Cefepime-taniborbactam (FTB) epidemiological cutoff values (ECOFFs) against key Enterobacterales species and *Pseudomonas aeruginosa*

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Background

- Taniborbactam is an investigational cyclic boronate β-lactamase inhibitor that restores cefepime activity against cefepime-, carbapenem-, and multidrug-resistant isolates of Enterobacterales and *P. aeruginosa* producing serine- and metallo-β-lactamases (Hamrick 2020)
- Susceptibility breakpoints for new agents are informed by epidemiological cutoff values (ECOFFs) for the wild-type MIC distribution, which represent the highest MIC for organisms that lack phenotypically detectable acquired resistance mechanisms (EUCAST SOP 10.2)
- One objective of determining ECOFFs is to avoid splitting the wild-type MIC distribution when setting susceptibility breakpoints, thereby limiting excessive categorical errors due to inherent technical variation associated with MIC determinations (Arendrup 2009; Kahlmeter 2022)
- We determined cefepime-taniborbactam ECOFFs for clinical isolates of *Enterobacter cloacae* complex, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *P. aeruginosa*

Results

- Six to eight cefepime-taniborbactam MIC distributions per species were aggregated (red curves; Figure 1) from 18,279 isolates of Enterobacterales and 9,607 isolates of *P. aeruginosa*
- The modeled wild-type MIC distributions for each of the five species (green curves; Figure 1) were primarily symmetrical and were either centered around the modal MIC or contained the modal MIC with a substantial shoulder 1 to 2 doubling dilutions higher than the mode
- Cefepime-taniborbactam ECOFFs to encompass ≥97.5% to ≥99.9% of the modeled wild-type populations ranged from 0.125 to 0.25 mg/L for Enterobacterales species and from 16 to 32 mg/L for *P. aeruginosa* (Table 1)

Conclusions

- A cefepime-taniborbactam ECOFF of 0.125 mg/L encompassed ≥99.0% of the modeled wild-type populations of *E. cloacae* complex, *E. coli*, *K. pneumoniae*, and *P. mirabilis*
- Whereas 92.6% of *P. aeruginosa* isolates in the aggregated MIC distribution were inhibited at ≤8 mg/L cefepime-taniborbactam, 17.3% of isolates had a cefepime-taniborbactam MIC = 8 mg/L
  - Given this 'shoulder' of isolates at 8 mg/L in the wild-type MIC distribution, a breakpoint of Susceptible ≤8 mg/L would split the wild-type distribution and lead to excessive categorical errors due to technical variation
  - Since only 3.5% of *P. aeruginosa* isolates in the aggregated distribution had a cefepime-taniborbactam MIC = 16 mg/L, a breakpoint of Susceptible ≤16 mg/L would largely alleviate this concern by leaving the wild-type MIC distribution intact
- A cefepime-taniborbactam ECOFF of 16 mg/L supports considerations for a breakpoint of Susceptible ≤16 mg/L for Enterobacterales species and *P. aeruginosa*, and is further supported by PK/PD analyses, mouse infection models (Abdelraouf 2020), and analyses of outcomes by MIC in the Phase 3 study CERTAIN-1 (Moeck 2024)

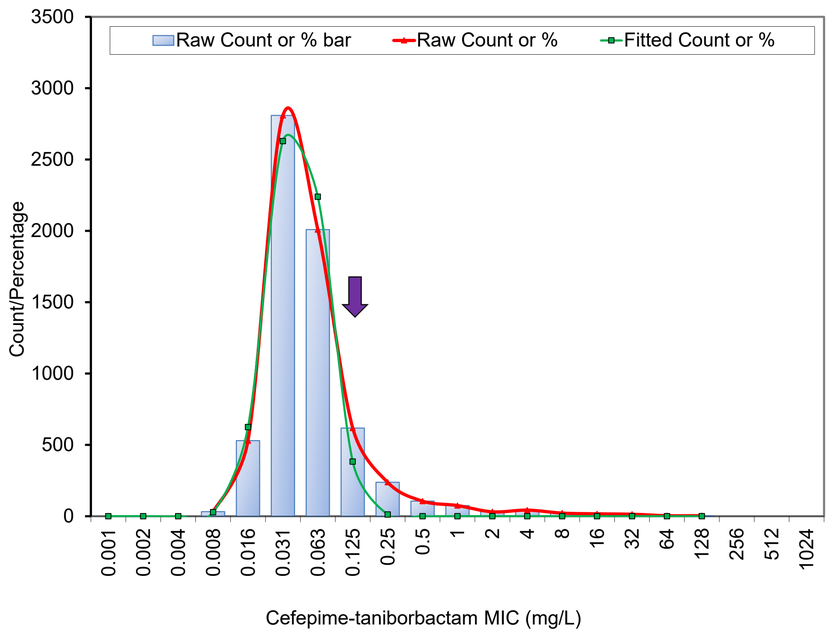
Methods

- Enterobacterales and *P. aeruginosa* isolates were from ongoing global surveillance between 2018 and 2023 (Karlowsky 2024), two additional independent surveillance studies, and a Phase 3 study in patients with complicated urinary tract infections (CERTAIN-1; Wagenlehner 2024).
- FTB MICs were determined by reference broth microdilution (ISO 20776-1:2019; CLSI 2018) at three central microbiology laboratories (IHMA, Schaumburg, IL; LabCorp, Indianapolis, IN; LabCorp, Shanghai, China) and at the Venatorx Pharmaceuticals laboratory (Malvern, PA).
- ECOFFs were determined for each species using ECOFFinder_XL_2010_v2.1 (https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/MIC_distributions/ECOFFinder_XL_2010_v2.1_web_version.xlsm) (EUCAST SOP 10.2 2021; CLSI 2023).

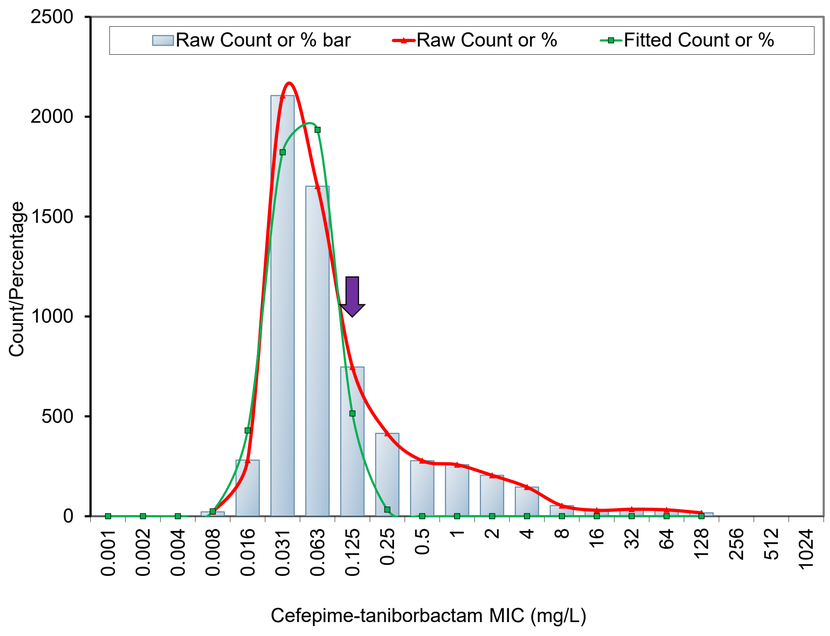
Results, continued

Figure 1. Statistical characterization of wild-type cefepime-taniborbactam MIC distributions for Enterobacterales species and *P. aeruginosa* (purple arrow in each distribution represents ECOFF value encompassing 99.0% of the wild-type population)

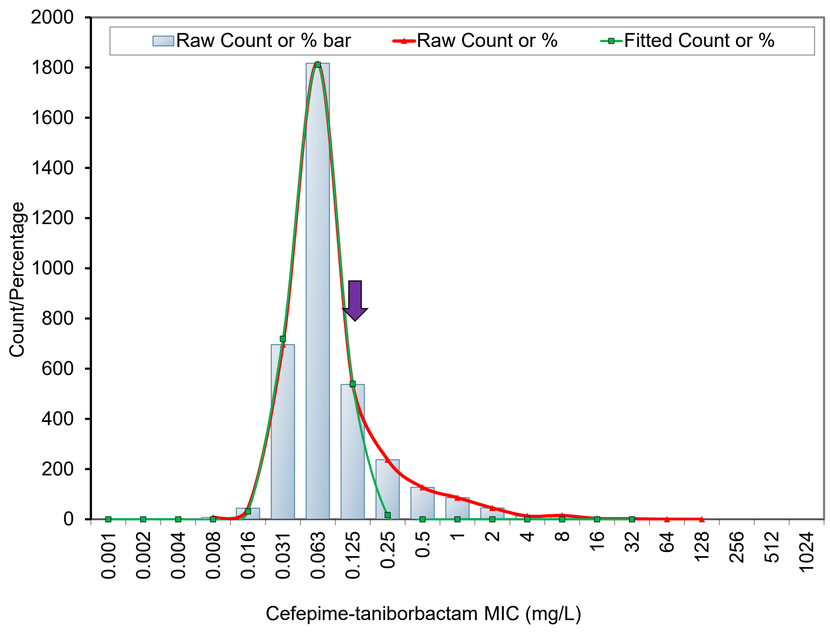
A. *E. coli* (n=6,552)



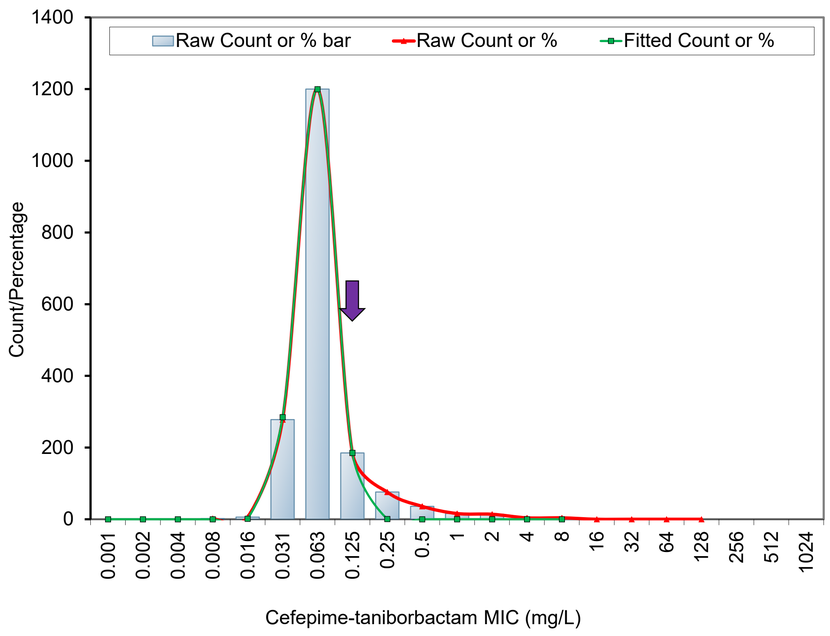
B. *K. pneumoniae* (n=6,277)



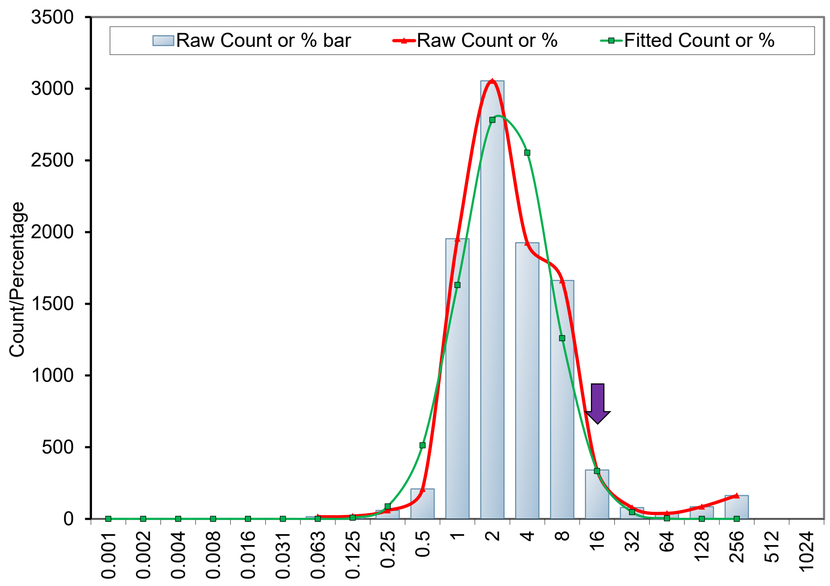
C. *E. cloacae* complex (n=3,629)



D. *P. mirabilis* (n=1,821)



E. *P. aeruginosa* (n=9,607)



Purple arrow in each panel represents the ECOFF value encompassing 99.0% of the modeled wild-type population

Table 1. Cefepime-taniborbactam ECOFFs for *E. cloacae* complex, *E. coli*, *K. pneumoniae*, *P. mirabilis*, and *P. aeruginosa*, by %inhibition threshold

		% inhibition threshold				
Organism (n)	**Parameter**	**95.0%**	**97.5%**	**99.0%**	**99.5%**	**99.9%**
E. coli (6,552)	ECOFF (mg/L)	0.125	0.125	0.125	0.125	0.25
	%Obs > ECOFF	8.5%	8.5%	8.5%	8.5%	4.8%
	%Obs = ECOFF	6.5%	6.5%	6.5%	6.5%	0.2%
E. cloacae complex (3,629)	ECOFF (mg/L)	0.125	0.125	0.125	0.25	0.25
	%Obs > ECOFF	14.5%	14.5%	14.5%	8.0%	8.0%
	%Obs = ECOFF	17.3%	17.3%	17.3%	0.5%	0.5%
K. pneumoniae (6,277)	ECOFF (mg/L)	0.125	0.125	0.125	0.25	0.25
	%Obs > ECOFF	23.4%	23.4%	23.4%	16.8%	16.8%
	%Obs = ECOFF	10.8%	10.8%	10.8%	0.7%	0.7%
P. mirabilis (1,821)	ECOFF (mg/L)	0.125	0.125	0.125	0.125	0.125
	%Obs > ECOFF	8.2%	8.2%	8.2%	8.2%	8.2%
	%Obs = ECOFF	11.1%	11.1%	11.1%	11.1%	11.1%
P. aeruginosa (9,607)	ECOFF (mg/L)	8	16	16	32	32
	%Obs > ECOFF	7.4%	3.8%	3.8%	3.0%	3.0%
	%Obs = ECOFF	13.7%	3.6%	3.6%	0.5%	0.5%

ECOFF, epidemiological cutoff value (in mg/L)
%Obs > ECOFF, percentage of cefepime-taniborbactam MICs above the ECOFF
%Obs = ECOFF, percentage of cefepime-taniborbactam MIC equal to the ECOFF.

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