

Global Activity of Imipenem-Relebactam and Comparators against Clinical Gram-Negative Pathogens – SMART 2017

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INTRODUCTION

Relebactam (REL), formerly MK-7655, is an inhibitor of class A and C β -lactamases that is in development in combination with imipenem (IMI). In this study, we evaluated the activity of IMI/REL against recent clinical isolates of gram-negative bacilli (GNB) collected globally as part of the Study for Monitoring Antimicrobial Resistance Trends (SMART) surveillance program.

METHODS

In 2017, 188 hospitals in 54 countries, excluding China and India, each collected up to 100 consecutive gram-negative aerobic or facultatively anaerobic pathogens from lower respiratory tract infections (RTI), 75 from intra-abdominal infections (IAI), and 75 from urinary tract infections (UTI). MICs were determined for 41,510 GNB, including 30,994 *Enterobacteriaceae* and 6,975 *P. aeruginosa* isolates, using CLSI broth microdilution. MICs were interpreted with CLSI breakpoints; for comparison purposes, IMI susceptible breakpoints were applied to IMI/REL [1, 2]. Colistin susceptibility was assessed using EUCAST breakpoints [3].

Enterobacteriaceae isolates that were nonsusceptible to ceftolozane-tazobactam (MIC >2 μ g/ml) and non-*Proteaeae* *Enterobacteriaceae* isolates that were nonsusceptible to ertapenem (MIC >0.5 μ g/ml) or IMI (MIC >1 μ g/ml) were screened for genes encoding β -lactamases using published multiplex PCR assays, followed by full-gene DNA sequencing.

RESULTS

Figure 1. Species distribution among all collected gram-negative isolates

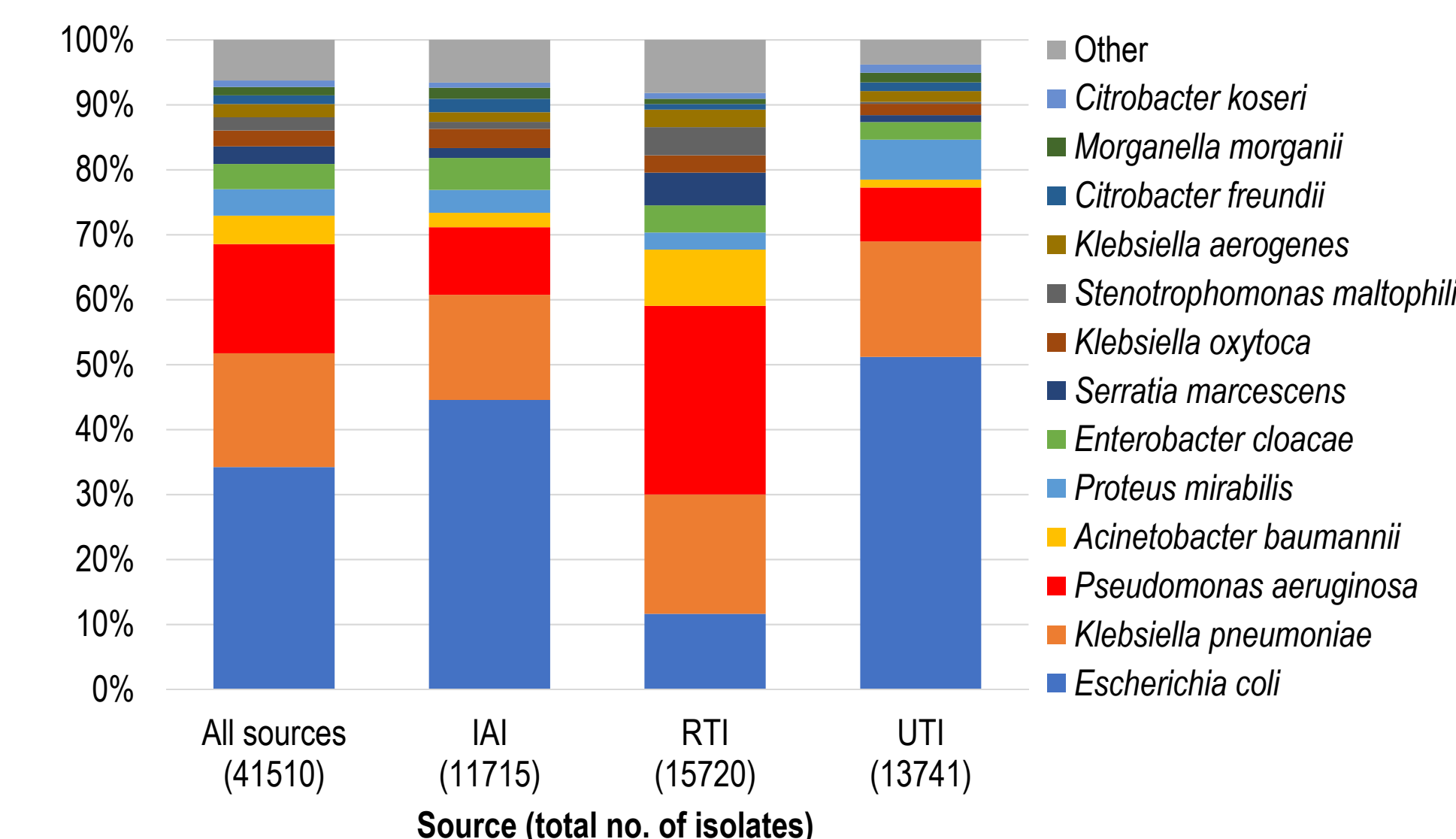


Table 1. Antimicrobial susceptibility (%) of the ten most common *Enterobacteriaceae* species and *P. aeruginosa*, all specimen sources^a

Organism	n	IMI/REL	IMI	FEP	CAZ	P/T	ATM	CIP	AMK	CST
All <i>Enterobacteriaceae</i>	30994	93.1	89.8	76.2	75.4	84.7	74.4	69.8	97.5	85.3
<i>E. coli</i>	14194	99.6	99.1	75.9	79.1	91.1	76.2	64.5	99.0	99.6
<i>K. pneumoniae</i>	7280	93.0	87.5	59.4	58.6	69.2	58.9	60.9	94.0	95.1
<i>P. mirabilis</i>	1687	63.0	63.7	88.9	91.3	98.1	94.9	66.2	96.2	0.4
<i>E. cloacae</i>	1609	96.8	93.9	75.5	62.6	72.4	63.5	82.0	97.8	93.2
<i>S. marcescens</i>	1133	70.6	52.0	91.6	92.1	92.9	90.6	90.0	98.1	5.2
<i>K. oxytoca</i>	1013	99.4	98.8	94.5	94.1	87.0	87.2	94.4	99.7	99.2
<i>K. aerogenes</i>	831	97.6	88.6	92.8	72.2	75.2	75.5	94.2	98.8	98.6
<i>C. freundii</i>	568	98.9	97.5	90.7	71.0	79.8	72.0	87.2	99.1	99.8
<i>M. morganii</i>	538	32.0	5.6	95.0	84.6	97.6	94.2	77.0	99.3	0.6
<i>C. koseri</i>	403	99.8	97.3	98.5	98.3	97.8	97.5	98.8	99.8	100
<i>P. aeruginosa</i>	6975	89.2	68.9	74.9	73.5	68.5	64.0	75.1	90.9	99.5

^aIMI, imipenem; REL, relebactam; FEP, cefepime; CAZ, ceftazidime; P/T, piperacillin-tazobactam; ATM, aztreonam; CIP, ciprofloxacin; AMK, amikacin; CST, colistin

Table 2. Antimicrobial susceptibility (%) of the ten most common *Enterobacteriaceae* species and *P. aeruginosa*, IAI^a

Organism	n	IMI/REL	IMI	FEP	CAZ	P/T	ATM	CIP	AMK	CST
All <i>Enterobacteriaceae</i>	9948	94.2	91.3	78.5	77.1	85.2	76.0	73.0	97.9	88.4
<i>E. coli</i>	5220	99.5	98.9	78.4	81.2	91.0	78.2	68.7	99.0	99.5
<i>K. pneumoniae</i>	1897	92.6	87.3	61.7	60.9	70.1	61.4	62.9	94.3	95.4
<i>P. mirabilis</i>	413	65.9	65.1	92.7	93.0	99.0	96.9	71.2	97.8	0.0
<i>E. cloacae</i>	575	97.0	93.7	77.7	63.8	71.1	65.0	85.2	97.9	93.0
<i>S. marcescens</i>	180	71.7	49.4	87.2	89.4	87.8	86.1	89.4	95.0	3.9
<i>K. oxytoca</i>	345	99.4	99.1	95.1	95.7	87.3	90.1	96.5	99.7	99.4
<i>K. aerogenes</i>	174	96.0	87.9	91.4	61.5	66.7	66.7	96.0	98.3	99.4
<i>C. freundii</i>	246	99.6	97.6	91.1	68.3	80.1	71.5	89.4	99.6	99.6
<i>M. morganii</i>	200	29.0	5.0	95.5	84.0	98.0	93.5	82.5	100	0.5
<i>C. koseri</i>	91	100	94.5	98.9	97.8	95.6	96.7	97.8	100	100
<i>P. aeruginosa</i>	1219	91.4	75.0	78.9	75.5	72.9	67.4	81.0	93.6	99.6

^aIMI, imipenem; REL, relebactam; FEP, cefepime; CAZ, ceftazidime; P/T, piperacillin-tazobactam; ATM, aztreonam; CIP, ciprofloxacin; AMK, amikacin; CST, colistin

Table 3. Antimicrobial susceptibility (%) of the ten most common *Enterobacteriaceae* species and *P. aeruginosa*, RTI^a

Organism	n	IMI/REL	IMI	FEP	CAZ	P/T	ATM	CIP	AMK	CST
All <i>Enterobacteriaceae</i>	8491	90.5	84.9	75.1	73.0	80.9	72.5	72.9	96.4	78.8
<i>E. coli</i>	1829	99.5	98.9	70.5	74.5	86.5	71.1	59.8	98.5	99.7
<i>K. pneumoniae</i>	2883	92.1	85.9	59.0	58.2	68.6	58.3	62.5	92.8	94.4
<i>P. mirabilis</i>	412	61.9	62.4	83.7	87.1	97.3	91.0	64.6	94.4	0.2
<i>E. cloacae</i>	658	96.8	94.7	78.6	67.3	77.5	67.8	86.3	98.8	93.6
<i>S. marcescens</i>	795	70.3	51.3	92.7	92.8	94.0	91.6	91.1	98.6	5.7
<i>K. oxytoca</i>	416	99.8	98.6	95.0	94.2	87.5	85.8	95.2	99.8	99.3
<i>K. aerogenes</i>	427	97.9	88.1	93.9	74.9	76.4	77.3	91.8	98.4	98.4
<i>C. freundii</i>	136	100	98.5	91.2	70.6	77.9	70.6	84.6	99.3	100
<i>M. morganii</i>	128	40.6	10.2	95.3	88.3	99.2	96.9	77.3	99.2	0.8
<i>C. koseri</i>	139	100	97.1	97.8	97.8	99.3	97.1	99.3	100	100
<i>P. aeruginosa</i>	4565	89.0	65.9	73.0	71.7	66.3	62.2	74.0	90.9	99.5

^aIMI, imipenem; REL, relebactam; FEP, cefepime; CAZ, ceftazidime; P/T, piperacillin-tazobactam; ATM, aztreonam; CIP, ciprofloxacin; AMK, amikacin; CST, colistin

Table 4. Antimicrobial susceptibility (%) of the ten most common *Enterobacteriaceae* species and *P. aeruginosa*, UTI^a

Organism	n	IMI/REL	IMI	FEP	CAZ	P/T	ATM	CIP	AMK	CST
All <i>Enterobacteriaceae</i>	12313	94.0	91.9	75.0	75.6	87.0	74.5	65.2	98.0	87.3
<i>E. coli</i>	7033	99.7	99.4	75.5	78.8	92.4	76.1	62.5	99.1	99.6
<i>K. pneumoniae</i>	2442	94.5	89.6	58.0	57.4	69.5	57.7	57.8	95.3	95.8
<i>P. mirabilis</i>	845	62.1	63.2	89.6	92.3	98.0	95.7	64.5	96.2	0.6
<i>E. cloacae</i>	370	96.8	92.7	66.8	52.4	65.4	53.5	69.5	95.7	92.4
<i>S. marcescens</i>	148	71.6	58.1	90.5	91.2	92.6	89.9	84.5	98.7	4.7
<i>K. oxytoca</i>	240	99.2	99.2	93.3	92.1	85.8	85.4	90.4	99.6	98.8
<i>K. aerogenes</i>	228	98.3	90.4	91.7	75.0	79.4	78.5	97.4	100	98.3
<i>C. freundii</i>	182	97.3	96.7	89.6	74.7	80.8	73.6	85.7	98.4	100
<i>M. morganii</i>	207	29.0	2.9	94.7	83.1	96.1	93.7	72.0	98.6	0.5
<i>C. koseri</i>	172	99.4	98.8	98.8	98.8	97.7	98.3	98.8	99.4	100
<i>P. aeruginosa</i>	1143	87.9	74.4	78.3	78.6	72.4	67.9	73.3	88.7	99.4

^aIMI, imipenem; REL, relebactam; FEP, cefepime; CAZ, ceftazidime; P/T, piperacillin-tazobactam; ATM, aztreonam; CIP, ciprofloxacin; AMK, amikacin; CST, colistin

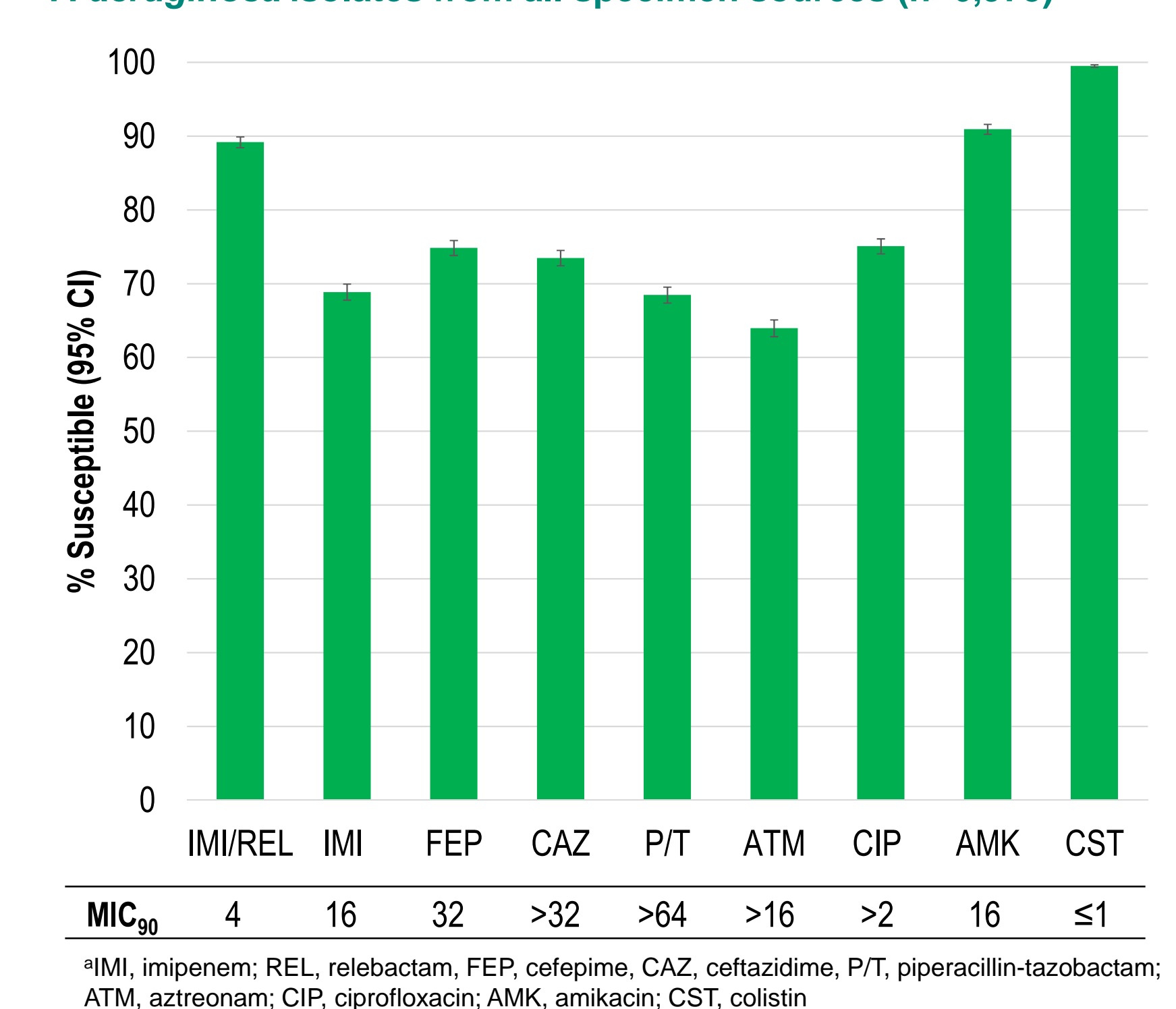
Table 5. Antimicrobial susceptibility (%) of KPC-positive *Enterobacteriaceae*, all specimen sources^a

Organism	n	IMI/REL	IMI	FEP	CAZ	P/T	ATM	CIP	AMK	CST
All <i>Enterobacteriaceae</i>	425	94.6	3.1	4.0	5.2	0.5	0.9	13.6	70.6	73.2
<i>K. pneumoniae</i>	355	96.1	2.5	1.7	2.0	0.6	0.6	8.7	68.2	71.3
<i>E. coli</i>	18	100	16.7	27.8	33.3	0.0	0.0	38.9	88.9	100
<i>E. cloacae</i>	13	100	7.7	7.7	0.0	0.0	0.0	23.1	76.9	100
<i>S. marcescens</i>	12	66.7	0.0	0.0	16.7	0.0	0.0	16.7	66.7	0.0
Other species ^b	27	81.5	0.0	18.5	25.9	0.0	7.4	55.6	88.9	100

^aIMI, imipenem; REL, relebactam; FEP, cefepime; CAZ, ceftazidime; P/T, piperacillin-tazobactam; ATM, aztreonam; CIP, ciprofloxacin; AMK, amikacin; CST, colistin

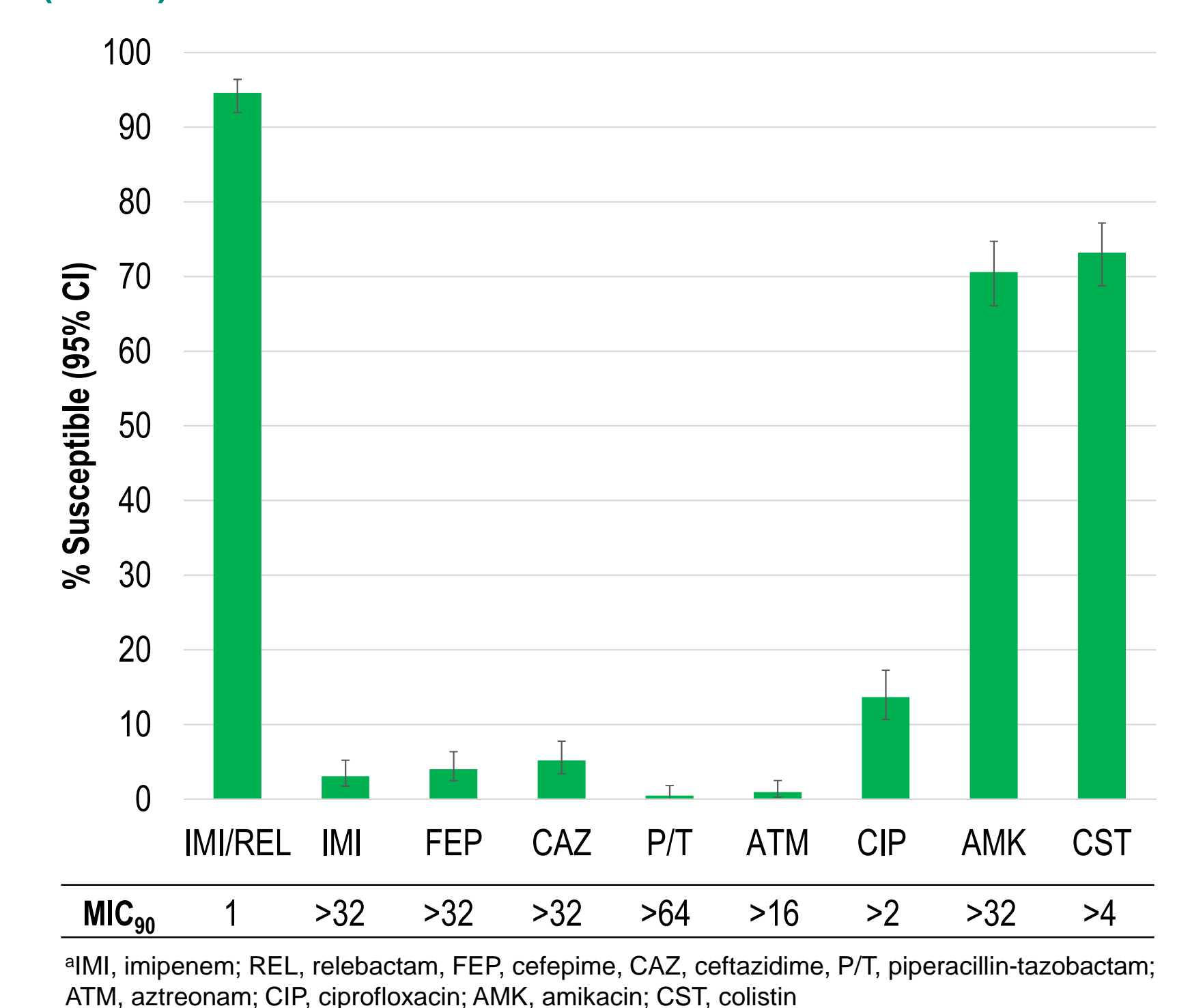
^bIncludes *K. aerogenes* (n=9), *K. oxytoca* (n=7), *C. freundii* (n=4), *K. variicola* (n=4), *R. ornithinolytica* (n=1), *C. farmeri* (n=1), *P. gergoviae* (n=1)

Figure 2. Antimicrobial susceptibility and MIC₉₀ (μ g/mL) of *P. aeruginosa* isolates from all specimen sources (n=6,975)^a



^aIMI, imipenem; REL, relebactam; FEP, cefepime; CAZ, ceftazidime; P/T, piperacillin-tazobactam; ATM, aztreonam; CIP, ciprofloxacin; AMK, amikacin; CST, colistin

Figure 3. Antimicrobial susceptibility and MIC₉₀ (μ g/mL) of KPC-positive *Enterobacteriaceae* isolates from all specimen sources (n=425)^a



^aIMI, imipenem; REL, relebactam; FEP, cefepime; CAZ, ceftazidime; P/T, piperacillin-tazobactam; ATM, aztreonam; CIP, ciprofloxacin; AMK, amikacin; CST, colistin

RESULTS SUMMARY

- E. coli*, *K. pneumoniae*, and *P. aeruginosa* comprised 69% of all collected gram-negative pathogens and were the three most common species collected from all specimen sources (Figure 1).
- IMI/REL showed potent *in vitro* activity against 7 of the 10 most common *Enterobacteriaceae* species (>90% susceptible, S), typically ~5-35 percentage points higher than that of most β -lactam comparators tested. Against *P. aeruginosa* (89% S), IMI/REL activity was ~15-25% higher than that of the β -lactam comparators. Only amikacin and colistin showed similar or higher activity against most species (Table 1, Figure 2).
- IMI/REL showed similarly potent activity against *Enterobacteriaceae* (>90% S) and *P. aeruginosa* (88-91% S) from IAI, RTI, and UTI sources (Tables 2-4).
- IMI/REL showed modest activity against isolates of *Proteaeae* (intrinsic resistant to imipenem and colistin) and *Serratia* spp. (intrinsic resistant to colistin); however, these species comprised <10% of all collected GNB (Figure 1).
- Against KPC+ *Enterobacteriaceae* (>90% S), IMI/REL maintained activity typically ~20 to 90 percentage points higher than all other comparators tested (Table 5 and Figure 3).

CONCLUSIONS

IMI/REL showed potent *in vitro* activity against *P. aeruginosa* and most *Enterobacteriaceae*, including KPC-positive isolates. It could provide an important treatment option against infections caused by gram-negative pathogens, especially because other agents such as amikacin and colistin are associated with significant morbidity, including nephrotoxicity and ototoxicity, and are seldom used as monotherapy.

References and Acknowledgments:

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- The European Committee on Antimicrobial Susceptibility Testing – EUCAST Clinical Breakpoints 2018; http://www.eucast.org/clinical_breakpoints/

Funding for this research was provided by Merck & Co., Inc., Kenilworth, NJ USA. The authors thank all the participants in the SMART program for their continuing contributions to its success.



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