P1451

# *In vitro* Activity of Cefepime-Taniborbactam and Comparators Against European Isolates of Enterobacterales and *P. aeruginosa* with Defined β-lactamase Carriage, 2018-2022

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## INTRODUCTION

Taniborbactam is a novel cyclic boronate-based broad-spectrum β-lactamase inhibitor that is undergoing development in combination with cefepime for use against Enterobacterales and *Pseudomonas aeruginosa* resistant to current standard-of-care antibiotics. Taniborbactam inhibits serine-β-lactamases, as well as NDM and VIM metallo-β-lactamases [1]. This study reports on the susceptibility of a recent (2018-2022) European collection of clinical isolates of Enterobacterales and *P. aeruginosa* to cefepime-taniborbactam (FTB) and comparator agents stratified by their β-lactamase content.

## METHODS

- For this study, 8,760 Enterobacterales and 3,480 *P. aeruginosa* isolates collected in 25 European countries from 2018 to 2022 were assessed.
- MICs of cefepime with taniborbactam fixed at 4 mg/L and comparator antimicrobial agents were determined using the ISO 20776-1:2019 reference method [2] and interpreted with 2023 EUCAST breakpoints [3].
- For FTB, a provisional susceptible MIC breakpoint of ≤16 mg/L was employed for comparative purposes [4].
- Organisms with FTB MIC ≥16 mg/L were characterized by whole genome sequencing [5], while those resistant to meropenem by 2023 CLSI criteria [6] were screened for acquired β-lactamase carriage by PCR followed by Sanger sequencing, as previously described [7]. To examine geographic variation in carbapenemase production, countries were divided into two European regions: North/Western Europe (Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Latvia, Lithuania, Netherlands, Portugal, Spain, Sweden, Switzerland, and the United Kingdom) and Central/Eastern Europe (Croatia, Czech Republic, Greece, Hungary, Poland, Romania, Russia, Slovenia, Turkey, and Ukraine).

## RESULTS SUMMARY

- Overall, 841 Enterobacterales and 914 *P. aeruginosa* were subjected to molecular testing. Countries contributing the most isolates included Russia (12.1%), Italy (11.1%), and Ukraine (10.8%; Figure 1). *P. aeruginosa* and *K. pneumoniae* accounted for >85% of the molecularly-characterized isolates. (Figure 2).
- Among the carbapenemases detected in meropenem-resistant (MIC ≥ 4 mg/L; CLSI 2023 [5]) Enterobacterales, isolates from the North/Western European countries were more likely to carry KPC and less likely to carry NDM or OXA-48-like enzymes than those from Central/Eastern Europe (Figure 3A).
- Among the meropenem-resistant *P. aeruginosa* (MIC ≥8 mg/L; CLSI 2023 [5]), the isolates in Central/Eastern Europe were more likely to carry a carbapenemase (~40%) than those originating from North/Western Europe (~14%; Figure 3B). VIM was the most frequently encountered carbapenemase in both geographies.
- FTB was the sole agent among comparators with activity against NDM-carrying Enterobacterales, as approximately 75% of the isolates were inhibited at ≤16 mg/L (Table 1, Figure 4A).
- FTB at ≤16 mg/L inhibited 94.6% of VIM-carrying Enterobacterales, 46 percentage points higher than the most active comparator, meropenem-vaborbactam.
- FTB also demonstrated potent antimicrobial activity against Enterobacterales harboring KPC, OXA-48-group, ESBL and acquired AmpC-type enzymes, with 100%, 98.6%, 99.3%, and 96.2% of the isolates inhibited at ≤16 mg/L, respectively.
- FTB was the sole agent among comparators active versus VIM-carrying *P. aeruginosa*, inhibiting 86.2% of these isolates at ≤16 mg/L (Table 1, Figure 4B).
- Against *P. aeruginosa* harboring GES, VEB, and PER-type enzymes, FTB was also the most active agent with 100%, 91.9% and 100% of the isolates in the respective groups inhibited at ≤16 mg/L.

## CONCLUSIONS

The addition of taniborbactam to cefepime greatly enhanced its *in vitro* activity against most isolates of Enterobacterales carrying NDM and VIM-type metallo-β-lactamases and serine β-lactamases, as well as most *P. aeruginosa* carrying VIM-type metallo-β-lactamases and GES-, PER- and VEB-type serine β-lactamases. Continued development of FTB is warranted.

## REFERENCES

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## DISCLOSURES

This project has been supported in part or whole with federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services (HHS); Biomedical Advanced Research and Development Authority (BARDA), Administration for Strategic Preparedness and Response (ASPR), HHS, under Contract No. HHSO100201900007C and 75A50122C00080, and The Wellcome Trust under Award No. 360G-Wellcome-101999/Z/13/Z

## RESULTS

Figure 1. Country of collection for molecularly characterized isolates included in this study

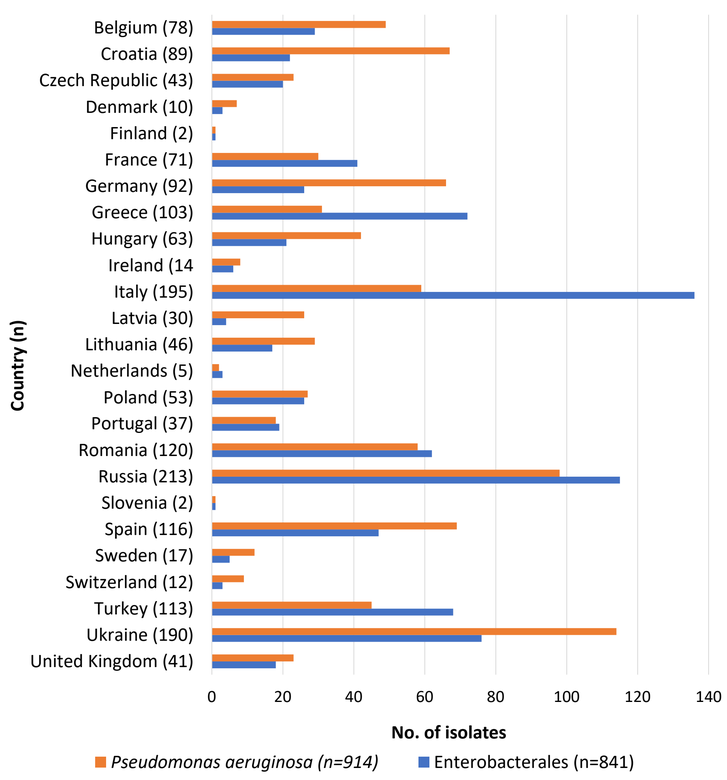



Figure 2. Taxon distribution of molecularly characterized isolates included in this study

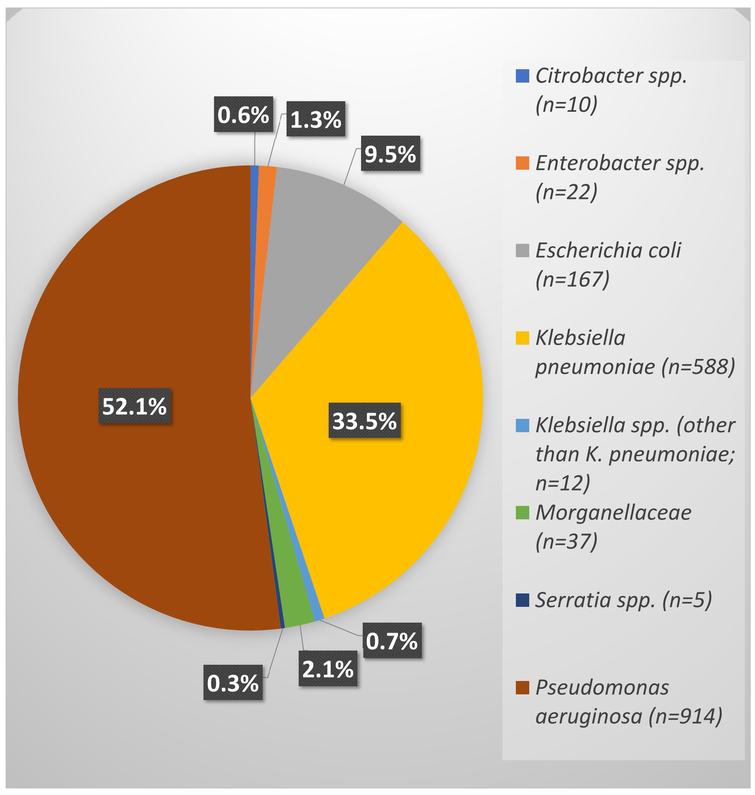
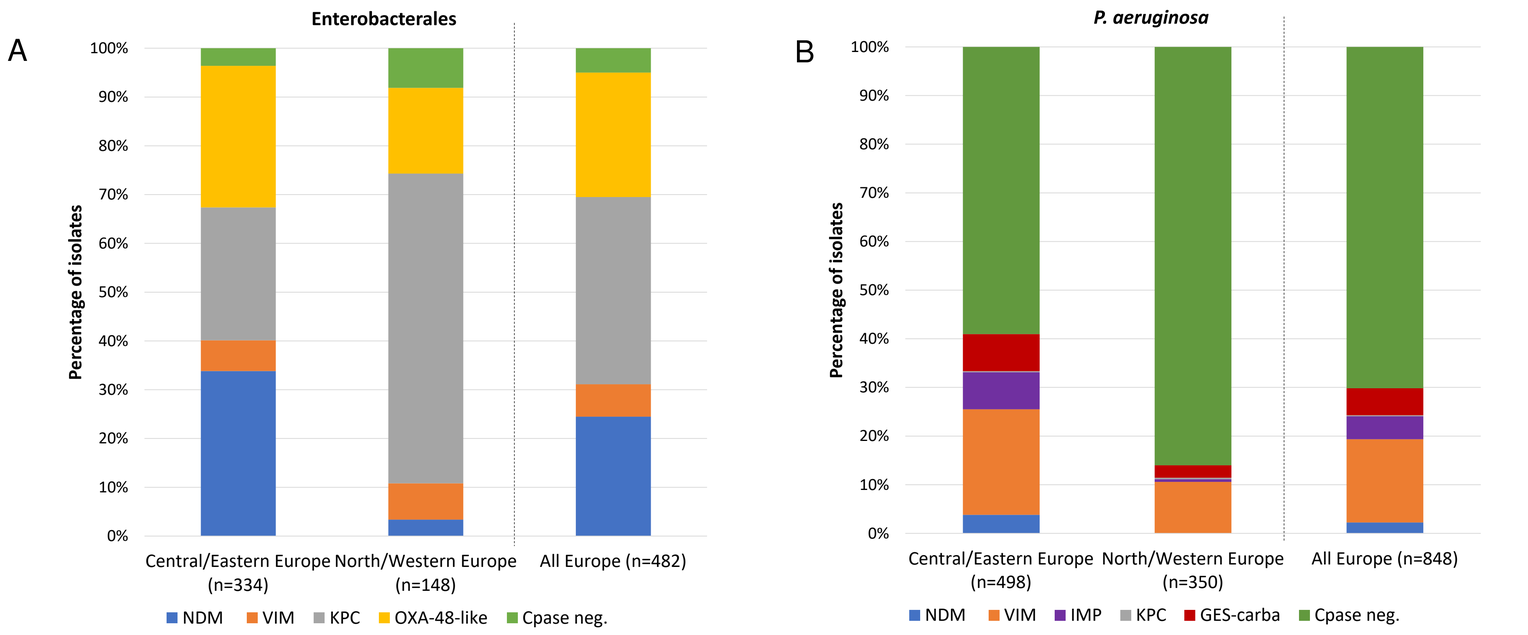



Figure 3. Diversity of carbapenemases detected among meropenem-resistant (CLSI 2023 [5]) Enterobacterales (A) and *P. aeruginosa* (B) by European region*



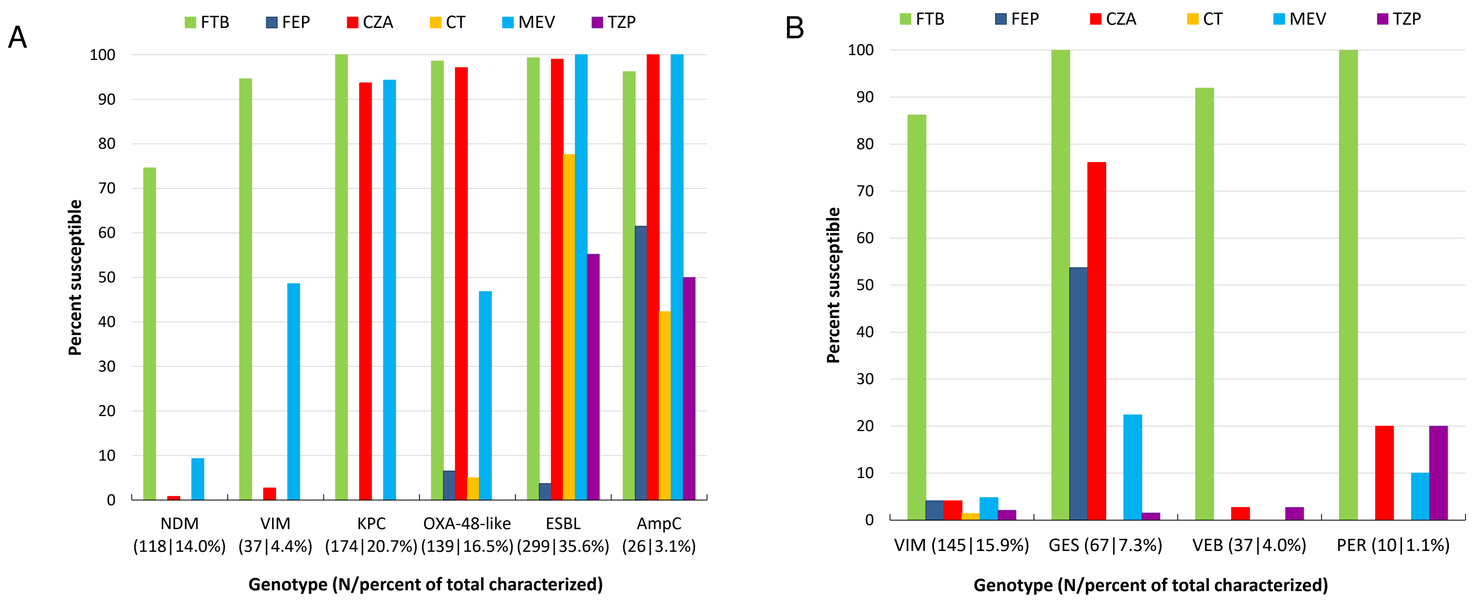

*Central/Eastern: Croatia, Czech Republic, Greece, Hungary, Poland, Romania, Russia, Slovenia, Turkey, Ukraine. North/Western: Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Latvia, Lithuania, Netherlands, Portugal, Spain, Sweden, Switzerland, United Kingdom. Isolates that carried multiple carbapenemases were counted for each carbapenemase type. "GES-carba" only tallies GES variants with reported carbapenemase activity. "Cpase neg" = no carbapenemases were detected.

Table 1. *In vitro* activity of FTB and comparator agents against molecularly characterized Enterobacterales and *P. aeruginosa* by genotypic subset

| Organism / Genotype | n (%)[a] | $MIC_{90}$ (mg/L)/Percent susceptible | | | | | |
|---|---|---|---|---|---|---|---|
| | | FTB[b] | FEP[c] | CZA | CT | MEV | TZP[c] |
| **Enterobacterales** | | | | | | | |
| **NDM** | 118 (14.0%) | 32/74.6 | >16/0.0 | >16/0.8 | >8/0.0 | >16/9.3 | >128/0.0 |
| **VIM** | 37 (4.4%) | 16/94.6 | >16/0.0 | >16/2.7 | >8/0.0 | >16/48.6 | >128/0.0 |
| **KPC[d]** | 174 (20.7%) | 4/100 | >16/0.0 | 8/93.7 | >8/0.0 | 4/94.3 | >128/0.0 |
| **OXA-48 group[e]** | 139 (16.5%) | 4/98.6 | >16/6.5 | 2/97.1 | >8/5.0 | >16/46.8 | >128/0.0 |
| **ESBL[f]** | 299 (35.6%) | 1/99.3 | >16/3.7 | 1/99.0 | >8/77.6 | 0.12/100 | >128/55.2 |
| **AmpC[g]** | 26 (3.1%) | 1/96.2 | 8/61.5 | 1/100 | >8/42.3 | 0.12/100 | >128/50.0 |
| ***P. aeruginosa*[h]** | | | | | | | |
| **VIM** | 145 (15.9%) | >32/86.2 | >32/4.1 | >16/4.1 | >16/1.4 | >16/4.8 | >128/2.1 |
| **GES[d]** | 67 (7.3%) | 16/100 | 32/53.7 | 16/76.1 | >16/0.0 | >16/22.4 | >128/1.5 |
| **VEB[d]** | 37 (4.0%) | 16/91.9 | >32/0.0 | >16/2.7 | >16/0.0 | >16/0.0 | >128/2.7 |
| **PER[d]** | 10 (1.1%) | 8/100 | >32/0.0 | 16/20.0 | >16/0.0 | >16/10.0 | >128/20.0 |

Abbreviations: FTB, cefepime with taniborbactam fixed at 4 mg/L; FEP, cefepime; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEV, meropenem-vaborbactam; TZP, piperacillin-tazobactam.
[a] Percentage is based on total molecularly characterized isolates (Enterobacterales, n=841; *P. aeruginosa*, n=914)
[b] "Percent susceptible" corresponds to percentage of isolates inhibited by ≤16 mg/L FTB (for comparative purposes).
[c] For FEP and TZP against *P. aeruginosa*, "Percent Susceptible, Increased Exposure" value is given.
[d] Excludes isolates co-producing MBLs
[e] Excludes isolates co-producing MBLs and/or KPC.
[f] Excludes isolates co-producing carbapenemases.
[g] Excludes isolates expected to possess intrinsic (chromosomal) AmpC, and those co-producing carbapenemases and ESBLs.
[h] *P. aeruginosa* isolates carrying IMP (n=41) are not represented in table as taniborbactam does not inhibit IMP, and all tested agents were inactive.

Figure 4. Antimicrobial susceptibility of Enterobacterales (A) and *P. aeruginosa* (B) to FTB and comparators, by β-lactamase carriage




FTB, cefepime with taniborbactam fixed at 4 mg/L; FEP, cefepime; CZA, ceftazidime-avibactam; CT, ceftolozane-tazobactam; MEV, meropenem-vaborbactam; TZP, piperacillin-tazobactam. Total N of Enterobacterales = 841; total N of *P. aeruginosa* = 914. For FTB, percent susceptible corresponds to percentage of isolates inhibited by ≤16 mg/L (for comparative purposes only). KPC-, OXA-48-like-, GES-, VEB- and PER-carrying groups exclude any isolates co-producing MBLs. ESBL-carrying group excludes isolates co-producing carbapenemases. AmpC carrying group excludes isolates co-producing carbapenemases and/or ESBLs.

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