



News from EUCAST and EDL

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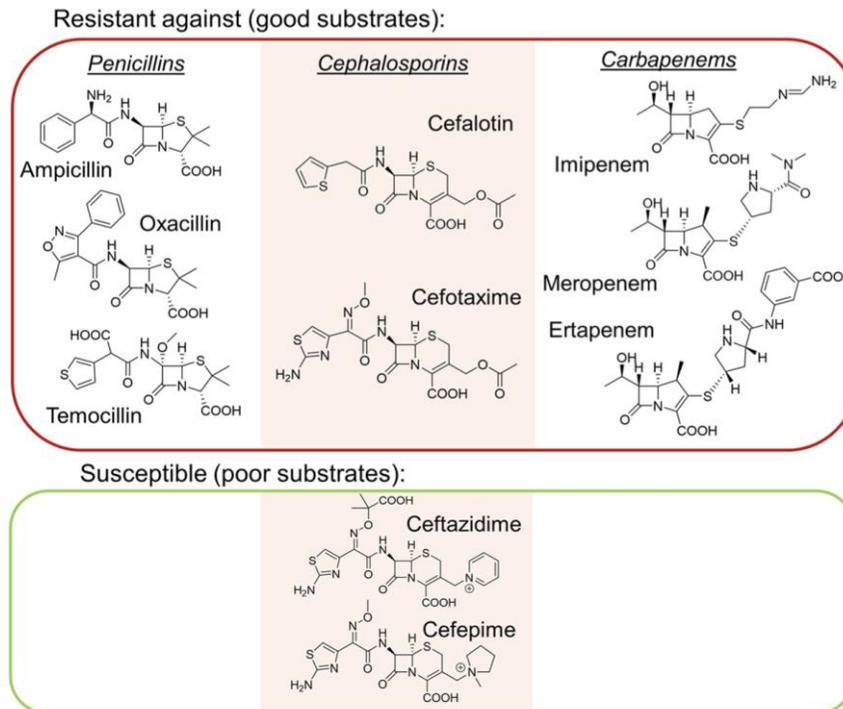
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News from EUCAST

Cefepime-enmetazobactam (Allecra)

- Phase 3 study
 - 2+0.5 g x 3 vs pip-tazo 4.5 g x 3 in cUTI
- Stable against ESBL, AmpC



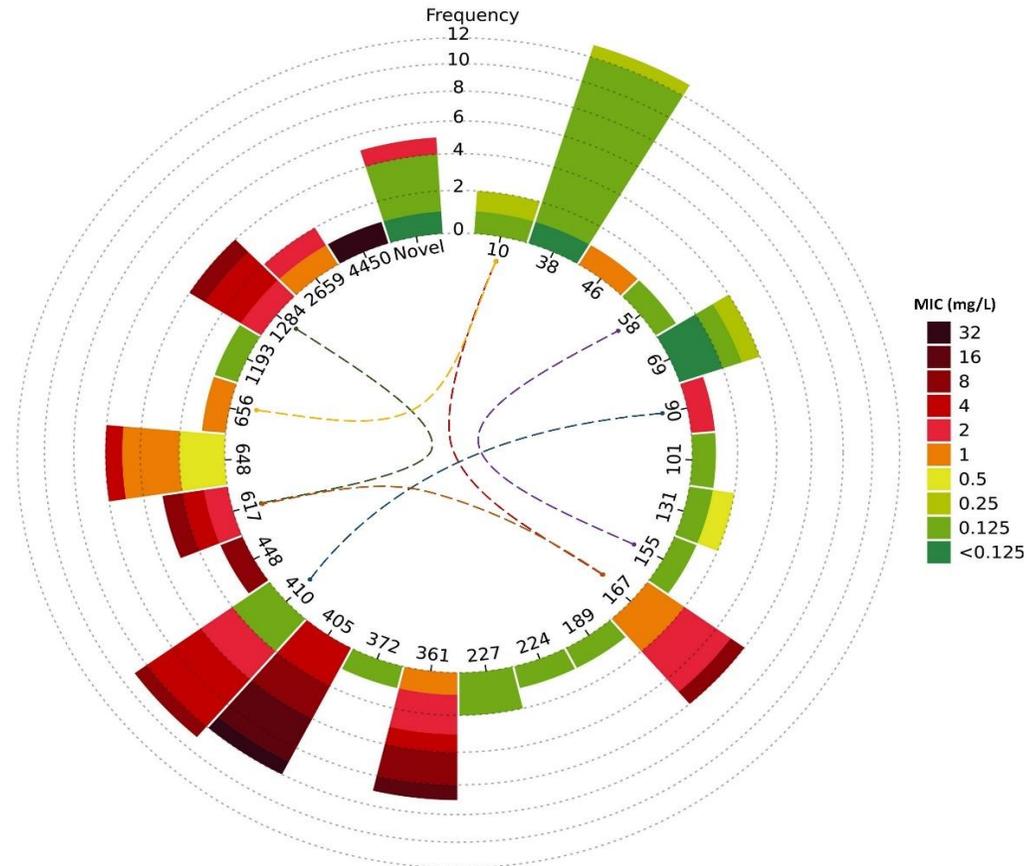
Stability vs OXA-48

Enmetazobactam does not inhibit, but cefepime is poorly hydrolysed

Hirvonen VHA. AAC 2021

Aztreonam-avibactam (Pfizer)

- ASSEMBLE: ATM-AVI vs best available therapy for treatment cIAI, HAP/VAP, cUTI, BSI caused by MBL-producing Gram-negatives
 - 15 patients included
 - 5/12 cure ATM-AVI (vs 0/3)
- REVIST: ATM-AVI +/- MZL vs MER +/- COL for treatment of cIAI, HAP/VAP caused by Gram-negatives (including MBL)
 - All-cause mortality 10.8 % vs 19.4% (422 pts in total)
- Dosing: 1.5+0.5 g x 4



102 clinical isolates of CP *E. coli* (unpubl.)
MIC>4 mg/L occurred among NDM-producers

New breakpoints

- *Enterobacterales*
 - Aztreonam-avibactam: S \leq 4 mg/L, R $>$ 4 mg/L
 - Cefepime-enmetazobactam: S \leq 4 mg/L, R $>$ 4 mg/L
- *P. aeruginosa*
 - Aztreonam-avibactam: IE (ECOFF is 16 mg/L....)
 - Cefepime-enmetazobactam: IE (inhibitor does not add clinical benefit)
- *Acinetobacter*
 - Both lack clinically useful activity
- *S. maltophilia*
 - Aztreonam-avibactam: IE (ECOFF 8 mg/L)
 - Cefepime-enmetazobactam: inhibitor does not add clinical benefit
- Disk breakpoints are available

Endocarditis breakpoints

EUCAST guidance document on Infective Endocarditis:

Reporting of antimicrobial susceptibility testing results

December 2024

- Because of reduced antimicrobial penetration into vegetations, the dosages used in endocarditis are higher than the EUCAST standard and high dosages, and no I-breakpoints
- Endocarditis-breakpoints are based on epidemiological cut-off values (ECOFFs)
- Only when endocarditis breakpoints differ from the breakpoint for other indications, are they included in the breakpoint table as an additional line
- Clinical guidance on treatment, including recommended dosing regimens, is provided in the ESC guidelines or national guidelines
- There are no situations where MIC-testing is needed (exception vancomycin)
- Moxifloxacin has been dealt with and there is new guidance on the previous I-group for benzylpenicillin vs viridans streptococci (now low-level resistance)

Challenging infection sites and special situations

Information on EUCAST breakpoints and dosing for challenging infection sites and on special situations for antimicrobial treatment

EUCAST breakpoints are based on standard and, if applicable, high exposure to antimicrobial agents. The dosing regimens are either those listed in the Summary of Product Characteristics approved by EMA (European Medicines Agency) or, especially with older agents, doses that are commonly administered in European countries. For some more common infections or when the usual severity of the infection requires special attention, EUCAST has produced additional dosing guidance (e.g. urinary tract infections) and/or breakpoints (e.g. meningitis).

There are other sites and infections where the antibiotic exposure of the organism may be impaired and where therapy may require higher dosing or a change in the mode of administration to ensure the desired exposure. Such situations include, but are not limited to, endocarditis, bone and joint infections, and abscesses in the central nervous system.

Since EUCAST is a breakpoint committee it will not give dosing or other treatment recommendations for such conditions, but will list specific breakpoints for challenging infections when applicable. Refer to textbooks or national/international treatment guidelines for more information on dosing regimens in challenging infections.

In addition to these clinical situations, rare resistance mechanisms may require tailored or unusual therapeutic approaches and often these therapies are still discussed in the community. Examples include borderline resistant *S. aureus* (BORSA), vancomycin-variable enterococci and *A. baumannii* producing KPC. For such isolates, EUCAST currently does not give specific recommendations, neither for testing nor for selection of the appropriate antimicrobial agent.

The EUCAST tables cannot be used as a treatment guideline

Cefiderocol and non-fermenters

Cephalosporins	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes
	S ≤	R >	ATU		S ≥	R <	ATU	
Ceftazidime	-	-			-	-		1. Broth microdilution MIC determination must be performed in iron-depleted Mueller-Hinton broth and specific reading instructions must be followed. For testing conditions and reading instructions, see https://www.eucast.org/eucastguidancedocuments/ . 2/A. The <i>in vitro</i> activity of cefiderocol against <i>Stenotrophomonas maltophilia</i> is comparable to the activity of the agent against <i>Enterobacterales</i> and there is also animal data to suggest efficacy. However, there is insufficient clinical data to determine a clinical breakpoint. Isolates with MIC values ≤0.5 mg/L (zone diameter ≥28 mm) are mostly devoid of resistance mechanisms. Isolates with MICs 1-2 mg/L have acquired resistance mechanisms which may result in impaired clinical response. Isolates with MIC values >2 mg/L (zone diameter <22 mm) will likely be resistant.
Cefepime	-	-			-	-		
Cefiderocol ¹	Note ²	Note ²		30	Note ^A	Note ^A		

Cephalosporins	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes
	S ≤	R >	ATU		S ≥	R <	ATU	
Cefaclor	-	-			-	-		1. Broth microdilution MIC determination must be performed in iron-depleted Mueller-Hinton broth and specific reading instructions must be followed. For testing conditions and reading instructions, see https://www.eucast.org/eucastguidancedocuments/ . 2/A. The <i>in vitro</i> activity of cefiderocol against <i>Acinetobacter</i> spp. is comparable to the activity of the agent against <i>Enterobacterales</i> and there is also animal data to suggest efficacy. However, there is insufficient clinical data to determine a clinical breakpoint. Isolates with MIC values ≤0.5 mg/L (zone diameter ≥21 mm) are mostly devoid of resistance mechanisms. Isolates with MICs 1-2 mg/L have acquired resistance mechanisms which may result in impaired clinical response. Isolates with MIC values >2 mg/L (zone diameter <17 mm) will likely be resistant.
Cefadroxil	-	-			-	-		
Cefalexin	-	-			-	-		
Cefazolin	-	-			-	-		
Cefepime	-	-			-	-		
Cefepime-enmetazobactam	-	-			-	-		
Cefiderocol ¹	Note ²	Note ²		30	Note ^A	Note ^A		

Cephalosporins	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)			Notes
	S ≤	R >	ATU		S ≥	R <	ATU	
Cefiderocol ¹	Note ²	Note ²		30	Note ^A	Note ^A		1. Broth microdilution MIC determination must be performed in iron-depleted Mueller-Hinton broth and specific reading instructions must be followed. For testing conditions and reading instructions, see https://www.eucast.org/eucastguidancedocuments/ . 2/A. The <i>in vitro</i> activity of cefiderocol against <i>Achromobacter xylosoxidans</i> is comparable to the activity of the agent against <i>Enterobacterales</i> and there is also animal data to suggest efficacy. However, there is insufficient clinical data to determine a clinical breakpoint. Isolates with MIC values ≤0.5 mg/L (zone diameter ≥26 mm) are mostly devoid of resistance mechanisms. Isolates with MICs 1-2 mg/L have acquired resistance mechanisms which may result in impaired clinical response. Isolates with MIC values >2 mg/L (zone diameter <22 mm) will likely be resistant.

S. aureus and cephalosporins

MIC distributions for *Staphylococcus aureus*

AGENT	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	Distributions	(T)ECOFF
Cefazolin	0	0	0	0	0	18	359	3277	7870	4718	878	250	181	157	1343	0	0	0	201	5	2
Cefepime	0	0	1	12	10	4	8	34	180	548	2043	854	98	33	13	64	8	12	0	38	8
Cefotaxime	0	0	2	0	1	3	18	103	383	2174	2383	400	92	25	242	10	6	15	0	41	4
Ceftriaxone	0	0	0	0	0	0	0	0	0	4	119	211	8	9	1	3	1	1	0	3	(8)
Cefuroxime	0	0	0	2	3	2	55	363	1265	7230	1429	234	124	890	247	1	0	8	0	8	4

Cefotaxime [ECOFF = 4]

Healthy volunteers. PB(%): 36.6 ± 5.9; Vd (L): 16.6 ± 8.1; t_{1/2β} (h): 1.1 ± 0.4 [Appendix-3,Appendix-13]

f%T>MIC 25%					f%T>MIC 30%					f%T>MIC 35%				
Regimen					Regimen					Regimen				
0.25	0.5	1	2	4	0.25	0.5	1	2	4	0.25	0.5	1	2	4
1 g x 3	2 g x 3	1 g x 4	2 g x 4		1 g x 3	2 g x 3	1 g x 4	2 g x 4		1 g x 3	2 g x 3	1 g x 4	2 g x 4	
98	99	99	99		98	98	99	99		97	98	98	99	
98	98	99	99		97	98	98	99		95	97	98	98	
97	98	98	99		95	97	97	98		92	95	96	97	
94	97	97	98		91	95	96	98		86	92	94	96	
88	94	94	97		80	91	91	95		71	86	86	93	
65	88	82	94		51	80	73	91		38	71	62	86	
25	65	42	82		17	51	31	72		12	38	22	62	

The EUCAST recommendation is that for MSSA, susceptibility can be inferred for the following parenteral agents:

- Cefazolin, provided a dosage of 2 g x 3
- Cefuroxime iv, provided a dosage of 1.5 g x 3
- Cefotaxime, provided dosages of 2 g x 3-4
- Ceftriaxone, provided dosages of 2 g x 2 iv or 4 g x 1 iv are used, and preferably only as follow-on therapy after initial response to other more established agents
- Cefepime, provided a dosage of 2 g x 3

Other work in progress

- Detection of resistance mechanisms
 - Warning comment related to detection of carbapenemases – clinical response may be impaired and carbapenems should normally be avoided since better treatment options occur
- Revision of carbapenem breakpoints
 - Potential for reducing the MIC-breakpoints one dilution step, which would be favourable for PK-PD
 - Carbapenems are often used in critically ill patients, where the T>MIC should be far more than 40-50%
- Revision of trimethoprim and trimethoprim-sulfa breakpoints
 - Making the breakpoints ECOFF-based
 - Removing I-groups, as there is no evidence supporting them
- Fluoroquinolone breakpoints
 - Bringing MIC-breakpoints downwards for systemic infections
 - Bringing MIC-breakpoints upwards for UTI
 - Avoiding thus one breakpoint trying to fit both, but in fact fitting neither, and causing testing issues

News from EDL

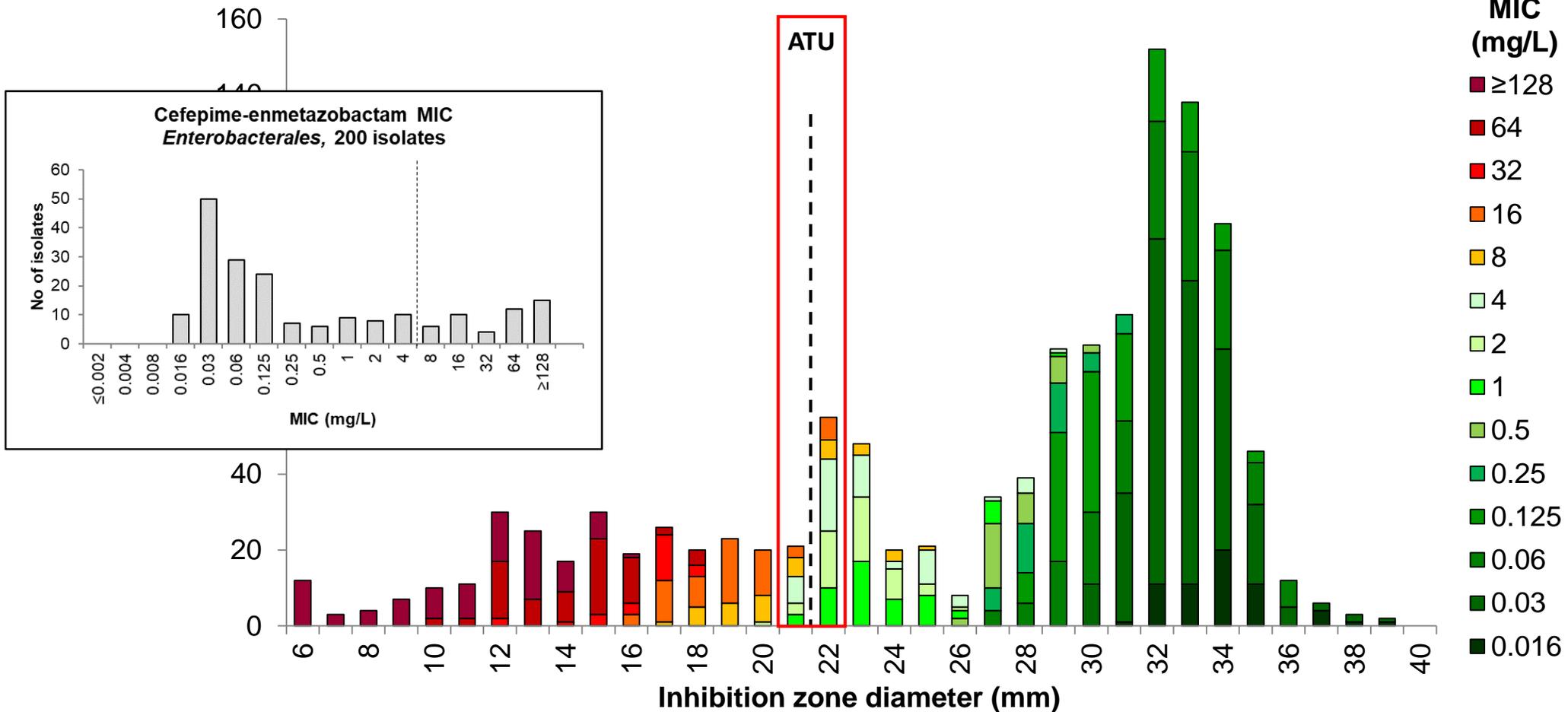
Cefepime-enmetazobactam

Clinical MIC and zone diameter breakpoints

Organism	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
<i>Enterobacterales</i>	4	4		30-20	22	22	21-22
<i>Pseudomonas</i> spp.	Note	Note			Note	Note	

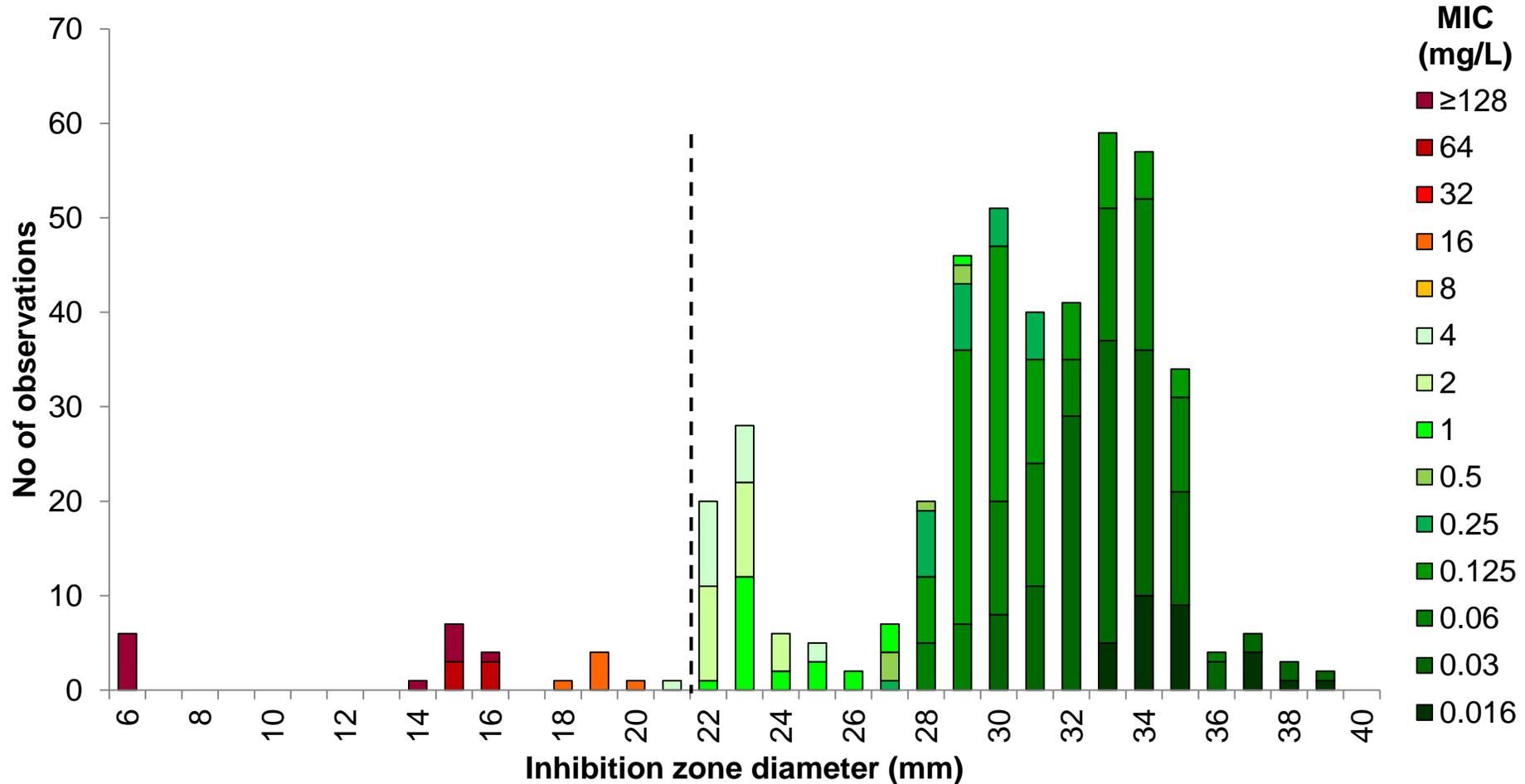
- For MIC determination, the concentration of enmetazobactam is fixed at 8 mg/L.
- For *Pseudomonas* spp., the addition of a beta-lactamase inhibitor does not add clinical benefit.

Cefepime-enmetazobactam 30-20 µg vs. MIC *Enterobacterales*, 200 isolates (1197 correlates)



Breakpoints	ATU
MIC	S≤4, R>4 mg/L
Zone diameter	S≥22, R<22 mm

Cefepime-enmetazobactam 30-20 µg vs. MIC *E. coli*, 75 isolates (456 correlates)



Breakpoints		ATU
MIC	S ≤ 4, R > 4 mg/L	
Zone diameter	S ≥ 22, R < 22 mm	21-22 mm

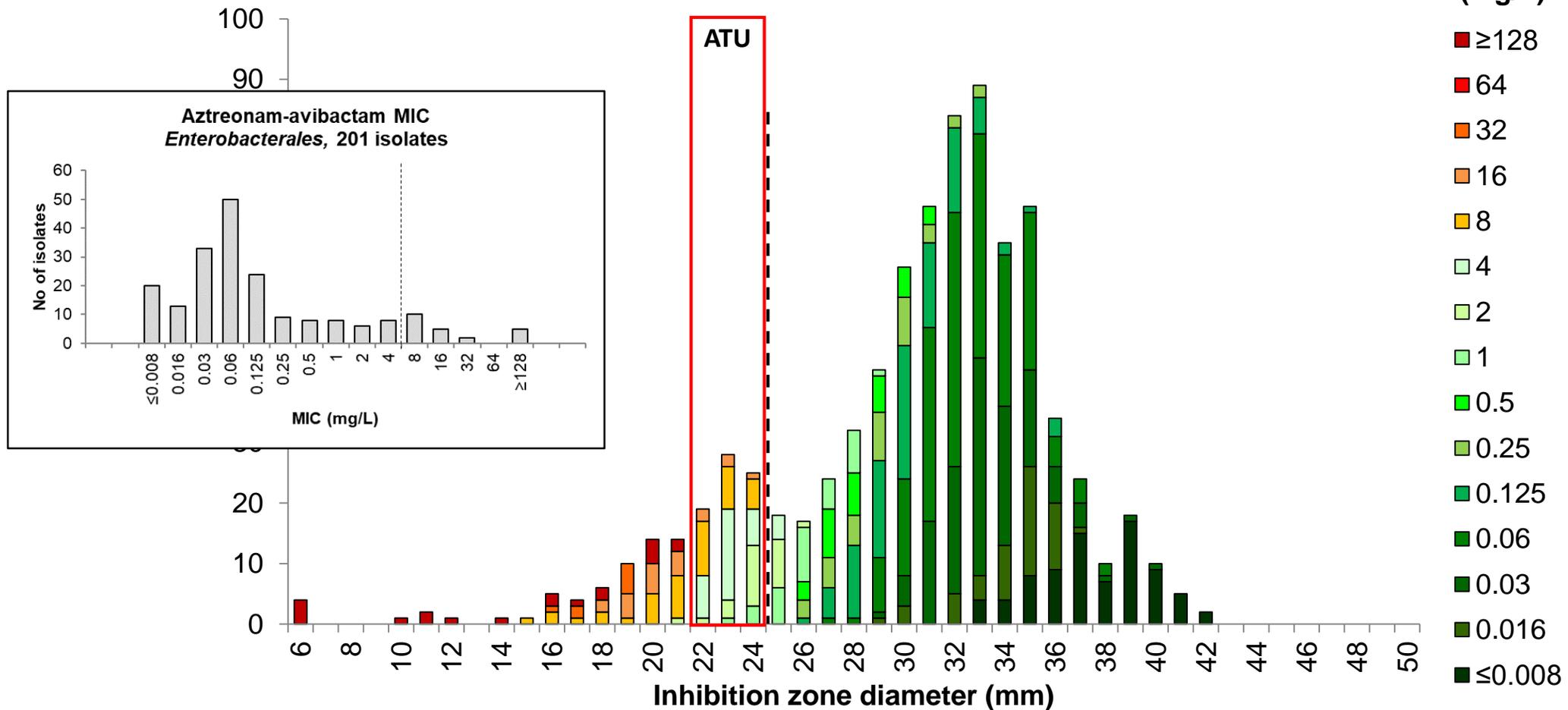
Aztreonam-avibactam

Clinical MIC and zone diameter breakpoints

Organism	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
<i>Enterobacterales</i>	4	4		30-20	25	25	22-24
<i>Pseudomonas</i> spp.	IE	IE			IE	IE	

- For MIC determination, the concentration of avibactam is fixed at 4 mg/L.
- IE = Insufficient Evidence

Aztreonam-avibactam 30-20 µg vs. MIC *Enterobacterales*, 201 isolates (804 correlates)



Breakpoints	ATU
MIC	S≤4, R>4 mg/L
Zone diameter	S≥25, R<25 mm
	22-24 mm

Quality Control criteria

β-lactam-inhibitor combinations must be tested both with a susceptible QC strain and a β-lactamase-producing QC strain!

Cefepime-enmetazobactam

QC strain	MIC (mg/L)		Disk content (µg)	Inhibition zone diameter	
	Target	Range		Target	Range
<i>Escherichia coli</i> ATCC 25922	0.06	0.03-0.125	30-20	35	32-38
<i>Escherichia coli</i> NCTC 13353 ¹	0.06	0.03-0.125	30-20	30	27-33

¹ CTX-M-15 and OXA-1 producing strain to control the inhibitor component.

Aztreonam-avibactam

QC strain	MIC (mg/L)		Disk content (µg)	Inhibition zone diameter	
	Target	Range		Target	Range
<i>Escherichia coli</i> ATCC 25922	0.06	0.03-0.125	30-20	35	32-38
<i>Klebsiella pneumoniae</i> ATCC 700603 ¹	0.125-0.25	0.06-0.5	30-20	29	26-32

¹ SHV-18 ESBL producing strain to control the inhibitor component.

Breakpoints for *Enterococcus* spp.

- Breakpoints valid for all species of enterococci but originally based mainly on data for *E. faecalis* och *E. faecium*.
- Now validated for 8 additional species:
 - *E. avium*
 - *E. casseliflavus*
 - *E. durans*
 - *E. gallinarum*
 - *E. hirae*
 - *E. lactis*
 - *E. raffinosus*
 - *E. mundtii*

Breakpoints for *Enterococcus* spp.

- **Ampicillin/Amoxicillin:**

- I category removed.
- New breakpoints: 4/4 mg/L.
- For *E. faecalis* that test resistant to ampicillin with disk diffusion, confirm with an MIC test.

- **Piperacillin-tazobactam, imipenem and nitrofurantoin (uncomplicated UTI):**

- Breakpoints valid for *E. faecalis* only.

Enterococci Screening disks

- **Fluoroquinolone resistance:**
 - Norfloxacin 10 µg can be used for all species.
 - Susceptibility to ciprofloxacin and levofloxacin (uncomplicated UTI) can be inferred from the norfloxacin disk.
 - Screening breakpoint: 12/12 mm.
- **High-level aminoglycoside resistance (presence of aminoglycoside-modifying enzymes):**
 - Gentamicin 30 µg can be used for all species.
 - HLAR: GEN zone <8 mm or MIC >128 mg/L.

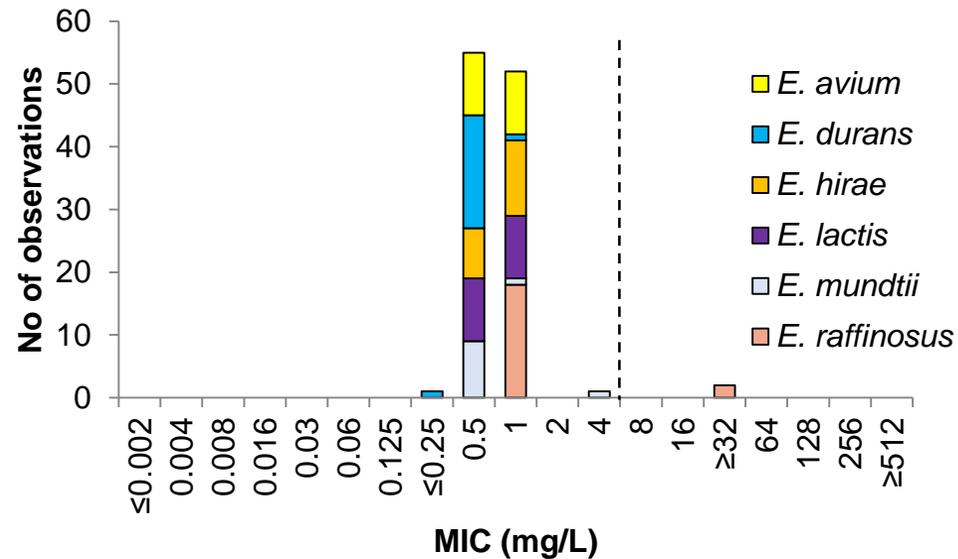
Enterococci and Vancomycin

- No breakpoints for *E. casseliflavus* and *E. gallinarum*.
- Examine the zone edge (sharp or fuzzy) only for *E. faecalis* and *E. faecium*!
- For other species, interpret according to separate breakpoints without examining the zone edge.

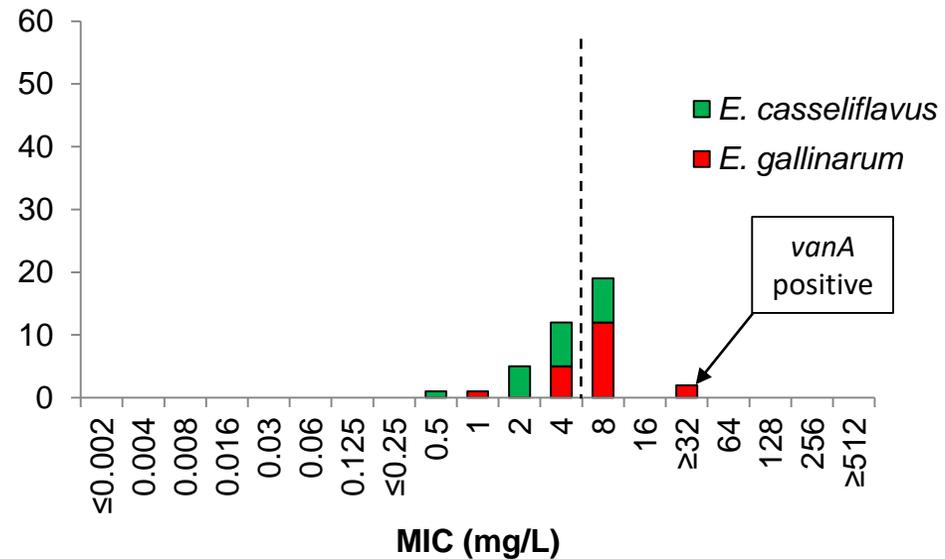
Glycopeptides	MIC breakpoints		Disk content (µg)	Zone diameter	
	S ≤	R >		S ≥	R <
Vancomycin, <i>E. faecalis</i> and <i>E. faecium</i>	4	4	5	12	12
Vancomycin, <i>E. casseliflavus</i> and <i>E. gallinarum</i>	-	-		-	-
Vancomycin, other enterococci	4	4	5	15	15

Enterococci and Vancomycin

Enterococci other than *E. casseliflavus* and *E. gallinarum*



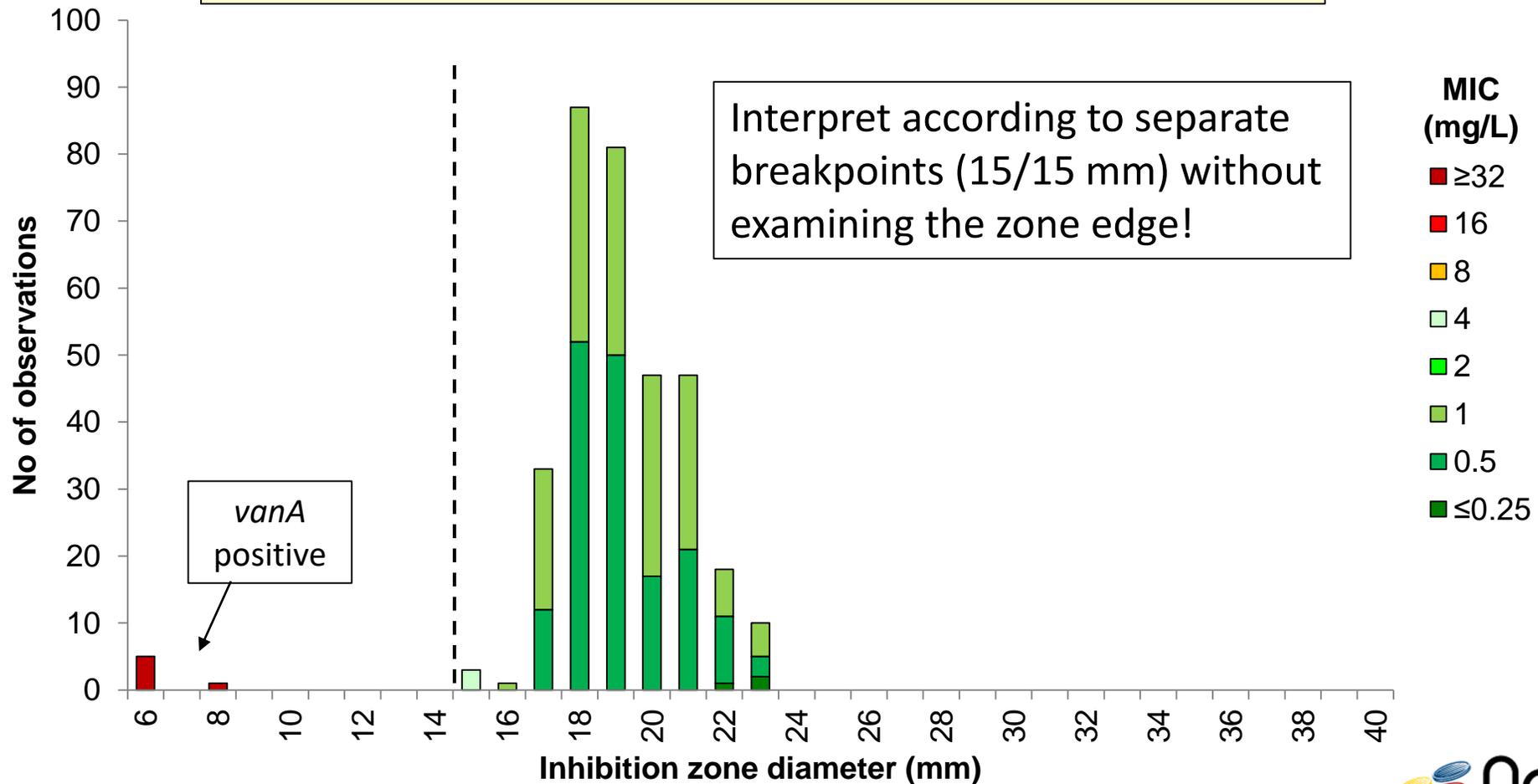
E. casseliflavus and *E. gallinarum*



E. casseliflavus and *E. gallinarum* is the expected phenotype due to the presence of the *vanC* gene → Low level resistance.

Enterococci and Vancomycin

Enterococci other than *E. faecalis* and *E. faecium*



Enterococci and Tigecycline

Breakpoint Table v. 14.0, 2024

Tetracyclines	MIC breakpoints		Disk content (μg)	Zone diameter	
	S \leq	R $>$		S \geq	R $<$
Tigecycline, <i>E. faecalis</i>	0.25	0.25	15	20	20
Tigecycline, <i>E. faecium</i>	0.25	0.25	15	22	22

Breakpoint Table v. 15.0, 2025

Tetracyclines	MIC breakpoints		Disk content (μg)	Zone diameter	
	S \leq	R $>$		S \geq	R $<$
Tigecycline	0.5	0.5	15	20	20

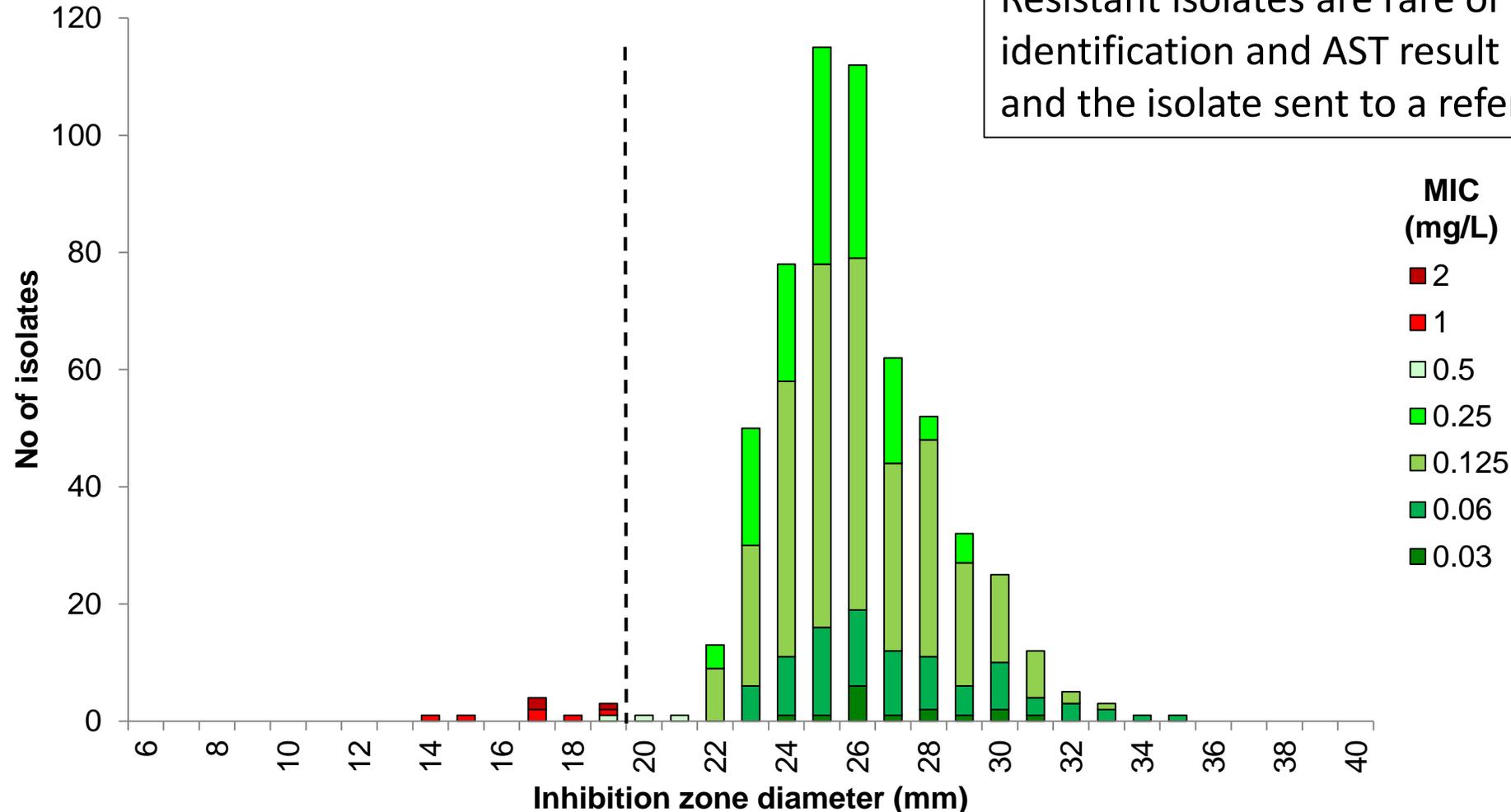
- Breakpoints common for all species of enterococci!

Enterococci and Tigecycline

Breakpoints

MIC	0.5/0.5 mg/L
Zone diameter	20/20 mm

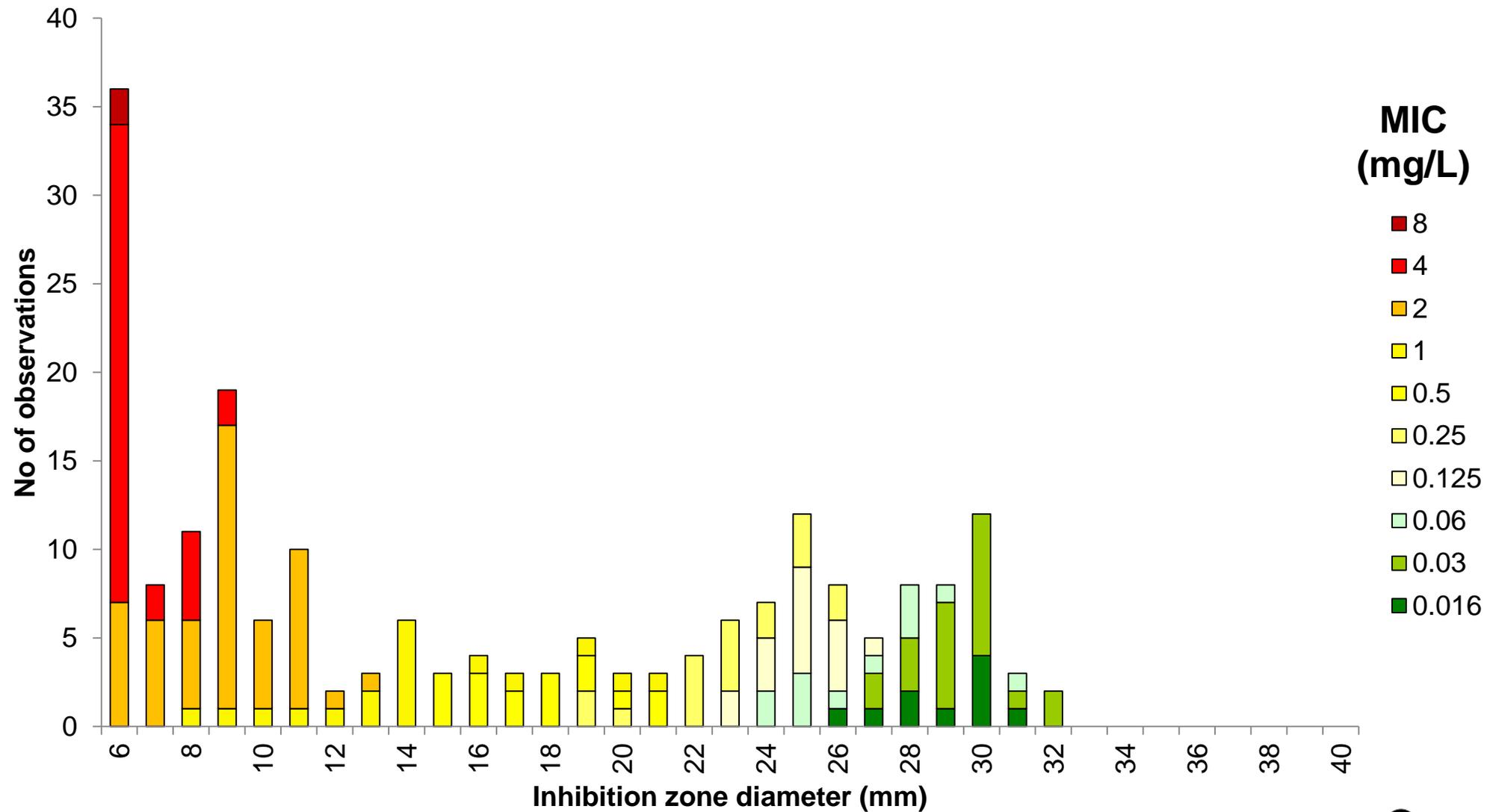
Resistant isolates are rare or not yet reported. The identification and AST result must be confirmed and the isolate sent to a reference laboratory.



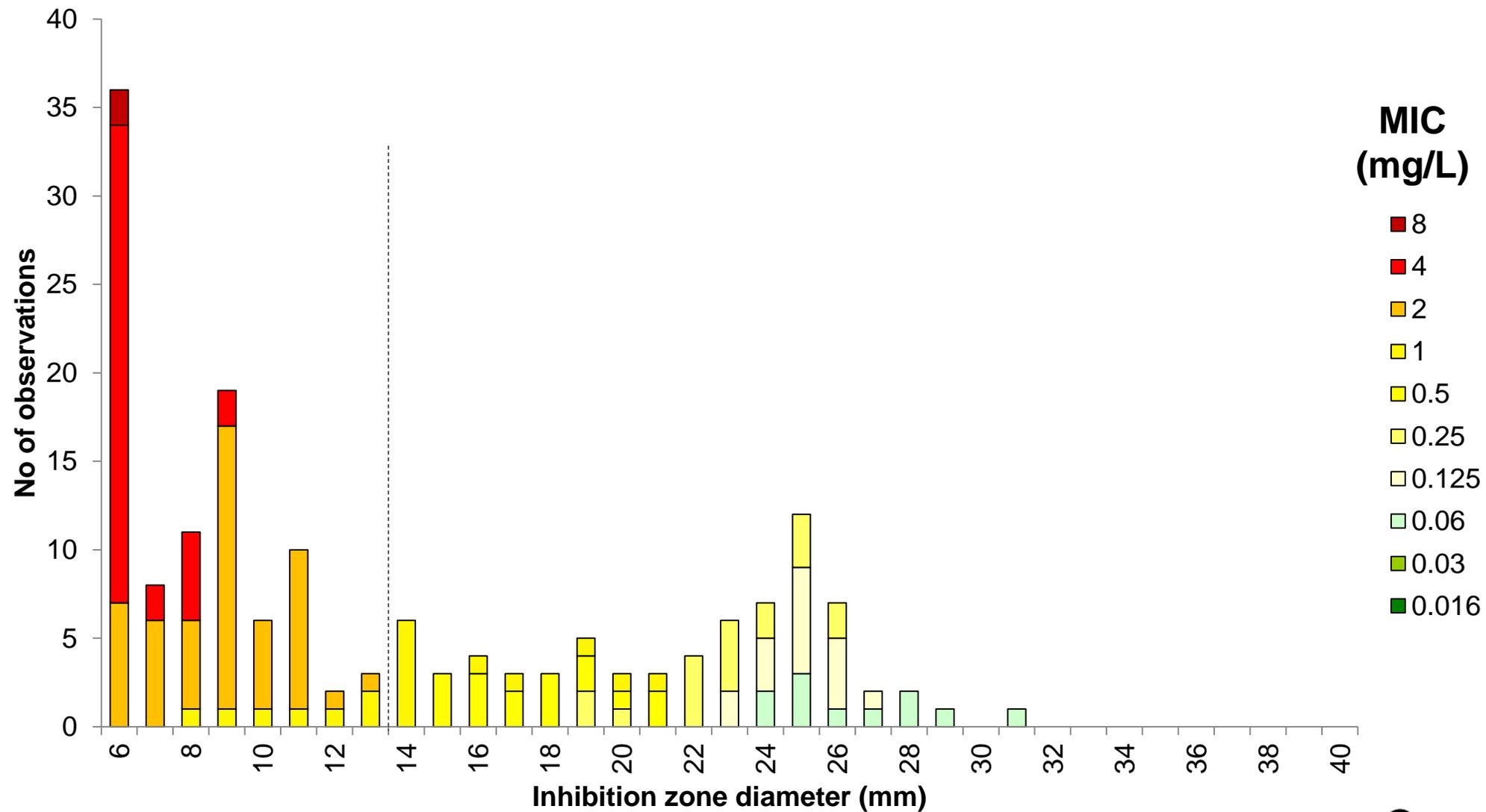
Development of a new method to categorise benzylpenicillin in *S. pneumoniae*

- 100 *S. pneumoniae* with benzylpenicillin MICs 0.016-8 mg/L.
- Broth microdilution and disk diffusion performed in parallel
 - Disk diffusion on MH-F agar from 2 manufacturers
 - Benzylpenicillin 1 unit
 - Ampicillin 2 µg
 - Piperacillin-tazobactam 30-6 µg
 - Oxacillin 1 µg
 - Cefadroxil 30 µg
 - Cefaclor 30 µg
 - Cefoxitin 30 µg
 - Ceftazidime 10 µg
 - Cefotaxime 5 µg
 - Ceftaroline 5 µg

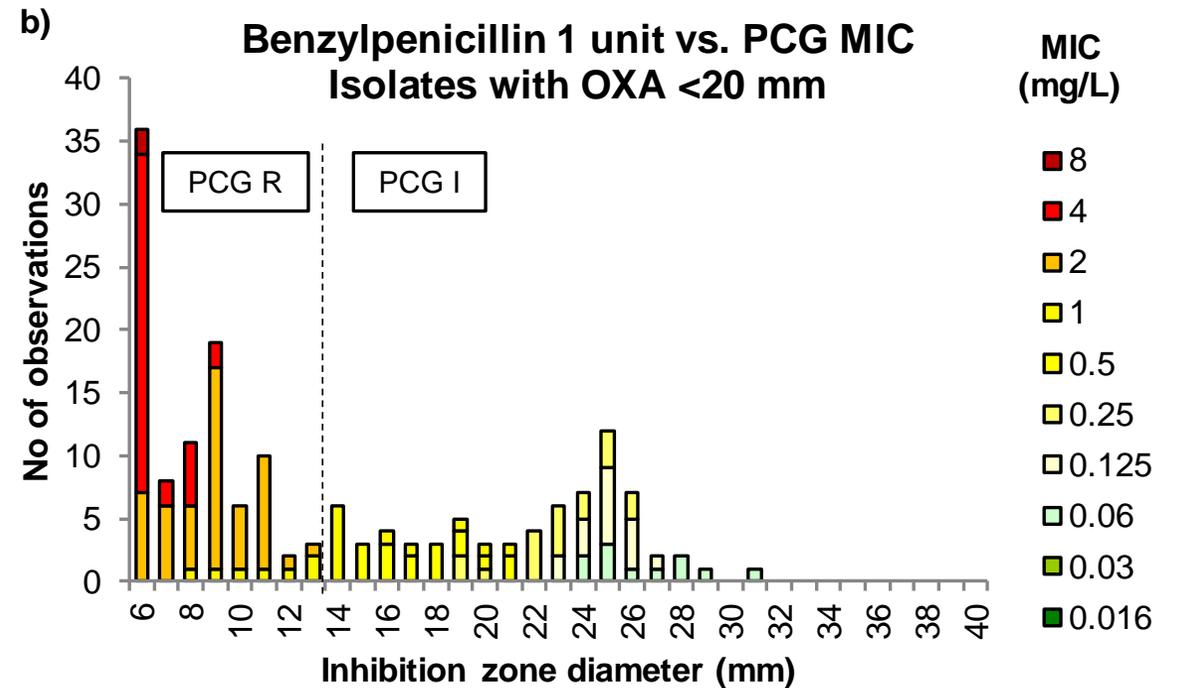
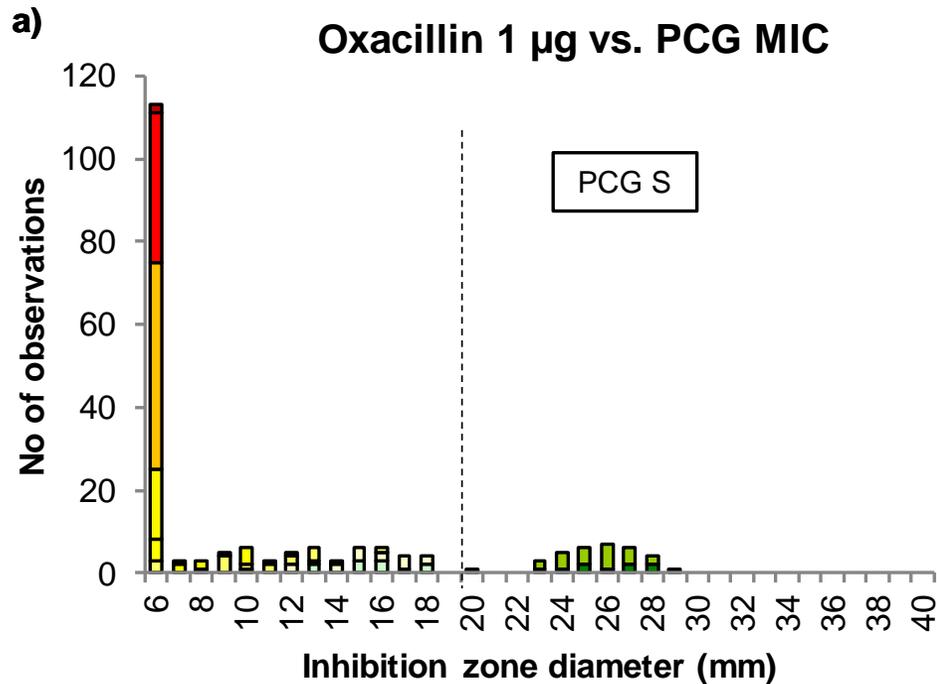
Benzylpenicillin 1 unit vs. MIC *S. pneumoniae*, 100 isolates (200 correlates)



Benzylpenicillin 1 unit vs. MIC, **OXA <20 mm** *S. pneumoniae*, 84 isolates (167 correlates)



Combined testing algorithm with oxacillin 1 µg and benzylpenicillin 1 unit



***Streptococcus pneumoniae*: Flow chart based on screen tests for beta-lactam resistance mechanisms**

Following the flow chart avoids delays in reporting benzylpenicillin susceptibility in *S. pneumoniae*.
Include both the oxacillin (1 µg) and the benzylpenicillin (1 unit) disks already from the beginning.
Read and interpret the benzylpenicillin disk **only** for isolates with oxacillin zones <20 mm.

**Oxacillin 1 µg zone diameter ≥20 mm
(or benzylpenicillin MIC ≤0.06 mg/L)**

Mechanism: excludes all beta-lactam resistance mechanisms

Report susceptible (**S**) to beta-lactam agents for which clinical breakpoints are available, including those with “Note”.

Exception: Cefaclor is reported “susceptible, increased exposure” (**I**).

No further testing required.

**Oxacillin 1 µg zone diameter <20 mm
(or benzylpenicillin MIC >0.06 mg/L)**

Mechanism: beta-lactam resistance detected

Report resistant (**R**) to benzylpenicillin in endocarditis and meningitis and to phenoxymethylpenicillin (all indications).

For benzylpenicillin in indications other than endocarditis and meningitis,
read and interpret the benzylpenicillin disk:
If zone ≥14 mm, report benzylpenicillin “susceptible, increased exposure” (**I**),
If zone <14 mm, report benzylpenicillin resistant (**R**).

For other beta-lactam agents, see below.

Oxacillin 1 µg zone diameter 9-19 mm

Report susceptible (**S**) without further testing to: ampicillin, amoxicillin and piperacillin (without and with beta-lactamase inhibitor), cefepime, cefotaxime, ceftaroline, ceftobiprole, ceftriaxone, imipenem and meropenem. For beta-lactam agents not listed, perform susceptibility test and interpret according to breakpoints.

Oxacillin 1 µg zone diameter <9 mm

For beta-lactam agents other than benzylpenicillin, perform susceptibility testing and interpret according to breakpoints.

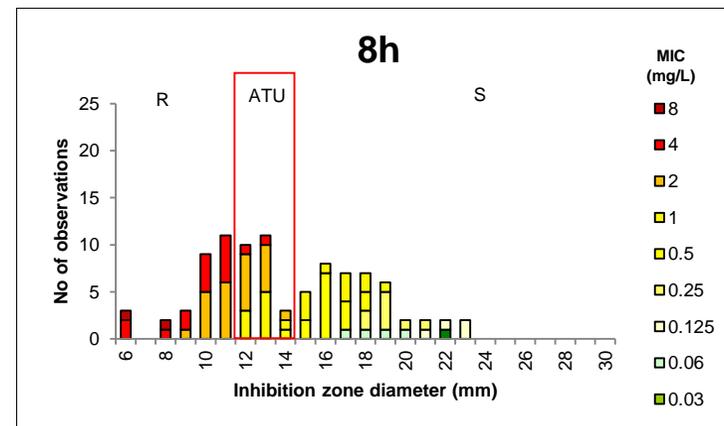
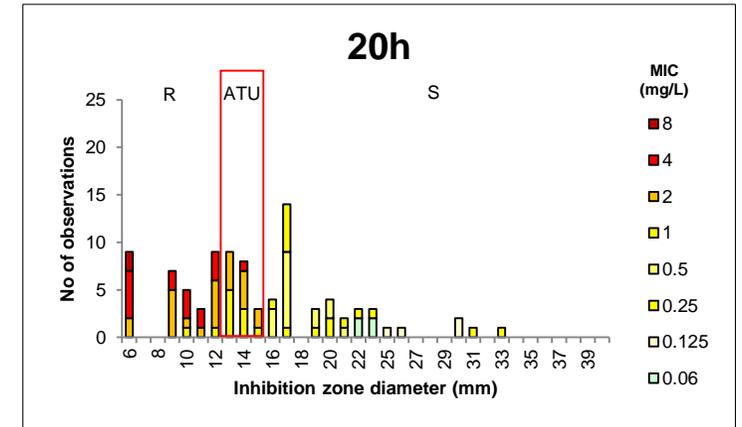
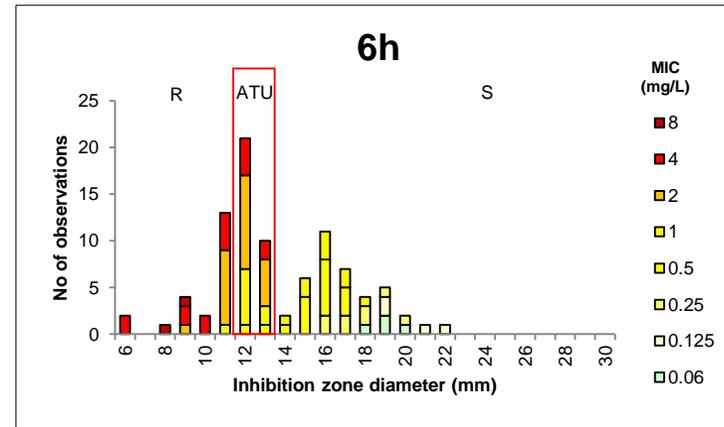
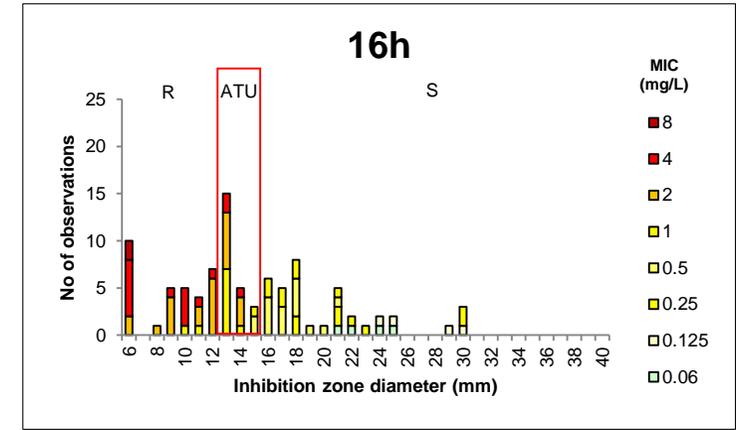
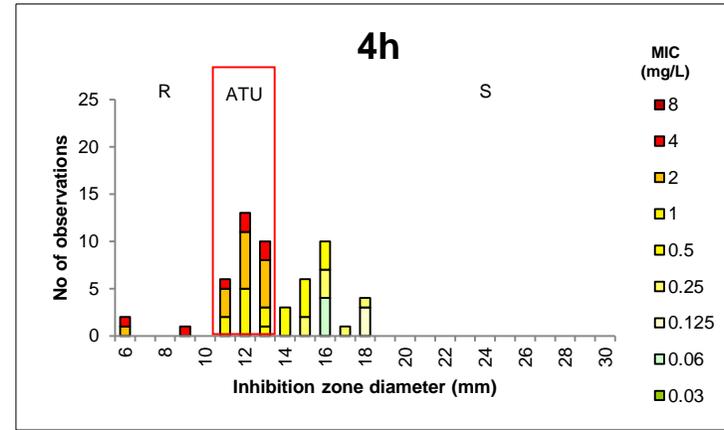
S. pneumoniae and benzylpenicillin with RAST

RAST Breakpoint Tables v. 8.0, 2025

In oxacillin screen positive isolates and for indications other than meningitis and endocarditis, read the benzylpenicillin 1 unit disk and interpret according to the table below.

Antimicrobial agent	Disk content	4 hours			6 hours			8 hours			16-20 hours		
		S ≥	ATU	R <	S ≥	ATU	R <	S ≥	ATU	R <	S ≥	ATU	R <
Benzypenicillin (indications other than meningitis and endocarditis)	1 unit	14	11-13	11	14	12-13	12	15	12-14	12	16	13-15	13

***S. pneumoniae* and PCG
RAST vs. reference BMD
Oxacillin screen positive
isolates (resistant or
within ATU)**



Recommendations on dalbavancin in staphylococci

- Previous recommendation to infer dalbavancin from vancomycin (*S. aureus*) or vancomycin + teicoplanin (CoNS) removed in Breakpoint Tables v. 15.0.
- Reports on dalbavancin resistance in vancomycin-susceptible staphylococci.
- Glycopeptide MICs are method dependent and should be determined by broth microdilution (ISO standard 20776-1).
 - Warning on teicoplanin Etest and CoNS from bioMerieux.
- Resistance to glycopeptides and lipoglycopeptides is rare, and it is difficult to get reliable data to recommend inference from vancomycin.

EDL data for 9 CoNS resistant to dalbavancin

Organism	Dalbavancin	Teicoplanin	Vancomycin	Category
Staphylococcus hominis	1	16	2	VAN S, TEI R
Staphylococcus epidermidis	>1	>16	2	VAN S, TEI R
Staphylococcus epidermidis	1	16	4	VAN S, TEI R
Staphylococcus epidermidis	>1	16	4	VAN S, TEI R
Staphylococcus epidermidis	1	8	8	VAN R, TEI R
Staphylococcus epidermidis	1	>16	8	VAN R, TEI R
Staphylococcus epidermidis	1	>16	8	VAN R, TEI R
Staphylococcus epidermidis	>1	>16	8	VAN R, TEI R
Staphylococcus epidermidis	>1	16	>16	VAN R, TEI R

4 of 9 dalbavancin-resistant isolates were susceptible to vancomycin.

EUCAST Breakpoint Tables v 15.0: Test dalbavancin separately (BMD)

Update on cefiderocol testing

- MIC determination of cefiderocol is difficult
 - Endpoints difficult to read for some isolates
 - Differences in results due to CAMHB brand used to produce ID-CAMHB
 - Collaboration with CLSI to better understand the difficulties
- The warning on the EUCAST website is still valid
 - Problems with accuracy of commercial MIC products
 - Disk diffusion can be trusted when mean results from ≥ 5 tests are on QC target ± 1 mm for both *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853
 - Re-evaluation of disk potency for cefiderocol (collaboration with CLSI)

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

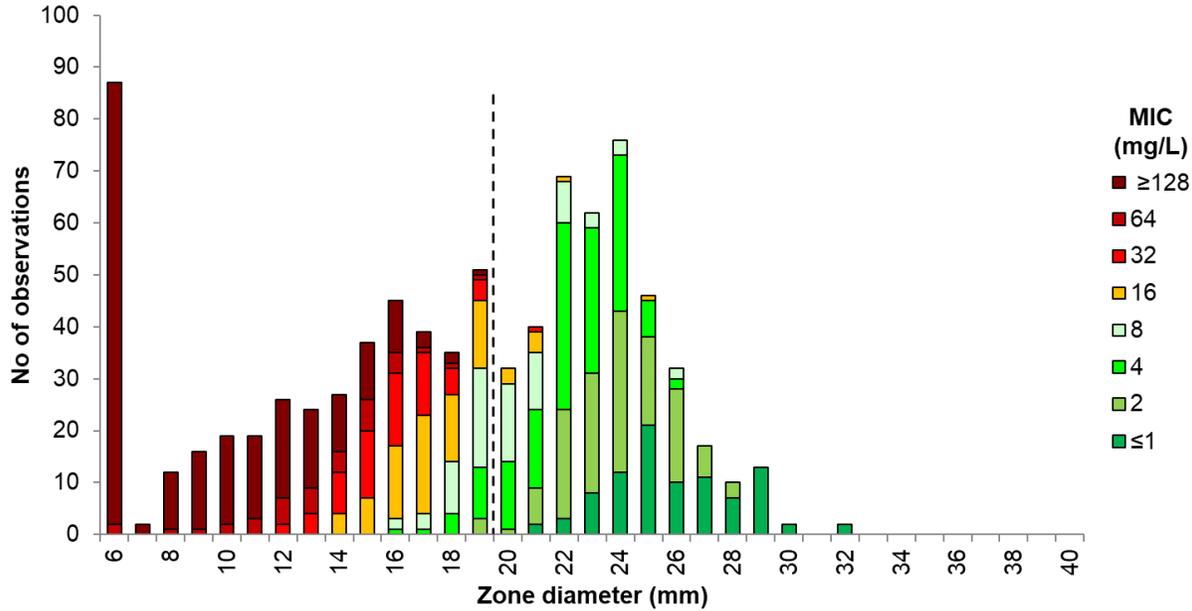
Ongoing work with CLSI

Joint working group on AST methods and QC

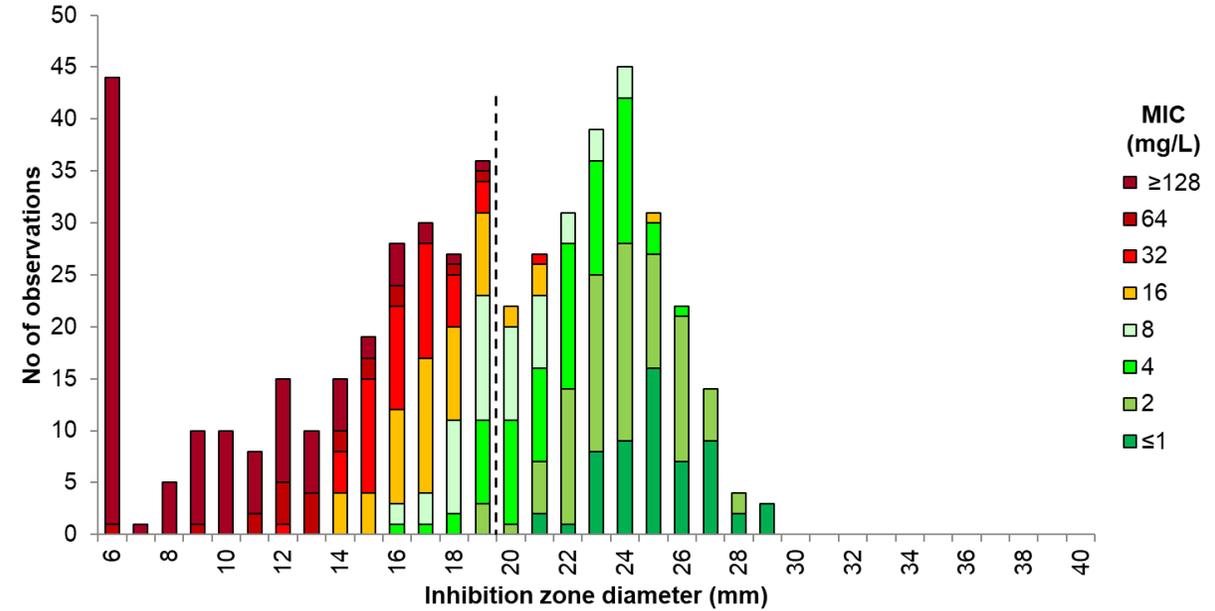
- Development of disk potencies for new antimicrobial agents
- Importance of standardisation in MIC testing
 - CLSI-EUCAST joint procedure for development of modified MIC methods
 - Avoid modifications as much as possible
 - Standardise when modifications are needed
- Re-evaluation of the disk potency for piperacillin-tazobactam with focus on *Enterobacterales* and *P. aeruginosa*

Enterobacterales and piperacillin-tazobactam

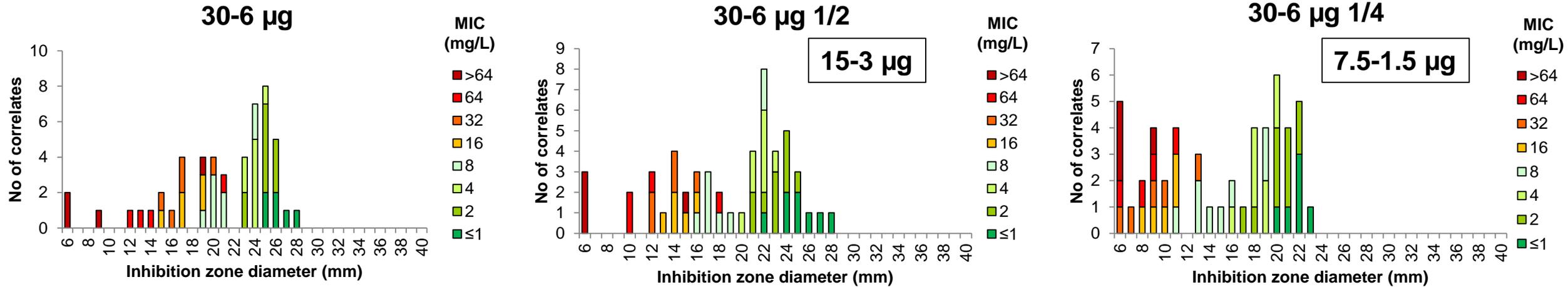
Piperacillin-tazobactam 30-6 µg vs. MIC
Enterobacterales, 531 isolates (840 correlates)



Piperacillin-tazobactam 30-6 µg vs. MIC
E. coli, 294 isolates (496 correlates)



E. coli and piperacillin-tazobactam



P. aeruginosa and piperacillin-tazobactam

