EUCAST

EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

The intermediate category – what does it mean?

ECCMID 2016 Workshop

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A change in the EUCAST definitions of the **intermediate** category is under discussion.

- a proposal is undergoing public consultation

EUCAST is exploring how to make the definition of INTERMEDIATE clear, relevant and unequivocal.

The proposal is not to remove the INTERMEDIATE category!

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Susceptible and Resistant categories

No change suggested!

- A microorganism is defined as susceptible/resistant by a level of antimicrobial activity associated with a high likelihood of therapeutic success/therapeutic failure.
- A [illegible] ying th[illegible]
- This breakpoint may be altered with legitimate changes in circumstances

Unequivocal definitions

Popular definitions of I:

- I equals R
- I equals S (if the patient is not ill, otherwise R)
- I equals “indeterminate” (uncertainty)
- I don´t know
- I don´t care
- I will not use
- ID consultants only

Intermediate - current definition

(1) A micro-organism is defined as intermediate by a level of antimicrobial ag

(2)
tre a
hig

(3)
technical factors from causing major discrepancies in interpretations.

Three definitions rolled into one but the report does not say which applies!

A micro-organism is categorized as intermediate (I) by applying the appropriate breakpoints in a defined phenotypic test system

These breakpoints may be altered with legitimate changes in circumstances

The EUCAST process for setting breakpoints

is related to the PK/PD, dosing and mode of administration

EUCAST breakpoints are related to defined doses:

The standard dose corresponds to the S-breakpoint and, when available, a high dose to the I-breakpoint.

"High-dose" may relate to a **larger amount** of the agent with the same frequency as the normal dose, a **higher frequency** of dosing or prolonged **infusion**, but will improve PK/PD by at least one dilution step.

The doses and PK/PD on which breakpoints are based are shown in EUCAST rationale documents and in the last tabs of the EUCAST breakpoint tables.

The listing has been revised and extended in v6.0, 2016.

8. Clinical breakpoints

From the Ciprofloxacin rationale document

Non-species-related breakpoints	Non-species related breakpoints have been determined using Pk/Pd data and are independent of MIC distributions of specific species. They are for use only for organisms that do not have specific breakpoints. Breakpoints are S≤0.5 mg/L, R>1 mg/L. These render wild type Enterobacteriaceae, *Pseudomonas* spp., *Acinetobacter* spp., *Staphylococcus* spp., *Haemophilus influenzae*, *Moraxella catarrhalis* and *Neisseria* spp. susceptible.
Species-related breakpoints	The wild type MIC distributions of most Enterobacteriaceae, including *Salmonella* spp, exhibit MIC values <0.125 mg/L. A breakpoint of ≤0.5 mg/L allows low-level quinolone resistant Enterobacteriaceae to be categorised as susceptible to ciprofloxacin. For *Acinetobacter* spp. and *Staphylococcus* spp. the S/I breakpoint was increased to 1 mg/L to avoid dividing wild type MIC distributions. Therefore these breakpoints relate to the higher dosages of ciprofloxacin. For *S. pneumoniae*, more than 95% of wild type strains have MICs of 0.25, 0.5 or 1 mg/L, which means that neither of the non-species-related values can be used as a breakpoint without causing major splitting of the wild type distribution and thus problems with the reproducibility of S, I and R categorisation. A breakpoint of S≤0.125 mg/L categorises wild type *S. pneumoniae* as intermediate to ciprofloxacin and a breakpoint of R>2 mg/L categorises non-wild type *S. pneumoniae* as resistant to ciprofloxacin. Both consequences were intended. The breakpoints allow *Haemophilus influenzae* and *Moraxella catarrhalis* with low-level fluoroquinolone resistance to be categorized as susceptible to ciprofloxacin. Many laboratories screen for fluoroquinolone resistance with a nalidixic acid 30 µg disc; but note that *Neisseria gonorrhoeae* and *Salmonella typhi* that are ciprofloxacin resistant but not clearly nalidixic acid resistant have been reported.
Species without breakpoints	*Streptococcus* spp., *Enterococcus* spp. and anaerobic bacteria were considered poor targets for ciprofloxacin therapy and for that reason did not receive breakpoints.
Clinical qualifications	There is clinical evidence for ciprofloxacin to indicate a poor response in systemic infections caused by *Salmonella* spp with low-level fluoroquinolone resistance (MIC>0.064 mg/L). EUCAST has suggested that the epidemiological cut off value (S≤0.064/R>0.064 mg/L) be used in *Salmonella* spp. systemic infections.
Dosage	Breakpoints apply to an oral dose of 500 mg x 2 (or as low as 250 mg x 2 for uncomplicated urinary tract infections) to 750 mg x 2 and an intravenous dose of 400 mg x 2 to 400 mg x 3.
Additional comment	

Dosages

EUCAST Clinical Breakpoint Table v. 6.0, valid from 2016-01-01

Fluoroquinolones	Standard dose	High dose
Ciprofloxacin	500 mg x 2 oral or 400 mg x 2 iv	750 mg x 2 oral or 400 mg x 3 iv
Levofloxacin	500 mg x 1 oral or 500 mg x 1 iv	500 mg x 2 oral or 500 mg x 2 iv
Moxifloxacin	400 mg x 1 oral or 400 mg x 1 iv	None
Nalidixic acid		
Norfloxacin	400 mg x 2 oral	None
Ofloxacin	200 mg x 2 oral or 200 mg x 2 iv	400 mg x 2 oral or 400 mg x 2 iv

Aminoglycosides	Standard dose	High dose
Amikacin	20 mg/kg x 1 iv	25 mg/kg x 1 iv
Gentamicin	5 mg/kg x 1 iv	7 mg/kg x 1 iv
Netilmicin	5 mg/kg x 1 iv	7 mg/kg x 1 iv
Tobramycin	5 mg/kg x 1 iv	7 mg/kg x 1 iv

Glycopeptides and lipoglycopeptides	Standard dose	High dose
Dalbavancin	1 g x 1 iv over 30 minutes on day 1 If needed, 500 mg x 1 iv over 30 minutes on day 8	None
Oritavancin	1.2 g x 1 (single dose) iv over 3 h	None
Teicoplanin	400 mg x 1 iv	800 mg x 1 iv or 400 mg x 2 iv
Telavancin	10 mg/kg x 1 iv over 1 h	None
Vancomycin	500 mg x 4 iv or 1 g x 2 iv or 2 g x 1 by continuous infusion	None

Macrolides, lincosamides and streptogramins	Standard dose	High dose
Azithromycin	500 mg x 1 oral or 500 mg x 1 iv	None
Clarithromycin	250 mg x 2 oral	500 mg x 2 oral
Erythromycin	500 mg x 2-4 oral or 500 mg x 2-4 iv	1 g x 4 oral or 1 g x 4 iv
Roxithromycin	150 mg x 2 oral	None
Telithromycin	800 mg x 1 oral	None
Clindamycin	300 mg x 2 oral or 600 mg x 3 iv	300 mg x 4 oral or 1200 mg x 2 iv
Quinupristin-dalfopristin		

Tab: PK/PD breakpoints

PK/PD (Non-species related) breakpoints

EUCAST Clinical Breakpoint Table v. 6.0, valid from 2016-01-01

These breakpoints are used only when there are no species-specific breakpoints or other recommendations (a dash or a note) in the species-specific tables.

Penicillins	MIC breakpoint (mg/L)		Notes
	S ≤	R >	
Benzylpenicillin	0.25	2	1. For susceptibility testing purposes, the concentration of sulbactam is fixed at 4 mg/L.
Ampicillin	2	8	2. For susceptibility testing purposes, the concentration of clavulanic acid is fixed at 2 mg/L.
Ampicillin-sulbactam	2[1]	8[1]	3. For susceptibility testing purposes, the concentration of tazobactam is fixed at 4 mg/L.
Amoxicillin	2	8	
Amoxicillin-clavulanic acid	2[2]	8[2]	
Piperacillin	4	16	
Piperacillin-tazobactam	4[3]	16[3]	
Ticarcillin	8	16	
Ticarcillin-clavulanic acid	8[2]	16[2]	
Phenoxymethylpenicillin	IE	IE	
Oxacillin	IE	IE	
Cloxacillin	IE	IE	
Dicloxacillin	IE	IE	
Flucloxacillin	IE	IE	
Mecillinam	IE	IE	

The proportion of numerical breakpoints WITH an intermediate category in EUCAST and CLSI.

	Enterobact-eriaceae	Pseudo-monas	Staphylo-cocci	S. pneu-moniae	H. influenzae
EUCAST	56 %	41 %	43 %	64 %	39 %
CLSI	77 %	100 %	77 %	88 %	69 %

The proportion of numerical breakpoints where an intermediate category was included is higher in the CLSI than in EUCAST.
In EUCAST, each intermediate category is related to a dose or administration which is higher than the standard.

The EUCAST Intermediate category

	Entero-bacteriaceae	Pseudo-monas	Staphylo-cocci	S.pneu-moniae	Haemo-philus
No of numerical breakpoints	45	17	40	36	33
WITHOUT intermediate	20	10	23	13	20
WITH intermediate	25	7	17	23	13
Uncertain clinical effect[I]	0	1	0	3	6
Intermediate for high dose	25	5	17	20	7
I for buffer	0	1[II]	0	0	0

[I]The whole Wild Type population placed in intermediate (see next slide)
[II]Where a buffer is considered a major reason for an I-category (Amikacin vs. *Pseudomonas aeruginosa*)

I - current definition

(1)

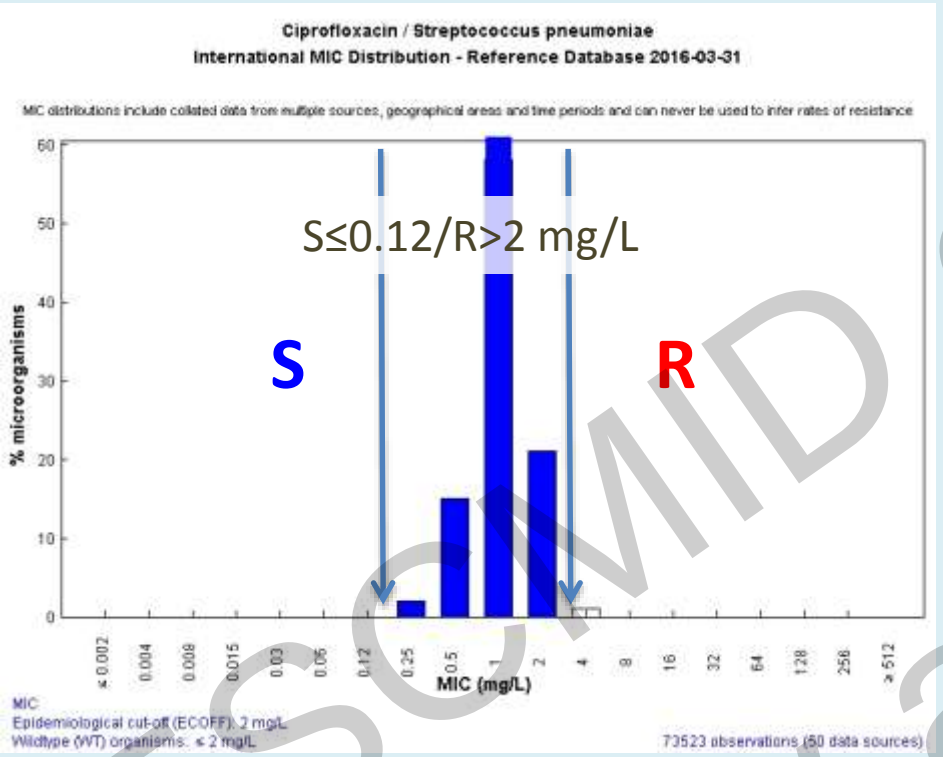
A micro-organism is defined as intermediate by a level of antimicrobial agent activity associated with uncertain therapeutic effect.

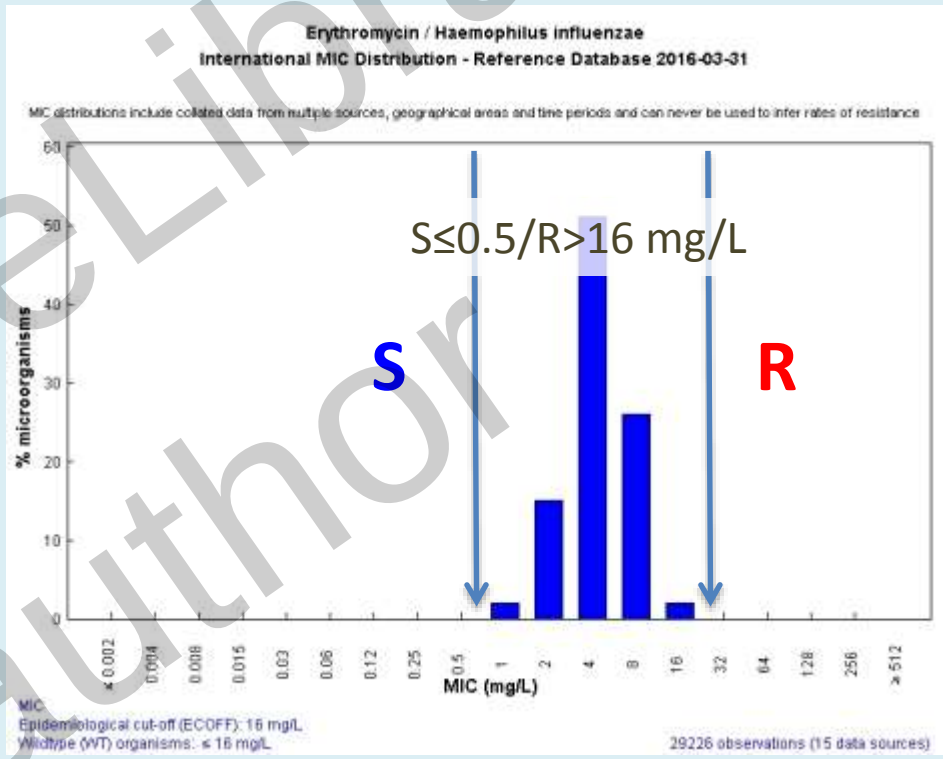
EUCAST has used this to place whole wild type distributions in the Intermediate category rather than dividing the wild type into S, I and R categories.

Typically, the literature on clinical efficacy is ambiguous and PK/PD cuts into the wild type. There is general agreement that IF the agent is considered for therapy, the dose needs to be the highest possible and that non-wild type isolate should be categorised “R”.

Uncertain therapeutic effect of standard dose (the whole wild type in intermediate)

Species	Agents where Wild Type categorised as intermediate
Enterobacteriaceae	-
Pseudomonas spp.	Aztreonam
Staphylococcus spp.	-
Enterococcus spp.	Trimethoprim, TrimSulfa
S. pneumoniae	Cefaclor, Ciprofloxacin, Ofloxacin
Haemophilus spp.	Cefuroxime axetil, Macrolides (4), Telithromycin
Moraxella catarrhalis	Cefuroxime axetil
All others	-





I - current definition

(2)

It implies that an infection due to the isolate may be appropriately treated when a high dose can be used (or in body sites where the agent is physically concentrated).

This pertains to most of the current EUCAST intermediate categories!

The PK/PD analyses will suggest an I-breakpoint ≥1 dilution higher than the S-breakpoint.

The higher dose is usually at least twice the regular dose.

The typical I-category (which fits this definition) is one dilution wide (84 % of breakpoints) but for some betalactam agents it may be wider (16 % of breakpoints).

The EUCAST Intermediate category

	Entero-bacteriaceae	Pseudo-monas	Staphylo-cocci	S.pneu-moniae	Haemo-philus
No of numerical breakpoints	45	17	40	36	33
WITHOUT intermediate	20	10	23	13	20
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Uncertain clinical effect[I]	0	1	0	3	6
Intermediate for high dose	25	5	17	20	7
I for buffer	0	1[II]	0	0	0

[I]The whole Wild Type population placed in intermediate (see next slide)
[II]Where a buffer is considered a major reason for an I-category (Amikacin vs. *Pseudomonas aeruginosa*)

Some breakpoints pertain to UTI only - there is no intermediate category and the breakpoint table gives clear instructions.

Penicillins[1] Enterobacteriaceae	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Benzylpenicillin	-	-		-	-
Ampicillin	8[1]	8	10	14[A,B]	14[B]
Ampicillin-sulbactam	8[1,2]	8[2]	10-10	14[A,B]	14[B]
Amoxicillin	8[1]	8	-	Note[C]	Note[C]
Amoxicillin-clavulanic acid	8[1,3]	8[3]	20-10	19[A,B]	19[B]
Amoxicillin-clavulanic acid (uncomplicated UTI only)	32[1,3]	32[3]	20-10	16[A,B]	16[B]
Piperacillin	8	16	30	20	17
Piperacillin-tazobactam	8[4]	16[4]	30-6	20	17
Ticarcillin	8	16	75	23	23
Ticarcillin-clavulanic acid	8[3]	16[3]	75-10	23	23
Phenoxymethylpenicillin	-	-		-	-
Oxacillin	-	-		-	-
Cloxacillin	-	-		-	-
Dicloxacillin	-	-		-	-
Flucloxacillin	-	-		-	-
Mecillinam (uncomplicated UTI only) *E. coli*, *Klebsiella* spp. and *P. mirabilis*	8	8	10	15[D]	15[D]

Agents where breakpoints pertain to “UTI only”.
Enterobacteriaceae

- Amoxicillinclavulanic acid (UTI breakpoint higher than the systemic breakpoints)
- Cefadroxil
- Cefalexin
- Cefixime
- Cefpodoxime
- Ceftibuten
- Cefuroximeaxetil
- Pivmecillinam
- Fosfomycin, oral
- Nitrofurantoin
- Trimethoprim*
- (Nitroxoline)

For all these, the Wild Type is categorised as S and, with one exception*, there is no intermediate category!

*Only one of these (trimethoprim) has an intermediate category – unclear why!.

I - current definition

(3)

“It also indicates a buffer zone that should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations.”

EUCAST has systematically strived to avoid splitting wild type distributions of target organisms, thereby minimizing consequences of inherent technical variation (which varies with antimicrobial but which is often approximated to ±1 dilution for MICs and ±3 mm for disk diffusion.

EUCAST has not included an I-category with the aim to achieve a buffer zone.

The EUCAST Intermediate category

	Entero-bacteriaceae	Pseudo-monas	Staphylo-cocci	S.pneu-moniae	Haemo-philus
No of numerical breakpoints	45	17	40	36	33
WITHOUT intermediate	20	10	23	13	20
WITH intermediate	25	7	17	23	13
Uncertain clinical effect[I]	0	1	0	3	6
Intermediate for high dose	25	5	17	20	7
I for buffer	0	1[II]	0	0	0

[I]The whole Wild Type population placed in intermediate (see next slide)
[II]Where a buffer is considered a major reason for an I-category (Amikacin vs. *Pseudomonas aeruginosa*)

Proposed new definition

Susceptible (S)

- A microorganism is defined as susceptible by a level of antimicrobial activity associated with a high likelihood of therapeutic success.

Intermediate (I)

- A microorganism is defined as intermediate by a level of antimicrobial activity associated with a high likelihood of therapeutic success but only when a higher dosage of the agent than normal can be used or when the agent is physiologically concentrated at the site of infection.

Resistant (*R*)

- A microorganism is defined as resistant by a level of antimicrobial activity associated with a high likelihood of therapeutic failure.

Consequences of a new defition

~~(1) A micro-organism is defined as intermediate by a level of antimicrobial agent activity associated with **uncertain therapeutic** effect.~~
Consequence: 10 breakpoints where the wild type is categorised as intermediate need to be reviewed – most will fit the new definition.

(2) It implies that an infection due to the isolate may be appropriately treated when a higher dosage of the agent than normal can be used or when the agent is physiologically concentrated at the site of infection.

Consequence: None

~~(3) it **also indicates a buffer zone** that should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations.~~
Consequence: we have to address the issue of technical uncertainty in a systematic but alternative way.

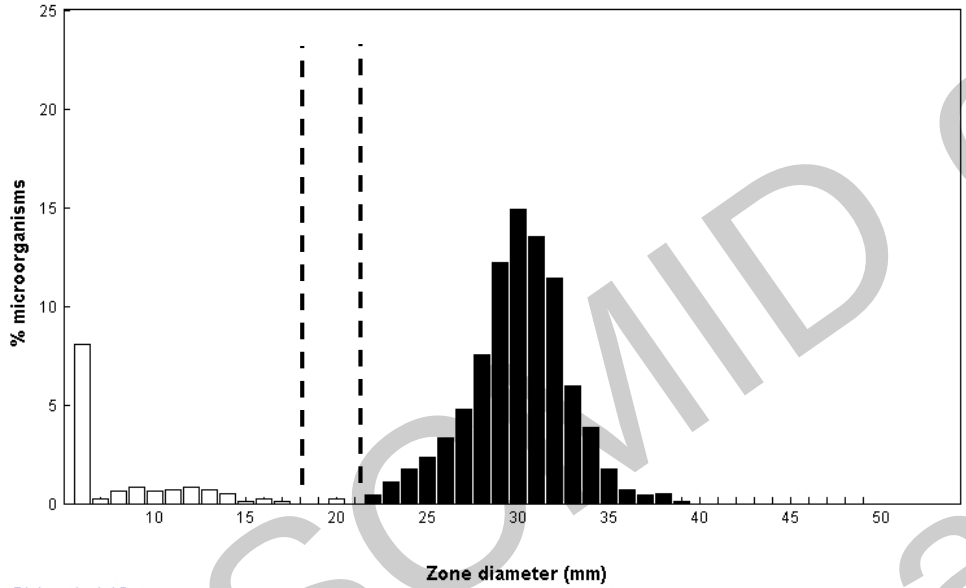
The need for a “buffer zone” differs between agents and species

Erythromycin / Streptococcus pneumoniae

International wild type zone diameter distribution - Reference database 2016-04-05

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

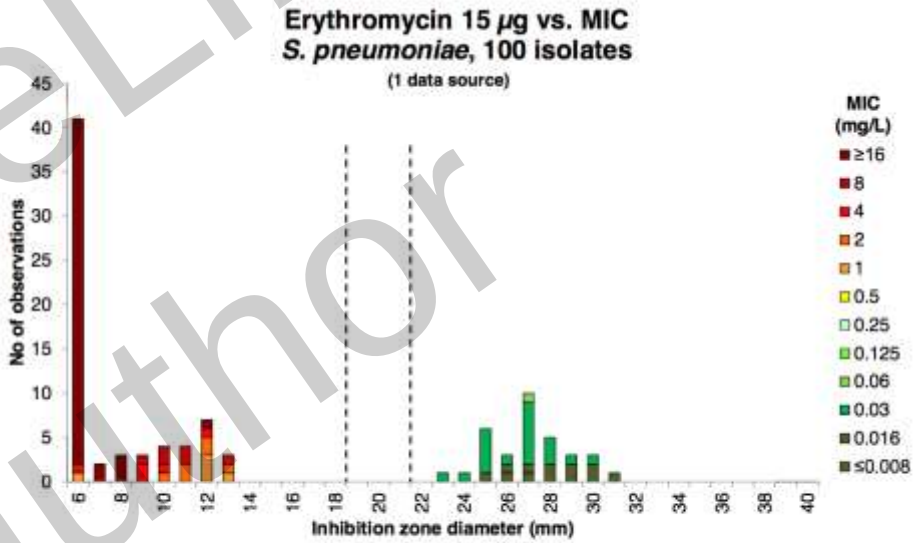


Disk content: 15

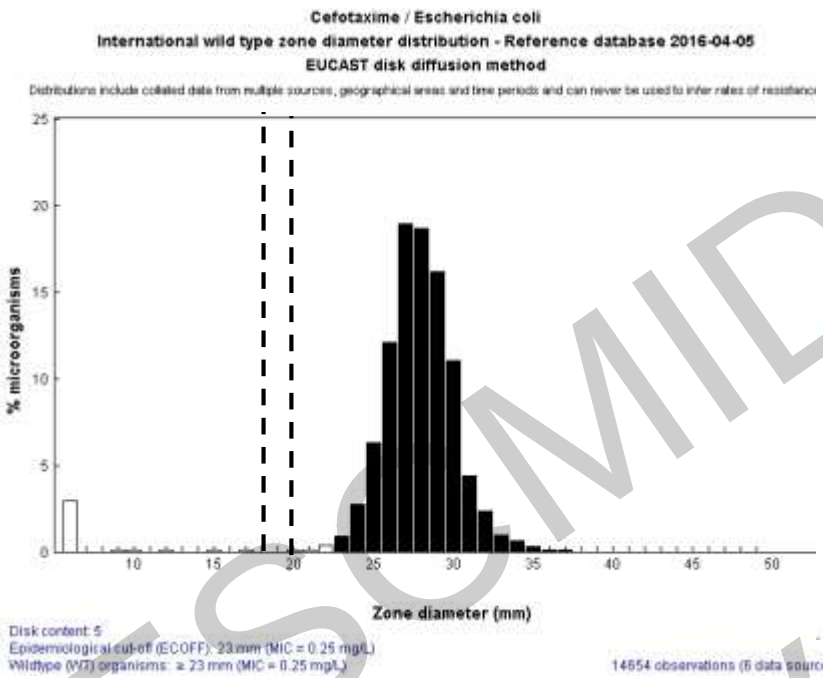
Epidemiological cut-off (ECOFF): 22 mm (MIC = 0.25 mg/L)

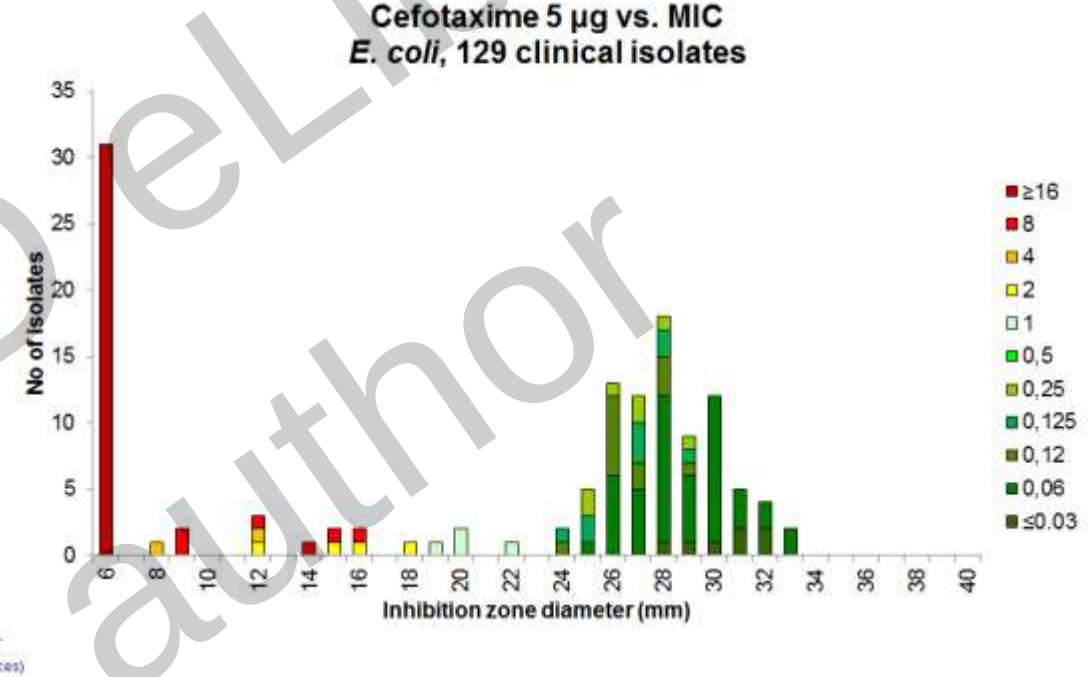
Wildtype (WT) organisms: ≥ 22 mm (MIC = 0.25 mg/L)

992 observations (5 data sources)



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



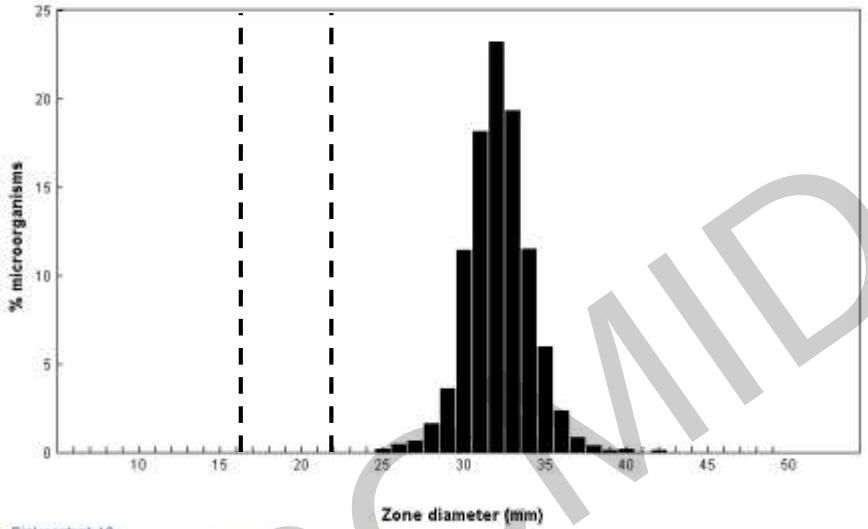


Meropenem / Escherichia coli

International wild type zone diameter distribution - Reference database 2016-04-05

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



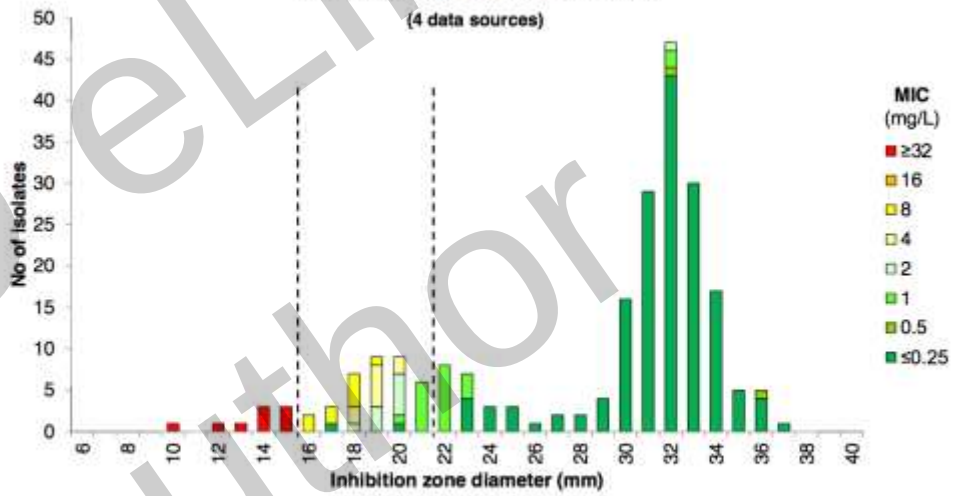
Disk content: 10
Epidemiological cut-off (ECOFF): 25 mm (MIC = 0.125 mg/L)
Wildtype (WT) organisms: ≥ 25 mm (MIC = 0.125 mg/L)

7033 observations (8 data sources)

Meropenem 10 µg vs. MIC

***E. coli*, 225 clinical isolates**

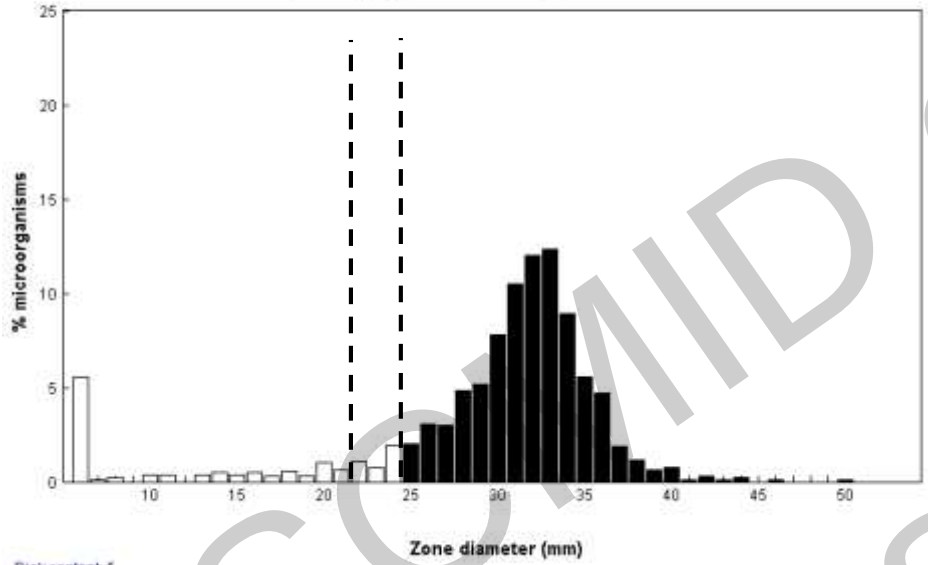
(4 data sources)



Breakpoints		**ECOFF**
MIC	S≤2, R>8 mg/L	0.125 mg/L
Zone diameter	S≥22, R<16 mm	

Ciprofloxacin / Pseudomonas aeruginosa
International wild type zone diameter distribution - Reference database 2016-04-05
EUCAST disk diffusion method

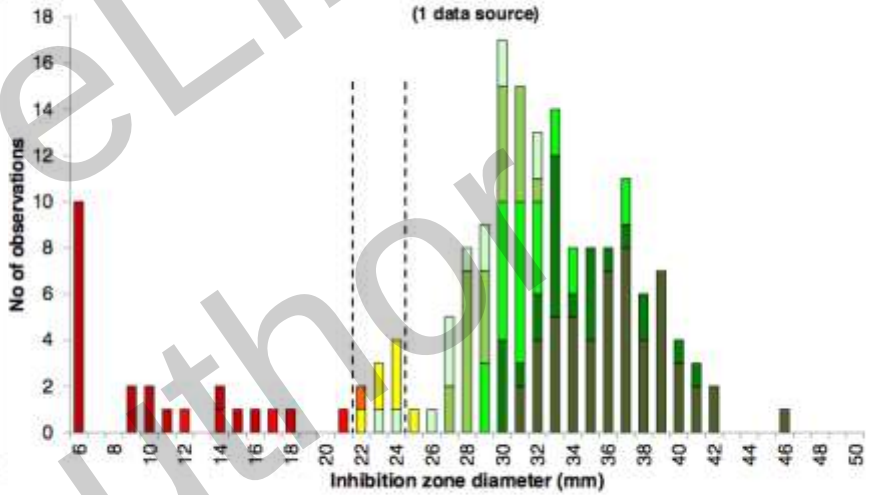
Distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



Disk content: 5
Epidemiological cut-off (ECOFF): 25 mm (MIC = 0.5 mg/L)
Wildtype (WT) organisms: ≥ 25 mm (MIC = 0.5 mg/L)

1283 observations (5 data sources)

Ciprofloxacin 5 µg vs. MIC
***Pseudomonas* non-*aeruginosa*, 173 isolates**
(1 data source)



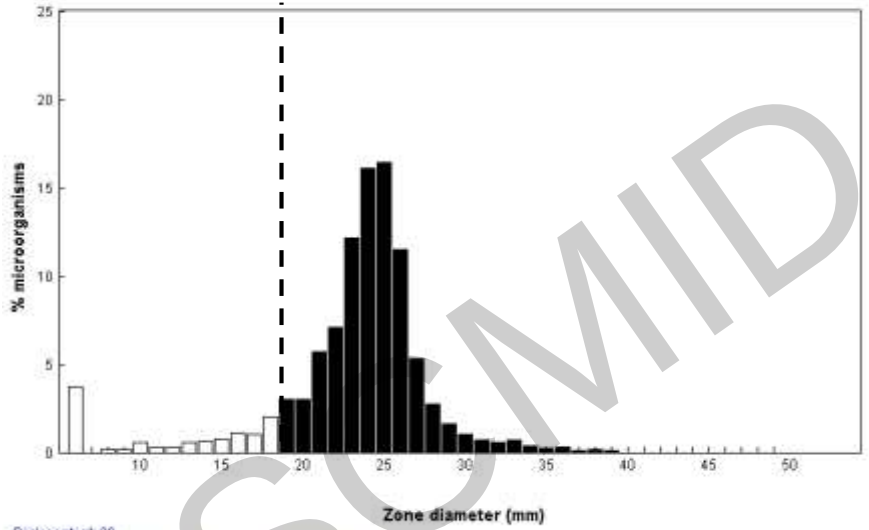
Breakpoints	
MIC	S≤0.5, R>1 mg/L
Zone diameter	S≥25, R<22 mm

Piperacillin-tazobactam / Pseudomonas aeruginosa

International wild type zone diameter distribution - Reference database 2016-04-05

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



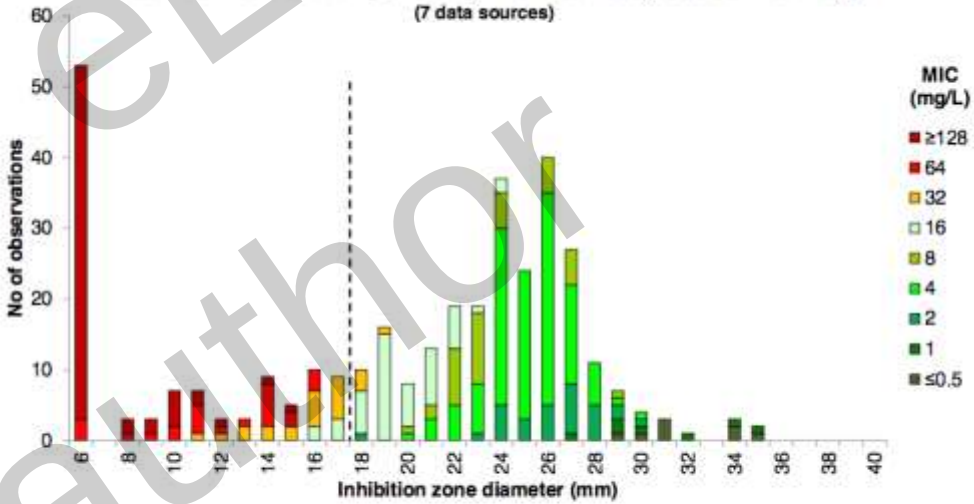
Disk content: 36
Epidemiological cut-off (ECOFF): 19 mm (MIC = 16 mg/L)
Wildtype (WT) organisms: ≥ 19 mm (MIC = 16 mg/L)

1283 observations (5 data sources)

Piperacillin-tazobactam 30-6 µg vs. MIC

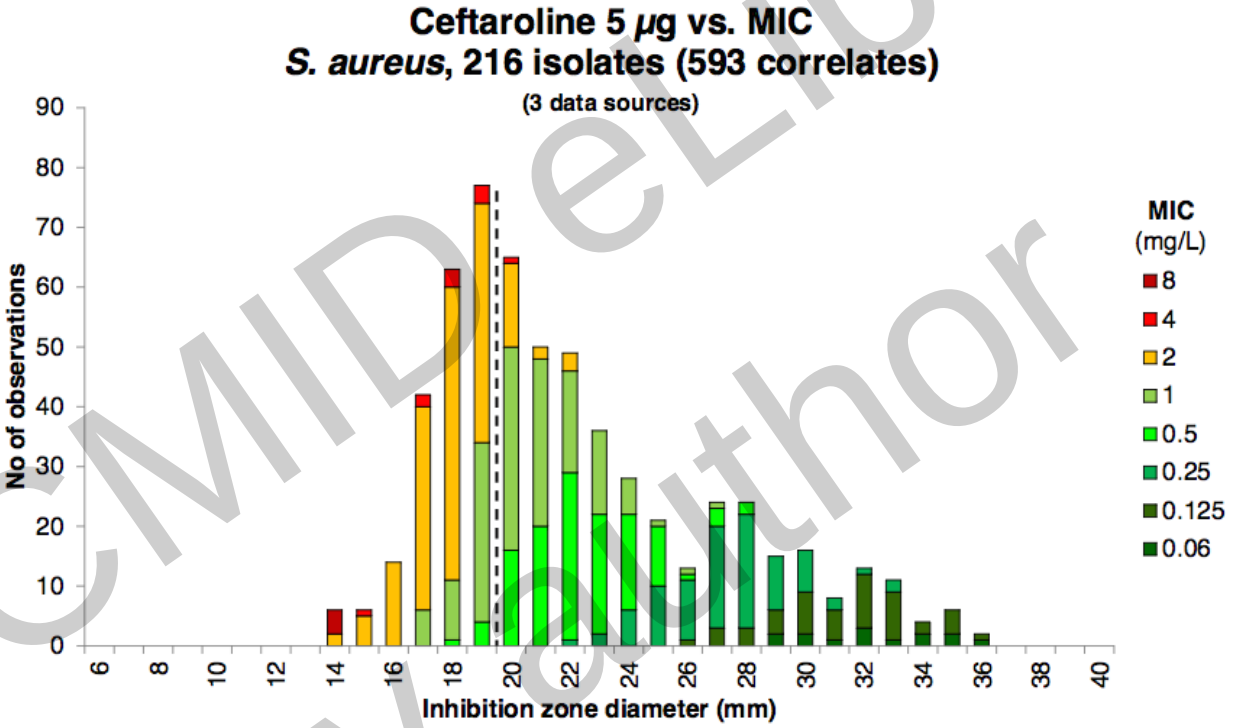
***Pseudomonas aeruginosa*, 249 isolates (356 correlates)**

(7 data sources)



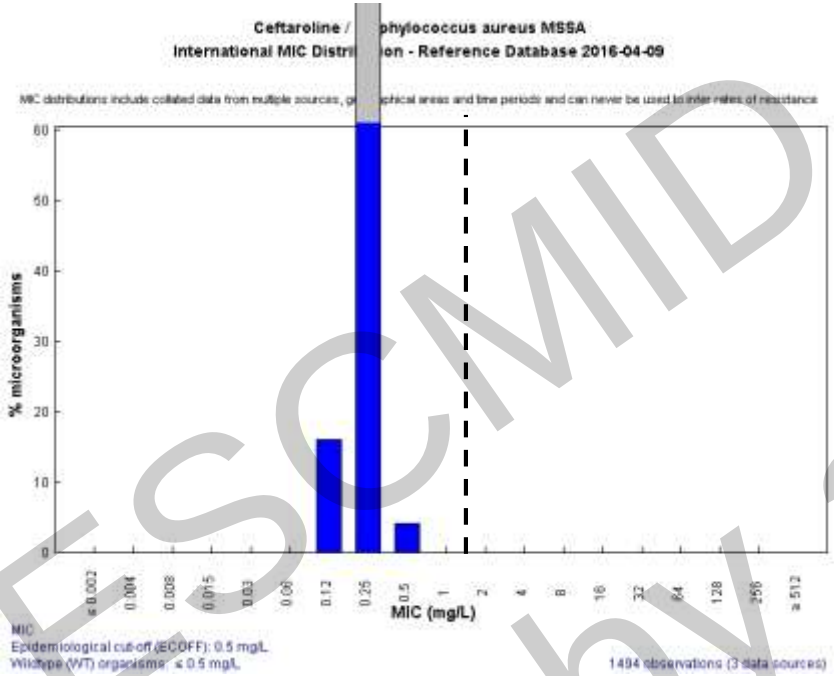
Breakpoints		ECOFF
MIC	S≤16, R>16 mg/L	16 mg/L
Zone diameter	S≥18, R<18 mm	

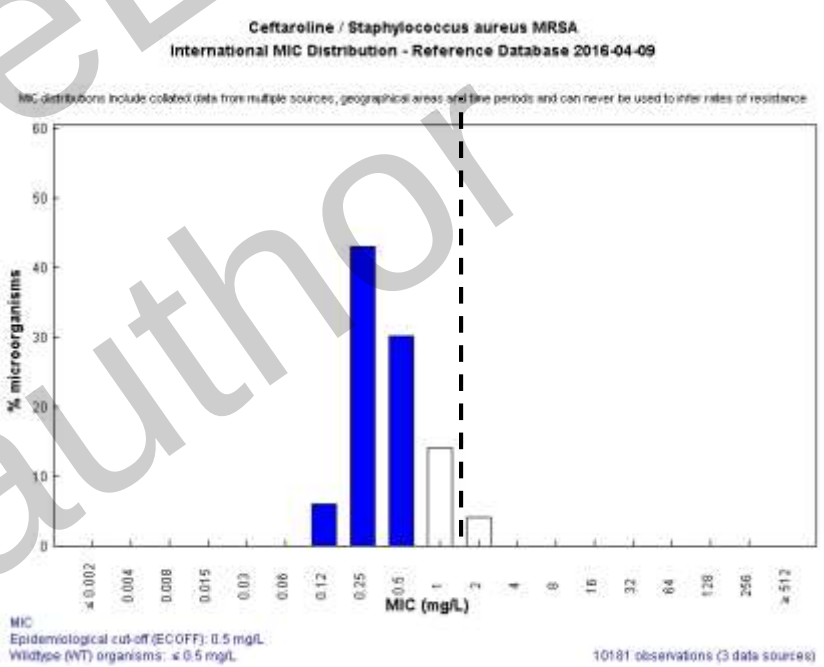
An intermediate category will not solve this problem!



Breakpoints		ECOFF
MIC	S≤1, R>1 mg/L	0.5 mg/L
Zone diameter	S≥20, R<20 mm	

Ceftaroline vs. S. aureus





Alternative ways forward

- No change – leave it as is and let people cope as best they can.
- Remove the “increase the dose” and “concentration” from the definition and change the definition of intermediate to “The intermediate category represents an area of uncertainty caused by the inherent technical variation in the tests used by clinical laboratories. The organism may be susceptible or resistant and the test will not guide therapy.
- Change the definition as proposed by EUCAST – remove the “buffer zone” from the definition.
- Change the definition as proposed by EUCAST – remove the “buffer zone” from the definition but also introduce an **Area of Technical Uncertainty** in the laboratory for **relevant** species/agent combinations as a warning and for action in the lab.

Area of Technical Uncertainty

Is it possible to introduce a technical buffer zone as a warning in the laboratory, not to the clinician?

How wide (in MIC and in mm) should the UNCERTAIN RESULT be?

- for MIC breakpoints 1 dilution step.
- for zone diameter breakpoints 3 mm (corresponds to 1 dilution, and also to the +/-variation in the disk diffusion test; see the EUCAST QC Tables).
- Not all agent/species combinations are in need of an ATU.

Area of Technical Uncertainty

What to do with an UNCERTAIN result?

1. **Report the result but as "uncertain"**
   - add a comment; report the result in brackets or parenthesis
2. **Repeat uncertain results**
   - repeat the test – the same test or use another test. What to do with discrepant result (revert to plan 1)
   - an MIC-test will "automatically give an unambiguous result!", "the right result?"
3. **"Play it safe" – a result in the ATU is downsized to one category lower** (S to I, I to R).
4. **Do not report antimicrobials with results in the UNCERTAIN AREA – leave blank or "IE" in report.**
5. **……**

- EUCAST has not decided on how to proceed
- We believe we have to abandon the ambiguous definition of INTERMEDIATE
- Whatever the decision, we will consult with national committees and our colleagues at large.
- All the well written and carefully thought through comments to our consultations are much appreciated.

Thank you!

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