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In vitro activity of Ceftazidime-Avibactam and Comparators against Gram-negative Pathogens in Europe - The International Network For Optimal Resistance Monitoring (INFORM) Global Surveillance Study 2012

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Introduction

Avibactam (AVI) is a novel non-β-lactam, β-lactamase inhibitor, being developed for use in combination with ceftazidime (CAZ). Avibactam does not have any clinically meaningful antibacterial activity in its own right, but is capable of protecting β-lactams from hydrolysis in Gram-negative bacteria that produce extended-spectrum β-lactamases (ESBLs) and carbapenemases including Ambler class A and/or class C enzyme producers, and some class D enzymes. Although ceftazidime is active against many Gram-negative bacteria, it is inactive against strains that produce ESBLs and/or highly-expressed class C β-lactamases. Avibactam is being evaluated in combination with ceftazidime to assess whether it enhances ceftazidime's spectrum of antibacterial activity against Gram-negative bacteria that produce ESBLs and/or carbapenemases. The INFORM study began monitoring the activity of ceftazidime-avibactam and comparators in 2012. This report describes their activity against Gram-negative pathogens collected in Europe.

Materials and Methods

In this first year, 5,169 clinically relevant Gram-negative pathogens were collected from 62 sites in 17 European countries (n): Austria (237), Belgium (313), Czech Republic (228), Denmark (116), France (333), Germany (362), Greece (382), Hungary (229), Italy (343), the Netherlands (196), Portugal (455), Romania (271), Russia (465), Spain (485), Sweden (270), Turkey (298), and the United Kingdom (190). Each site collected and identified consecutive fresh clinical isolates from documented intra-abdominal infections (IAI), urinary tract infections (UTI), skin and skin structure infections (SSSI), and lower respiratory tract infections (LRTI). Fourteen isolates came from unknown sources. All isolates were sent to a central laboratory, International Health Management Associates, Inc (IHMA) in Schaumburg, Illinois, where the isolates were further evaluated and stored.

Minimum inhibitory concentrations (MICs) were determined using broth microdilution panels prepared at IHMA. All broth microdilution testing, including panel manufacture, inoculation, incubation, was conducted following current CLSI guidelines [1], and interpreted using EUCAST 2013 guidelines [2]. *Escherichia coli, Klebsiella oxytoca, K. pneumoniae* and *Proteus mirabilis* were screened and confirmed for ESBL activity according to CLSI guidelines [3]. Quality control testing (QC) using the appropriate ATCC strains was performed on each day of testing following CLSI guidelines.

Statistical analyses were performed by Fisher's exact test, two tailed, using GraphPad Quick Calcs (GraphPad Software, Inc, 2014). Any $p<0.05$ was considered statistically significant.

Acknowledgements

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Results

Table 1. *In vitro* activity of ceftazidime, ceftazidime-avibactam, and comparators against Gram-negative pathogens from 15 EARS-Net countries representing the European Union (EU), Russia, and Turkey; bolded numbers show a significant decrease in %S compared to EU isolates ($p<0.5$).

Organism, Region (N)		CAZ	CAZ-AVI	AMK	DOR	LVX	MEM	TZP	TGC
Enterobacteriaceae									
EU (3557)	%S	80	99	95	98	80	98	80	77
	MIC_{90}	64	0.5	8	0.25	> 4	0.12	128	4
EU, ESBL (575)	%S	5	99	73	94	27	94	31	81
	MIC_{90}	> 128	1	32	0.5	> 4	0.25	> 128	2
Russia (394)	%S	**46**	100	**76**	**95**	**49**	**95**	**58**	74
	MIC_{90}	> 128	1	> 32	1	> 4	0.25	> 128	4
Russia, ESBL (151)	%S	1	100	59	97	16	98	30	72
	MIC_{90}	> 128	1	> 32	1	> 4	0.25	> 128	4
Turkey (195)	%S	**65**	100	**90**	98	78	99	**66**	**68**
	MIC_{90}	64	0.5	16	0.25	> 4	0.12	> 128	4
Turkey, ESBL (50)	%S	12	100	68	100	52	100	30	92
	MIC_{90}	> 128	0.5	16	0.12	> 4	0.06	> 128	1
A. baumannii									
EU (182)	%S	na	na	37	25	23	30	na	na
	MIC_{90}	> 128	128	> 32	> 4	> 4	> 8	> 128	4
Russia (31)	%S	na	na	**3**	**3**	**3**	**10**	na	na
	MIC_{90}	> 128	> 128	> 32	> 4	> 4	> 8	> 128	4
Turkey (43)	%S	na	na	28	**9**	9	16	na	na
	MIC_{90}	> 128	128	> 32	> 4	> 4	> 8	> 128	8
P. aeruginosa									
EU (613)	%S	85	98	90	73	68	79	80	na
	MIC_{90}	32	8	8	> 4	> 4	8	128	> 8
Russia (40)	%S	**70**	100	**68**	**58**	**43**	68	68	na
	MIC_{90}	64	8	> 32	> 4	> 4	> 8	128	> 8
Turkey (56)	%S	86	100	86	61	61	71	79	na
	MIC_{90}	16	4	32	> 4	> 4	8	128	> 8

AMK-amikacin, **CAZ**-ceftazidime, **CAZ-AVI**-ceftazidime-avibactam at a fixed concentration of 4 mg/L, **DOR**-doripenem, **LVX**-levofloxacin, **MEM**-meropenem, **TZP**-piperacillin-tazobactam, **TGC**-tigecycline; **%S**-percent susceptible; MIC_{90} in mg/L; **na**-no EUCAST breakpoint defined
*CAZ-AVI %S reported as % isolates with MIC ≤8mg/L.

Table 2. *In vitro* activity of ceftazidime, ceftazidime-avibactam, and comparators against *H. influenzae* from 15 EARS-Net countries representing the European Union (EU) and Turkey.

Organism	Location (N)		AMX	AMP	SAM	CAZ	CAZ-AVI	CRO	DOR	LVX	MEM
H. influenzae	EU (56)	%S	96	84	71	na	na	100	100	100	100
		MIC_{90}	2	2	4	0.12	0.06	≤ 0.03	1	0.015	0.25
	Turkey (4)	%S	75	75	75	na	na	100	75	100	100
		MIC_{90}	--	--	--	--	--	--	--	--	--

AMX-amoxicillin, **AMP**-ampicillin, **SAM**- ampicillin-sulbactam, **CAZ**-ceftazidime, **CAZ-AVI**-ceftazidime-avibactam at a fixed concentration of 4 mg/L, **CRO** -ceftriaxone, **DOR**-doripenem, **LVX**-levofloxacin, **MEM**-meropenem; **%S**-percent susceptible; MIC_{90} in mg/L; **na**-no EUCAST breakpoint defined; -- MIC_{90} not determined for n<10; no *H. influenzae* were collected in Russia.

Figure 1. Cumulative frequency distribution of ceftazidime (CAZ) and ceftazidime-avibactam (CAZ-AVI) MICs against *Enterobacteriaceae* from European Union (EU) countries, Russia and Turkey combined.

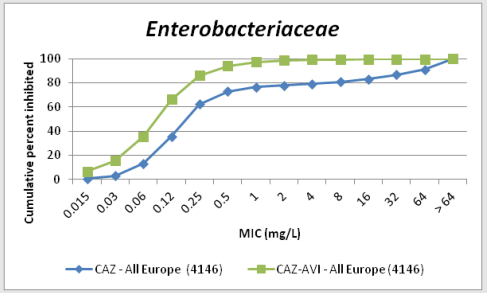
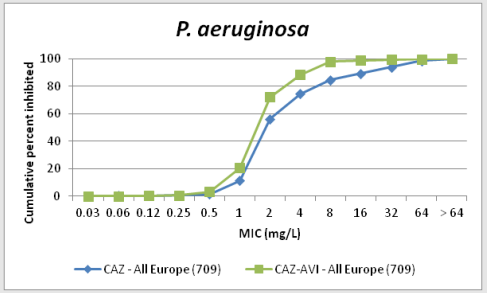


Figure 2. Cumulative frequency distribution of ceftazidime (CAZ) and ceftazidime-avibactam (CAZ-AVI) MICs against *P. aeruginosa* from European Union (EU) countries, Russia and Turkey combined.



Cumulative frequency distribution of ceftazidime (CAZ) and ceftazidime-avibactam (CAZ-AVI) MICs against *H. influenzae* from European Union (EU) countries and Turkey combined.

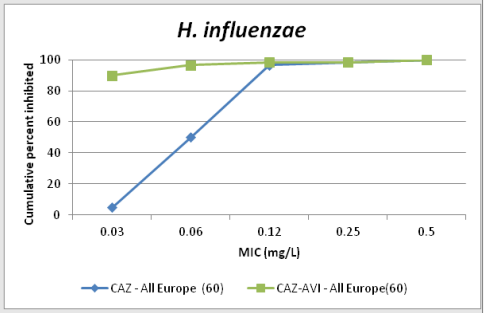
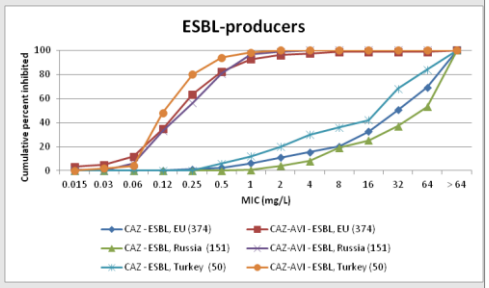


Figure 4. Cumulative frequency distribution of ceftazidime (CAZ) and ceftazidime-avibactam (CAZ-AVI) MICs against ESBL-producing *Enterobacteriaceae* from European Union (EU) countries, Russia and Turkey combined.



Conclusions

- Ceftazidime-avibactam demonstrated potent *in vitro* activity against *Enterobacteriaceae* from Europe, including ESBL-producing isolates, lowering the MIC_{90} values at least 128-fold.
- While isolates from Russia and Turkey were significantly more resistant to many of the antimicrobials tested, including ceftazidime, 100% of *Enterobacteriaceae* from these countries had a ceftazidime-avibactam MIC of ≤8 mg/L.
- Avibactam restored the *in vitro* activity of ceftazidime 4-fold against *P. aeruginosa*, and 2- to 4-fold against *H. influenzae*. All tested antimicrobials were ineffective against *A. baumannii*.