

# Can mecillinam breakpoints be established for *Enterobacterales* beyond *E. coli* and *Klebsiella*?

## The Danish Study

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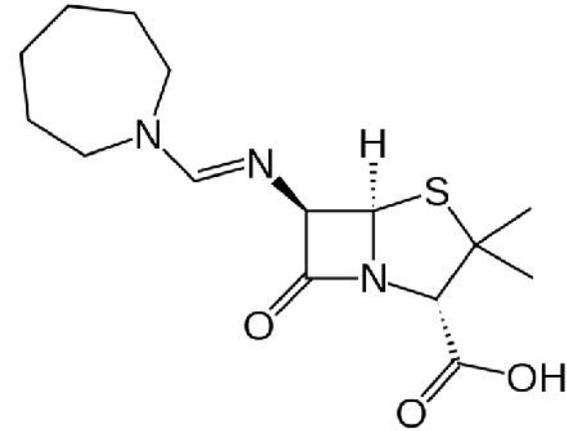
NordicAST workshop Göteborg, 8.5.2018

PRELIMINARY RESULTS

## Mecillinam (amdinocillin)

6-beta-amidinopenicillanic acid

Prodrug for oral use: pivmecillinam



developed by Leo Pharmaceutical Laboratories  
marketed in the 1970's

antibacterial activity against gram negative rods  
binds to Penicillin binding protein 2 (PBP2)

## DK: Pivmecillinam first line drug for uncomplicated UTI

### Behandling

#### Anbefalet behandling

##### Voksne

Pivmecillinam 400 mg p.o. x 3 i 3 dage

##### eller

Nitrofurantoin 50-100 mg p.o. x 4 i 3 dage

##### eller

Sulfamethizol 1 g p.o. x 2 i 3 dage.

##### Ved allergi over for ovennævnte stoffer

##### Voksne

Trimethoprim 200 mg p.o. x 2 i 3 dage.

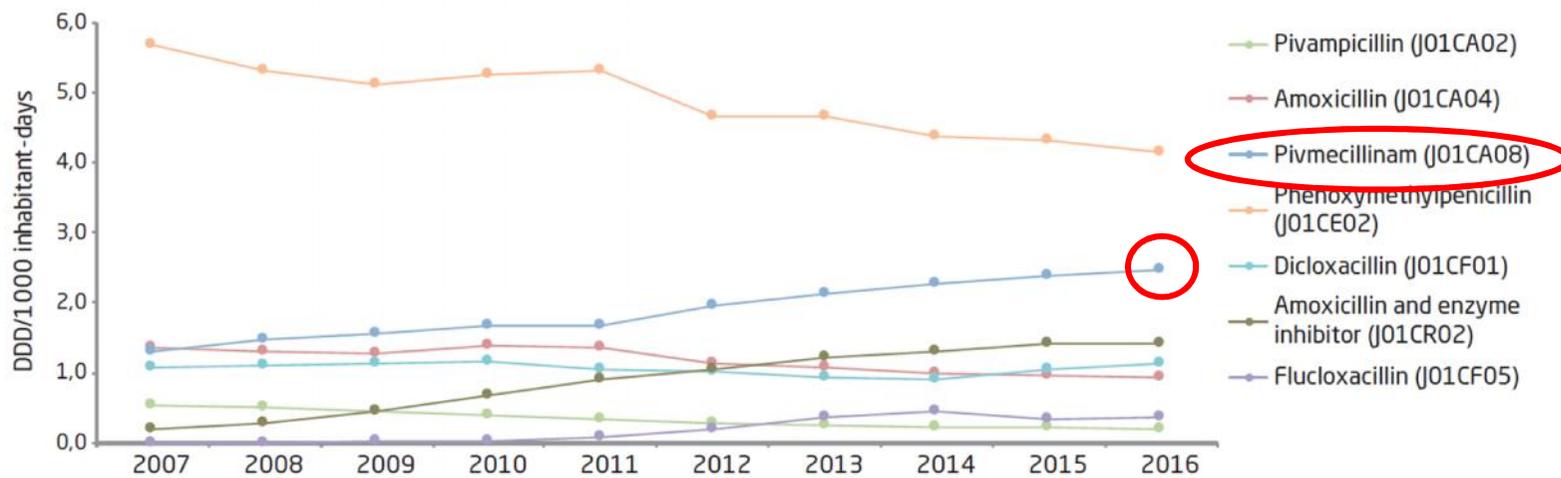
<http://pro.medicin.dk/Specielleemner/Emner/318565#a000>

Also used for complicated UTI and iv mecillinam for urosepsis

# DK: pivmecillinam consumption in primary health care

Figure 5.4. Consumption of leading penicillins in primary health care, Denmark

DANMAP 2016



[https://www.danmap.org/~media/Projekt%20sites/Danmap/DANMAP%20reports/DANMAP%202016/DANMAP\\_2016\\_web.ashx](https://www.danmap.org/~media/Projekt%20sites/Danmap/DANMAP%20reports/DANMAP%202016/DANMAP_2016_web.ashx)

## Resistance rates remain low.

**Table 1** Percentage susceptibility of *Escherichia coli* isolated from women with acute uncomplicated urinary tract infection in 2000, 2008, and 2014

Country	Year	No. of isolates	Mecillinam	Amoxicillin-clavulanic acid	Cefadroxil	Nitrofurantoin	Ciprofloxacin	Trimethoprim
France	2014	166	97.0	94.0	97.0	100	95.2	82.5
	2000	199	98.5	NA <sup>a</sup>	99.0	99.0	98	84.4
Germany	2014	133	97.0	91.7	88.0	97.7	79.7 <sup>b</sup>	63.2
	2000	138	97.8	NA <sup>a</sup>	98.6	99.3	97.8	77.5
Spain	2014	169	93.5	79.9	91.7	100	69.2	62.7
	2000	191	99.0	NA <sup>a</sup>	96.9	95.8	85.3	74.9
Sweden	2014	137	98.5	94.3	97.1	98.5	92.7 <sup>b</sup>	83.1 <sup>b</sup>
	2008	203	99.5	NA <sup>a</sup>	98.5	100	97.5	83.7
	2000	193	98.4	NA <sup>a</sup>	94.8	100	100	91.2
United Kingdom	2014	124	95.2	86.3	95.2	94.4	84.7	54.0
	2008	201	99.0	NA <sup>a</sup>	98.5	100	99.5	85.1
	2000	180	98.3	NA <sup>a</sup>	98.3	100	99.4	86.7

<sup>a</sup> See text for why data for amoxicillin-clavulanic acid are not applicable (NA)

<sup>b</sup> Additional 1% intermediate susceptibility

Kahlmeter et al. Infect Dis Ther. 2015 Dec;4(4):417-23.

## Low impact on normal intestinal flora

Sullivan et al. Journal of Chemotherapy 2001; 13:3, 299-308

# Clinical breakpoints for Enterobacterales

only for *E. coli*, *Klebsiella* spp. and *P. mirabilis*

<b>Mecillinam</b> (SE - endast okomplicerad UVI) <i>E. coli</i> , <i>Klebsiella</i> spp. och <i>P. mirabilis</i>	8	8	10	15	15
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Bortse från isolerade kolonier i hämningszonen för *E. coli*.

Agarspädning är referensmetod för MIC-bestämning av mecillinam.

MIC reference method: agar dilution

<b>Mecillinam</b> (DK och NO) <i>E. coli</i> , <i>Klebsiella</i> spp. och <i>P. mirabilis</i>	8	8	10	15	15
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Bortse från isolerade kolonier i hämningszonen för *E. coli*.

Agarspädning är referensmetod för MIC-bestämning av mecillinam.

Det saknas klinisk evidens för effekt av mecillinam vid andra infektioner än okomplicerad UVI. För laboratorier i Danmark och Norge hänvisas till AFAs hemsidor för mer information om användning vid andra indikationer.

<https://unn.no/Documents/Kompetansetjenester,%20-sentre%20og%20fagråd/AFA%20-%20arbeidsgruppen%20for%20antibiotikaspørsmål/Farmakokinetikk%20og%20-dynamikk%20amoxicillin%20og%20mecillinam%202012-05-10.pdf>

Mecillinam MIC distributions  
in *Enterobacterales* (non-*E. coli*, *Klebsiella*, *P. mirabilis*)  
from blood culture isolates from Denmark  
determined by agar dilution

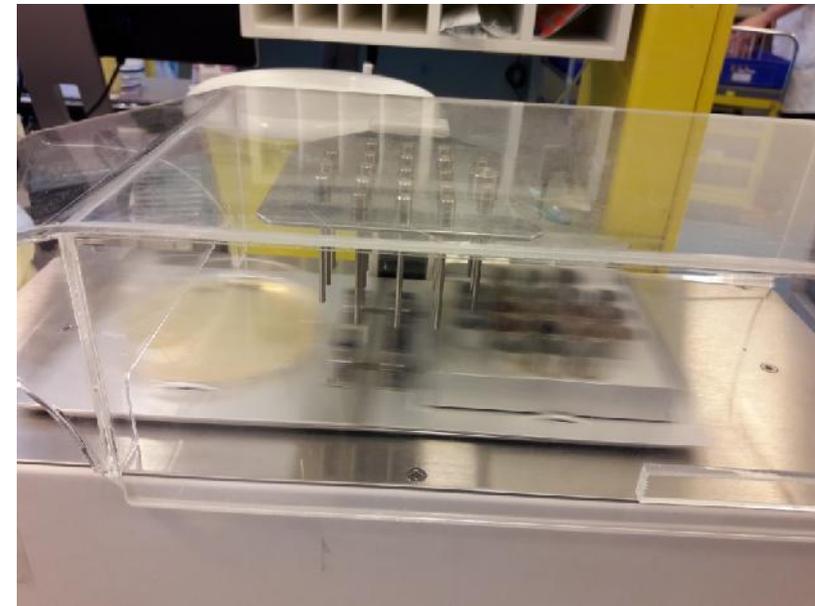
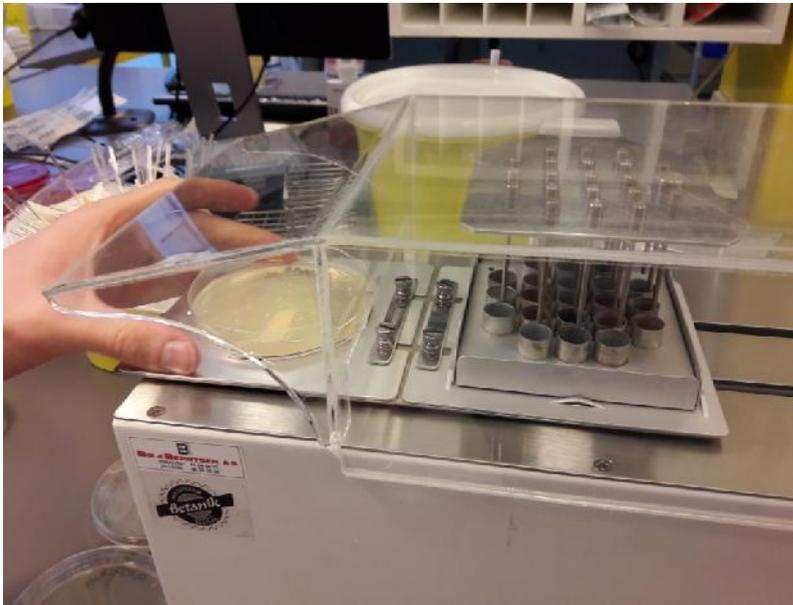
All 10 Danish dept. of clinical microbiology participated  
493 isolates, 11 species

Retrospectively collected, frozen isolates from blood  
cultures

<i>Escherichia coli</i>	45
<i>Klebsiella pneumoniae</i>	43
<i>Klebsiella oxytoca</i>	42
<i>Citrobacter freundii</i>	42
<i>Citrobacter koseri</i>	49
<i>Enterobacter aerogenes</i>	45
<i>Enterobacter cloacae</i>	47
<i>Morganella morganii</i>	46
<i>Serratia marcescens</i>	48
<i>Proteus mirabilis</i>	43
<i>Proteus vulgaris</i>	43

## Agar dilution

2-fold serial dilution of mecillinam in MH-plates  
bacterial suspension  $10^7$  CFU/mL



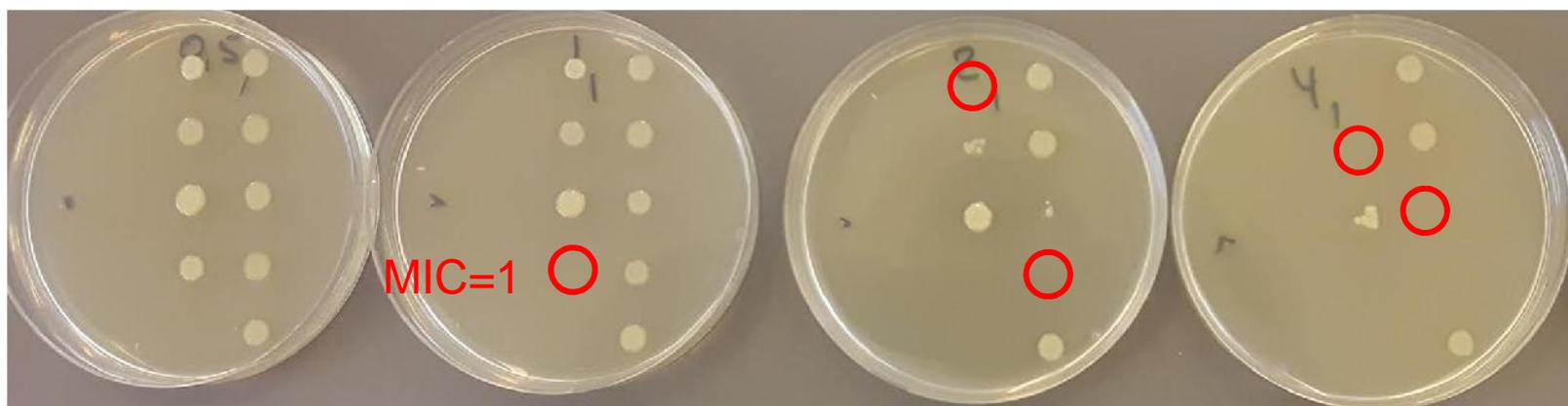
Inoculation  
Final inoculum ca.  $10^4$  CFU/spot

0,5 mg/L

1 mg/L

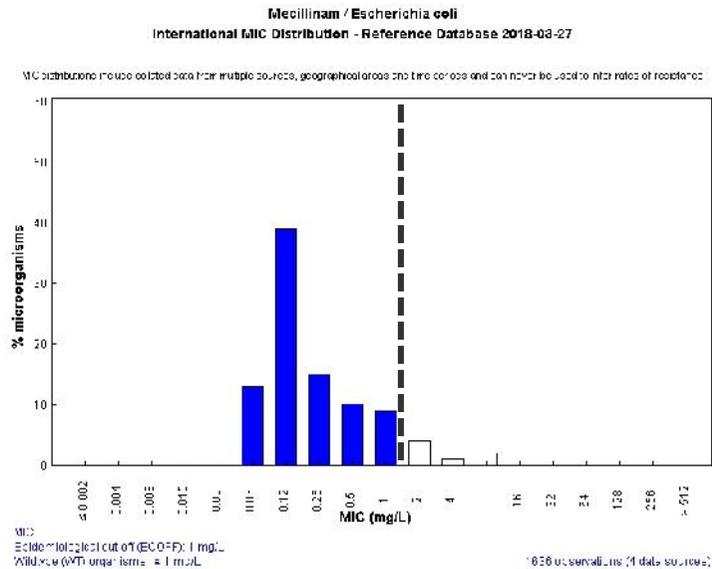
2 mg/L

4 mg/L

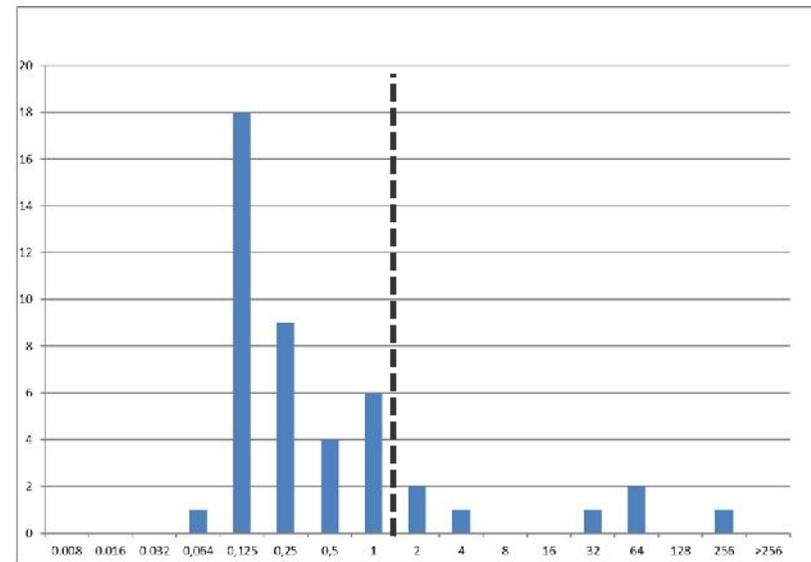


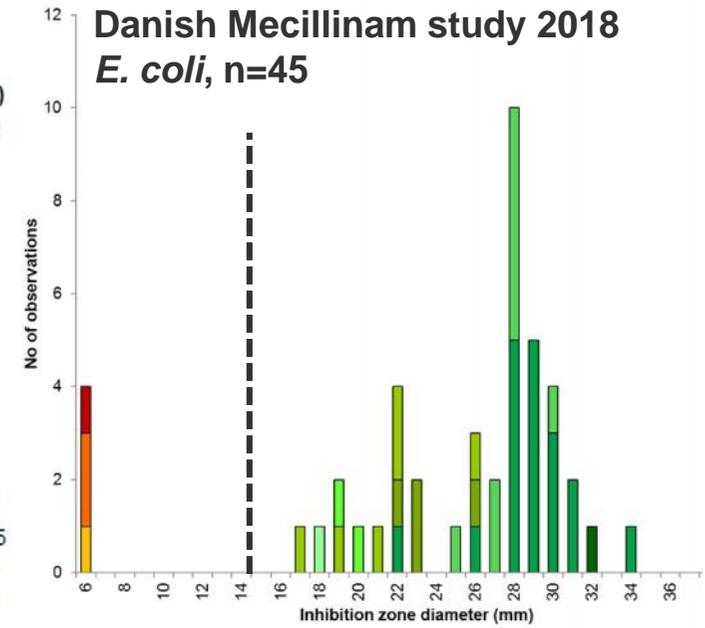
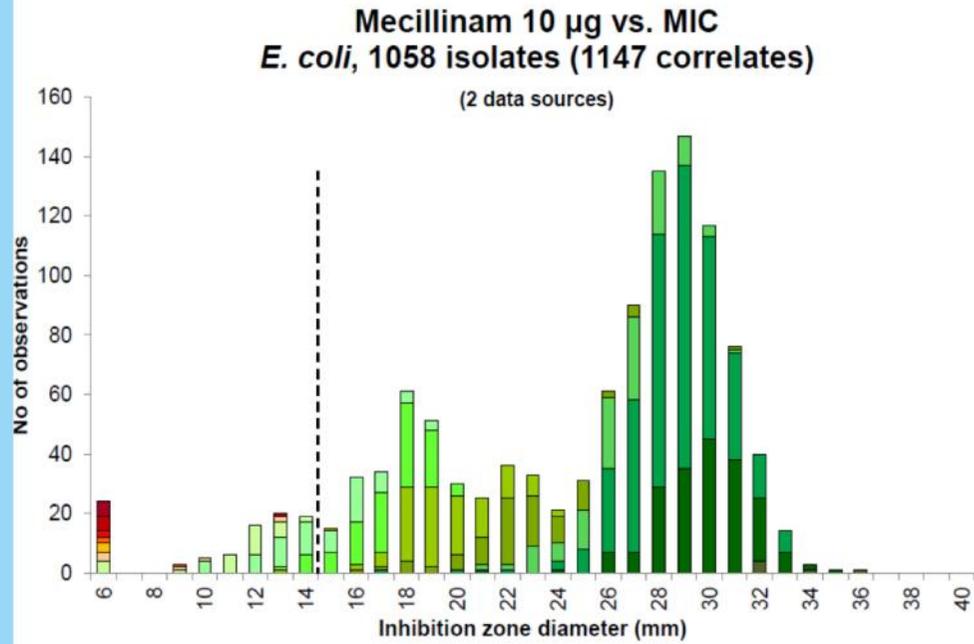
# Calibration: *E. coli* MIC distribution

*E. coli*, EUCAST  
 (n=1636, 4 datasources)



Danish Mecillinam study 2018  
*E. coli*, n=45

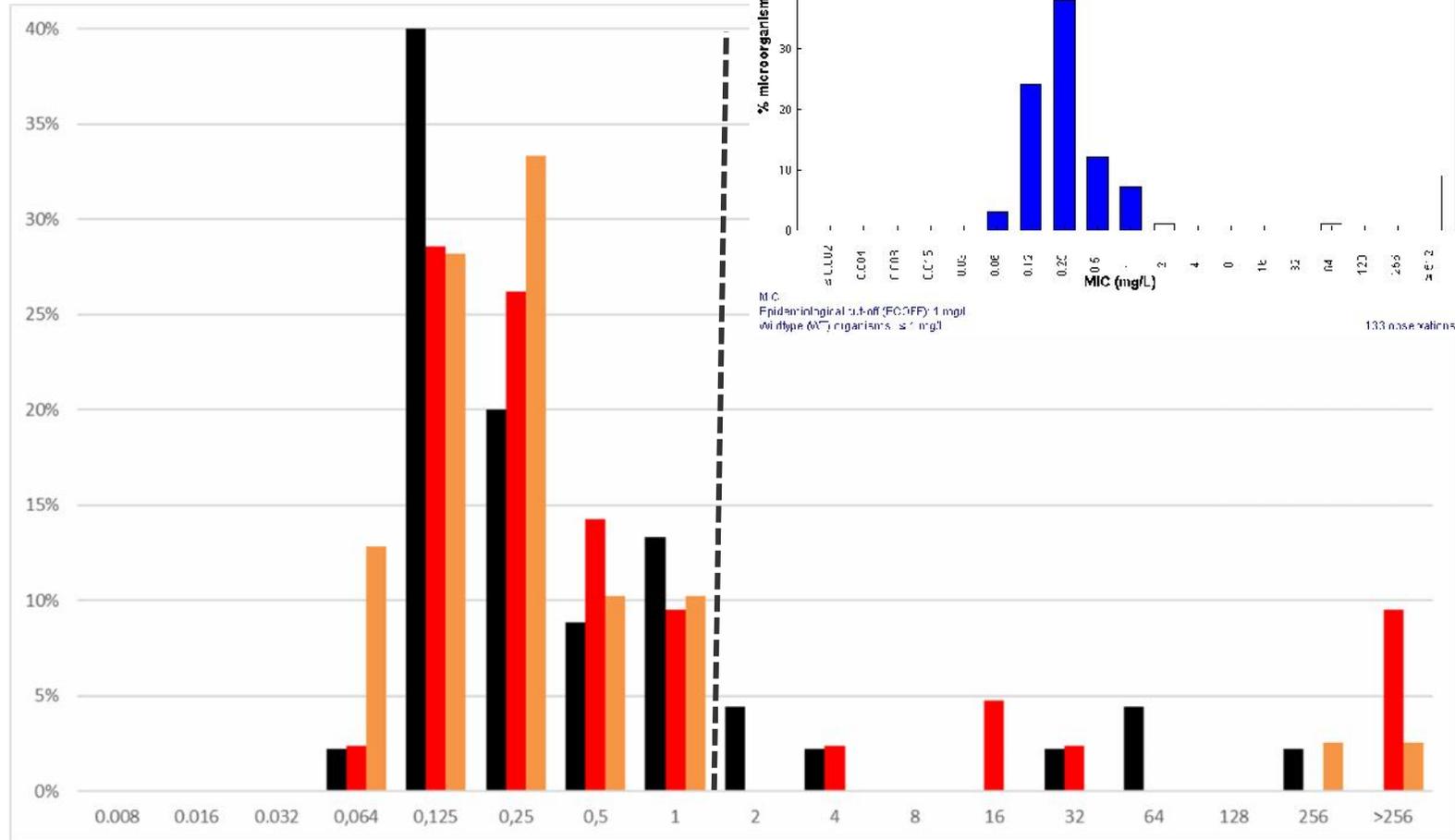




Breakpoints		ECOFF
MIC	S≤8, R>8 mg/L	1 mg/L
Zone diameter	S≥15, R<15 mm	

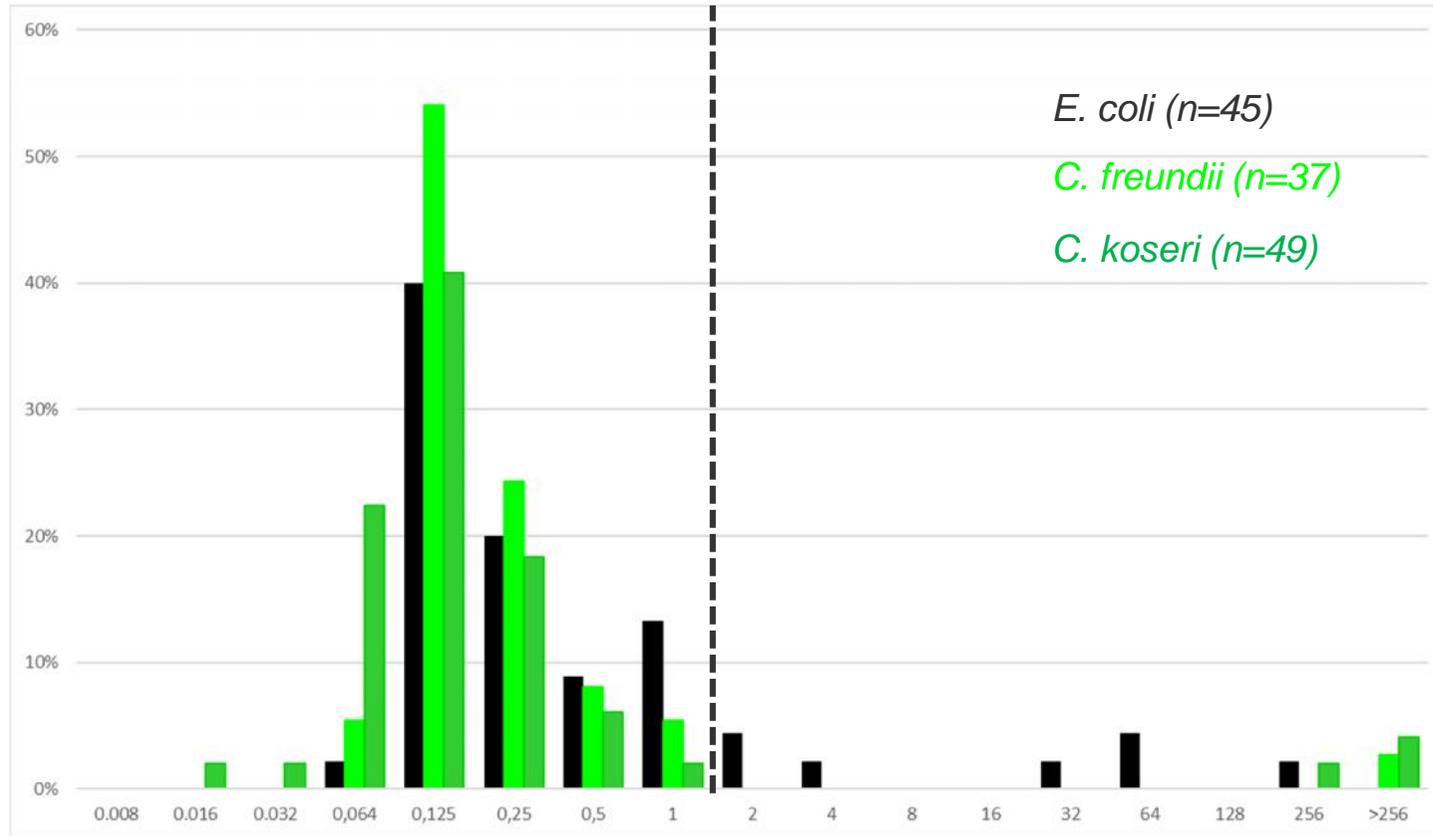
MIC distributions include isolated data from multiple countries, geographical areas and time periods and can never be used to infer rates of resistance

# MIC distribution *Klebsi*



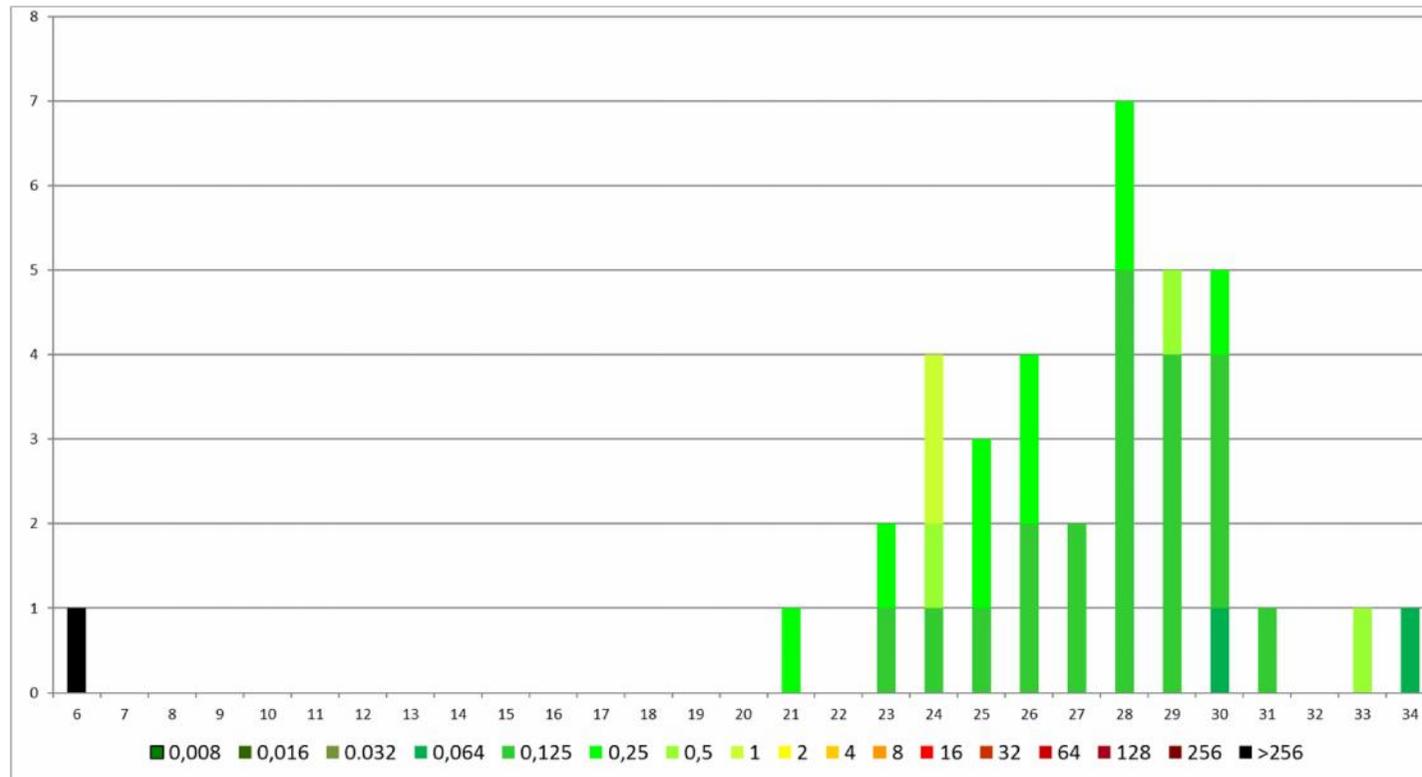
PRELIMINARY RESULTS

## Citrobacter spp.



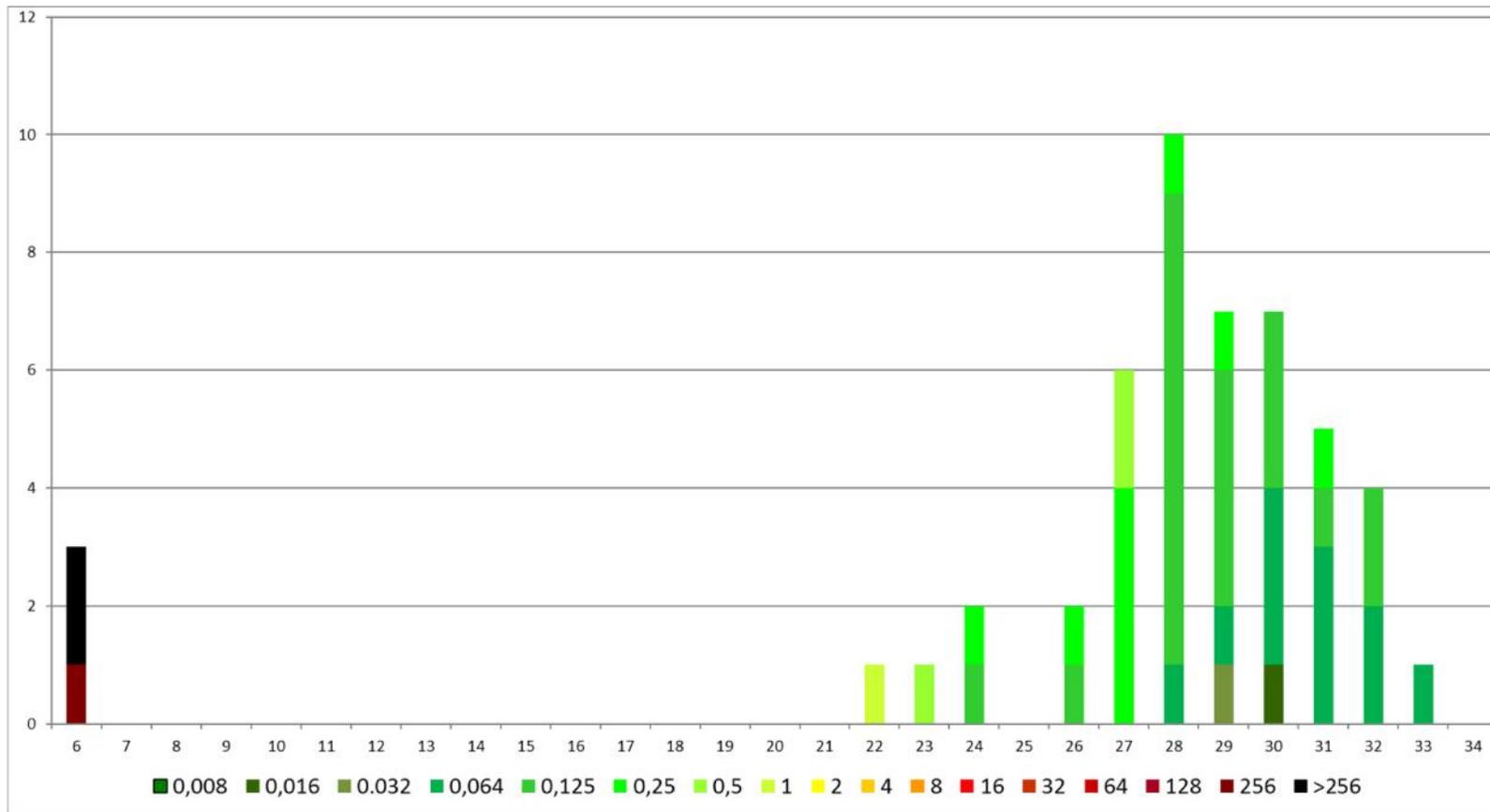
PRELIMINARY RESULTS

## *Citrobacter freundii* (n=37)



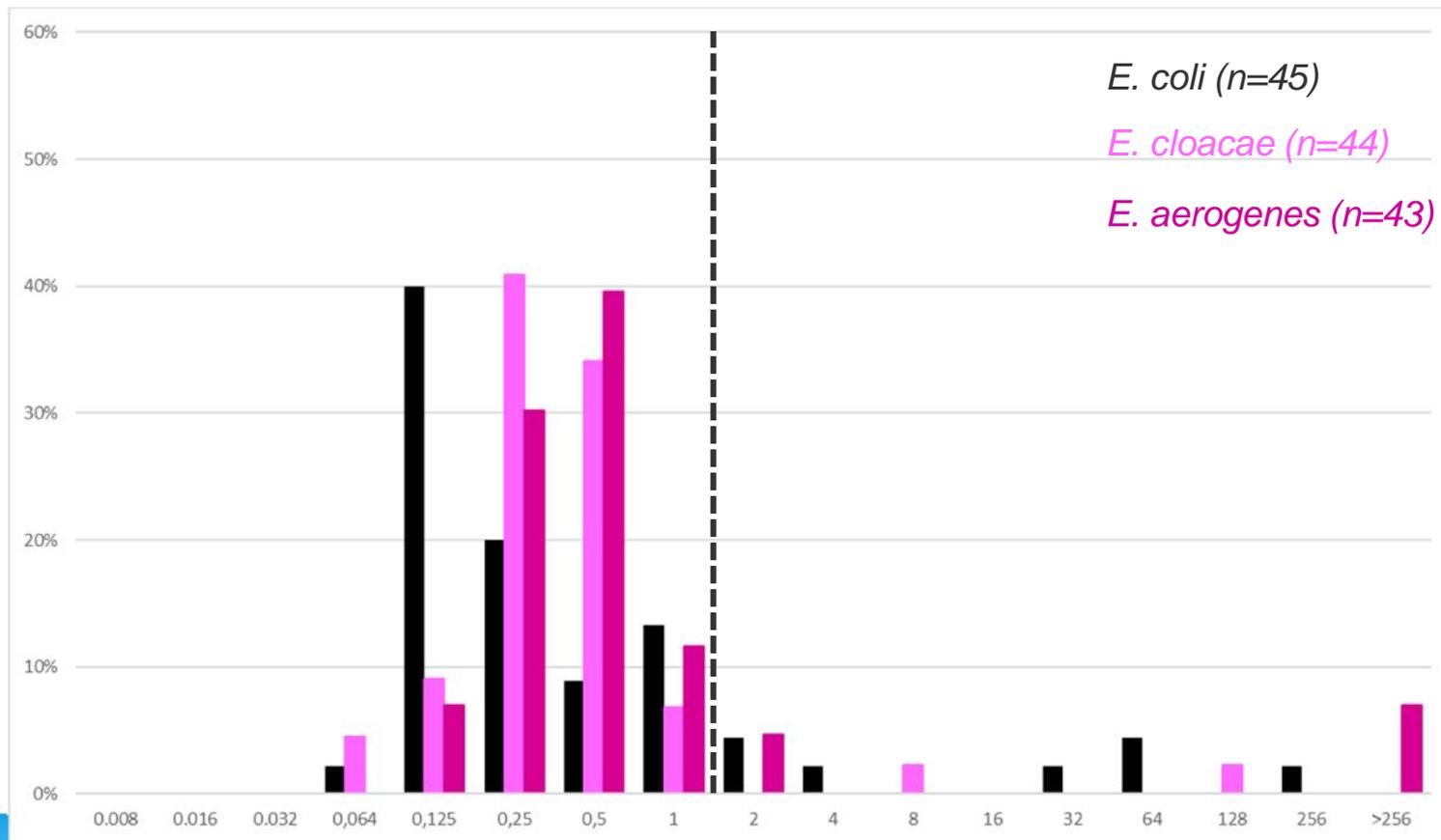
PRELIMINARY RESULTS

## *Citrobacter koseri* (n=49)



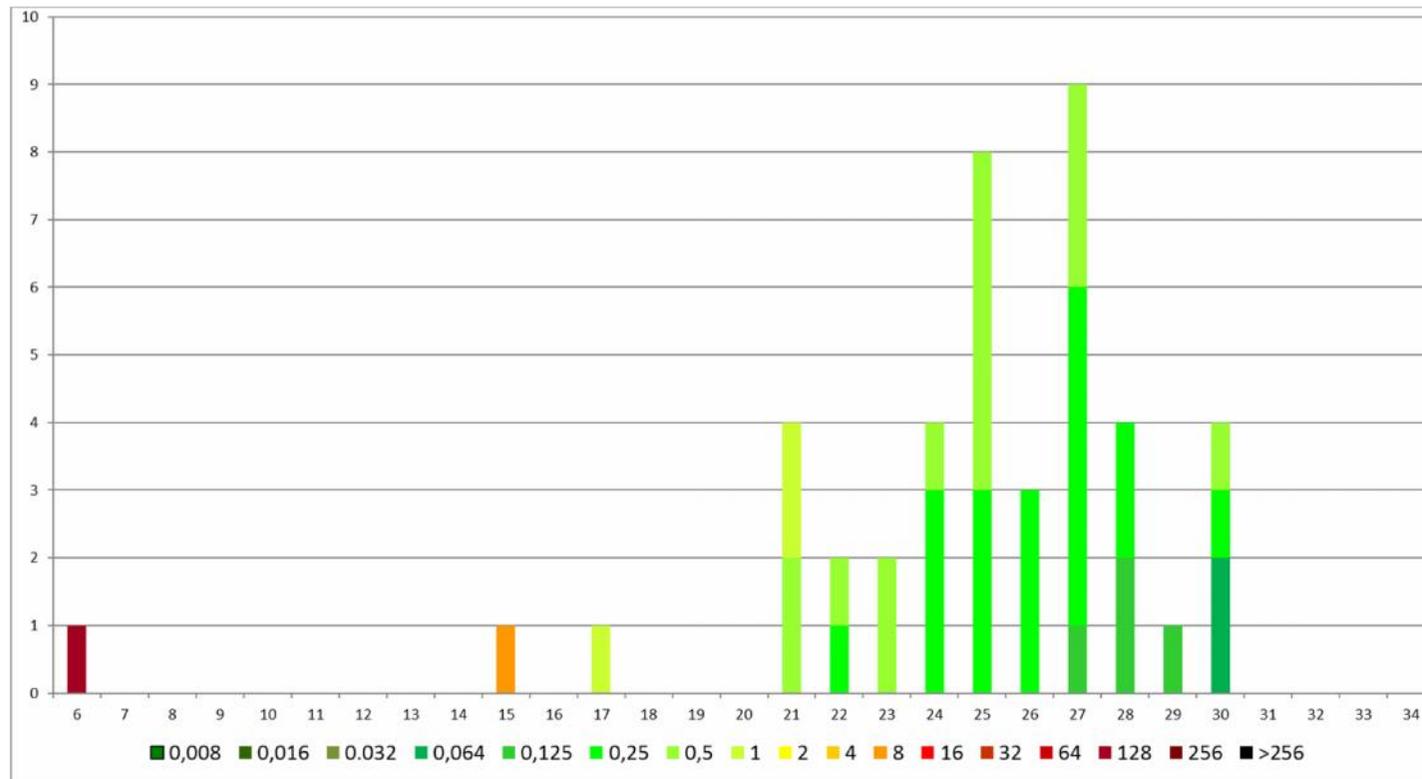
PRELIMINARY RESULTS

## Enterobacter spp.



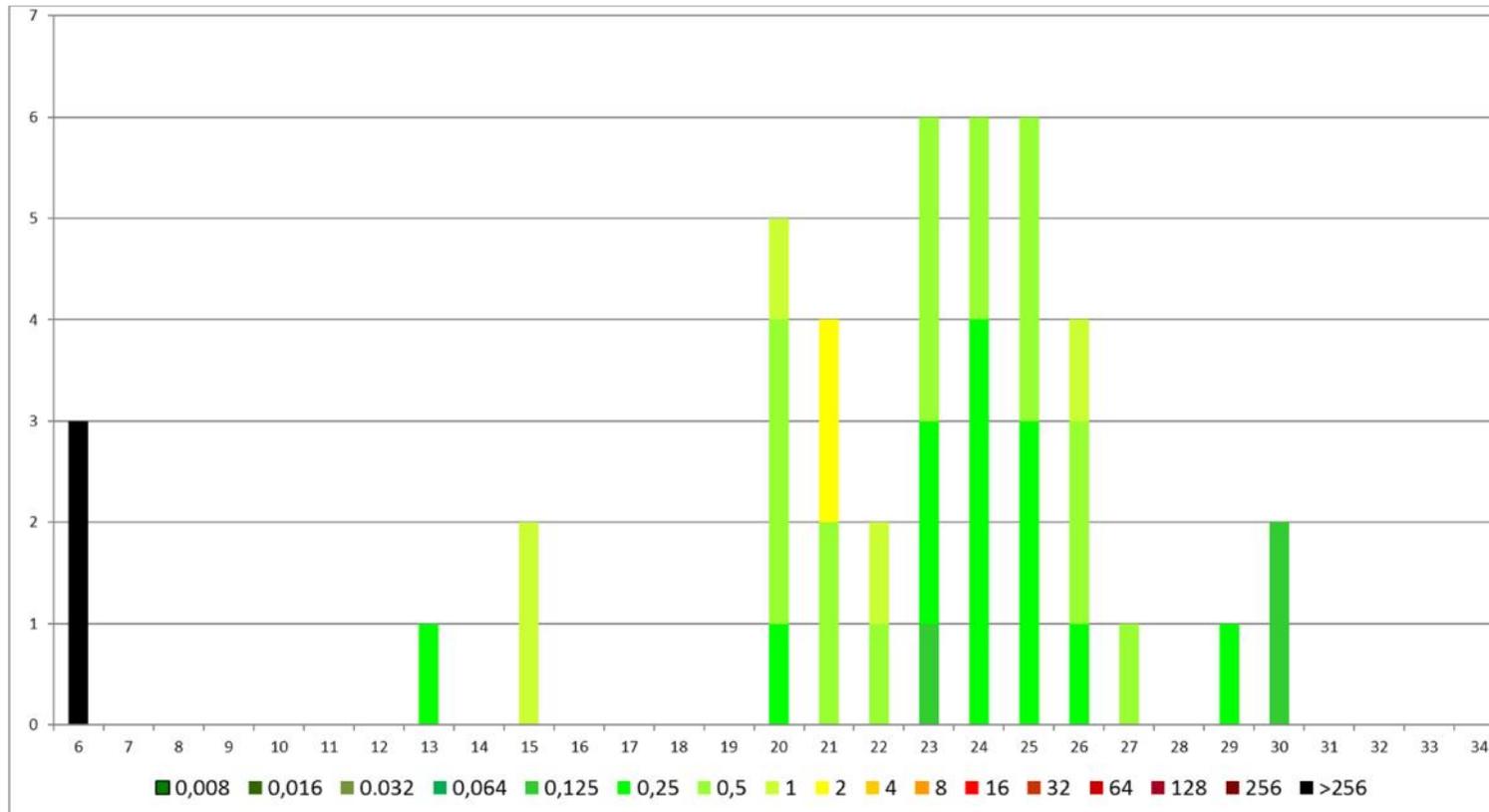
PRELIMINARY RESULTS

## *Enterobacter cloacae* (n=44)



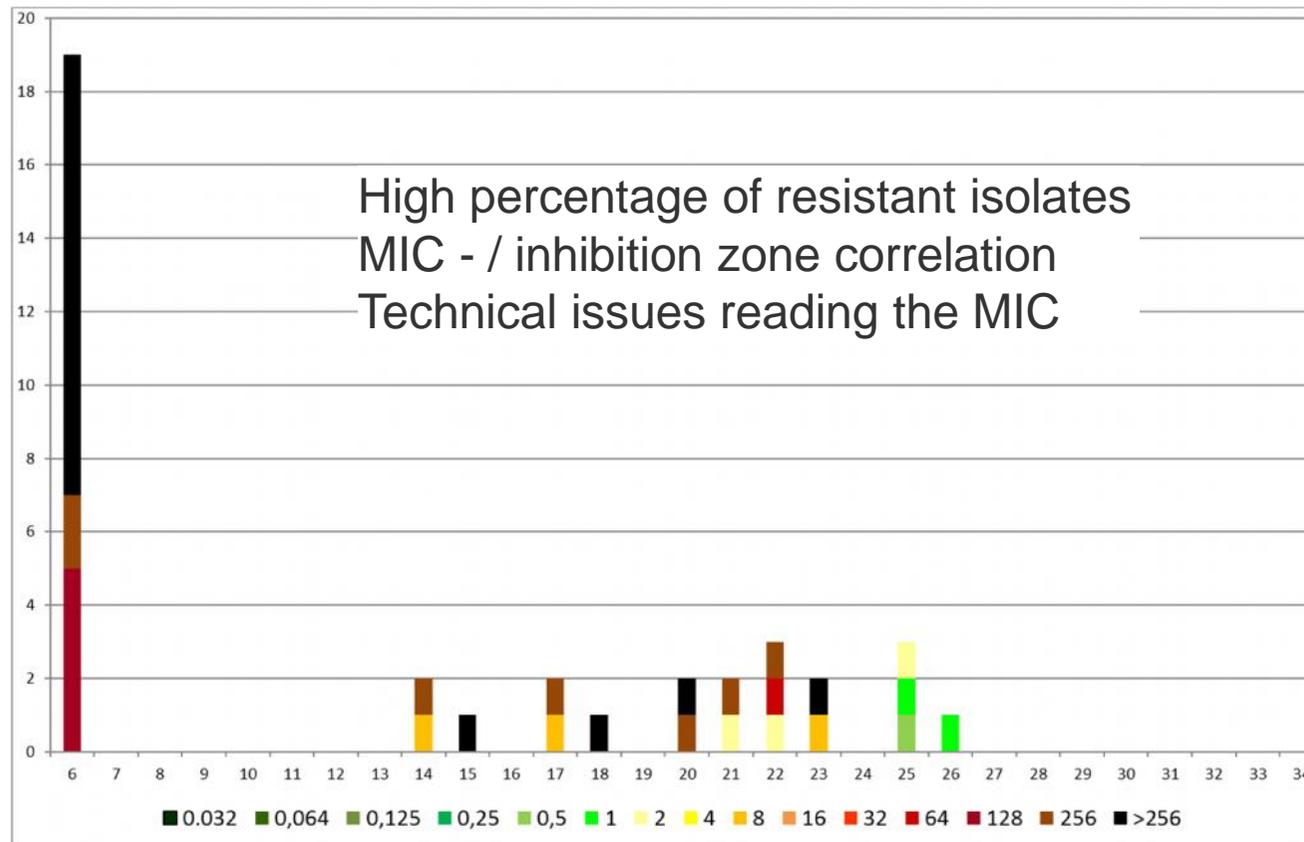
PRELIMINARY RESULTS

## *Enterobacter aerogenes* (n=43)



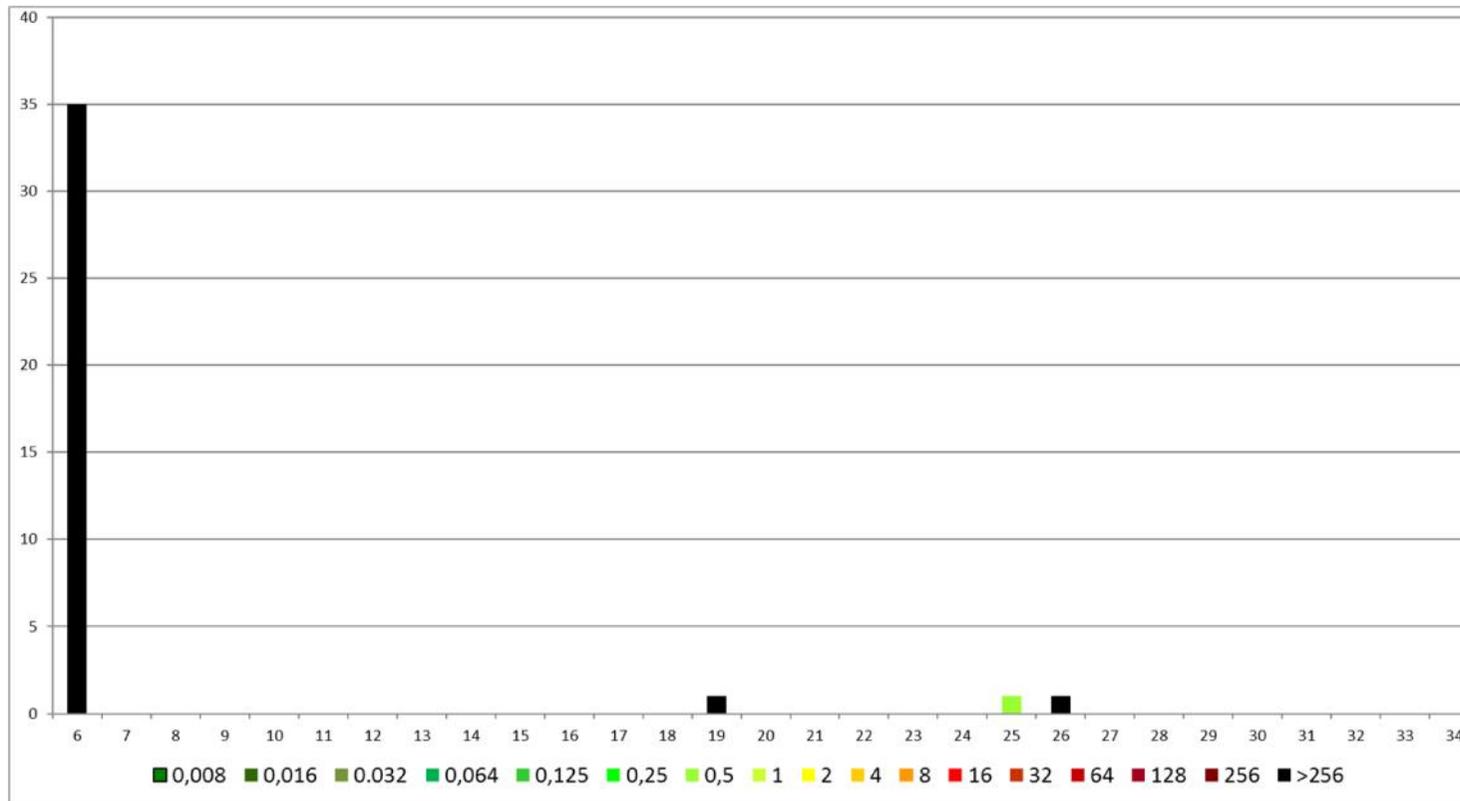
PRELIMINARY RESULTS

## *Serratia marcescens* (n=38)



PRELIMINARY RESULTS

## *Morganella morganii* (n=38)



## ***Proteus spp.***

Technical issues reading MICs  
work in progress

## Conclusions

ECOFF 1 seems to be adequate for *Citrobacter spp.* and *Enterobacter cloacae*.

ECOFF for *E. aerogenes* might be one dilution step higher, further work is to be done.

*Serratia marcescens* and *Morganella morganii*: high percentage intrinsically resistant + technical problems.  
proposed "-": no BP/ AST not recommended

**TAK!**

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