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Global perspective on imipenem non-susceptible Pseudomonas aeruginosa isolates collected as part of the SMART surveillance programme, 2015

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Background: Relebactam (REL) is a non-β-lactam β-lactamase inhibitor in development for use with imipenem/ cilastatin. REL inhibits Class A and Class C enzymes and potentiates the activity of imipenem (IMI) against multidrug-resistant *P. aeruginosa* isolates and isolates non-susceptible to IMI (IMI-NS) due to overproduction of chromosomal AmpC or porin loss. In this study, we evaluated the *in vitro* activity of IMI/REL against *P. aeruginosa* isolates collected globally as part of the SMART surveillance program in 2015.

Material/methods: 154 medical centers in 51 countries collected consecutive, non-duplicate Gram-negative isolates from patients with respiratory tract, intra-abdominal, and urinary tract infections. Antimicrobial susceptibility was determined by broth microdilution and interpreted using CLSI guidelines. REL was tested at a fixed concentration of 4 mg/L in combination with IMI. *P. aeruginosa* isolates that were IMI-NS (MIC ≥ 4 mg/L) were screened for the presence of acquired β-lactamases (ESBLs, AmpCs, serine- and metallo- carbapenemases) by multiplex PCR. All detected β-lactamases and the chromosomal AmpC common to *P. aeruginosa* were sequenced.

Results: 5491 isolates of *P. aeruginosa* were collected from respiratory tract (n=3620), intra-abdominal (n=1303), urinary tract (n=534), and unknown (n=34) infection sources. Of these, 31.3%, 24.2%, 25.5%, and 23.5% of isolates, respectively, were IMI-NS. The percentage of susceptibility to IMI and IMI/REL of overall and IMI-NS isolates is shown in the table.

Region	*P. aeruginosa*, All			*P. aeruginosa*, IMI-NS		
	n	IMI (% S)	IMI/REL (% S)	n	IMI (% S)	IMI/REL (% S)
Global	5491	71.0	92.1	1593	0.0	72.7
Europe	1705	67.9	92.7	547	0.0	77.3
North America	1152	71.9	93.8	324	0.0	77.8
Asia	769	78.9	94.8	162	0.0	75.3
Latin America	673	63.6	85.3	245	0.0	59.6
South Pacific	468	85.9	96.8	66	0.0	77.3
Africa	368	66.0	85.1	125	0.0	56.0
Middle East	356	65.2	91.6	124	0.0	75.8

IMI, imipenem; REL, relebactam; NS, non-susceptible; % S, percent susceptible. For the purpose of comparison, the CLSI susceptible breakpoint of 2 mg/L for IMI was applied to IMI/REL.

The percentage of *P. aeruginosa* isolates non-susceptible to IMI ranged from 14.1% (South Pacific) to 36.4% (Latin America). The addition of REL restored susceptibility to IMI (MICs ≤ 2 mg/L) to 75.3 – 77.8% of IMI-NS isolates collected in Europe, North America, Asia, South Pacific, and the Middle East region, for overall susceptibilities of 91.6 – 96.8%. A lower percentage of IMI-NS isolates (56.0 – 59.6%) collected in Africa and Latin America were rendered susceptible by the addition of REL, resulting in overall susceptibilities of 85.1-85.3% in these regions. Of the 435 isolates collected globally that were IMI/REL-NS, 40.7% carried metallo-β-lactamases, 9.4% carried GES β-lactamases, and no acquired β-lactamases that contribute to reduced susceptibility were detected in the remaining isolates.

Conclusions: REL restored the *in vitro* activity of IMI against many isolates of *P. aeruginosa* collected globally that were otherwise non-susceptible to carbapenem treatment. Further development of IMI/REL/cistatin could provide a valuable therapeutic option for treating infections caused by resistant isolates of this important pathogen.