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Activity of Meropenem-Vaborbactam against *Enterobacteriaceae* Isolates Collected during 2016

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Introduction

- Carbapenem-resistant *Enterobacteriaceae* (CRE) isolates are a growing issue worldwide
  - Most CRE isolates carry carbapenemase-encoding genes embedded in mobile genetic elements that harbour resistance genes to other antimicrobial classes
- Among carbapenemases detected in *Enterobacteriaceae* species, *Klebsiella pneumoniae* carbapenemases (KPCs) are the most prevalent, followed by New Delhi metallo-beta-lactamase (NDM)
  - KPC-producing isolates have been reported in Germany, Poland, Belgium, Hungary, Croatia, the United Kingdom, Israel, and China
  - These isolates are considered endemic in Greece, Italy, Brazil, and the East Coast in the United States
- Vaborbactam (formerly RPX7009) is a cyclic boronic acid β-lactamase inhibitor that has activity against Ambler class A, including KPC, and C enzymes
  - Vaborbactam has been combined with meropenem and enhances the activity of this carbapenem against KPC-producing isolates when compared to meropenem tested alone
  - Meropenem-vaborbactam has been approved by the United States Food and Drug Administration (US FDA) for the treatment of complicated urinary tract infections
- We evaluated the activity of meropenem-vaborbactam against 7,142 *Enterobacteriaceae* clinical isolates collected in Europe, Asia-Pacific, and Latin America during 2016
  - CRE isolates were screened for the presence of carbapenemase-encoding genes using whole genome analysis

Materials and Methods

- A total of 7,142 *Enterobacteriaceae* clinical isolates collected during 2016 from 62 hospitals located in Europe (n=5,742), Asia-Pacific (n=828), and Latin America (n=572) were included in the study
- Isolates were limited to 1 per patient episode and were collected from bloodstream infections (n=2,614), intra-abdominal infections (n=532), pneumonia in hospitalised patients (n=1,487), skin and skin structure infections (n=1,263), urinary tract infections (n=1,161), and other sources (n=85)
- Species identification was confirmed, when necessary, by matrix-assisted laser desorption ionization-time of flight mass spectrometry
- Isolates were tested for susceptibility against meropenem-vaborbactam (inhibitor at fixed 8 mg/L) and comparator agents using the reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI; M07, 2018)
  - Quality control (QC) was performed according to CLSI guidelines, and all QC MIC results were within acceptable ranges, as published in CLSI documents (M100, 2018)
  - Categorical interpretations for all comparator agents were those found in CLSI criteria in M100 (2018), EUCAST breakpoint tables (version 7.0, January 2018), and/or the US FDA website
- CRE was defined as any isolate exhibiting doripenem, imipenem, and/or meropenem MIC values at ≥2 mg/L (*Proteus mirabilis* and indole-positive Proteeae used only meropenem due to intrinsically elevated imipenem MIC values)
  - CRE isolates were submitted to whole genome sequencing on a MiSeq (Illumina, San Diego, California, US) instrument targeting a 30X coverage
  - Sequences were *de novo* assembled and searched for the presence of acquired carbapenemases using a curated library and applying criteria of >94% sequencing identity and 40% minimum length coverage

Table 1 Activity of meropenem-vaborbactam tested against CRE and CPE isolates collected in Europe, Asia-Pacific, and Latin America

Continent	Organism group (no. of isolates)	% susceptible[a]							
		Meropenem-vaborbactam	Meropenem	Piperacillin-tazobactam	Cefepime	Amikacin	Gentamicin	Colistin	Tigecycline
All	CRE (281)	66.2	6.0	0.0	2.5	50.5	48.4	77.8	86.1
	Carrying bla_{KPC} (120)	98.3	0.8	0.0	0.0	42.5	62.5	71.7	90.8
	Carrying bla_{OXA-48}-like (69)	30.4	13.0	0.0	8.7	66.7	40.6	85.5	84.1
	Carrying MBL genes (55)	9.1	7.3	0.0	0.0	32.7	29.1	83.6	80.0
Asia-Pacific	CRE (28)	25.0	3.6	0.0	0.0	64.3	46.4	89.3	82.1
	Carrying bla_{KPC} (2)	50.0	0.0	0.0	0.0	50.0	0.0	50.0	100.0
	Carrying bla_{OXA-48}-like (6)	0.0	0.0	0.0	0.0	50.0	66.7	83.3	100.0
	Carrying MBL genes (19)	5.3	5.3	0.0	0.0	63.2	47.4	100.0	89.5
Europe	CRE (220)	70.0	7.3	0.0	3.2	46.8	51.4	78.9	86.8
	Carrying bla_{KPC} (93)	100.0	1.1	0.0	0.0	37.6	74.2	76.3	91.4
	Carrying bla_{OXA-48}-like (62)	33.9	14.5	0.0	9.7	67.7	38.7	85.5	83.9
	Carrying MBL genes (31)	12.9	9.7	0.0	0.0	9.7	16.1	77.4	74.2
Latin America	CRE (33)	75.8	0.0	0.0	0.0	63.6	30.3	60.6	84.8
	Carrying bla_{KPC} (25)	96.0	0.0	0.0	0.0	60.0	24.0	56.0	88.0
	Carrying bla_{OXA-48}-like (1)	0.0	0.0	0.0	0.0	100.0	0.0	100.0	0.0
	Carrying MBL genes (5)	0.0	0.0	0.0	0.0	60.0	40.0	60.0	80.0

[a] EUCAST breakpoints were applied for all comparator agents. Meropenem-vaborbactam breakpoints were from US FDA (susceptible, ≤4 mg/L).

Results

- Meropenem-vaborbactam ($MIC_{50/90}$, 0.03/0.06 mg/L) inhibited 7,047/7,142 (98.7%) *Enterobacteriaceae* isolates at the susceptible breakpoint established by the US FDA (≤4 mg/L)
  - Applying the EUCAST breakpoint, 96.3% of the *Enterobacteriaceae* isolates were susceptible to meropenem (data not shown)
- A total of 281 isolates were CRE, and the highest CRE rates were noted in Poland (33.6%), Russia (16.2%), Brazil (11.5%), Italy (10.9%), and Taiwan (10.7%; Figure 1)
  - CRE rates >5% were observed in Malaysia (8.9%), Thailand (8.7%), Turkey (7.7%), Belarus (7.6%), Romania (7.1%), and the Philippines (6.8%)
  - CRE isolates were not detected in Australia, New Zealand, Singapore, Czech Republic, France, Israel, Slovenia, Sweden, and Chile
- CRE isolates were predominantly *K. pneumoniae* (n=237), but 10 other species were observed
  - *Enterobacter cloacae* species complex (n=19), *Escherichia coli* (n=9), and *Klebsiella oxytoca* (n=4) were the most common species after *K. pneumoniae*
- Carbapenemase-encoding genes were detected among 235 (82.2%) CRE (Figure 2)
  - 120 isolates carried bla_{KPC}: 74 bla_{KPC-3} (mostly from Italy), 45 bla_{KPC-2} (9 countries, all regions), and 1 bla_{KPC-12} (Greece)
  - 39 isolates harboured bla_{NDM-1} (12 countries, all regions); bla_{NDM-5} (United Kingdom) and bla_{NDM-7} (Philippines) were also detected
  - 69 isolates harboured bla_{OXA-48}-like (12 countries; 9 from Europe) genes that included bla_{OXA-48}, $bla_{OXA-232}$, $bla_{OXA-244}$, and $bla_{OXA-370}$ were observed among 69 isolates; 7 isolates carried these genes along with bla_{KPC-3} or bla_{NDM}
  - 1 *Proteus mirabilis* carried bla_{OXA-23}
- Meropenem-vaborbactam ($MIC_{50/90}$, 2/>32 mg/L) inhibited 66.2% of the 281 CRE when applying the US FDA breakpoint (Table 1)
  - Meropenem ($MIC_{50/90}$, 32/>32 mg/L; 6.0% susceptible) had limited activity against CREs and isolates producing carbapenemases (0.8% to 13.0% susceptible)
  - Comparator agents had limited activity against CREs, and colistin and tigecycline had the highest susceptibility rates (77.8% and 86.1%, respectively)
- Meropenem-vaborbactam ($MIC_{50/90}$, 0.25/2 mg/L) inhibited 98.3% of isolates carrying bla_{KPC} at ≤4 mg/L (Table 1)
  - The activity of this combination and most comparator agents was limited against isolates carrying MBL genes
- The activity of meropenem-vaborbactam against *Enterobacteriaceae* and CRE isolates was greater in Europe (98.9% and 70.0%) and Latin America (98.6% and 75.8%) when compared to Asia-Pacific (97.5% and 25.0%, respectively; Table 1)

Figure 1 Prevalence of CRE and carbapenemase-producing *Enterobacteriaceae* (CPE) isolates in the surveyed countries

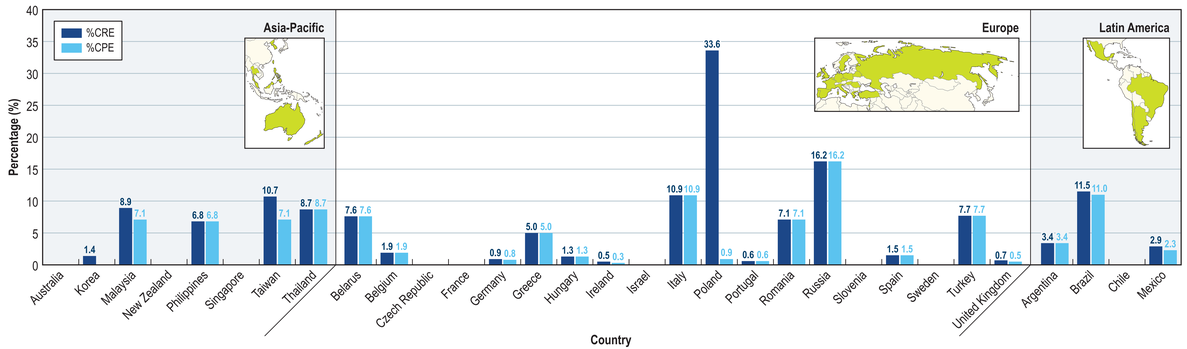
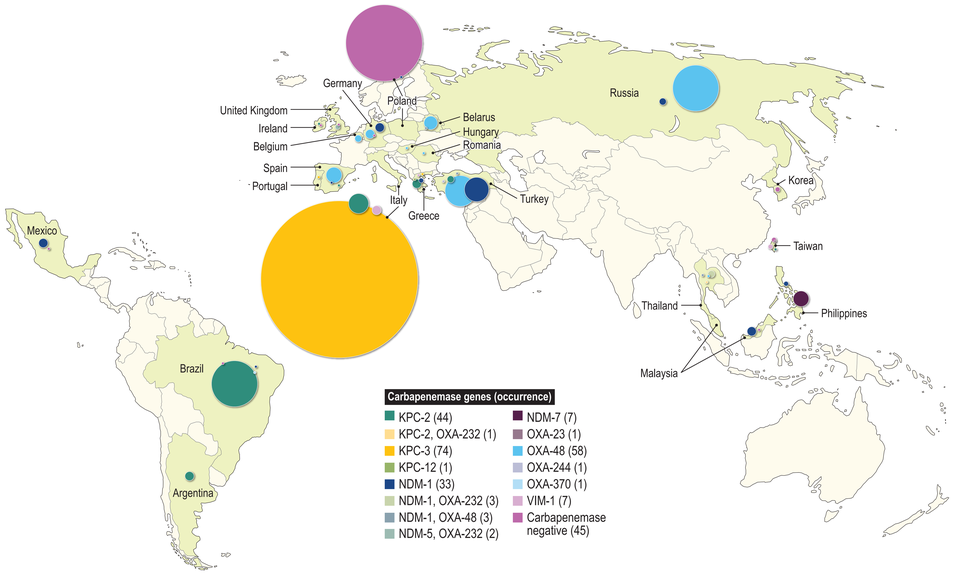


Figure 2 Occurrence of carbapenemase genes in the countries surveyed



Conclusions

- CRE- and carbapenemase-producing isolates are a problem worldwide
  - The prevalence of carbapenemase genes varied in the countries analysed; however, isolates carrying bla_{KPC} were detected in all 3 regions evaluated
- As the incidence of CRE was relatively low, the activity of meropenem-vaborbactam was only slightly greater than the activity of meropenem alone against the collection of *Enterobacteriaceae* isolates tested
  - Meropenem-vaborbactam was the most active agent against isolates carrying bla_{KPC} and was only less active than colistin and tigecycline against CRE isolates
- Meropenem-vaborbactam is a valuable therapeutic option for the treatment of infections caused by KPC-producing isolates

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