)								
Ceftolozane-tazobactam	0.25	0.5	97.5	0.8	1.6	96.9		3.1
Amikacin	2	4	99.2	0.7	0.2	97.9	1.3	0.8
Cefepime	≤0.5	>16	81.7	3.5[b]	14.8	80.3	2.8	16.9
Ceftazidime	0.12	16	86	2.5	11.5	80.4	5.6	14
Ceftriaxone	≤0.06	>8	78.9	0.2	20.9	78.9	0.2	20.9
Colistin	≤0.5	≤0.5				100		0.0
Levofloxacin	≤0.12	>4	82.0	2.0	16.0	80.0	1.7	18.3
Meropenem	≤0.06	≤0.06	99.7	0.2	0.2	99.8	0.2	0
Piperacillin-tazobactam	2	16	90.8	3.1	6.1	87.7	3.1	9.2
Klebsiella pneumoniae (*n*=280)								
Ceftolozane-tazobactam	0.5	16	83.6	3.2	13.2	80.0		20.0
Amikacin	1	16	91.1	2.1	6.8	88.9	2.1	8.9
Cefepime	≤0.5	>16	55.0	5.0[b]	40.0	53.9	3.2	42.9
Ceftazidime	0.5	>32	58.9	6.1	35	56.1	2.9	41.1
Ceftriaxone	0.25	>8	52.5	1.4	46.1	52.5	1.4	46.1
Colistin	≤0.5	1				97.1		2.9
Levofloxacin	≤0.12	>4	84.5	3.6	11.9	75.1	7.9	17
Meropenem	≤0.06	1	91.8	1.8	6.5	93.5	1.8	4.7
Piperacillin-tazobactam	4	>64	76.3	6.5	17.3	70.9	5.4	23.7
Pseudomonas aeruginosa (*n*=413)								
Ceftolozane-tazobactam	0.5	4	93.2	1.7	5.1	93.2		6.8
Amikacin	4	32	89.6	4.4	6.1	85.5	4.1	10.4
Cefepime	2	16	84.0	8.7	7.3	84.0		16.0
Ceftazidime	2	32	80.9	3.9	15.3	80.9		19.1
Ceftriaxone	>8	>8						
Colistin	1	2	98.3		1.7	98.3		1.7
Levofloxacin	0.5	>4	80.1	3.9	16	71.1		28.9
Meropenem	0.5	>8	77.0	5.6	17.4	77.0	12.3	10.7
Piperacillin-tazobactam	4	>64	78.5	9.0	12.6	78.5		21.5

MIC, minimal inhibitory concentration; S, susceptible; I, intermediate; R, resistant.
[a] Criteria as published by Clinical Laboratory Standards Institute and European Committee on Antimicrobial Susceptibility Testing [12,14].
[b] Intermediate interpreted as susceptible-dose dependent.Organisms include: *Citrobacter braakii* (1), *C. freundii* (14), *C. freundii* species complex (8), *C. koseri* (21), *Enterobacter aerogenes* (21), *E. asburiae* (4), *E. cloacae* (96), *E. cloacae* species complex (30), *Escherichia coli* (608), *Hafnia alvei* (2), *Klebsiella oxytoca* (88), *K. pneumoniae* (280), *Leclercia adecarboxylata* (1), *Morganella morganii* (25), *Pantoea agglomerans* (2), *Pluralibacter gergoviae* (1), *Proteus mirabilis* (51), *P. penneri* (1), *P. vulgaris* (10), *Providencia rettgeri* (4), *Raoultella ornithinolytica* (1), *Serratia liquefaciens* (6), *S. marcescens* (69) and unspeciated *Raoultella* spp. (3).

time of flight technology mass spectrometry (Bruker, Billerica, MA, USA) or other methods, as needed.

2.2. Antimicrobial susceptibility testing

Minimal inhibitory concentrations (MICs) for all antibiotics were determined using broth microdilution panels according to the Clinical and Laboratory Standards Institute (CLSI) method [12]. Antibiotic powders were obtained from manufacturers or Sigma-Aldrich (St. Louis, MO, USA), and stock solutions were made according to CLSI or the manufacturer's instructions. All ceftolozane-tazobactam and piperacillin-tazobactam MIC tests used a fixed tazobactam concentration of 4 mg/L. Other comparators tested were amikacin, cefepime, ceftazidime, colistin, levofloxacin and meropenem. Interpretation of results was performed according to CLSI M100 and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [13,14]. EUCAST Enterobacteriaceae breakpoints were used for colistin. Quality control was performed according to CLSI. MIC results for CLSI quality control strains were within published ranges.

2.3. Resistant subsets

Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca and *Proteus mirabilis* were grouped as 'ESBL screen-positive phenotype' based on the CLSI screening criteria for potential ESBL production with MIC values ≥2 mg/L for ceftazidime, ceftriaxone and aztreonam [12]. CRE isolates were defined as displaying MIC values ≥4 mg/L for imipenem (*P. mirabilis* and indole-positive Proteeae were not included due to the intrinsically elevated MIC values), meropenem and/or doripenem. Since carbapenemase-producing isolates may also appear to have an ESBL phenotype, non-carbapenem-resistant ESBL-screen-positive phenotype (ESBL, non-CRE) isolates were analysed.

P. aeruginosa isolates were considered to be non-susceptible to meropenem if the MIC value was ≥4 mg/L, non-susceptible

Table 5
Susceptibility for ceftolozane-tazobactam by country.

Organism/organism group Country	*n*	% susceptible[a]
Enterobacteriaceae		
Europe	1347	89.4%
Austria	18	100.0%
Belgium	42	97.6%
Czech Republic	12	100.0%
France	104	94.2%
Germany	157	89.8%
Ireland	65	95.4%
Israel	45	93.3%
Italy	115	95.7%
Netherlands	25	96.0%
Norway	10	100.0%
Poland	29	44.8%
Portugal	41	100.0%
Russia	53	67.9%
Spain	53	96.2%
Sweden	35	97.1%
Turkey	380	84.7%
United Kingdom	114	96.5%
Ukraine	25	76.0%
Pseudomonas aeruginosa		
Europe	413	93.2%
France	21	100.0%
Germany	18	100.0%
Israel	16	100.0%
Italy	36	94.4%
Poland	22	90.9%
Russia	38	84.2%
Spain	13	92.3%
Turkey	149	90.6%
UK	35	100.0%
Ukraine	17	82.4%

[a] European Committee on Antimicrobial Susceptibility Testing, 2018. Only countries contributing at least 10 isolates of either Enterobacteriaceae or *P. aeruginosa* during the study period are listed.

to ceftazidime or cefepime if the MIC was ≥16 mg/L, and non-susceptible to piperacillin-tazobactam if the MIC was ≥32 mg/L, in accordance with CLSI and EUCAST criteria [13,14].

3. Results

The most common infection types caused by Gram-negative bacteria in hospitalized paediatric patients in the USA and Europe were pneumonia (35.6% USA and 25.6% Europe), urinary tract infection (27.2% USA and 21.0% Europe) and bloodstream infection (18.5% USA and 22.6% Europe). In total, 4316 Enterobacteriaceae (2969 USA and 1347 Europe) and 1765 non-enterics (1152 USA and 613 Europe) were isolated. The three most common Gram-negative species isolated were *E. coli* (1311 and 608 isolates from USA and Europe, respectively), *P. aeruginosa* (823 and 413 isolates from USA and Europe, respectively) and *K. pneumoniae* (429 and 280 isolates from USA and Europe, respectively). The age group that contributed the largest number of isolates was ≤1 year, with <1-year-olds accounting for 33.8% (*n*=2058) of isolates and 1-year-olds accounting for 10.3% (*n*=624) of isolates. The number of infants (<1 year old) who were in neonatal intensive care units was unknown, but the number of infants recorded as being in an ICU was 1072 (52.1%).

MIC distributions of ceftolozane-tazobactam for the most common species and resistant phenotypes are shown in Table 1 for US isolates and Table 2 for European isolates. Susceptibilities and $MIC_{50/90}$ values for ceftolozane-tazobactam and comparators for the main species and resistant phenotypes are shown in Table 3 for US isolates and Table 4 for European isolates. The susceptibility of ceftolozane-tazobactam by European country is shown in Table 5. Only countries that contributed at least 10 isolates of Enterobacteriaceae and/or *P. aeruginosa* are listed.

Against US Enterobacteriaceae isolates (Table 3), ceftolozane-tazobactam [$MIC_{50/90}$ 0.25/0.5 mg/L, 96.1% susceptible (S) by CLSI and 94.2%S by EUCAST breakpoints] had a higher percentage susceptibility than other cephalosporins (cefepime $MIC_{50/90}$ ≤0.5/≤0.5 mg/L, 95.2%/93.5%S; ceftazidime $MIC_{50/90}$ 0.12/2 mg/L, 91.0%/89.5%S by CLSI/EUCAST breakpoints) and piperacillin-tazobactam ($MIC_{50/90}$ 2/8 mg/L, 94.0%/91.7%S by CLSI/EUCAST breakpoints); only meropenem ($MIC_{50/90}$ ≤0.06/0.06 mg/L, 99.7%/99.8%S by CLSI/EUCAST breakpoints) and amikacin ($MIC_{50/90}$ 2/4 mg/L, 99.8%/99.4%S by CLSI/EUCAST breakpoints) had higher susceptibility rates. For 119 *E. coli* with the ESBL, non-CRE phenotype, ceftolozane-tazobactam had excellent susceptibility (92.4/89.1%S by CLSI/EUCAST breakpoints), with a higher susceptibility rate than ceftazidime (32.8/10.9%S by CLSI/EUCAST breakpoints), cefepime (35.3/29.4%S by CLSI/EUCAST breakpoints) and piperacillin-tazobactam (84.0/72.3%S by CLSI/EUCAST breakpoints). Against 44 *K. pneumoniae* with an ESBL, non-CRE phenotype, ceftolozane-tazobactam was less active (86.4/65.9%S by CLSI/EUCAST breakpoints) compared with *E. coli* with the ESBL, non-CRE phenotype. Only seven of 2969 US Enterobacteriaceae (0.2%) were CRE in this study. In the USA, ceftolozane-tazobactam was the most active agent tested against 823 *P. aeruginosa* isolates ($MIC_{50/90}$ 0.5/1 mg/L, 99.5/99.5%S by CLSI/EUCAST breakpoints) and was similar to colistin ($MIC_{50/90}$ 1/2 mg/L, 99.3/99.3%S by CLSI/EUCAST breakpoints) in activity. Twelve isolates were non-susceptible to the other beta-lactams tested in this study: ceftazidime, cefepime, meropenem and piperacillin-tazobactam. Ceftolozane-tazobactam maintained activity against 10 of 12 isolates (83.3%/83.3%S by CLSI/EUCAST breakpoints). Colistin was the other antimicrobial to which these isolates were susceptible (100%/100% by CLSI/EUCAST breakpoints).

For European isolates (Table 4), the overall susceptibility of Enterobacteriaceae for ceftolozane-tazobactam was 91.4/89.4% ($MIC_{50/90}$ 0.25/2 mg/L) by CLSI and EUCAST breakpoints, respectively. Ceftolozane-tazobactam had a higher susceptibility rate compared with other cephalosporins, including cefepime (79.0/76.8%S by CLSI/EUCAST breakpoints), ceftazidime (78.5/74.4%S by CLSI/EUCAST breakpoints) and piperacillin-tazobactam (86.2/82.8%S by CLSI/EUCAST breakpoints). The antimicrobials with the highest susceptibility rates, as seen with US isolates, were amikacin (97.2/95.9%S by CLSI/EUCAST breakpoints) and meropenem (97.3/98.0%S by CLSI/EUCAST breakpoints). Ceftolozane-tazobactam susceptibility against 131 ESBL, non-CRE *E. coli* was 89.3/87.0% by CLSI/EUCAST breakpoints; ceftolozane-tazobactam susceptibility was lower (75.2/67.3%S by CLSI/EUCAST breakpoints) against 113 ESBL, non-CRE *K. pneumoniae*. There were 35 European CRE isolates (2.6%). Against European *P. aeruginosa*, ceftolozane-tazobactam was the second most active agent tested (93.2/93.2%S by CLSI/EUCAST breakpoints), and colistin was the most active agent (98.3/98.3%S by CLSI/EUCAST breakpoints). Ceftolozane-tazobactam was more active than other β-lactams when tested against isolates that were not susceptible to ceftazidime, cefepime, meropenem or piperacillin-tazobactam, where ceftolozane-tazobactam maintained 59.1–72.6%S by CLSI and EUCAST breakpoints. Susceptibility of 43 *P. aeruginosa* isolates, resistant to all other β-lactams tested in this study, to ceftolozane-tazobactam was 44.2/44.2%S by CLSI/EUCAST breakpoints.

The differences in ceftolozane-tazobactam susceptibility using EUCAST criteria in the participating European countries is shown in Table 5. For Enterobacteriaceae isolates, 11 countries had >95% susceptibility, and Poland had the lowest susceptibility rate at 44.8%. For *P. aeruginosa* isolates, four countries had no resistant isolates and only two countries had <90% susceptibility [Russia (84.2%) and Ukraine (82.4%)].

As stated previously, the most common age group from which isolates were collected was ≤1 year. The susceptibility of

ceftolozane-tazobactam for isolates from European patients aged ≤1 year was 89.9/87.5% vs 92.7/91.0% by CLSI/EUCAST breakpoints for children aged 2–17 years for Enterobacteriaceae, and 92.9/92.9% (≤1 year) vs 93.4/93.4% (2–17 years) for *P. aeruginosa*. For isolates from US patients, ceftolozane-tazobactam susceptibilities were 95.6/93.6% (≤1 year) and 96.5/94.7% (2–17 years) for Enterobacteriaceae and 100.0/100.0% (≤1 year) and 99.3/99.3% (2–17 years) for *P. aeruginosa*.

4. Conclusions

This study examined the susceptibility of Enterobacteriaceae and *P. aeruginosa* isolates from paediatric infections in the USA and Europe, and, to the best of the authors' knowledge, is the first study to report the susceptibility of ceftolozane-tazobactam against paediatric surveillance isolates. This study confirms a higher resistance rate to β-lactams and quinolones in European paediatric isolates compared with US isolates reported by others [15,16]. These reports suggest that effective antimicrobials to treat serious paediatric infections are becoming more difficult to identify, particularly as fewer broad-spectrum antimicrobials are approved for use in paediatric patients [4,17,18]. Carbapenems are often the last option for serious paediatric infections, with a corresponding increase in carbapenem resistance reported [19,20].

Overall susceptibility of ceftolozane-tazobactam against US Enterobacteriaceae was 96.1/ 94.2% by CLSI/EUCAST breakpoints; amikacin and meropenem were the most active drugs with >99% susceptibility by both CLSI and EUCAST breakpoints. Overall susceptibility of ceftolozane-tazobactam against European Enterobacteriaceae was 91.4/89.1% by CLSI/EUCAST breakpoints. Although a large number of isolates were from infants aged ≤1 year, the susceptibility of ceftolozane-tazobactam was similar between this group and children aged 2–17 years for both US and European isolates. This study also confirms the activity of ceftolozane-tazobactam against ESBL screen-positive *E. coli* that are susceptible to carbapenems, with a lower susceptibility rate for ESBL, non-CRE *K. pneumoniae* as reported in other studies [21]. Livermore et al. found that susceptibility of ESBL, non-CRE isolates to ceftolozane-tazobactam differed between *E. coli* and *K. pneumoniae*, and suggested that cell wall permeability changes and/or secondary β-lactamases in *K. pneumoniae* may be responsible [22]. Differences in susceptibilities to β-lactam antibiotics among European countries were also observed in this study for paediatric populations, consistent with reports by others for primarily adult populations [23,24]. The difference in ceftolozane-tazobactam susceptibility of US and European ESBL, non-CRE isolates is likely due to differences in prevalence of β-lactamases and/or cell wall permeability changes in the various countries studied. No β-lactamases were characterized in this study.

For *P. aeruginosa* isolates, ceftolozane-tazobactam demonstrated potent activity with 99.5/99.5%S by CLSI/EUCAST breakpoints for US isolates, and was the most potent antibiotic tested with activity similar to colistin (99.3/99.3%S by CLSI/EUCAST breakpoints). For European isolates, overall ceftolozane-tazobactam susceptibility was 93.2/93.2%, second only to colistin (98.3/98.3%S by CLSI/EUCAST breakpoints). Ceftolozane-tazobactam retained activity against *P. aeruginosa* resistant to other β-lactams tested in this study.

A single-dose ceftolozane-tazobactam study in paediatric patients demonstrated that the pharmacokinetics are generally comparable between children and adults [25]. The pharmacokinetics and the in-vitro data of this study suggest that ceftolozane-tazobactam may be a useful treatment option for serious infections in paediatric patients, and support continued study in ongoing paediatric treatment trials.

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Competing interests

JMI Laboratories was contracted to perform services in 2017 for Achaogen, Allecra Therapeutics, Allergan, Amplyx Pharmaceuticals, Antabio, API, Astellas Pharma, AstraZeneca, Athelas, Basilea Pharmaceutica, Bayer AG, BD, Becton, Dickinson and Co., Boston, CEM-102 Pharma, Cempra, Cidara Therapeutics, Inc., CorMedix, CSA Biotech, Cutanea Life Sciences, Inc., Entasis Therapeutics, Inc., Geom Therapeutics, Inc., GSK, Iterum Pharma, Medpace, Melinta Therapeutics, Inc., Merck & Co., Inc., MicuRx Pharmaceuticals, Inc., N8 Medical, Inc., Nabriva Therapeutics, Inc., NAEJA-RGM, Novartis, Paratek Pharmaceuticals, Inc., Pfizer, Polyphor, Ra Pharma, Rempex, Riptide Bioscience Inc., Roche, Scynexis, Shionogi, Sinsa Labs Inc., Skyline Antiinfectives, Sonoran Biosciences, Spero Therapeutics, Symbiotica, Synlogic, Synthes Biomaterials, TenNor Therapeutics, Tetraphase, The Medicines Company, Theravance Biopharma, VenatoRx Pharmaceuticals, Inc., Wockhardt, Yukon Pharma, Zai Laboratory, Zavante Therapeutics, Inc. There are no speakers' bureaus or stock options to declare.

Ethical approval

Not required.

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