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In Vitro Activity of Aztreonam-Avibactam and Comparator Agents Against Multidrug-Resistant Enterobacterales Collected Globally as Part of the ATLAS Surveillance Program, 2016-2018

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Introduction

Avibactam is a serine-β-lactamase inhibitor in development with aztreonam for treatment of infections caused by drug-resistant Enterobacterales, especially carbapenem-resistant isolates co-producing serine- and metallo-β-lactamases, which are often resistant to agents from multiple drug classes. This study evaluated the *in vitro* activity of aztreonam-avibactam (ATM-AVI) and comparators against Enterobacterales collected globally as part of the Antimicrobial Testing Leadership and Surveillance (ATLAS) program.

Methods

44,671 non-duplicate clinical isolates were collected in 2016-2018 in 51 countries in Europe, Asia/Pacific (excluding China and India), Middle East/Africa, and Latin America. Susceptibility testing was performed by CLSI broth microdilution and interpreted using CLSI 2020 and FDA (tigecycline) breakpoints (1-3). ATM-AVI was tested at a fixed concentration of 4 μg/mL AVI. Drug-resistant phenotypes were defined as: multidrug resistant (MDR), resistant to ≥3 of 7 sentinel agents (amikacin, aztreonam, cefepime, colistin, levofloxacin, meropenem, piperacillin-tazobactam); extensively drug resistant (XDR), susceptible to ≤2 sentinel agents; and pandrug resistant (PDR), non-susceptible to all sentinel agents. Isolates with meropenem MIC >1 μg/mL were screened for β-lactamase genes by PCR and sequencing (4).

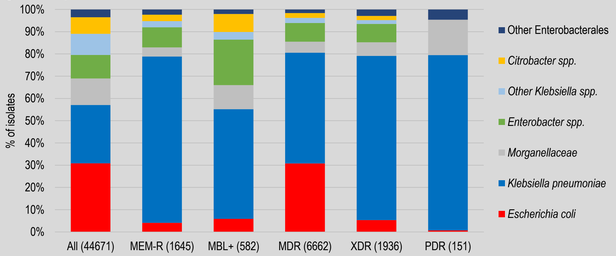
Results

Table. *In vitro* activity of aztreonam-avibactam and comparators against overall and resistant subsets of Enterobacterales isolates

Region[a]	Phenotype (n)[b]	Drug (MIC_{50} [μg/mL]/% Susceptible)[c]											
		ATM-AVI		ATM		MEM		AMK		TGC		CST[d]	
		MIC_{50}	%S	MIC_{50}	%S	MIC_{50}	%S	MIC_{50}	%S	MIC_{50}	%S	MIC_{50}	%S
Global	All (44671)	0.12	NA	64	74.2	0.12	95.7	8	97.4	1	97.0	>8	0.0
	MEM-R (1645)	0.5	NA	>128	10.7	>8	0.0	>32	64.1	2	91.9	>8	0.0
	MBL+ (582)	0.5	NA	>128	19.6	>8	5.2	>32	59.1	4	87.1	>8	0.0
	MDR (6662)	0.5	NA	>128	4.8	>8	73.0	>32	84.4	2	94.2	>8	0.0
	XDR (1936)	0.5	NA	>128	4.0	>8	16.8	>32	55.7	2	91.0	>8	0.0
	PDR (151)	0.5	NA	>128	0.0	>8	0.0	>32	0.0	4	75.5	>8	0.0
APAC	All (7256)	0.12	NA	64	73.9	0.12	97.2	4	98.4	1	97.2	>8	0.0
	MEM-R (175)	1	NA	>128	13.7	>8	0.0	>32	84.0	4	86.9	>8	0.0
	MBL+ (126)	0.5	NA	>128	17.5	>8	4.8	>32	88.1	4	88.9	2	0.0
	MDR (1015)	0.5	NA	>128	5.3	>8	82.2	16	90.4	2	92.6	>8	0.0
	XDR (207)	1	NA	>128	3.4	>8	25.6	>32	65.2	4	87.0	>8	0.0
	PDR (3)	0.25-1	NA	128->128	0.0	8->8	0.0	32->32	0.0	1->8	33.3	>8	0.0
EUR	All (24803)	0.12	NA	64	76.5	0.12	95.4	8	97.2	1	96.9	>8	0.0
	MEM-R (983)	0.5	NA	>128	11.1	>8	0.0	>32	58.9	2	91.0	>8	0.0
	MBL+ (319)	0.5	NA	>128	18.2	>8	4.7	>32	49.2	4	84.6	>8	0.0
	MDR (3371)	0.5	NA	>128	4.6	>8	67.8	>32	81.1	2	93.7	>8	0.0
	XDR (1161)	0.5	NA	>128	4.3	>8	15.0	>32	53.4	4	89.8	>8	0.0
	PDR (119)	0.5	NA	>128	0.0	>8	0.0	>32	0.0	4	71.4	>8	0.0
LATAM	All (8196)	0.12	NA	128	68.7	0.12	94.7	8	96.6	1	97.4	>8	0.0
	MEM-R (376)	0.5	NA	>128	6.9	>8	0.0	>32	68.9	2	96.5	>8	0.0
	MBL+ (76)	0.25	NA	>128	27.6	>8	6.6	>32	55.3	4	89.5	>8	0.0
	MDR (1648)	0.5	NA	>128	3.6	>8	75.3	32	85.8	2	96.7	>8	0.0
	XDR (442)	0.5	NA	>128	2.3	>8	17.9	>32	57.9	2	96.2	>8	0.0
	PDR (26)	0.5	NA	>128	0.0	>8	0.0	>32	0.0	2	100	>8	0.0
MEA	All (4416)	0.12	NA	64	71.8	0.12	96.9	8	98.0	1	96.7	>8	0.0
	MEM-R (111)	0.5	NA	>128	15.3	>8	0.0	>32	62.2	2	91.9	>8	0.0
	MBL+ (61)	0.25	NA	>128	21.3	>8	6.6	>32	55.7	2	93.4	>8	0.0
	MDR (628)	0.5	NA	>128	7.6	>8	79.9	32	89.0	2	92.8	>8	0.0
	XDR (126)	0.5	NA	>128	7.9	>8	15.1	>32	53.2	2	90.5	>8	0.0
	PDR (3)	0.12-4	NA	16->128	0.0	>8->8	0.0	32->32	0.0	0.25-4	66.7	>8	0.0

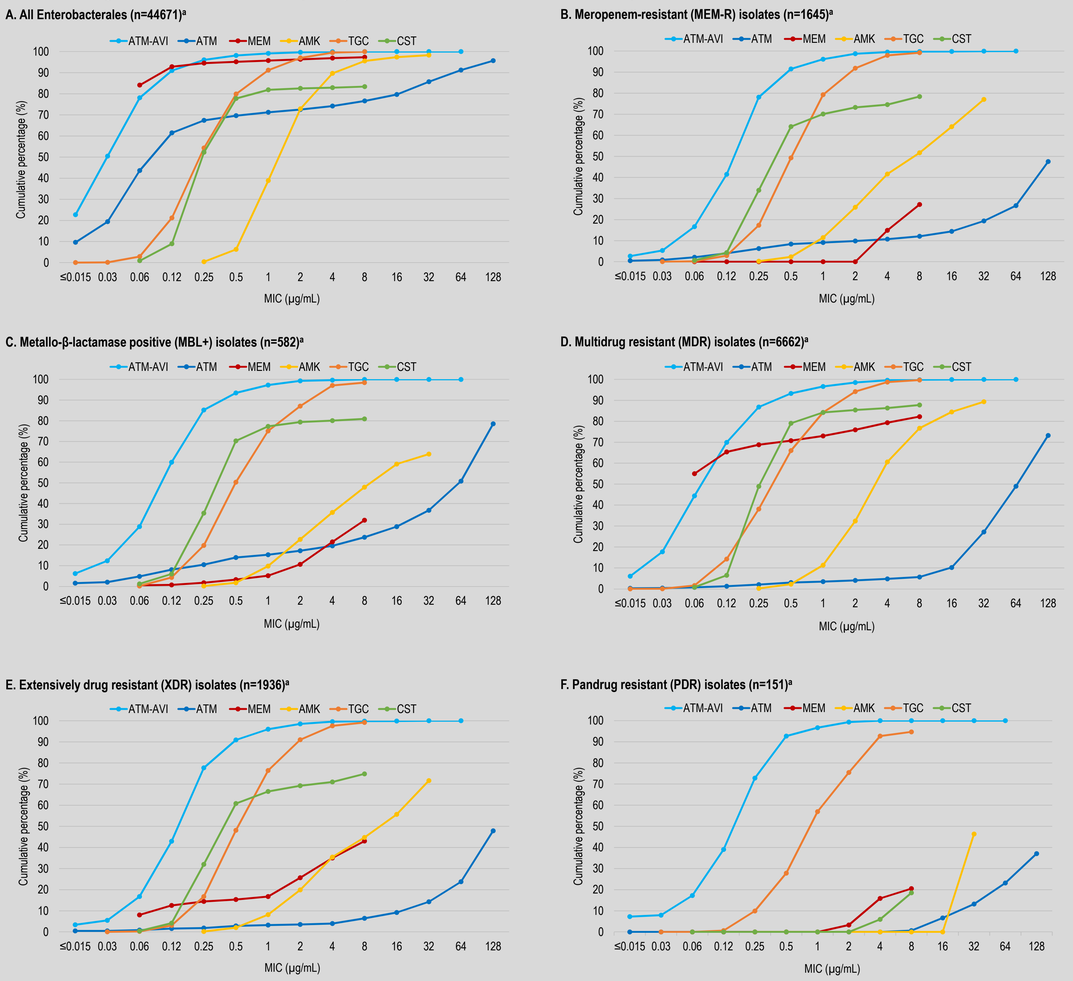
[a]Regions: APAC, Asia/South Pacific (Australia, Hong Kong, Japan, Malaysia, Philippines, Singapore, South Korea, Taiwan, Thailand); EUR, Europe (Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Netherlands, Poland, Portugal, Romania, Russia, Spain, Sweden, Switzerland, Turkey, Ukraine, United Kingdom); LATAM, Latin America (Argentina, Brazil, Chile, Colombia, Costa Rica, Dominican Republic, Guatemala, Mexico, Panama, Venezuela); MEA, Middle East/Africa (Israel, Jordan, Kuwait, Morocco, Nigeria, Saudi Arabia, South Africa).
[b]MEM-R, meropenem-resistant; MBL+, metallo-β-lactamase positive (a gene encoding an MBL was detected by PCR); MDR, multidrug resistant (resistant to ≥3 of 7 sentinel agents [AMK, ATM, CST, MEM, cefepime, levofloxacin, piperacillin-tazobactam]); XDR, extensively drug resistant (susceptible to ≤2 sentinel agents); PDR, pandrug resistant (non-susceptible to all sentinel agents).
[c]ATM-AVI, aztreonam-avibactam; ATM, aztreonam; MEM, meropenem; AMK, amikacin; TGC, tigecycline; CST, colistin; NA, no breakpoints available. % Susceptible was determined using CLSI 2020 breakpoints for all agents except TGC. TGC MICs were interpreted using U.S. FDA breakpoints.
[d]CLSI approved new breakpoints for colistin in 2020. A susceptible breakpoint is no longer defined for colistin due to clinical and PK/PD data that demonstrated limited clinical efficacy for this agent.

Figure 1. Species distribution of resistant subsets of Enterobacterales[a]



[a]*Citrobacter* spp. included *C. amalonaticus*, *C. braakii*, *C. farmeri*, *C. freundii*, *C. gillenii*, *C. koseri*, *C. murliniae*, *C. sedlakii*, *C. youngae*, and *Citrobacter*, species not determined; *Enterobacter* spp. included *E. asburiae*, *E. cloacae*, *E. hormaechei*, *E. kobei*, *E. ludwigii*, and *Enterobacter*, species not determined; *Morganellaceae* included *Morganella morganii*, *Proteus* spp. (*P. hauseri*, *P. mirabilis*, *P. penneri*, *P. vulgaris*, *Proteus*, species not determined), and *Providencia* spp. (*P. alcalifaciens*, *P. rettgeri*, *P. stuartii*, *Providencia*, species not determined); Other *Klebsiella* spp. included *K. aerogenes*, *K. oxytoca*, and *K. variicola*; Other Enterobacterales included *Cronobacter sakazakii*, *Escherichia vulneris*, *Kluyvera ascorbata*, *Kosakonia cowanii*, *Lelliottia amnigena*, *Pantoea* spp. (*P. agglomerans*, *P. dispersa*, *P. septica*, *Pantoea*, species not determined), *Pluribacter gergoviae*, *Raoultella* spp. (*R. ornithinolytica*, *R. planticola*, *R. terrigena*), *Salmonella*, species not determined, and *Serratia* spp. (*S. fonticola*, *S. liquefaciens*, *S. marcescens*, *S. rubidaea*, *S. ureilytica*, *Serratia*, species not determined).

Figure 2. Cumulative MIC susceptibility curves for aztreonam-avibactam and comparators against overall and resistant isolates



[a]ATM-AVI, aztreonam-avibactam; ATM, aztreonam; MEM, meropenem; AMK, amikacin; TGC, tigecycline; CST, colistin. The endpoints shown represent the highest concentration tested of each drug. The remaining tested isolates had MICs higher than their endpoint values.

Results

- 14.9%, 4.3%, 3.7%, 1.3%, and 0.3% of Enterobacterales collected globally were MDR, XDR, MEM-R, MBL+, and PDR, respectively. *Klebsiella pneumoniae* composed the majority of isolates with resistant phenotypes, ranging from 49% of MBL+ isolates to 79% of PDR isolates. *Enterobacter* spp. and *Citrobacter* spp. were more common among MBL+ isolates and *E. coli* was more common among MDR isolates than in other resistant subsets (Figure 1).
- ATM-AVI tested with MIC_{90} values of 0.12 μg/mL against all Enterobacterales and 0.5 μg/mL against subsets of resistant isolates (Table 1, Figure 2A-Figure 2F).
- On the regional level, similar ATM-AVI values were observed against all (MIC_{90}, 0.12 μg/mL) and resistant isolates (MIC_{90}, 0.25-1 μg/mL) collected in Asia/South Pacific, Europe, Latin America, and Middle East/Africa (Table 1).
- The tested comparators, excluding tigecycline, showed percentages of susceptibility <90% against regional and global subsets of resistant isolates in most cases (Table 1).
- 99.97% (44658 of 44671) Enterobacterales, including all MBL-positive and PDR isolates, were inhibited by ≤8 μg/mL of ATM-AVI (Figure 2A-Figure 2F).

Conclusions

Based on MIC_{90} values, ATM-AVI demonstrated potent *in vitro* activity against resistant and MBL-positive subsets of Enterobacterales collected globally.

ATM-AVI could be an effective therapy for difficult-to-treat infections caused by drug-resistant Enterobacterales.

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Disclosures

This study was sponsored by Pfizer. AZ's rights to aztreonam-avibactam were acquired by Pfizer in December 2016. IHMA received financial support from Pfizer in connection with the study and the development of this poster. K. Kazmierczak and D. Sahm are employees of IHMA. G. Stone, an employee of and shareholder in AZ at the time of the study, is currently an employee of Pfizer. F. Arhin is an employee of Pfizer. This study has been funded in part by BARDA, under OT number HHSO100201500029C.