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In Vitro Activity of Novel Ceftazidime-Avibactam and Aztreonam-Avibactam Combinations against Carbapenem-Non-Susceptible *Enterobacteriaceae* Isolates by Phenotype Collected in Latin America from 2014-2017 as part of the INFORM Surveillance Program

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Introduction

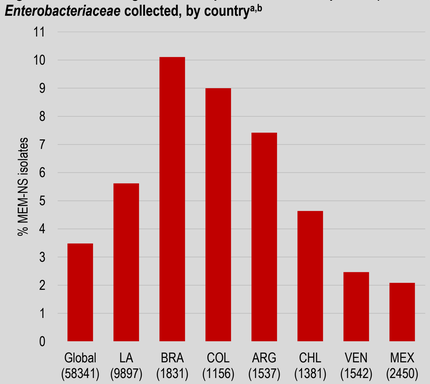
Carbapenem-nonsusceptible *Enterobacteriaceae* (CRE) are often multidrug-resistant and infections caused by these organisms are associated with increased morbidity and mortality. The combinations of avibactam, a non-β-lactam β-lactamase inhibitor of Class A, C, and some Class D serine β-lactamases, with ceftazidime and aztreonam are being launched and developed, respectively, to treat infections caused by CRE. Ceftazidime-avibactam (CAZ-AVI) demonstrates potent *in vitro* activity against CRE, except those producing metallo-β-lactamases (MBLs), whereas aztreonam-avibactam (ATM-AVI) inhibits the growth of both MBL-positive and MBL-negative CRE. We evaluated the *in vitro* activity of CAZ-AVI and ATM-AVI against *Enterobacteriaceae* isolates non-susceptible to meropenem (MEM-NS) collected in 2014-2017 in Latin America through the International Network for Optimal Resistance Monitoring (INFORM) global surveillance program.

Methods

- 9897 non-duplicate, clinically significant *Enterobacteriaceae* isolates were collected from 2014-2017 from 29 hospital laboratories located in Argentina, Brazil, Chile, Colombia, Mexico, and Venezuela.
- Susceptibility testing was performed by Clinical and Laboratory Standards Institute (CLSI) broth microdilution methodology and interpreted according to CSLI 2018 guidelines [1,2].
- Avibactam was tested at a fixed concentration of 4 μg/mL in combination with ceftazidime and aztreonam.
- 556 meropenem non-susceptible *Enterobacteriaceae* isolates (MEM-NS, MIC >1 μg/mL) were collected from patients with urinary tract (n=149, 26.8%), intra-abdominal (n=107, 19.2%), respiratory tract (n=104, 18.7%), skin and soft tissue (n=98, 17.6%), and bloodstream (n=98, 17.6%) infections.
- MEM-NS isolates were screened for the presence of β-lactamase genes (ESBLs, plasmid-mediated AmpCs, serine carbapenemases, and MBLs) by PCR and sequencing [3].

Results

Figure 1. Percentage of meropenem non-susceptible (MEM-NS) *Enterobacteriaceae* collected, by country[a,b]



[a]Global, Europe (Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Netherlands, Poland, Portugal, Romania, Russia, Spain, Sweden, Turkey, United Kingdom), Middle East/Africa (Israel, Kenya, Kuwait, Nigeria, South Africa), Asia/Pacific (Australia, Hong Kong, Japan, Malaysia, Philippines, South Korea, Taiwan, Thailand), and Latin America.
[b]LA, Latin America; ARG, Argentina; BRA, Brazil; CHL, Chile; COL, Colombia; MEX, Mexico; VEN, Venezuela..

Figure 2A-2C. Species distribution of all MEM-NS, serine carbapenemase-positive and metallo-β-lactamase (MBL)-positive *Enterobacteriaceae*

2A) MEM-NS isolates (n=556)

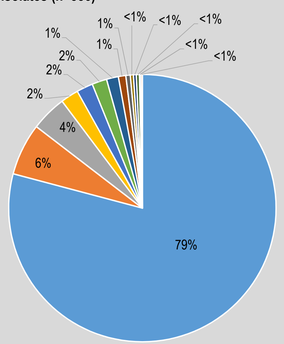
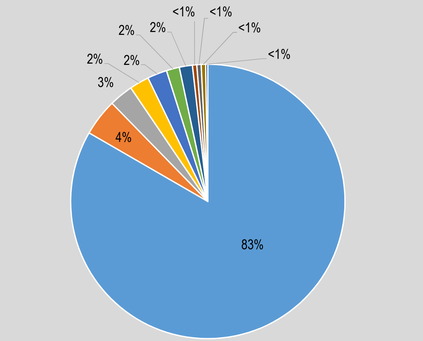
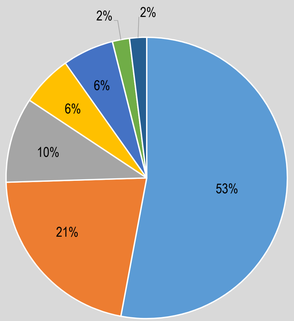


Figure 2B. Serine carbapenemase-producing isolates (n=390)[a]



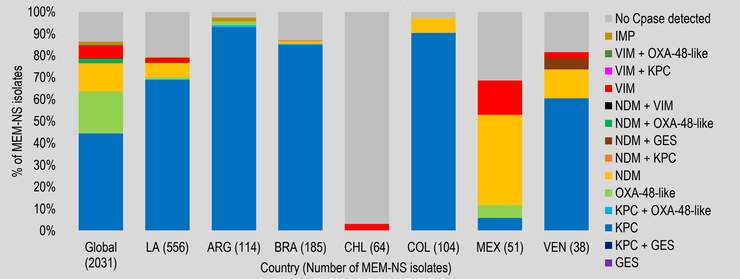
[a] Includes isolates carrying KPC-2 (n=336), KPC-3 (n=45), KPC-30 (n=1), KPC-type (n=1), OXA-163 (n=2), OXA-232 (n=2), OXA-181 (n=1), KPC-2 + OXA-163 (n=1), and KPC-2 + OXA-370 (n=1) carbapenemases. Excludes 3 isolates co-carrying serine carbapenemases and MBLs.

Figure 2C. MBL-producing isolates (n=51)[a,b]



[a] Includes isolates carrying NDM-1 (n=35), VIM-23 (n=8), VIM-1 (n=2), VIM-24 (n=1), IMP-8 (n=2), NDM-1 and GES-2 (n=2), and NDM-1 and KPC-2 (n=1).
[b] 86.3% (n=44) of MBL-producing isolates carried an Ambler Class A or Class C β-lactamase capable of hydrolyzing third-generation cephalosporins or monobactams.

Figure 3. Distribution of carbapenem resistance mechanisms among MEM-NS *Enterobacteriaceae*[a,b]



[a]Global, Europe (Austria, Belgium, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Netherlands, Poland, Portugal, Romania, Russia, Spain, Sweden, Turkey, United Kingdom), Middle East/Africa (Israel, Kenya, Kuwait, Nigeria, South Africa), Asia/Pacific (Australia, Hong Kong, Japan, Malaysia, Philippines, South Korea, Taiwan, Thailand), and Latin America.
[b]LA, Latin America; ARG, Argentina; BRA, Brazil; CHL, Chile; COL, Colombia; MEX, Mexico; VEN, Venezuela. No Cpase detected, no gene encoding an acquired carbapenemase (Cpase) was detected by PCR.

Table 1. *In vitro* activity of ceftazidime-avibactam (CAZ-AVI), aztreonam-avibactam (ATM-AVI) and comparators against isolates collected in Latin America

Region/ Country	Phenotype/ β-lactamase carriage (n)[a]	MIC$_{90}$ [μg/mL]/% Susceptible[b]											
		CAZ		CAZ-AVI		ATM		ATM-AVI		TGC		CST	
		MIC$_{90}$	%S	MIC$_{90}$	%S	MIC$_{90}$	%S	MIC$_{90}$	%S	MIC$_{90}$	%S	MIC$_{90}$	%S
Latin America	All *Eba* (9897)	64	70.2	0.5	99.4	128	68.5	0.12	NA	2	96.2	>4	82.9
	MEM-NS *Eba* (556)	>128	6.1	8	90.7	>128	5.8	0.5	NA	2	95.0	>4	75.9
	Cpase- (115)	>128	9.6	4	99.1	>128	8.7	1	NA	2	95.7	>4	73.9
	KPC+, MBL- (385)	>128	5.5	2	100	>128	0.3	0.5	NA	2	96.6	>4	75.6
	OXA-48+, MBL- (5)	0.5->128	2 of 5	0.12-1	5 of 5	0.5-64	2 of 5	0.06-0.5	NA	0.25-2	5 of 5	0.25-1	5 of 5
	MBL+ (51)	>128	0	>128	0	>128	37.3	0.25	NA	4	80.4	>4	80.4
Argentina	All *Eba* (1537)	64	74.0	0.5	99.6	128	73.3	0.12	NA	2	95.8	>4	80.6
	MEM-NS *Eba* (114)	>128	0.9	2	98.3	>128	1.8	0.5	NA	2	98.3	>4	62.3
	Cpase- (3)	16-32	0 of 3	0.06-0.25	3 of 3	0.25->128	1 of 3	0.06-0.06	NA	0.25-1	3 of 3	0.25-1	3 of 3
	KPC+, MBL- (107)	>128	0.9	2	100	>128	0.9	0.5	NA	2	98.1	>4	59.8
	OXA-48+, MBL- (2)	128->128	0 of 2	1-1	2 of 2	64-64	0 of 2	0.5-0.5	NA	1-1	2 of 2	0.5-1	2 of 2
	MBL+ (2)	>128->128	0 of 2	>128->128	0 of 2	16-64	0 of 2	0.5-0.5	NA	0.12-2	2 of 2	0.25-0.5	2 of 2
Brazil	All *Eba* (1831)	64	73.1	0.5	99.8	128	70.1	0.25	NA	2	96.8	>4	82.0
	MEM-NS *Eba* (185)	>128	6.5	2	97.8	>128	2.2	0.5	NA	2	93.5	>4	79.5
	Cpase- (24)	>128	20.8	2	95.8	>128	16.7	1	NA	1	95.8	>4	87.5
	KPC+, MBL- (158)	>128	4.4	2	100	>128	0	0.5	NA	2	93.0	>4	77.8
	MBL+ (3)	>128->128	0 of 3	>128->128	0 of 3	>128->128	0 of 3	0.06-0.25	NA	0.5-1	3 of 3	0.25-0.5	3 of 3
Chile	All *Eba* (1381)	128	69.1	1	99.9	128	66.6	0.25	NA	2	95.6	>4	82.8
	MEM-NS *Eba* (64)	>128	3.1	4	96.9	>128	4.7	1	NA	2	95.3	>4	65.6
	Cpase- (62)	>128	3.2	4	100	>128	3.2	1	NA	2	95.2	>4	64.5
	MBL+ (2)	>128->128	0 of 2	>128->128	0 of 2	2-8	1 of 2	0.12-0.12	NA	1-1	2 of 2	0.25-0.5	2 of 2
Colombia	All *Eba* (1156)	64	74.2	0.5	99.3	64	69.7	0.12	NA	2	96.6	>4	82.4
	MEM-NS *Eba* (104)	>128	13.5	4	93.3	>128	3.9	0.5	NA	2	96.2	>4	82.7
	Cpase- (3)	4->128	1 of 3	0.12-2	3 of 3	32-64	0 of 3	0.03-4	NA	0.25-0.5	3 of 3	0.25-1	3 of 3
	KPC+, MBL- (94)	>128	13.8	4	100	>128	0	0.5	NA	2	100	>4	85.1
	MBL+ (7)	64->128	0 of 7	64->128	0 of 7	≤0.015-64	4 of 7	≤0.015-0.25	NA	0.5-4	3 of 7	0.25->4	3 of 7
Mexico	All *Eba* (2450)	64	61.4	0.5	98.8	128	61.4	0.12	NA	2	95.9	>4	84.5
	MEM-NS *Eba* (51)	>128	5.9	>128	43.1	>128	29.4	1	NA	4	88.2	>4	80.4
	Cpase- (16)	>128	6.3	2	100	>128	6.3	4	NA	2	100	>4	75.0
	KPC+, MBL- (3)	8->128	0 of 3	0.5-8	3 of 3	64->128	0 of 3	0.12-1	NA	0.25-1	3 of 3	0.25-2	3 of 3
	OXA-48+, MBL- (3)	0.5-32	2 of 3	0.12-1	3 of 3	0.5-32	2 of 3	0.06-0.25	NA	0.25-2	3 of 3	0.25-0.25	3 of 3
	MBL+ (29)	>128	0	>128	0	>128	41.4	0.25	NA	4	79.3	>4	79.3
Venezuela	All *Eba* (1542)	32	75.0	0.25	99.3	64	73.7	0.12	NA	1	96.9	>4	84.0
	MEM-NS *Eba* (38)	>128	5.3	>128	79.0	>128	10.5	0.5	NA	2	97.4	2	92.1
	Cpase- (7)	0.5->128	2 of 7	0.25-2	7 of 7	0.06->128	2 of 7	0.06-0.5	NA	0.12-4	6 of 7	0.25->4	6 of 7
	KPC+, MBL- (23)	>128	0	1	100	>128	0	0.5	NA	1	100	2	91.3
	MBL+ (8)	64->128	0 of 8	16->128	0 of 8	0.12->128	2 of 8	0.03-0.5	NA	0.25-2	8 of 8	0.12-1	8 of 8

[a] *Eba*, *Enterobacteriaceae*, MEM-NS, meropenem non-susceptible; Cpase, carbapenemase; MBL, metallo-β-lactamase; CAZ, ceftazidime; CAZ-AVI, ceftazidime-avibactam; ATM, aztreonam; ATM-AVI, aztreonam-avibactam; TGC, tigecycline; CST, colistin; NA, no breakpoints available; n, number of isolates.
[b] % Susceptible was defined using CLSI 2018 breakpoints except for TGC (U.S. FDA [4]) and CST (EUCAST [5]). MIC ranges instead of MIC$_{90}$ values were provided for subsets of fewer than 10 isolates.

Results

- 5.6% of *Enterobacteriaceae* collected in Latin American (LA) countries were MEM-NS, compared to 3.5% of isolates collected worldwide. Percentages of MEM-NS isolates ranged from 10.1% (Brazil, BRA) to 2.1% (Mexico, MEX) (Figure 1).
- *Klebsiella pneumoniae* composed 83.3% of serine carbapenemase (cpase)-positive and 52.9% of MBL-positive isolates (Figures 2A-2C).
- 70.1% of MEM-NS isolates collected in LA carried serine cpases (KPC and OXA-48-like), 8.6% carried MBLs (NDM-, VIM-, and IMP-type), and 0.5% co-carried MBLs and serine cpases. No acquired cpase was detected in 20.7% of isolates, which were presumed to possess alterations in drug permeability or efflux combined with ESBL or AmpC production (Figure 3).
- There were substantial differences in carbapenem resistance mechanism found in the different countries.
- CAZ-AVI showed potent *in vitro* activity against all *Enterobacteriaceae* collected in LA (99.4% susceptible, S), as well as against the subsets of all MEM-NS isolates (90.7% S), cpase-negative isolates (99.1% S), and KPC- and OXA-48-like-positive MBL-negative isolates (100% S) (Table 1).
- As expected, CAZ-AVI was not active against MBL-positive *Enterobacteriaceae* (0% S), which composed 9.2% of all MEM-NS isolates collected in LA and ranged from <2% (ARG, BRA) to 57% (MEX) (Table 1, Figure 3).
- ATM-AVI tested with an MIC$_{90}$ of 0.12 μg/mL against all collected *Enterobacteriaceae*. MIC$_{90}$ values were 0.25 μg/mL against MBL-positive isolates, 0.5 μg/mL against all MEM-NS and KPC-positive isolates, and 1 μg/mL against cpase-negative isolates. MICs were ≤0.5 μg/mL against isolates carrying OXA-48-like cpases (n=5) (Table 1).
- At the country level, ATM-AVI MIC$_{90}$ values against MEM-NS isolates ranged from 0.5-1 μg/mL (Table 1). 100% of MEM-NS *Enterobacteriaceae* were inhibited by ≤8 μg/mL of ATM-AVI.
- In comparison, percentages of susceptibility to tigecycline and colistin were 95.0% and 75.9%, respectively, among all MEM-NS isolates and 80.4% among MBL-positive isolates (Table 1).

Conclusions

- CAZ-AVI and ATM-AVI displayed potent *in vitro* activity against MEM-NS *Enterobacteriaceae* collected in LA (90.7% susceptible and 100% inhibited at ≤8 μg/mL, respectively).
- Based on MIC$_{90}$ values, ATM-AVI was the most potent agent tested against MEM-NS *Enterobacteriaceae* collected in the region.
- CAZ-AVI was highly active against cpase-negative and serine cpase-positive isolates, but not active against MBL-positive *Enterobacteriaceae*. As a result, in countries with a higher incidence of MBL-producing isolates, activity of CAZ-AVI against MEM-NS isolates was reduced (MEX, VEN).
- Both agents could serve as promising options for treatment of infections caused by CRE in LA.

References

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Disclosures

This study was sponsored by AstraZeneca (AZ) and Pfizer. AZ's rights to ceftazidime-avibactam and aztreonam-avibactam were acquired by Pfizer in December 2016. IHMA received financial support from AZ in connection with the study and from Pfizer for the development of this poster. K. Kazmierczak and D. Sahm are employees of IHMA. G. Stone and B.L. de Jonge, employees of and shareholders in AZ at the time of the study, are currently employees of Pfizer.

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