



Challenges in cefiderocol antimicrobial susceptibility testing

Erika Matuschek, PhD
EUCAST Development Laboratory, EDL

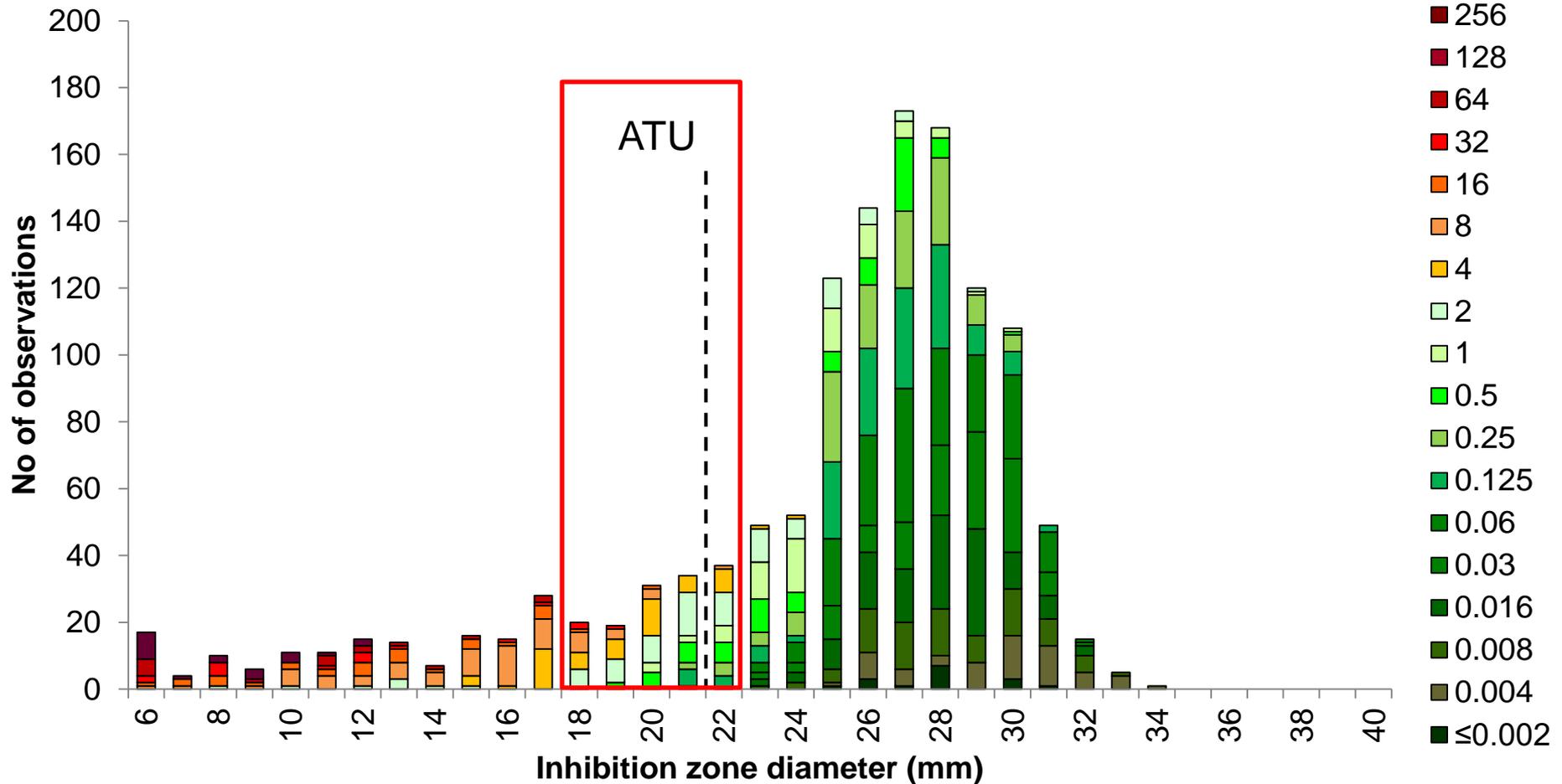
Cefiderocol AST

- Broth microdilution in iron-depleted Mueller-Hinton broth (ID-CAMHB)
 - See EUCAST Guidance document for MIC methodology and specific reading instructions for cefiderocol, <https://www.eucast.org/eucastguidancedocuments>
- Disk diffusion on standard un-supplemented Mueller-Hinton agar
 - Zone diameter breakpoints for *Enterobacterales* and *P. aeruginosa*
 - Zone diameter cut-off values corresponding to the PK-PD breakpoint for *Acinetobacter* spp. and *S. maltophilia*

<https://www.eucast.org/ast-of-bacteria/warnings>

Cefiderocol 30 µg vs. MIC

Enterobacterales, 382 isolates (1302 correlates)

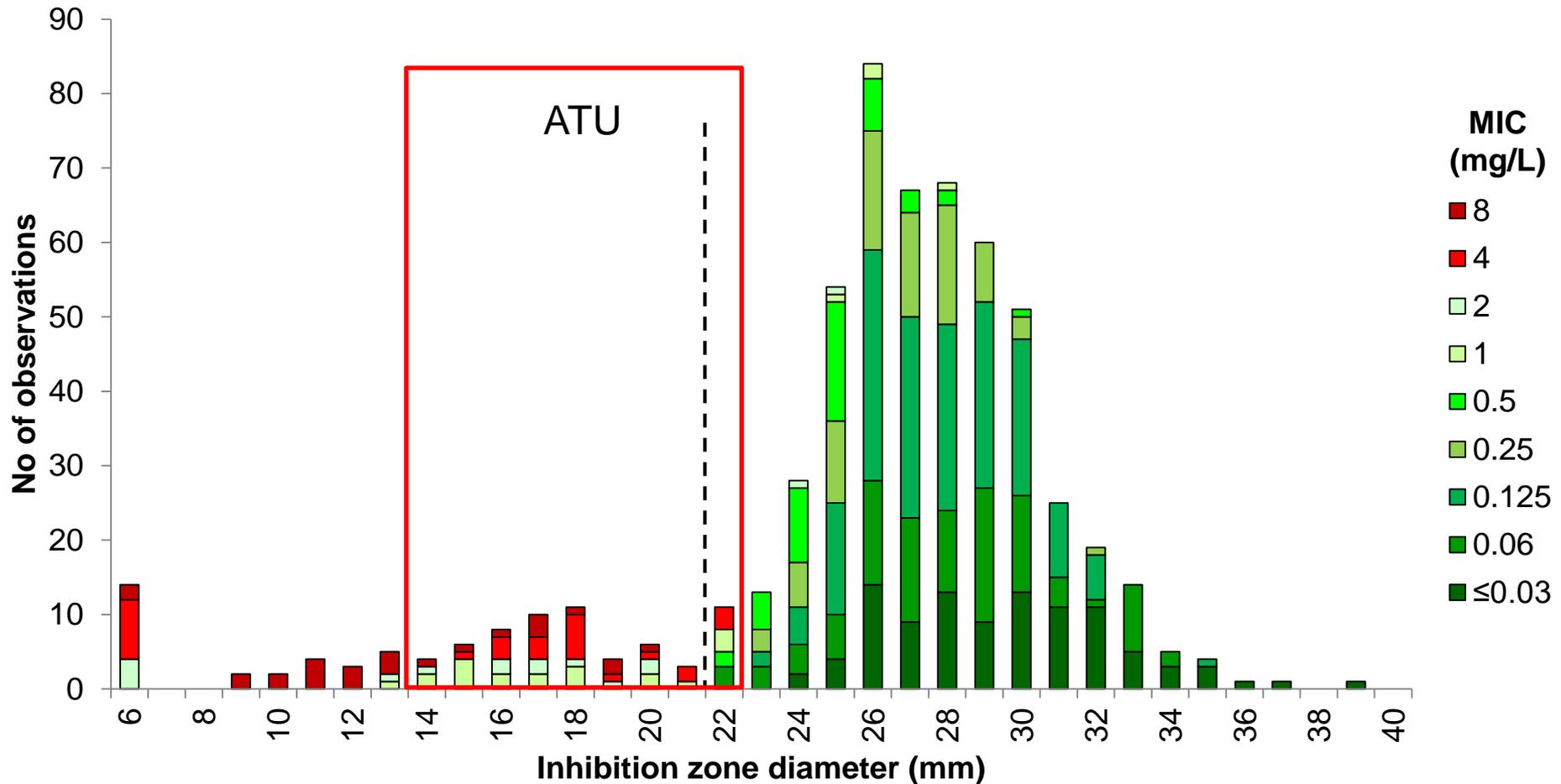


Breakpoints

MIC S ≤ 2 , R > 2 mg/L

Zone diameter S ≥ 22 , R < 22 mm

Cefiderocol 30 μg vs. MIC *P. aeruginosa*, 152 isolates (588 correlates)



Breakpoints	
MIC	S \leq 2, R $>$ 2 mg/L
Zone diameter	S \geq 22, R $<$ 22 mm

AST of bacteria

[Organization](#)
[Consultations](#)
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[Rapid AST in blood cultures](#)
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[AST of mycobacteria](#)
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12. Cefiderocol: EUCAST has evaluated (August 2022) commercially available tests and all have problems with accuracy, reproducibility, bias and/or for some, with skipped wells. For this reason, it is difficult to resolve the susceptibility interpretation of isolates in the ATU (area of technical uncertainty) in routine testing. Considering the current limitations and the need for testing in multiresistant bacteria, these are the recommendations of EUCAST until the issue of confirmatory MIC determination is solved.

- Disk diffusion. Laboratories are recommended to start testing cefiderocol with disk diffusion. Resistance to beta-lactam agents is increasing and therapeutic alternatives are few. Disk diffusion, when correctly performed and calibrated using quality material and recommended quality control guidelines, is predictive of susceptibility and resistance outside the ATU.
Template zone diameter distributions for relevant species against which to calibrate in-house
- Inside the ATU, and as long as there is no alternative method to resolve interpretative uncertainties (eg MIC-testing in the routine laboratory or assistance from a reference laboratory), EUCAST recommends colleagues to ignore the ATU and interpret using the zone diameter breakpoints in the breakpoint table.
- However, as with all AST methods and for all antimicrobial agents, results depend on the quality of materials used. EUCAST does not have the resources to systematically investigate all products from all manufacturers. Below a few commonly used manufacturers of disks and MH agars are mentioned but others are not. Assume that those that are not mentioned may have undisclosed problems.

For cefiderocol, using a cross-over protocol, disks from three manufacturers and Mueller-Hinton media from five manufacturers were evaluated.

If care is taken to ensure that the EUCAST QC criteria for the two strains, *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853, are met, i.e. with the mean of at least 5 repeated tests is within +/-1 mm of the target values, disk diffusion using EUCAST breakpoints performed well. When the mean value was more than +/-1 mm from the target, an increasing proportion of results were erroneous. This was particularly problematic for *Pseudomonas aeruginosa*.

Among the evaluated cefiderocol 30 µg disks (Liofilchem, Mast and Oxoid) and Muller-Hinton agars (BBL, bioMérieux, Bio-Rad, Liofilchem and Oxoid), disks from Oxoid and MH agar from Bio-Rad produced larger than acceptable zone diameters for both QC strains and clinical isolates. Combining Oxoid disks with Bio-Rad MH agar increased the problem further.

Further work to elucidate the problems surrounding cefiderocol susceptibility testing is ongoing. Two commercial products currently under investigation, are UMIC (Bruker) and ComASP (Liofilchem).

The issue has been discussed by the EUCAST Steering Committee, January 2023, and it was decided that issues have not yet been resolved and that the warning should remain.

A EUCAST evaluation is ongoing and results will be made available as soon as testing is completed and an analysis by the committee performed.



Warnings!



Cefiderocol disk diffusion

- Perform frequent quality control and evaluate the data
 - Mean values from ≥ 5 tests should be on target ± 1 mm for both *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853
- EDL evaluation of disks from 3 manufacturers on MH agar from 5 manufacturers
 - Larger zones with Oxoid disks and Bio-Rad MH agar (especially when in combination) resulted in false susceptible results

<https://www.eucast.org/ast-of-bacteria/warnings>

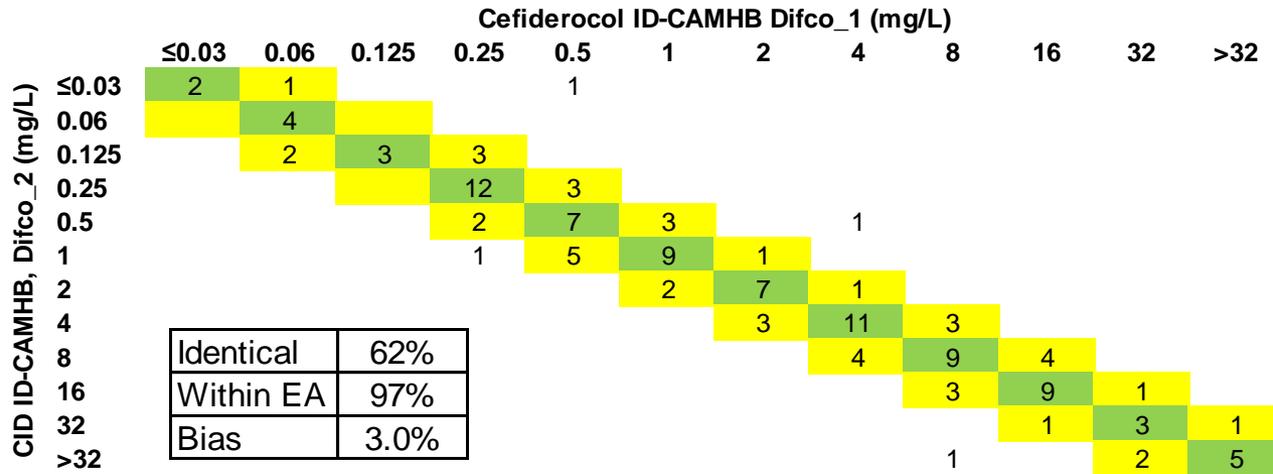
Evaluation of cefiderocol BMD

Ongoing evaluations at EDL:

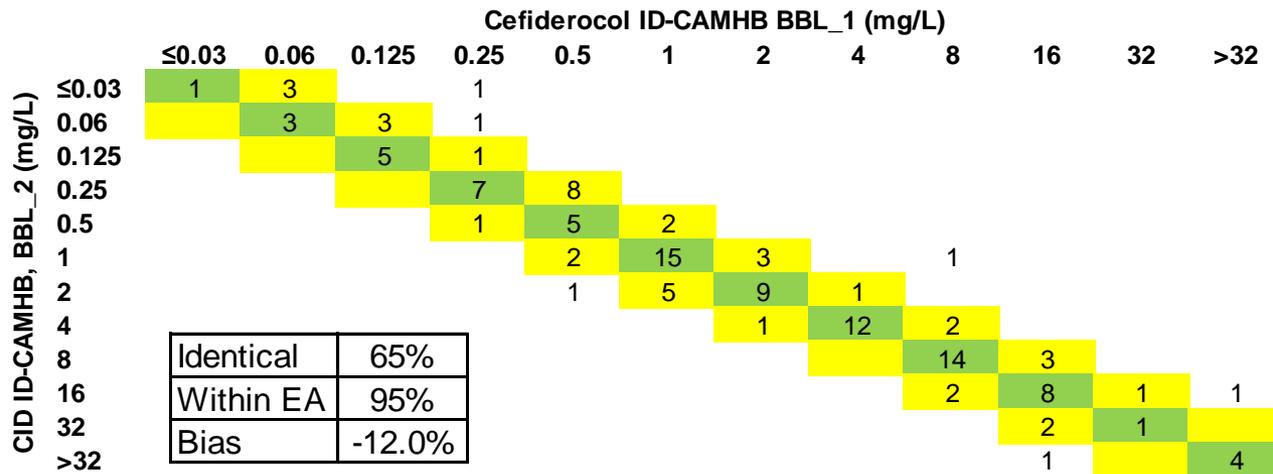
- Reproducibility of reference methodology
- Comparison of two different CAMHB powder media (BBL and Difco) for preparation of ID-CAMHB
- Evaluation of two commercial MIC products for cefiderocol (freeze-dried panels)
 - ComASP (Liofilchem)
 - UMIC (Bruker)
- A challenge collection of 130 isolates: *E. coli* (n=30), *K. pneumoniae* (n=30), *P. aeruginosa* (n=30), *A. baumannii* (n=20) and *S. maltophilia* (n=20)

Reproducibility of reference method

ID-CAMHB Difco from two tests

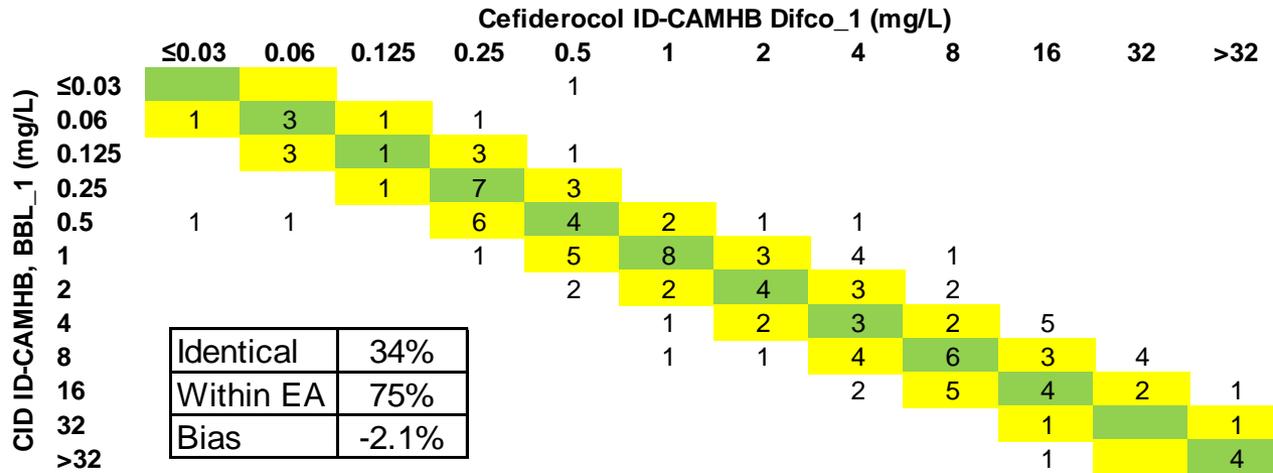


ID-CAMHB BBL from two tests



Reproducibility of reference method

ID-CAMHB BBL vs ID-CAMHB Difco



Comparative data

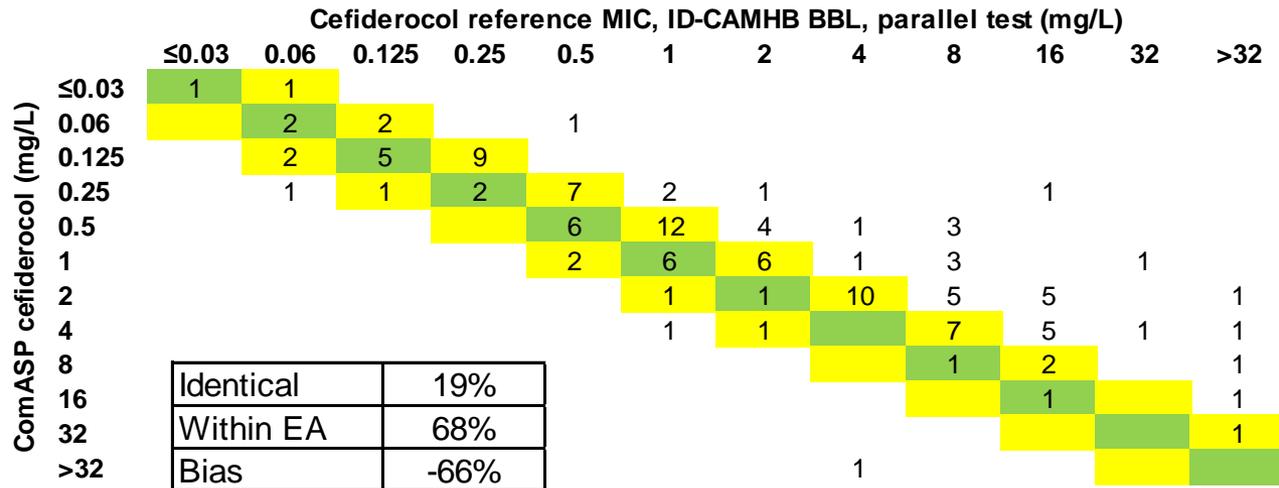
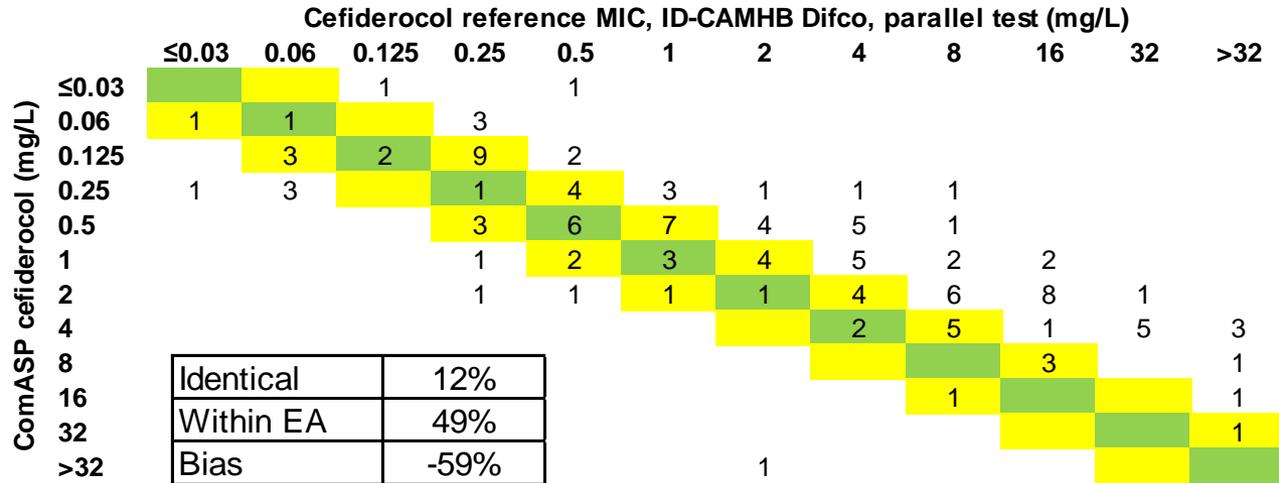
Difco vs Difco

Identical	62%
Within EA	97%
Bias	3.0%

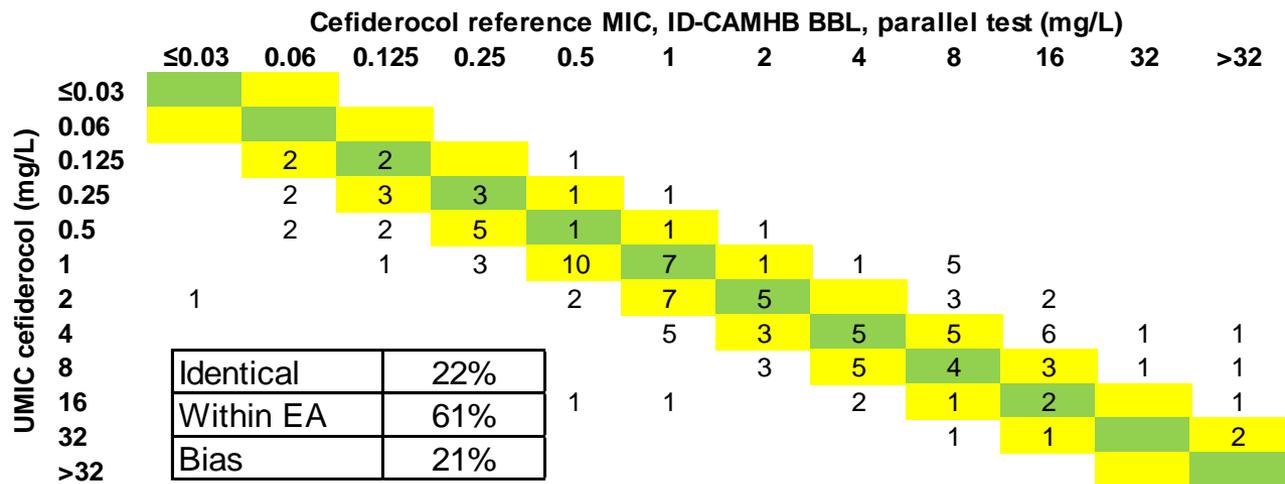
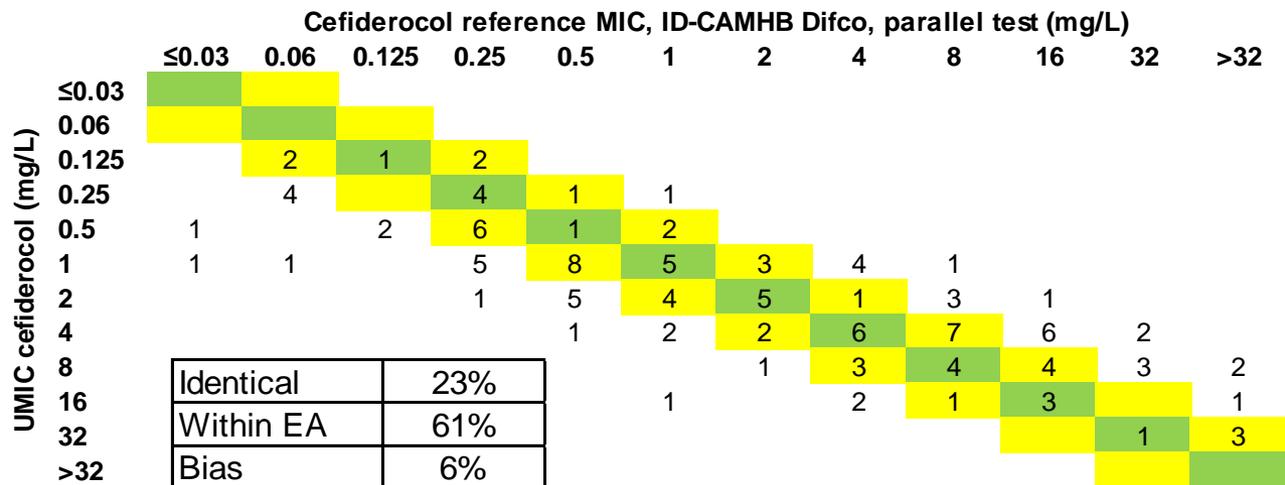
BBL vs BBL

Identical	65%
Within EA	95%
Bias	-12.0%

Commercial method: ComASP



Commercial method: UMIC



Conclusions and further work

- Cefiderocol MIC determination is difficult!
- The MIC reference method must be further evaluated
 - Including evaluation of different reading instructions
- Data for commercial products will be further evaluated
 - Evaluation of Thermo Fisher panels if/when available
- ATUs in disk diffusion to be reviewed by EUCAST
- EUCAST warning to be updated

