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Activity of Cefiderocol against Metallo-β-Lactamase-Carrying *Pseudomonas aeruginosa* of the SENTRY Antimicrobial Surveillance Program (2020–2024)

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INTRODUCTION

- Cefiderocol is a siderophore-conjugated cephalosporin with activity against Gram-negative pathogens including metallo-β-lactamase (MBL)-carrying carbapenem-resistant strains.
- Cefiderocol was approved for clinical use in the USA in 2019 and in Europe in 2020.
- In this study, we assessed the *in vitro* activity of cefiderocol and comparators against MBL-carrying *Pseudomonas aeruginosa* collected between 2020–2024 in the USA and Europe as part of the SENTRY Antimicrobial Surveillance Program.

MATERIALS AND METHODS

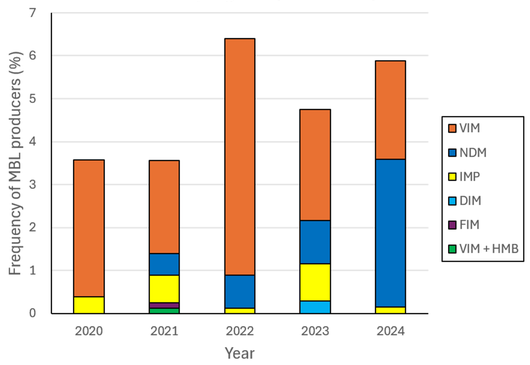
Bacterial strains

- Of the 11,757 isolates of *P. aeruginosa* which were collected in the USA and Europe during 2020 to 2024 as part of SENTRY surveillance program, 3,743 were carbapenem- or cephalosporin-nonsusceptible, and the genomes of these were sequenced.
- 180 of these isolates carried MBL genes and were used for analysis.

Susceptibility testing

- Minimum inhibitory concentrations (MICs) for cefiderocol and comparators (β-lactam/β-lactamase inhibitor combinations [BL/BLI]) were determined according to CLSI guidelines using broth microdilution with cation-adjusted Mueller–Hinton broth (CAMHB) for comparators and iron-depleted CAMHB for cefiderocol.
- Susceptibility percentage (%S) to cefiderocol and comparators were determined using 2026 CLSI, EUCAST, and FDA breakpoints.

Figure 1. Frequency of MBL producers of 3,743 carbapenem- or cephalosporin-nonsusceptible *P. aeruginosa* isolates by year from the US and EU hospitals collected as part of the SENTRY surveillance program (2020–2024)

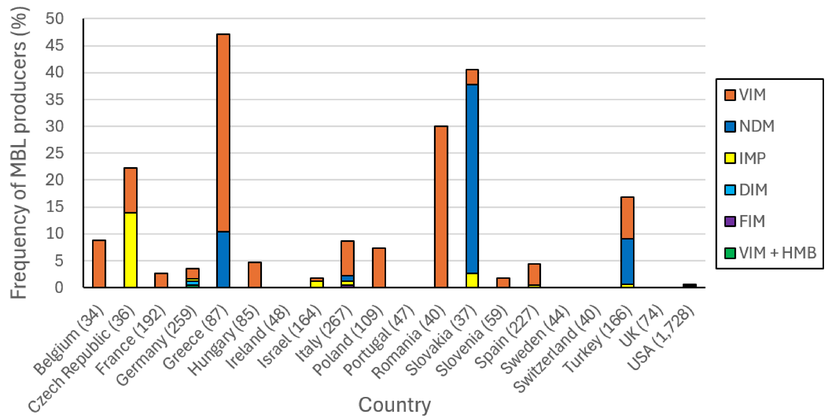


VIM (119 isolates): Includes VIM-1 (12), VIM-2 (93), VIM-4 (9), VIM-5 (2), VIM-20 (2), VIM-43 (1)
NDM (41 isolates): Includes NDM-1 (41)
IMP (16 isolates): Includes IMP-1 (2), IMP-7 (6), IMP-8 (1), IMP-10 (1), IMP-13 (5), IMP-83 (1)
DIM (2 isolates): Includes DIM-1 (2)
FIM (1 isolate): Includes FIM-1 (1)
VIM + HMB (1 isolate): Includes VIM-1 + HMB-1 (1)

RESULTS

- The 180 MBL-carrying *P. aeruginosa* were identified at the frequency of 1.5% among total isolates and 4.8% of carbapenem- or cephalosporin-nonsusceptible isolates.
- In the 180 MBL producers, VIM was encountered most frequently (120 isolates), followed by NDM (41 isolates), IMP (16 isolates) and other MBLs (4 isolates; DIM, 2 isolates; FIM, 1 isolate; HMB, 1 isolate) with 1 isolate co-producing two MBLs (VIM + HMB) (**Figure 1**).
- The frequency of MBL-producing isolates remained similar (3.5–6.5%) over these 5 years. VIM and IMP producers appeared with the frequency of 2–5% and <1%, respectively. A large increase in NDM-producing isolates was observed (from <1% to >3%) in 2024 (**Figure 1**).
- The majority of MBL-carrying *P. aeruginosa* came from Europe (n=170), with the incidence and MBL allele varying by country. NDM producers appeared mainly in Greece, Turkey, and Slovakia. IMP producers appeared mainly in Czech Republic (**Figure 2**).
- Cefiderocol showed MIC_{50}/MIC_{90} values of 0.25/4 μg/mL and %S of 90.6/83.9/74.4% (based on CLSI/EUCAST/FDA breakpoint) against these 180 isolates (**Figure 3**, **Table 1**).
- Cefiderocol showed significantly lower MIC_{50}, MIC_{90} values and significantly higher %S compared with other BL/BLI comparators (**Figure 3**, **Table 1**).

Figure 2. Frequency of MBL producers of 3,743 carbapenem- or cephalosporin-nonsusceptible *P. aeruginosa* isolates by country from the US and EU hospitals collected as part of the SENTRY surveillance program (2020–2024)



DIM, Dutch imipenemase; FIM, Florence imipenemase; HMB, Hamburg metallo-β-lactamase; IMP, imipenemase; NDM, New Delhi metallo-β-lactamase; VIM, Verona integron-encoded metallo-β-lactamase.

Acknowledgments
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Conflicts of interest
YY, BLMD, STG, SS, HY, and CL are employees of Shionogi.

Figure 3. Cumulative percentage of isolates inhibited by cefiderocol and comparators against 180 MBL-carrying *P. aeruginosa* collected as part of the SENTRY surveillance program (2020–2024)

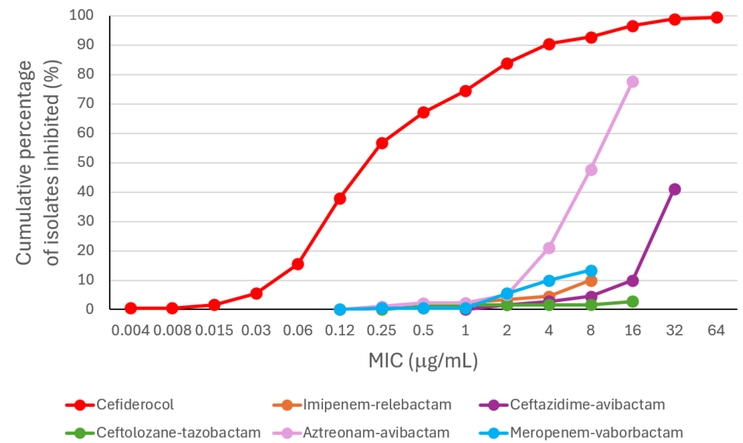


Table 1. Activity of cefiderocol and comparators against 180 MBL-carrying *P. aeruginosa* collected as part of the SENTRY surveillance program (2020–2024)

	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	%S		
			CLSI	EUCAST	FDA
Cefiderocol	0.25	4	90.6	83.9	74.4
Imipenem-relebactam	>8	>8	3.3	3.3	3.3
Ceftazidime-avibactam	>32	>32	4.4	4.4	4.4
Ceftolozane-tazobactam	>8	>8	1.7	1.7	1.7
Meropenem-vaborbactam	>8	>8	NA	13.3	NA
Aztreonam-avibactam	16	>16	NA	NA	NA

NA: not available

CONCLUSIONS

- MBL-carrying *P. aeruginosa* appeared at a frequency of 4.8% of carbapenem- or cephalosporin-nonsusceptible isolates, with varied frequency between countries mainly from Europe.
- Cefiderocol showed higher activity against MBL-carrying *P. aeruginosa* than β-lactam/β-lactamase inhibitor comparators with 74.4–90.6% susceptibility based on CLSI/EUCAST/FDA breakpoint. Continued monitoring of cefiderocol susceptibility is warranted.