

# ATU

# Area of Technical Uncertainty

Gunnar Kahlmeter  
Klinisk mikrobiologi, Växjö  
EUCAST

# Errors in phenotypic susceptibility testing

- **Random errors – can be minimized but not prevented.**
  - Variation between individuals (inocula, reading practices, ...)
  - Variation in materials (disks, plates, concentrations, ...)
  - Variation in appliances (temperature, atmosphere, ...)
- **Systematic errors – can be prevented**
  - Differences in methodology
  - Differences in materials (disks and media from different manufacturers)
  - ....

# Intermediate – current definition

- uncertain therapeutic effect
- where the drugs are physiologically concentrated
- when a high dosage of drug can be used
- a buffer zone

## Proposed definitions 2018

All definitions of susceptibility testing categories relate to the degree of exposure of the infecting organism to the antimicrobial agent. Exposure is a function of how the mode of administration, dose, dosing interval, infusion time, as well as distribution and excretion of the antimicrobial agent will influence the infecting organism at the site of infection.

### **S - Susceptible, standard dosing regimen:**

A microorganism is categorised as *Susceptible, standard dosing regimen*, when there is a high likelihood of therapeutic success using a standard dosing regimen of the agent.

### **I – Susceptible, increased exposure:**

A microorganism is categorised as *Susceptible, Increased exposure* when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.

### **R - Resistant:**

A microorganism is categorised as *Resistant* when there is a high likelihood of therapeutic failure even when there is increased exposure.

## **Proposed guidance for laboratories on how to handle technical uncertainty in antimicrobial susceptibility testing.**

**Consultation (3<sup>rd</sup>) February 20 – April 10, 2018**

All measurements are affected by random variation and some by systematic variation. Systematic variation should be avoided and random variation reduced as much as possible. Antimicrobial susceptibility testing (AST), irrespective of method, is no exception.

EUCAST strives to advise laboratories by providing standardised methods for both MIC determination and disk diffusion and by avoiding setting breakpoints which seriously affect the reproducibility of the test.

# ATU

ATU is an area inside which the interpretation of the phenotypic result is uncertain.

- MIC
- Zone diameter
- Any other phenotypic measurement

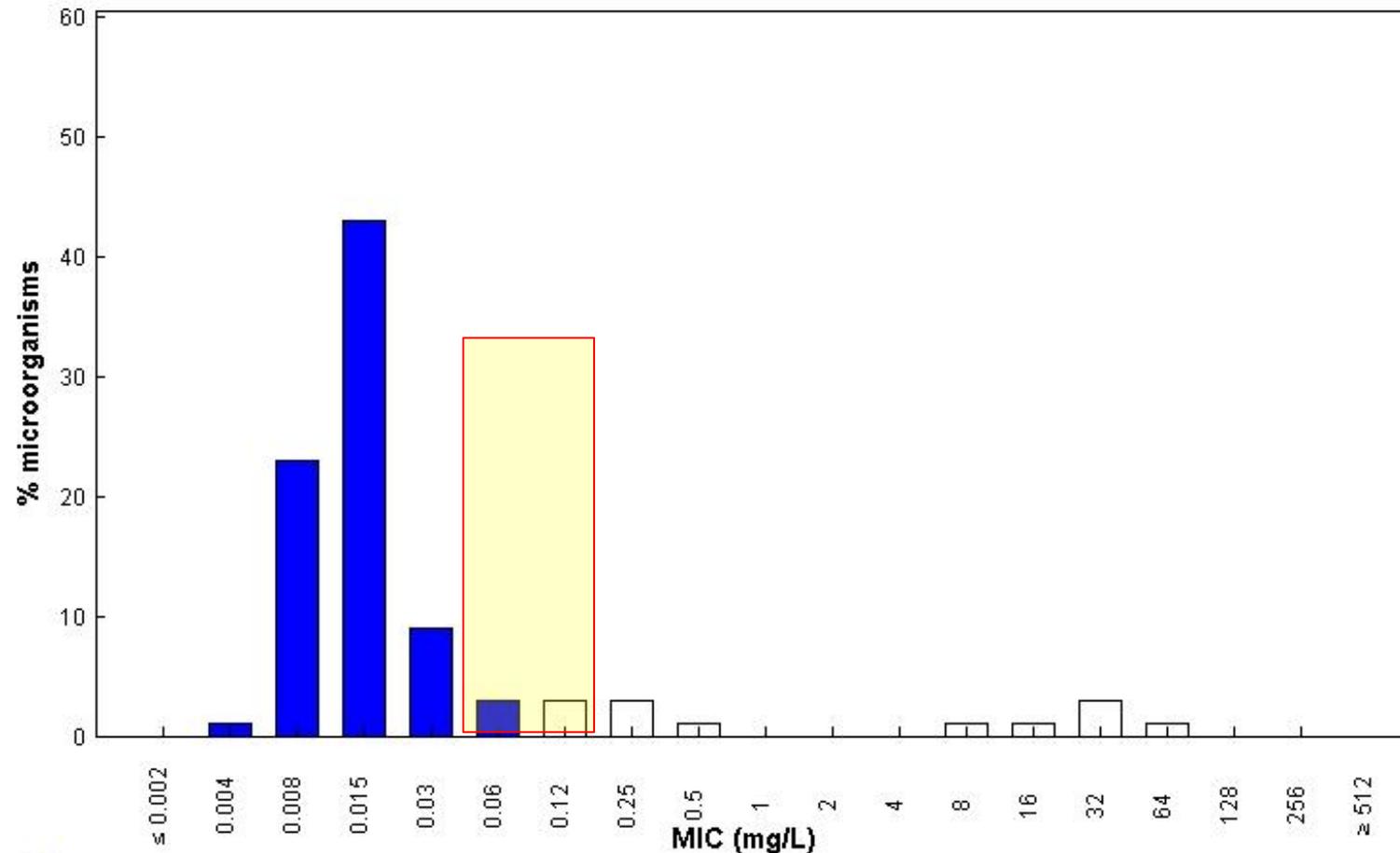
# ATU

- To reduce the number of very major (false susceptible) and major (false resistant) errors.
- To increase the reliability of and confidence in S, I and R.

# ATU – Area of Technical Uncertainty in phenotypic AST

## Ciprofloxacin / *Escherichia coli* International MIC Distribution - Reference Database 2018-05-07

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

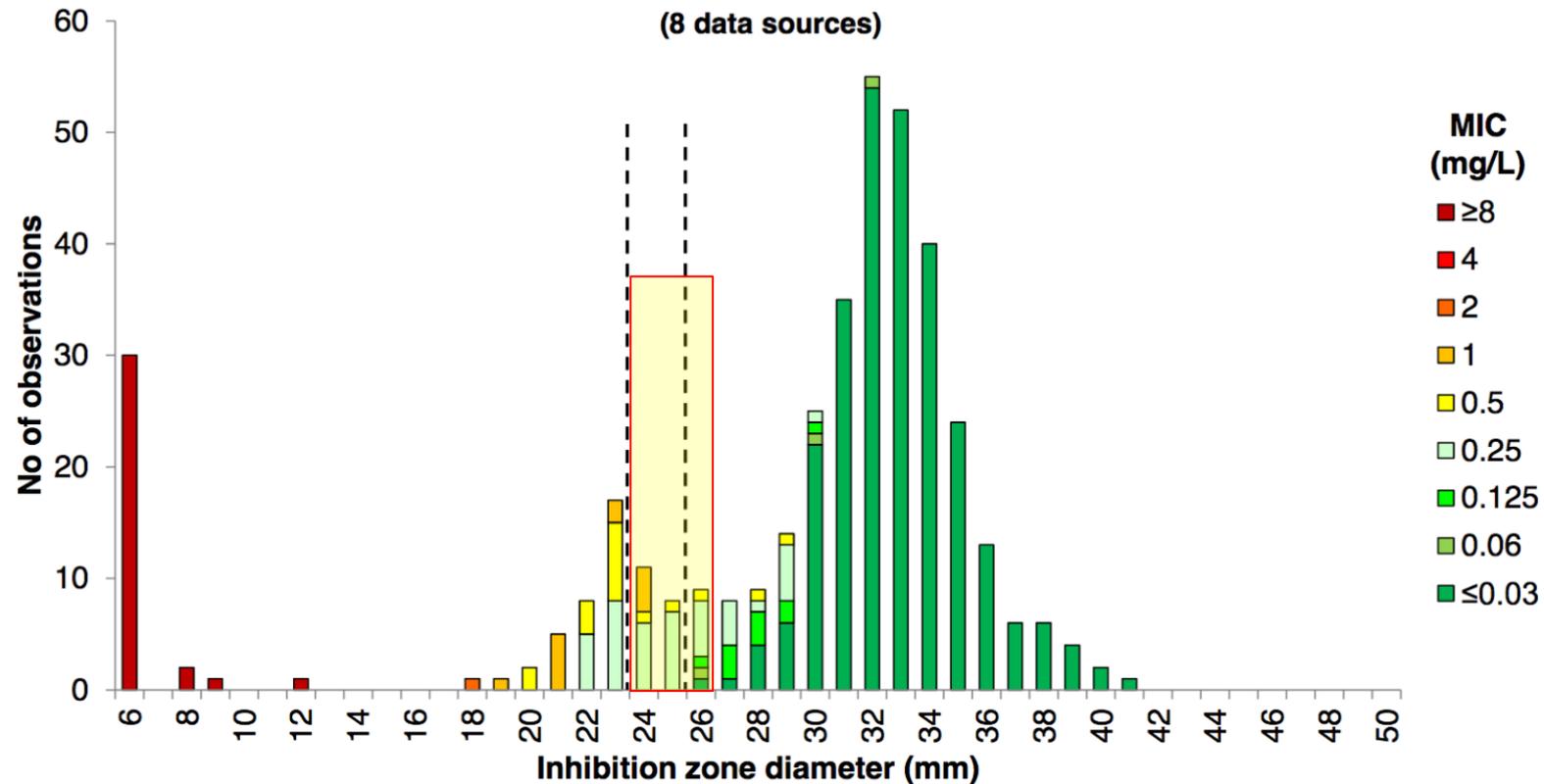


MIC  
Epidemiological cut-off (ECOFF): 0.064 mg/L  
Wildtype (WT) organisms: ≤ 0.064 mg/L

16702 observations (55 data sources)

# ATU – Area of Technical Uncertainty in phenotypic AST

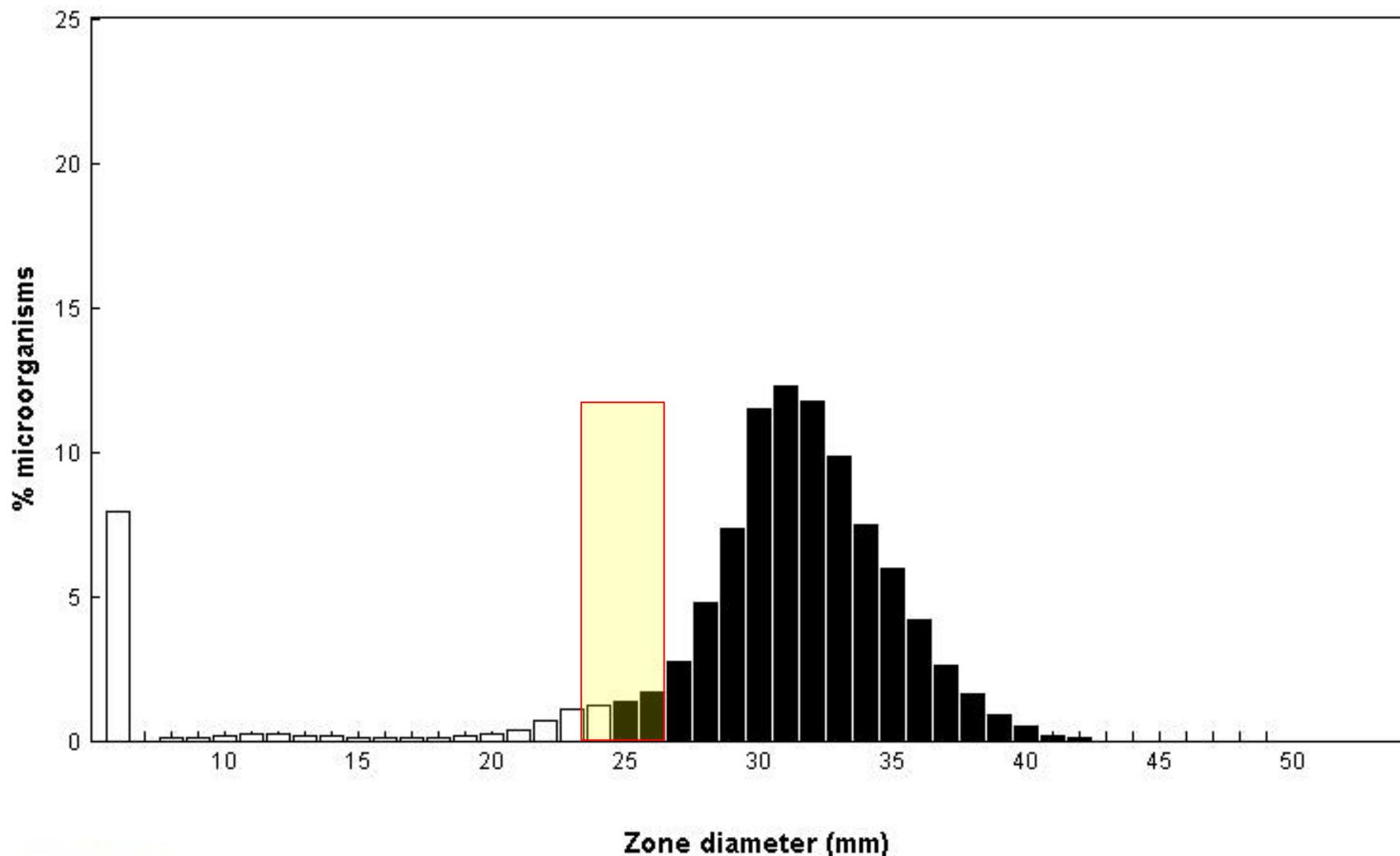
**Ciprofloxacin 5 µg vs. MIC**  
*E. coli*, 376 isolates (390 correlates)



Breakpoints		ECOFF
MIC	S≤0.25, R>0.5 mg/L	0.06 mg/L
Zone diameter	S≥26, R<24 mm	

**Ciprofloxacin / Escherichia coli**  
**International wild type zone diameter distribution - Reference database 2018-05-07**  
**EUCAST disk diffusion method**

Distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



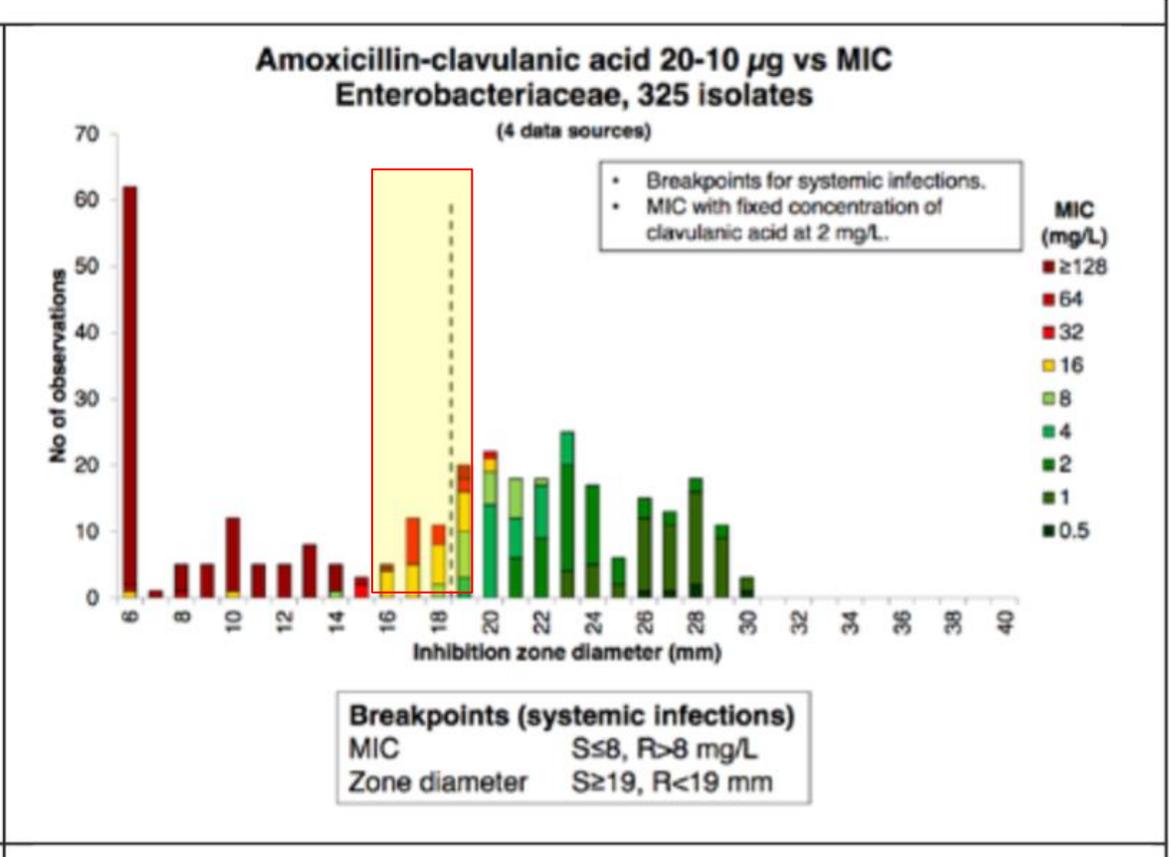
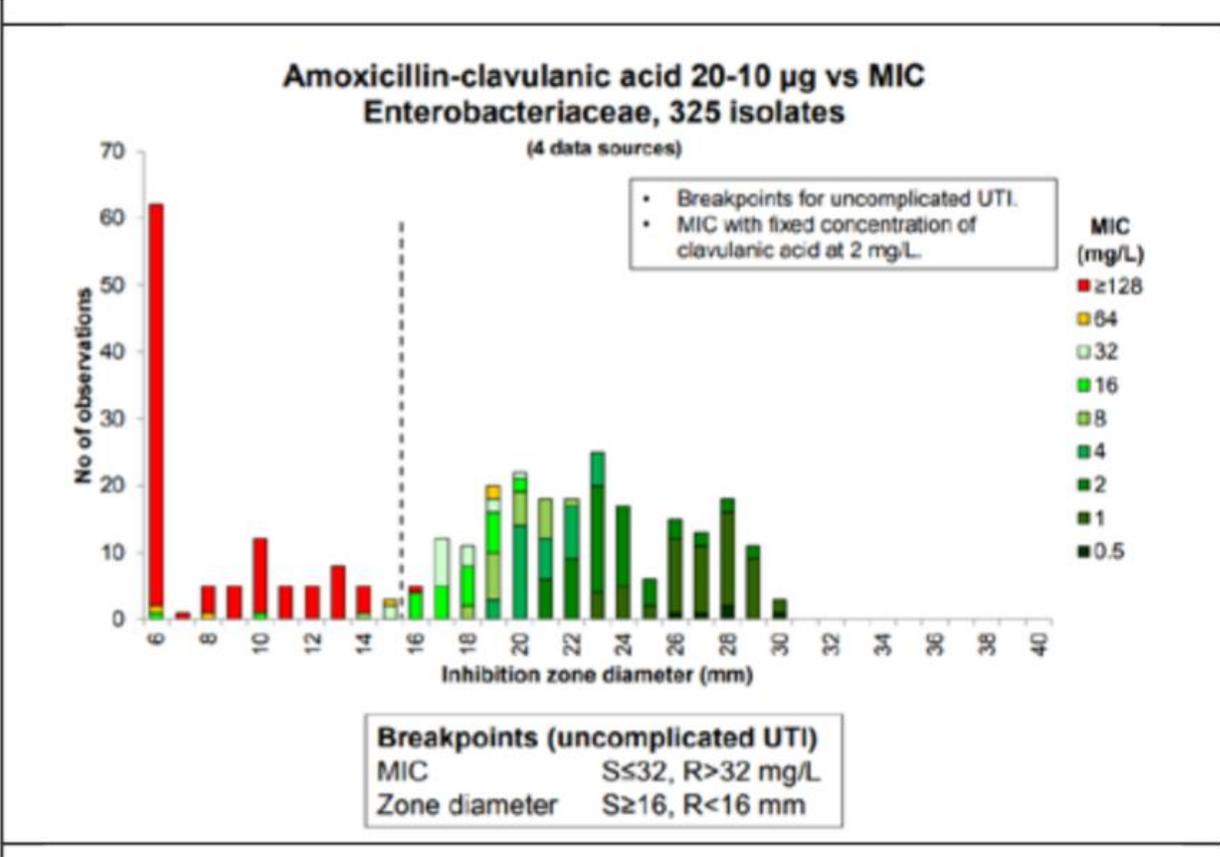
Disk content: 5

Epidemiological cut-off (ECOFF): 25 mm (MIC = 0.064 mg/L)

Wildtype (WT) organisms:  $\geq 25$  mm (MIC = 0.064 mg/L)

36774 observations (13 data sources)

# ATU may or may not be needed depending on where breakpoints are set.



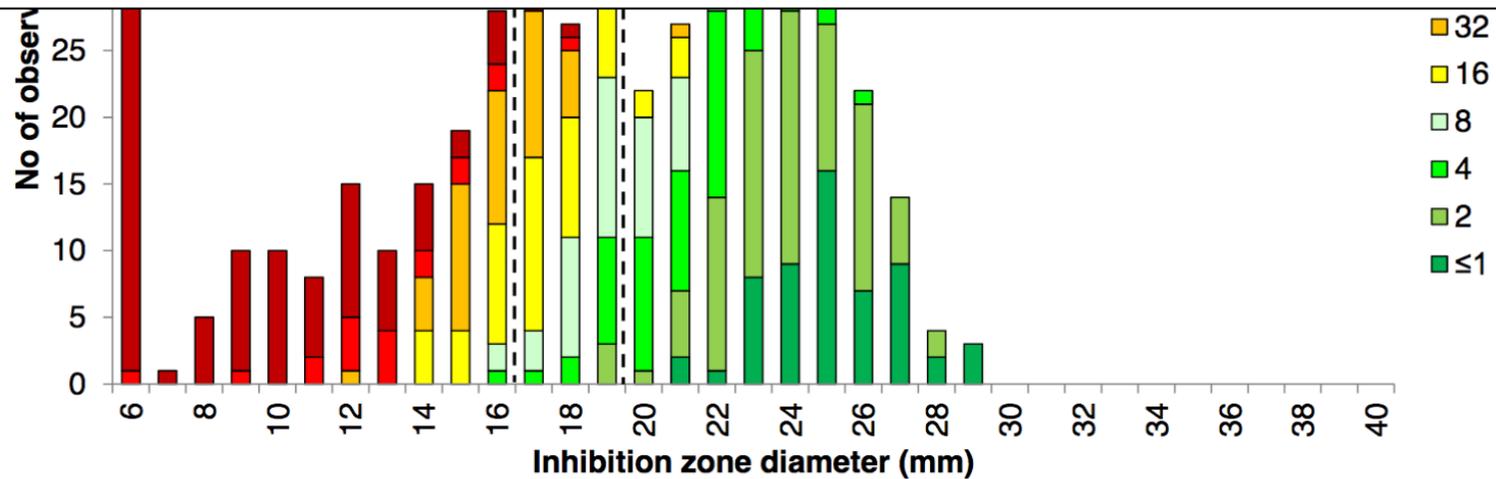
Some distributions are fraught with "overlap"  
and just hopeless to handle...

# Piperacillintazobactam vs. *E. coli*

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

(7 data sources)

MIC and zone diameter correlation is perfect –  
 but overlap causes major problems



**Breakpoints**

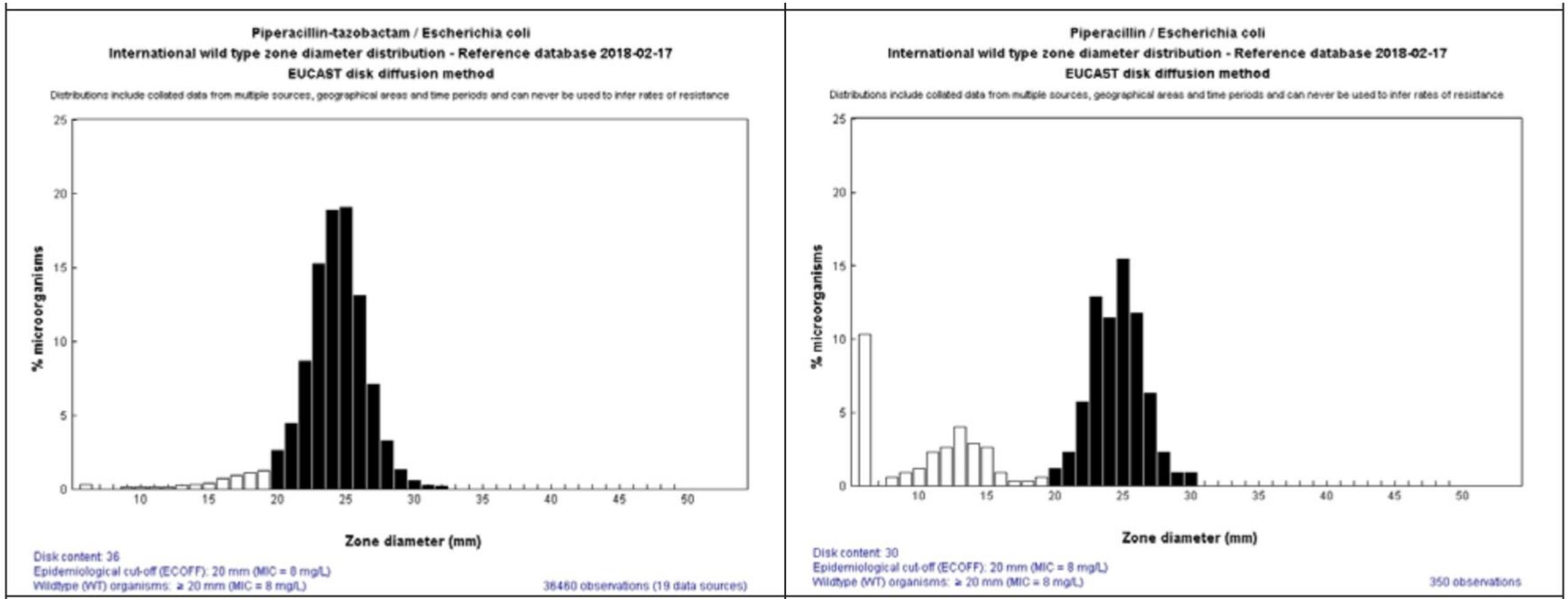
MIC S≤8, R>16 mg/L

Zone diameter S≥20, R<17 mm

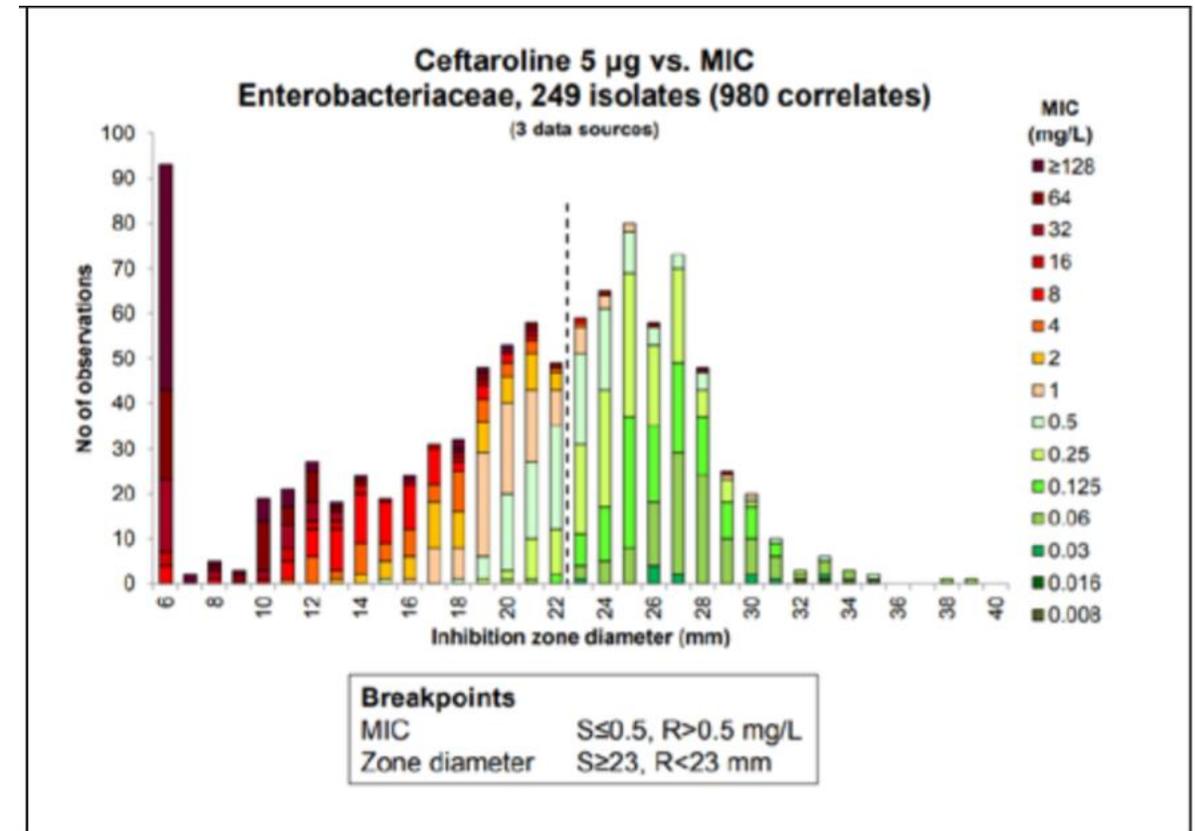
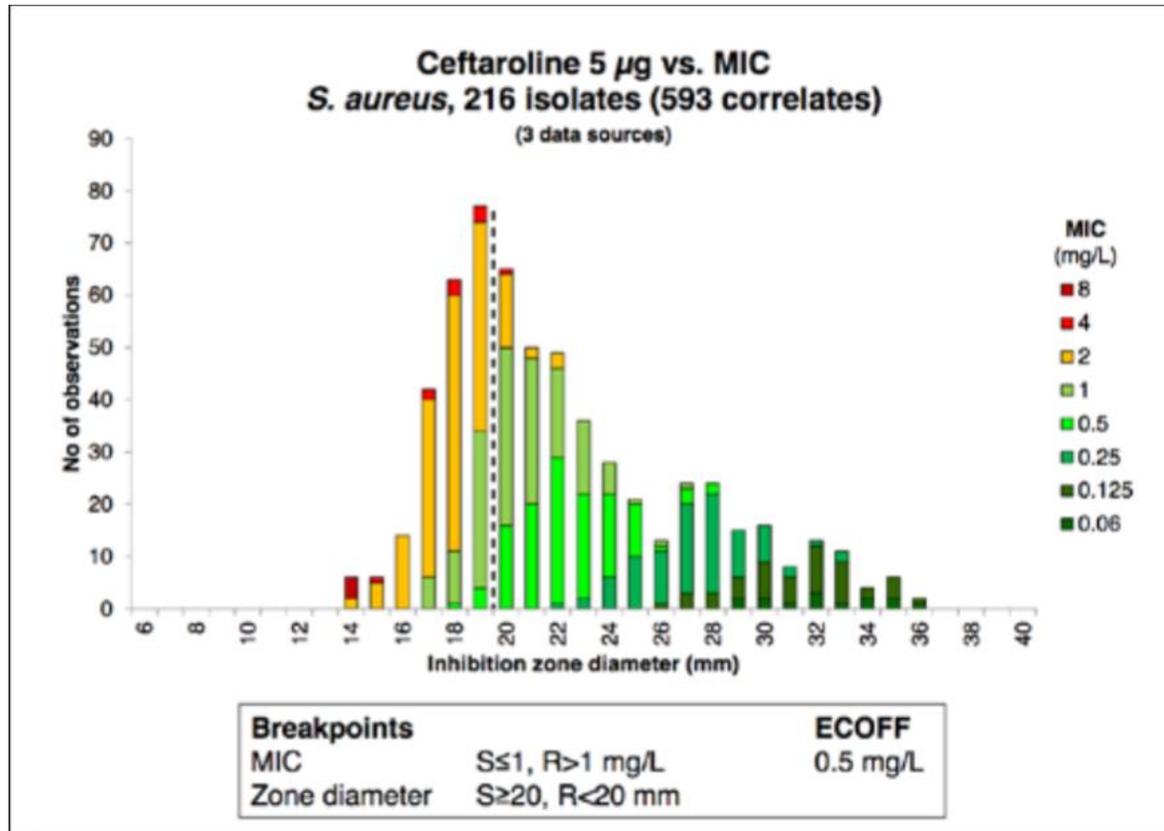
**ECOFF**

8 mg/L

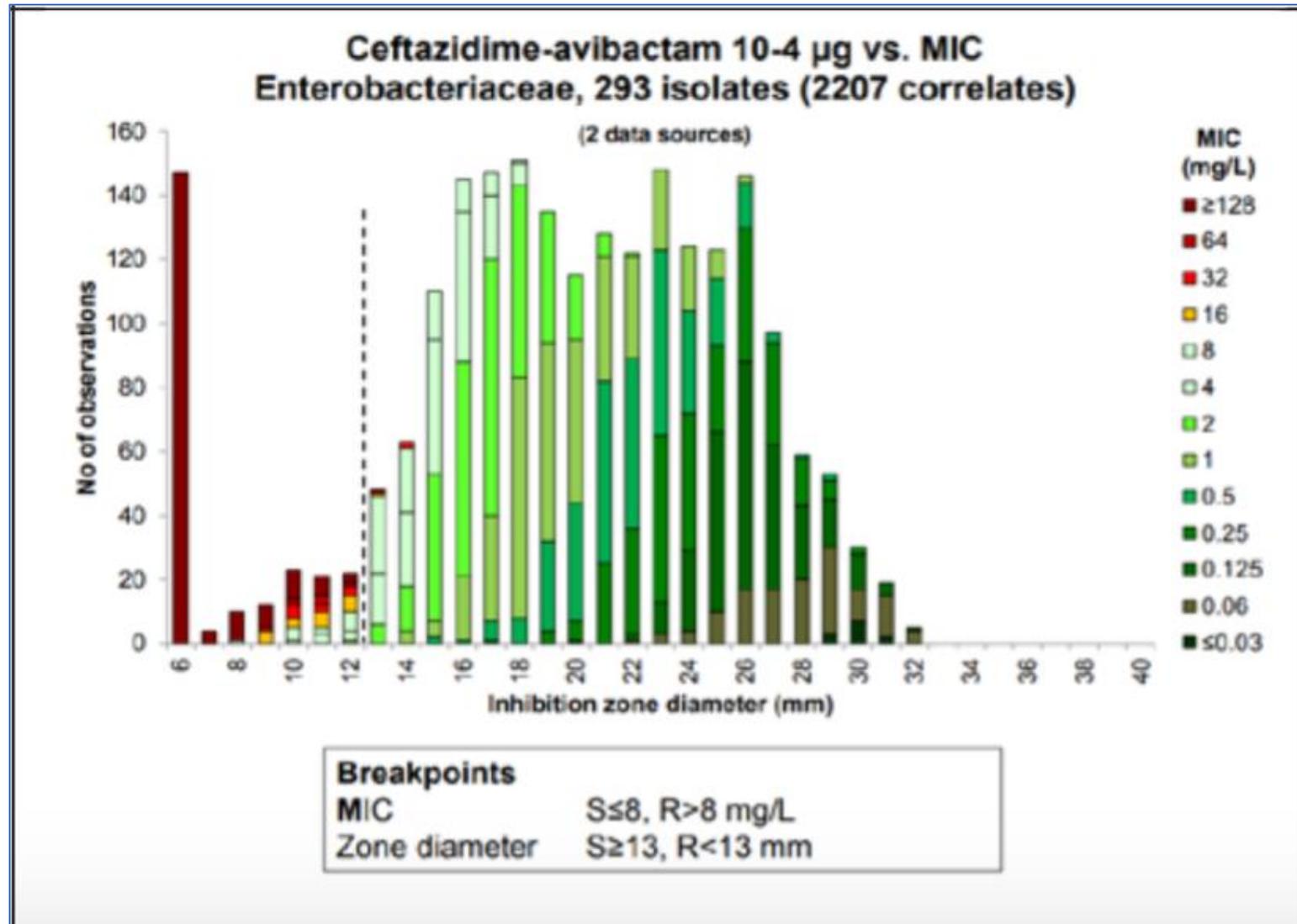
# Piperacillin vs. piperacillintazobactam



# ATU may be needed because of where the breakpoint is set



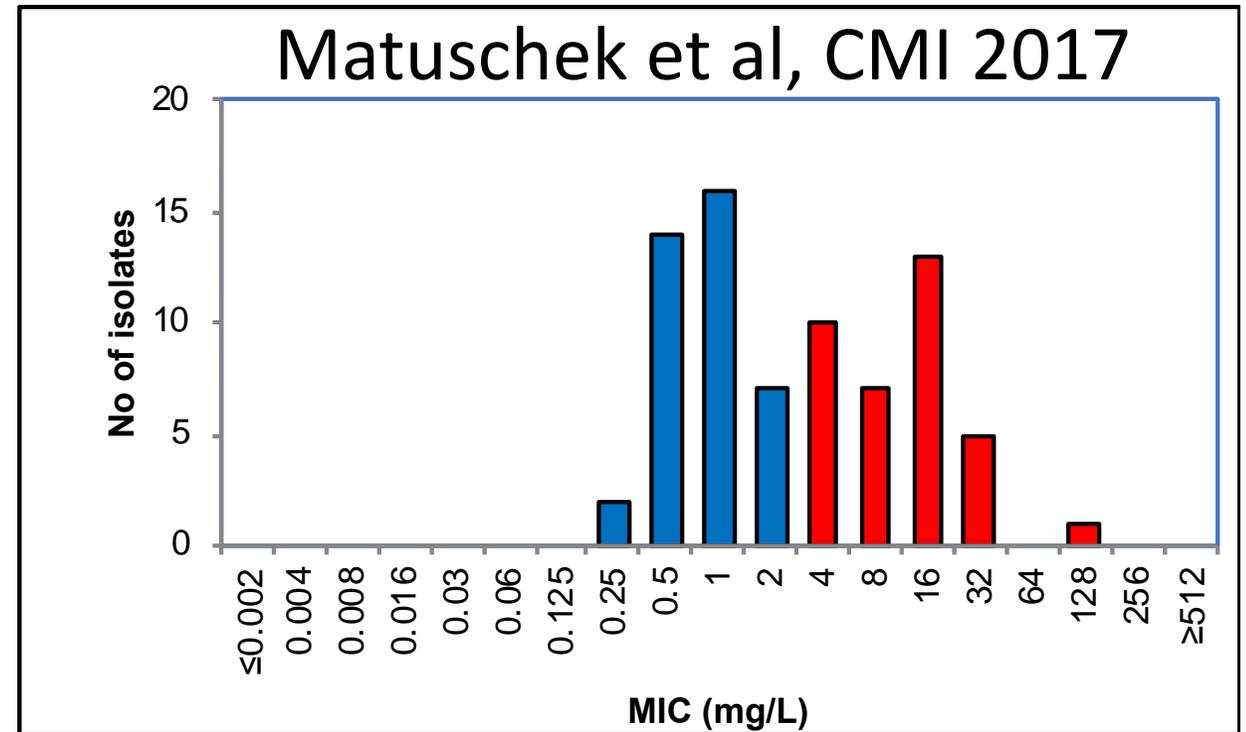
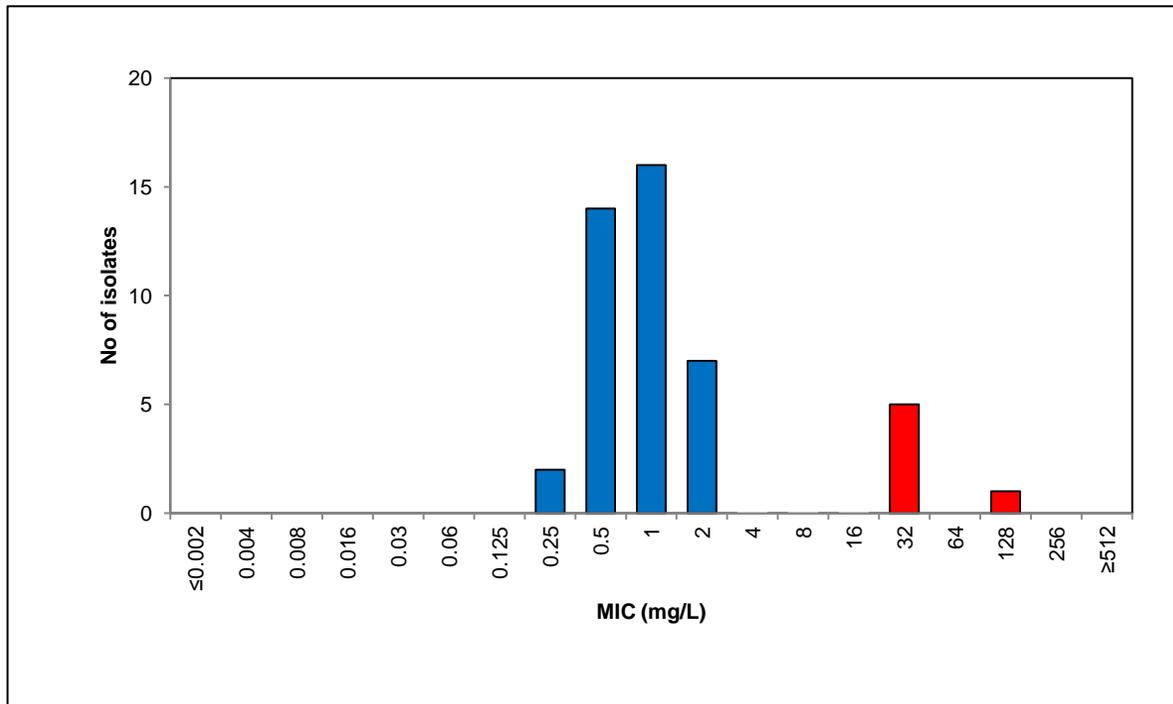
# ATU needed, or?....



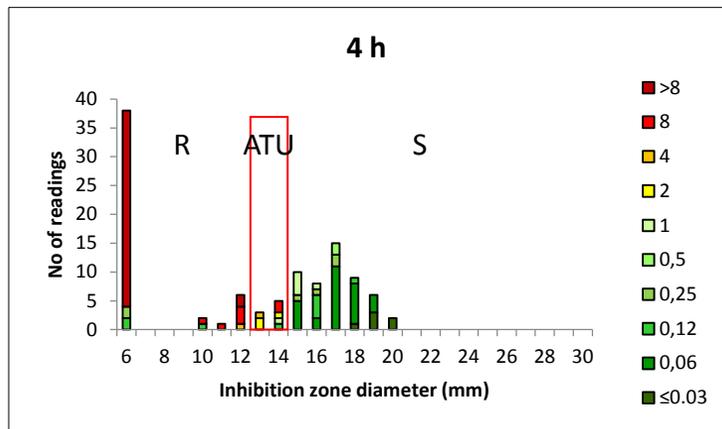
**ATU may be needed because of how resistance mechanisms and their clinical significance develop**

## **Colistin MICs of**

***E. coli, K. pneumoniae, Ps. aeruginosa and Acinetobacter baumannii***



4h

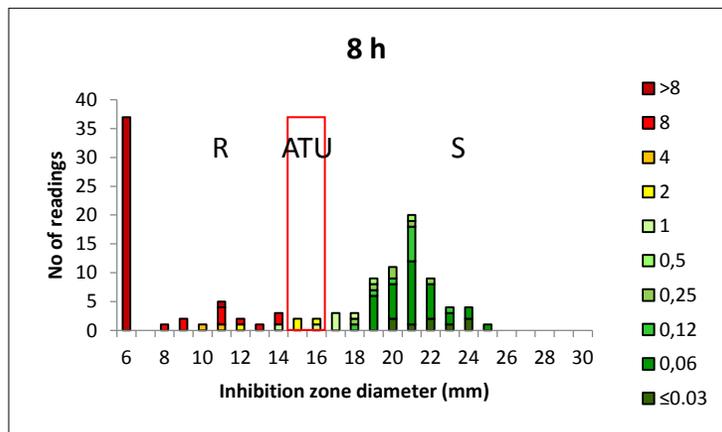


Rapid AST directly from positive blood culture bottles:  
*E. coli* vs cefotaxime 5 µg – zone diameters at 4h, 6h and 8h.

6

ATU may be needed because of uncertainties in the system used.

8h



Appropriate ATUs for the situations exemplified in Table 2 (a dash is for situations where an ATU is not needed):

Agent	Species	ATU – MIC	ATU – disk diffusion
Piperacillin-tazobactam	Enterobacteriaceae	16 mg/L	15 – 19 mm
Ceftaroline	<i>S. aureus</i>	2 mg/L	18 – 20 mm
Ceftaroline	Enterobacteriaceae	1 & 2 mg/L	20 – 23 mm
Tetracycline	<i>S. aureus</i>	-	-
Amoxicillin-clavulanate	Enterobacteriaceae	- (UTI brpt)	- (UTI brpt)
Tobramycin	Enterobacteriaceae	-	-
Cefotaxime	Enterobacteriaceae	-	-
etc			

Dash in this table – ATU not needed.

# EUCAST never used INTERMEDIATE as a buffer

EUCAST has always used INTERMEDIATE as a signal that the organism needed "higher exposure" to the agent (higher dose, a change in administration mode, high exposure at the site of infection).

CLSI has used INTERMEDIATE to signal the need for higher exposure, as a buffer between S and R, and to prevent VME and ME – the wider the intermediate, the fewer VME/Mes.

# **ACTIONS** **in the ATU**

Methodological uncertainty...

is the responsibility of the laboratory

# 1. Repeat the test.

- This is only relevant if there is reason to suspect a mistake or technical error in the primary AST.

## 2. Use an alternative test (perform an MIC)

- This may be relevant if only few therapeutic alternatives.  
If the organism is multi-resistant and one or two of the results are in ATUs, it is advisable to perform an MIC determination for several antibiotics
- Extend the AST with antibiotics such as new cephalosporine-inhibitor combinations and colistin.

NB. concerns about accuracy and precision of MIC determination.

### 3. Do not interpret (report) results in the ATU.

- If therapeutic alternatives, it is reasonable to classify the result in the ATU as “not possible to interpret” or to downgrade it to the nearest category “below”
  - S – I or I – R
  - include a comment or “See note” and perhaps save the isolate.

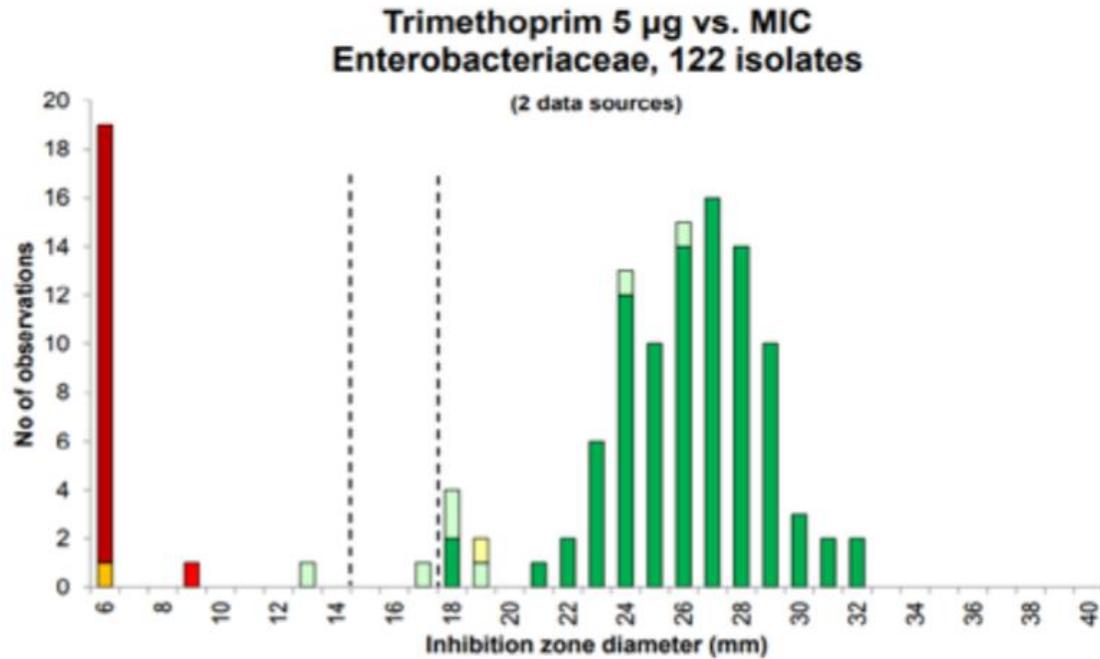
**Do NOT leave blank!**

## 4. Include the ATU in the report.

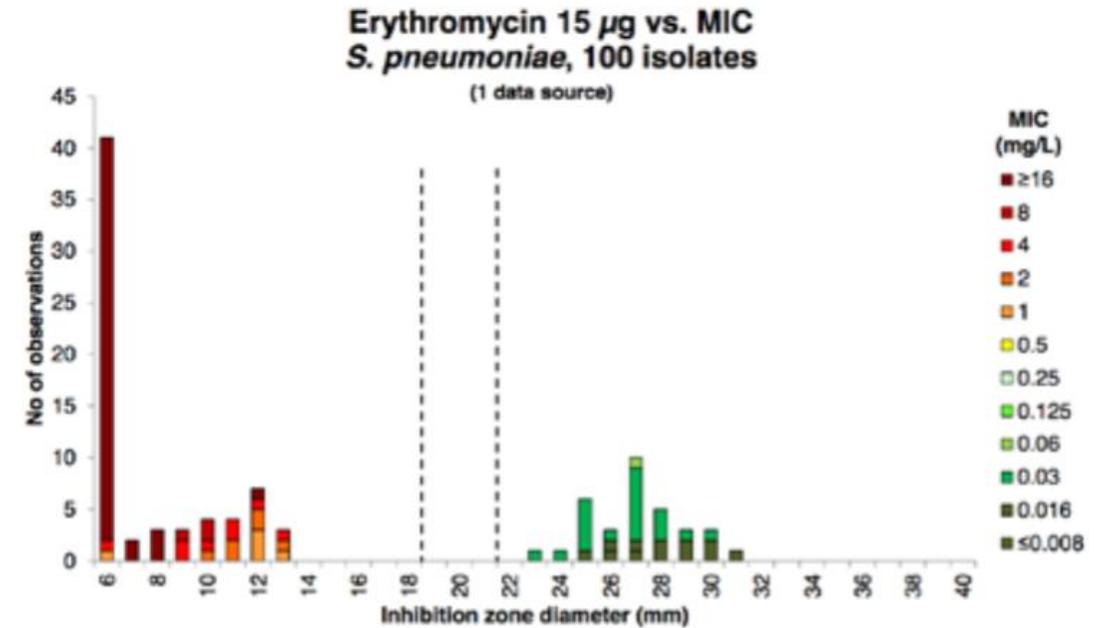
- It is common practice in many other laboratory settings to include information on the **uncertainty** of the reported result. Alternatives:
  - Categorise the result according to breakpoints and include a symbol for which there is an agreed interpretation such as “the technical result is in an area where interpretation is uncertain” or
  - For serious situations, take the opportunity to contact the clinical colleague to explain and discuss the results.

ATU is mostly not needed

# ATU not needed...

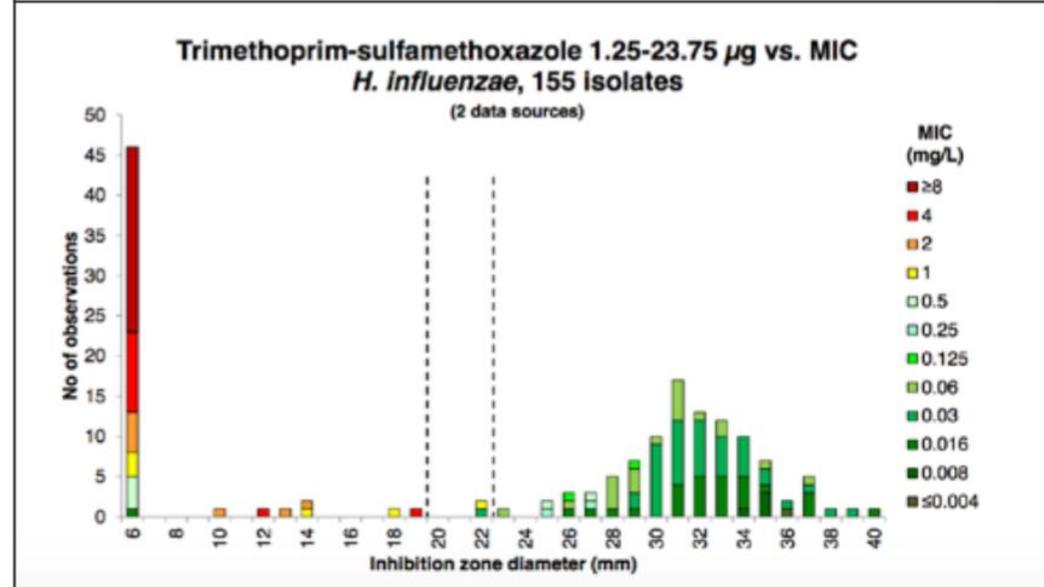
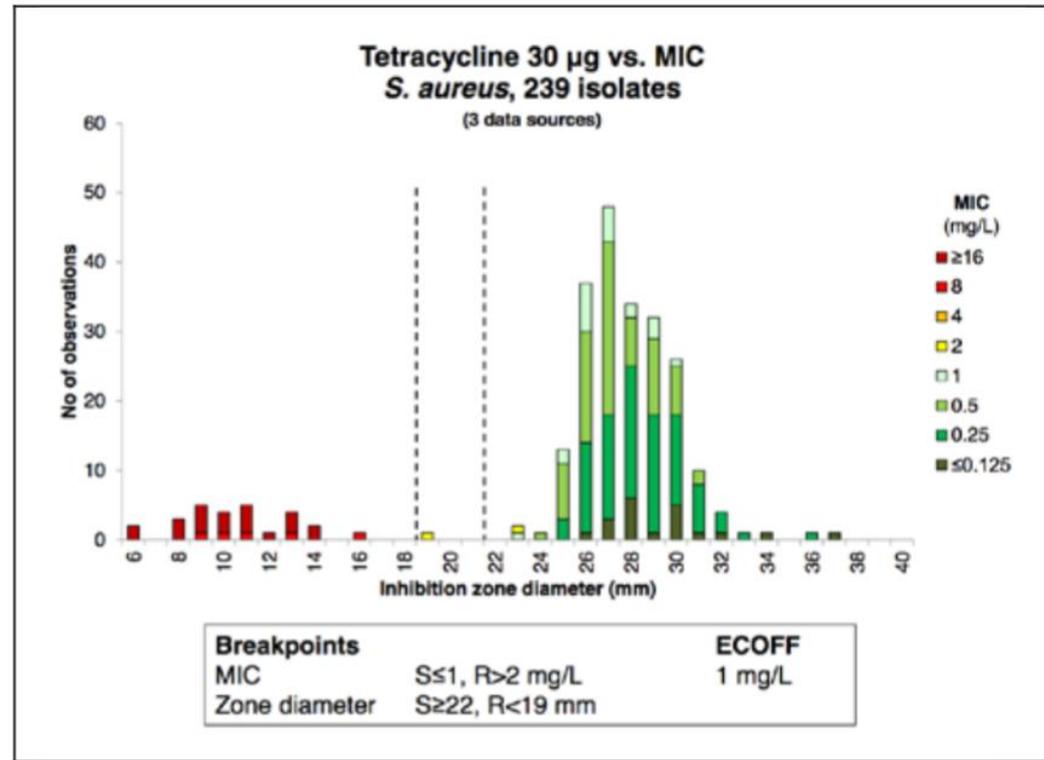


Breakpoints	
MIC	S≤2, R>4 mg/L
Zone diameter	S≥18, R<15 mm

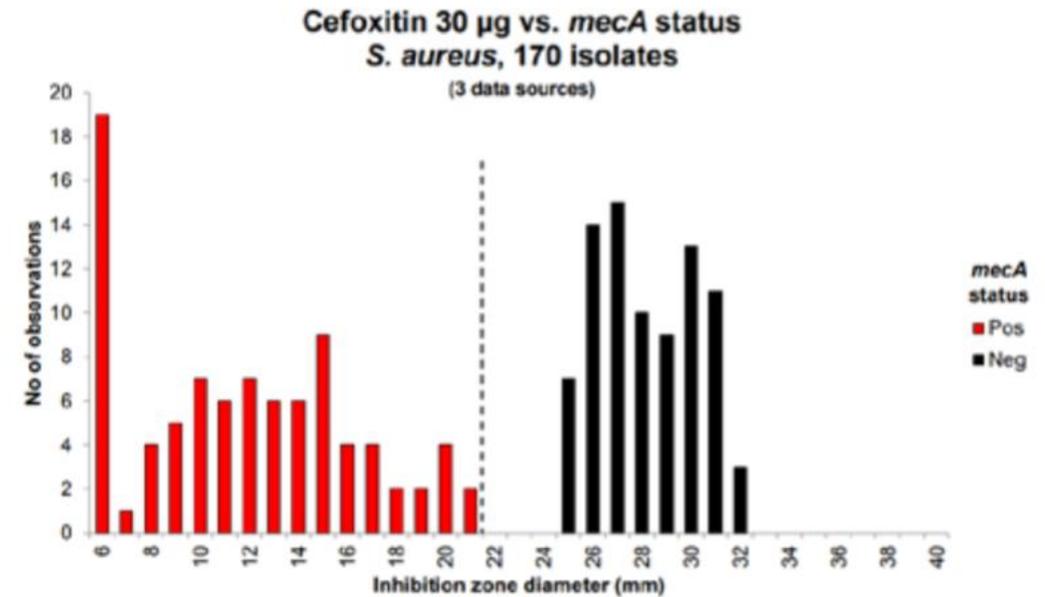
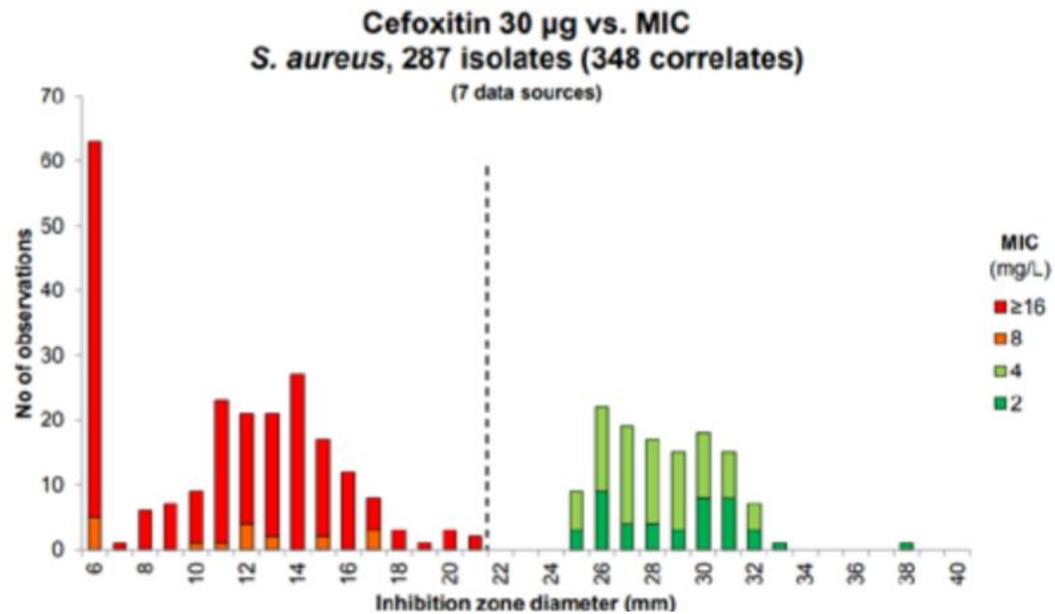


Breakpoints		ECOFF
MIC	S≤0.25, R>0.5 mg/L	0.25 mg/L
Zone diameter	S≥22, R<19 mm	

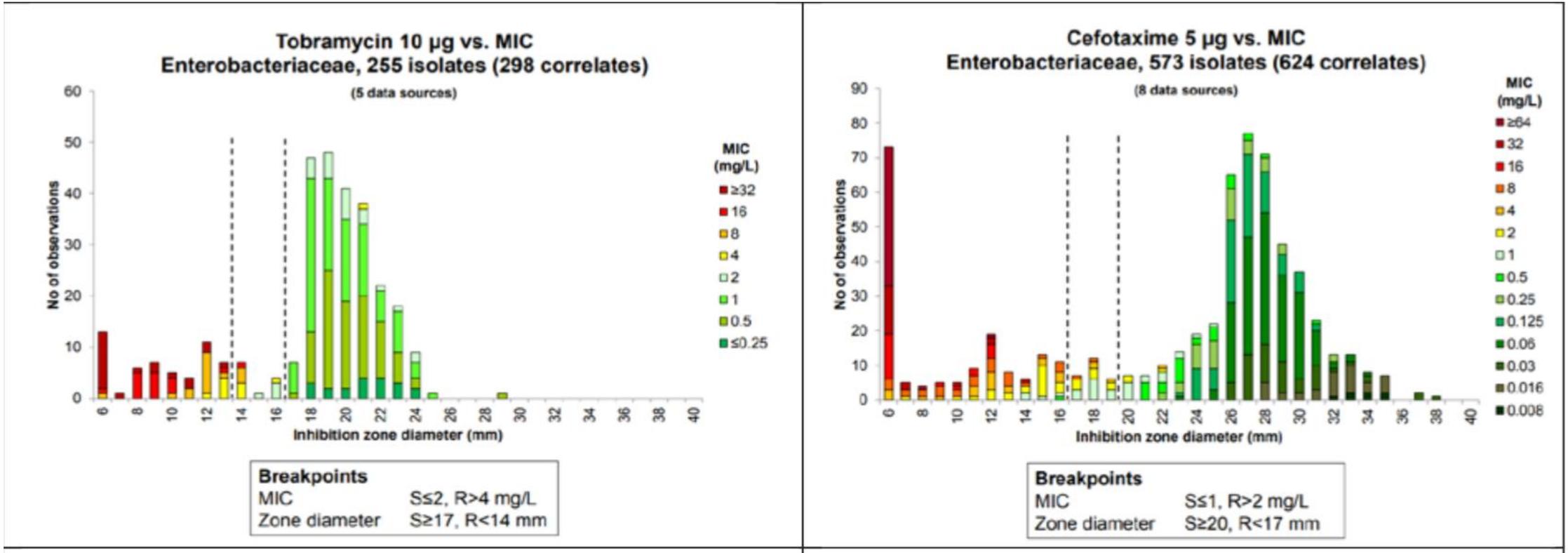
ATU not needed...



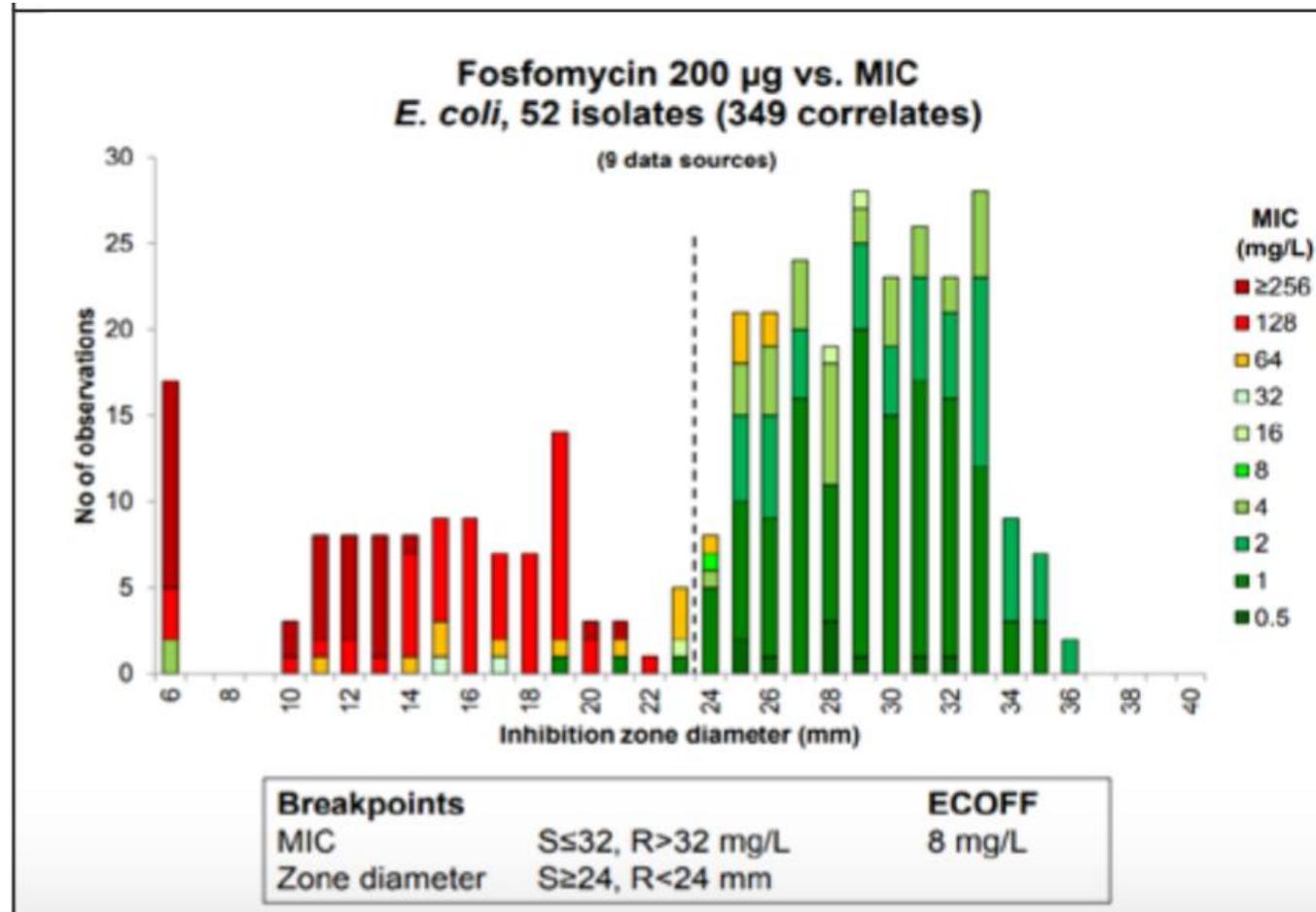
# ATU not needed...



# ATU not needed...



ATU not needed... provided you know how to perform the test properly



**Results in the ATU**

**Discussion**