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Ceftibuten-avibactam (fixed 4 μ g/mL), Ceftibuten, and Ceftazidimeavibactam (fixed 4 μ g/mL) Broth Microdilution Quality Control Ranges Using a CLSI M23 (2018) Multi-Laboratory Study Design

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Introduction

- Ceftibuten-avibactam (fixed 4 μ g/mL) is an orally active antibacterial combination being developed for the treatment of Gram-negative bacterial infections, particularly those responsible for urinary tract infection.
- A Clinical and Laboratory Standards Institute (CLSI) M23 (Tier 2) quality control (QC) study was conducted to establish ceftibutenavibactam (fixed 4 µg/mL) broth microdilution QC ranges against 5 CLSI QC strains and to provide additional QC ranges for ceftibuten and ceftazidime-avibactam (fixed 4 μ g/mL).
- Establishing ceftibuten-avibactam (fixed 4 µg/mL) broth microdilution QC ranges will assist both clinical and reference laboratories in generating reliable, accurate susceptibility testing results during clinical trials and in clinical microbiology practice.

Materials and Methods

- Eight institutions participated in the CLSI M23 (2018) Tier 2 broth microdilution QC study for ceftibuten-avibactam (fixed 4 μ g/mL), ceftibuten, and ceftazidime-avibactam (fixed 4 µg/mL).
- Reference broth microdilution susceptibility testing panels were prepared in a certified GMP facility (Trek Diagnostic Systems/Thermo Fisher Scientific, Oakwood Village, Ohio) using 3 lots of Mueller-Hinton broth obtained from at least 2 different manufacturers (n=3).
- Mueller-Hinton broth was obtained from Difco (Becton Dickinson, Lot 9156821), BBL (Becton Dickinson, Lot 0252344), and Oxoid (Thermo Fisher Scientific, Lot 3163254).
- Testing was performed over multiple days (\geq 3) and \geq 10 replicate tests/QC strain.

Results

QC Strain	Approved broth microdilution QC range (µg/mL) (% in range; no. of dilutions)		
	Ceftibuten-avibactam (fixed 4 μg/mL)	Ceftibuten	Ceftazidime-avibactam (fixed 4 µg/mL)
E. coli	0.016/4 – 0.12/4	0.12 – 0.5ª	0.06/4 – 0.5/4ª
ATCC 25922	(100.0%; 4)	(100.0%; 3)	(100.0%; 4)
E. coli	0.03/4 – 0.12/4	16 – 64ª	0.12/4 – 0.5/4
NCTC 13353	(100.0%; 3)	(100.0%; 3)	(100.0%; 3)
K. pneumoniae	0.06/4 – 0.25/4	0.25 – 1	0.25/4 – 2/4 ^a
ATCC 700603	(98.8%; 3)	(99.2%; 3)	(100.0%; 4)
K. pneumoniae	0.03/4 – 0.25/4	4 – 32ª	0.25/4 – 2/4
ATCC BAA-1705	(100.0%; 4)	(100.0%; 4)	(100.0%; 4)
K. pneumoniae	0.12/4 – 0.5/4	8 – 32ª	1/4 – 4/4
ATCC BAA-2814	(99.6%; 3)	(100.0%; 3)	(100.0%; 3)

 Three dilution QC ranges were approved for ceftibuten-avibactam (fixed 4 µg/mL) against *Escherichia coli* NCTC 13353 (0.03/4-0.12/4; 100.0%), Klebsiella pneumoniae ATCC 700603 (0.06/4-0.25/4; 98.8%), and K. pneumoniae ATCC BAA-2814 (0.12/4-0.5/4; 99.6%) Table 1 and Figures 2-3 and 5).

Four dilution QC ranges were approved for *E. coli* ATCC 25922 (0.016/4-0.12/4; 100.0%) and K. pneumoniae ATCC BAA-1705 (0.03/4-0.25/4; 100.0%) based on the bimodal distribution of MIC values (Table 1 and Figures 1 and 4).

• All (100.0%) of the ceftibuten MIC values against *E. coli* ATCC 25922, E. coli NCTC 13353, K. pneumoniae ATCC BAA-1705, and *L. pneumoniae* ATCC BAA-2814 were within current CLSI-approved QC ranges listed in the M100 (2022) document providing validated internal controls on each day of susceptibility testing (Table 1).

 All (100.0%) of the ceftazidime-avibactam (fixed 4 µg/mL) MIC values against E. coli ATCC 25922 and K. pneumoniae ATCC 700603 were within current CLSI-approved QC ranges listed in the M100 (2022) document providing validated internal controls on each day of susceptibility testing (Table 1).

• Comparator agent QC ranges were also approved for ceftibuten against *K. pneumoniae* ATCC 700603 (0.25-1 µg/mL; 99.2%) and ceftazidime-avibactam (fixed 4 µg/mL) against *E. coli* NCTC 13353 (0.12/4-0.5/4; 100.0%), K. pneumoniae ATCC BAA-1705 (0.25/4-2/4; 100.0%), and *K. pneumoniae* ATCC BAA-2814 (1/4-4/4; 100.0%) (Table 1).

Figure 1. Ceftibuten-avibactam (fixed 4 µg/mL) MIC distributions by medium lot for *E. coli* ATCC 25922

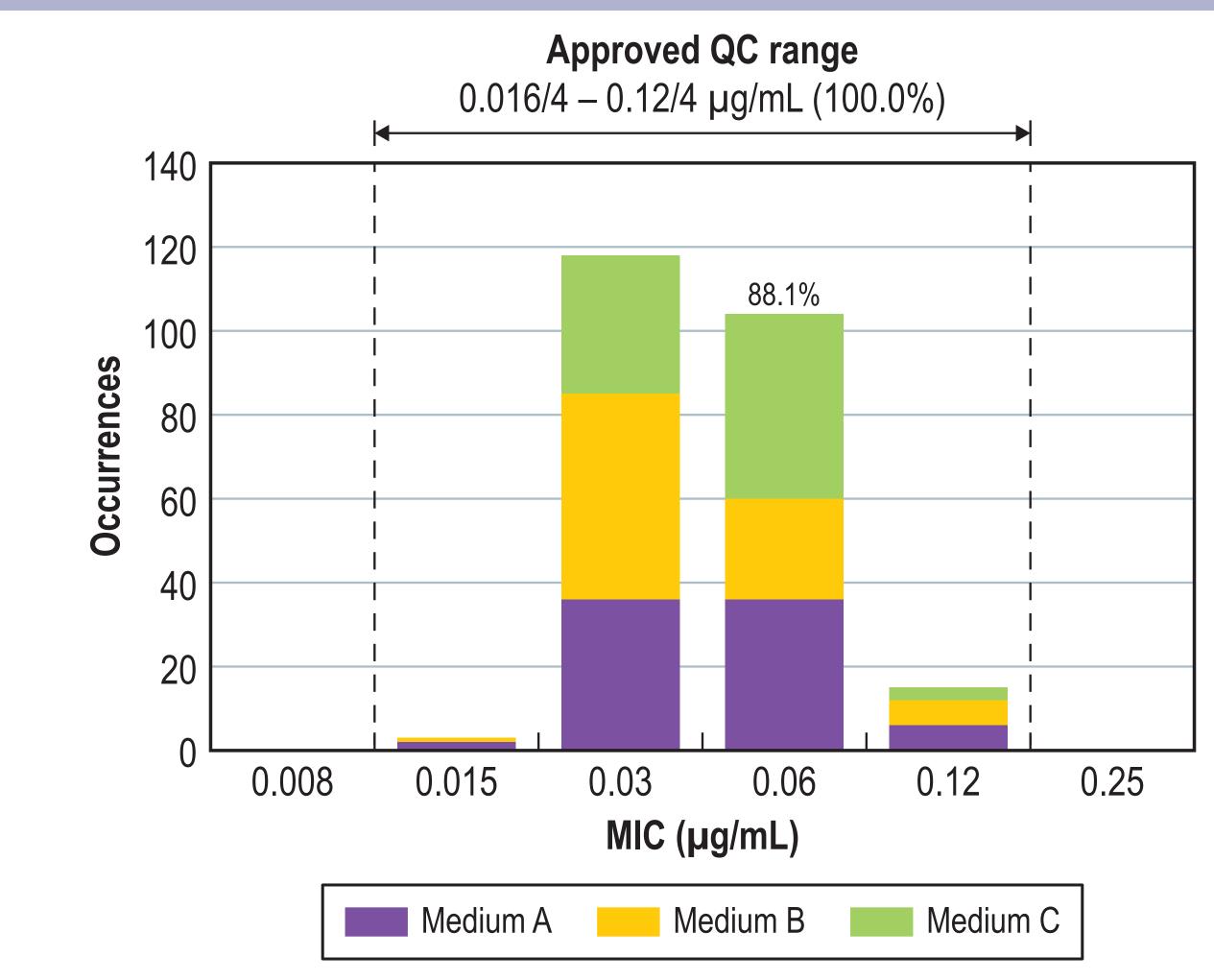


Figure 3. Ceftibuten-avibactam (fixed 4 µg/mL) MIC distributions by medium lot for K. pneumoniae ATCC 700603

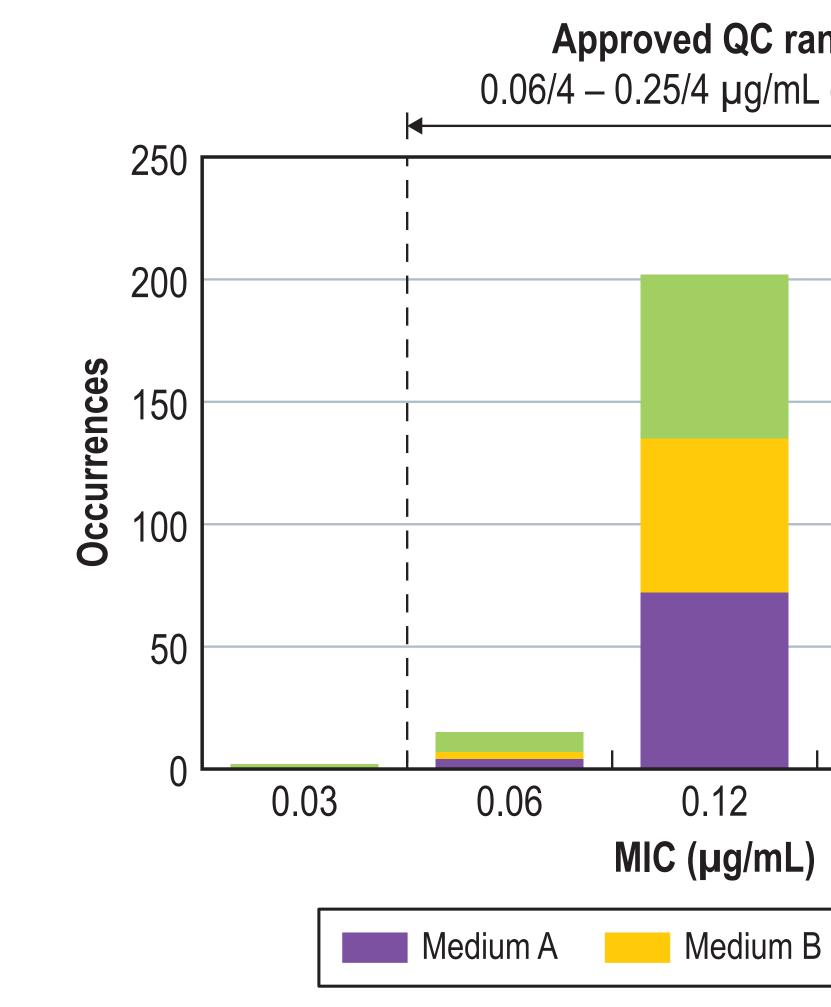
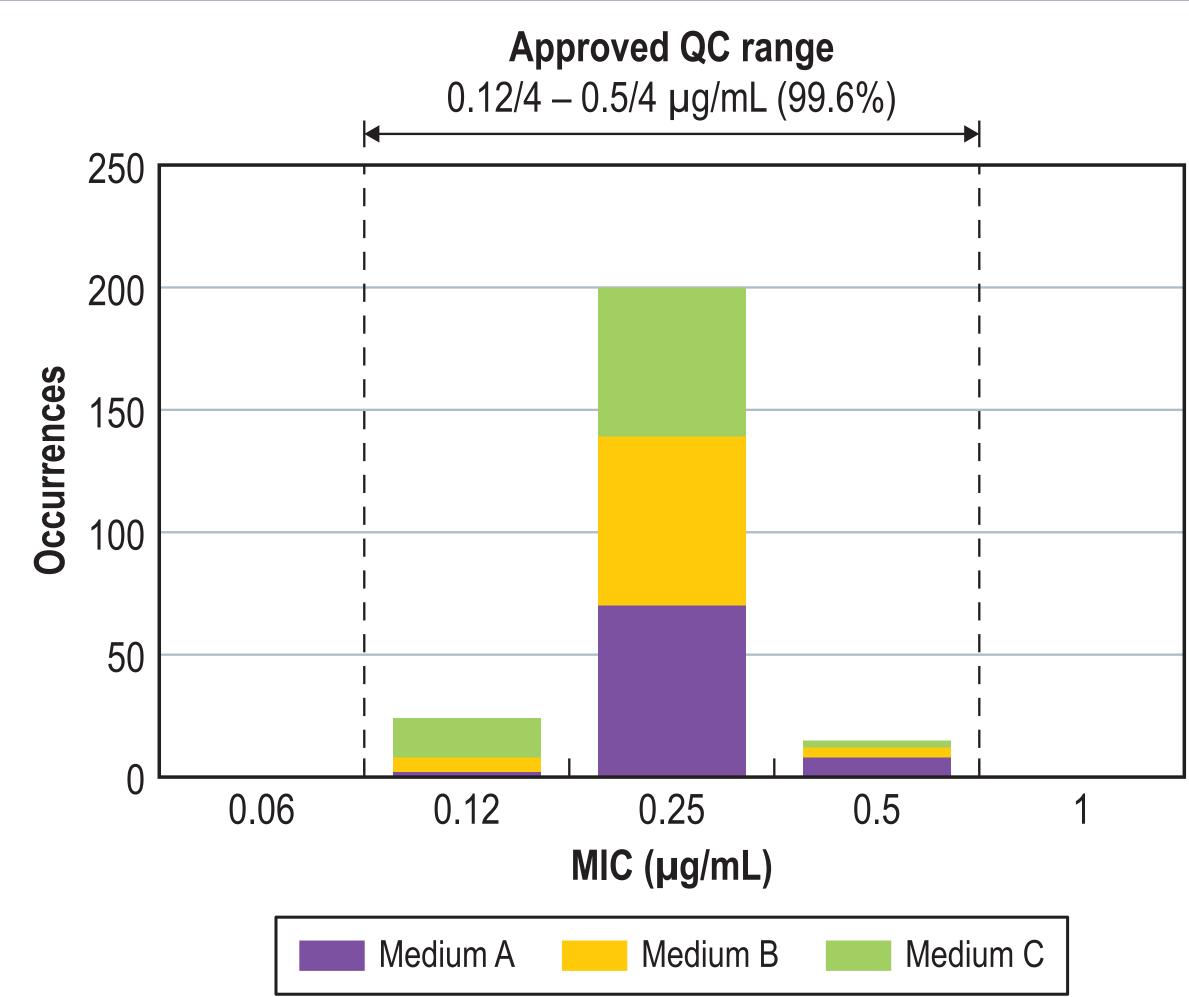


Figure 5. Ceftibuten-avibactam (fixed 4 µg/mL) MIC distributions by medium lot for *K. pneumoniae* ATCC BAA-2814



Approved QC range 0.06/4 – 0.25/4 µg/mL (98.8%)

Medium A Medium B Medium C

Figure 2. Ceftibuten-avibactam (fixed 4 µg/mL) MIC distributions by medium lot for *E. coli* NCTC 13353

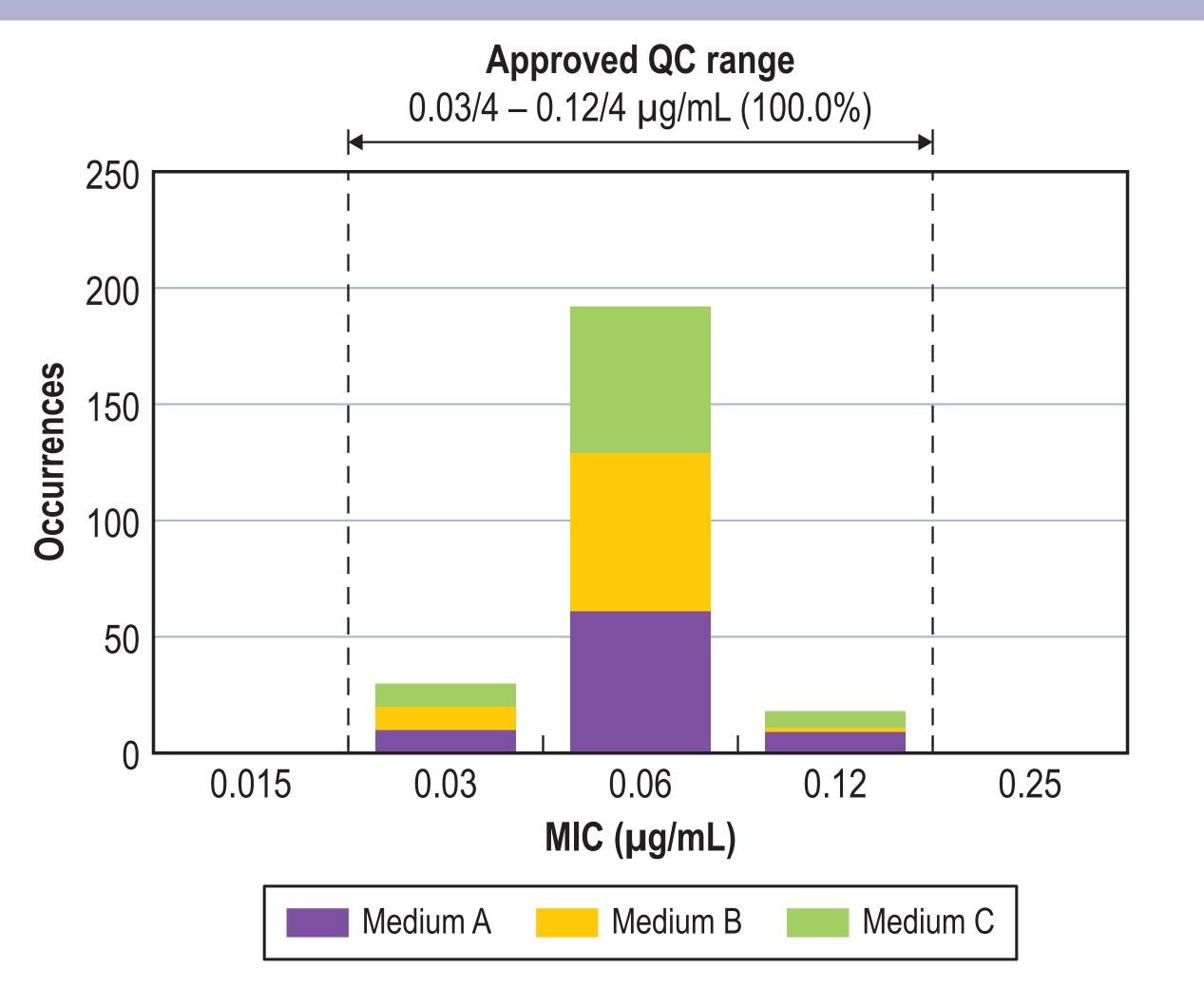
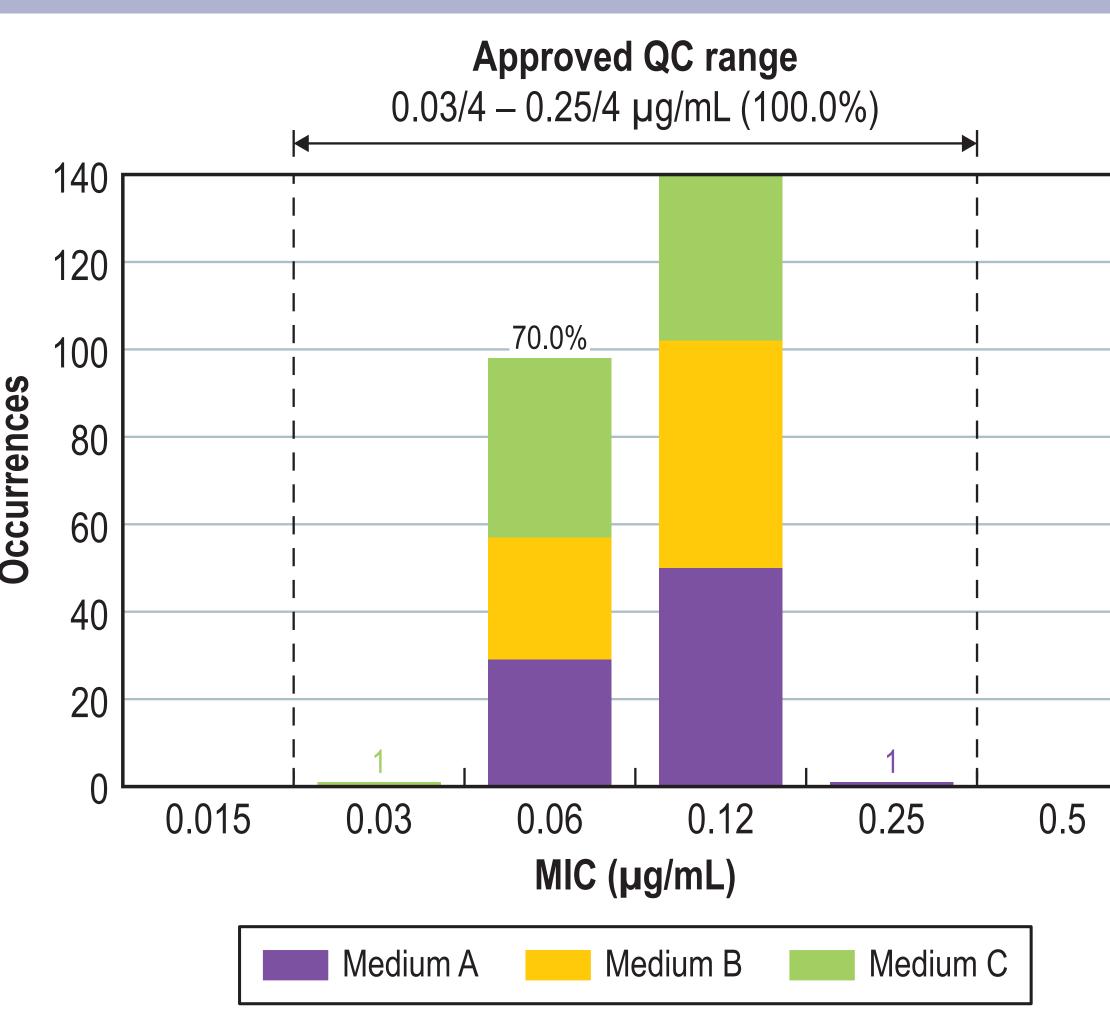


Figure 4. Ceftibuten-avibactam (fixed 4 µg/mL) MIC distributions by medium lot for *K. pneumoniae* ATCC BAA-1705





Conclusions

- The CLSI committee on Antimicrobial Susceptibility Testing approved ceftibuten-avibactam (fixed 4 μ g/mL) broth microdilution QC ranges for E. coli ATCC 25922, E. coli NCTC 13353, K. pneumoniae ATCC 700603, K. pneumoniae ATCC BAA-1705, and K. pneumoniae ATCC BAA-2814; ceftibuten QC ranges for *K. pneumoniae* ATCC 700603; and ceftazidime-avibactam (fixed 4 µg/mL) QC ranges for E. coli NCTC 13353, K. pneumoniae ATCC BAA-1705, and K. pneumoniae ATCC BAA-2814 at the January 2022 CLSI meeting.
- Approved ceftibuten-avibactam (fixed 4 μ g/mL), ceftibuten, and ceftazidime-avibactam (fixed 4 μ g/mL) broth microdilution QC ranges will be published in Table 5A-2 of the 2023 CLSI M100 document.
- E. coli NCTC 13353, K. pneumoniae ATCC BAA-1705, and K. pneumoniae ATCC BAA-2814 should be utilized as routine QC strains when evaluating the activity of ceftibuten-avibactam (fixed 4 μ g/mL) as they provide QC for both the ceftibuten and avibactam components of the antimicrobial combination.
- The approved broth microdilution QC ranges for ceftibuten-avibactam (fixed 4 µg/mL), ceftibuten, and ceftazidime-avibactam (fixed 4 µg/ mL) will assist both clinical laboratories and reference laboratories participating in clinical trials.

Acknowledgements

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