In Vitro Activity of Ceftazidime-Avibactam and Comparators Against *Pseudomonas aeruginosa* from Europe 2012–2014

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Revised Abstract

Background: Avibactam is a novel non-β-lactam β-lactamase inhibitor that is being developed for use in combination with ceftazidime. Avibactam does not have any clinically meaningful intrinsic antibacterial activity, but inhibits Ambler class A β-lactamases including extended-spectrum enzymes and KPCs, class C β-lactamases, and some class D enzymes. It is able to restore the activity of ceftazidime against the often resistant ESKAPE pathogen *Pseudomonas aeruginosa.* This study reports ceftazidime-avibactam susceptibility data for recent clinical isolates from Europe generated through the INFORM Surveillance initiative. **Methods:** 3,893 clinically relevant *P. aeruginosa* isolates from multiple sources were collected between 2012 and 2014 in 19 European countries. MICs were determined as specified by CLSI broth microdilution and interpreted following FDA guidelines for ceftazidime-avibactam (≤8 µg/mL susceptible), and EUCAST 2015 guidelines for comparators. **Results**: The table below shows the *in vitro* activities based on MIC_{90}/% susceptible (S) of ceftazidime-avibactam and comparators against *P. aeruginosa* according to various resistant phenotypes. Ceftazidime-avibactam exhibited potent *in vitro* antimicrobial activity against *P. aeruginosa* collected in Europe, with 92.6% of all isolates testing as susceptible. Of the meropenem-non-susceptible isolates, 74.2% were susceptible to ceftazidime-avibactam, but that increased to 86.2% in the metallo-β-lactamase (MBL)-negative subset. Country differences in *in vitro* activity were noted, with consistently high activity in countries with no MBLs (exemplified by Denmark and The Netherlands), and decreased activity in countries where MBLs are more prevalent (exemplified by Russia and Romania).

***In Vitro* Activity of Ceftazidime-Avibactam and Comparators Against *P. aeruginosa* from Europe**

		MIC_{90}/%S					
Region	N	CAZ-AVI	CAZ	CEP	MEM	TZP	COL
Europe	3893	8/92.6	64/77.4	16/78.8	>8/72.9	>128/69.4	2/99.5
Europe-MEM NS	1056	32/74.2	128/41.3	>16/41.0	>8/0	>128/27.0	2/99.4
Europe, no MBL	3740	8/96.2	32/80.5	16/81.9	>8/75.8	128/72.1	2/99.5
Europe-MEM NS, no MBL	904	16/86.2	128/47.9	>16/47.6	>8/0	>128/31.1	4/99.2
Russia	376	32/75.3	64/57.5	>16/57.7	>8/52.7	>128/50.7	2/100
Russia, no MBL	309	8/90.9	64/69.3	>16/70.2	>8/64.1	>128/61.8	2/100
Romania	114	32/79.0	128/64.9	>16/61.4	>8/61.4	>128/53.5	2/100
Romania, no MBL	103	16/87.4	128/71.8	>16/68.0	>8/68.0	>128/59.2	2/100
Denmark	149	4/99.3	8/93.3	8/93.3	2/91.3	32/85.2	2/100
Denmark, no MBL	149	4/99.3	8/93.3	8/93.3	2/91.3	32/85.2	2/100
Netherlands	79	4/100	16/89.9	8/98.7	4/89.9	16/91.1	2/100
Netherlands, no MBL	79	4/100	16/89.9	8/98.7	4/89.9	16/91.1	2/100

CAZ-AVI, ceftazidime-avibactam; CAZ, ceftazidime; CEP, cefepime; MEM, meropenem; TZP, piperacillin-tazobactam; COL, colistin; MEM-NS, meropenem non-susceptible; MBL, metallo-β-lactamase.

Conclusions: Ceftazidime-avibactam showed potent *in vitro* antimicrobial activity against *P. aeruginosa* collected in Europe, but activity was compromised by MBLs. The incidence of these play a role in the reduced activity of ceftazidime-avibactam in some countries.

Introduction

P. aeruginosa is a cause of serious healthcare-associated infections and exhibits resistance to a number of different antimicrobials used to treat these infections, including currently available β-lactams. Ceftazidime-avibactam is a combination of ceftazidime with the non-β-lactam β-lactamase-inhibitor avibactam that is under clinical development as a potential therapeutic option for the treatment of infections caused by *P. aeruginosa* in Europe. To evaluate this potential, ceftazidime-avibactam susceptibility data generated through the International Network for Optimal Resistance Monitoring (INFORM) surveillance initiative were analyzed, and compared to other agents according to various *P. aeruginosa* resistance phenotypes among European isolates.

Materials & Methods

- 3,893 clinically relevant *P. aeruginosa* isolates from multiple sources were collected between 2012 and 2014 in 19 European countries. Isolates were tested centrally at International Health Management Associates, Inc. (IHMA).
- MICs were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method [1]. Ceftazidime-avibactam MIC interpretive criteria followed FDA guidelines [2]; comparator antimicrobials were interpreted following EUCAST 2016 guidelines [3].
- Multidrug-resistant (MDR) phenotype was defined as resistance to three or more antimicrobial classes.
- Presence of β-lactamase genes for metallo-β-lactamases (MBL) was assessed via multiplex PCR, followed by sequencing.

Table 1. *In Vitro* Activity of Ceftazidime-Avibactam and Comparators Against *P. aeruginosa*, Including Non-MBL Resistant Phenotypes.

			Ceftazidime-avibactam			Ceftazidime			Meropenem			Piperacillin-tazobactam			Amikacin			Colistin			
Region (# of sites/%MBL)	Phenotype	N	%S	MIC_{90}	Range	%S	MIC_{90}	Range	%S	MIC_{90}	Range	%S	MIC_{90}	Range	%S	MIC_{90}	Range	N*	%S	MIC_{90}	Range
Europe (92/4.3)	All *P. aeruginosa*	3893	92.6	8	0.06 - > 128	77.4	64	0.06 - > 128	72.9	> 8	≤ 0.06 - > 8	69.4	> 128	≤ 0.25 - > 128	83.8	32	≤ 0.25 - > 32	2091	99.6	2	0.12 - > 8
	All *P. aeruginosa*, no MBL	3740	96.2	8	0.06 - > 128	80.5	32	0.06 - > 128	75.8	> 8	≤ 0.06 - > 8	72.1	128	≤ 0.25 - > 128	86.7	16	≤ 0.25 - > 32	2001	99.6	2	0.12 - > 8
	MEM NS, no MBL	904	86.2	16	0.25 - > 128	47.9	128	0.5 - > 128	0	> 8	4 - > 8	31.1	> 128	≤ 0.25 - > 128	64.8	> 32	≤ 0.25 - > 32	486	99.2	4	0.25 - > 8
	CAZ NS, no MBL	730	80.7	16	0.5 - > 128	0	128	16 - > 128	35.5	> 8	≤ 0.06 - > 8	6.2	> 128	1 - > 128	64.1	> 32	≤ 0.25 - > 32	414	99.0	2	0.25 - > 8
	MDR, no MBL	899	84.3	16	0.25 - > 128	27.1	128	0.5 - > 128	28.0	> 8	≤ 0.06 - > 8	7.1	> 128	≤ 0.25 - > 128	59.1	> 32	≤ 0.25 - > 32	499	99.0	4	0.25 - > 8
Austria (5/1.1)	All *P. aeruginosa*	180	95.6	4	0.5 - > 128	87.8	16	0.5 - > 128	85.0	8	≤ 0.06 - > 8	84.4	64	2 - > 128	93.3	8	≤ 0.25 - > 32	106	100	4	0.5 - 4
	All *P. aeruginosa*, no MBL	178	96.6	4	0.5 - > 128	88.8	16	0.5 - > 128	86.0	4	≤ 0.06 - > 8	85.4	64	2 - > 128	94.4	8	≤ 0.25 - > 32	105	100	4	0.5 - 4
	MEM NS, no MBL	25	80.0	16	1 - > 128	56.0	128	1 - > 128	0	> 8	4 - > 8	52.0	> 128	2 - > 128	80.0	16	≤ 0.25 - > 32	14	100	2	0.5 - 2
	CAZ NS, no MBL	20	70.0	32	1 - > 128	0	128	16 - > 128	45.0	> 8	0.25 - > 8	20.0	> 128	16 - > 128	90.0	8	≤ 0.25 - 16	9	100	2	0.5 - 2
	MDR, no MBL	25	76.0	32	1 - > 128	36.0	128	1 - > 128	40.0	> 8	0.25 - > 8	16.0	> 128	4 - > 128	72.0	16	≤ 0.25 - > 32	13	100	2	0.5 - 2
Belgium (5/4.0)	All *P. aeruginosa*	227	89.9	16	0.25 - 128	74.0	64	0.25 - > 128	73.1	> 8	≤ 0.06 - > 8	69.6	> 128	≤ 0.25 - > 128	84.1	16	0.5 - > 32	126	99.2	2	0.12 - > 8
	All *P. aeruginosa*, no MBL	218	93.6	8	0.25 - 128	77.1	64	0.25 - > 128	76.2	> 8	≤ 0.06 - > 8	72.0	> 128	≤ 0.25 - > 128	87.6	16	0.5 - > 32	122	99.2	2	0.12 - > 8
	MEM NS, no MBL	52	75.0	32	0.5 - 128	46.2	> 128	2 - > 128	0	> 8	4 - > 8	36.5	> 128	4 - > 128	73.1	32	0.5 - > 32	23	95.7	4	0.5 - > 8
	CAZ NS, no MBL	50	72.0	32	2 - 128	0	> 128	16 - > 128	44.0	> 8	0.12 - > 8	12.0	> 128	4 - > 128	76.0	32	2 - > 32	30	96.7	4	0.25 - > 8
	MDR, no MBL	56	75.0	32	0.5 - 128	23.2	> 128	2 - > 128	32.1	> 8	0.5 - > 8	14.3	> 128	4 - > 128	73.2	32	2 - > 32	32	96.9	2	0.25 - > 8
Czech Republic (4/4.0)	All *P. aeruginosa*	198	89.9	16	0.12 - > 128	70.2	64	0.12 - > 128	62.1	> 8	≤ 0.06 - > 8	55.6	> 128	≤ 0.25 - > 128	81.3	16	≤ 0.25 - > 32	113	100	2	0.25 - 4
	All *P. aeruginosa*, no MBL	190	93.7	8	0.12 - 32	73.2	64	0.12 - > 128	64.7	> 8	≤ 0.06 - > 8	57.9	> 128	≤ 0.25 - > 128	84.2	16	≤ 0.25 - > 32	107	100	2	0.25 - 4
	MEM NS, no MBL	67	83.6	16	1 - 32	40.3	64	2 - 128	0	> 8	4 - > 8	14.9	> 128	2 - > 128	68.7	32	≤ 0.25 - > 32	44	100	2	0.5 - 4
	CAZ NS, no MBL	51	76.5	16	1 - 32	0	64	16 - > 128	21.6	> 8	≤ 0.06 - > 8	5.9	> 128	1 - > 128	76.5	32	≤ 0.25 - > 32	29	100	4	0.5 - 4
	MDR, no MBL	74	83.8	16	1 - 32	35.1	64	2 - 128	20.3	> 8	0.25 - > 8	5.4	> 128	16 - > 128	67.6	32	≤ 0.25 - > 32	45	100	2	0.5 - 4
Denmark (3/0)	All *P. aeruginosa*	149	99.3	4	0.25 - 32	93.3	8	0.25 - > 128	91.3	2	≤ 0.06 - > 8	85.2	32	≤ 0.25 - > 128	92.6	8	≤ 0.25 - 32	102	100	2	0.5 - 4
	All *P. aeruginosa*, no MBL	149	99.3	4	0.25 - 32	93.3	8	0.25 - > 128	91.3	2	≤ 0.06 - > 8	85.2	32	≤ 0.25 - > 128	92.6	8	≤ 0.25 - 32	102	100	2	0.5 - 4
	MEM NS, no MBL	13	92.3	8	2 - 32	38.5	128	2 - > 128	0	> 8	4 - > 8	30.8	> 128	4 - > 128	84.6	16	0.5 - 32	8	100	2	1 - 2
	CAZ NS, no MBL	10	90.0	8	2 - 32	0	128	16 - > 128	20.0	8	0.5 - > 8	10.0	> 128	16 - > 128	90.0	8	0.5 - 16	6	100	2	1 - 2
	MDR, no MBL	15	93.3	8	2 - 32	40.0	128	4 - > 128	33.3	> 8	0.5 - > 8	6.7	> 128	16 - > 128	86.7	16	0.5 - 32	7	100	2	1 - 2
France (9/0.3)	All *P. aeruginosa*	331	97.3	8	0.12 - 128	81.6	32	0.25 - > 128	80.7	8	≤ 0.06 - > 8	73.1	> 128	≤ 0.25 - > 128	86.4	16	≤ 0.25 - > 32	203	99.0	4	0.5 - > 8
	All *P. aeruginosa*, no MBL	330	97.6	4	0.12 - 128	81.8	32	0.25 - > 128	80.9	4	≤ 0.06 - > 8	73.3	> 128	≤ 0.25 - > 128	86.4	16	≤ 0.25 - > 32	202	99.0	4	0.5 - > 8
	MEM NS, no MBL	63	88.9	16	1 - 128	49.2	64	1 - > 128	0	> 8	4 - > 8	28.6	> 128	≤ 0.25 - > 128	76.2	> 32	1 - > 32	35	100	4	1 - 4
	CAZ NS, no MBL	60	86.7	16	1 - 128	0	128	16 - > 128	46.7	> 8	0.25 - > 8	8.3	> 128	16 - > 128	78.3	32	0.5 - > 32	38	100	4	1 - 4
	MDR, no MBL	74	89.2	16	1 - 128	28.4	128	2 - > 128	39.2	> 8	≤ 0.06 - > 8	9.5	> 128	≤ 0.25 - > 128	73.0	> 32	0.5 - > 32	43	100	4	1 - 4
Germany (8/1.8)	All *P. aeruginosa*	330	95.2	8	0.25 - > 128	81.5	64	0.5 - > 128	76.1	> 8	≤ 0.06 - > 8	74.6	128	≤ 0.25 - > 128	92.1	8	≤ 0.25 - > 32	177	100	2	1 - 4
	All *P. aeruginosa*, no MBL	324	96.9	8	0.25 - > 128	83.0	32	0.5 - > 128	77.5	> 8	≤ 0.06 - > 8	75.9	128	≤ 0.25 - > 128	92.9	8	≤ 0.25 - > 32	173	100	2	1 - 4
	MEM NS, no MBL	73	87.7	16	0.5 - > 128	53.4	128	1 - > 128	0	> 8	4 - > 8	35.6	> 128	2 - > 128	80.8	16	≤ 0.25 - > 32	37	100	4	1 - 4
	CAZ NS, no MBL	55	81.8	16	1 - > 128	0	> 128	16 - > 128	38.2	> 8	0.25 - > 8	9.1	> 128	4 - > 128	78.2	32	≤ 0.25 - > 32	30	100	2	1 - 4
	MDR, no MBL	64	84.4	16	1 - > 128	23.4	128	2 - > 128	26.6	> 8	0.25 - > 8	4.7	> 128	16 - > 128	78.1	32	≤ 0.25 - > 32	34	100	2	1 - 4
Greece (3/12.7)	All *P. aeruginosa*	204	84.8	16	0.5 - > 128	79.9	32	0.5 - > 128	69.6	> 8	≤ 0.06 - > 8	71.1	64	2 - > 128	76.5	> 32	0.5 - > 32	103	100	2	1 - 4
	All *P. aeruginosa*, no MBL	178	96.6	8	0.5 - 128	91.6	8	0.5 - > 128	79.8	> 8	≤ 0.06 - > 8	80.9	32	2 - > 128	87.1	16	0.5 - > 32	90	100	4	1 - 4
	MEM NS, no MBL	36	83.3	16	2 - 128	75.0	128	2 - 128	0	> 8	4 - > 8	50.0	> 128	4 - > 128	69.4	16	1 - > 32	19	100	4	1 - 4
	CAZ NS, no MBL	15	60.0	16	2 - 128	0	128	16 - > 128	40.0	> 8	0.25 - > 8	6.7	> 128	8 - > 128	40.0	> 32	1 - > 32	8	100	4	1 - 4
	MDR, no MBL	29	79.3	16	2 - 128	51.7	128	2 - > 128	41.4	> 8	0.25 - > 8	17.2	> 128	8 - > 128	34.5	> 32	1 - > 32	11	100	4	1 - 4
Hungary (4/4.2)	All *P. aeruginosa*	165	93.3	8	0.25 - 128	76.4	32	0.5 - 128	64.2	> 8	≤ 0.06 - > 8	67.3	128	≤ 0.25 - > 128	86.7	16	0.5 - > 32	95	99.0	2	0.5 - 8
	All *P. aeruginosa*, no MBL	158	96.8	8	0.25 - 64	79.8	32	0.5 - 64	67.1	> 8	≤ 0.06 - > 8	70.3	128	≤ 0.25 - > 128	90.5	8	0.5 - > 32	89	98.9	2	0.5 - 8
	MEM NS, no MBL	52	90.4	8	0.25 - 64	57.7	64	0.5 - 64	0	> 8	4 - > 8	44.2	> 128	4 - > 128	80.8	16	0.5 - > 32	31	100	2	0.5 - 2
	CAZ NS, no MBL	32	84.4	16	0.5 - 64	0	64	16 - 64	31.3	> 8	0.12 - > 8	6.3	> 128	16 - > 128	87.5	16	0.5 - > 32	21	100	2	0.5 - 2
	MDR, no MBL	43	88.4	16	0.25 - 64	37.2	64	0.5 - 64	23.3	> 8	0.25 - > 8	11.6	> 128	8 - > 128	76.7	> 32	0.5 - > 32	26	100	2	0.5 - 2
Italy (7/2.0)	All *P. aeruginosa*	307	94.1	8	0.25 - > 128	70.7	64	0.5 - > 128	70.7	> 8	≤ 0.06 - > 8	63.2	> 128	≤ 0.25 - > 128	78.5	32	≤ 0.25 - > 32	35	100	2	0.5 - 4
	All *P. aeruginosa*, no MBL	301	96.0	8	0.25 - 128	72.1	32	0.5 - > 128	72.1	> 8	≤ 0.06 - > 8	64.5	> 128	≤ 0.25 - > 128	78.7	32	≤ 0.25 - > 32	35	100	2	0.5 - 4
	MEM NS, no MBL	84	86.9	16	1 - 128	33.3	128	2 - > 128	0	> 8	4 - > 8	19.1	> 128	2 - > 128	48.8	> 32	0.5 - > 32	1	100	4	4 - 4
	CAZ NS, no MBL	84	85.7	16	1 - 128	0	> 128	16 - > 128	33.3	> 8	0.12 - > 8	3.6	> 128	2 - > 128	58.3	> 32	0.5 - > 32	6	100	2	2 - 2
	MDR, no MBL	91	86.8	16	1 - 128	19.8	128	4 - > 128	23.1	> 8	0.12 - > 8	5.5	> 128	≤ 0.25 - > 128	47.3	> 32	0.5 - > 32	2	100	2	2 - 2
Netherlands (2/0)	All *P. aeruginosa*	79	100	4	0.25 - 8	89.9	16	0.25 - 64	89.9	4	≤ 0.06 - 8	91.1	16	≤ 0.25 - > 128	97.5	8	≤ 0.25 - 32	97	99.0	4	1 - 8
	All *P. aeruginosa*, no MBL	79	100	4	0.25 - 8	89.9	16	0.25 - 64	89.9	4	≤ 0.06 - 8	91.1	16	≤ 0.25 - > 128	97.5	8	≤ 0.25 - 32	97	99.0	4	1 - 8
	MEM NS, no MBL	8	100	4	1 - 4	87.5	32	1 - 32	0	8	4 - 8	75.0	128	1 - 128	87.5	32	1 - 32	20	95.0	4	2 - 8
	CAZ NS, no MBL	8	100	8	1 - 8	0	64	16 - 64	87.5	4	0.25 - 4	50.0	> 128	4 - > 128	100	8	2 - 8	17	94.1	4	2 - 8
	MDR, no MBL	6	100	4	1 - 4	33.3	32	4 - 32	50.0	8	0.5 - 8	16.7	> 128	16 - > 128	83.3	32	4 - 32	18	94.4	4	2 - 8
Poland (3/0.7)	All *P. aeruginosa*	142	97.2	8	0.25 - 64	83.1	32	0.25 - > 128	78.9	8	≤ 0.06 - > 8	78.9	128	≤ 0.25 - > 128	84.5	16	0.5 - > 32	123	98.4	4	0.5 - 8
	All *P. aeruginosa*, no MBL	141	97.9	4	0.25 - 32	83.7	32	0.25 - > 128	79.4	8	≤ 0.06 - > 8	79.4	64	≤ 0.25 - > 128	85.1	16	0.5 - > 32	121	98.4	4	0.5 - 8
	MEM NS, no MBL	29	93.1	8	1 - 32	51.7	32	1 - > 128	0	> 8	4 - > 8	44.8	> 128	2 - > 128	72.4	> 32	2 - > 32	39	100	4	0.5 - 4
	CAZ NS, no MBL	23	87.0	16	2 - 32	0	64	16 - > 128	39.1	> 8	0.5 - > 8	4.4	> 128	8 - > 128	56.5	> 32	4 - > 32	38	100	4	0.5 - 4
	MDR, no MBL	25	88.0	16	1 - 32	16.0	64	1 - > 128	32.0	> 8	0.5 - > 8	4.0	> 128	8 - > 128	52.0	> 32	2 - > 32	43	97.7	4	0.5 - 8
Portugal (4/2.1)	All *P. aeruginosa*	234	97.0	8	0.5 - 32	72.7	64	0.5 - 128	70.5	> 8	≤ 0.06 - > 8	60.7	> 128	≤ 0.25 - > 128	82.1	32	≤ 0.25 - > 32	44	100	2	1 - 4
	All *P. aeruginosa*, no MBL	229	99.1	8	0.5 - 32	74.2	64	0.5 - 128	72.1	> 8	≤ 0.06 - > 8	61.6	> 128	≤ 0.25 - > 128	82.5	32	≤ 0.25 - > 32	40	100	2	1 - 4
	MEM NS, no MBL	64	98.4	8	1 - 16	34.4	128	2 - 128	0	> 8	4 - > 8	25.0	> 128	4 - > 128	53.1	32	0.5 - > 32	16	100	4	1 - 4
	CAZ NS, no MBL	59	96.6	8	1 - 32	0	128	16 - 128	28.8	> 8	≤ 0.06 - > 8	1.7	> 128	16 - > 128	47.5	32	0.5 - > 32	10	100	2	1 - 4
	MDR, no MBL	66	97.0	8	1 - 32	16.7	128	4 - 128	28.8	> 8	0.12 - > 8	0	> 128	32 - > 128	48.5	32	0.5 - > 32	15	100	4	1 - 4
Romania (4/9.6)	All *P. aeruginosa*	114	79.0	32	0.5 - > 128	64.9	128	1 - > 128	61.4	> 8	≤ 0.06 - > 8	53.5	> 128	≤ 0.25 - > 128	65.8	> 32	1 - > 32	178	100	2	1 - 4
	All *P. aeruginosa*, no MBL	103	87.4	16	0.5 - > 128	71.8	128	1 - > 128	68.0	> 8	≤ 0.06 - > 8	59.2	> 128	≤ 0.25 - > 128	71.8	> 32	1 - > 32	137	100	2	1 - 4
	MEM NS, no MBL	33	66.7	32	2 - > 128	36.4	> 128	2 - > 128	0	> 8	4 - > 8	18.2	> 128	4 - > 128	30.3	> 32	2 - > 32	51	100	2	1 - 4
	CAZ NS, no MBL	29	55.2	64	2 - > 128	0	> 128	16 - > 128	27.6	> 8	0.5 - > 8	6.9	> 128	16 - > 128	31.0	> 32	2 - > 32	46	100	2	1 - 4
	MDR, no MBL	38	65.8	32	2 - > 128	26.3	> 128	2 - > 128	23.7	> 8	0.25 - > 8	7.9	> 128	8 - > 128	23.7	> 32	2 - > 32	52	100	2	1 - 4
Russia (10/17.8)	All *P. aeruginosa*	376	75.3	32	0.12 - > 128	57.5	64	0.25 - > 128	52.7	> 8	≤ 0.06 - > 8	50.7	> 128	≤ 0.25 - > 128	60.1	> 32	0.5 - > 32	173	99.4	2	0.5 - > 8
	All *P. aeruginosa*, no MBL	309	90.9	8	0.12 - > 128	69.3	64	0.25 - > 128	64.1	> 8	≤ 0.06 - > 8	61.8	> 128	≤ 0.25 - > 128	71.2	> 32	0.5 - > 32	172	99.4	2	0.5 - > 8
	MEM NS, no MBL	111	75.7	32	0.5 - > 128	39.6	> 128	1 - > 128	0	> 8	4 - > 8	27.9	> 128	2 - > 128	36.0	> 32	1 - > 32	51	98.0	4	0.5 - > 8
	CAZ NS, no MBL	95	70.5	64	1 - > 128	0	> 128	16 - > 128	29.5	> 8	≤ 0.06 - > 8	2.1	> 128	8 - > 128	35.8	> 32	0.5 - > 32	37	97.3	2	0.5 - > 8
	MDR, no MBL	111	74.8	32	1 - > 128	19.8	> 128	1 - > 128	23.4	> 8	≤ 0.06 - > 8	7.2	> 128	8 - > 128	29.7	> 32	0.5 - > 32	52	98.1	2	0.5 - > 8
Spain (7/0.3)	All *P. aeruginosa*	330	97.3	8	0.06 - 64	81.2	32	0.06 - > 128	73.3	> 8	≤ 0.06 - > 8	70.9	> 128	≤ 0.25 - > 128	94.2	8	≤ 0.25 - > 32	35	100	2	1 - 4
	All *P. aeruginosa*, no MBL	329	97.6	8	0.06 - 64	81.5	32	0.06 - > 128	73.6	> 8	≤ 0.06 - > 8	71.1	> 128	≤ 0.25 - > 128	94.5	8	≤ 0.25 - > 32	35	100	2	1 - 4
	MEM NS, no MBL	87	90.8	8	1 - 64	48.3	64	2 - > 128	0	> 8	4 - > 8	24.1	> 128	4 - > 128	87.4	32	0.5 - > 32	5	100	4	1 - 4
	CAZ NS, no MBL	61	86.9	16	1 - 64	0	64	16 - > 128	26.2	> 8	0.5 - > 8	3.3	> 128	16 - > 128	86.9	16	1 - > 32	7	100	4	1 - 4
	MDR, no MBL	85	90.6	8	2 - 64	35.3	64	2 - > 128	20.0	> 8	0.5 - > 8	4.7	> 128	16 - > 128	84.7	32	1 - > 32	8	100	4	1 - 4
Sweden (4/0)	All *P. aeruginosa*	128	96.9	4	0.5 - 32	90.6	8	0.5 - > 128	87.5	4	≤ 0.06 - > 8	85.9	64	≤ 0.25 - > 128	96.1	8	0.5 - > 32	106	100	4	1 - 4
	All *P. aeruginosa*, no MBL	128	96.9	4	0.5 - 32	90.6	8	0.5 - > 128	87.5	4	≤ 0.06 - > 8	85.9	64	≤ 0.25 - > 128	96.1	8	0.5 - > 32	105	100	4	1 - 4
	MEM NS, no MBL	16	87.5	16	1 - 32	75.0	128	2 - > 128	0	> 8	4 - > 8	56.3	> 128	4 - > 128	68.8	32	1 - > 32	32	100	4	1 - 4
	CAZ NS, no MBL	12	66.7	16	2 - 32	0	128	16 - > 128	66.7	> 8	0.25 - > 8	0	> 128	32 - > 128	75.0	32	2 - > 32	18	100	2	1 - 2
	MDR, no MBL	15	73.3	16	2 - 32	26.7	128	8 - > 128	53.3	> 8	0.25 - > 8	6.7	> 128	8 - > 128	66.7	32	2 - > 32	24	100	2	1 - 4
Turkey (5/1.0)	All *P. aeruginosa*	208	96.6	8	0.25 - 128	79.3	32	0.25 - > 128	67.8	> 8	≤ 0.06 - > 8	72.1	> 128	≤ 0.25 - > 128	83.2	16	≤ 0.25 - > 32	100	100	2	0.5 - 4
	All *P. aeruginosa*, no MBL	206	97.1	8	0.25 - 64	80.1	32	0.25 - > 128	68.0	> 8	≤ 0.06 - > 8	72.3	> 128	≤ 0.25 - > 128	83.5	16	≤ 0.25 - > 32	100	100	2	0.5 - 4
	MEM NS, no MBL	66	93.9	8	1 - 64	59.1	64	1 - > 128	0	> 8	4 - > 8	33.3	> 128	2 - > 128	54.6	32	1 - > 32	13	100	2	1 - 2
	CAZ NS, no MBL	41	85.4	16	1 - 64	0	128	16 - > 128	34.2	> 8	0.25 - > 8	4.9	> 128	8 - > 128	43.9	32	2 - > 32	13	100	2	1 - 4
	MDR, no MBL	52	88.5	16	1 - 64	28.9	128	2 - > 128	21.2	> 8	0.25 - > 8	3.9	> 128	4 - > 128	40.4	> 32	1 - > 32	17	100	2	1 - 4
United Kingdom (5/0.6)	All *P. aeruginosa*	179	98.3	4	0.12 - > 128	87.2	16	0.25 - > 128	86.0	4	≤ 0.06 - > 8	75.4	128	≤ 0.25 - > 128	95.0	8	≤ 0.25 - > 32	100	100	2	0.5 - 4
	All *P. aeruginosa*, no MBL	178	98.3	4	0.12 - > 128	87.1	16	0.25 - > 128	86.5	4	≤ 0.06 - > 8	75.3	128	≤ 0.25 - > 128	94.9	8	≤ 0.25 - > 32	100	100	2	0.5 - 4
	MEM NS, no MBL	24	91.7	8	1 - > 128	62.5	64	1 - > 128	0	> 8	4 - > 8	37.5	> 128	2 - > 128	87.5	16	0.5 - > 32	13	100	2	1 - 2
	CAZ NS, no MBL	23	87.0	16	1 - > 128	0	128	16 - > 128	60.9	> 8	0.12 - > 8	0	> 128	32 - > 128	82.6	16	1 - > 32	13	100	2	1 - 4
	MDR, no MBL	28	89.3	16	1 - > 128	25.0	128	2 - > 128	46.4	> 8	0.12 - > 8	3.6	> 128	16 - > 128	85.7	16	0.5 - > 32	17	100	2	1 - 4

*Colistin not tested in 2012; %S, percent susceptible based on EUCAST or FDA (ceftazidime-avibactam) breakpoints; MIC_{90} and range in mg/L; MBL, metallo β-lactamase; MEM NS, meropenem non- susceptible; CAZ NS, ceftazidime non- susceptible; MDR, multidrug-resistant

Results Summary

- **92.6% of all *P. aeruginosa* isolates were susceptible to ceftazidime-avibactam at the FDA breakpoint of ≤8 mg/L.**
- **Ceftazidime-avibactam showed the highest percentage of susceptibility compared to other β-lactams and amikacin. Only colistin showed a higher percentage of susceptibility.**
- **Ceftazidime-avibactam had the highest percentage of susceptibility against ceftazidime-non-susceptible, meropenem-non-susceptible, and MDR non-MBL-containing isolates, with the exception of colistin.**
- **Overall, 4.3% of *P. aeruginosa* were MBL-positive; 68% (104/153) of MBL isolates came from three countries (Russia, Greece, Romania). Ceftazidime-avibactam had decreased activity in countries with higher numbers of MBL-producing isolates. This is consistent with the lack of activity of avibactam against MBLs.**
- **High percentages of susceptibility to ceftazidime-avibactam were seen across all countries, with a few exceptions (Table 1):**
  - **Countries with a high number of MBL-producing isolates (Russia, Romania, and Greece) showed reduced susceptibility to ceftazidime-avibactam.**
  - **Percentage susceptibility of ceftazidime-non-susceptible non-MBL-producing isolates was lower in Greece, Romania, and Sweden.**

Conclusions

- **Regardless of the resistant phenotype analyzed, ceftazidime-avibactam and colistin were the most active agents against non-MBL-containing *P. aeruginosa* isolates from Europe.**
- **Country differences in *in vitro* activity of CAZ AVI were noted, with consistently high activity in countries with no MBLs (exemplified by Denmark and The Netherlands), and decreased activity in countries with higher number of MBLs (exemplified by Russia and Romania).**
- **These findings demonstrate the extent to which β-lactam resistance exists among *P. aeruginosa* isolates and show the potent *in vitro* activity of ceftazidime-avibactam against these isolates from Europe.**

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