

# Evaluation of Etests and the disk diffusion method for assessment of the activity of ceftazidime-avibactam against *Enterobacterales* and *Pseudomonas aeruginosa* in China

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## Research article

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# Abstract

**Background:** Gram-negative bacilli, particularly *Enterobacterales* and *Pseudomonas aeruginosa*, often acquire antimicrobial resistance. Ceftazidime-avibactam was approved for use in China in 2019. However, currently available commercial antimicrobial susceptibility test kits have not yet been developed. Here, we evaluated the Etest and disk diffusion method for assessment of the efficacy of ceftazidime-avibactam against *Enterobacterales* and *P. aeruginosa* in China.

**Results:** In total, 194 *Enterobacterales* and 77 *P. aeruginosa* isolates, which were divided into a random selection group (140 *Enterobacterales* and 54 *P. aeruginosa* isolates) and a stock group (46 *Enterobacterales* and 31 *P. aeruginosa* isolates), were assessed by the Etest, disk diffusion, and broth microdilution (BMD) methods. Minimum inhibitory concentrations (MICs) and zone diameters were interpreted according to the CLSI M100 30<sup>th</sup> edition. For all 271 *Enterobacterales* and *P. aeruginosa* isolates, no very major errors were found using Etests. The overall categorical agreement rates (CA%) of Etests for *Enterobacterales* and *P. aeruginosa* were 99.5% (193/194) and 96.1% (74/77), respectively. The overall essential agreement rates (EA%) of Etests for *Enterobacterales* and *P. aeruginosa* were 95.9% (186/194) and 94.8% (73/77), respectively. In both the random selection and stock groups, EA% and CA% values of Etests exceeded 90%. Overall CA% values of the disk diffusion method for *Enterobacterales* and *P. aeruginosa* were 98.5% (191/194) and 93.5% (71/77), respectively. There was no linear relationship between zone diameter and BMD MIC.

**Conclusions:** For *Enterobacterales* and *P. aeruginosa*, Etests and the disk diffusion method could have better performance as alternative methods to meet the needs of clinical treatment interpretation. Application of the disk diffusion method in *Enterobacterales* was superior to that in *P. aeruginosa*.

## Background

Gram-negative bacilli, particularly carbapenem-resistant *Enterobacterales* (CRE) and *Pseudomonas aeruginosa*, exhibit major antimicrobial resistance worldwide, including in European countries, the United States of America (USA), and China [1–3]. The approval of ceftazidime-avibactam for clinical use in Europe and the USA has brought new treatment options to CRE-infected patients, particularly those with serine-carbapenemase resistance mechanisms [4, 5]. Ceftazidime-avibactam was approved for use in China in 2019. However, currently available commercial antimicrobial susceptibility test kits have not yet been developed for analysis of ceftazidime-avibactam resistance in China, and in patients with infections caused by CRE, which are resistant to multiple antimicrobials, the results of ceftazidime-avibactam susceptibility tests are urgently needed to facilitate appropriate targeted treatment. Although ceftazidime-avibactam has excellent in vitro activity against carbapenem-resistant *Klebsiella pneumoniae* (CRKP) and *Pseudomonas aeruginosa* strains, a small number of resistant strains will still appear during treatment [6–8]. Therefore, susceptibility test results for ceftazidime-avibactam are even more critical.

In most of the laboratories in China, performing the standard broth microdilution method (BMD) is challenging. Therefore, other rapid, simple methods are required as alternatives to determine ceftazidime-avibactam susceptibility. In this study, we evaluated two antimicrobial susceptibility test methods for ceftazidime-avibactam, i.e., the Etest method and the disk diffusion method with the standard BMD, to evaluate whether these easy-to-use methods could replace standard methods when required in the clinical setting.

## Materials And Methods

### Groups

Isolates were divided into two groups, i.e., the random selection group and the stock group. For the random selection group, we randomly selected 140 *Enterobacterales* and 46 *Pseudomonas aeruginosa* strains from clinical nonrepeated isolates obtained at Peking University People's Hospital. Among these samples, 59.3% (83/140) of *Enterobacterales* and 56.5% (26/46) of *Pseudomonas aeruginosa* strains were defined as fresh strains from clinical isolates obtained within 1 month prior to testing (November 2019 to March 2020). The remaining strains in the random selection group were obtained from the strain repository of Peking University People's Hospital from January 2018 to October 2019. The 140 strains of *Enterobacterales* used in the testing included 13 species, i.e., 25 *K. pneumoniae*, 19 *Escherichia coli*, 18 *Proteus mirabilis*, 17 *Enterobacter cloacae*, 16 *Serratia marcescens*, 15 *Citrobacter freundii*, 14 *K. oxytoca*, four *Proteus vulgaris*, three *Morganella morganii*, three *Providencia stuartii*, two *Providencia rettgeri*, two *K. aerogenes*, and two *Citrobacter koseri* strains. For the stock group, we selected 54 strains of *Enterobacterales* from 15 hospitals in the CRE China-Network from January 2015 to October 2019 and requested that the minimum inhibitory concentration (MIC) of ceftazidime-avibactam be between 2 and 256 µg/mL. Among these strains, six strains (11.1%) showed MICs for ceftazidime-avibactam of between 8 and 16 µg/mL, and 15 strains (27.8%) showed MIC between 4 and 32 µg/mL. The carbapenem-resistance genes present in these strains were elucidated in previous studies [9]. The 54 strains of *Enterobacterales* used in this study included 29 *K. pneumoniae* (18 strains having the *bla*<sub>KPC</sub> gene and 10 strains having the *bla*<sub>NDM</sub> gene), 12 *Escherichia coli* (two strains having the *bla*<sub>KPC</sub> gene and seven strains having the *bla*<sub>NDM</sub> gene), eight *Enterobacter cloacae* (one strain having the *bla*<sub>KPC</sub> gene, five strains having the *bla*<sub>NDM</sub> gene, one strain having the *bla*<sub>IMP</sub> gene, and one strain having *bla*<sub>VIM</sub> gene), three *K. oxytoca* (two strains having the *bla*<sub>IMP</sub> gene and one strain having the *bla*<sub>NDM</sub> gene), and two *Citrobacter freundii* (one strain having the *bla*<sub>IMP</sub> gene and one strain having the *bla*<sub>NDM</sub> gene).

We selected 31 strains of *Pseudomonas aeruginosa* from the eight hospitals involved in the CARES 2018 project as stock group strains and required the MIC of ceftazidime-avibactam to be between 2 and 256 µg/mL. Among these strains, 12 strains (38.7%) had MICs for ceftazidime-avibactam between 8 and 16 µg/mL, and 25 strains (80.6%) had MICs between 4 and 32 µg/mL.

All strains were removed from a -80 °C ultra-low temperature refrigerator and transferred to Columbia blood agar twice before antimicrobial susceptibility testing.

## Antimicrobial susceptibility testing

For the disk diffusion method, ceftazidime-avibactam disks were obtained from Oxoid (Thermo Scientific, China) The content of ceftazidime-avibactam in each disk was 30 µg/20 µg. The operation process was strictly tested following the requirements of the CLSI standardized method [10].

For the Etest gradient diffusion method, ceftazidime-avibactam Etest strips were obtained from BioMérieux (Marcy l'Etoile, France). The test was performed in strict accordance with the manufacturer's instructions. The ceftazidime-avibactam concentration gradient ranged from 0.016 to 256 µg/mL. When the Etest MIC value was between the standard value and twice the standard value (0.016, 0.032, 0.064, 0.125, 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 128, and 256), the high standard value will be read as the MIC.

The MH agar used for both the disk diffusion method and the Etest gradient diffusion method for antimicrobial susceptibility testing was obtained from Oxoid (Thermo Scientific Inc).

The BMD was performed strictly following CLSI guidelines [11]. Ceftazidime and avibactam powers were obtained from Pfizer (USA). The concentration ranged from the standard double dilution of 0.016 µg/mL to 256 µg/mL.

Quality control and colony counting are performed simultaneously for each batch of experiments. *Escherichia coli* ATCC 25922, *K. pneumoniae* ATCC 700603, *Escherichia coli* ATCC 35218, and *Pseudomonas aeruginosa* ATCC 27853 were

used as experimental quality control strains. The experiment was considered valid only when the experimental values of all the quality control strains were within the acceptable range.

The MICs and zone diameters of ceftazidime-avibactam for *Enterobacterales* and *Pseudomonas aeruginosa* were interpreted according to CLSI M100 30th edition [11]. Briefly, MICs of less than or equal to 8/4 µg/mL or a zone diameter of greater than or equal to 21 mm indicated that the strain was susceptible, whereas MICs of greater than or equal to 16/4 µg/mL or a zone diameter of less than or equal to 20 mm indicated that the strain was resistant.

Essential agreement (EA) indicated that the difference between the MIC value measured by Etest and the BMD did not exceed one dilution factor. Categorical agreement (CA) indicated that the BMD method was consistent with the classification results from the disk diffusion method and Etest method based on the same CLSI breakpoints.

Very major errors (VMEs) indicated that the strain was susceptible by Etest or the disk diffusion method but resistant by the BMD. Major errors (MEs) indicated that the strain was susceptible by the BMD but resistant by Etest or the disk diffusion method.

## Result

### Etest versus the BMD

For 194 *Enterobacterales* strains, no VMEs were found using the Etest method. As shown in Table 1, the overall CA rate was 99.5%, and the overall EA rate was 95.9%. The CA rate of the stock group was 90.7%, and the CA rate in the random selection group was 97.9%. When comparing Etest results with BMD results, we found that the MICs of eight strains exceeded the two dilution factors. As shown in Fig. 1, the Etest MICs of 102 (52.5%) strains were consistent with the BMD MICs. The Etest MICs of 71 (36.6%) strains were a dilution multiple higher than the BMD MICs. Only 12 (6.2%) strains had Etest MICs that were a dilution multiple lower than the BMD MICs.

Table 1

Evaluation of essential and categorical agreement between the BMD method and Etests or the disk diffusion method for analysis of ceftazidime-avibactam antimicrobial susceptibility

Organisms	No. of strains tested	Etest						Disk diffusion			
		No. of EA	EA%	No. of CA	CA%	No. of VMEs	No. of MEs	No. of CA	CA%	No. of VMEs	No. of MEs
Enterobacterales											
Random selection Group	140	137	97.9%	140	100.0%	0	0	140	100.0%	0	0
Stock group:	54	49	90.7%	53	98.1%	0	1	51	94.4%	2	1
Total in <i>Enterobacterales</i>	194	186	95.9%	193	99.5%	0	1	191	98.5%	2	1
<i>Pseudomonas aeruginosa</i>											
Random selection Group	46	45	97.8%	46	100.0%	0	0	43	93.5%	0	3
Stock group:	31	28	90.3%	28	90.3%	0	3	29	93.5%	1	1
Total in <i>Pseudomonas aeruginosa</i>	77	73	94.8%	74	96.1%	0	3	72	93.5%	1	4
<b>Total in all tested strains</b>	271	259	95.6%	267	98.5%	0	4	263	97.0%	3	5
EA: essential agreement; CA: categorical agreement; VMEs: very major errors (false susceptible); MEs: major errors (false resistant)											

For 77 *Pseudomonas aeruginosa* strains, no VMEs were found using the Etest method. As shown in Table 1, the overall CA rate was 96.1%, and the overall EA rate was 94.8%. The CA rate in the stock group was 90.3%, and the CA rate in the random selection group was 100%. As shown in Fig. 2, the Etest MICs of 45 (58.4%) strains were consistent with the MICs obtained by the BMD. The Etest MICs of 22 (28.6%) strains were one dilution higher than those obtained by the BMD, whereas those of six (7.8%) strains were one dilution lower than the MICs obtained by the BMD. For one strain, the Etest MIC was two dilutions higher than those obtained by the BMD. Three MEs appeared in the stock group when the Etest method was used.

## Disk diffusion method versus BMD

A comparison of the disk diffusion method and BMD results for 194 *Enterobacterales* strains (Fig. 3) showed that there were no linear relationships between zone diameter and MIC. The overall CA rate in the 194 *Enterobacterales* strains was 98.5%. Two VMEs and one ME were found using the disk diffusion method in the stock group; all were for *K. pneumoniae* strains. No VMEs or MEs were found using the disk diffusion method in the random selection group. There were 22 strains of *Enterobacterales* with zone diameters of 2 mm (19–22 mm susceptibility breakpoint). Forty-one of the 45 resistant strains obtained by BMD had zone diameters in the range of 13–20 mm.

In a comparison of the results of the disk diffusion method and BMD for 77 *Pseudomonas aeruginosa* strains, the number of MEs was four, and the number of VMEs was 1. As shown in Table 1, the overall CA rate was 93.5%. Moreover,

as shown in Fig. 4, when the zone diameter was 20 mm, the MICs obtained by the BMD method were 4, 8, 16, or 64 µg/mL.

## Discussion

In the past ten years, the incidence of CRE, particularly CRKP, has increased significantly in China. The latest China Antimicrobial Resistance Surveillance System (CARSS) data show that the incidence of CRKP nationwide is as high as 10.1% (<http://www.carss.cn/Report/Details?ald=648>). However, few active antibacterial agents, such as tigecycline and colistin, are available to treat CRKP in the clinical setting [12, 13], resulting in high mortality worldwide. Previous molecular epidemiological data show that more than 70% of CRE isolated in China from 2012 to 2016 produce KPC-type carbapenemases [9]. Ceftazidime-avibactam, a drug with potent antibacterial activity against serine-carbapenemase, was approved for use in China in 2019. Recent retrospective studies have shown that ceftazidime-avibactam treatment of CRKP and *Pseudomonas aeruginosa* infection in patients who have undergone solid organ transplantation improves clinical success rates [14, 15]. Despite these promising findings, ceftazidime-avibactam antimicrobial susceptibility test results are essential for clinical use of this treatment. However, no ceftazidime-avibactam combination kits are available for assessing resistance in China.

To the best of our knowledge, this is the first study comparing Etests, the disk diffusion method, and the BMD with regard to detection of ceftazidime-avibactam susceptibility in China. Compared with the standard BMD method, no VMEs were found using the Etest method. The results of Etest MICs and BMD MICs were reasonably well correlated for both *Enterobacterales* and *Pseudomonas aeruginosa*. The overall of EA% of 271 tested strains was 95.6%. Compared with the BMD method, the Etest method exhibited an excellent linear correlation, supporting the use of this approach as an alternative to the standard clinical method without considering economic costs. This result was similar to the previous research findings of other authors [16]. The disk diffusion method is easy to implement in the clinical setting from an economic standpoint. The CA% values of the ceftazidime-avibactam disk diffusion method against *Enterobacterales* and *Pseudomonas aeruginosa* were 98.5% and 93.5%, respectively, similar to the findings of Shields and other scholars [16, 17]. Indeed, our results showed that application of the disk diffusion method was more appropriate for *Enterobacterales* than for *Pseudomonas aeruginosa*. Notably, however, the disk diffusion method did not have an excellent linear correlation with BMD. Therefore, the zone diameters of strains near the breakpoints ( $\pm 2$  mm) should be checked by the BMD carefully, consistent with other research results [17, 18]. This should also be considered when users refer to the new version of CLSI M100, which suggests using the disk diffusion method [11].

## Conclusions

In conclusion, for *Enterobacterales* and *Pseudomonas aeruginosa*, Etests and the disk diffusion method showed good performance as alternative methods to meet the needs of clinical treatment interpretation. The application of the disk diffusion method was superior for *Enterobacterales* compared with *Pseudomonas aeruginosa*.

## Declarations

**Ethics approval and consent to participate:** Not applicable

**Consent for publication:** Not applicable

**Competing interests:** The authors declare that they have no competing interests

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**Authors' contributions:** HW conceived and designed the study. QW, FZ, HC, XW, YZ and SL performed experiments described in this study. QW wrote the draft, and HW revised it. All authors approved the final version.

**Competing Interests:** The authors declare no conflicts of interest in this work.

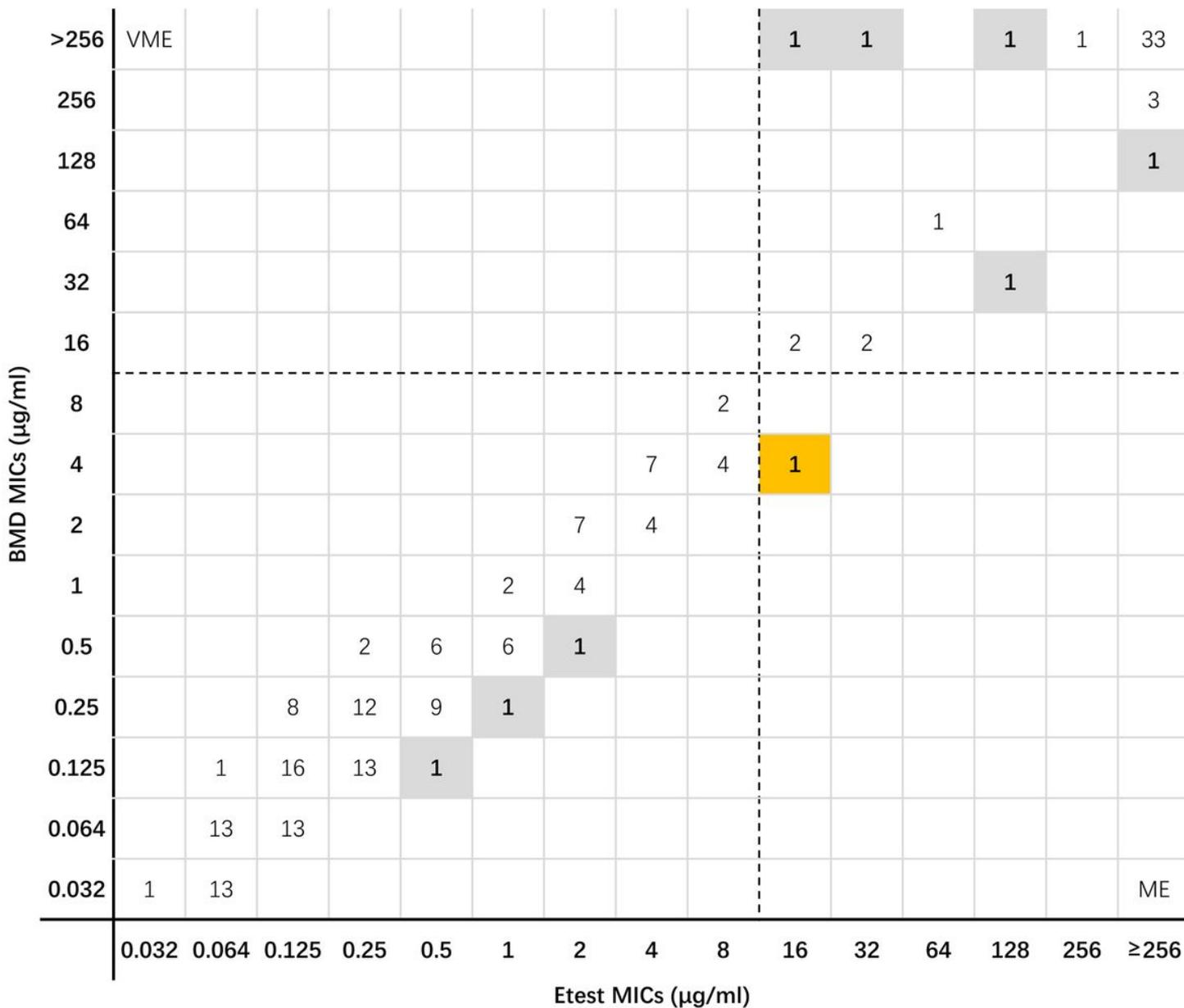
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## Figures



**Figure 1**

Scatter plot of ceftazidime-avibactam Etest MICs versus BMD MICs against Enterobacterales. Dotted lines represent the susceptibility breakpoint for ceftazidime-avibactam. VMEs: very major errors (false susceptible); MEs: major errors (false resistant). The gray background indicates that the MIC of the Etest did not satisfy the essential agreement compared with the MIC of the BMD; the yellow background indicates that a major error occurred in the MIC result of the Etest compared with the MIC of the BMD.

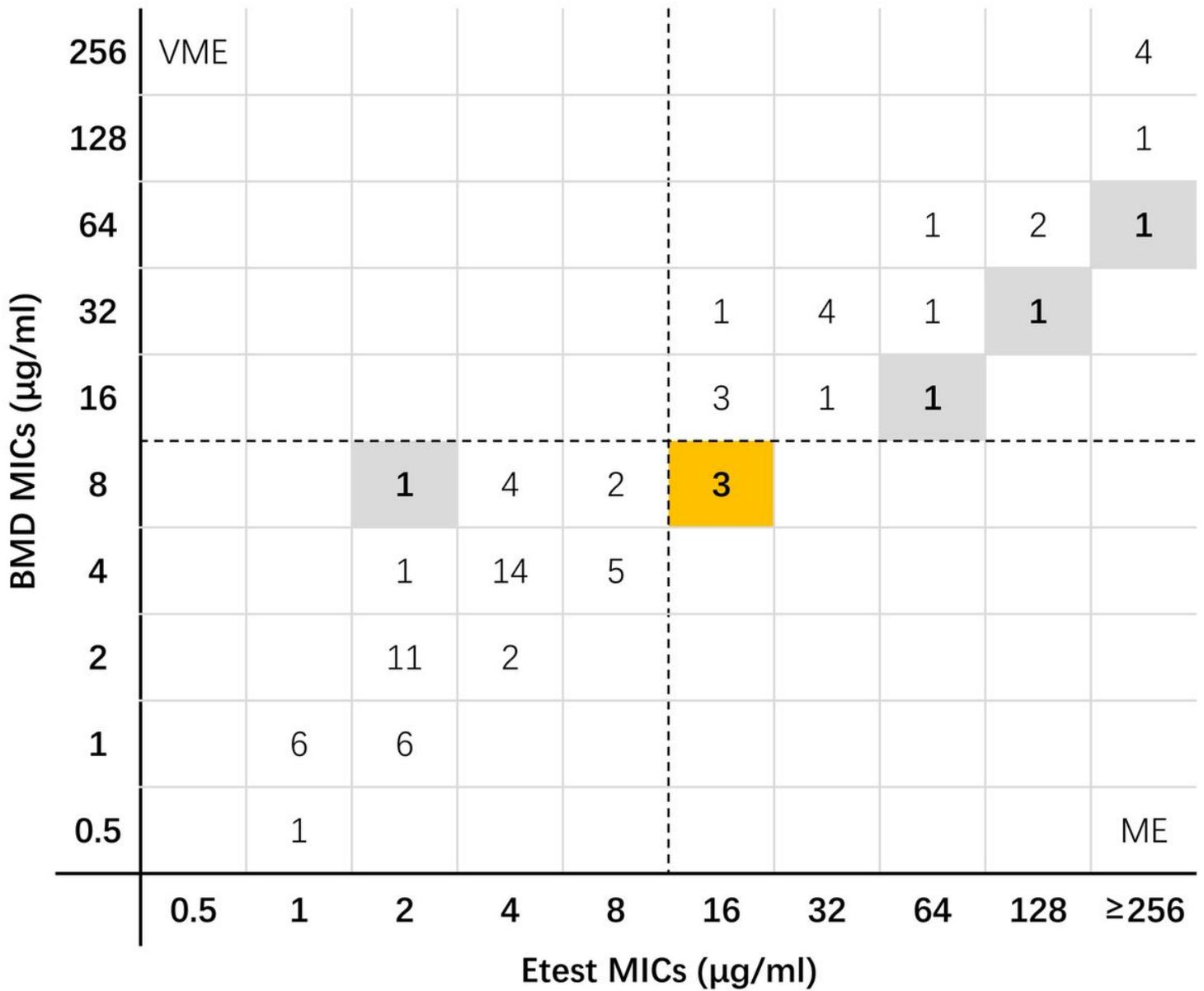


Figure 2

Scatter plot of ceftazidime-avibactam Etest MICs versus BMD MICs against *Pseudomonas aeruginosa*. Dotted lines represent the susceptibility breakpoint for ceftazidime-avibactam. VMEs: very major errors (false susceptible); MEs: major errors (false resistant). The gray background indicates that the MIC of the Etest did not satisfy the essential agreement compared with the MIC of the BMD; the yellow background indicates that three major errors occurred in the MIC results of the Etest compared with the MIC of the BMD.

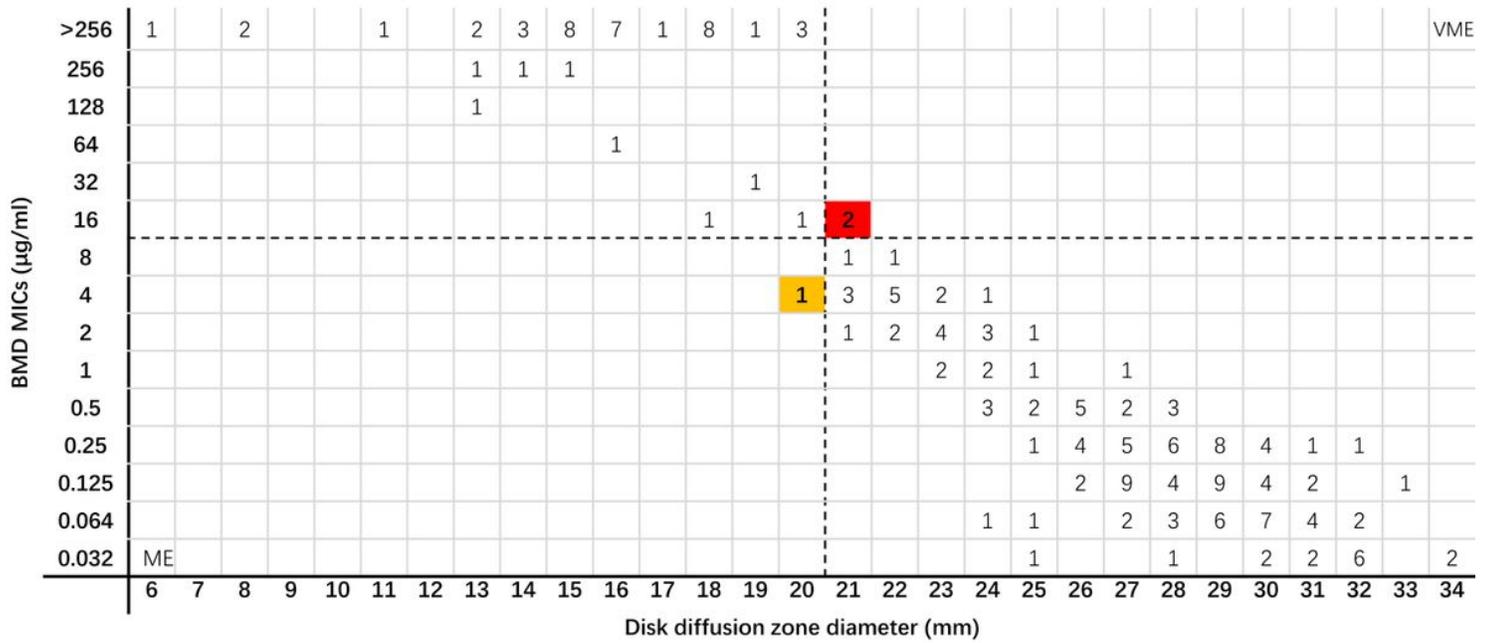


Figure 3

Scatter plot of ceftazidime-avibactam zone diameters versus BMD MICs against Enterobacterales. Dotted lines represent the susceptibility breakpoint for ceftazidime-avibactam. VMEs: very major errors (false susceptible); MEs: major errors (false resistant). The yellow background indicates that a major error occurred when comparing the results of the disk diffusion method with the results of the BMD. The red background indicates that two very major errors occurred when comparing the results of the disk diffusion method with the results of the BMD.

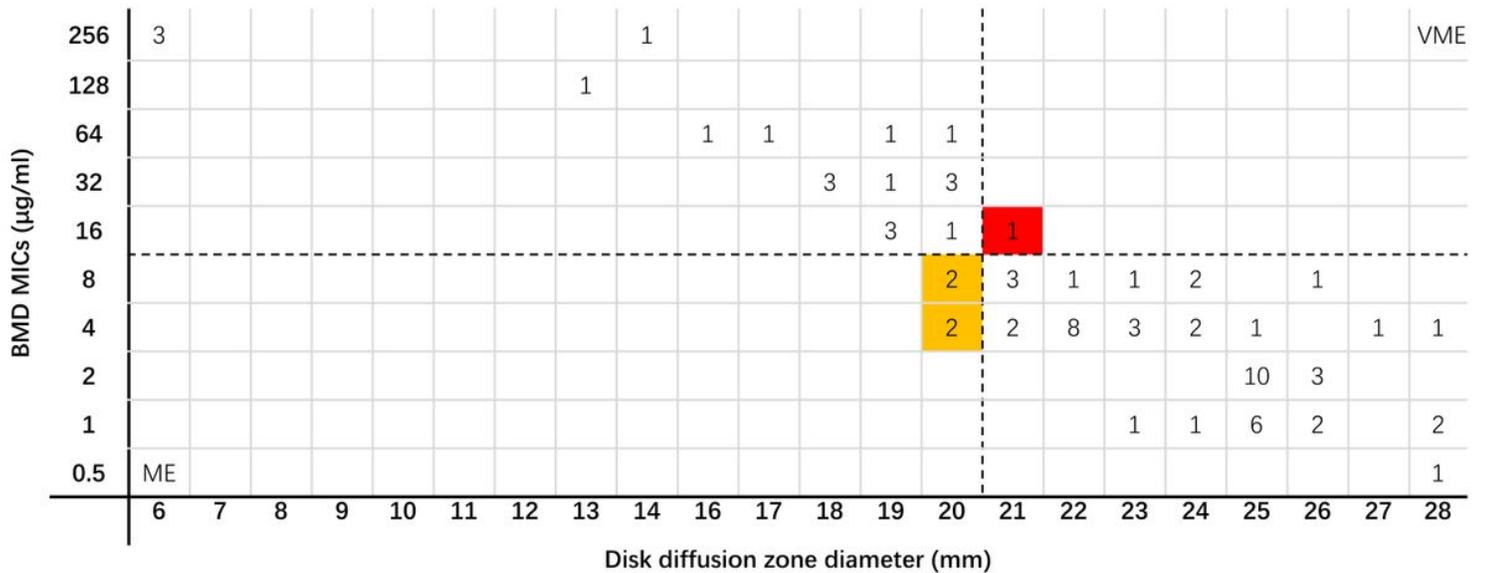


Figure 4

Scatter plot of ceftazidime-avibactam zone diameters versus BMD MICs against *Pseudomonas aeruginosa*. Dotted lines represent the susceptibility breakpoint for ceftazidime-avibactam. VMEs: very major errors (false susceptible); MEs: major errors (false resistant). The yellow background indicates that four major errors occurred when comparing the results of the disk diffusion method with the results of the BMD. The red background indicates that a very major error occurred when comparing the results of the disk diffusion method with the results of the BMD.