P0330

Global Activity of Meropenem Against Gram-negative Isolates Collected in 2012-2014

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Revised Abstract

Objectives: Increasing resistance in gram-negative pathogens, especially due to extended-spectrum β-lactamases (ESBLs) and carbapenemases, has been reported worldwide, seriously limiting treatment options in some regions. Meropenem is a broad-spectrum carbapenem antibiotic that is highly refractory to degradation by many β-lactamases. This report uses data from a global surveillance study over the years 2012-2014 to examine susceptibility patterns of gram-negative pathogens to meropenem.
Methods: 48,626 clinically relevant gram-negative isolates from multiple body sources were collected in 2012-2014 from 202 sites in 39 countries. MICs were determined by CLSI broth microdilution and results were interpreted following EUCAST 2015 guidelines. Presence of extended-spectrum β-lactamase (ESBL), and carbapenemase (KPC, OXA-48-like, GES and metallo-β-lactamase) genes were determined using PCR in ceftazidime and carbapenem non-susceptible isolates.
Results: The percent susceptible (%S) of gram-negative isolates to meropenem in different geographic regions is shown in the table. Meropenem exhibited good activity against all *Enterobacteriaceae*, including the ESBL-producing subset. Slight regional differences were seen, which appears to be associated with regional differences in the incidence of carbapenemase enzymes. Meropenem exhibited moderate activity against *P. aeruginosa*, with differences across the different regions. The lower activity could not be fully attributed to the presence of carbapenemases, pointing to additional resistance mechanisms in this species. Meropenem showed reduced activity against *A. baumannii*.

	AP		EU		LA		MEA		NA	
	N	%S	N	%S	N	%S	N	%S	N	%S
Enterobacteriaceae	7,087	98.8	18,377	97.6	5,317	96.1	3,281	98.1	4,204	98.5
Enterobacteriaceae, ESBL-containing	1,434	96.3	3,070	92.1	1,350	91.3	803	96.3	281	94.7
Enterobacteriaceae minus carbapenemase-containing isolates	7,002	99.6	17,812	99.6	5,119	98.1	3,215	99.8	4,139	99.8
Escherichia coli	2,496	99.6	6,182	99.9	1,928	99.5	1,164	99.5	1,433	99.7
Klebsiella spp.	2,233	97.7	5,977	93.4	1,682	89.4	1,114	96.1	1,331	96.3
Citrobacter spp.	442	98.4	1,014	99.5	269	98.9	164	99.4	264	98.9
Enterobacter spp.	838	98.3	2,133	98.6	602	97.5	358	98.3	535	99.1
Pseudomonas aeruginosa	1,392	77.4	3,893	72.9	1,088	64.9	689	74.8	948	77.4
P. aeruginosa minus carbapenemase-containing isolates	1,337	80.6	3,703	76.6	982	71.5	642	80.2	945	77.7
Acinetobacter baumannii	398	42.2	1,229	34.0	299	20.1	189	23.3	235	42.1

AP, Asia/Pacific; EU, Europe; LA, Latin America; MEA, Middle East/Africa; NA, North America; ESBL, extended-spectrum β-lactamase MBL, metallo-β-lactamase

Conclusions: Despite being on the market for many years, resistance in *Enterobacteriaceae* and *P. aeruginosa* is still low and meropenem continues to display significant *in vitro* activity against these gram-negative pathogens. Resistance in *Enterobacteriaceae* seems to be primarily mediated by carbapenemase enzymes, while for *P. aeruginosa* other mechanisms are also in play.

Introduction

Increasing resistance in gram-negative pathogens, especially due to extended-spectrum β-lactamases (ESBLs) and carbapenemases, has been reported worldwide, seriously limiting treatment options in some regions. Meropenem is a broad-spectrum carbapenem antibiotic that is highly refractory to degradation by many β-lactamases. This report uses data from a global surveillance study over the years 2012-2014 to examine susceptibility patterns of gram-negative pathogens to meropenem.

Materials & Methods

- 48,626 clinically relevant gram-negative isolates from multiple body sources were collected in 2012-2014 from 202 sites in 39 countries. MICs were determined by the Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method [1]. MIC interpretive criteria followed EUCAST guidelines [2]. Colistin was tested in 2014 only.
- Isolates were screened for ESBL activity according to CLSI guidelines using ceftazidime and/or aztreonam followed by confirmation by the clavulanic inhibition test [3].
- An isolate of *Enterobacteriaceae* was defined as CRE if it was not susceptible to meropenem using EUCAST interpretive criteria [2].
- The presence of extended-spectrum β-lactamase (ESBL), and carbapenemase (KPC, OXA-48-like, GES and metallo-β-lactamase) genes were determined using PCR followed by amplification of the full-length genes and sequencing in ceftazidime and carbapenem non-susceptible isolates.

Results

Table 1. *In Vitro* Activity of Meropenem and Comparators Against Gram-negative Clinical Isolates and Subgroups

Organism Group	Region		Meropenem			Cefepime			Piperacillin-tazobactam			Levofloxacin			Amikacin			Tigecycline				Colistin		
		N	%S	MIC_{90}	Range	%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
All *Enterobacteriaceae*	Asia/Pacific	7087	**98.8**	0.12	≤ 0.004 - > 8	75.3	> 16	≤ 0.12 - > 16	81.2	64	≤ 0.25 - > 128	71.3	> 4	≤ 0.03 - > 4	**95.3**	8	≤ 0.25 - > 32	83.4	2	≤ 0.015 - > 8	2078	83.5	> 4	≤ 0.12 - > 4
	Europe	18377	**97.6**	0.12	≤ 0.004 - > 8	78.5	> 16	≤ 0.12 - > 16	76.8	128	≤ 0.25 - > 128	75.9	> 4	≤ 0.03 - > 4	**93.6**	8	≤ 0.25 - > 32	81.6	2	≤ 0.015 - > 8	7453	82.7	> 4	≤ 0.12 - > 4
	Latin America	5317	**96.1**	0.12	≤ 0.004 - > 8	67.5	> 16	≤ 0.12 - > 16	73.4	> 128	≤ 0.25 - > 128	64.4	> 4	≤ 0.03 - > 4	**89.7**	16	≤ 0.25 - > 32	82.2	2	≤ 0.015 - > 8	2168	82.2	> 4	≤ 0.12 - > 4
	MidEast/Africa	3281	**98.1**	0.12	≤ 0.004 - > 8	70.7	> 16	≤ 0.12 - > 16	75.0	64	≤ 0.25 - > 128	71.5	> 4	≤ 0.03 - > 4	**93.5**	8	≤ 0.25 - > 32	84.0	2	≤ 0.015 - > 8	1478	83.5	> 4	≤ 0.12 - > 4
	North America	4204	**98.5**	0.12	≤ 0.004 - > 8	89.9	2	≤ 0.12 - > 16	86.4	16	≤ 0.25 - > 128	80.1	> 4	≤ 0.03 - > 4	**97.1**	4	≤ 0.25 - > 32	84.0	2	≤ 0.015 - > 8	1573	84.6	> 4	≤ 0.12 - > 4
Enterobacteriaceae, no carbapenemase	Asia/Pacific	7002	**99.7**	0.12	≤ 0.004 - > 8	76.2	> 16	≤ 0.12 - > 16	82.1	32	≤ 0.25 - > 128	71.8	> 4	≤ 0.03 - > 4	**95.7**	8	≤ 0.25 - > 32	**93.7**	2	≤ 0.015 - > 8	2057	83.5	>4	≤ 0.12 - > 4
	Europe	17887	**99.7**	0.12	≤ 0.004 - > 8	80.5	> 16	≤ 0.12 - > 16	78.9	64	≤ 0.25 - > 128	77.5	> 4	≤ 0.03 - > 4	**95.2**	8	≤ 0.25 - > 32	**92.3**	2	≤ 0.015 - > 8	7236	82.9	>4	≤ 0.12 - > 4
	Latin America	5119	**99.1**	0.12	≤ 0.004 - > 8	69.9	> 16	≤ 0.12 - > 16	76.2	64	≤ 0.25 - > 128	66.1	> 4	≤ 0.03 - > 4	**91.1**	8	≤ 0.25 - > 32	**93.1**	2	≤ 0.015 - > 8	2062	82.4	>4	≤ 0.12 - > 4
	MidEast/Africa	3215	**99.8**	0.12	≤ 0.004 - > 8	71.9	> 16	≤ 0.12 - > 16	76.5	32	≤ 0.25 - > 128	72.3	> 4	≤ 0.03 - > 4	**94.3**	8	≤ 0.25 - > 32	**94.0**	2	≤ 0.015 - > 8	1446	83.4	>4	≤ 0.12 - > 4
	North America	4139	**99.9**	0.12	≤ 0.004 - > 8	**91.2**	> 16	≤ 0.12 - > 16	87.8	16	≤ 0.25 - > 128	81.2	> 4	≤ 0.03 - > 4	**97.9**	4	≤ 0.25 - > 32	**93.4**	2	≤ 0.015 - > 8	1550	84.6	>4	≤ 0.12 - > 4
Enterobacteriaceae, ESBL+	Asia/Pacific	1385	**99.1**	0.12	0.008 - > 8	4.6	> 16	≤ 0.12 - > 16	58.8	> 128	≤ 0.25 - > 128	31.0	> 4	≤ 0.03 - > 4	86.6	16	≤ 0.25 - > 32	86.6	2	0.06 - 8	412	**96.6**	1	≤ 0.12 - > 4
	Europe	2791	**98.9**	0.12	≤ 0.004 - > 8	4.0	> 16	≤ 0.12 - > 16	37.3	> 128	≤ 0.25 - > 128	28.5	> 4	≤ 0.03 - > 4	80.3	32	≤ 0.25 - > 32	84.0	2	0.03 - > 8	1238	**94.2**	1	0.25 - > 4
	Latin America	1258	**97.1**	0.25	≤ 0.004 - > 8	3.7	> 16	≤ 0.12 - > 16	40.8	> 128	≤ 0.25 - > 128	24.6	> 4	≤ 0.03 - > 4	77.7	32	≤ 0.25 - > 32	85.0	2	≤ 0.015 - > 8	511	**93.0**	1	0.25 - > 4
	MidEast/Africa	770	**99.5**	0.12	0.015 - > 8	2.7	> 16	≤ 0.12 - > 16	41.3	> 128	≤ 0.25 - > 128	37.4	> 4	≤ 0.03 - > 4	84.9	16	≤ 0.25 - > 32	86.5	2	0.06 - 8	368	**94.6**	1	0.25 - > 4
	North America	263	**100**	0.12	≤ 0.004 - > 8	9.9	> 16	≤ 0.12 - > 16	55.5	> 128	0.5 - > 128	18.3	> 4	≤ 0.03 - > 4	83.7	16	0.5 - > 32	86.7	2	0.06 - 8	102	**97.1**	1	≤ 0.12 - > 4
All *K. pneumoniae*	Asia/Pacific	1889	**97.5**	0.06	≤ 0.004 - > 8	70.1	> 16	≤ 0.12 - > 16	72.3	> 128	≤ 0.25 - > 128	76.2	> 4	≤ 0.03 - > 4	**94.2**	4	≤ 0.25 - > 32	86.2	2	≤ 0.015 - > 8	639	**98.1**	1	0.25 - > 4
	Europe	4830	**91.9**	0.5	≤ 0.004 - > 8	60.2	> 16	≤ 0.12 - > 16	58.3	> 128	≤ 0.25 - > 128	67.0	> 4	≤ 0.03 - > 4	89.3	16	≤ 0.25 - > 32	84.5	2	0.03 - > 8	2297	**95.7**	1	≤ 0.12 - > 4
	Latin America	1424	87.7	4	0.008 - > 8	52.2	> 16	≤ 0.12 - > 16	53.7	> 128	≤ 0.25 - > 128	62.3	> 4	≤ 0.03 - > 4	85.8	32	≤ 0.25 - > 32	84.1	2	0.06 - 8	643	**91.6**	2	0.25 - > 4
	MidEast/Africa	955	**95.7**	0.06	≤ 0.004 - > 8	51.0	> 16	≤ 0.12 - > 16	54.9	> 128	0.5 - > 128	70.5	> 4	≤ 0.03 - > 4	**91.0**	8	≤ 0.25 - > 32	86.8	2	0.06 - 8	485	**98.8**	1	0.25 - > 4
	North America	1057	**95.4**	0.06	≤ 0.004 - > 8	86.2	8	≤ 0.12 - > 16	81.5	64	≤ 0.25 - > 128	85.0	> 4	≤ 0.03 - > 4	**93.8**	4	≤ 0.25 - > 32	87.8	2	≤ 0.015 - 8	478	**98.7**	1	0.25 - > 4
K. pneumoniae, no carbapenemase	Asia/Pacific	1844	**99.7**	0.06	≤ 0.004 - > 8	71.7	> 16	≤ 0.12 - > 16	73.8	> 128	≤ 0.25 - > 128	77.5	> 4	≤ 0.03 - > 4	**95.2**	4	≤ 0.25 - > 32	86.4	2	≤ 0.015 - >8	625	**98.4**	1	0.25 - > 4
	Europe	4414	**99.3**	0.06	≤ 0.004 - > 8	65.6	> 16	≤ 0.12 - > 16	63.8	> 128	≤ 0.25 - > 128	72.3	> 4	≤ 0.03 - > 4	**94.5**	8	≤ 0.25 - > 32	85.9	2	0.03 - >8	2109	**97.8**	1	≤ 0.12 - > 4
	Latin America	1261	**97.5**	0.12	0.008 - > 8	58.3	> 16	≤ 0.12 - > 16	60.5	> 128	≤ 0.25 - > 128	68.5	> 4	≤ 0.03 - > 4	**90.6**	8	≤ 0.25 - > 32	86.0	2	0.06 - 8	556	**94.1**	1	0.25 - > 4
	MidEast/Africa	913	**99.6**	0.06	≤ 0.004 - > 8	53.3	>16	≤ 0.12 - > 16	57.4	128	≤ 0.5 - > 128	72.8	> 4	≤ 0.03 - > 4	**93.5**	8	≤ 0.25 - > 32	87.7	2	0.06 - 8	462	**99.1**	1	0.25 - > 4
	North America	1003	**100**	0.06	≤ 0.004 - > 8	**90.7**	1	≤ 0.12 - > 16	85.8	16	≤ 0.25 - > 128	89.1	4	≤ 0.03 - > 4	**97.1**	2	≤ 0.25 - > 32	89.1	2	≤ 0.015 - 8	457	**99.3**	1	0.25 - > 4
K. pneumoniae, ESBL+	Asia/Pacific	525	**99.2**	0.12	0.015 - > 8	6.7	> 16	≤ 0.12 - > 16	34.7	> 128	0.5 - > 128	45.5	> 4	≤ 0.03 - > 4	86.1	16	≤ 0.25 - > 32	72.4	2	0.06 - 8	188	**96.3**	1	0.25 - > 4
	Europe	1486	**98.2**	0.12	≤ 0.004 - > 8	2.0	> 16	≤ 0.12 - > 16	20.3	> 128	0.5 - > 128	33.8	> 4	≤ 0.03 - > 4	86.1	16	≤ 0.25 - > 32	77.5	2	0.03 - 8	727	**96.6**	1	0.25 - > 4
	Latin America	537	**94.4**	2	0.015 - > 8	5.2	> 16	≤ 0.12 - > 16	24.0	> 128	0.5 - > 128	40.6	> 4	≤ 0.03 - > 4	81.8	32	≤ 0.25 - > 32	76.7	2	0.06 - 8	230	**90.4**	2	0.25 - > 4
	MidEast/Africa	425	**99.3**	0.06	0.015 - > 8	3.3	> 16	≤ 0.12 - > 16	28.9	> 128	1 - > 128	53.9	> 4	≤ 0.03 - > 4	88.2	16	≤ 0.25 - > 32	83.5	2	0.06 - 8	215	**98.6**	1	0.25 - > 4
	North America	85	**100**	0.12	0.015 - 1	9.4	> 16	≤ 0.12 - > 16	36.5	> 128	2 - > 128	25.9	> 4	0.06 - > 4	78.8	32	0.5 - > 32	67.1	4	0.25 - 8	31	**100**	1	0.5 - 1
All *P. aeruginosa*	Asia/Pacific	1392	77.4	> 8	≤ 0.06 - > 8	80.2	16	≤ 0.12 - > 16	71.3	> 128	≤ 0.25 - > 128	69.8	> 4	≤ 0.03 - > 4	**91.0**	8	≤ 0.25 - > 32	NA	> 8	0.25 - > 8	632	**99.4**	4	0.12 - > 8
	Europe	3893	72.9	> 8	≤ 0.06 - > 8	78.8	16	≤ 0.12 - > 16	69.4	> 128	≤ 0.25 - > 128	62.8	> 4	≤ 0.03 - > 4	83.8	32	≤ 0.25 - > 32	NA	> 8	0.06 - > 8	2091	**99.6**	2	0.12 - > 8
	Latin America	1088	64.9	> 8	≤ 0.06 - > 8	73.2	> 16	≤ 0.12 - > 16	62.3	> 128	≤ 0.25 - > 128	54.7	> 4	≤ 0.03 - > 4	77.0	> 32	≤ 0.25 - > 32	NA	> 8	0.5 - > 8	595	**100**	2	0.5 - 4
	MidEast/Africa	689	74.8	> 8	≤ 0.06 - > 8	79.5	16	0.25 - > 16	68.8	> 128	≤ 0.25 - > 128	65.2	> 4	0.06 - > 4	85.2	16	0.5 - > 32	NA	> 8	0.12 - > 8	446	**99.1**	4	1 - > 8
	North America	948	77.4	8	≤ 0.06 - > 8	80.8	16	≤ 0.12 - > 16	72.7	> 128	≤ 0.25 - > 128	63.7	> 4	≤ 0.03 - > 4	**91.1**	8	≤ 0.25 - > 32	NA	> 8	0.5 - > 8	480	**99.8**	2	0.5 - 8
All *P. aeruginosa*, no carbapenemase	Asia/Pacific	1337	80.6	8	≤ 0.06 - > 8	83.3	16	≤ 0.12 - > 16	74.0	> 128	≤ 0.25 - > 128	72.4	> 4	≤ 0.03 - > 4	**93.9**	8	≤ 0.25 - > 32	NA	> 8	0.25 - > 8	600	**99.3**	4	0.12 - > 8
	Europe	3703	76.6	> 8	≤ 0.06 - > 8	82.4	16	≤ 0.12 - > 16	72.8	128	≤ 0.25 - > 128	65.9	> 4	≤ 0.03 - > 4	87.5	16	≤ 0.25 - > 32	NA	> 8	0.06 - > 8	1978	**99.5**	2	0.12 - > 8
	Latin America	982	71.5	> 8	≤ 0.06 - > 8	80.3	>16	≤ 0.12 - > 16	68.6	> 128	≤ 0.25 - > 128	59.5	> 4	≤ 0.03 - > 4	82.9	32	≤ 0.25 - > 32	NA	> 8	0.5 - > 8	534	**100**	2	0.5 - 4
	MidEast/Africa	642	80.2	8	≤ 0.06 - > 8	85.4	16	0.25 - > 16	73.5	128	≤ 0.25 - > 128	69.9	> 4	0.06 - > 4	**90.7**	8	≤ 0.5 - > 32	NA	> 8	0.12 - > 8	410	**99.0**	4	1 - > 8
	North America	945	77.7	8	≤ 0.06 - > 8	81.1	16	≤ 0.12 - > 16	72.8	> 128	≤ 0.25 - > 128	63.8	> 4	≤ 0.03 - > 4	**91.3**	8	≤ 0.25 - > 32	NA	> 8	0.5 - > 8	478	**99.8**	2	0.5 - 8
A. baumannii	Asia/Pacific	398	42.2	> 8	≤ 0.06 - > 8	NA	> 16	0.25 - > 16	NA	> 128	≤ 0.25 - > 128	38.9	> 4	≤ 0.03 - > 4	49.8	> 32	≤ 0.25 - > 32	NA	2	≤ 0.015 - > 8	172	**98.8**	2	0.5 - > 8
	Europe	1229	34.0	> 8	≤ 0.06 - > 8	NA	> 16	≤ 0.12 - > 16	NA	> 128	≤ 0.25 - > 128	24.1	> 4	≤ 0.03 - > 4	36.9	> 32	≤ 0.25 - > 32	NA	4	≤ 0.015 - > 8	588	**93.0**	2	0.5 - > 8
	Latin America	299	20.1	> 8	≤ 0.06 - > 8	NA	> 16	0.25 - > 16	NA	> 128	≤ 0.25 - > 128	15.1	> 4	≤ 0.03 - > 4	22.7	> 32	≤ 0.25 - > 32	NA	2	0.06 - > 8	152	**99.3**	2	≤ 0.06 - 8
	MidEast/Africa	189	23.3	> 8	0.12 - > 8	NA	> 16	0.5 - > 16	NA	> 128	≤ 0.25 - > 128	24.9	> 4	≤ 0.03 - > 4	35.5	> 32	0.5 - > 32	NA	2	0.12 - 8	114	**95.6**	2	0.5 - 8
	North America	235	42.1	> 8	≤ 0.06 - > 8	NA	> 16	≤ 0.12 - > 16	NA	> 128	≤ 0.25 - > 128	34.0	> 4	≤ 0.03 - > 4	60.4	> 32	≤ 0.25 - > 32	NA	4	0.06 - 8	105	**93.3**	2	0.5 - > 8

%S, percent susceptible; MIC_{50}, MIC_{90} range in mg/L; ns, non-susceptible; N*, colistin tested in 2014 only

Table 2. MIC Frequency Distribution (N) and Cumulative Percent Inhibited for Meropenem Against *Enterobacteriaceae, Enterobacteriaceae* with No Carbapenemases, ESBL-positive *Enterobacteriaceae,* and *P. aeruginosa*

Organism	N	Value Type	Meropenem MIC (mg/L)								
			≤0.06	**0.12**	**0.25**	**0.5**	**1**	**2**	**4**	**8**	**>8**
Enterobacteriaceae	38,266	N	32,670	3,477	800	179	111	162	143	139	585
		Cumulative %	85.4	**94.5**	96.6	97	97.3	97.7	98.1	98.4	100
Enterobacteriaceae, no carbapenemase	37,362	N	32,658	3474	787	148	81	93	59	28	34
		Cumulative %	87.4	**96.7**	98.8	99.2	99.4	99.6	99.8	99.9	100
Enterobacteriaceae, ESBL+	6,467	N	5427	592	190	51	47	77	42	23	18
		Cumulative %	83.9	**93.1**	96.0	96.8	97.5	98.7	99.3	99.7	100
P. aeruginosa	8,010	N	401	874	1,378	1,496	1,166	555	482	492	1,166
		Cumulative %	5	15.9	33.1	51.8	66.4	73.3	79.3	85.4	**100**

Dotted line indicates EUCAST breakpoint

Figure 1. Distribution of Carbapenemases in Meropenem-non-susceptible *Enterobacteriaceae* by Geographic Region

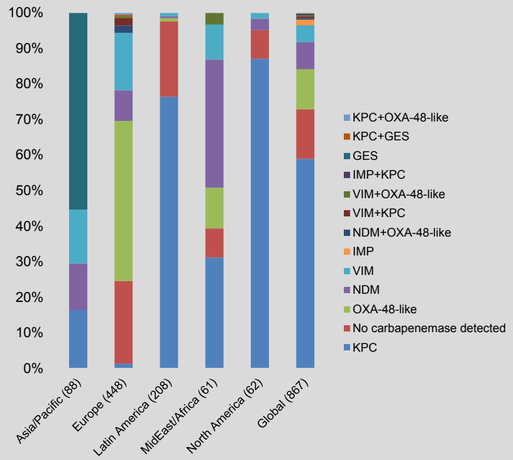
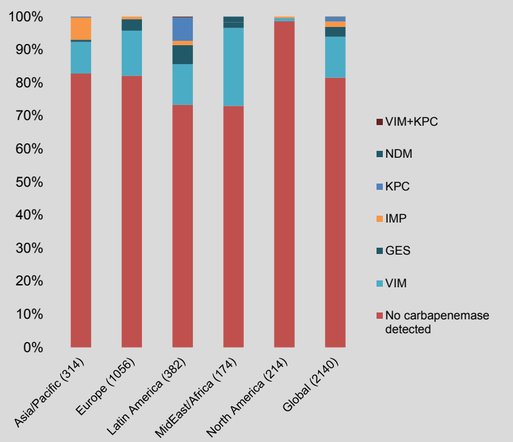


Figure 2. Distribution of Carbapenemases in Meropenem-non-susceptible *Pseudomonas aeruginosa* by Geographic Region



Results Summary

- Meropenem and amikacin were the most active antimicrobials against all *Enterobacteriaceae* in all regions (Table 1). Meropenem inhibited ≥ 96.1% of all *Enterobacteriaceae* across all regions at the EUCAST susceptible breakpoint of ≤ 2 mg/L (Table 2).
- Meropenem and colistin were the most active antimicrobials against ESBL-positive *Enterobacteriaceae* in all regions (Table 1).
- Reduced activity of meropenem against *Enterobacteriaceae* was mainly due to the presence of carbapenemases; 2.4% of *Enterobacteriaceae* produced carbapenemases. Distribution of carbapenemase enzyme classes varied by region (Figure 1).
- Meropenem was less active *in vitro* against *P. aeruginosa*, with percent susceptible ranging from 64.9% (Latin America) to 77.4% (North America and Asia/Pacific). These percentages increased to 71.5% (Latin America) and 80.6% (Asia/Pacific), against isolates which were carbapenemase-negative. However, the majority of meropenem-non-susceptible *P. aeruginosa* (81.5% globally) did not produce known carbapenemases (Figure 2).
- Meropenem showed even less activity against *A. baumannii*, with percent susceptible ≤ 42.2% (Table 1).

Conclusions

- Despite being on the market for many years, resistance to meropenem in *Enterobacteriaceae* and *P. aeruginosa* is still low and meropenem continues to display significant *in vitro* activity against these gram-negative pathogens.
- Resistance in *Enterobacteriaceae* seems to be primarily mediated by carbapenemase enzymes, while for *P. aeruginosa* other mechanisms are also in play.

References and Acknowledgments:

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