

Activity of Imipenem/Relebactam Against Clinical Isolates of *P. aeruginosa* and *K. pneumoniae* Collected in Asia/Pacific Countries – SMART 2016-2018

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Introduction

Relebactam (REL) inhibits class A and C β -lactamases, including KPC, and was approved in the United States in combination with imipenem/cilastatin (IMI) for the treatment of complicated urinary tract and intraabdominal infections in patients with limited treatment options, and for hospital-acquired and ventilator-associated bacterial pneumonia. We evaluated the activity of IMI/REL against recent clinical isolates collected in Asia/Pacific for the Study for Monitoring Antimicrobial Resistance Trends (SMART) global surveillance program.

Methods

In 2016-2018, 57 laboratories each collected up to 250 consecutive, aerobic or facultatively anaerobic, gram-negative pathogens from bloodstream (added in 2018), intraabdominal, lower respiratory tract, and urinary tract infections. Susceptibility was determined for 4,528 *P. aeruginosa* and 5,844 *K. pneumoniae* isolates using CLSI broth microdilution and CLSI breakpoints [1-3]. IMI-nonsusceptible isolates were screened by PCR and sequenced for genes encoding β -lactamases [4], except isolates from India (2016-2018), Vietnam (2017), one Vietnam site in 2018 (Enterobacterales only), and a small number of other isolates that were not available for molecular characterization and were not included in the denominators for the carbapenemase rate calculations.

Results

Table 1. Antimicrobial susceptibility and MBL gene carriage of all collected *P. aeruginosa* isolates^a

Country (no. of sites)	n	% Susceptible										% MBL
		IMI/REL	IMI	MEM	FEP	CAZ	ATM	P/T	LVX	AMK	% MBL	
Australia (5)	753	96.3	80.2	87.8	87.5	86.1	77.7	82.5	78.1	97.2	0.1	
Hong Kong (3)	94	88.3	66.0	73.4	75.5	73.4	60.6	68.1	69.2	98.9	0.0	
India (7)	439	63.8	42.4	52.9	56.0	50.8	46.2	51.5	46.0	64.7	N/A	
South Korea (7)	394	88.6	68.0	71.3	70.8	68.5	60.7	60.2	51.5	94.7	1.8	
Malaysia (4)	344	92.7	78.5	84.6	83.1	77.6	69.5	75.0	81.7	95.1	4.7	
New Zealand (5)	399	98.0	83.5	90.0	87.0	90.0	79.2	88.2	74.4	97.7	0.0	
Philippines (4)	173	89.6	77.5	75.1	80.4	77.5	65.3	76.3	65.3	96.5	4.0	
Taiwan (9)	1152	96.9	79.5	82.0	82.6	80.2	67.5	74.1	71.0	99.0	0.2	
Thailand (5)	446	81.2	62.8	66.6	69.7	67.7	56.1	62.8	61.9	88.3	11.0	
Vietnam (7)	298	60.4	45.3	44.3	48.3	51.0	43.0	51.3	38.6	61.1	41.2	
Asia/Pacific (57)	4528	88.9	71.7	76.2	77.0	75.1	65.2	71.1	66.5	91.8	--^c	

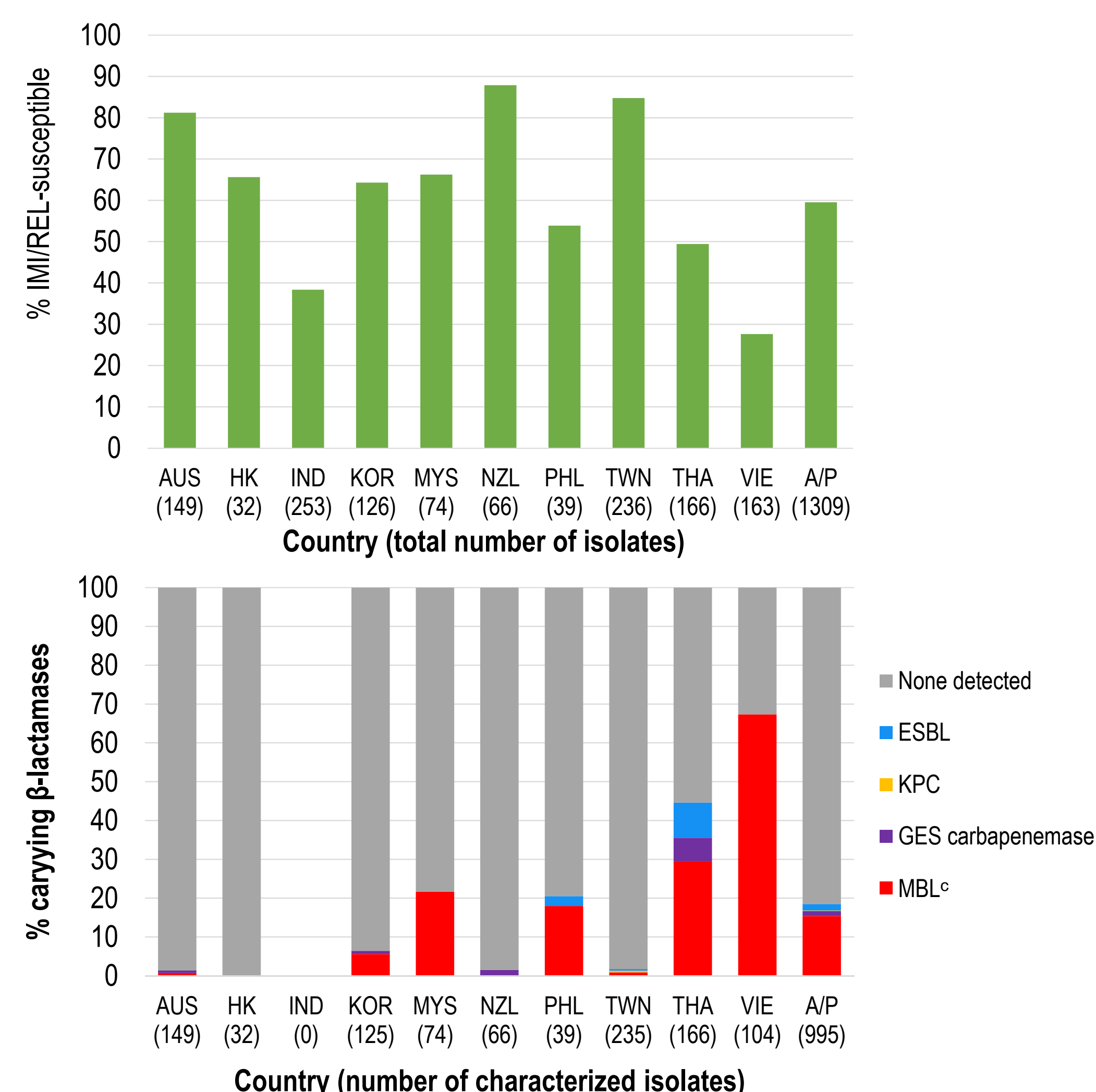
^aShowing individually only countries with at least 2 participating sites; Singapore not shown.

^bResults for colistin are not shown because *P. aeruginosa* are no longer considered susceptible to colistin per 2020 CLSI guidelines.

^cNo regional proportion calculated as molecular data was not available for isolates from India, Vietnam (2017), and one Vietnam site in 2018.

IMI, imipenem; REL, relebactam; MEM, meropenem; FEP, cefepime; CAZ, ceftazidime; ATM, aztreonam; P/T, piperacillin/tazobactam; LVX, levofloxacin; AMK, amikacin; MBL, metallo- β -lactamase; N/A, not available.

Figure 1. Proportion of IMI-nonsusceptible *P. aeruginosa* isolates testing as susceptible to imipenem/relebactam (top) and gene carriage of all IMI-nonsusceptible isolates (bottom)^{a, b}



^aOriginal spectrum β -lactamases (e.g., TEM-1) and intrinsic AmpC are not shown.

^bMolecular data not available for isolates from India, Vietnam (2017), one Vietnam site in 2018, and a small number of other isolates. Only countries with at least 10 IMI-nonsusceptible isolates are shown; Singapore not shown.

^cAny isolate carrying an MBL (MBL \pm other carbapenemase \pm ESBL \pm AmpC).

AUS, Australia; HK, Hong Kong; IND, India; KOR, South Korea; MYS, Malaysia; NZL, New Zealand; PHL, Philippines; TWN, Taiwan; THA, Thailand; VIE, Vietnam.

Table 2. Antimicrobial susceptibility and carbapenemase gene carriage of all collected *K. pneumoniae* isolates^a

Country (no. of sites)	n	% Susceptible											% MBL and/or OXA-48-like	
		IMI/REL	IMI	MEM	ETP	FEP	CAZ	ATM	P/T	CIP	AMK	% KPC	OXA-48-like	
Australia (5)	490	98.2	97.6	98.4	95.9	89.0	90.0	89.8	93.1	85.2	99.2	0.0	1.7	
Hong Kong (3)	157	98.7	97.5	98.7	98.7	86.0	86.0	84.7	93.6	72.6	100.0	0.0	0.0	
India (7)	604	58.8	55.3	56.6	53.2	36.8	33.8	33.6	47.5	27.7	60.1	N/A	N/A	
South Korea (7)	694	98.8	96.3	97.4	94.4	70.9	69.2	69.3	77.2	58.5	97.0	2.2	0.0	
Malaysia (4)	658	97.0	94.4	97.0	93.2	69.0	67.2	67.9	79.6	68.7	99.1	0.0	2.7	
New Zealand (5)	225	99.6	98.2	99.6	98.2	81.3	81.3	81.3	87.1	77.4	99.6	0.0	0.0	
Philippines (4)	385	95.1	91.7	92.7	90.1	70.9	63.4	64.7	78.7	52.7	97.7	2.3	4.4	
Taiwan (9)	1331	98.4	91.4	94.9	88.0	80.2	68.8	75.4	78.1	60.8	95.3	3.2	0.6	
Thailand (5)	665	80.5	79.9	79.7	77.7	44.5	43.3	43.6	57.3	35.9	97.3	0.0	21.5	
Vietnam (7)	556	77.9	69.6	71.4	67.5	45.0	43.7	45.0	52.3	32.1	85.3	6.9	20.2	
Asia/Pacific (57)	5844	90.0	86.2	88.0	84.2	66.4	62.4	64.2	72.5	56.4	92.4	1.7	--^c	

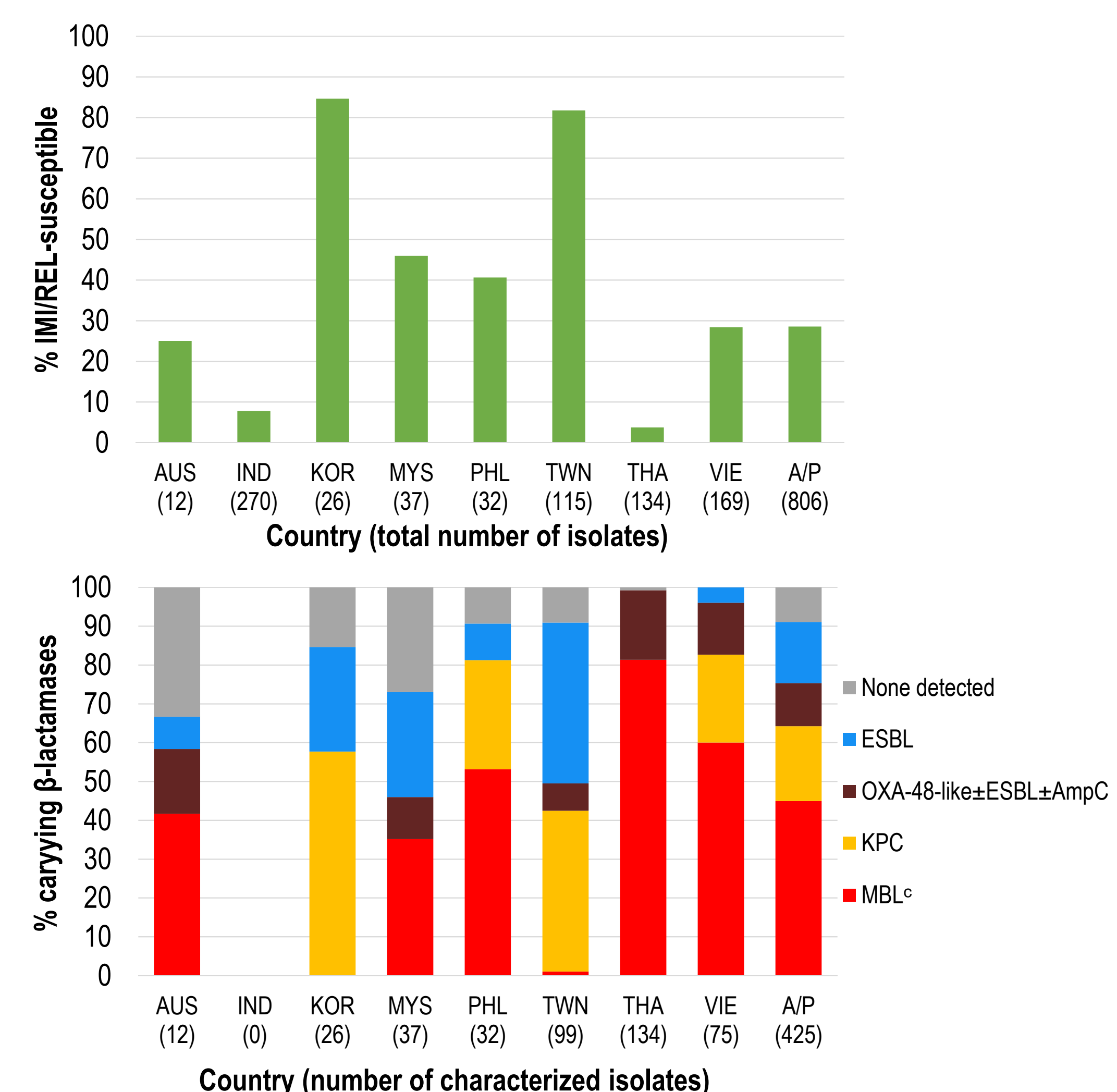
^aShowing individually only countries with at least 2 participating sites; Singapore not shown.

^bResults for colistin are not shown because Enterobacterales are no longer considered susceptible to colistin per 2020 CLSI guidelines.

^cNo proportion calculated as data was not available for isolates from India, Vietnam (2017), and one Vietnam and one Taiwan site in 2018.

IMI, imipenem; REL, relebactam; MEM, meropenem; ETP, ertapenem; FEP, cefepime; CAZ, ceftazidime; ATM, aztreonam; P/T, piperacillin/tazobactam; CIP, ciprofloxacin; AMK, amikacin; MBL, metallo- β -lactamase; N/A, not available.

Figure 2. Proportion of IMI-nonsusceptible *K. pneumoniae* isolates testing as susceptible to imipenem/relebactam (top) and gene carriage of all IMI-nonsusceptible isolates (bottom)^{a, b}



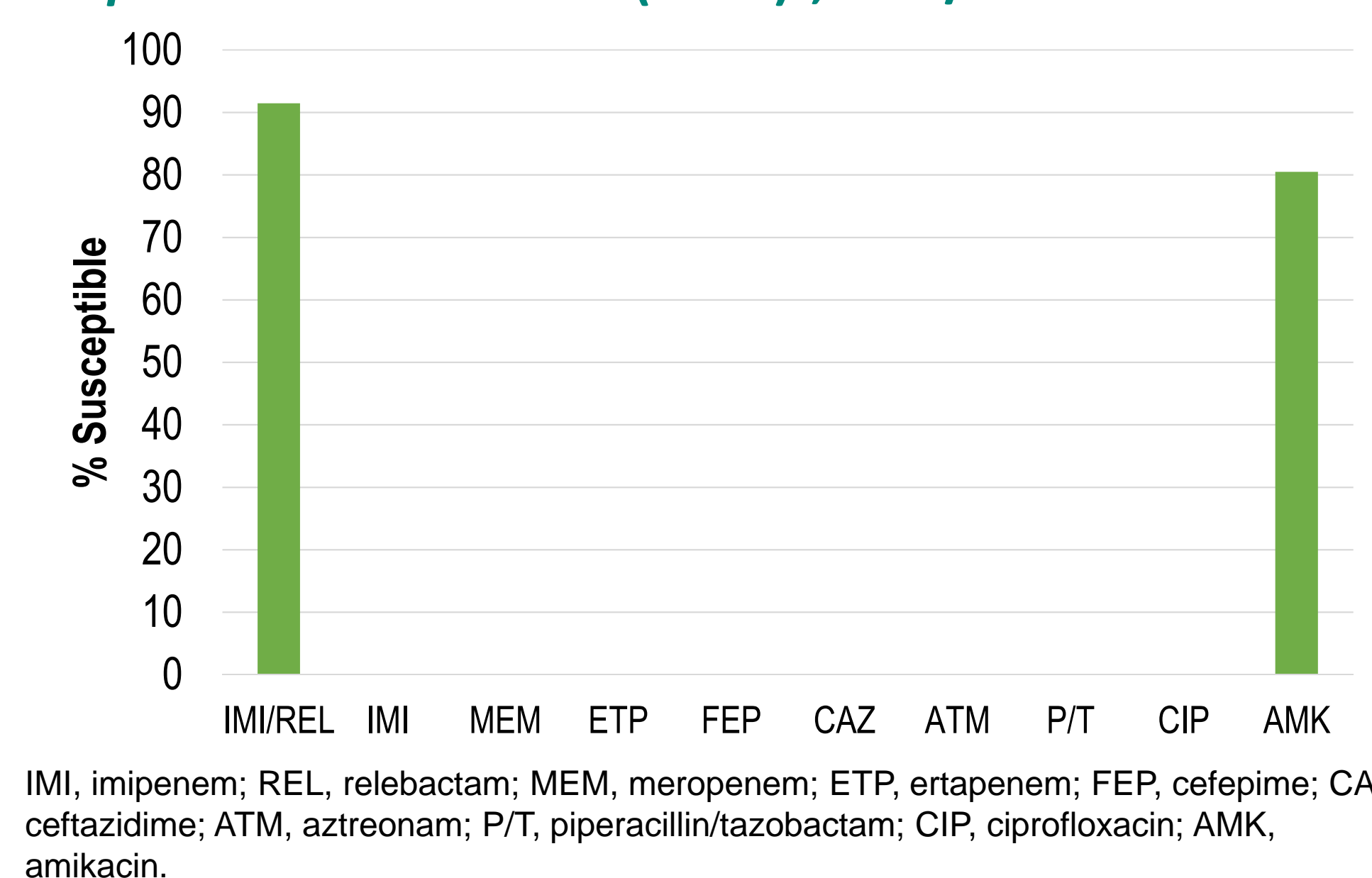
^aOriginal spectrum β -lactamases (e.g., TEM-1) are not shown.

^bMolecular data not available for isolates from India, Vietnam (2017), and one Vietnam and one Taiwan site in 2018. Only countries with at least 10 IMI-nonsusceptible isolates are shown; Hong Kong, New Zealand, and Singapore not shown.

^cAny isolate carrying an MBL (MBL \pm other carbapenemase \pm ESBL \pm AmpC).

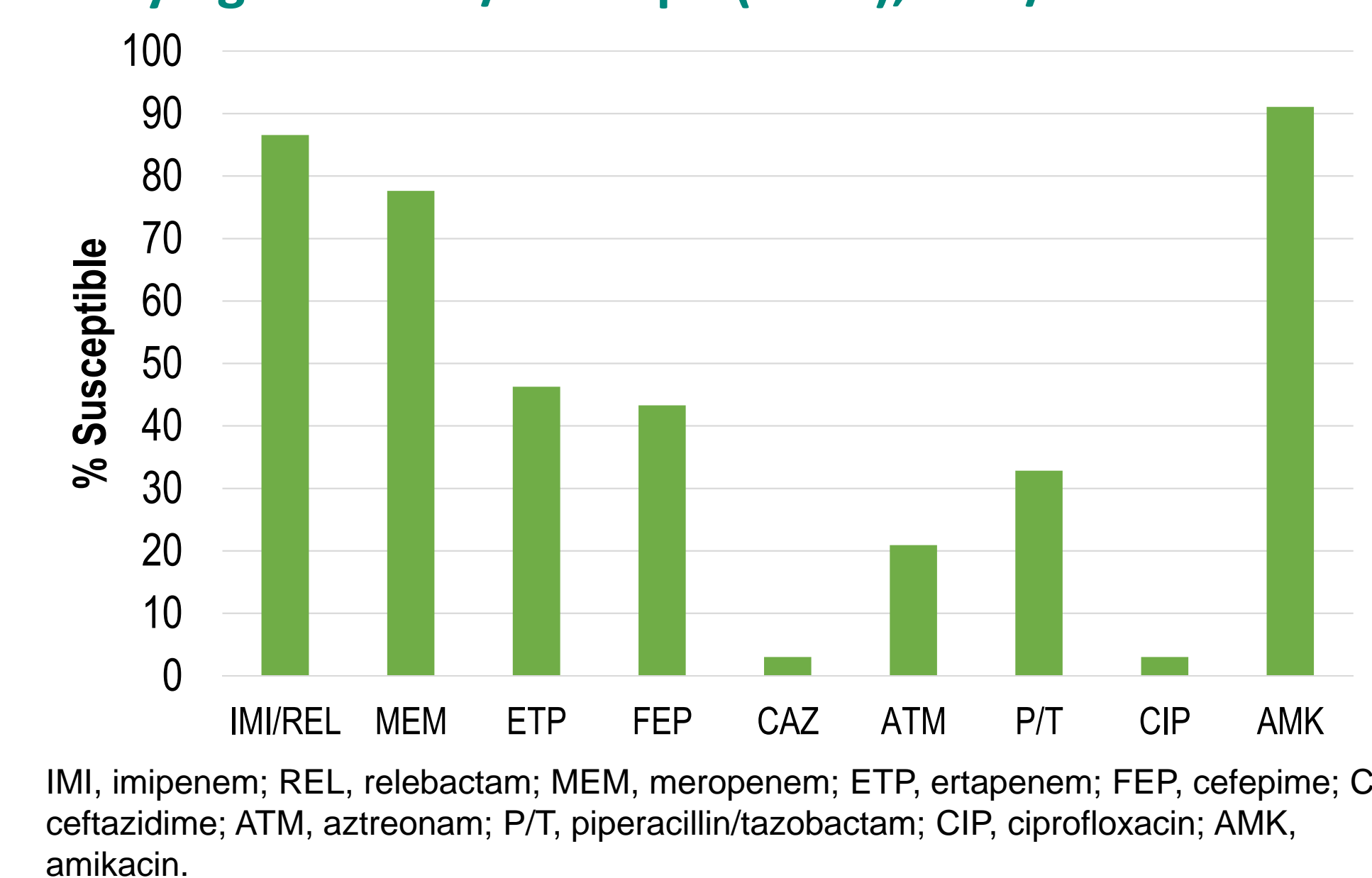
AUS, Australia; IND, India; KOR, South Korea; MYS, Malaysia; PHL, Philippines; TWN, Taiwan; THA, Thailand; VIE, Vietnam.

Figure 3. Susceptibility of MBL-negative KPC-positive *K. pneumoniae* isolates (n=82)^a, Asia/Pacific



IMI, imipenem; REL, relebactam; MEM, meropenem; ETP, ertapenem; FEP, cefepime; CAZ, ceftazidime; ATM, aztreonam; P/T, piperacillin/tazobactam; CIP, ciprofloxacin; AMK, amikacin.

Figure 4. Susceptibility of IMI-nonsusceptible carbapenemase-negative *K. pneumoniae* isolates carrying ESBL and/or AmpC (n=67), Asia/Pacific



IMI, imipenem; REL, relebactam; MEM, meropenem; ETP, ertapenem; FEP, cefepime; CAZ, ceftazidime; ATM, aztreonam; P/T, piperacillin/tazobactam; CIP, ciprofloxacin; AMK, amikacin.

Results Summary

- Among all *P. aeruginosa*, 88.9% of isolates were IMI/REL-susceptible (S) in Asia/Pacific overall, ranging from ~60% in India and Vietnam to >90% in 4 countries (Table 1).
- Among all *K. pneumoniae*, 90.0% of isolates were IMI/REL-S in Asia/Pacific overall, ranging from 58.8% in India to >95% in 7 countries (Table 2).
- Among IMI-nonsusceptible (NS) *P. aeruginosa*, 59.5% were IMI/REL-S, ranging from 27.6% in Vietnam (where 67.3% of characterized IMI-NS isolates carried class B MBL, which REL does not inhibit) to >80% in Australia, New Zealand, and Taiwan (where <1% carried MBL) (Figure 1).
- Among IMI-NS *K. pneumoniae*, 28.5% were IMI/REL-S, ranging from 3.7% in Thailand (where 99.3% of IMI-NS isolates carried MBL and/or class D OXA-48-like carbapenemases, which REL does not inhibit) to >80% in South Korea and Taiwan (where >70% of isolates carried KPC or only ESBL and/or AmpC, and \leq 7% carried MBL and/or OXA-48-like carbapenemases) (Figure 2).
- Among KPC-positive *K. pneumoniae*, 91.5% of isolates were IMI/REL-S; of the tested comparator agents only amikacin showed activity (Figure 3).
- Among IMI-NS *K. pneumoniae* isolates that carried only ESBL and/or AmpC, 86.6% of isolates were IMI/REL-S; only amikacin showed higher activity (Figure 4).

Conclusions

IMI/REL was active against 89% of *P. aeruginosa* and 90% of *K. pneumoniae* isolates collected in Asia/Pacific and maintained activity against 91% of KPC-positive *K. pneumoniae*. Susceptibility to IMI/REL among IMI-nonsusceptible isolates varied across the region, with higher activity in countries with low proportions of MBL-positive isolates and low proportions of OXA-48-like-positive *K. pneumoniae*. IMI/REL promises to be an important treatment option for IMI-nonsusceptible MBL-negative isolates, including KPC-producing *K. pneumoniae*.

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