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Activity of ceftolozane/tazobactam and imipenem/relebactam against clinical isolates of Enterobacterales and *Pseudomonas aeruginosa* collected in central and northern Europe (Belgium, Norway, Sweden, Switzerland)—SMART 2017–21

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Objectives: To evaluate the *in vitro* activities of ceftolozane/tazobactam and imipenem/relebactam against clinical isolates of Gram-negative bacilli collected in four central and northern European countries (Belgium, Norway, Sweden, Switzerland) during 2017–21.

Methods: Participating clinical laboratories each collected up to 250 consecutive Gram-negative isolates per year from patients with bloodstream, intraabdominal, lower respiratory tract or urinary tract infections. MICs were determined by CLSI broth microdilution and interpreted using 2022 EUCAST breakpoints. β-Lactamase genes were identified in select β-lactam-non-susceptible isolate subsets.

Results: Ninety-five percent of all Enterobacterales ($n=4158$), 95% of ESBL-positive non-carbapenem-resistant Enterobacterales (non-CRE) phenotype *Escherichia coli* and 85% of ESBL-positive non-CRE phenotype *Klebsiella pneumoniae* were ceftolozane/tazobactam susceptible. By country, 88% (Belgium), 91% (Sweden, Switzerland) and 96% (Norway) of ESBL-positive non-CRE phenotype Enterobacterales were ceftolozane/tazobactam susceptible. Greater than ninety-nine percent of non-Morganellaceae Enterobacterales and all ESBL-positive non-CRE phenotype Enterobacterales were imipenem/relebactam susceptible. Ceftolozane/tazobactam (96%) and imipenem/relebactam (95%) inhibited most *Pseudomonas aeruginosa* ($n=823$). Both agents retained activity against ≥75% of cefepime-resistant, ceftazidime-resistant and piperacillin/tazobactam-resistant isolates; 56% and 43% of meropenem-resistant isolates were ceftolozane/tazobactam susceptible and imipenem/relebactam susceptible, respectively. By country, 94% (Belgium), 95% (Sweden) and 100% (Norway, Switzerland) of *P. aeruginosa* were ceftolozane/tazobactam susceptible and 93% (Sweden) to 98% (Norway, Switzerland) were imipenem/relebactam susceptible. Carbapenemase gene carriage among Enterobacterales and *P. aeruginosa* isolates was generally low (<1%) or completely absent with one exception: an estimated 2.7% of *P. aeruginosa* isolates from Belgium carried an MBL.

Conclusions: Recent clinical isolates of Enterobacterales and *P. aeruginosa* collected in four central and northern European countries were highly susceptible (≥95%) to ceftolozane/tazobactam and imipenem/relebactam.

Introduction

Ceftolozane/tazobactam, an antipseudomonal cephalosporin combined with a β-lactamase inhibitor, is approved by the EMA and the FDA for the treatment of complicated urinary tract infection, complicated intraabdominal infection and hospital-acquired and ventilator-associated bacterial pneumonia (HAP and VAP). Imipenem/relebactam is a combination of imipenem/cilastatin with relebactam, an inhibitor of class A and C β-lactamases. Imipenem/relebactam is approved by the EMA and the FDA for HAP and VAP, bacteraemia associated with HAP and VAP (EMA only) and infections due to aerobic Gram-negative bacilli in adults

with limited treatment options (e.g. complicated urinary tract infection, complicated intraabdominal infection). Previous publications have not described country-specific *in vitro* susceptibility testing data for ceftolozane/tazobactam and imipenem/relebactam against clinical isolates of Gram-negative bacilli collected in central and northern Europe.[1–4] We evaluated the activity of these two agents and relevant comparators against clinical isolates of Gram-negative bacilli collected by clinical laboratories in Belgium, Norway, Sweden and Switzerland as part of the Study for Monitoring Antimicrobial Resistance Trends (SMART) global surveillance programme.

Materials and methods

Bacterial isolates and antimicrobial susceptibility testing

During 2017–21, five clinical laboratories in central and northern Europe (two in Belgium and one each in Norway, Sweden and Switzerland) participated in the SMART global surveillance programme. Each laboratory collected consecutive aerobic or facultative Gram-negative isolates from intraabdominal infections (75 isolates in 2017 and 50 isolates/year during 2018–21), urinary tract infections (75 isolates in 2017 and 50 isolates/year during 2018–21), lower respiratory tract infections (100 isolates/year) and bloodstream infections (50 isolates/year during 2018–21 only). Only one isolate per patient per species per year was accepted. All isolates were sent to a central laboratory (IHMA, Monthey, Switzerland), where species identity was confirmed using MALDI-TOF MS (Bruker Daltonics, Billerica, MA, USA) and antimicrobial susceptibility testing was performed.

MICs were determined by the CLSI reference broth microdilution method[5] using custom-made dehydrated broth microdilution panels manufactured by TREK Diagnostic Systems (Thermo Fisher Scientific, Oakwood Village, OH, USA) in 2017 and broth microdilution panels prepared at IHMA during 2018–21. MICs were interpreted using 2022 EUCAST breakpoints.[6] EUCAST does not publish breakpoints for imipenem/relebactam against Morganellaceae (*Proteus*, *Providencia* and *Morganella* spp.) isolates because they are known to have intrinsic, lowered susceptibility to imipenem by a mechanism independent of β-lactamase production,[7] and relebactam does not improve the activity of imipenem against Morganellaceae. Therefore, imipenem/relebactam susceptibility was analysed for non-Morganellaceae Enterobacterales (NME) only. An ESBL-positive non-carbapenem-resistant Enterobacterales (non-CRE) phenotype was defined by an isolate of *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae* or *Proteus mirabilis* testing with a ceftriaxone MIC of ≥2 mg/L (ceftriaxone non-susceptible using CLSI and EUCAST breakpoints) and an ertapenem MIC of ≤0.5 mg/L (ertapenem susceptible using CLSI and EUCAST breakpoints).[6,7]

Screening for β-lactamase genes

Isolates meeting the following phenotypic criteria were screened for β-lactamase genes: NME isolates (excluding *Serratia* spp.) testing with imipenem or imipenem/relebactam MIC values of ≥2 mg/L and *Pseudomonas aeruginosa* isolates testing with imipenem or imipenem/relebactam MIC values of ≥4 mg/L collected during 2017–21; NME and *Serratia* spp. isolates testing with ertapenem MIC values of ≥1 mg/L collected during 2017–18 only; isolates of *Serratia* spp. testing with imipenem MIC values of ≥4 mg/L collected during 2017–18; and Enterobacterales and *P. aeruginosa* isolates testing with ceftolozane/tazobactam MIC values of ≥4 mg/L and ≥8 mg/L, respectively, collected during 2017–21. Published multiplex PCR assays were used to screen for the following β-lactamase genes: ESBLs (CTX-M, GES, PER, SHV, TEM, VEB); acquired AmpC β-lactamases (ACC, ACT, CMY, DHA, FOX, MIR, MOX) and the chromosomal AmpC intrinsic to *P. aeruginosa* (PDC); serine carbapenemases [GES, KPC, OXA-48-like (Enterobacterales), OXA-24-like (*P. aeruginosa*)]; and MBLs (GIM, IMP, NDM, SPM, VIM).[8,9] All detected genes encoding carbapenemases, ESBLs and PDC were amplified using gene-flanking primers and sequenced (Sanger). For *P. aeruginosa* collected in 2020 and 2021 only, isolates were characterized by short-read WGS (Illumina HiSeq 2×150 bp reads) to a targeted coverage depth of 100×[10] and analysed using the CLC Genomics Workbench (QIAGEN). The ResFinder database was used to detect β-lactamase genes.[11] Per SMART protocol for Enterobacterales isolates collected in 2021, a representative sample of approximately 95% of isolates meeting the criteria for molecular characterization were characterized. Accordingly, of the 62 isolates that met the testing criteria, two randomly selected isolates were not molecularly characterized. Per SMART protocol for *P. aeruginosa* isolates collected in 2020 and 2021, a representative sample of approximately 75% of isolates meeting the criteria for molecular characterization were characterized (16 randomly selected isolates of 88 qualified isolates were not characterized). For each clinical laboratory, the percentage of qualified isolates collected in 2020 and 2021 that were not characterized was considered when calculating estimated carbapenemase rates.

Results

A brief summary of the demographic and clinical characteristics (patient location, length of hospital stay at the time of specimen collection, and infection source) associated with all isolates of Gram-negative bacilli collected in Belgium, Norway, Sweden and Switzerland (combined) in 2017–21 is presented in Table S1 (available as Supplementary data at *JAC-AMR* Online).

Ceftolozane/tazobactam inhibited 95.0% of all Enterobacterales isolates, 94.9% of ESBL-positive non-CRE phenotype *E. coli* isolates, 85.2% of ESBL-positive non-CRE phenotype *K. pneumoniae* isolates and 89.5% of all ESBL-positive non-CRE phenotype Enterobacterales (*E. coli*, *K. pneumoniae*, *K. oxytoca*, *P. mirabilis*) isolates (Tables 1 and 2). Imipenem/relebactam inhibited 99.6% of NME and 100% of ESBL-positive non-CRE phenotype *E. coli*, *K. pneumoniae* and *K. oxytoca*. Meropenem (99.4% susceptible) and amikacin (98.6%) also inhibited most Enterobacterales isolates, while cefepime, ceftazidime, ceftriaxone, piperacillin/tazobactam, levofloxacin and colistin (NME, 92.1% susceptible) all tested with percent susceptible values between 81% and 88%. Levofloxacin was the least active agent tested against *E. coli* (79.1% susceptible) and cefepime, ceftazidime, ceftriaxone, piperacillin/tazobactam and levofloxacin (80%–83% susceptible) were least active against *K. pneumoniae*. Less than 36% of ESBL-positive non-CRE phenotype isolates of *E. coli* and *K. pneumoniae* were levofloxacin susceptible; 75.7% of ESBL-positive non-CRE phenotype *E. coli* and 44.4% of ESBL-positive non-CRE phenotype *K. pneumoniae* were piperacillin/tazobactam susceptible.

By country, ceftolozane/tazobactam susceptibility for all Enterobacterales isolates was 93.6% for Belgium, 94.7% for Switzerland and 97.4% for both Norway and Sweden, while imipenem/relebactam susceptibility for NME was 99.2% for Belgium, 99.9% for Sweden and 100% for both Norway and Switzerland (Table 3). In subset analysis, ceftolozane/tazobactam susceptibility for ESBL-positive non-CRE phenotype Enterobacterales (i.e. *E. coli*, *K. pneumoniae*, *K. oxytoca* and *P. mirabilis*) ranged from 88.2% (Belgium, $n=271$) to 96.0% (Norway, $n=25$) while imipenem/relebactam percent susceptible values for ESBL non-CRE NME (i.e. *E. coli*, *K. pneumoniae* and

Table 1. Antimicrobial susceptibility of clinical isolates of Gram-negative bacilli collected in Belgium, Norway, Sweden and Switzerland (combined) during 2017–21

		% Susceptible											
Organism	*n*	C/T	IPM/REL	MEM	IPM[a,b]	ETP	FEP[b]	CAZ[b]	CRO	TZP[b]	LVX[b,c]	AMK	CST
Enterobacterales	4158	95.0	NA	99.4	99.5	97.9	87.5	82.0	81.4	84.9	84.9	98.6	85.0
NME	3833	94.7	99.6	99.4	99.1	97.7	86.7	81.3	80.6	83.7	85.0	98.7	92.1
E. coli	1842	98.9	99.9	99.8	99.8	99.5	85.6	84.4	84.6	89.0	79.1	98.9	99.7
ESBL non-CRE[d]	276	94.9	100	100	100	100	15.9	9.8	0	75.7	35.5	94.9	99.3
K. pneumoniae	654	95.4	98.6	98.3	98.6	97.6	81.0	79.5	81.5	80.9	83.2	98.0	98.0
ESBL non-CRE[d]	108	85.2	100	99.1	100	100	8.3	3.7	0	44.4	32.1	98.1	96.3
P. aeruginosa	823	95.7	94.5	81.7	80.0	NA	80.9	79.1	NA	77.0	84.2	93.6	99.9
FEP resistant	157	78.3	74.5	42.0	42.0	NA	0	15.3	NA	17.2	58.6	73.2	99.4
CAZ resistant	172	80.2	77.9	45.9	45.9	NA	22.7	0	NA	11.0	63.4	78.5	99.4
MEM resistant	54	55.6	42.6	0	3.7	NA	14.8	11.1	NA	3.7	24.1	63.0	98.1
TZP resistant	189	83.1	80.4	47.6	49.7	NA	31.2	19.0	NA	0	62.4	83.1	99.5
	% Susceptible												

C/T, ceftolozane/tazobactam; IPM/REL, imipenem/relebactam; MEM, meropenem; ETP, ertapenem; FEP, cefepime; CAZ, ceftazidime; CRO, ceftriaxone; TZP, piperacillin/tazobactam; LVX, levofloxacin; AMK, amikacin; CST, colistin; NA, not applicable or MIC breakpoint not available.
[a]The results provided for Enterobacterales combine % susceptible, increased exposure values for Morganellaceae and % susceptible values for NME.[6]
[b]The results provided for *P. aeruginosa* are % susceptible, increased exposure values.[6]
[c]Levofloxacin was only tested against Enterobacterales isolates from 2018 to 2021.
[d]ESBL non-CRE was defined by an isolate testing with a ceftriaxone MIC of ≥2 mg/L and an ertapenem MIC of ≤0.5 mg/L.

Table 2. Antimicrobial susceptibility of ESBL non-CRE phenotype Enterobacterales and NME, by country during 2017–21

Organism	*n*	C/T	IPM/REL	MEM	IPM[a]	FEP	CAZ	TZP	LVX[b]	AMK	CST
ESBL non-CRE Enterobacterales[c,d]											
Belgium	271	88.2	NA	99.6	99.6	15.5	8.5	60.5	34.8	93.0	95.9
Norway	25	96.0	NA	100	100	40.0	8.0	56.0	52.0	100	100
Sweden	77	90.9	NA	100	100	18.2	19.5	62.3	41.3	97.4	100
Switzerland	55	90.9	NA	100	100	16.4	16.4	74.5	38.2	92.7	98.2
Central/northern Europe	428	89.5	NA	99.8	99.8	17.5	11.4	62.4	37.8	94.2	97.2
ESBL non-CRE NME[c,e]											
Belgium	265	88.7	100	99.6	100	14.3	8.3	59.6	34.2	93.2	98.1
Norway	25	96.0	100	100	100	40.0	8.0	56.0	52.0	100	100
Sweden	77	90.9	100	100	100	18.2	19.5	62.3	41.3	97.4	100
Switzerland	55	90.9	100	100	100	16.4	16.4	74.5	38.2	92.7	98.2
Central/northern Europe	422	89.8	100	99.8	100	16.8	11.4	61.8	37.4	94.3	98.6

C/T, ceftolozane/tazobactam; IPM/REL, imipenem/relebactam; MEM, meropenem; FEP, cefepime; CAZ, ceftazidime; TZP, piperacillin/tazobactam; LVX, levofloxacin; AMK, amikacin; CST, colistin; NA, not applicable or MIC breakpoint not available.
[a]The results provided for ESBL non-CRE Enterobacterales combine % susceptible, increased exposure values for Morganellaceae and % susceptible values for NME.[6]
[b]Levofloxacin against Enterobacterales only available for 2018–21.
[c]ESBL non-CRE was defined by an isolate testing with a ceftriaxone MIC of ≥2 mg/L and an ertapenem MIC of ≤0.5 mg/L.
[d]*E. coli*, *K. pneumoniae*, *K. oxytoca* and *P. mirabilis*.
[e]*E. coli*, *K. pneumoniae* and *K. oxytoca*.

K. oxytoca) were 100% for isolates from all four countries (Table 2).

Ceftolozane/tazobactam (95.7% susceptible) and imipenem/relebactam (94.5%) both inhibited ∼95% of all *P. aeruginosa* isolates (*n* = 823) and retained activity against 78%–83% (ceftolozane/tazobactam) and 75%–80% (imipenem/relebactam) of cefepime-resistant, ceftazidime-resistant and piperacillin/tazobactam-resistant isolates; 56% and 43% of meropenem-resistant isolates were ceftolozane/tazobactam and imipenem/relebactam susceptible, respectively (Table 1).

Table 3. Antimicrobial susceptibility and estimated carbapenemase rates among clinical isolates of Enterobacterales, NME and *P. aeruginosa*, by country during 2017–21

		% Susceptible											Estimated % carrying carbapenemase[a]			
Organism	*n*	C/T	IPM/REL	MEM	IPM[b,c]	ETP	FEP[c]	CAZ[c]	CRO	TZP[c]	LVX[c,d]	AMK	CST	MBL	KPC	OXA-48-like	GES
Enterobacterales																	
Belgium	2039	93.6	NA	99.1	98.5	97.0	83.3	76.7	76.7	80.5	80.9	97.9	83.8	0.5	0	0.9	0
Norway	495	97.4	NA	99.8	99.6	98.4	94.9	90.5	90.3	92.3	91.7	99.6	90.1	0	0	0	0
Sweden	778	97.4	NA	100	99.7	99.2	88.9	86.8	84.7	89.2	84.2	99.2	87.0	0.1	0	0	0
Switzerland	846	94.7	NA	99.6	99.5	98.5	92.2	85.5	84.5	87.1	89.1	99.3	83.1	0	0.1	0	0
NME																	
Belgium	1865	93.2	99.2	99.0	98.6	96.7	82.1	75.8	75.4	78.9	81.2	98.0	91.5	0.5	0	1.0	0
Norway	474	97.3	100	99.8	99.6	98.3	94.7	90.3	90.3	92.0	91.6	99.8	94.1	0	0	0	0
Sweden	716	97.2	99.9	100	99.7	99.2	88.3	86.2	84.1	88.4	83.8	99.2	94.6	0.1	0	0	0
Switzerland	778	94.2	100	99.6	99.6	98.3	91.5	84.7	83.8	86.0	89.5	99.2	90.1	0	0.1	0	0
P. aeruginosa																	
Belgium	360	94.2	93.9	81.4	80.8	NA	79.2	77.5	NA	75.6	83.1	92.8	100	2.7	0	0	0
Norway	42	100	97.6	81.0	83.3	NA	85.7	78.6	NA	78.6	85.7	100	100	0	0	0	0
Sweden	280	95.0	93.2	80.0	75.7	NA	79.3	77.9	NA	76.8	79.3	90.7	99.6	0	0	0	0
Switzerland	141	100	97.9	85.8	85.1	NA	87.2	85.8	NA	80.9	96.5	99.3	100	0	0	0	0

C/T, ceftolozane/tazobactam; IPM/REL, imipenem/relebactam; MEM, meropenem; ETP, ertapenem; FEP, cefepime; CAZ, ceftazidime; CRO, ceftriaxone; TZP, piperacillin/tazobactam; LVX, levofloxacin; AMK, amikacin; CST, colistin; NA, not applicable or MIC breakpoint not available.

[a]No isolates carried both an MBL and another carbapenemase.

[b]The results provided for Enterobacterales combine % susceptible, increased exposure values for Morganellaceae and % susceptible values for NME.[6]

[c]The results provided for *P. aeruginosa* are % susceptible, increased exposure values.[6]

[d]Levofloxacin was only tested against Enterobacterales isolates from 2018 to 2021.

Ceftolozane/tazobactam inhibited 51.1% (23/45) of imipenem/relebactam-resistant (MIC >2 mg/L) *P. aeruginosa* and imipenem/relebactam inhibited 37.1% (13/35) of ceftolozane/tazobactam-resistant (MIC >4 mg/L) *P. aeruginosa*. Colistin (99.9% susceptible) was the agent with the highest percent susceptible value for *P. aeruginosa*, while only 77%–82% of isolates were susceptible to meropenem, cefepime, ceftazidime and piperacillin/tazobactam. Levofloxacin (24.1% susceptible), amikacin (63.0%) and colistin (98.1%) were all least active against meropenem-resistant *P. aeruginosa* compared with other β-lactam-resistant isolate subsets.

By country, ceftolozane/tazobactam susceptibility for all *P. aeruginosa* isolates was 94.2% for Belgium, 95.0% for Sweden and 100% for both Norway and Switzerland, while percent susceptible values for imipenem/relebactam were 93.2% for Sweden, 93.9% for Belgium, 97.6% for Norway and 97.9% for Switzerland (Table 3).

In considering the colistin and amikacin data, it is important to note that given the limitations associated with colistin and aminoglycoside use in treating Gram-negative infections, EUCAST only publishes bracketed colistin, amikacin (systemic infections) and gentamicin (systemic infections) susceptible and resistant MIC breakpoints with a warning against the use of any of these agents without additional therapeutic measures.[6,12] Similarly, CLSI does not publish a susceptible MIC breakpoint for colistin for any Gram-negative pathogen.[7]

Carbapenemase gene carriage among isolates of Enterobacterales and *P. aeruginosa* from the four central and northern European countries studied was low (1% or less) or completely absent in all countries with one exception: an estimated 2.7% of *P. aeruginosa* isolates from Belgium were MBL positive (Table 3). Carbapenemase genes were not identified in *P. aeruginosa* isolates from other countries. MBLs among Enterobacterales were only identified in Belgium (0.5% of isolates) and Sweden (0.1%). KPCs were only identified in Enterobacterales isolates from Switzerland (0.1%) and OXA-48-like enzymes only in isolates from Belgium (0.9%). GES carbapenemase genes were not identified in any isolate.

Discussion

Carbapenem-resistant and ESBL-producing Enterobacterales rates are lower in northern, central and western European countries than in southern and eastern Europe.[2,13–15] Meropenem-resistant Enterobacterales were rarely identified (<1%) in the current study of clinical isolates from central and northern Europe; 15% of *E. coli* and 17% of *K. pneumoniae* had an ESBL, non-CRE phenotype (Table 1). Approximately 18% of *P. aeruginosa* in the current study were meropenem non-susceptible (Table 3), accounting for 14% of isolates from Switzerland, 19% of isolates from Belgium and Norway, and 20% of isolates from Sweden. Our observations agree with previous studies that reported carbapenem-resistant *P. aeruginosa* rates to be lower in northern, central and western European countries than in southern and eastern Europe (≥30%).[2,13]

Ceftolozane/tazobactam inhibited 95% of Enterobacterales, including 95% of ESBL-positive non-CRE phenotype *E. coli* and 85% of ESBL-positive non-CRE phenotype *K. pneumoniae*, confirming data in earlier publications.[16] Ceftolozane/tazobactam maintained activity against most ESBL-positive Enterobacterales that do not possess carbapenemases and is more active *in vitro* than piperacillin/tazobactam.[1,16] Imipenem/relebactam inhibited >99% of NME (an estimated 0.3% of NME isolates carried an MBL and 0.5% an OXA-48-like enzyme) and 100% of ESBL-positive non-CRE phenotype *E. coli* and *K. pneumoniae*, again confirming earlier publications.[16,17]

Ceftolozane/tazobactam and imipenem/relebactam both inhibited ~95% of all *P. aeruginosa* isolates but were less active against isolates with β-lactam-resistant phenotypes. Imipenem/relebactam generally retains *in vitro* activity against isolates without MBL carbapenemases although limited numbers of *P. aeruginosa* isolates without these mechanisms have tested imipenem/relebactam non-susceptible.[16–18] Geographical differences in β-lactamase prevalence and other resistance mechanisms do affect the *in vitro* activities of all currently available β-lactams and β-lactam/β-lactamase inhibitor combinations, including ceftolozane/tazobactam and imipenem/relebactam.[3,4] In the current study, we observed low numbers of MBLs, KPC, OXA-48-like and GES carbapenemases in both Enterobacterales and *P. aeruginosa* (Table 3). Therefore, mechanisms of carbapenem resistance other than β-lactamases (e.g. OprD mutations in combination with AmpC hyperproduction)[19] must have predominated in the isolates of *P. aeruginosa* collected from the four central and northern European countries we studied.

The data presented in this study are limited by the small annual sample size (250 Gram-negative isolates per medical centre per year) and the small number of participating medical centres. The data generated from isolates submitted by participating medical centres within central and northern Europe should not be extrapolated to represent all isolates or geographical areas within these regions.

In conclusion, recent (2017–21) clinical isolates of Enterobacterales and *P. aeruginosa* collected in four central and northern European countries were highly susceptible (≥95%) to ceftolozane/tazobactam and imipenem/relebactam. Based on these *in vitro* data, ceftolozane/tazobactam and imipenem/relebactam may be important treatment options for patients in central and northern Europe with infections caused by Gram-negative pathogens, including ESBL-positive non-CRE phenotype Enterobacterales and many β-lactam-resistant phenotypes of *P. aeruginosa*.

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Supplementary data

Table S1 is available as Supplementary data at *JAC-AMR* Online.

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