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Plan Nacional  
Resistencia  
Antibióticos

CoESAnt

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# I Jornada del Comité Español del Antibiograma (COESANT)

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Madrid 24 de noviembre de 2022



# Área de Incertidumbre Técnica

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I JORNADA COESANT

I Jornada del Comité Español del Antibiograma (COESANT)

# Definición



Valores únicos de CMI o rango de valores de diámetros de halo (**superposición** de organismos sensibles y resistentes)



**incertidumbre** en la asignación correcta de la categoría clínica



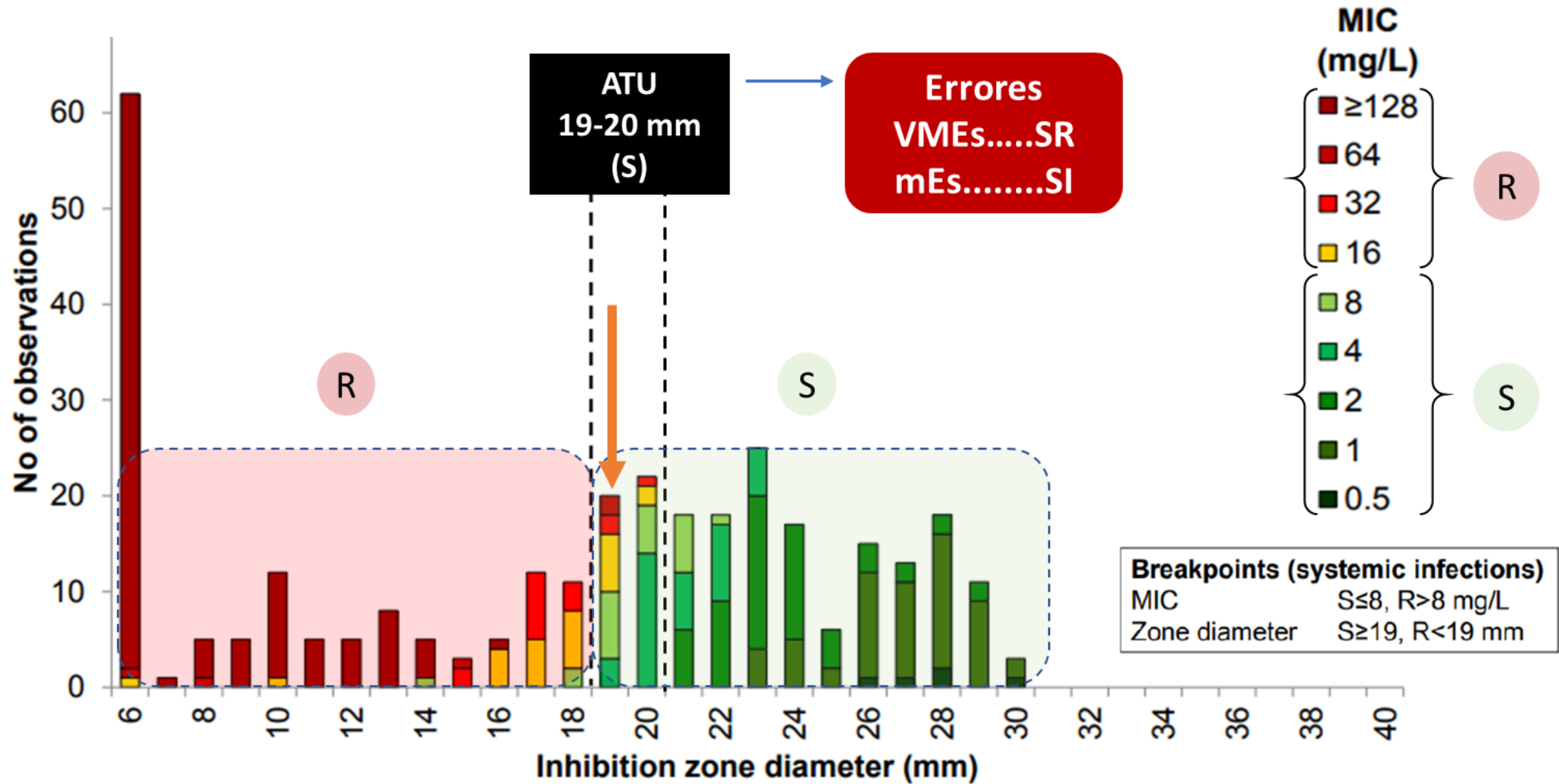
**Errores de categoría clínica**



Resolver las ATUs en el **LABORATORIO**

# Ejemplo

## Amoxicillin-clavulanic acid/Enterobacterales



# ATUS en Bacterias

## ***H. Influenzae (PBP3)***

- Cefuroxime
- Ceftriaxone
- Cefotaxime
- Cefpodoxima
- Cefepime
- Imipenem
- Piperacilina-tazobactam

## ***Pseudomonas spp.***

- Piperacilina
- Piperacilina-tazobactam
- Ceftazidima-avibactam
- Cefiderocol

## ***Enterobacterales***

- Amoxicilina-clavulánico
- Piperacilina-tazobactam
- Ceftolozano-tazobactam
- Meropenem-varbobaactam
- Ceftarolina
- Cefiderocol
- Ciprofloxacino

## ***Staphylococcus spp.***

- Cefoxitina (*S. epidermidis*, *S. lugdunensis*)
- Ceftarolina (*S. aureus*)
- Ceftobiprol (*S. aureus*)
- Tedizolid

# Origen de las ATUS



Difusión con disco



Todas las ATUs

Métodos basdos en la CMI

Tiras de gradiente



Sistemas automatizados de microdilución en caldo

MicroScan WA 96

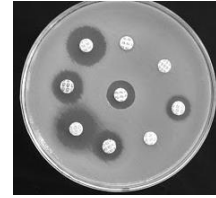
Vitek-2

Phoenix 100

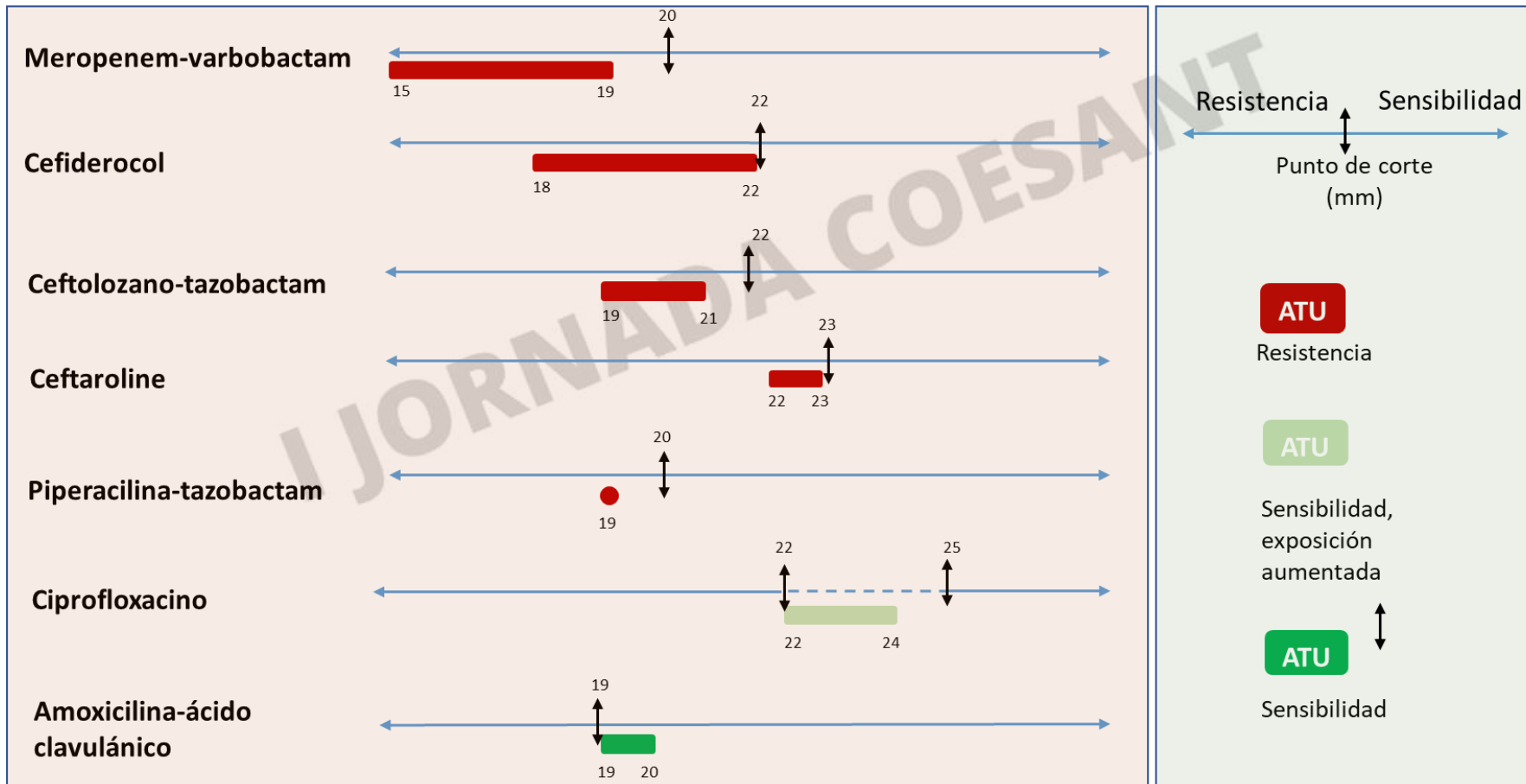
Sensitre

Antimicrobial	MIC breakpoints (mg/L)			Zone diameter breakpoints (mm)		
	S ≤	R >	ATU	S ≥	R <	ATU
<i>Enterobacterales</i>						
• Piperacillin-tazobactam	8	8	16	20	20	19
• Ciprofloxacin	0,25	0,5	0,5	25	22	22-24
<i>S. aureus</i>						
• Ceftaroline	1	2	1	20	17/20	19-20
• Ceftobiprole	2	2	2	17	17	16-17
<i>H. influenzae</i>						
• Cefuroxime iv	1	2	2	27	25	25-27

# ATUs (Difusión con disco)

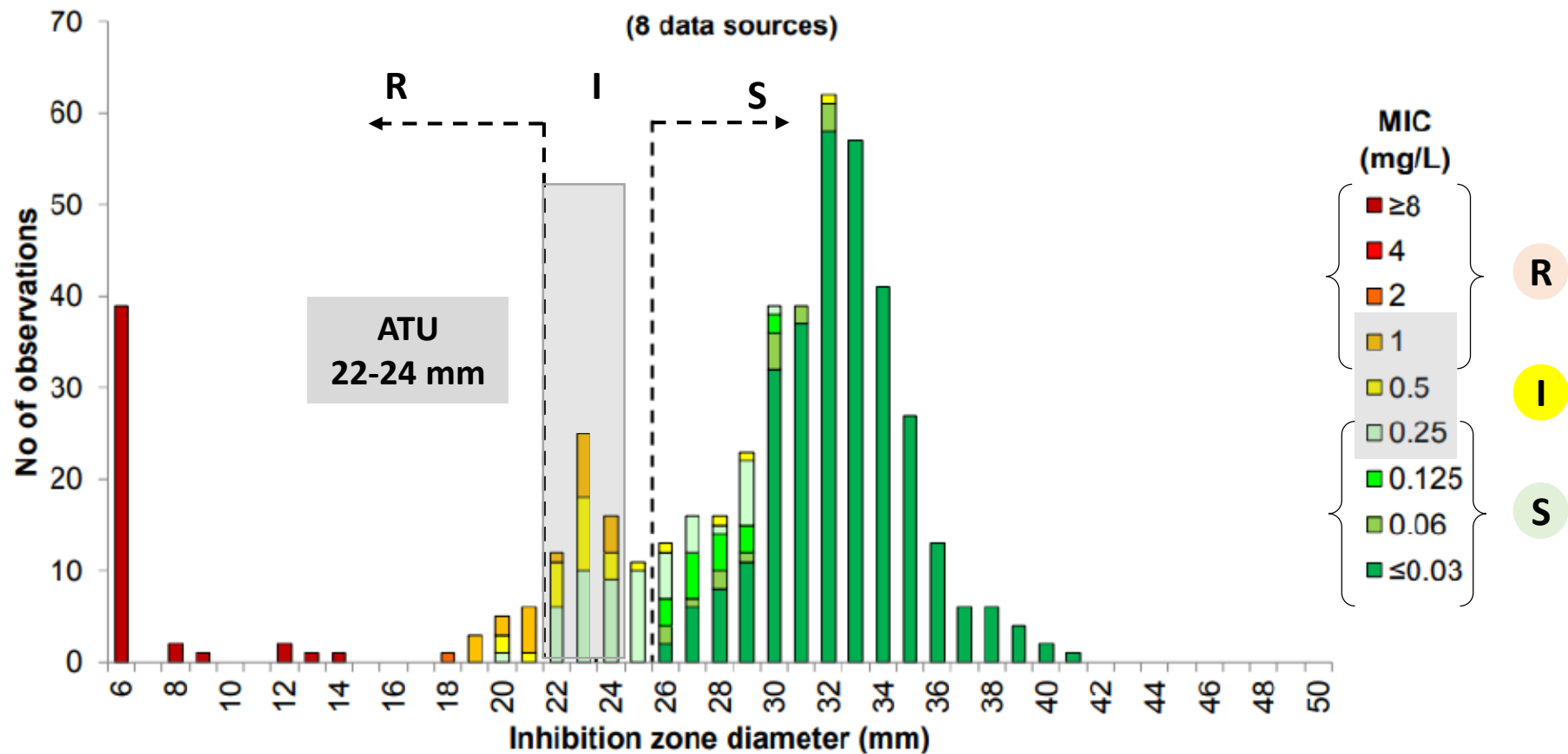


*Enterobacteriales*



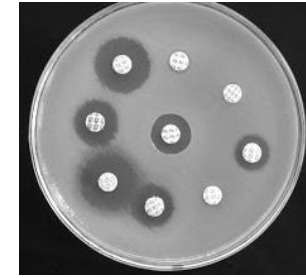
# Ejemplo

## Ciprofloxacin 5 µg vs. MIC Enterobacteriaceae, 471 isolates (490 correlates)

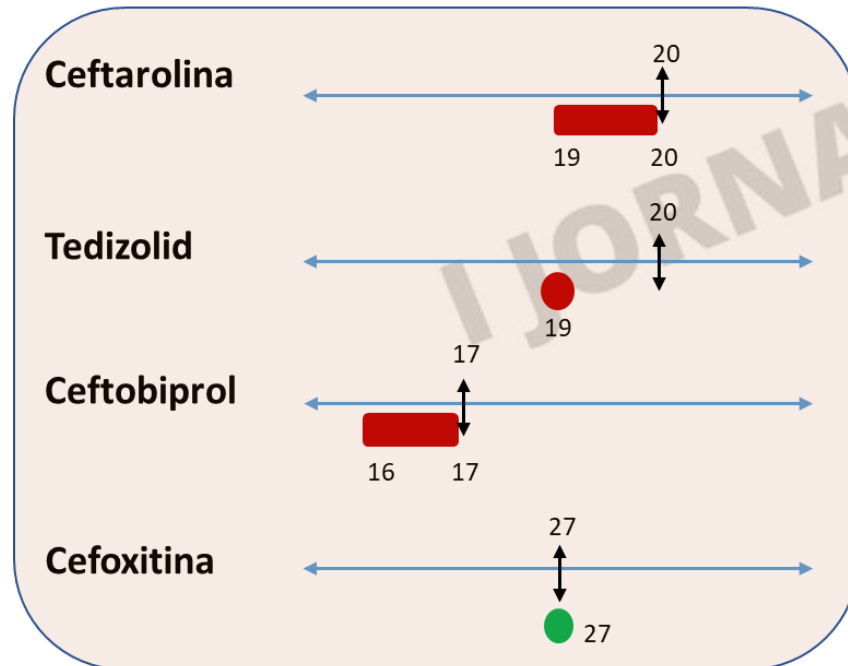




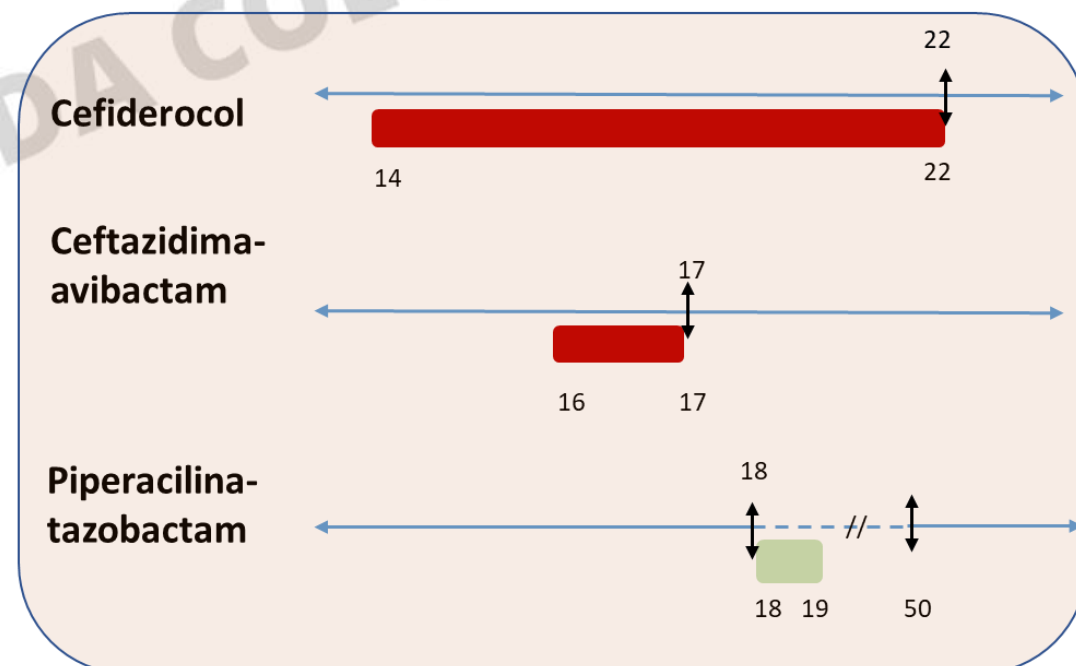
# ATUs (Difusión con disco)



*Staphylococcus spp*



*Pseudomonas spp*

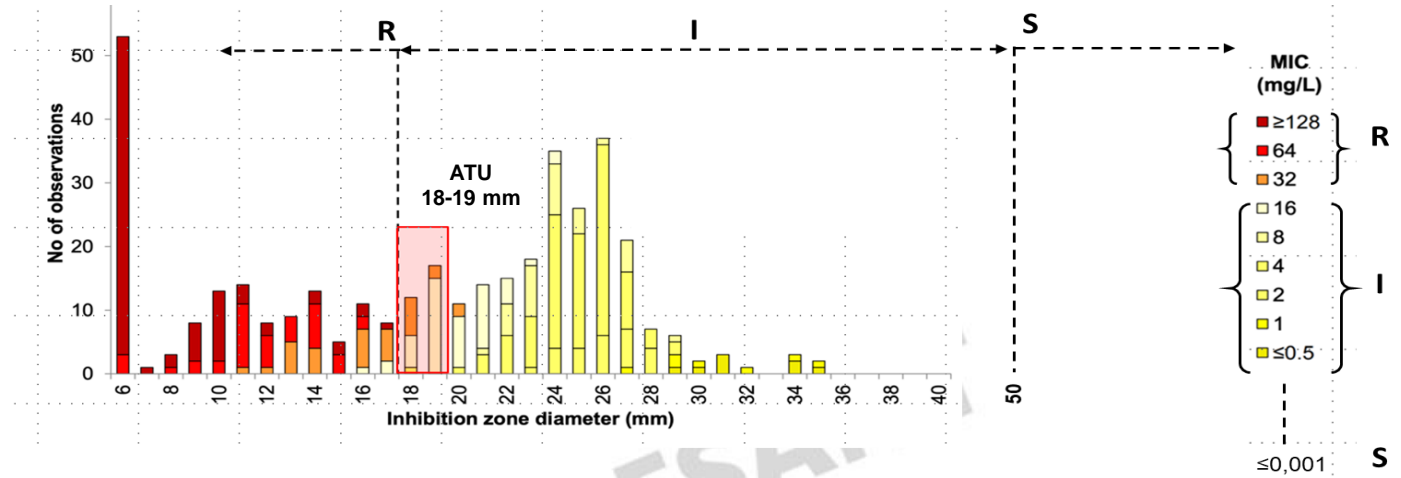


# Ejemplos

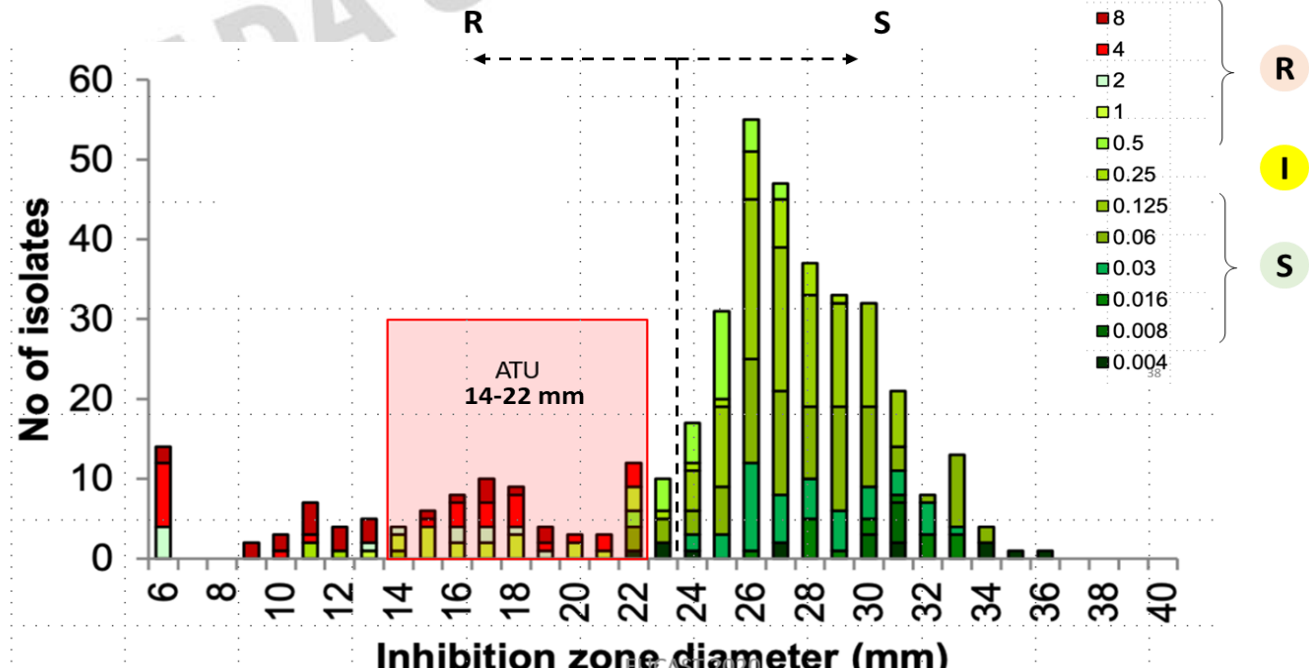

**EUCAST** EUROPEAN COMMITTEE  
ON ANTIMICROBIAL  
 SUSCEPTIBILITY TESTING  
European Society of Clinical Microbiology and Infectious Diseases

*P. aeruginosa*

## Piperacilina-tazobactam

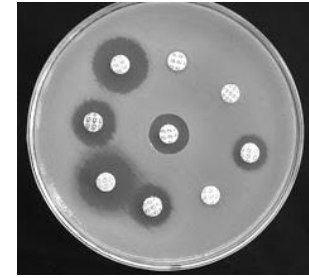


## Cefiderocol

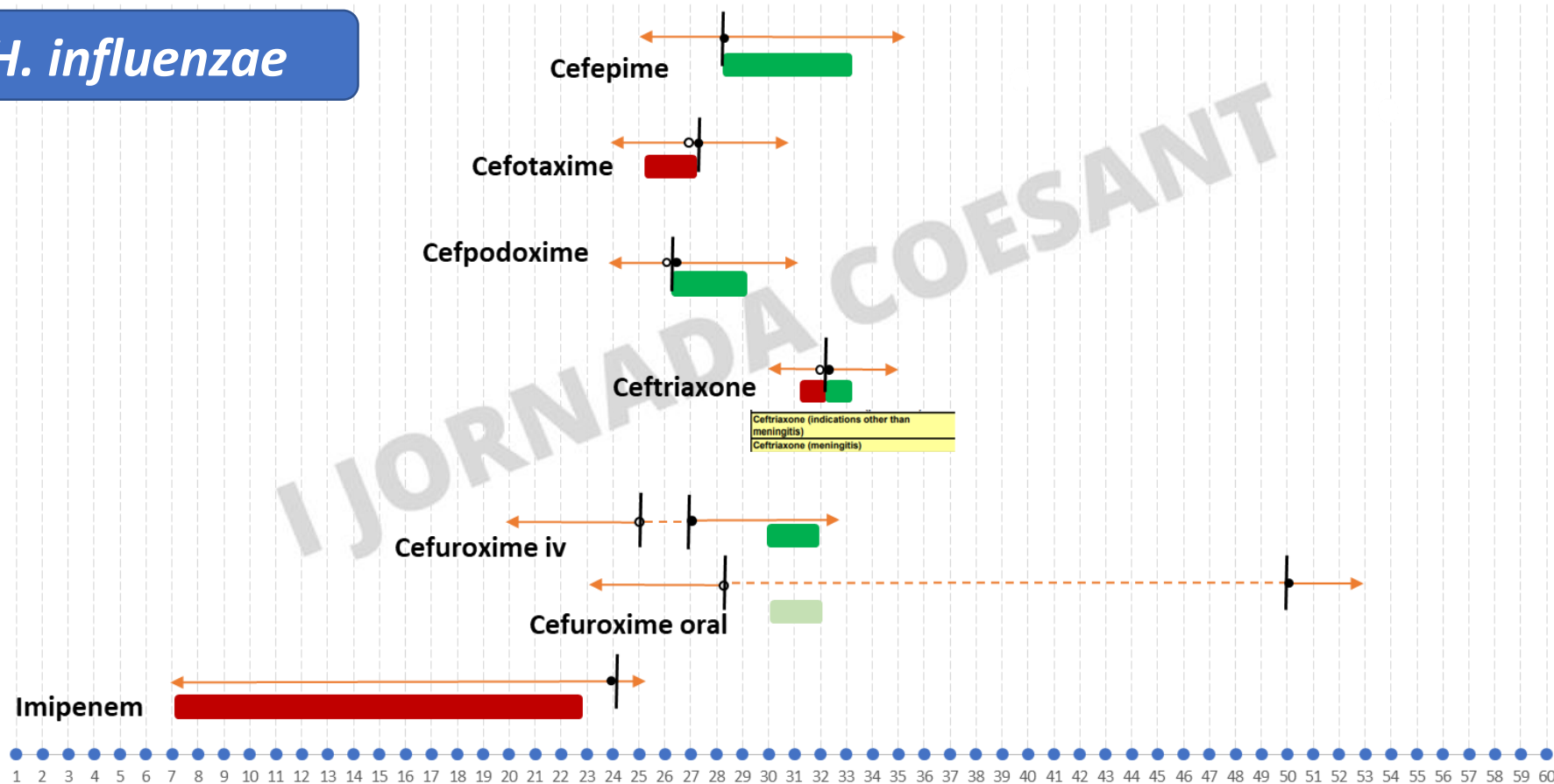


*P. aeruginosa*

# ATUs (Difusión con disco)



*H. influenzae*



Diámetro halo (mm)

# ATUs (métodos de antibiograma basados en la CMI)

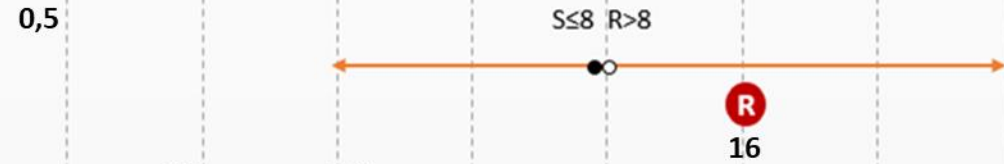


*Enterobacterales*

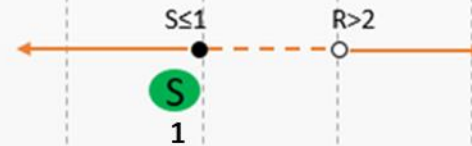
Cirpofloxacino



Piperacilina-tazobactam



Ceftarolina

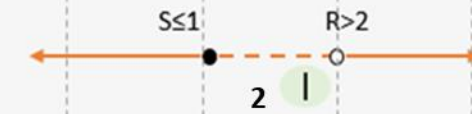


Ceftobiprol



*H. influenzae*

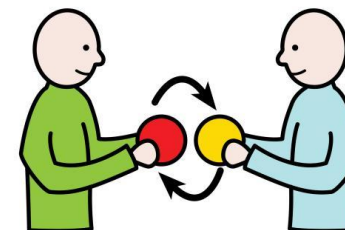
Cefuroxima iv



0,06    0,125    0,25    0,5    1    2    4    8    16    32    64

MIC (mg/L)

# Implementación de las ATUs en el Laboratorio (I)



MicroScan WA 96



Vitek-2



Phoenix 100



Sensititre



- Comprobar que las concentraciones de antimicrobianos de los paneles o tarjetas incluyen los valores de CMI s de las ATU.
- Si las ATUs están fuera de la serie de diluciones, es imposible el control.

ATU ciprofloxacino = 0,5 mg/L

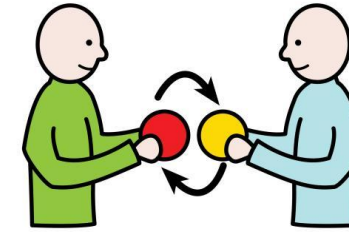
## Gram-negative MIC panels

Panel name	Neg MIC 42	Neg MIC 43	Neg MIC 45	Neg MIC 46	ES:L plus	
MicroScan catalog number	B1017-419	B1017-420	B1017-424	B1017-425	B1027-101	
Languages	EN, ES, FR, PT	EN, ES, FR, PT	EN, ES, FR, PT	EN, ES, FR, PT	EN, ES, FR, PT	
Antimicrobial agent	µg/mL	µg/mL	µg/mL	µg/mL	µg/mL	Abbr.
Ciprofloxacin	0.5-4	0.5-2	1-2	1-2	-	Cp

## Gram-negative combo panels

Panel name	Neg Combo 67	Neg Combo 68	Neg/Urine Combo 51	Neg/Urine Combo 55	Neg/Urine Combo 61	Neg/Urine Combo 62	Neg/Urine Combo 73
MicroScan catalog number	B1017-421	B1017-422	B1017-407	B1017-409	B1017-414	B1017-416	B1017-423
Languages	EN, ES, FR, PT	EN, ES, FR, PT	EN, ES, FR, P T	EN, ES, FR, PT	EN, ES, FR, PT	EN, ES, FR, PT	EN, ES, FR, PT
Antimicrobial agent	µg/mL	µg/mL	µg/mL	µg/mL	µg/mL	µg/mL	µg/mL
Ciprofloxacin	0.5-2	1-2	1-4	1-2	1-2	1-2	1-2

# Implementación de las ATUs en el Laboratorio (II)



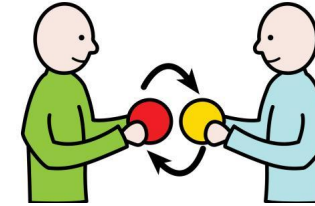
**SIN** soporte informático

- Listado **manual** de especies bacterianas y antimicrobianos con ATUs.
- Categorización clínica **manual** (S, I y R) a partir de resultados de CMI o de difusión con discos.

**Enterobacterales\***  
Expert Rules and Intrinsic Resistance Tables

Cephalosporins <sup>1</sup>	MIC breakpoints (mg/L)			Disk content (µg)	Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Cefaclor	-	-			-	-	
Cefadroxil (uncomplicated UTI only)	16	16		30	12	12	
Cefalexin (uncomplicated UTI only)	16	16		30	14	14	
Cefazolin (infections originating from the urinary tract), <i>E. coli</i> , and <i>Klebsiella</i> spp. (except <i>K. aerogenes</i> )	0.001 <sup>2</sup>	4 <sup>2</sup>		30	50 <sup>A</sup>	20 <sup>A</sup>	
Cefepime	1	4		30	27	24	
Cefiderocol	2 <sup>3</sup>	2 <sup>3</sup>		30	22	22	18-22
Cefixime (uncomplicated UTI only)	1	1		5	17	17	
Cefotaxime (indications other than meningitis)	1	2		5	20	17	
Cefotaxime (meningitis)	1	1		5	20	20	
Cefoxitin (screen only) <sup>4</sup>	Note <sup>4</sup>	Note <sup>4</sup>		30	19	19	
Cefpodoxime (uncomplicated UTI only)	1	1		10	21	21	
Ceftaroline	0.5	0.5		5	23	23	22-23
Ceftazidime	1	4		10	22	19	
Ceftazidime-avibactam	8 <sup>5</sup>	8 <sup>5</sup>		10-4	13	13	
Ceftibuten (infections originating from the urinary tract)	1	1		30	23	23	
Ceftobiprole	0.25	0.25		5	23	23	
Ceftolozane-tazobactam <sup>6</sup>	2 <sup>7</sup>	2 <sup>7</sup>		30-10	22	22	19-21
Ceftriaxone (indications other than meningitis)	1	2		30	25	22	
Ceftriaxone (meningitis)	1	1		30	25	25	
Cefuroxime iv, <i>E. coli</i> , <i>Klebsiella</i> spp. (except <i>K. aerogenes</i> ), <i>Raoultella</i> spp. and <i>P. mirabilis</i>	0.001	8		30	50	19	
Cefuroxime oral (uncomplicated UTI only), <i>E. coli</i> , <i>Klebsiella</i> spp. (except <i>K. aerogenes</i> ), <i>Raoultella</i> spp. and <i>P. mirabilis</i>	8	8		30	19	19	

# Implementación de las ATUs en el Laboratorio (III)



**CON** soporte informático

- **Reglas de experto:**
  - ❖ Si *E. coli* y piperacilina-tazobactam y CMI 16 mg/L (o diámetro de halo 18-19 mm), ENTONCES realizar la ACCION\*...
- Una "señal de aviso" (sonido, luz, asterisco en el informe) de ATU.
- La categorización clínica (S, I y R) se realiza **automáticamente** al introducir los resultados de CMI o de difusión con discos.

Cefoxitin zone-mm within ATU – marked by the system with an orange colour.

Antibiotic	Result
Oxacillin_OX (beregnet)	S
Cefoxitin_FOX_D	S (26)
Gentamicin_CN_D	S (28)
Erytromycin_E_D	R (6)
Klindamycin_DA_D	R (30)
Fusidin_FD_D	S (34)
MLS	Induserbar

Cefoxitin ATU is resolved with *mecA*-PCR. Consequently, oxacillin is reported **R** ATU is marked as resolved, and changes colour to purple.

Antibiotic	Result
Oxacillin_OX (beregnet)	R
Cefoxitin_FOX_D	S (26)
Gentamicin_CN_D	S (28)
Erytromycin_E_D	R (6)
Klindamycin_DA_D	R (30)
Fusidin_FD_D	S (34)
MLS	Induserbar

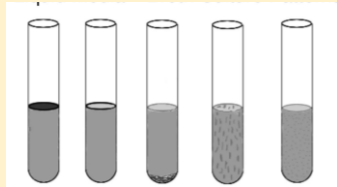




# Acciones del Laboratorio de Microbiología

## Acciones técnicas

- **Repetir** la prueba (sospecha de error técnico; ej preparación inóculo).



- **Método alternativo** (cefotaxima vs PCR mecA, Etest) si escasas opciones de tratamiento (infecciones graves).



## Acciones informativas

- Informar como “**valor obtenido incierto**” (sin incluir categoría clínica) ± **comentario**.
- Informar **resistente** (si existen otras alternativas terapéuticas).
- **Discutir** las ATUs con el clínico.



# Impacto de las ATUs en el laboratorio

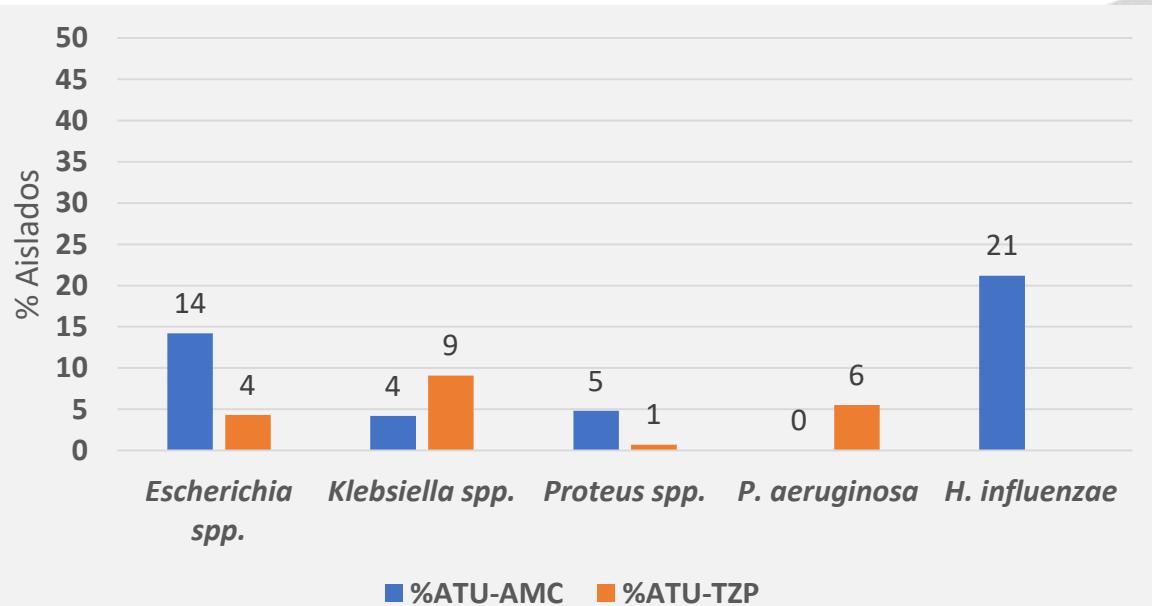
European Journal of Clinical Microbiology & Infectious Diseases (2022) 41:203–207  
<https://doi.org/10.1007/s10096-021-04364-6>

ORIGINAL ARTICLE

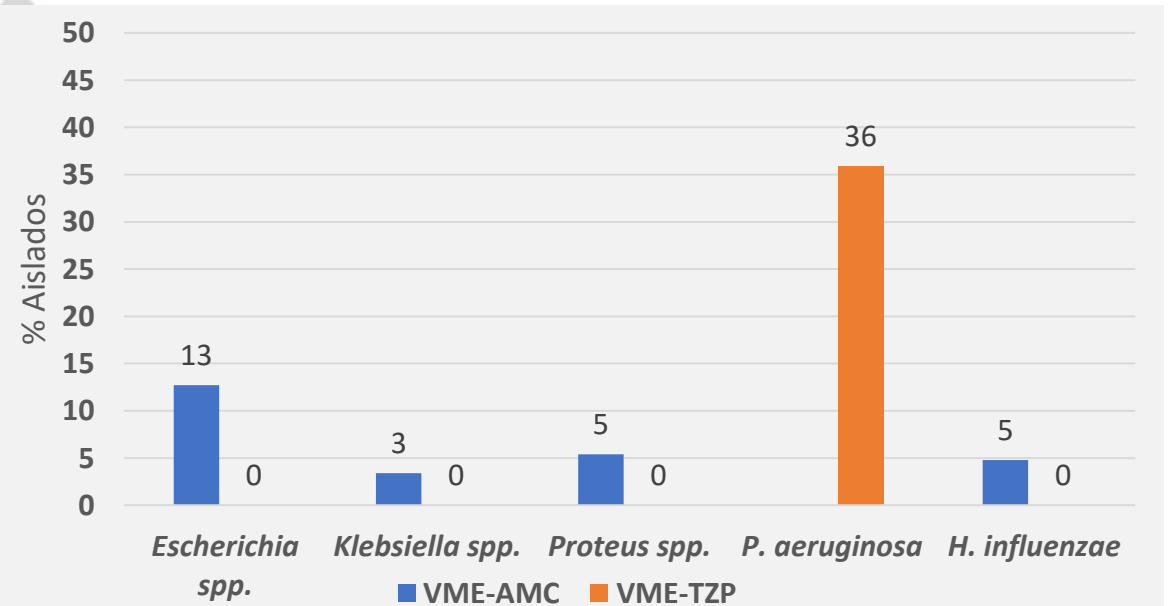
## Impact of the introduction of EUCAST's concept of "area of technical uncertainty"

Eveline Van Honacker<sup>1</sup> · S. Vandendriessche<sup>1</sup> · L. Coorevits<sup>1</sup> · B. Verhasselt<sup>1,2</sup> · J. Boelens<sup>1,2</sup>

### A % ATU



### B % VMEs (Falsa sensibilidad)



- **Disk diffusion** antibiotic susceptibility testing was read and interpreted by ADAGIO 93400 automated system (Bio-Rad).
- **AMC and TZP.**
- In case of an inhibition zone in the **ATU**, strains were retested using gradient minimal inhibitory concentration method (**Etest**, BioMérieux).

# ¿Impacto ATU ciprofloxacino?

HUVM  
Enterobacterias  
abril-octubre 2022

Neg Multidrug Resistant MIC 1  
MicoScan WalkAway 96

CMI 0,5 mg/L

Comprobación con  
disco de  
ciprofloxacina

## A % ATUs

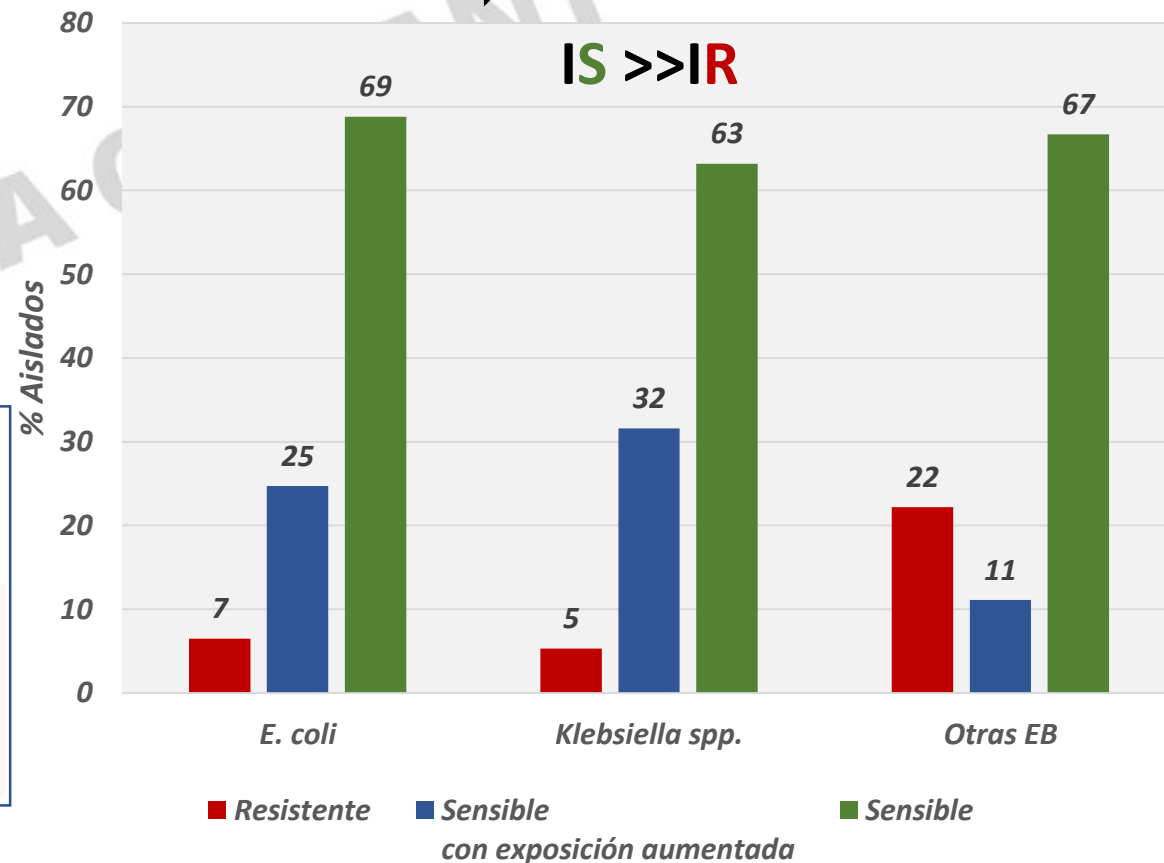
- 2,9% *E. coli* (N=2696)
- 1,6% *K. pneumoniae* (n=1096)

## B Errores de categoría

IS + IR

Errores  
menores

75%..... *E. coli*  
69%..... *Klebsiella* spp.  
89%..... otras EB



# CONCLUSIONES

1. Las ATUs están **definidas** por un único valor de CMI o un rango generalmente corto de valores de diámetro de halo de inhibición.
2. Son muy útiles para **alertar** al personal del **laboratorio** cuando hay un problema de interpretación/categorización (S, I, R).
3. Correcta **categorización** para evitar **errores** de categoría clínica (**VMES**>>MEs).
4. La forma de **resolver** las ATUs dependerá de factores microbiológicos (antimicrobiano, microorganism....) y estratégicos (posibilidad de incorporar reglas de expert.....).

# Gracias

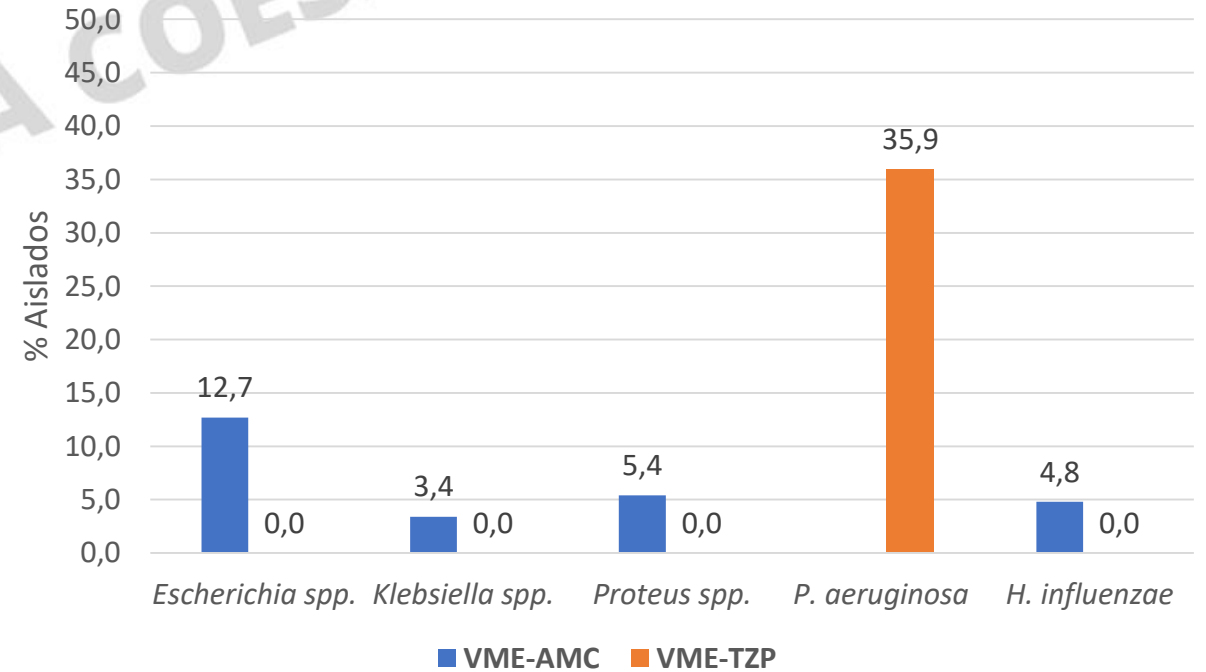
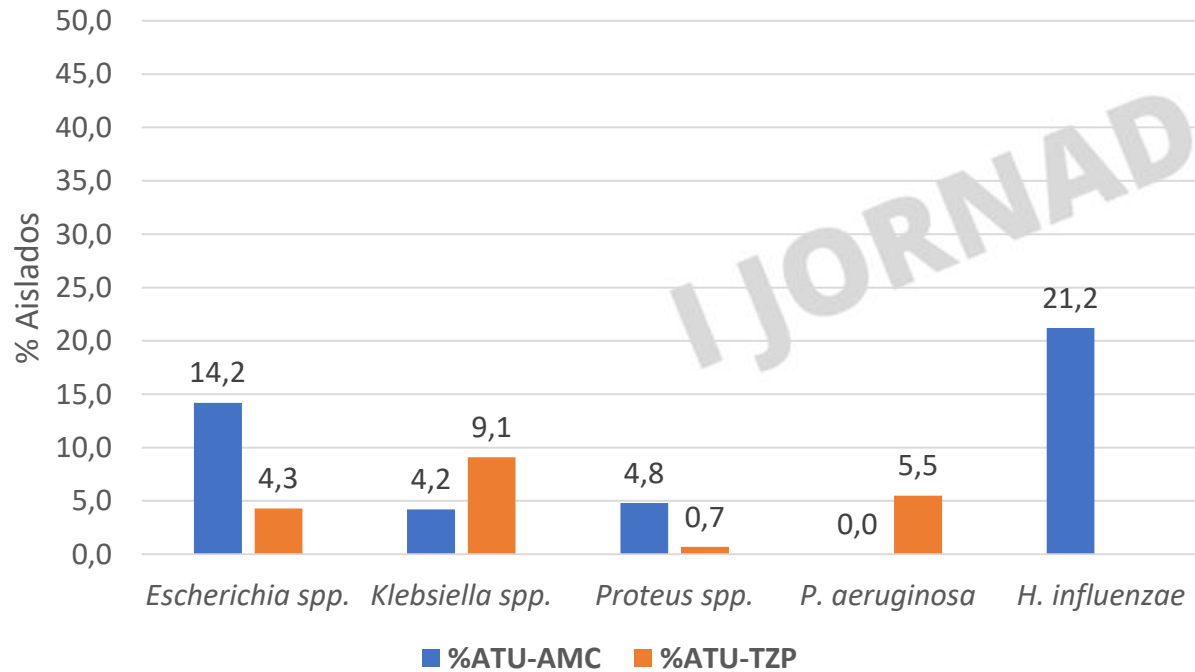


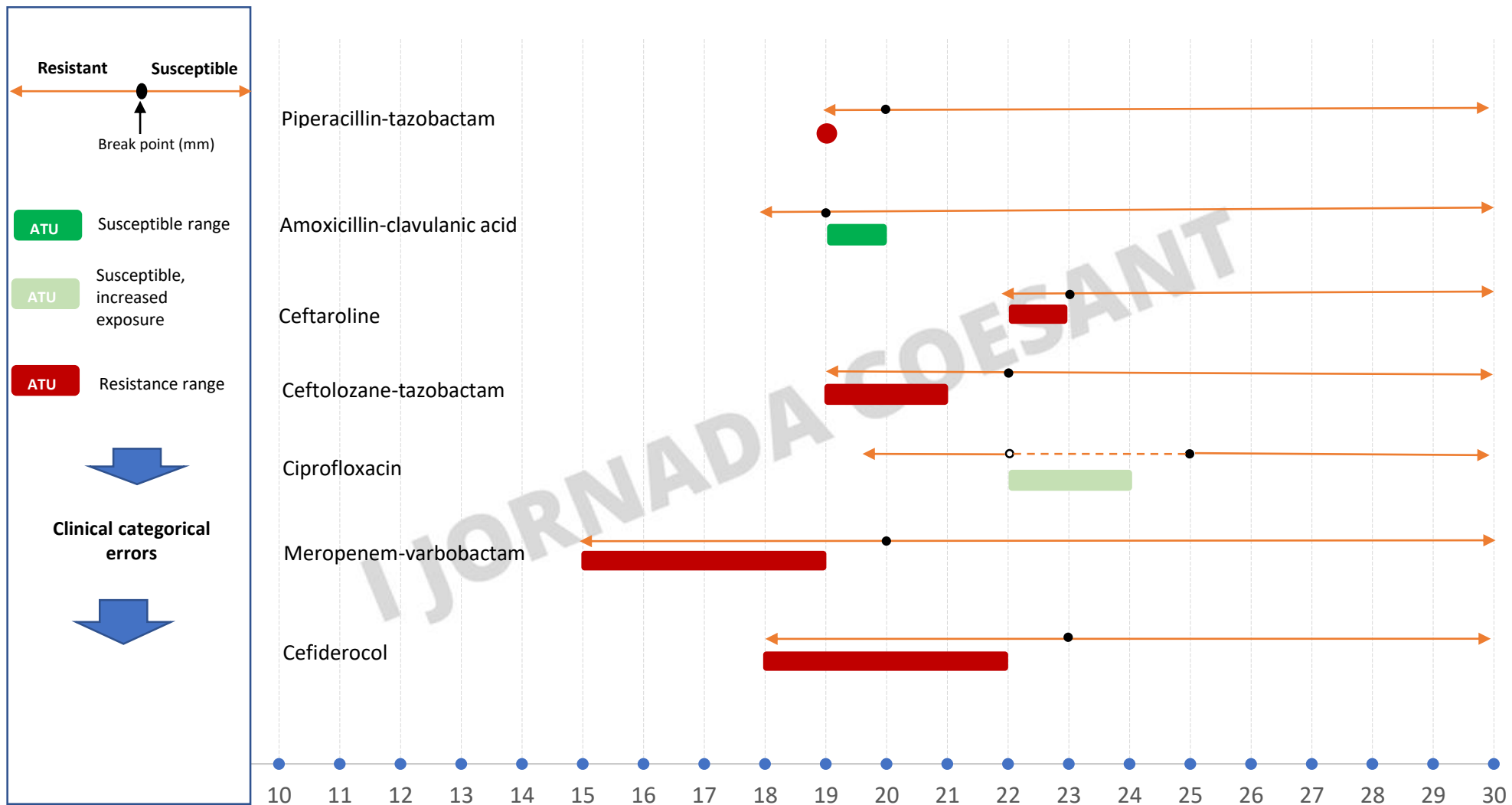


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## Impact of the introduction of EUCAST's concept of "area of technical uncertainty"

Eveline Van Honacker<sup>1</sup> · S. Vandendriessche<sup>1</sup> · L. Coorevits<sup>1</sup> · B. Verhasselt<sup>1,2</sup> · J. Boelens<sup>1,2</sup>





## EUCAST Clinical Breakpoint Tables v. 12.0, valid from 2022-01-01

### *Enterobacterales*

Antimicrobial	MIC breakpoints (mg/L)				Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Amoxicillin-clavulanic acid*	8	8			19	19	19-20
Piperacillin-tazobactam	8	8	16		20	20	19
Cefiderocol	2	2			22	22	18-22
Ceftaroline	0,5	0,5			23	23	22-23
Ceftolozane-tazobactam	2	2			22	22	19-21
Meropenem-varbobaactam	8	8			20	20	15-19
Ciprofloxacin	0,25	0,5	0,5		25	22	22-24

\*Systemic infections

### *Pseudomonas spp.*

Antimicrobial	MIC breakpoints (mg/L)				Zone diameter breakpoints (mm)		
	S ≤	R >	ATU		S ≥	R <	ATU
Cefiderocol	2	2			22	22	14-22
Ceftazidime-avibactam	8	8			17	17	16-17

## *Staphylococcus spp.*

Antimicrobial	MIC breakpoints (mg/L)			Zone diameter breakpoints (mm)		
	S ≤	R >	ATU	S ≥	R <	ATU
<b>Cefoxitin</b> ( <i>S. epidermidis</i> , <i>S. lugdunensis</i> )	-	-		27	27	27
<b>Ceftaroline</b> ( <i>S. aureus</i> )	1	2	<b>1</b>	20	17/20*	19-20
<b>Ceftobiprole</b> ( <i>S. aureus</i> )	2	2	<b>2</b>	17	17	16-17
<b>Tedizolid</b>	0,5	0,5		20	20	19

\*17 mm: other than pneumonia

\*18 mm: pneumonia



## *H. influenzae*

Antimicrobial	MIC breakpoints (mg/L)			Zone diameter breakpoints (mm)		
	S ≤	R >	ATU	S ≥	R <	ATU
<b>Piperacillin-tazobactam</b>	0,25	0,25		27	27	24-27
<b>Cefepime</b>	0,25	0,25		28	28	28-33
<b>Cefotaxime (± meningitis)</b>	0,125	0,125		27	27	25-27
<b>Cefpodoxime</b>	0,25	0,25		26	26	26-29
<b>Ceftriaxone (± meningitis)</b>	0,125	0,125		32	32	31-33
<b>Cefuroxime</b>						
iv	1	2	<b>2</b>	27	25	25-27
oral	0,001	1		50	27	25-27
<b>Imipenem</b>	2	2		20	20	6-19

Cefoxitin zone-mm within ATU  
 – marked by the system with an orange colour.

- Funn 2 (STEPID / R) Uferdig

Staphylococcus epidermidis B S M F I rikelig

+ Identifikasjon F2

- Resistensbestemmelse F2 Uferdig

.TEAM2 biomic		
Hvite staf generell syk disk		
Oxacillin_OX (beregnet)	X	S
Cefoxitin_FOX_D		S (26)
Gentamicin_CN_D	X	S (28)
Erytromycin_E_D	X	R (6)
Klindamycin_DA_D	X	R (30)
Fusidin_FD_D	X	S (34)
MLS		Induserbar



Cefoxitin ATU is resolved with *mecA*-PCR.  
 Consequently, oxacillin is reported **R**  
 ATU is marked as resolved, and changes colour to purple.

- Funn 2 (STEPID / R) Ferdig

Staphylococcus epidermidis B S M F I rikelig

+ Identifikasjon F2

- Resistensbestemmelse F2

.TEAM2 biomic		Utført
Mec-A gen		Påvist
Hvite staf generell syk disk		
Oxacillin_OX (beregnet)	X	R
Cefoxitin_FOX_D		S (26)
Gentamicin_CN_D	X	S (28)
Erytromycin_E_D	X	R (6)
Klindamycin_DA_D	X	R (30)
Fusidin_FD_D	X	S (34)
MLS		Induserbar

Final report is not possible due to unresolved ATU!

«Antimicrobial agent within ATU - consider measures/supplemental tests and check what is reported»

- Funn 2 (STEPID / R)

Melding fra nettside

Staphylococcus epidermidis

+ Identifikasjon F2

- Resistensbestemmelse F2

.TEAM2 biomic		
Hvite staf generell syk disk		
Oxacillin_OX (beregnet)	X	S
Cefoxitin_FOX_D		S (26)
Gentamicin_CN_D	X	S (28)
Erytromycin_E_D	X	R (6) 28
Klindamycin_DA_D	X	R (30)
Fusidin_FD_D	X	S (34)
MLS		Induserbar

ATU-zoominar\_NOV\_2020.pdf - Adobe Acrobat Reader (64-bit)

Archivo Edición Ver Firmar Ventana Ayuda

Inicio Herramientas ATU-zoominar\_NO... x

28 / 43

Iniciar sesión

## Area of Technical Uncertainty (ATU)

- The ATU does **NOT** interfere with S, I and R interpretation.
- ATU is **NOT** a susceptibility category – it is to **alert laboratory staff** where there is a predictable issue with interpretation.
- The ATU is **NOT** to compensate for poor methodological skills – on the contrary, AST today require more skills than ever before.
- The ATU is defined by a **single MIC-value** or a **short range of zone diameter** values.
- How the ATU is dealt with depends on the situation (the sample, the agent, the infecting organism).

EUCAST 2020 30

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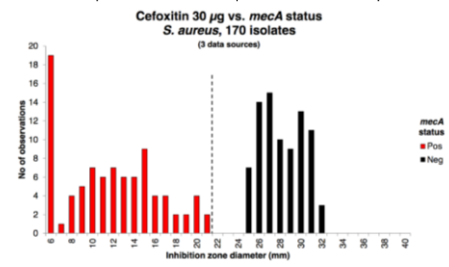
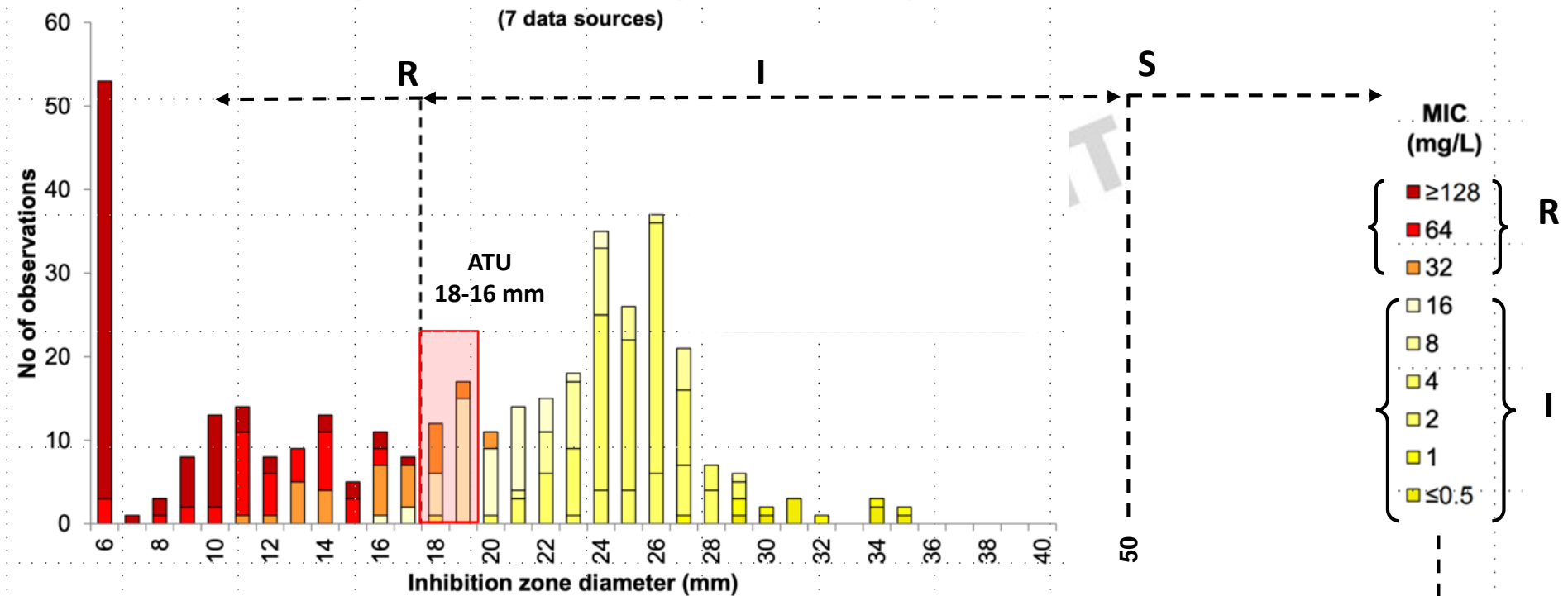
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Prueba gratis de 7 días

BCE 1.78% 13:45 21/11/2022

### Piperacillin-tazobactam 30-6 µg vs. MIC *P. aeruginosa*, 217 isolates (376 correlates)

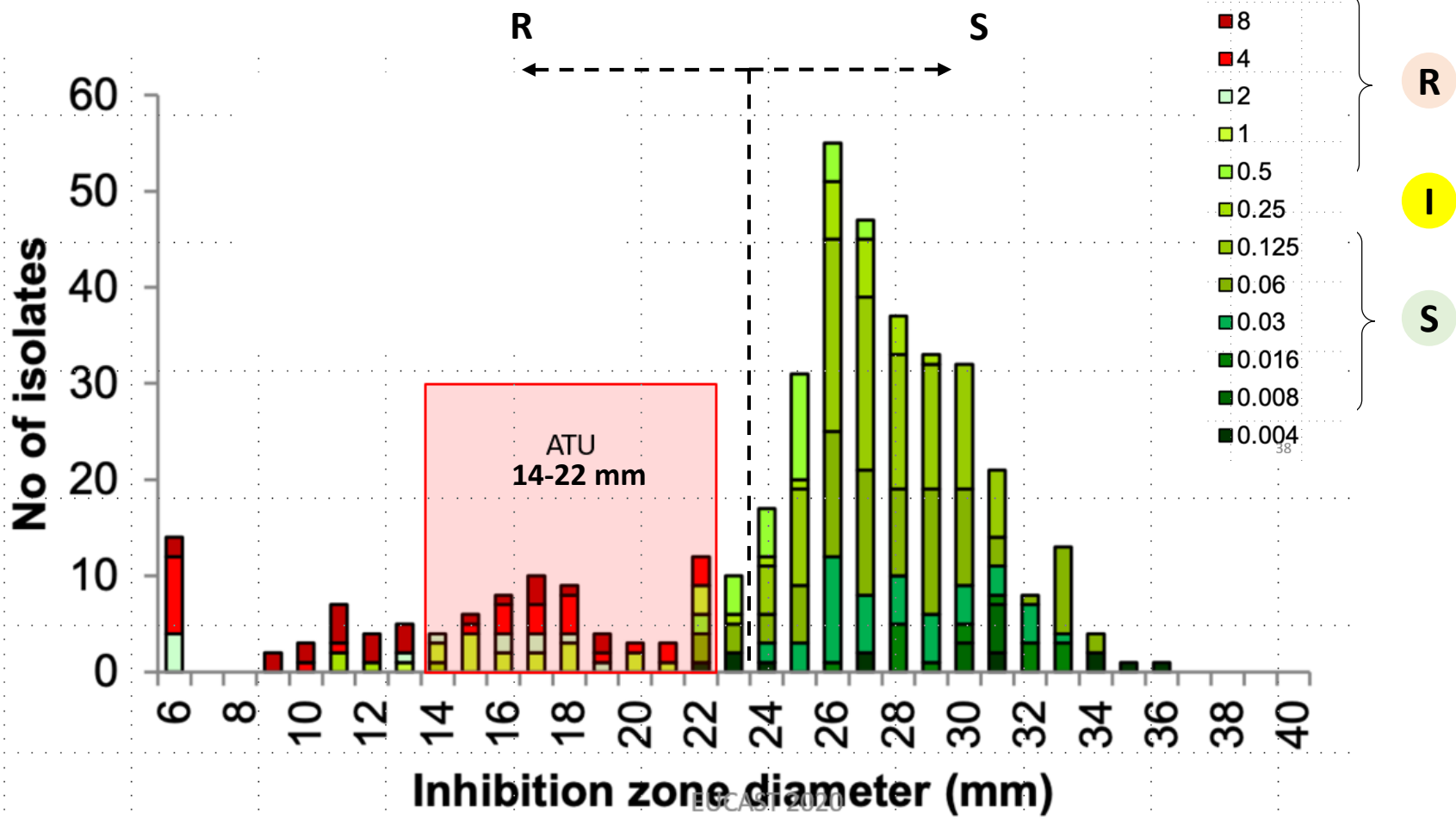
(7 data sources)



Breakpoints		ECOFF
MIC	S $\le 0.001$ , R $> 16$ mg/L	16 mg/L
Zone diameter	S $\ge 50$ , R $\le 18$ mm	

Breakpoints  
Zone diameter (szűrt) 2022 S  $\ge 22$ , R  $< 22$  mm

**Cefiderocol 30 µg vs. MIC**  
*P. aeruginosa*, 101 isolates (404 correlates)





Original Article

Area of technical uncertainty for susceptibility testing of amoxicillin/clavulanate against *Escherichia coli*: analysis of automated system, Etest and disk diffusion methods compared to the broth microdilution reference

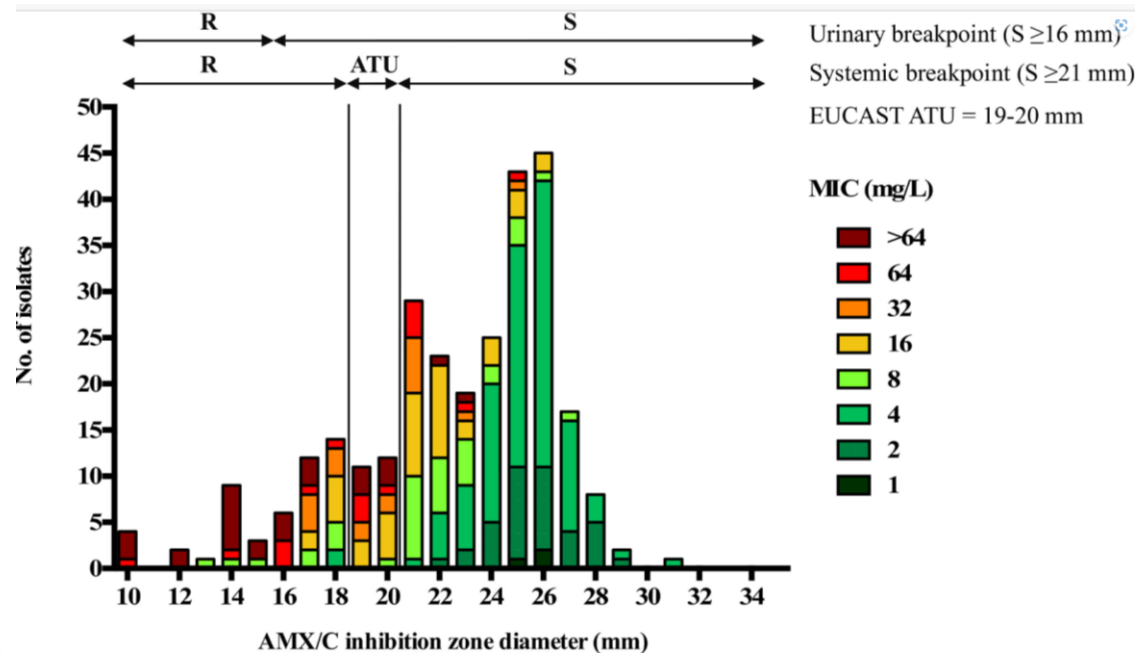
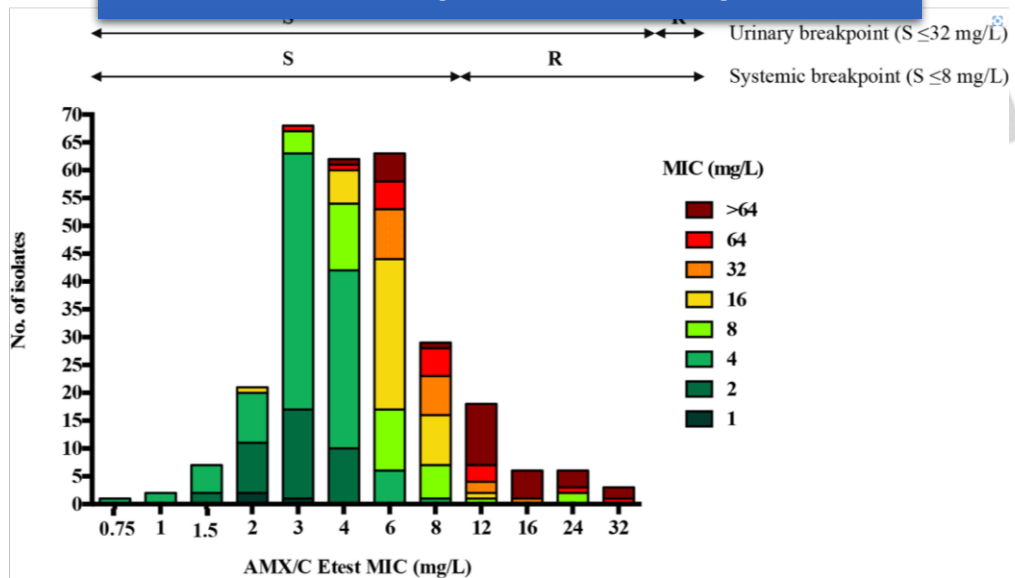
A. Soares<sup>1,2,\*</sup>, M. Pestel-Caron<sup>1,2</sup>, F. Leysour de Rohello<sup>2</sup>, G. Bourgoin<sup>2</sup>, S. Boyer<sup>1,2</sup>, F. Caron<sup>1,3</sup>

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<sup>2</sup> Microbiology Department, Rouen University Hospital, Rouen, France

<sup>3</sup> Infectious Diseases Department, Rouen University Hospital, Rouen, France

# Escasa correlación entre las CMI's obtenidas por E-test y BMD (referencia)



Method	Total set (n = 286)			
	AMX/C susceptibility (%)	Category agreement (%)	Very major error (%)	Major error (%)
Broth microdilution	62.2	—	—	—
Phoenix	66.8 <sup>a</sup>	83.6 <sup>d</sup>	10.5 <sup>d</sup>	5.9
Etest	88.5 <sup>b</sup>	71.7	27.3	1.0
Disk				
≥ 19 mm	82.2 <sup>c</sup>	73.1	23.4	3.5
≥ 20 mm	78.3	76.9	19.6	3.5
≥ 21 mm	74.1	80.5	15.7	3.8
≥ 22 mm	64.0	83.6	9.1	7.3

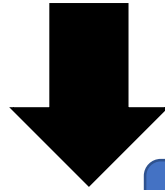
<sup>a</sup> p < 0.05 versus disk (for inhibition zone diameter ≥ 19 mm) and Etest (two-by-two comparisons)

<sup>b</sup> p < 0.05 versus broth microdilution, Phoenix and disk (for inhibition zone diameter ≥ 19 mm).

<sup>c</sup> p < 0.05 versus broth microdilution, Phoenix and Etest.

<sup>d</sup> p < 0.05 versus disk (for inhibition zone diameter ≥ 19 mm) and Etest.

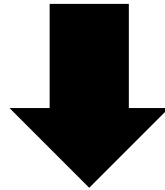
# ¿Impacto ATU ciprofloxacino?



CMI=0,5 mg/L

Hospital Virgen  
Macarena  
abril-octubre 2022

Neg Multidrug Resistant MIC 1  
MicoScan WalkAway 96

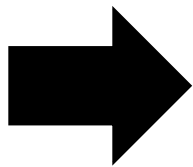


Comprobación con **disco** de  
ciprofloxacina

**Errores menores**

75%..... *E. coli*  
69%..... *Klebsiella* spp.  
89%..... otras EB

JORNADA COESANT



I JORNADA

**A**

**% ATUs**

- 2,9% *E. coli* (N=2696)
- 1,6% *K. pneumoniae* (n=1096)

**B**

**% Errores**

