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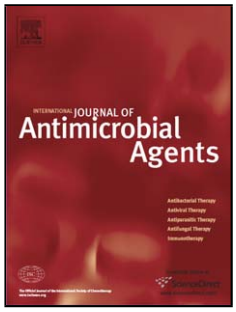

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In vitro activity of doripenem and other carbapenems against contemporary Gram-negative pathogens isolated from hospitalised patients in the Asia-Pacific region: results of the COMPACT Asia-Pacific Study

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ABSTRACT

The Comparative Activity of Carbapenems Testing (COMPACT) Study was designed to determine the in vitro potency of doripenem compared with imipenem and meropenem against a large number of contemporary Gram-negative pathogens from more than 100 centres across Europe and the Asia-Pacific region and to assess the reliability of Etest methodology for doripenem minimum inhibitory concentration (MIC) determination against these pathogens. Data from eight countries within the Asia-Pacific region, which collected 1612 bacterial isolates, are presented here. Etest methodology was found to be a reliable method for MIC determination. Doripenem showed in vitro activity similar to or better than meropenem and at least four-fold better than imipenem against Enterobacteriaceae. Against *Pseudomonas aeruginosa*, doripenem was also the most active of the three carbapenems in vitro. However, in vitro results do not necessary correlate with clinical outcome.

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1. Introduction

Antibiotic resistance amongst Gram-negative nosocomial pathogens continues to increase and to compromise treatment outcomes in the Asia-Pacific region [1,2]. The emergence of *Acinetobacter baumannii* as a cause of hospital-acquired pneumonia, increasing rates of infections caused by extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae such as *Klebsiella pneumoniae*, and the increasing resistance seen in *Pseudomonas aeruginosa* are just three examples [3].

Antibiotic resistance rates in some countries in the Asia-Pacific Rim are considerably higher than those in other parts of the world [4], e.g. 52% of *Escherichia coli* (ranging from 2.6% in Australia to 83% in India) and 52% of *K. pneumoniae* (ranging from 7.1% in Australia to 84% in India) were found to be ESBL-producers [5].

Infections caused by multidrug-resistant (MDR) Gram-negative pathogens have been associated with increased mortality, increased hospital stay and increased costs [6–9]. Furthermore, emergence of resistance during treatment of infections caused by pathogens such as *P. aeruginosa* and *Enterobacter* spp. has a dramatic effect both on outcome and costs [10,11].

Carbapenems now play a prominent therapeutic role, especially in hospitals and patient populations where MDR strains have become prevalent, due to their broad spectrum of activity and their activity against pathogens such as ESBL-producing Enterobacteriaceae, *P. aeruginosa* and *Acinetobacter* spp. [3,12,13]. Doripenem is a new, broad-spectrum, intravenous carbapenem antibiotic. Its in vitro antibacterial spectrum includes meticillin-susceptible staphylococci, streptococci (including

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penicillin-resistant *Streptococcus pneumoniae*), Enterobacteriaceae, *Haemophilus influenzae*, *P. aeruginosa*, *Moraxella catarrhalis*, ceftazidime-susceptible *Acinetobacter* spp., *Bordetella* spp., *Bacteroides* spp., *Prevotella* spp., *Clostridium* spp. and other Gram-positive anaerobes, including difficult-to-treat pathogens [14].

Doripenem is approved for the treatment of complicated urinary tract infections and complicated intra-abdominal infections (cIAIs) in the USA, Europe and Asia-Pacific region, and for nosocomial pneumonia (NP) [including ventilator-associated pneumonia (VAP)] both in Europe and several Asia-Pacific countries such as Thailand, Philippines, Malaysia, Australia and Indonesia.

The recommended dose of doripenem (500 mg) is administered as a 1-h infusion three times a day. However, in seriously ill patients (e.g. those with VAP), 500 mg three times a day given as a 4-h infusion is recommended to maximise therapeutic benefit [15]. Pharmacodynamic modelling suggests that prolonged infusion (over 4 h), thus increasing the time interval where drug levels exceed the minimum inhibitory concentration (MIC), would improve coverage of pathogens having a high doripenem MIC (4 mg/L) [16]. Clinical efficacy in patients known or suspected to be infected with pathogens having a high doripenem MIC needs to be confirmed in future clinical studies. Appropriate doripenem dose administration requires adequate epidemiological data and it is therefore essential to collect data on carbapenem MIC distribution against relevant species.

The Comparative Activity of Carbapenems Testing (COMPACT) Study had two objectives: first, to compare the MIC distribution of doripenem with that of imipenem

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and meropenem against Gram-negative pathogens causing serious infections in hospitalised patients, with a particular emphasis on *P. aeruginosa*; and, second, to assess the reliability of Etest methodology for the determination of doripenem MICs for these pathogens. Here we report the findings from the Asia-Pacific region, including Australia, Hong Kong, India, Indonesia, Malaysia, Philippines, Singapore and Thailand.

2. Materials and methods

2.1. Pathogens

The COMPACT Asia-Pacific Study Group consisted of 27 medical centres in eight countries, including Australia (3 centres), Hong Kong (2 centres), India (3 centres), Indonesia (1 centre), Malaysia (3 centres), Philippines (3 centres), Singapore (2 centres) and Thailand (10 centres). Participating centres collected a protocol-defined set and number of consecutive Gram-negative isolates during the latter half of 2008 and early 2009. Non-duplicate isolates were obtained from patients with cIAIs, bloodstream infections (BSIs) or NP (including VAP). The target number of isolates to be collected at each centre was 30 *P. aeruginosa*, 24 Enterobacteriaceae and 6 other Gram-negative pathogens.

2.2. In vitro investigations

Each collecting centre determined the MIC of doripenem, imipenem and meropenem against each pathogen collected using Etest methodology (AB BIODISK, Solna, Sweden) following the manufacturer's guidelines. Each centre, with the exception of the centre in Indonesia that was not permitted to export isolates out of the country,

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sent all isolates collected to the central reference laboratory (Quotient Bioresearch Ltd., Fordham, UK) for confirmation of pathogen identification. For quality control purposes, and for validation of Etest methodology for doripenem susceptibility testing, the central reference laboratory determined the MIC of doripenem, imipenem and meropenem by Etest and by broth microdilution (BMD) [17] against all isolates deemed to be resistant to either meropenem or imipenem or non-susceptible to doripenem according to the collecting centre's Etest result interpreted using current Clinical and Laboratory Standards Institute (CLSI) breakpoints for imipenem and meropenem (Table 1) [18] and US Food and Drug Administration (FDA) breakpoints for doripenem (Table 1) as there are no CLSI breakpoints. Further explanation on the rationale for the choice of breakpoints is included in the 'Discussion'. In addition, carbapenem susceptibility by Etest and BMD of a randomly selected 10% of susceptible isolates was determined. Quality control isolates used were *H. influenzae* ATCC 49766, *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853. All data were collated and analysed by Quotient Bioresearch Ltd.

3. Results

3.1. Isolates collected

A total of 1612 isolates were collected over a 6-month period, consisting of 656 Enterobacteriaceae (40.7%), 784 *Pseudomonas* spp. (48.6%) and 172 other Gram-negative isolates (10.7%). *Escherichia coli* (38.6%), *K. pneumoniae* (35.4%) and *Enterobacter* spp. (10.4%) were the most predominant Enterobacteriaceae collected. Of the *Enterobacter* spp. isolated, 72.1% were *Enterobacter cloacae*. *Pseudomonas aeruginosa* (99.5%) was the most commonly isolated *Pseudomonas* spp., and *A.*

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baumannii (74.4%) was the most isolated species amongst the other Gram-negatives collected.

Pathogens were most commonly isolated from patients with NP (49.7%), followed by patients with BSIs (36.6%) and patients with cIAIs (13.7%). Pathogens were isolated from patients in the Intensive Care Unit (ICU) in 38.5% of cases.

3.2. Etest minimum inhibitory concentration determination

The reference laboratory determined the BMD and Etest MICs of 454 isolates, consisting of 306 isolates deemed to be non-susceptible to doripenem or resistant to meropenem or imipenem according to the Etest MIC results (Table 1) generated at each collecting centre as well as for 148 randomly selected isolates that were susceptible to all three carbapenems.

The MIC determined by BMD and by Etest at the central reference laboratory was the same or within one doubling dilution for 89.6% of isolates tested and was the same or within two doubling dilutions for 98% of isolates.

The MIC determined by Etest at each centre and at the central reference laboratory was the same or within one doubling dilution for 83.2% of isolates and the same or within two doubling dilutions for 92.3% of isolates. Centre Etest MIC values were higher than reference laboratory values in 26.5% of cases and lower in 20.9%.

Table 2 summarises the in vitro activity of doripenem, imipenem and meropenem by Etest methodology as reported by the collecting centres, and Fig. 1 provides the

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cumulative percentage inhibition curves for Enterobacteriaceae, *A. baumannii* and *P. aeruginosa*.

3.2.1. Enterobacteriaceae

Doripenem and meropenem had activity against all Enterobacteriaceae, with MIC_{90} values (MIC for 90% of the organisms) of 0.06 mg/L and 0.12 mg/L, respectively, both being at least four-fold more active than imipenem (MIC_{90} = 0.5 mg/L) (Table 2; Fig. 1a). A similar pattern was seen against *E. coli*, *Klebsiella* spp. and *Enterobacter* spp. (Table 2). One *E. coli* isolate (from India) and one *Klebsiella oxytoca* isolate (from Singapore) was shown to have a high MIC for all three carbapenems (confirmed by the reference laboratory). One *Providencia rettgeri* isolate (from Thailand) had a doripenem MIC of 4 mg/L determined by the source site but this was not confirmed by the reference laboratory (doripenem MIC 0.12 mg/L at reference laboratory). One *E. cloacae* isolate (from Thailand) was found to have a doripenem MIC of 1 mg/L (i.e. just above the susceptible breakpoint) by the local laboratory but an MIC < 1 mg/L at the reference laboratory.

The activity of the three carbapenems against Enterobacteriaceae by country is given in Table 3. Doripenem and meropenem were comparable in activity, whilst both were more active than imipenem . Doripenem MICs were ≤0.5 mg/L in isolates from all countries except for the four isolates described above obtained from India, Thailand and Singapore.

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3.2.2. Other Gram-negative isolates

Doripenem and meropenem had a lower MIC_{50} (MIC for 50% of the organisms) (16 mg/L and 32 mg/L, respectively) than imipenem (≥64 mg/L). All three carbapenems had an MIC_{90} of ≥64 mg/L against other Gram-negatives combined (Table 2). None of the carbapenems was effective against *Stenotrophomonas maltophilia* isolates collected, but 6–8 of 11 isolates of *Burkholderia* spp. were carbapenem-susceptible (data not shown).

3.2.3. Pseudomonas aeruginosa

Doripenem had the lowest MIC_{90} against *P. aeruginosa* (8 mg/L), with meropenem and imipenem having MICs of ≥64 mg/L (Table 2). Rates of non-susceptibility to doripenem (MIC ≥ 4 mg/L) and meropenem (MIC ≥ 8 mg/L) were the same (21.3%), whilst the rate of non-susceptibility to imipenem (MIC ≥ 8 mg/mL) was 24.6%.

The activity of the three carbapenems against *P. aeruginosa* by country is given in Table 3.

Pseudomonas aeruginosa isolates from ICU patients tended to have higher carbapenem MICs than those collected outside of the ICU: the MIC_{90} for all carbapenems in the ICU was ≥64 mg/L compared with 4 mg/L for doripenem and 16 mg/L for the other two carbapenems outside the ICU (data not shown). Of the *P. aeruginosa* isolated from patients within the ICU, 30.0% were doripenem non-susceptible compared with 22.4% of those from outside the ICU (data not shown; see Table 1 for breakpoints).

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The carbapenems were equally active against *P. aeruginosa* isolates from BSIs, cIAIs and NP (data not shown).

3.3. Carbapenem resistance

Using CLSI breakpoints in place at the time of the study (Table 1) [18], ca. 17–18% of isolates were non-susceptible to imipenem or meropenem. Currently, the CLSI have not published breakpoints for doripenem, therefore using FDA breakpoints (only susceptible category published), 277 isolates (17.2%) were non-susceptible to doripenem (see Table 1 for breakpoints).

Almost full susceptibility was seen against the Enterobacteriaceae, with non-susceptibility rates <1% for all carbapenems (data not shown).

All *S. maltophilia* (*n* = 8) were non-susceptible to all three carbapenems (likely due to production of metallo-β-lactamase) and a high percentage of non-susceptibility was seen in *Burkholderia* spp., *Acinetobacter* spp. and *Pseudomonas* spp.

Eighty-six isolates (62.8%) of *Acinetobacter* spp. were resistant (MIC ≥ 16 mg/L) to both imipenem and meropenem and had high doripenem MICs (4 mg/L to ≥16 mg/L).

One hundred and twenty-four *P. aeruginosa* isolates (15.9%) were resistant (MIC ≥ 16 mg/L) to both imipenem and meropenem and all but one of these isolates were also doripenem non-susceptible.

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4. Discussion

The in vitro activity of the three carbapenems was determined in this study using Etest methodology. The Etest and BMD MIC values generated by the reference laboratory were in high agreement, and the Etest MIC values generated by each collecting centre were in high agreement with those of the reference laboratory. Etest methodology therefore appears to be a reliable method for doripenem MIC determination.

The in vitro activity of doripenem against Enterobacteriaceae was essentially no different to that of meropenem and was at least four-fold more potent than that of imipenem, including against the important pathogens *E. coli* and *K. pneumoniae.* A high percentage of these species are ESBL-producers in Asia-Pacific countries [5] and bacteraemic patients with ESBL-positive strains have been shown to have significantly higher average hospital costs, longer median hospital stays following onset of bacteraemia (11 days vs. 5 days; $P < 0.001$) and higher in-hospital mortality (35% vs. 18%; $P = 0.01$) compared with patients infected with non-ESBL-producing strains [8].

Doripenem had the lowest MIC distribution of the three carbapenems against *P. aeruginosa* regardless of whether the isolates were from patients within or outside the ICU and regardless of the type of infection. It is important to note, however, that there was a high proportion of isolates in the collection from Thailand, which may well affect the results of this study. Comparing Thailand with the other countries represented in this study would overestimate resistance in the region because Thailand has higher than average carbapenem MICs.

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Susceptibility analyses in this study were evaluated using breakpoints developed by the internationally recognised performance standards developing organisation (CLSI) at the time of study [18], which have not changed in the recent standards update [19]. The exception to this was doripenem, as there are no doripenem breakpoints in the CLSI standards. Organisations that establish breakpoints base their breakpoint decisions on the evaluation of MIC population distributions of organisms to include knowledge of resistance mechanisms and wild-type distributions, pharmacokinetics/pharmacodynamics, and correlation of MIC with clinical outcome. The organisations evaluate similar types of data but, owing to varying emphasis on key data sets, they may come to different conclusions regarding specific breakpoints. For example, for doripenem the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for *P. aeruginosa* and Enterobacteriaceae are susceptible ≤1 mg/L, intermediate 2–4 mg/L and resistant ≥8 mg/L, whilst the FDA breakpoints are susceptible ≤2 mg/L for *P. aeruginosa* and ≤0.5 mg/L for Enterobacteriaceae, with no intermediate/resistant categories defined. Other regulatory authorities around the world may also differ in how they establish breakpoints. The choice of the FDA breakpoint for doripenem in this study is a conservative approach as it is two-fold lower than those for meropenem and imipenem for *P. aeruginosa* and eight-fold lower for Enterobacteriaceae. It is pertinent to note that very recently the CLSI have published an update of the performance standards for antimicrobial susceptibility testing [20], where new carbapenem breakpoints for Enterobacteriaceae are presented, with reduced susceptible, intermediate and resistant breakpoints of ≤1, 2 and ≥4 mg/L, respectively, for all three carbapenems utilised in this study. Re-analysis of the data

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presented here for the Enterobacteriaceae has little effect on doripenem or meropenem non-susceptibility (0.3–0.6%), but imipenem non-susceptibility increases from 0.2% to 2% (data not shown). At present, no changes to *P. aeruginosa* CLSI breakpoints have been made, but if a similar change were introduced the relative shift in susceptibility would be in favour of doripenem.

Overall, non-susceptibility to meropenem and imipenem or doripenem was ca. 17–18% with little or no resistance observed in the Enterobacteriaceae. Nine percent of imipenem-resistant and 1% of meropenem-resistant isolates were doripenem-susceptible.

There was greater differentiation between the carbapenems against *P. aeruginosa* than with other bacterial species. Imipenem resistance in *P. aeruginosa* varied from country to country. The lowest rate was in Indonesia (5.1%) but this increased to as high as 35–38% in Thailand and India. As the rate of imipenem resistance increased, so did the resistance rate observed for meropenem and doripenem.

Pseudomonas aeruginosa is one of the leading causes of hospital-acquired infections for which treatment options are limited [21], and MDR *P. aeruginosa* has a significant impact on mortality and costs [6,7,10]. In addition, an increased carbapenem (imipenem and meropenem) MIC will clearly reduce the therapeutic options for *P. aeruginosa* infections where high levels of antibiotic resistance are common [5,7]. It has been postulated that extending the infusion time of a more active agent may overcome these difficulties by increasing the likelihood that the pharmacodynamic target is attained [13]. Furthermore, in vivo simulations support

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the use of prolonged infusions of doripenem at 1 g or 2 g doses as a potential treatment for *P. aeruginosa* isolates with raised doripenem MICs [22].

Although the in vitro activity of doripenem against *Pseudomonas* appears to be the best of the three carbapenems tested, geography and whether the patient is in or outside the ICU was shown to impact this activity. A real-time surveillance programme monitoring the susceptibility and MICs of these bacterial pathogens at the country or healthcare centre level appears to be a necessary tool to guide empirical treatment effectively. The Etest method for MIC determination is a rapid, convenient and reliable method for use in the clinical diagnostic laboratory. Confirmatory testing using a reference BMD method could be performed as required. Because in vitro data do not always extrapolate to the clinical setting, prospective controlled clinical trials are needed to demonstrate the efficacy of different infusion regimens or administration. Furthermore, there is generally a high prevalence of antibiotic resistance in Gram-negative bacteria in the Asia-Pacific region that will continue to be a problem for clinicians. These challenges will need to be overcome by alternative strategies with existing agents such as dosing manipulation (e.g. higher doses and/or prolonged infusion with doripenem) or combination therapy.

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Competing interests

Quotient Bioresearch Ltd. (Fordham, UK) carries out research on behalf of numerous pharmaceutical companies for the development of new antimicrobials.

Ethical approval

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Fig. 1. Cumulative minimum inhibitory concentration (MIC) distribution for doripenem, imipenem and meropenem against (a) Enterobacteriaceae, (b) *Acinetobacter baumannii* and (C) *Pseudomonas aeruginosa*.

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Table 1

Breakpoints (in mg/L) used to determine susceptibility of isolates for minimum inhibitory concentration testing

Isolates	FDA			CLSI					
	Doripenem			Imipenem			Meropenem		
	S	I	R	S	I	R	S	I	R
Pseudomonas aeruginosa	≤2	–	–	≤4	8	≥16	≤4	8	≥16
Enterobacteriaceae	≤0.5	–	–	≤4	8	≥16	≤4	8	≥16
Acinetobacter spp. (*A. baumannii*)	≤1	–	–	≤4	8	≥16	≤4	8	≥16
Stenotrophomonas maltophilia	≤2	–	–	≤4	8	≥16	≤4	8	≥16
Burkholderia cepacia	≤2	–	–	≤4	8	≥16	≤4	8	≥16
Other non-Enterobacteriaceae	≤1	–	–	≤4	8	≥ 16	≤4	8	≥16
Haemophilus influenzae	≤1	–	–	≤4	–	–	≤0.5	–	–

FDA, US Food and Drug Administration; CLSI, Clinical and Laboratory Standards Institute; S, susceptible, I, intermediate; R, resistant.

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Table 2

Summary minimum inhibitory concentration (MIC) data for doripenem (DOR), imipenem (IPM) and meropenem (MEM) against Gram-negative bacteria as determined using Etest methodology by the collecting centres

Isolates (*n*)	Antimicrobial agent	MIC (mg/L)		
		MIC_{50}	MIC_{90}	Range
Enterobacteriaceae (656)	DOR	0.03	0.06	0.008–8 [a,b]
	IPM	0.25	0.5	0.008–8 [a,b]
	MEM	0.03	0.12	0.008–16 [a,b]
Escherichia coli (253)	DOR	0.015	0.06	0.008–8 [a]
	IPM	0.12	0.25	0.015–8 [a]
	MEM	0.03	0.06	0.008–16 [a]
Klebsiella spp. (243)	DOR	0.03	0.06	0.008–4 [b]
	IPM	0.25	0.25	0.008–2 [b]
	MEM	0.03	0.06	0.008–8 [b]
Enterobacter spp. (68)	DOR	0.03	0.25	0.015–1
	IPM	0.25	1	0.015–4
	MEM	0.03	0.25	0.015–2
Salmonella spp. (30)	DOR	0.015	0.03	0.008–0.25
	IPM	0.12	0.25	0.03–1
	MEM	0.015	0.03	0.008–0.03
Proteus spp. (21)	DOR	0.06	0.25	0.03–0.25
	IPM	0.5	2	0.25–4
	MEM	0.06	0.25	0.03–0.5
Serratia spp. (13)	DOR	–	–	0.015–0.12
	IPM	–	–	0.25–1
	MEM	–	–	0.03–0.12
Citrobacter spp. (10)	DOR	–	–	0.015–0.5
	IPM	–	–	0.12–2
	MEM	–	–	0.015–0.5
Pseudomonas aeruginosa (780)	DOR	0.25	8	0.002 to ≥64

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	IPM	1	≥64	0.06 to ≥64
	MEM	0.5	≥64	0.008 to ≥64
Other Gram-negative isolates (172)	DOR	16	≥64	0.008 to ≥64
	IPM	≥64	≥64	0.015 to ≥64
	MEM	32	≥64	0.015 to ≥64
Acinetobacter baumannii (128)	DOR	32	≥64	0.008 to ≥64
	IPM	≥64	≥64	0.015 to ≥64
	MEM	≥64	≥64	0.015 to ≥64
Burkholderia spp. (11)	DOR	–	–	0.12 to ≥64
	IPM	–	–	0.25 to ≥64
	MEM	–	–	0.12 to ≥64

$MIC_{50/90}$, MICs for 50% and 90% of the organisms, respectively.

[a] One *E. coli* isolate was less susceptible to all three carbapenems (confirmed by the reference laboratory), with DOR, IPM and MEM MIC values of 8, 8 and 16 mg/L; the highest MICs excluding this isolate were 0.5, 1 and 0.5 mg/L, respectively.

[b] One *K. oxytoca* isolate was less susceptible to all three carbapenems (confirmed by the reference laboratory), with DOR, IPM and MEM MIC values 4, 2 and 8 mg/L; the highest MICs excluding this isolate were 0.5, 1 and 0.5 mg/L, respectively.

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Table 3

Carbapenem minimum inhibitory concentrations (MICs) (mg/L) against *Pseudomonas aeruginosa* and Enterobacteriaceae isolates evaluated by country

Country	Carbapenem	*P. aeruginosa* (*n* = 780)				Enterobacteriaceae (*n* = 656)			
		n	MIC_{50}	MIC_{90}	Range	*n*	MIC_{50}	MIC_{90}	Range
Australia	DOR	87	0.25	4	0.03 to ≥64	82	0.015	0.03	0.008–0.12
	IPM		1	8	0.06 to ≥64		0.25	0.25	0.12–2
	MEM		0.5	8	0.015 to ≥64		0.03	0.03	0.008–0.25
Hong Kong	DOR	59	0.25	2	0.06–8	47	0.03	0.12	0.015–0.5
	IPM		1	2	0.5 to ≥64		0.25	1	0.03–4
	MEM		0.25	2	0.03–16		0.03	0.12	0.015–0.25
India	DOR	66	0.25	≥64	0.03 to ≥64	65	0.015	0.06	0.008–8
	IPM		2	≥64	0.12 to ≥64		0.12	0.25	0.06–8
	MEM		0.5	≥64	0.06 to ≥64		0.03	0.06	0.008–16
Indonesia	DOR	39	0.25	4	0.03 to ≥64	36	0.06	0.25	0.008 – 0.5
	IPM		2	4	0.12 to ≥64		0.25	1	0.03–4
	MEM		0.5	4	0.03 to ≥64		0.06	0.5	0.008–1
Malaysia	DOR	89	0.25	2	0.015 to ≥64	71	0.03	0.06	0.008–0.5

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	IPM		1	16	0.12 to ≥64		0.25	0.5	0.12–2
	MEM		0.25	4	0.03 to ≥64		0.03	0.12	0.015–1
Philippines	DOR	85	0.25	8	0.03 to ≥64	67	0.03	0.12	0.008–0.5
	IPM		2	32	0.06 to ≥64		0.25	0.5	0.008–1
	MEM		0.5	32	0.008 to ≥64		0.03	0.12	0.008–0.5
Singapore	DOR	60	0.25	8	0.015 to ≥64	48	0.03	0.12	0.015–4
	IPM		1	≥64	0.25 to ≥64		0.25	0.5	0.12–2
	MEM		0.5	≥64	0.008 to ≥64		0.03	0.12	0.015–8
Thailand	DOR	295	0.5	16	0.002 to ≥64	240	0.03	0.06	0.008–4
	IPM		2	≥64	0.12 to ≥64		0.12	0.25	0.015–2
	MEM		0.5	≥64	0.03 to ≥64		0.03	0.06	0.008–2

$MIC_{50/90}$, MICs for 50% and 90% of the organisms, respectively; DOR, doripenem; IPM, imipenem; MEM, meropenem.

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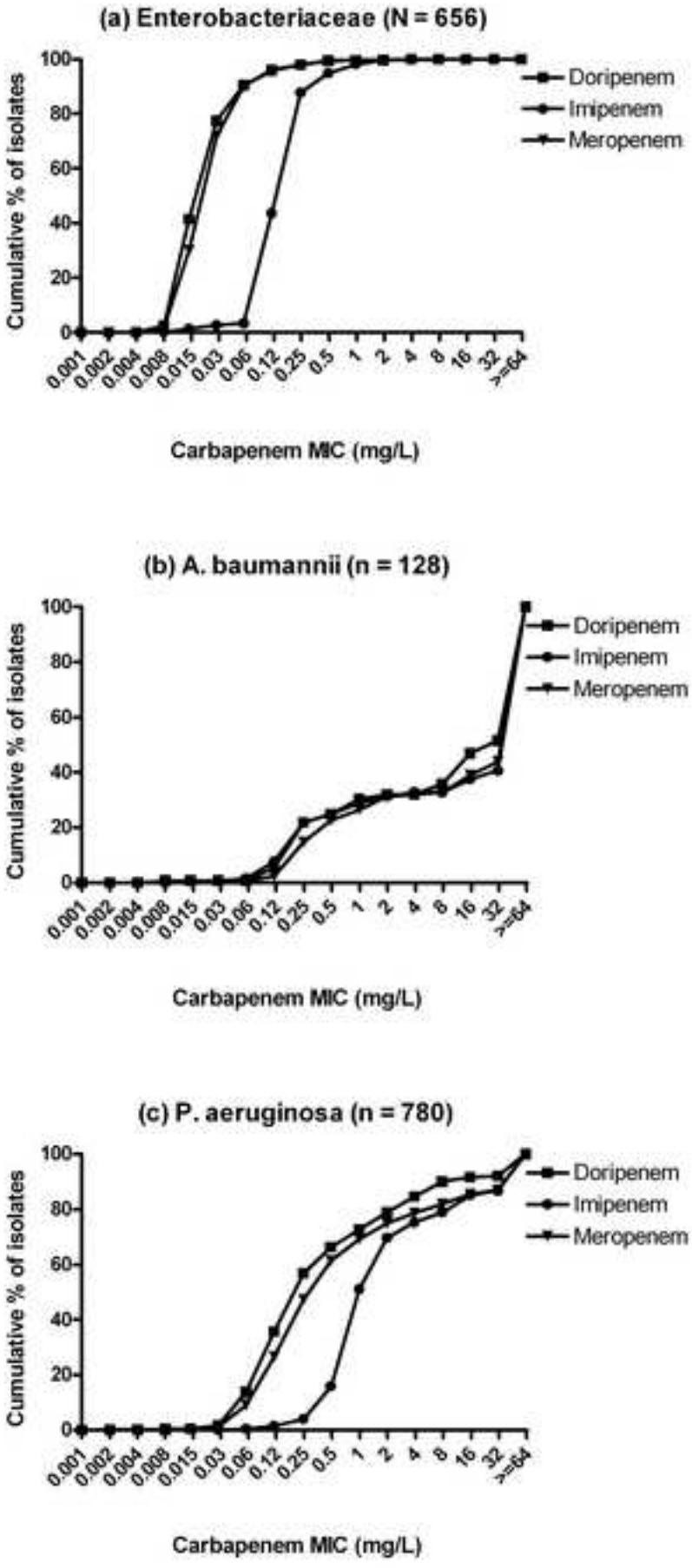
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