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Activity of Plazomicin and Comparator Agents Tested against Recent Clinical Isolates Collected in Asia-Pacific, Europe, and Latin America

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Amended Abstract

Background: Plazomicin is a next-generation aminoglycoside that was developed to overcome common aminoglycoside resistance mechanisms and is under development for the treatment of patients with serious bacterial infections due to MDR *Enterobacteriaceae*, including ESBL-producing and carbapenem-resistant *Enterobacteriaceae* (CRE). We evaluated the activity of plazomicin and comparators tested against 3,830 clinical isolates collected in hospitals from the Asia-Pacific (APAC) region, Europe, and Latin America (LATAM) during 2015.

Materials/methods: A total of 3,375 *Enterobacteriaceae*, 252 gram-positive cocci, 101 *Pseudomonas aeruginosa* (PSA), and 102 *Acinetobacter* spp. were collected in hospitals in APAC (n=851), Europe (n=2,365), and LATAM (n=614). Isolates were susceptibility (S) tested using the reference broth microdilution method. CLSI and EUCAST interpretive criteria were applied. CRE isolates were screened for carbapenemase encoding genes by PCR/sequencing.

Results: Overall, plazomicin (MIC_{50/90}, 0.5/1 mg/L) inhibited 90.9% and 95.8% of Enterobacteriaceae at ≤1 and ≤2 mg/L, respectively. Plazomicin displayed good activity against the main Enterobacteriaceae species, including E. coli (MIC_{50/90}, 0.5/1 mg/L), *K. pneumoniae* (MIC_{50/90}, 0.25/0.5 mg/L), and *E. cloacae* (MIC_{50/90}, 0.25/0.5 mg/L). Against ESBL-phenotype isolates that were not CRE (MIC_{50/90}, 0.25/1 mg/L), plazomicin inhibited 94.1% at ≤1 mg/L and 95.8% at ≤2 mg/L. Among 187 CRE isolates, 52 carried bla_{KPC-2} , 42 bla_{KPC-3} , 41 bla_{NDM-1} , 37 bla_{OXA-48} like, and 1 bla_{VIM-1} . Plazomicin (MIC_{50/90}, 0.25/>128 mg/L for CRE) inhibited 83/94 isolates carrying bla_{KPC} , 32/30 isolates carrying $bla_{OXA_{-48}}$ -like, and 11/42 isolates carrying metallo-beta-lactamase genes. The activity of plazomicin (MIC_{50/90}, 4/8 mg/L) against PSA was similar to the activity of amikacin (MIC_{50/90}, 2/16 mg/L) and lower than the activity of gentamicin (MIC_{50/90}, 1/8 mg/L) against these isolates. Plazomicin demonstrated good activity against coagulase-negative staphylococci (CoNS; MIC_{50/90}, 0.25/0.5 mg/L) and *S. aureus* (MIC_{50/90}, 0.5/1 mg/L). Plazomicin activity was limited against *Acinetobacter* spp. (MIC_{50/90}, 8/>128 mg/L), *Enterococcus* spp. (MIC_{50/90}, 32/64 mg/L), and *S. pneumoniae* (MIC_{50/90}, 32/64 mg/L). The activity of plazomicin and other aminoglycosides displayed slight variability according to geographic region (Table).

Conclusions: Plazomicin was active against *Enterobacteriaceae* isolates, including isolates displaying an ESBL phenotype and carrying genes encoding serine-carbapenemases. These data support the current development plan for plazomicin to treat serious infections caused by resistant *Enterobacteriaceae* where treatment options are limited.

	MIC ₅₀ /MIC ₉₀ in mg/L								
Organism/Group (no. tested)	Asia-Pacific			Europe			Latin America		
	PLZ	AMK	GEN	PLZ	AMK	GEN	PLZ	AMK	GEN
Enterobacteriaceae (3,375)	0.5/1	2/4	0.5/>8	0.5/1	2/8	0.5/>8	0.5/2	2/8	0.5/>8
ESBL-phenotype non-CRE (663)	0.5/1	2/8	1/>8	0.25/1	2/8	1/>8	0.5/1	2/8	>8/>8
CRE (187)	0.25/1	4/16	0.5/>8	0.25/>128	16/>32	>8/>8	0.25/>128	16/>32	>8/>8
P. aeruginosa (101)	4/8	4/4	1/4	4/8	2/16	1/>8	4/16	4/16	1/>8
S. aureus (65)	0.5/1	_	≤1/>8	0.5/1	_	≤1/≤1	0.5/0.5	_	≤1/>8
CoNS (64)	0.25/0.5		≤1/>8	0.25/0.5		≤1/>8	0.25/0.5		8/>8

Introduction

- Aminoglycosides are broad spectrum antimicrobial agents that bind to the 16S ribosomal RNA leading to inhibition of polypeptide synthesis and subsequent cell death
- Resistance to aminoglycosides may occur due to a variety of different resistance mechanisms
- The main mechanism in gram-positive and -negative bacteria is the enzymatic modification and inactivation of the aminoglycosides, mediated by aminoglycoside modifying enzymes (AME)
- Plazomicin is a semi-synthetic aminoglycoside derived from sisomicin and contains structural modifications that allow it to retain activity in the presence of AMEs

- Plazomicin is very active against *Enterobacteriaceae*, some *Pseudomonas* aeruginosa, and *Staphylococcus* spp., including methicillin-resistant (MRSA) isolates
- In this study, we evaluated the activity of plazomicin tested against a collection of 3,830 clinical isolates collected in Asia-Pacific, Europe, and Latin America during 2015 that comprised 3,375 *Enterobacteriaceae*, including molecular characterized carbapenem-resistant (CRE) isolates, 252 gram-positive cocci, 101 *P. aeruginosa*, and 102 *Acinetobacter* spp.

Materials and Methods

- A total of 3,830 bacterial isolates deemed cause of infection limited to 1 per patient episode were included in the study
- Isolates were collected during 2015 from 59 hospitals in Asia-Pacific (n=851), Europe (n=2,365), and Latin America (n=614) and included 3,375 *Enterobacteriaceae*, 252 gram-positive cocci, 101 *Pseudomonas aeruginosa*, and 102 *Acinetobacter* spp.
- Species identification was confirmed when necessary by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS)
- Isolates were susceptibility tested against plazomicin and comparator agents using the reference broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI)
- Quality control (QC) was performed according to CLSI guidelines (M100-S27) and all QC MIC results were within acceptable ranges as published in CLSI documents
- Categorical interpretations for all comparator agents were those found in CLSI criteria in M100-S27 (2017), EUCAST breakpoint tables (version 7.0, January 2017), or United States Food and Drug Administration (US FDA) package insert (tigecycline)
- ESBL-phenotype criterion was applied for *Escherichia coli*, *Klebsiella pneumoniae*, *K. oxytoca*, and *P. mirabilis* displaying an MIC value ≥2 mg/L for ceftriaxone, ceftazidime, or aztreonam (M100-S27)
- Carbapenem-resistant *Enterobacteriaceae* (CRE) was defined as any isolate exhibiting doripenem, imipenem, and/or meropenem MIC values at ≥2 mg/L
- Proteus mirabilis and indole-positive Proteeae were categorized as CRE if meropenem or doripenem MIC values at ≥2 mg/L due to intrinsically elevated imipenem MIC values
- CRE were screened for acquired carbapenemase encoding genes by PCR using custom primers
- Amplicons were sequenced on both strands and nucleotide sequences obtained were analyzed using the Lasergene® software package (DNAStar; Madison, Wisconsin, USA) and compared to available sequences via NCBI BLAST search (http://www.ncbi.nlm.nih.gov/blast/)

Results

- Plazomicin (MIC_{50/90}, 0.5/1 mg/L) inhibited 95.8% at ≤2 mg/L and 97.7% at ≤4 mg/L of 3,375 Enterobacteriaceae isolates collected in all regions (Figure 1)
- The activity of plazomicin was similar in all 3 regions, MIC $_{50}$ values were 0.5 mg/L for all 3 regions, and MIC $_{90}$ values were 1 mg/L (Asia-Pacific and Europe) or 2 mg/L (Latin America; Figure 1)
- Against Enterobacteriaceae, plazomicin (MIC₉₀, 1 mg/L) was more active than amikacin (MIC₉₀, 4 mg/L), gentamicin (MIC₉₀, >8 mg/L), and tobramycin (MIC₉₀, >8 mg/L; Table 1)
- Plazomicin was very active against ESBL-phenotype isolates, displaying no resistance to the carbapenems (ESBL non-CRE; MIC_{50/90}, 0.25/1 mg/L) and inhibiting 95.8% and 96.8% at ≤2 and ≤4 mg/L, respectively (Figure 1)
- A total of 187 CRE isolates were observed in this collection and plazomicin (MIC_{50/90}, 0.25/>128 mg/L) was considerably more active against these isolates when compared to amikacin (MIC_{50/90}, 16/>32 mg/L), gentamicin, or tobramycin (MIC_{50/90}, >8/>8 mg/L for both; Table 1)

- The majority of CRE isolates carried bla_{KPC} (94 isolates, 52 bla_{KPC-2}, and 42 bla_{KPC-3}; Figure 2) and plazomicin (MIC_{50/90}, 0.25/128 mg/L) displayed greater activity against these isolates when compared to amikacin (MIC_{50/90}, 16/>32 mg/L), gentamicin (MIC_{50/90}, 2/>8 mg/L) or tobramycin (MIC_{50/90}, >8/>8 mg/L; Table 2)
- A total of 30 isolates from Europe harboured bla_{OXA-48}, 41 isolates carried bla_{NDM-1},
 7 harboured bla_{OXA-232}, and bla_{VIM-1} was detected in 1 isolate (Figure 2)
- The activity of plazomicin and all other aminoglycosides (Table 2) was limited against NDM-1-producing organisms, but plazomicin (MIC_{50/90}, 0.25/128 mg/L) was more active against OXA-48-producers when compared to amikacin (MIC_{50/90}, 4/>32 mg/L) or gentamicin (MIC_{50/90}, >8/>8 mg/L)
- Plazomicin (MIC_{50/90}, 4/8 mg/L) activity was similar to the activity of amikacin (MIC_{50/90}, 2/16 mg/L) and four-fold lower than that of gentamicin (MIC_{50/90}, 1/8 mg/L) against *P. aeruginosa* isolates
- Plazomicin demonstrated activity against Staphylococcus spp. isolates (MIC_{50/90}, 0.5/1 mg/L; Figure 1), including coagulase-negative staphylococci (MIC_{50/90}, 0.25/0.5 mg/L) and S. aureus (MIC_{50/90}, 0.5/1 mg/L; data not shown)
- The activity of plazomicin was limited against *Acinetobacter* spp. (MIC_{50/90}, 8/>128 mg/L), *Enterococcus* spp. (MIC_{50/90}, 32/64 mg/L), and *S. pneumoniae* (MIC_{50/90}, 32/64 mg/L) isolates (data not shown)

Conclusions

- Plazomicin was active against *Enterobacteriaceae* isolates, including resistance groups such as cephalosporin-resistant isolates (ESBL non-CRE) and CRE
- The in vitro activity of plazomicin was greater compared to the activity of aminoglycosides against cephalosporin-resistant isolates and CRE, including isolates producing KPC or OXA-48
- Plazomicin displayed activity against *Staphylococcus* spp. and some *P. aeruginosa*, but its activity was limited against *Acinetobacter* spp., *Enterococcus* spp., and *S. pneumoniae*
- Plazomicin seems to be a valuable option for the treatment of infections caused by *Enterobacteriaceae* isolates, including isolates that may produce ESBLs and those carrying serine-carbapenemases

Acknowledgements

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References

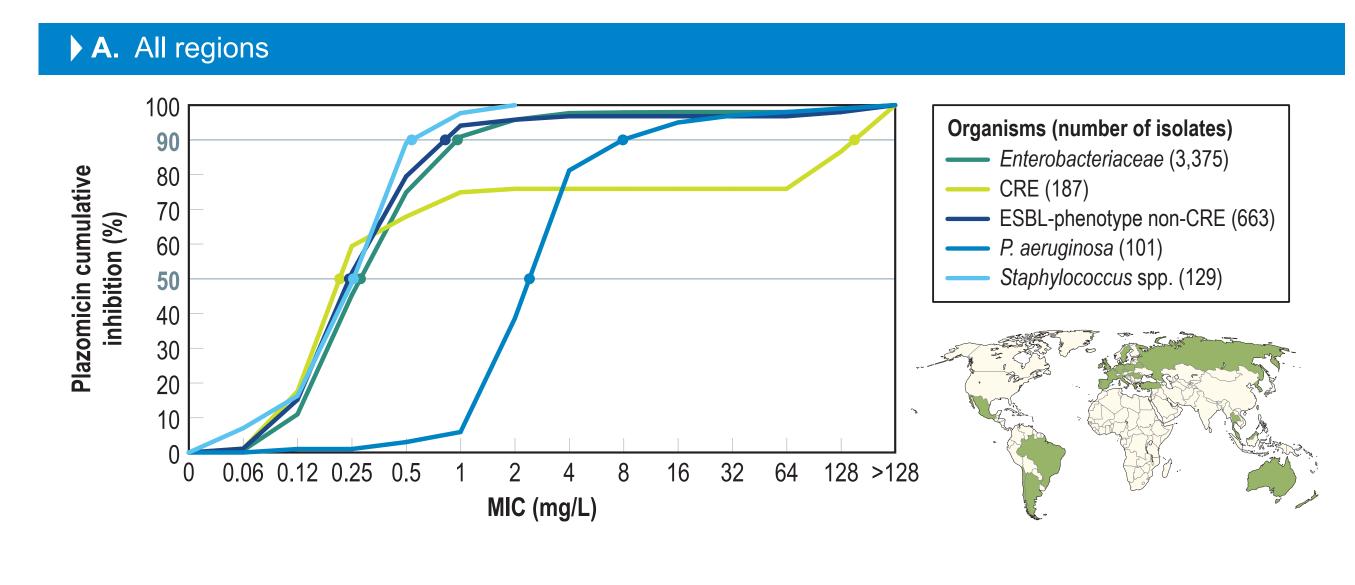
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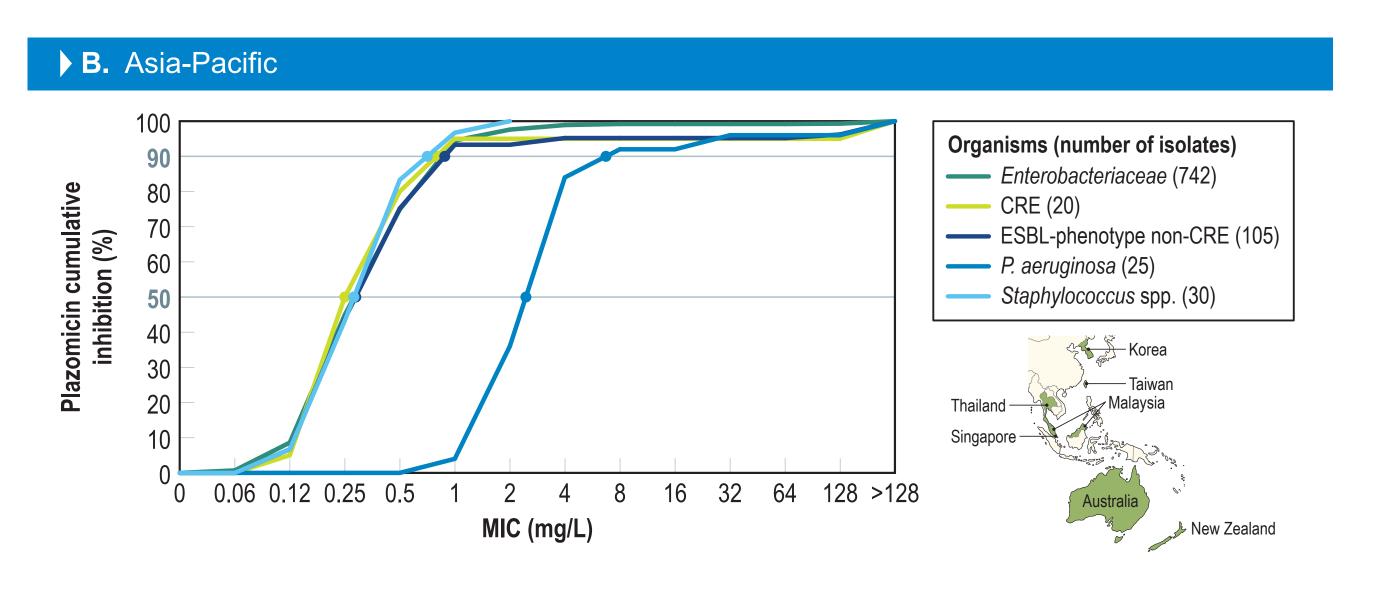
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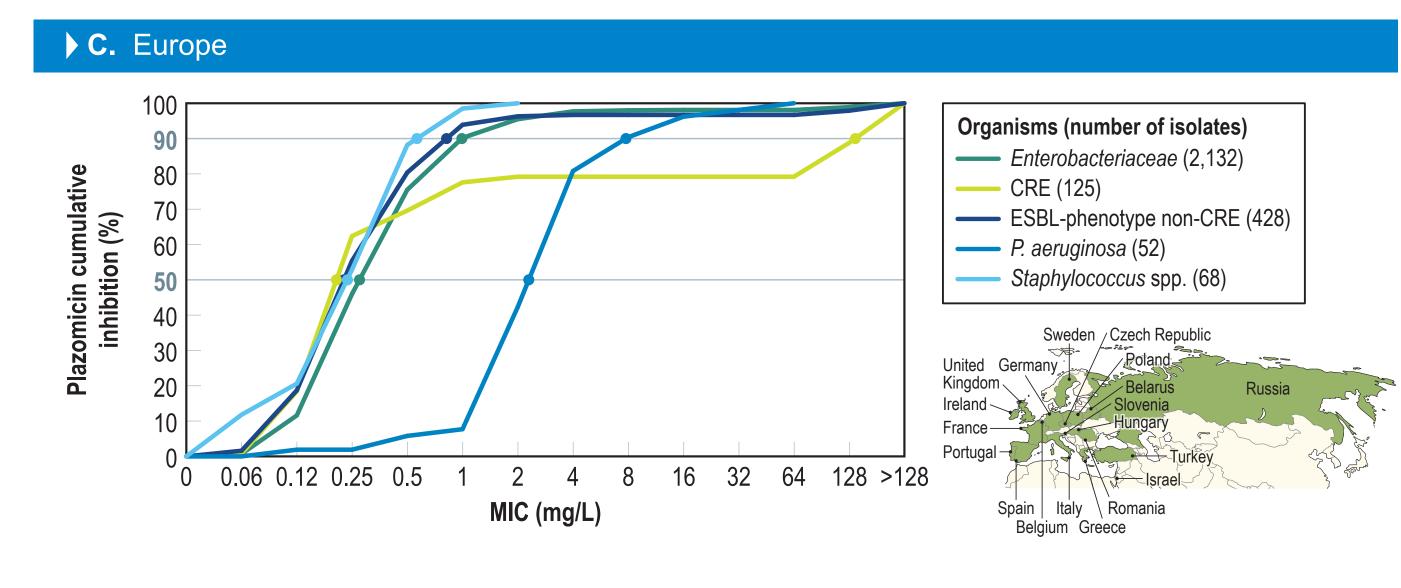
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Figure 1 Activity of plazomicin against main organism groups for geographic regions evaluated







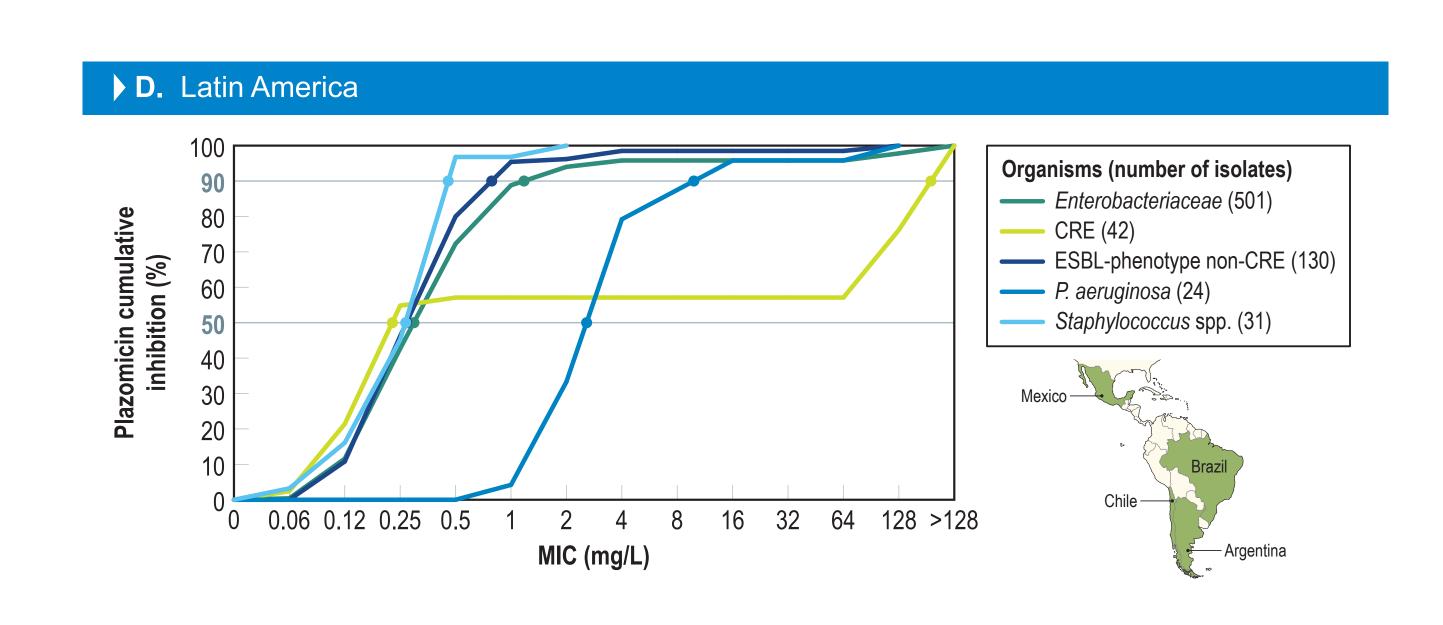


Figure 2 Distribution of CREs and carbapenemase genes by region

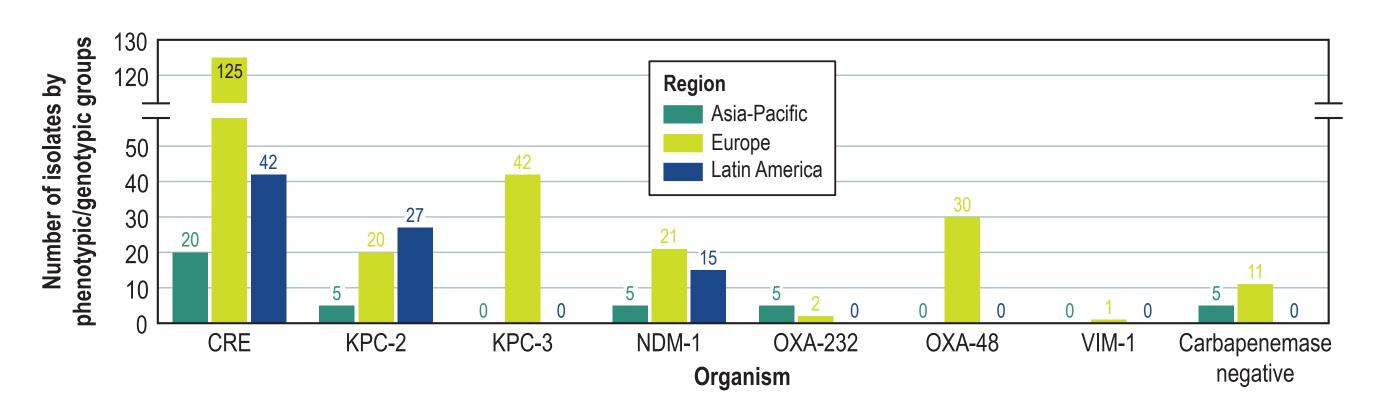


Table 1 Activity of plazomicin and comparator agents against main bacterial species analyzed

	Region (no. tested) MIC _{50/90} (mg/L)							
Organism								
antimicrobial agent	Overall	Asia-Pacific	Europe	Latin Americ				
Enterobacteriaceae	3,375	742	2,132	501				
Plazomicin	0.5 / 1	0.5 / 1	0.5 / 1	0.5 / 2				
Amikacin	2/4	2/4	2/8	2/8				
Gentamicin	0.5 / >8	0.5 / >8	0.5 / >8	0.5 / >8				
Tobramycin	0.5 / >8	0.5 / 8	0.5 / >8	1 / >8				
Ceftazidime	0.25 / >32	0.12 / 32	0.25 / >32	0.25 / >32				
Meropenem	0.03 / 0.06	0.03 / 0.06	0.03 / 0.12	0.03 / 1				
Piperacillin-tazobactam	2 / 128	2 / 16	2 / 128	2 / >128				
Colistin	0.12 / >8	0.12 / >8	0.12 / >8	0.12 / >8				
Tigecycline	0.25 / 1	0.25 / 0.5	0.25 / 1	0.25 / 1				
ESBL non-CRE	663	105	428	130				
Plazomicin	0.25 / 1	0.5 / 1	0.25 / 1	0.5 / 1				
Amikacin	2/8	2/8	2/8	2/8				
Gentamicin	1 / >8	1 / >8	1 / >8	>8 / >8				
Tobramycin	8 / >8	4 / >8	8 / >8	>8 / >8				
Ceftazidime	32 / >32	16 / >32	32 / >32	32 / >32				
Meropenem	0.03 / 0.12	0.03 / 0.06	0.03 / 0.12	0.03 / 0.5				
Piperacillin-tazobactam	8 / >128	8 / >128	8 / >128	8 / >128				
Colistin	0.12 / 0.25	0.12 / 0.25	0.12 / 0.25	0.12 / 1				
Tigecycline	0.25 / 1	0.25 / 1	0.25 / 1	0.25 / 1				
CRE	187	20	125	42				
Plazomicin	0.25 / >128	0.25 / 1	0.25 / >128	0.25 / >128				
Amikacin	16 / >32	4 / 16	16 / >32	16 / >32				
Gentamicin	>8 / >8	0.5 / >8	>8 / >8	>8 / >8				
Tobramycin	>8 / >8	8 / >8	>8 / >8	>8 / >8				
Ceftazidime	>32 / >32	>32 / >32	>32 / >32	>32 / >32				
Meropenem	32 / >32	16 / >32	32 / >32	32 / >32				
Piperacillin-tazobactam	>128 / >128	>128 / >128	>128 / >128	>128 / >128				
Colistin	0.25 / >8	0.12 / >8	0.25 / >8	0.25 / >8				
Tigecycline	0.5 / 2	0.25 / 0.5	0.5 / 2	0.5 / 2				
P. aeruginosa	101	25	52	24				
Plazomicin	4 / 8	4/8	4 / 8	4 / 16				
Amikacin	2 / 16	4 / 4	2 / 16	4 / 16				
Gentamicin	1 / 8	1 / 4	1 / >8	1 / >8				
Tobramycin	0.5 / 4	0.5 / 1	0.5 / 8	0.5 / >8				
Ceftazidime	2 / 16	2 / >32	2 / 16	2 / 16				
Meropenem	0.5 / 16	0.25 / 8	0.25 / 16	0.5 / 16				
Piperacillin-tazobactam	4 / >64	4 / >64	4 / >64	4 / 64				
Colistin	≤0.5 / 1	1/1	≤0.5 / 1	≤0.5 / 1				

Table 2 Activity of plazomicin and comparator agents against main carbapenemase

Region (no. tested) MIC_{50/90} (mg/L) **Latin America** 0.25 / >128 >32 / >32 >32 / >32 >32 / >32 >128 / >128 >128 / >128 0.25 / >8 OXA-48-producers 0.25 / 128 0.25 / 128 >128 / >128 >128 / >128 Piperacillin-tazobactam NDM producers 128 / >128 >128 / >128 >32 / >32 >32 / >32 32 / >32 >128 / >128 >128 / >128 >128 / >128 0.12 / 0.5 0.25 / >8 0.12 / >8 0.5 / 2 0.5 / 2 1/2