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Activity of cefiderocol against clinical isolates of *Pseudomonas aeruginosa* collected from five European countries as part of the SENTRY antimicrobial surveillance programme 2020–2023

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BACKGROUND

Pseudomonas aeruginosa (PA) is an important pathogen that is resistant to many first-line antibiotics and associated with high mortality. Cefiderocol (FDC) is a siderophore-conjugated cephalosporin with activity against *P. aeruginosa* including difficult-to-treat resistant isolates and is approved for treatment of aerobic Gram-negative bacterial infections with limited options.

In this study, the activity of cefiderocol against contemporary isolates of *P. aeruginosa* from patients in Europe was evaluated.

METHODS

- Isolates were collected between 2020–2023 as part of the SENTRY surveillance programme[1].
- Minimum inhibitory concentrations (MICs) were determined according to Clinical and Laboratory Standards Institute (CLSI) guidelines using broth microdilution with iron-depleted cation-adjusted Mueller-Hinton broth for cefiderocol and cation-adjusted Mueller–Hinton broth for comparator agents.
- Comparator agents included the β-lactam/β-lactamase inhibitor combinations ceftolozane-tazobactam (TOL-TAZ), ceftazidime-avibactam (CZA), imipenem-relebactam (IMI-REL) and aztreonam-avibactam (ATM-AVI).
- Susceptibility was interpreted according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) v14 breakpoints where available. Since aztreonam-avibactam has no EUCAST breakpoints for pathogens other than Enterobacterales, the percentage of isolates with MIC ≤4 mg/L is reported. Carbapenem resistance (CR) was defined as MIC ≥4 mg/L to meropenem or imipenem.

RESULTS

- 4,497 clinical isolates of PA were collected from Europe with 66% (n=2,945) from France, Germany, Italy, Spain or UK, of which 495 were carbapenem-resistant (17%).
- Of 47 carbapenemase-producing isolates, 74% contained metallo-β-lactamases, with VIM-2 the most frequent, while GES-5 was present in 26% **(Figure 1)**.
- Carbapenem susceptibility **(Figure 2)** varied from 10.4% in UK to 22.5% in Germany.
- Overall, 99.1% PA were susceptible to cefiderocol at the breakpoint of 2 mg/L (96% of CRPA isolates), including all GES-5 and 95% of metallo-β-lactamase producers.
- Cefiderocol MIC distributions for CRPA were similar between countries with a modal MIC of 0.12–0.25 mg/L **(Figure 3).**
- Overall isolates from all countries showed high susceptibility to comparators except aztreonam-avibactam, which was poorly active against *P. aeruginosa* **(Table 1).**
- 104 isolates (17% of CRPA) were resistant to TOL-TAZ. Of these, 76% were cross-resistant to ATM-AVI, 58% to CZA , 52% to IMI-REL but only 8% to FDC.

Table 1: Susceptibility rates of cefiderocol and comparator antibiotics against 2,945 *P. aeruginosa* isolates from 5 European countries: SENTRY 2020–2023

Country (n) Agent	France	Germany	Italy	Spain	UK
All *P. aeruginosa* (n=2,945)	**532**	**654**	**790**	**700**	**269**
Cefiderocol	99%	99%	99%	99%	100%
Ceftolozane-tazobactam	96%	98%	95%	96%	99%
Ceftazidime-avibactam	97%	97%	96%	97%	98%
Imipenem-relebactam	97%	98%	97%	96%	99%
Aztreonam-avibactam	62%	47%	52%	55%	48%
Carbapenem resistant (n=495)	**80**	**147**	**114**	**126**	**28**
Cefiderocol	96%	97%	98%	100%	100%
Ceftolozane-tazobactam	80%	93%	74%	79%	93%
Ceftazidime-avibactam	84%	91%	83%	87%	86%
Imipenem-relebactam	81%	92%	77%	79%	96%
Aztreonam-avibactam	48%	34%	24%	35%	11%
TOL-TAZ resistant (n=104)	**21**	**14**	**39**	**27**	**3**
Cefiderocol	81%	86%	95%	100%	3/3
Ceftazidime-avibactam	38%	36%	36%	63%	0/3
Imipenem-relebactam	48%	64%	49%	30%	2/3
Aztreonam-avibactam	19%	14%	13%	52%	0/3

n, number of isolates. Interpretations according to EUCAST breakpoint table v14 and Guidance on what to do when no breakpoints. Cefiderocol, breakpoint of ≤2 mg/L for *Pseudomonas* and other non-fermenters; Aztreonam-avibactam is reported at percentage with MIC ≤4 mg/L. **Key:** Green, >90%; Amber, 50-90%; Red <50% susceptible.

Figure 1: Summary of carbapenemases from 47/495 CR *P. aeruginosa*

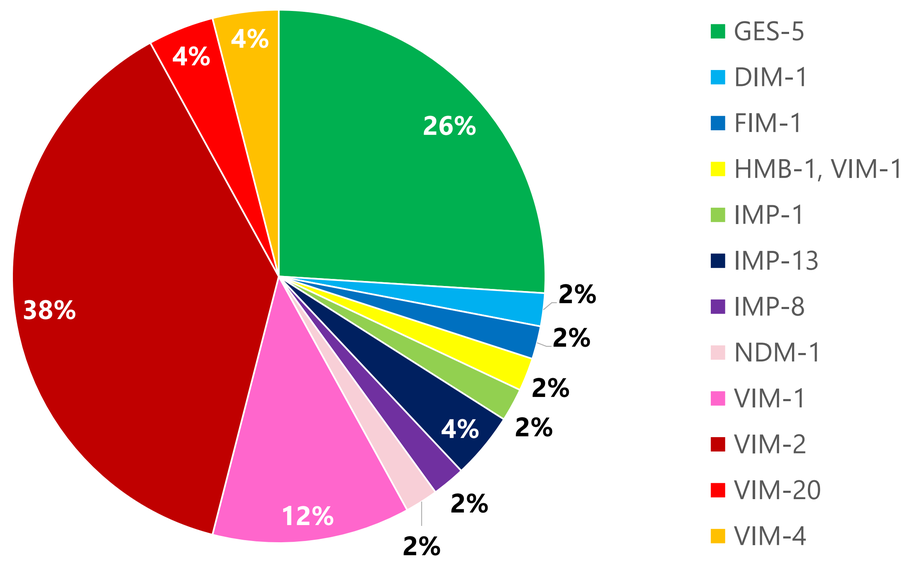


Figure 2: Carbapenem resistance in 2,945 isolates of *P. aeruginosa* from 5 European countries: SENTRY 2020–2023

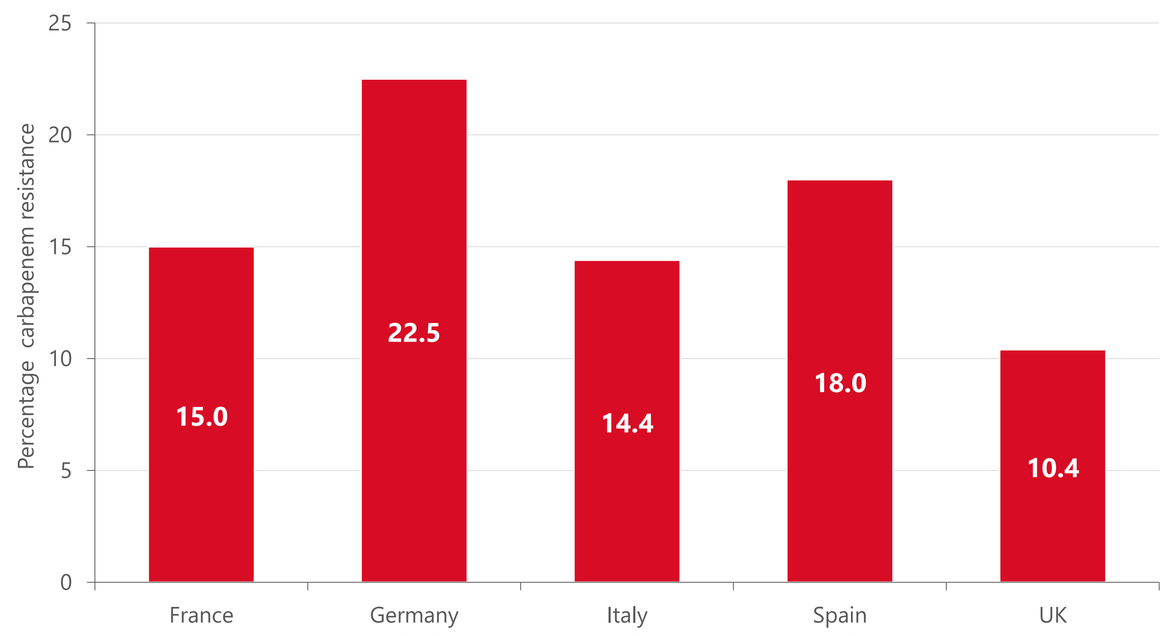
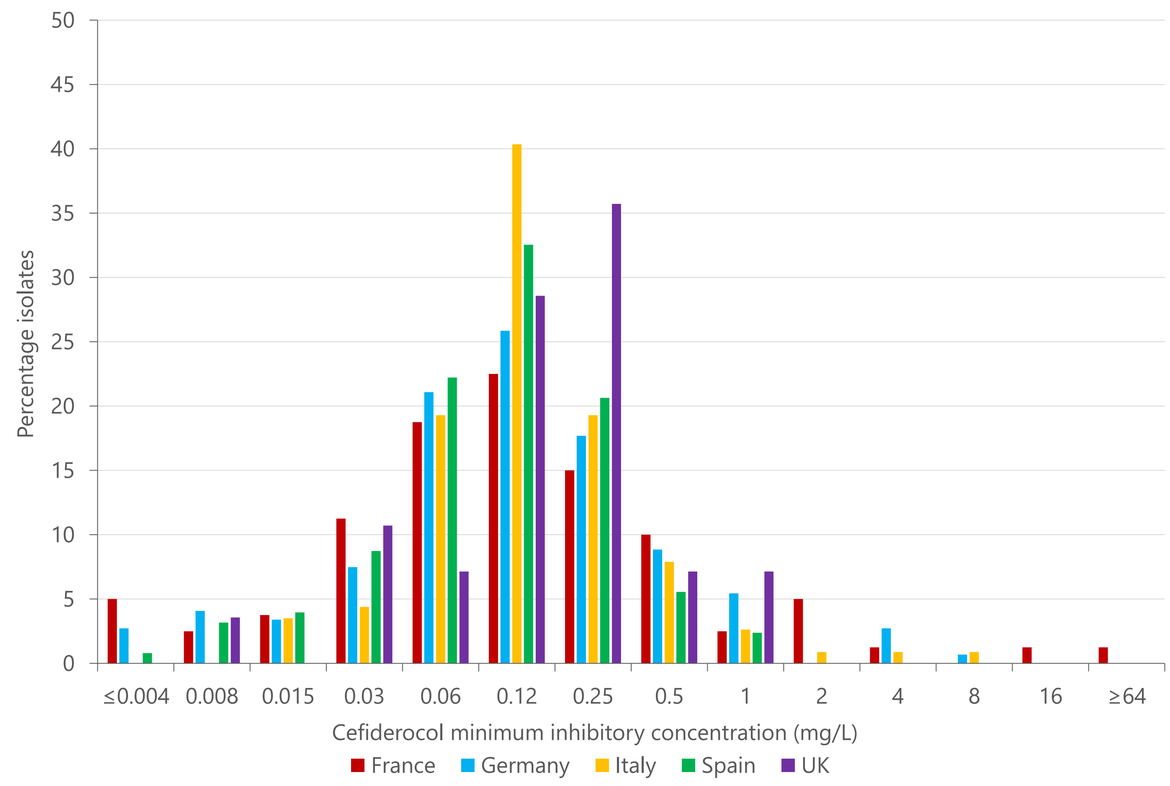


Figure 3: Cefiderocol MIC distributions for 495 CR *P. aeruginosa* isolates from 5 European countries: SENTRY 2020–2023



CONCLUSIONS

Cefiderocol showed the highest susceptibility rates against contemporary isolates of *P. aeruginosa*, including isolates resistant to carbapenems. High levels of cross-resistance between β-lactam/β-lactamase inhibitor combinations was observed, most of which remained susceptible to cefiderocol. Cefiderocol should be considered as a treatment for patients infected by *P. aeruginosa* with limited treatment options.

References

1. Shortridge D, et al. Microbiol Spectr. 2022;10(2):e0271221.

Acknowledgments

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