



The intermediate category – what does it mean?

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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 unambiguous.

The proposal is not to remove the INTERMEDIATE category!

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

Definitions unambiguous

- applying the appropriate breakpoint in a defined phenotypic test system.
- This breakpoint may be altered with legitimate changes in circumstances

Intermediate - current definition

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

(2)
tre
high

(3)
tec

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

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

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 R-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 on which breakpoints are based are shown in EUCAST rationale documents and in the last tab of the EUCAST breakpoint tables.

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

The EUCAST process for setting breakpoints

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

Where EUCAST has an INTERMEDIATE category there is a defined “standard” and “high” dose.

Dosages, both standard and high dose, are shown in the EUCAST breakpoint table.

Dosages		
EUCAST Clinical Breakpoint Table v. 6.0, valid from 2016-01-01		
EUCAST breakpoints are based on the following dosages (see section 8 in Rationale Documents).		
Penicillins	Standard dose	High dose
Benzylpenicillin	600 mg x 4 iv	2.4 g x 6 iv
Ampicillin	500 mg - 1 g x 3-4 iv	1 - 2 g x 4-6 iv
Ampicillin-sulbactam		
Amoxicillin	500 mg x 3 iv Oral dosage under discussion	2 g x 6 iv Oral dosage under discussion
Amoxicillin-clavulanic acid	500 mg x 3 iv Oral dosage under discussion	2 g x 6 iv Oral dosage under discussion
Piperacillin	4 g x 3 iv	4 g x 4 iv
Piperacillin-tazobactam	4 g x 3 iv	4 g x 4 iv
Ticarcillin	3 g x 4 iv	3 g x 6 iv
Ticarcillin-clavulanic acid	3 g x 4 iv	3 g x 6 iv
Phenoxymethylpenicillin		
Oxacillin		
Cloxacillin		
Dicloxacillin		
Flucloxacillin		
Mecillinam	200 - 400 mg x 3 oral	None
Cephalosporins	Standard dose	High dose
Cefaclor		
Cefadroxil	500 mg x 2 oral	1 g x 2 oral
Cefalexin		
Cefazolin		
Cefepime	2 g x 2 iv	2 g x 3 iv
Cefixime		
Cefotaxime	1 g x 3 iv	2 g x 3 iv
Cefoxitin		
Cefpodoxime		
Ceftaroline	600 mg x 2 iv over 1 hour	None
Ceftazidime	1 g x 3 iv	2 g x 3 iv

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. 2. For susceptibility testing purposes, the concentration of clavulanic acid is fixed at 2 mg/L. 3. For susceptibility testing purposes, the concentration of tazobactam is fixed at 4 mg/L.
Ampicillin	2	8	
Ampicillin-sulbactam	2 ¹	8 ¹	
Amoxicillin	2	8	
Amoxicillin-clavulanic acid	2 ¹	8 ¹	
Piperacillin	4	16	
Piperacillin-tazobactam	4 ¹	16 ¹	
Ticarcillin	8	16	
Ticarcillin-clavulanic acid	8 ¹	16 ¹	
Phenoxymethylpenicillin	IE	IE	
Oxacillin	IE	IE	
Cloxacillin	IE	IE	
Dicloxacillin	IE	IE	
Flucloxacillin	IE	IE	
Mecillinam	IE	IE	
Cephalosporins	MIC breakpoint (mg/L)		Notes
	S ≤	R >	
Cefaclor	IE	IE	1. Based on PK/PD target for Gram-negative organisms. 2. Breakpoints are based on ceftiozane data. 3. For susceptibility testing purposes, the concentration of tazobactam is fixed at 4 mg/L.
Cefadroxil	IE	IE	
Cefalexin	IE	IE	
Cefazolin	1	2	
Cefepime	4	8	
Cefixime	IE	IE	
Cefotaxime	1	2	
Cefoxitin	IE	IE	
Cefprozime	IE	IE	
Ceftazidime	0.5 ¹	0.5 ¹	
Ceftazidime	4	8	
Ceftibuten	IE	IE	
Ceftibiprole	4	4	
Ceftiozane-tazobactam	4 ^{1,2}	4 ^{1,2}	
Ceftriaxone	1	2	
Cefuroxime iv	4	8	
Cefuroxime oral	IE	IE	
Carbapenems	MIC breakpoint (mg/L)		Notes
	S ≤	R >	
Doripenem	1	2	
Ertapenem	0.5	1	
Imipenem	2	8	
Meropenem	2	8	
Monobactams	MIC breakpoint (mg/L)		Notes
	S ≤	R >	
Aztreonam	4	8	

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 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

^IThe 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 – 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 any non-wild type isolate should be categorised “R”.

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

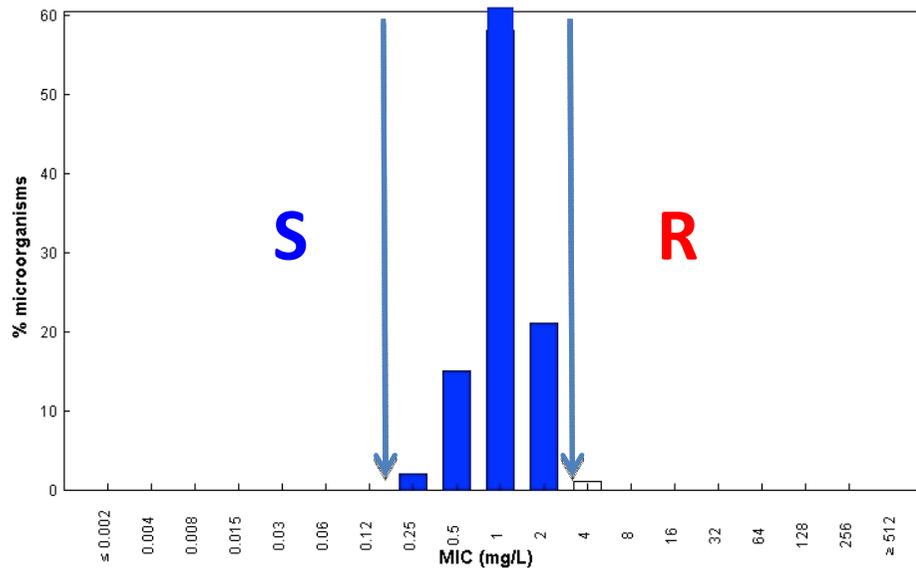
Species	Agents where Wild Type categorised as intermediate
<i>Enterobacteriaceae</i>	-
<i>Pseudomonas</i> spp.	Aztreonam
<i>Staphylococcus</i> spp.	-
<i>Enterococcus</i> spp.	Trimethoprim, TrimSulfa
<i>S. pneumoniae</i>	Cefaclor, Ciprofloxacin, Ofloxacin
<i>Haemophilus</i> spp.	Cefuroxime axetil, Macrolides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

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

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

Ciprofloxacin / *Streptococcus pneumoniae*
International MIC Distribution - Reference Database 2016-03-31

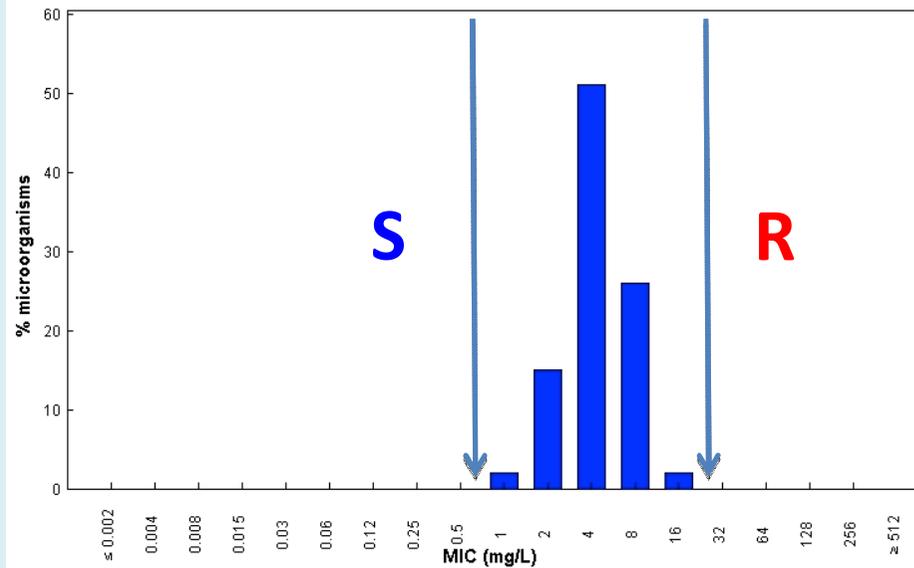
MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



MIC
 Epidemiological cut-off (ECOFF): 2 mg/L
 Wildtype (WT) organisms: ≤ 2 mg/L
 73523 observations (50 data sources)

Erythromycin / *Haemophilus influenzae*
International MIC Distribution - Reference Database 2016-03-31

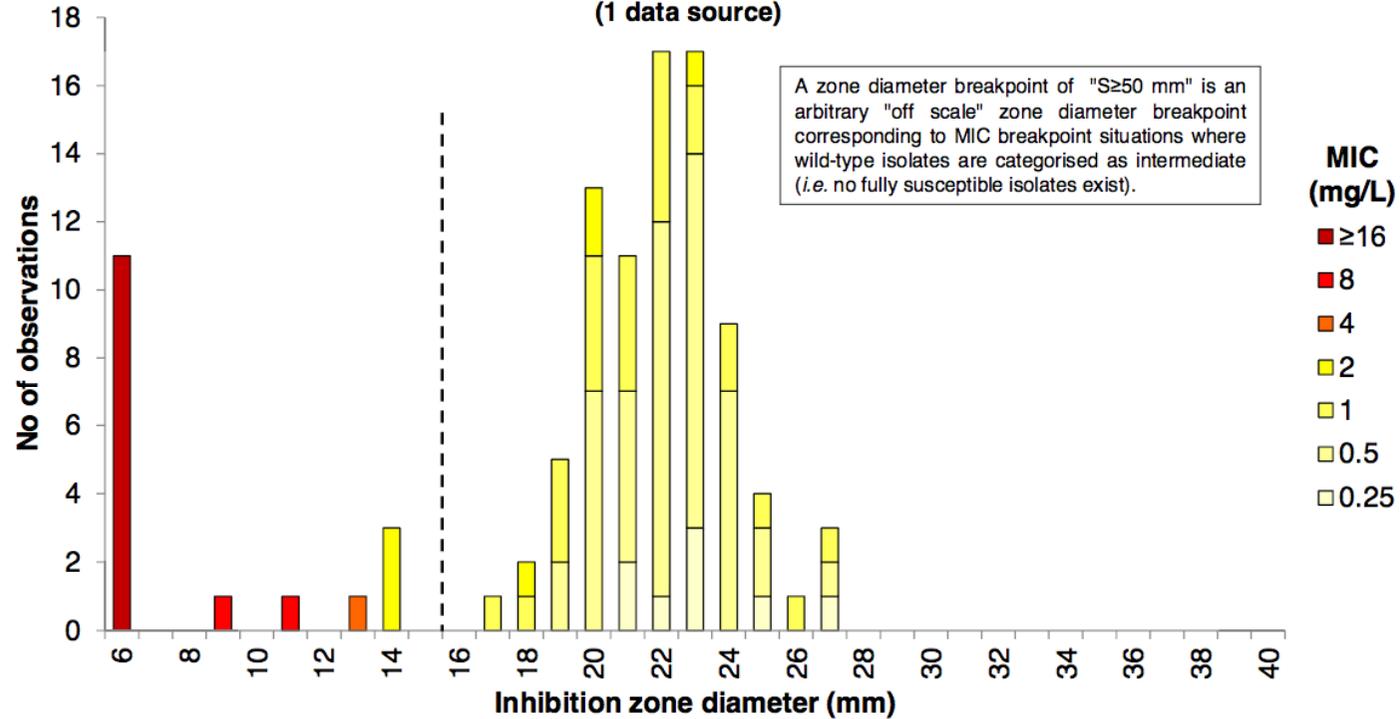
MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



MIC
 Epidemiological cut-off (ECOFF): 16 mg/L
 Wildtype (WT) organisms: ≤ 16 mg/L
 29226 observations (15 data sources)

Ciprofloxacin 5 μ g vs. MIC *S. pneumoniae*, 100 isolates

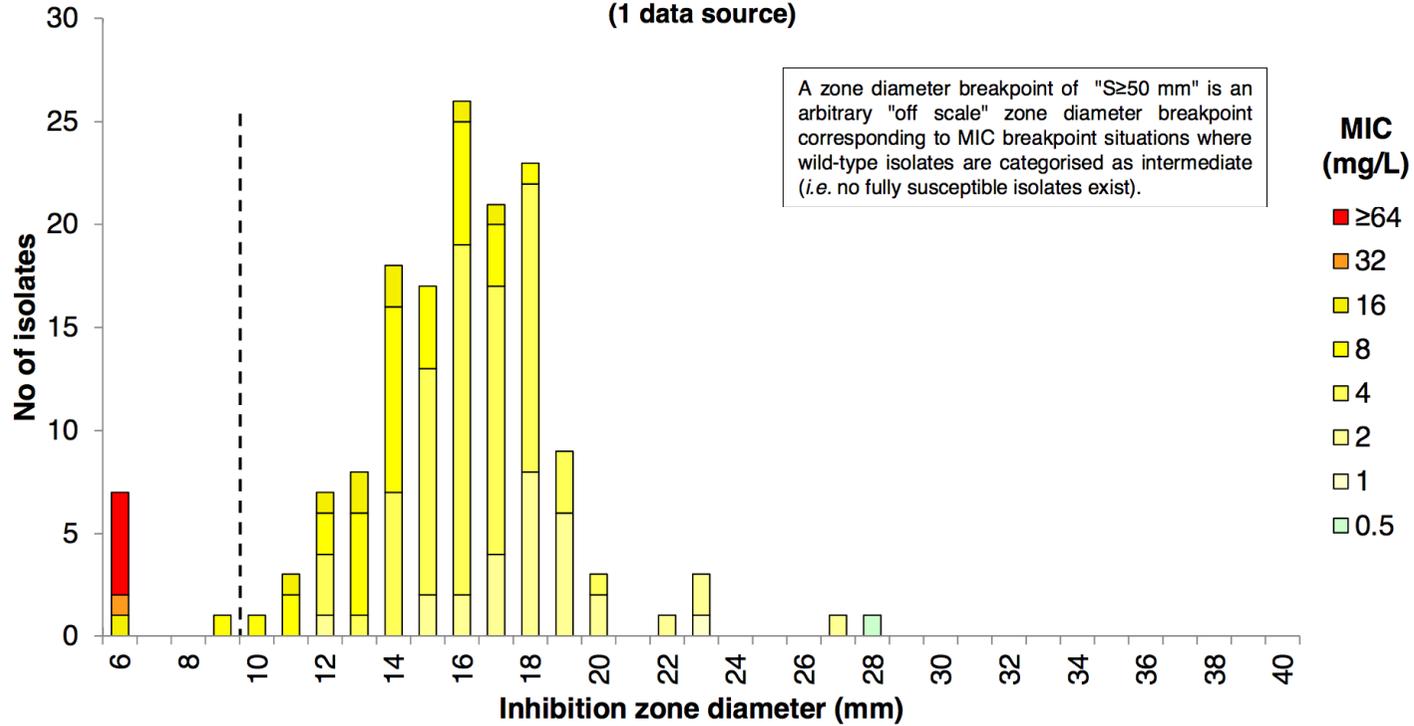
(1 data source)



Breakpoints		ECOFF
MIC	S \le 0.125, R $>$ 2 mg/L	2 mg/L
Zone diameter	S \ge 50, R $<$ 16 mm	

Erythromycin 15 µg vs. MIC *H. influenzae*, 150 clinical isolates

(1 data source)



Breakpoints		ECOFF
MIC	S≤0.5, R>16 mg/L	16 mg/L
Zone diameter	S≥50, R<10 mm	

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!

It fits PK/PD analyses. When the I-category is used, there is an accepted higher dose (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).

*For some agents, the breakpoints pertain to UTI only and in these cases there is no intermediate category.

I – standard and high dose

**This pertains to almost all of the current EUCAST
intermediate categories!**

I – agent concentrated at site of infection

Agents used only for UTI

Agents used both for systemic infections and UTI.

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

^IThe 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*)

Agents where breakpoints pertain to “UTI only”.

Enterobacteriaceae
(sometimes with limitations)

- Amoxicillinclavulanic acid (UTI breakpoint higher than the systemic breakpoints)
- Cefadroxil
- Cefalexin
- Cefixime
- Cefpodoxime
- Ceftibuten
- Cefuroximeaxetil
- Pivmecillinam
- Fosfomicin, 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!.

Agents, concentrated in urine, used for systemic infections and UTI .

Enterobacteriaceae

- Piperacillin-tazobactam
- Cefotaxime, Ceftriaxone, Ceftazidime, Cefepime
- Carbapenems
- Aztreonam
- Fluoroquinolones
- Aminoglycosides

I – as a “buffer zone”

To prevent uncontrolled, technical factors from causing major discrepancies in interpretations.

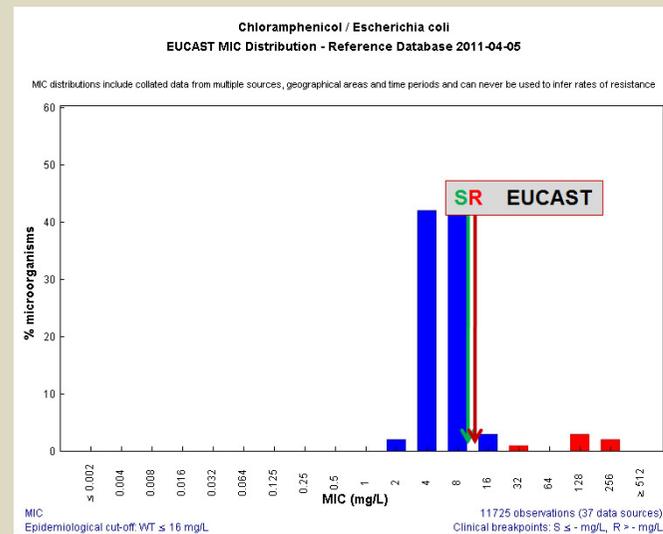
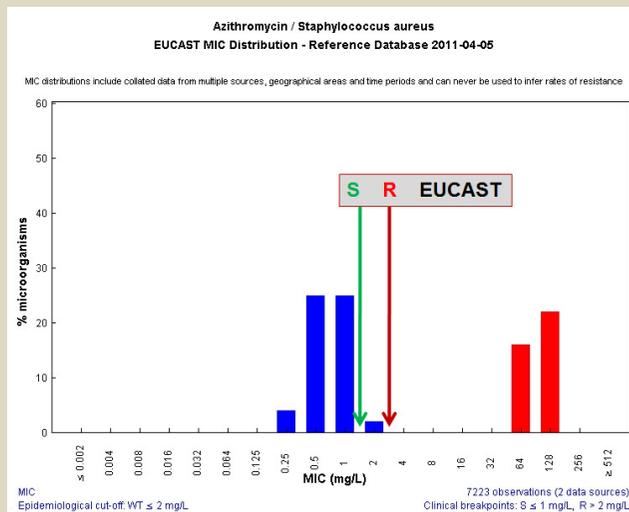
EUCAST avoid splitting wild type distributions of target organisms.

Zone diameter breakpoints are set to err on the side of safety.

EUCAST has not included an I-category as a buffer zone.

S/I-breakpoints splitting wild type MIC or zone diameter distributions

- S.aureus vs. azitromycin
- E. coli vs. chloramphenicol



Proposal in summary

~~(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 and checked to fit with the new definition.

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

Consequence: None

~~(3) it also indicates a buffer zone that should prevent small, uncontrolled, technical factors from causing major discrepancies in interpretations.~~

Consequence: the issue of technical uncertainty must be addressed in an alternative way.

Proposed new definitions

Susceptible (S)

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

Intermediate (I)

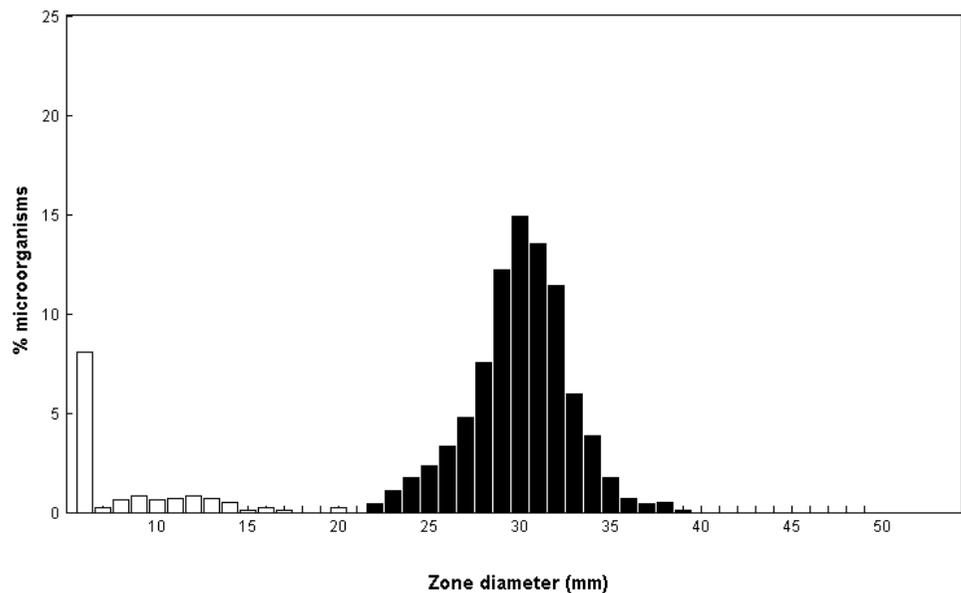
- A microorganism is defined as intermediate by a level of antimicrobial activity associated with a high likelihood of therapeutic success but only when a higher dosage of the agent than normal can be used or when the agent is physiologically concentrated at the site of infection.

Resistant (R)

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

Erythromycin / *Streptococcus pneumoniae*
International wild type zone diameter distribution - Reference database 2016-04-05
EUCAST disk diffusion method

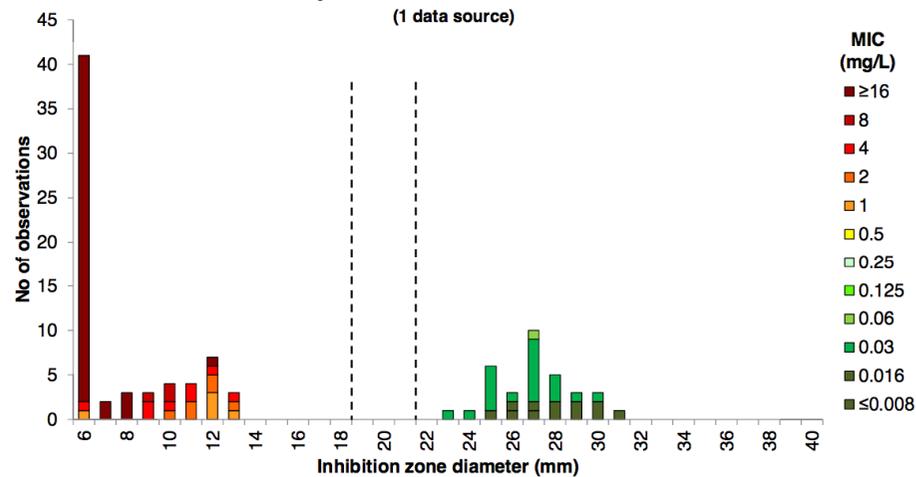
Distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



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)

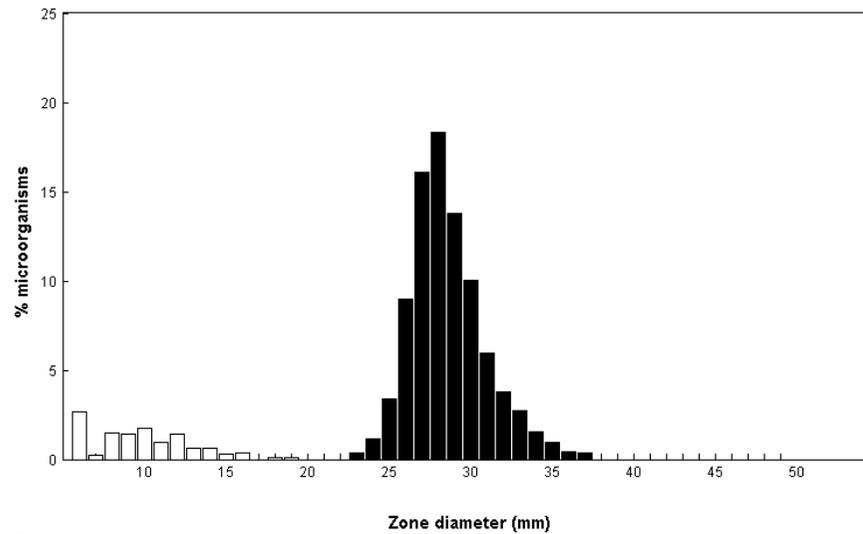
Erythromycin 15 μ g vs. MIC
***S. pneumoniae*, 100 isolates**
 (1 data source)



Breakpoints		ECOFF
MIC	S \leq 0.25, R $>$ 0.5 mg/L	0.25 mg/L
Zone diameter	S \geq 22, R $<$ 19 mm	

Tetracycline / *Staphylococcus aureus*
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

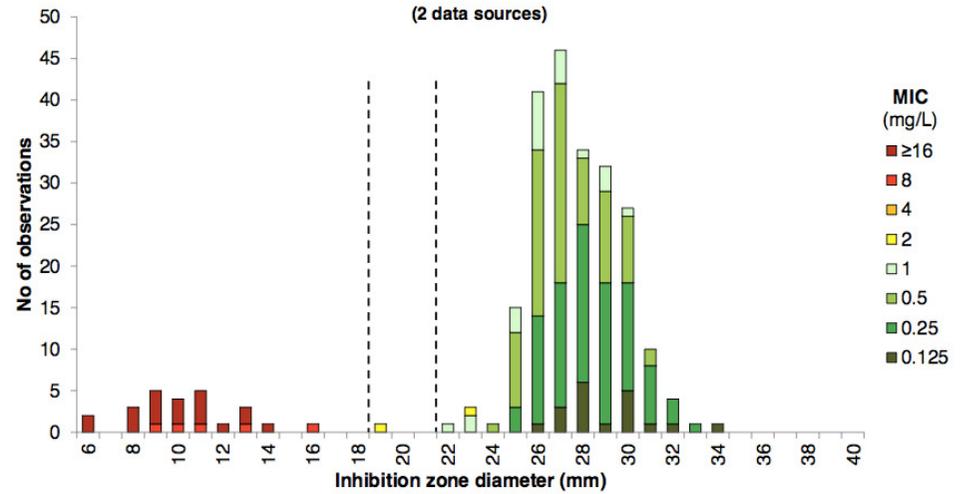


Disk content: 30
 Epidemiological cut-off (ECOFF): 22 mm (MIC = 1 mg/L)
 Wildtype (WT) organisms: ≥ 22 mm (MIC = 1 mg/L)

3520 observations (9 data sources)

Tetracycline 30 μ g vs. MIC
***S. aureus*, 242 isolates**

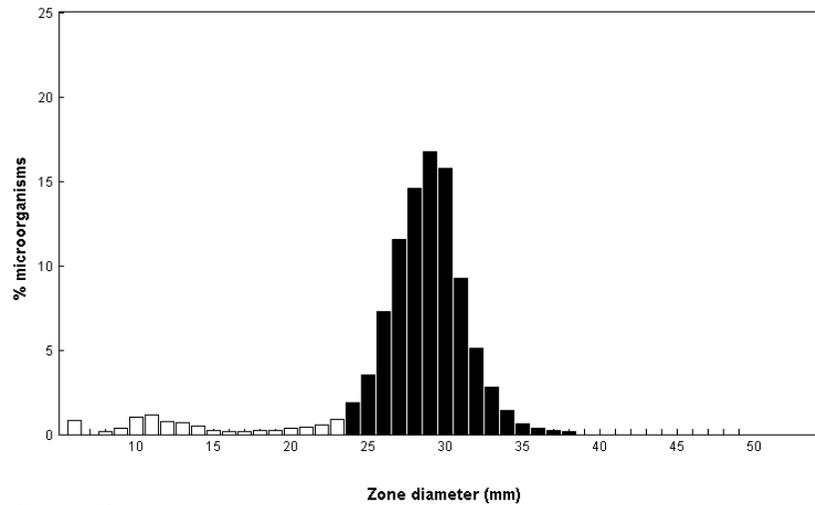
(2 data sources)



Breakpoints		ECOFF
MIC	S ≤ 1 , R >2 mg/L	1 mg/L
Zone diameter	S ≥ 22 , R <19 mm	

Fusidic acid / Staphylococcus aureus
International wild type zone diameter distribution - Reference database 2016-04-05
EUCAST disk diffusion method

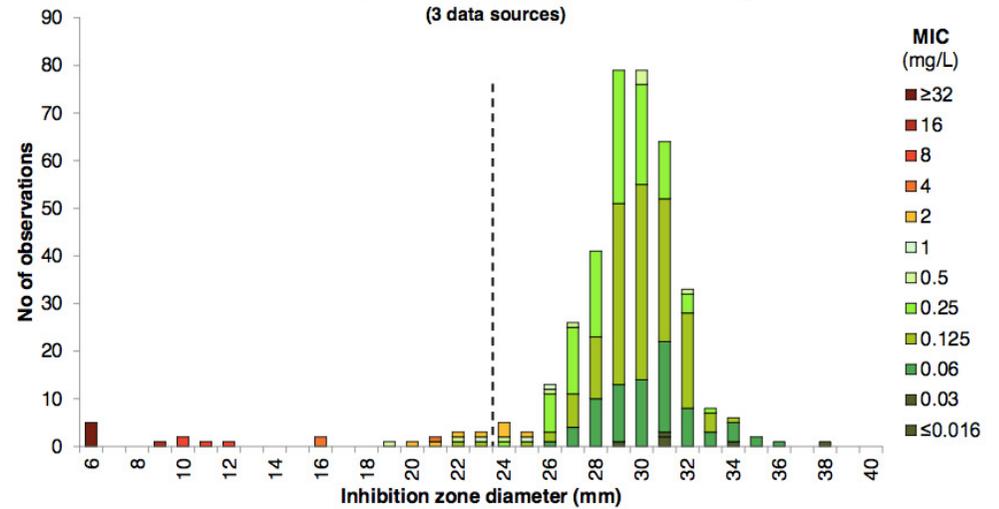
Distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



Disk content: 10
 Epidemiological cut-off (ECOFF): 24 mm (MIC = 0.5 mg/L)
 Wildtype (WT) organisms: ≥ 24 mm (MIC = 0.5 mg/L)

10838 observations (10 data sources)

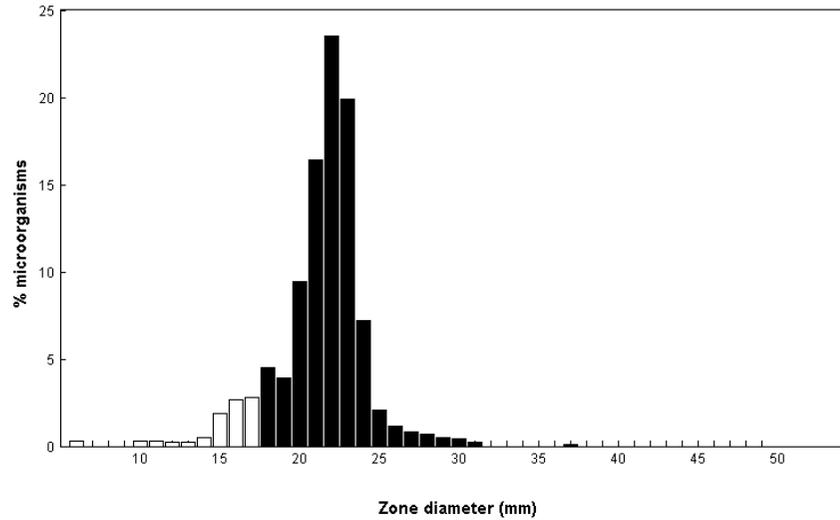
Fusidic acid 10 μ g vs. MIC
***S. aureus*, 350 isolates (383 correlates)**
 (3 data sources)



Breakpoints		ECOFF
MIC	S ≤ 1 , R >1 mg/L	0.5 mg/L
Zone diameter	S ≥ 24 , R <24 mm	

Amikacin / *Staphylococcus aureus*
International wild type zone diameter distribution - Reference database 2016-04-05
EUCAST disk diffusion method

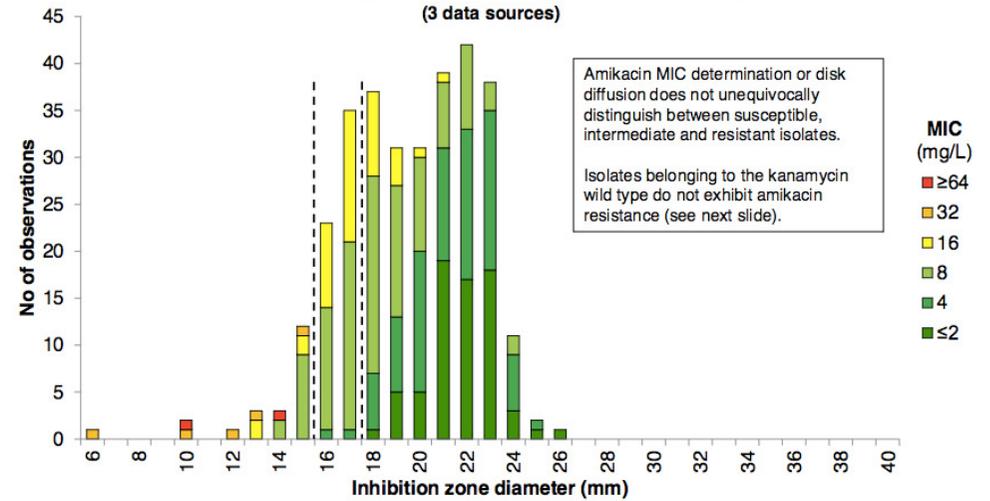
Distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



Disk content: 30
 Epidemiological cut-off (ECOFF): 18 mm (MIC = 8 mg/L)
 Wildtype (WT) organisms: ≥ 18 mm (MIC = 8 mg/L)

974 observations (6 data sources)

Amikacin 30 μ g vs. MIC
***S. aureus*, 173 isolates (312 correlates)**
 (3 data sources)

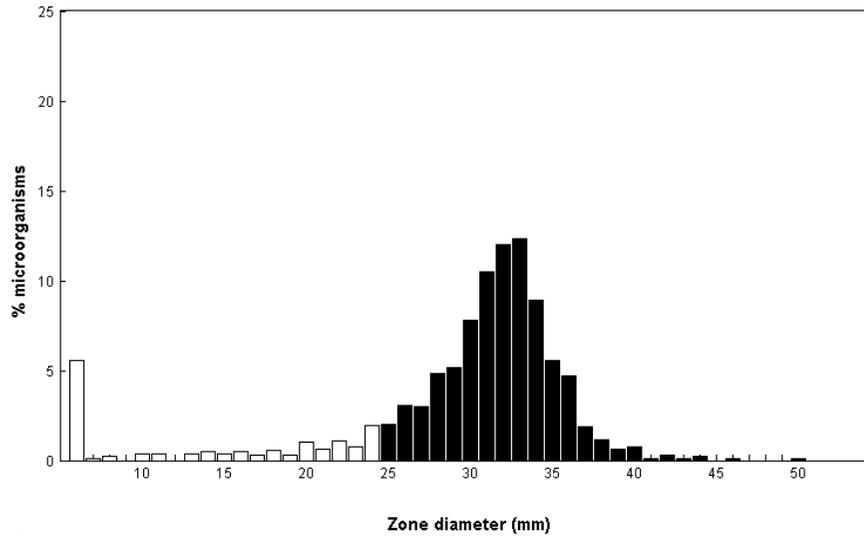


Amikacin MIC determination or disk diffusion does not unequivocally distinguish between susceptible, intermediate and resistant isolates.
 Isolates belonging to the kanamycin wild type do not exhibit amikacin resistance (see next slide).

Breakpoints		ECOFF
MIC	S ≤ 8 , R >16 mg/L	8 mg/L
Zone diameter	S ≥ 18 , R <16 mm	

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

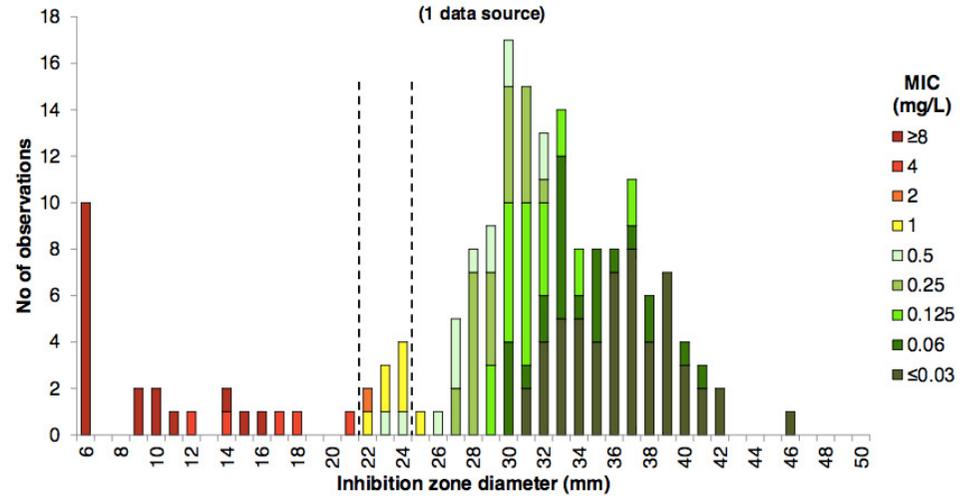
Distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



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)

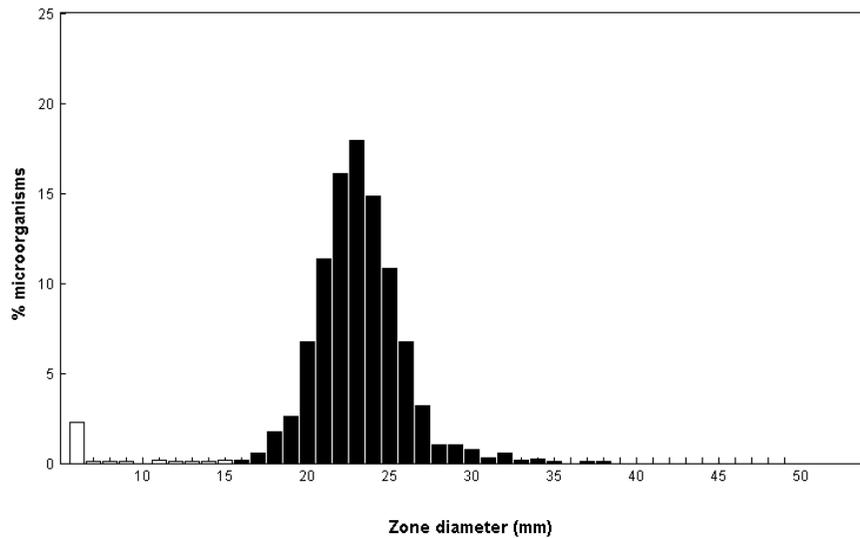
Ciprofloxacin 5 μ g vs. MIC
***Pseudomonas non-aeruginosa*, 173 isolates**
 (1 data source)



Breakpoints	
MIC	$S \leq 0.5$, $R > 1$ mg/L
Zone diameter	$S \geq 25$, $R < 22$ mm

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

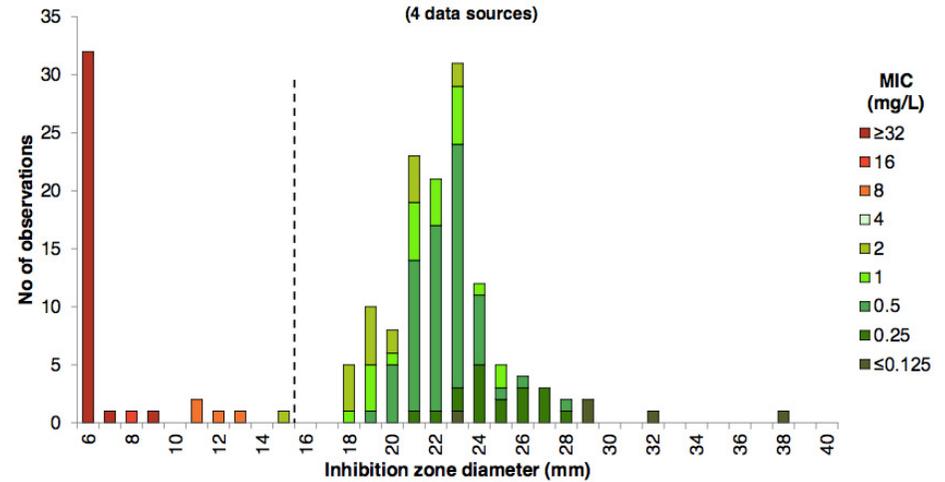
Distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



Disk content: 10
 Epidemiological cut-off (ECOFF): 16 mm (MIC = 2 mg/L)
 Wildtype (WT) organisms: ≥ 16 mm (MIC = 2 mg/L)

1281 observations (5 data sources)

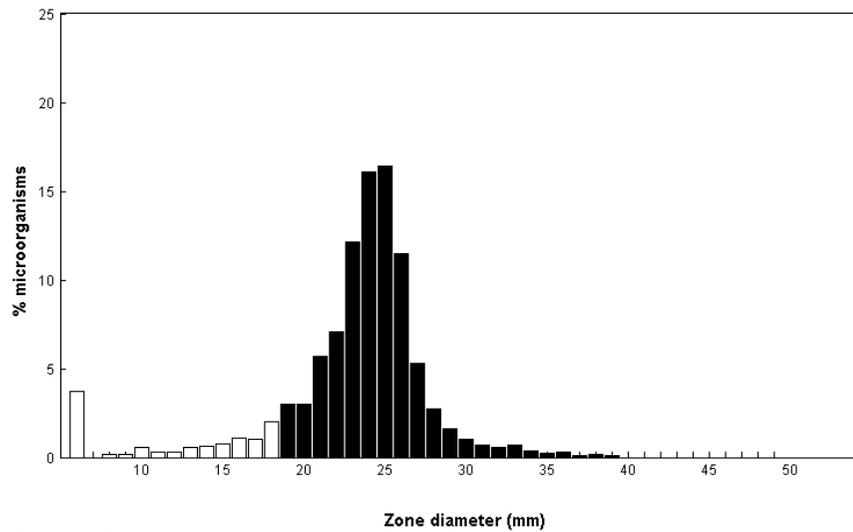
Tobramycin 10 μ g vs. MIC
***Pseudomonas aeruginosa*, 168 isolates**
(4 data sources)



Breakpoints		ECOFF
MIC	S \leq 4, R \geq 4 mg/L	2 mg/L
Zone diameter	S \geq 16, R $<$ 16 mm	

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

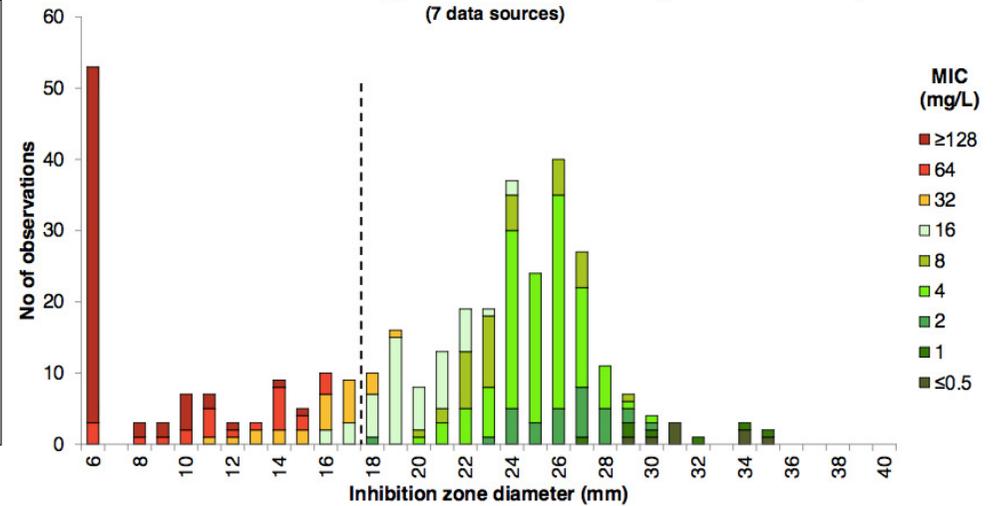
Distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



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)

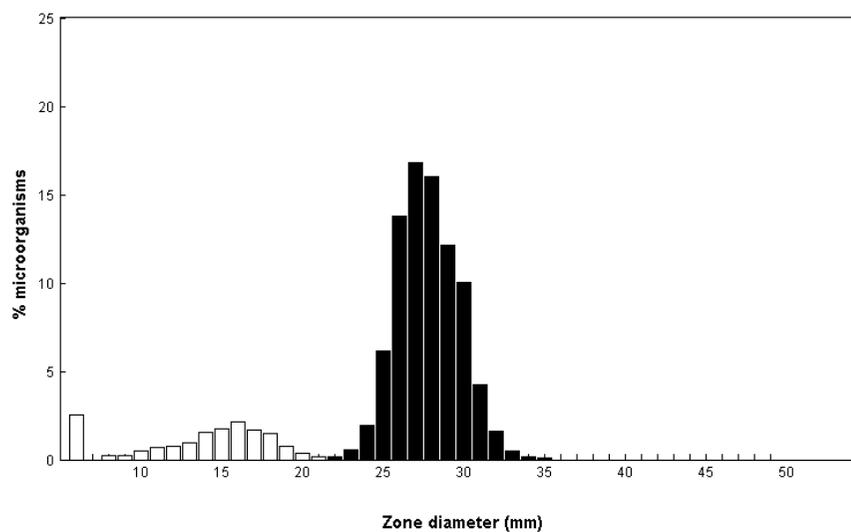
Piperacillin-tazobactam 30-6 μ g vs. MIC
***Pseudomonas aeruginosa*, 249 isolates (356 correlates)**
 (7 data sources)



Breakpoints		ECOFF
MIC	S \leq 16, R>16 mg/L	16 mg/L
Zone diameter	S \geq 18, R<18 mm	

Cefoxitin / *Staphylococcus aureus*
International wild type zone diameter distribution - Reference database 2016-04-05
EUCAST disk diffusion method

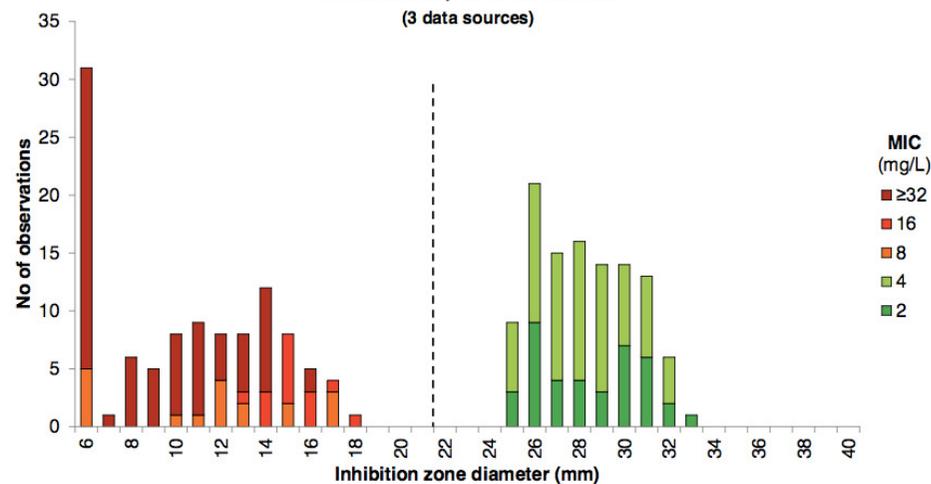
Distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



Disk content: 30
 Epidemiological cut-off (ECOFF): 22 mm (MIC = 4 mg/L)
 Wildtype (WT) organisms: ≥ 22 mm (MIC = 4 mg/L)

11190 observations (9 data sources)

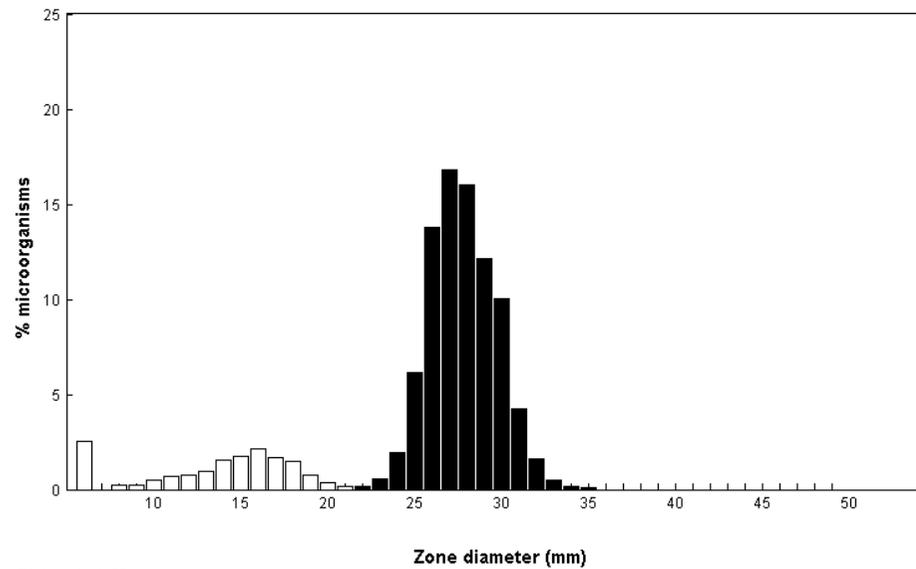
Cefoxitin 30 μ g vs. MIC
***S. aureus*, 215 isolates**
 (3 data sources)



Breakpoints		ECOFF
MIC (screen)	S \leq 4, R $>$ 4 mg/L	4 mg/L
Zone diameter (screen)	S \geq 22, R $<$ 22 mm	

Cefoxitin / *Staphylococcus aureus*
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

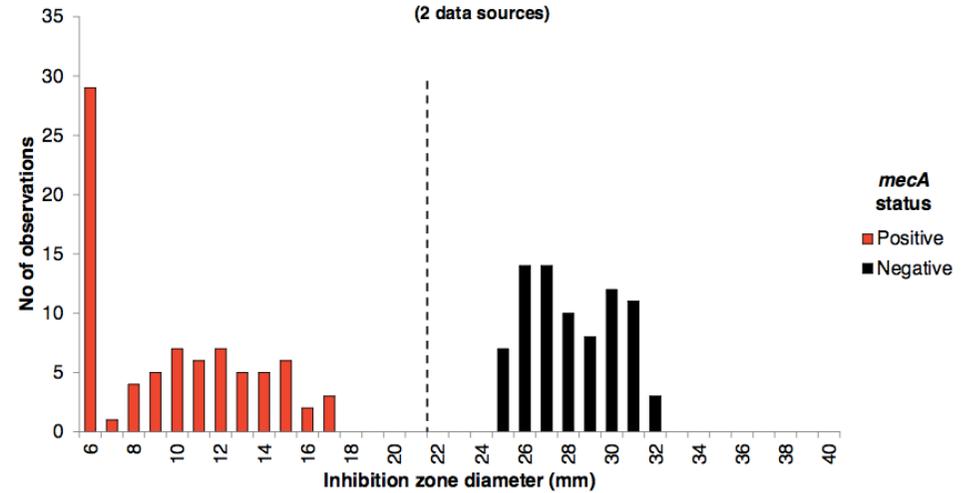


Disk content: 30
 Epidemiological cut-off (ECOFF): 22 mm (MIC = 4 mg/L)
 Wildtype (WT) organisms: ≥ 22 mm (MIC = 4 mg/L)

11190 observations (9 data sources)

Cefoxitin 30 μ g vs. *mecA* status
***S. aureus*, 159 isolates**

(2 data sources)



Breakpoints
 Zone diameter (screen) $S \geq 22$, $R < 22$ mm

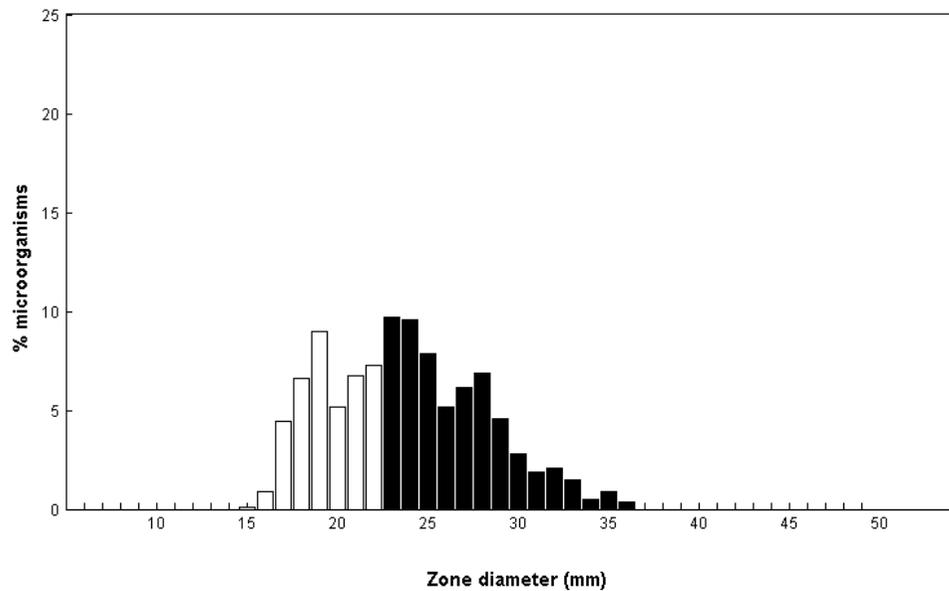
An intermediate category will not solve **this** problem!

Ceftaroline / *Staphylococcus aureus*

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

EUCAST disk diffusion method

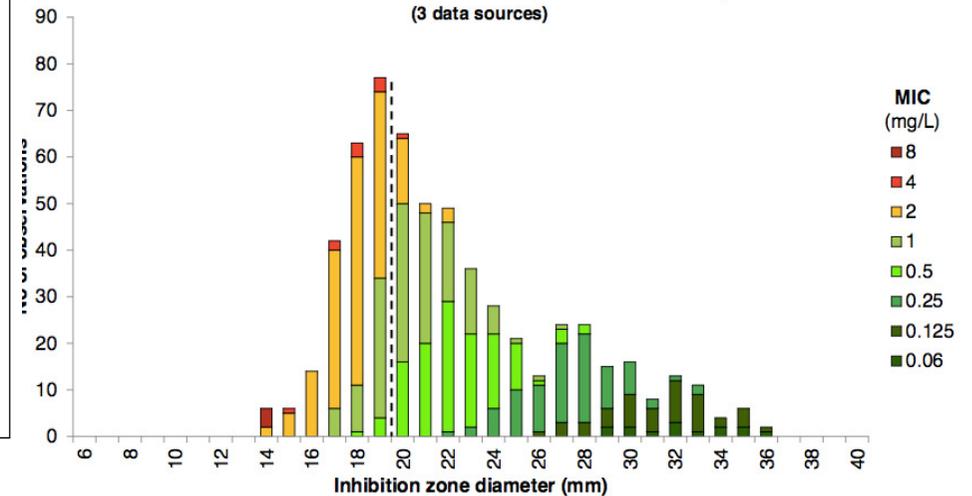
Distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



Disk content: 5
Epidemiological cut-off (ECOFF): 23 mm (MIC = 0.5 mg/L)
Wildtype (WT) organisms: ≥ 23 mm (MIC = 0.5 mg/L)

814 observations (7 data sources)

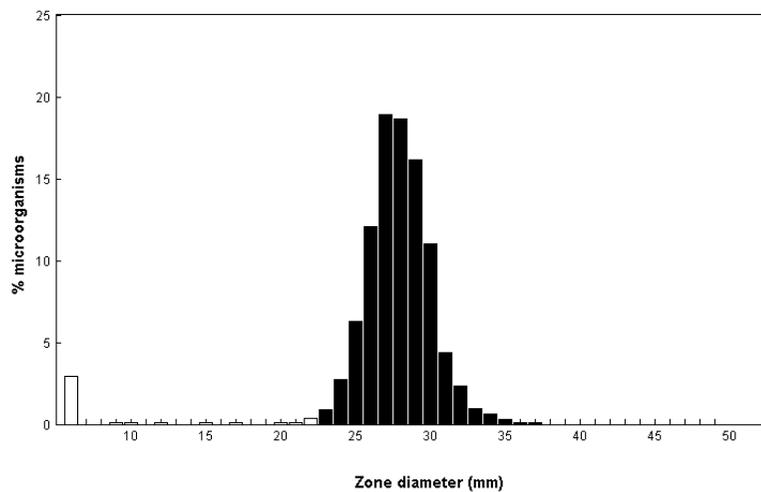
Ceftaroline 5 μg vs. MIC *S. aureus*, 216 isolates (593 correlates) (3 data sources)



Breakpoints		ECOFF
MIC	$S \leq 1, R > 1$ mg/L	0.5 mg/L
Zone diameter	$S \geq 20, R < 20$ mm	

Cefotaxime / Escherichia coli
International wild type zone diameter distribution - Reference database 2016-04-05
EUCAST disk diffusion method

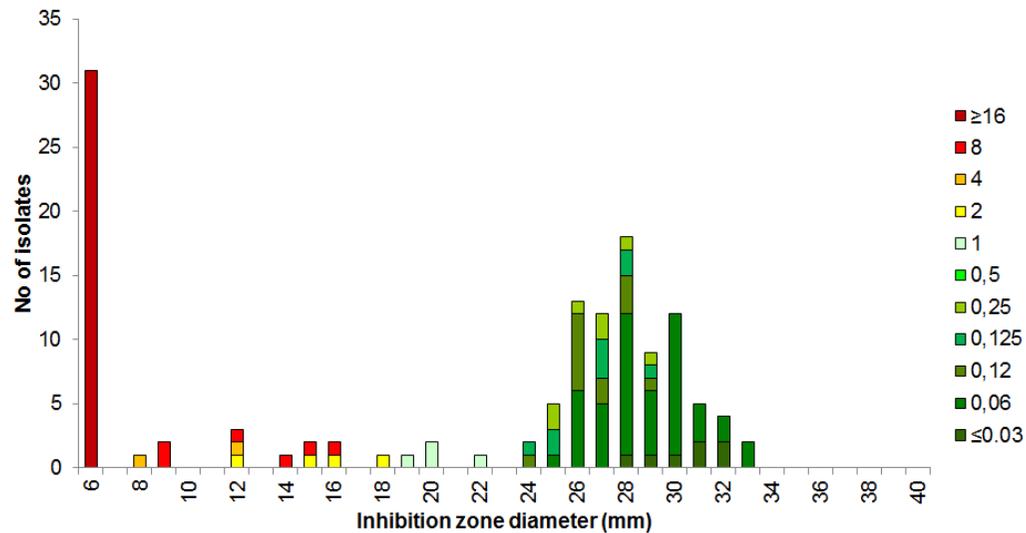
Distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



Disk content: 5
 Epidemiological cut-off (ECOFF): 23 mm (MIC = 0.25 mg/L)
 Wildtype (WT) organisms: ≥ 23 mm (MIC = 0.25 mg/L)

14654 observations (6 data sources)

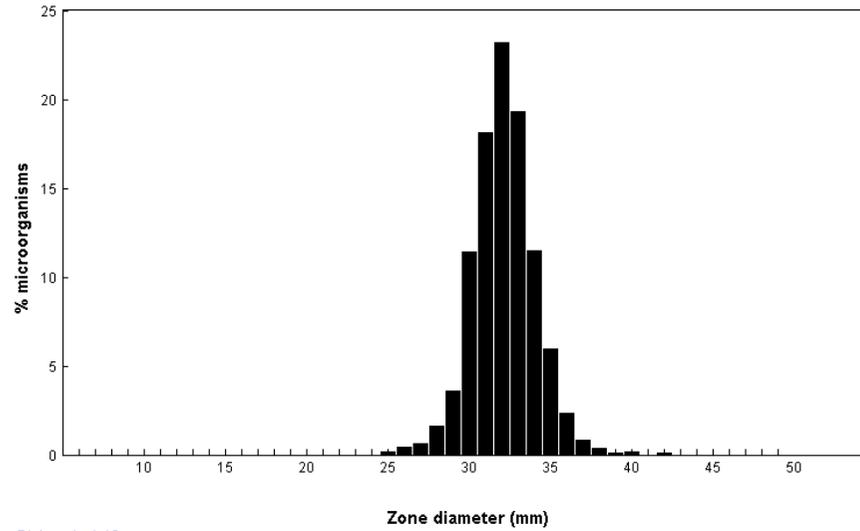
Cefotaxime 5 μ g vs. MIC
***E. coli*, 129 clinical isolates**



- ≥ 16
- 8
- 4
- 2
- 1
- 0,5
- 0,25
- 0,125
- 0,12
- 0,06
- ≤ 0.03

Meropenem / Escherichia coli
International wild type zone diameter distribution - Reference database 2016-04-05
EUCAST disk diffusion method

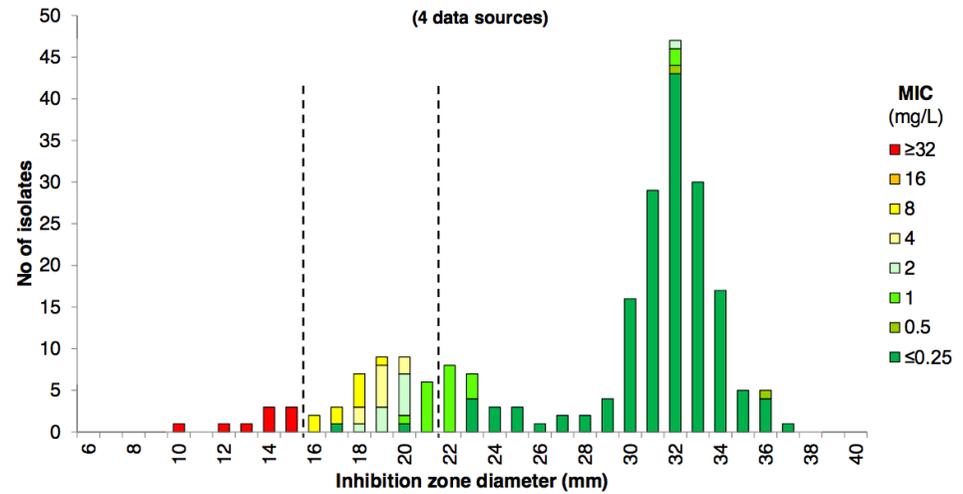
Distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



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)

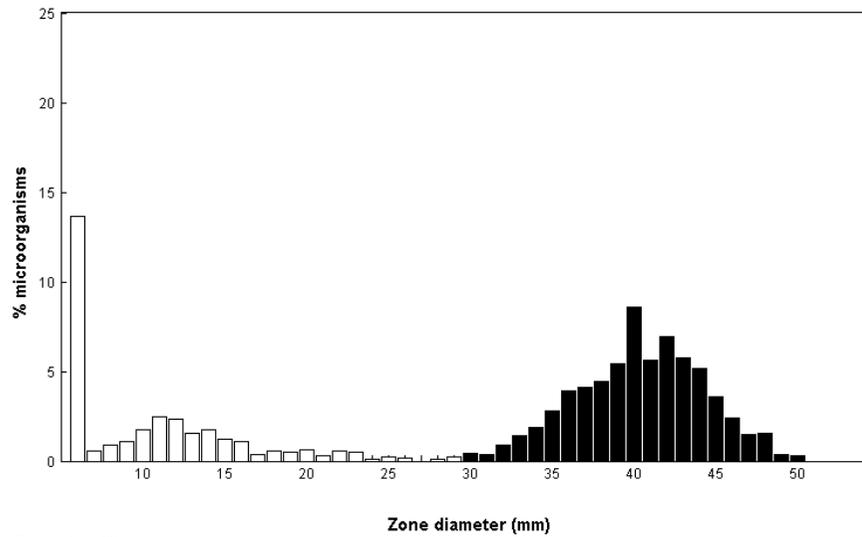
Meropenem 10 µg vs. MIC
***E. coli*, 225 clinical isolates**



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

Tetracycline / *Campylobacter jejuni*
International wild type zone diameter distribution - Reference database 2016-04-05
EUCAST disk diffusion method

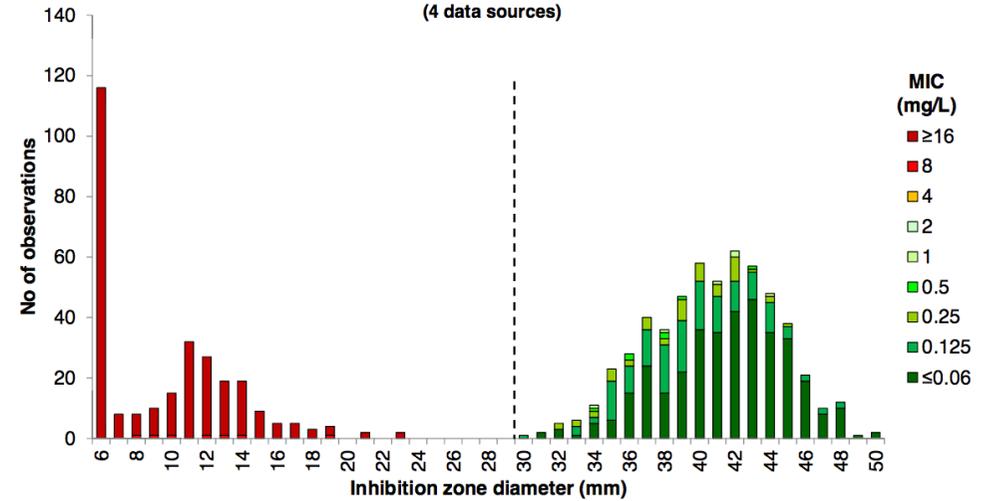
Distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



Disk content: 30
 Epidemiological cut-off (ECOFF): 30 mm (MIC = 1 mg/L)
 Wildtype (WT) organisms: ≥ 30 mm (MIC = 1 mg/L)

1585 observations (15 data sources)

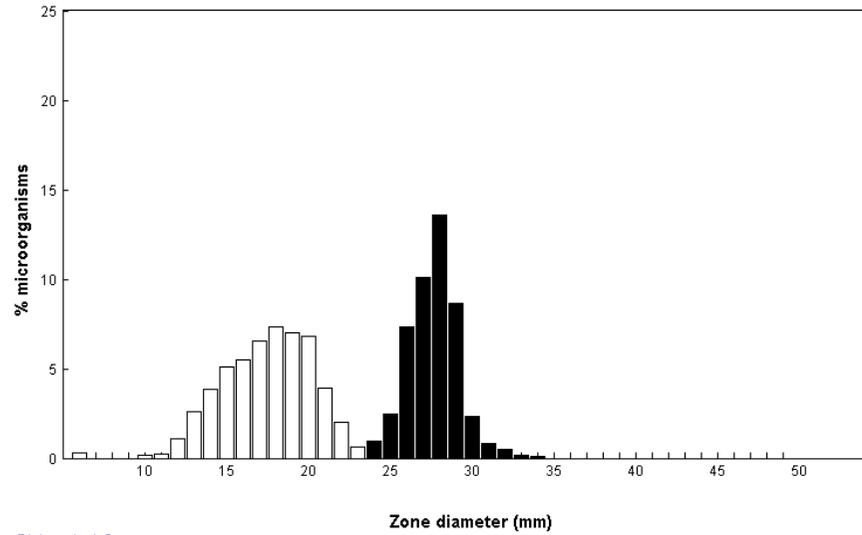
Tetracycline 30 μ g vs. MIC
***C. jejuni* and *coli*, 817 isolates (844 correlates)**
(4 data sources)



Breakpoints		ECOFF
MIC	S ≤ 2 , R > 2 mg/L	1 mg/L (<i>C. jejuni</i>), 2 mg/L (<i>C. coli</i>)
Zone diameter	S ≥ 30 , R < 30 mm	

Pefloxacin / Salmonella spp
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): 24 mm (MIC -)

Wildtype (WT) organisms: \geq 24 mm (MIC -)

1257 observations (15 data sources)

Trying to solve two different problems with one susceptibility category.

A. There is a need to inform clinicians about the fact that some intrinsically less susceptible organisms and some low level non-susceptible organisms can be overcome by an increase in dose (or concentration at infection site). This will only be for agents where the dose may be increased without ill effects.

B. When inherent natural variation is translated into dichotomous information (two or three categories), even the smallest variation will at times cause major shifts.

This is irrespective of test system (MIC, disk diffusion or any other test). When the measured result is close to one of the breakpoints (S/I or I/R or S/R - when no intermediate category) small variations may lead to major flips between categories. When it flips between R/S and S/R a very major (VME) or major error (ME) has occurred according to current terminology. The wider the INTERMEDIATE category, the less chance of VME/MEs.

This is the argument for retaining intermediate as a buffer zone between S and R. However, as much as half of EUCAST's breakpoints (and many of CLSI's breakpoints) lack an intermediate category.

EUCAST can not see how these two can be united in one common susceptibility category since there is nothing to inform the recipient of the report as to which meaning is relevant in individual cases. And at times both meanings may be relevant simultaneously.

Moreover, one is to warn the clinician that he may need to increase the dose, the other is to warn the laboratory that they may have to check their result (or warn the clinician that it may be erroneous).

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.

Alternativ

- Ingen ändring
- Inför en systematisk I-grupp i alla brytpunkter. Ändra definitionen till “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”.
- Ändra definition som EUCAST föreslagit – avlägsna buffertzonen från definitionen.
- Ändra definition som EUCAST föreslagit – avlägsna buffertzonen från definitionen och inför en laborieteknisk **Area of Technical Uncertainty**, men endast där det är relevant, som en varning på laboratoriet som kräver en åtgärd.

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.

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” – if not solved by other means, 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 in report

5.

Area of Technical Uncertainty

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

Hur bred ska ATU vara (MIC / Zon)?

- MIC 1 spädningssteg.
- zon diameter 3 mm (motsvarar 1 spädningssteg och +/- variationen i lappdiffusion).
- Inte alla brytpunkter måste ha en ATU.
- I flertalet fall kan detta lösas genom att medvetet flytta zonbrytpunkten 1 – 3 mm “uppåt”.

Area of Technical Uncertainty – Actions?

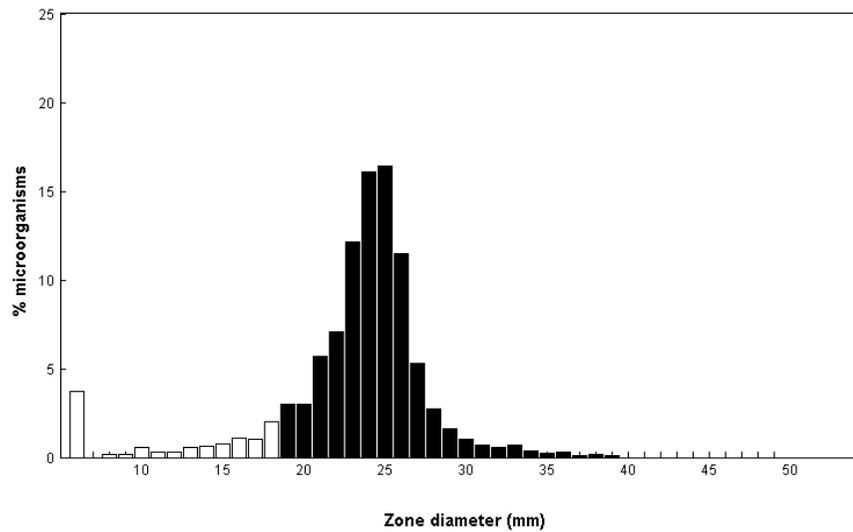
- 1. Report the result but as “uncertain”**
 - add a comment; report the result in brackets or parenthesis
 - requires changes in thousands of LIS systems
- 2. Repeat uncertain results**
 - repeat the test – the same test or use another test. What to do with discrepant result (revert to plan 1)
 - an MIC-test will “automatically give an unambiguous result!”, “the right result?”
- 3. “Play it safe” – if not solved by other means, 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 in report**
- 5.**

Area of Technical Uncertainty – Actions?

- 1. Rapportera resultatet men ange osäkerhet**
 - add a comment; report the result in brackets or parenthesis
 - requires changes in thousands of LIS systems
- 2. Upprepa testen**
 - samma test eller en ny test !
 - an MIC-test “ger alltid rätt resultat”!?
- 3. “Play it safe” – om man inte löst problemet på annat sätt, nedgradera resultat i ATU - S till I och I till R.**
- 4. Rapportera inte ATU-resultat – lämna blankt i resistensbestämningen.**
- 5.**

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

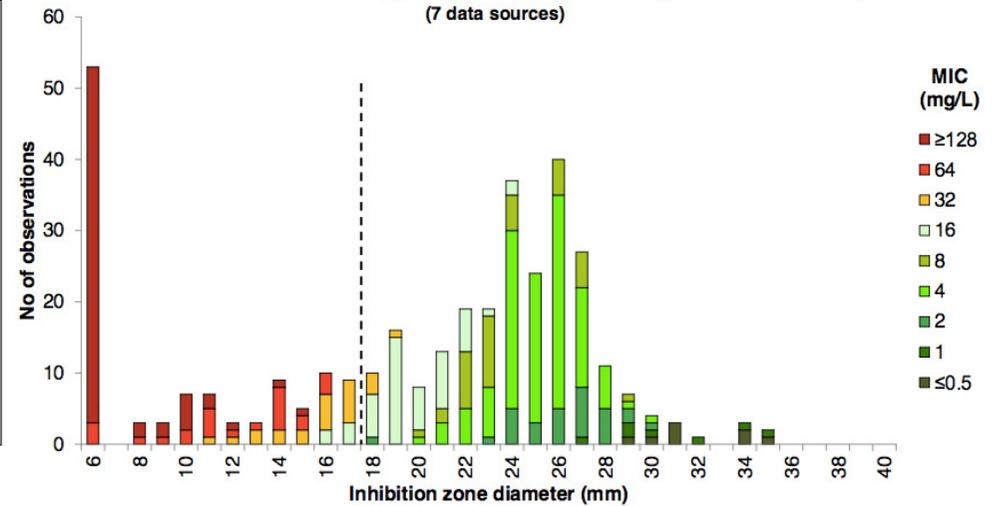
Distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



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)

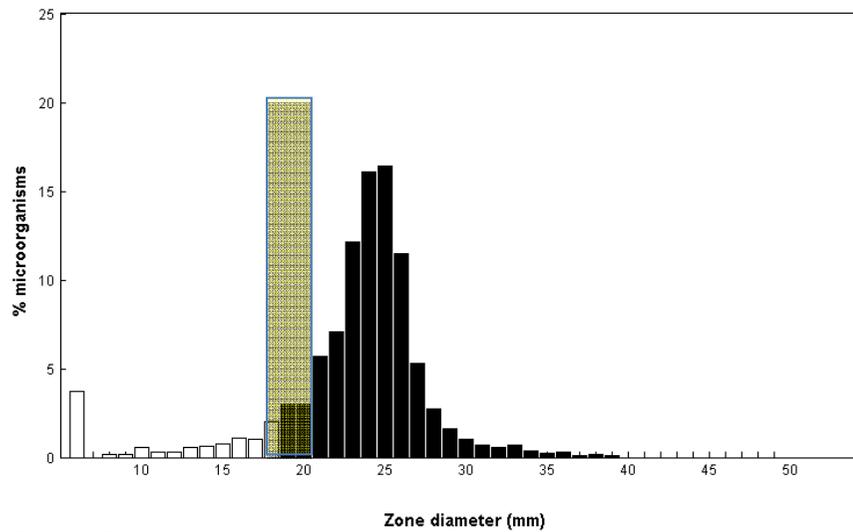
Piperacillin-tazobactam 30-6 μ g vs. MIC
***Pseudomonas aeruginosa*, 249 isolates (356 correlates)**
 (7 data sources)



Breakpoints		ECOFF
MIC	S \leq 16, R>16 mg/L	16 mg/L
Zone diameter	S \geq 18, R<18 mm	

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

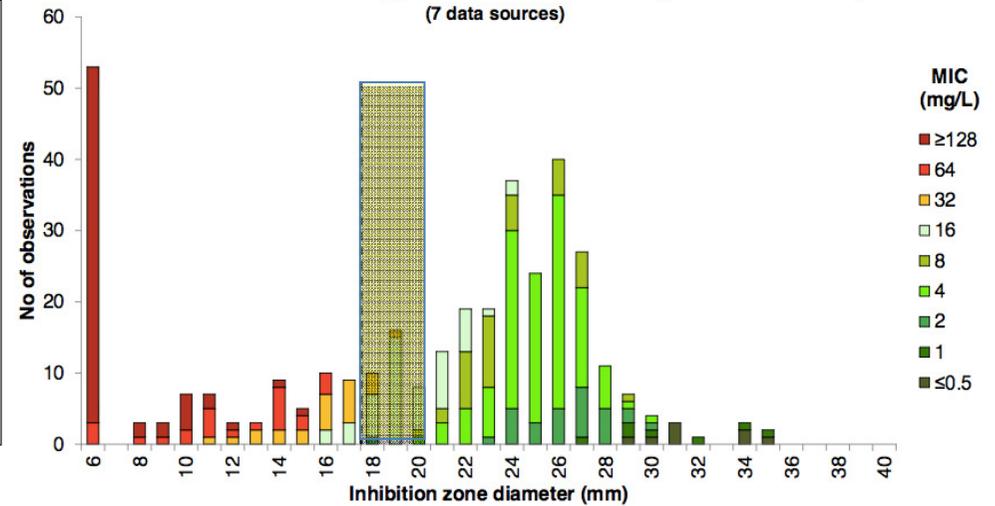
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Disk content: 36
 Epidemiological cut-off (ECOFF): 19 mm (MIC = 16 mg/L)
 Wildtype (WT) organisms: ≥ 19 mm (MIC = 16 mg/L)

1283 observations (5 data sources)

Piperacillin-tazobactam 30-6 μ g vs. MIC
***Pseudomonas aeruginosa*, 249 isolates (356 correlates)**
 (7 data sources)



Breakpoints		ECOFF
MIC	S \leq 16, R>16 mg/L	16 mg/L
Zone diameter	S \geq 18, R<18 mm	

Tack

Around each concentration or zone diameter,
there is variation -

- but the consequences may be small or large depending on agent, species, resistance rate and clonal outbreaks.
- to minimize consequences (to prevent a jump from a true R to an S; or from a true S to an R), an INTERMEDIATE category may be used.
- The wider the INTERMEDIATE category, the fewer very major and major errors – an infinite intermediate category will prevent all VME and ME.

The variation - MIC

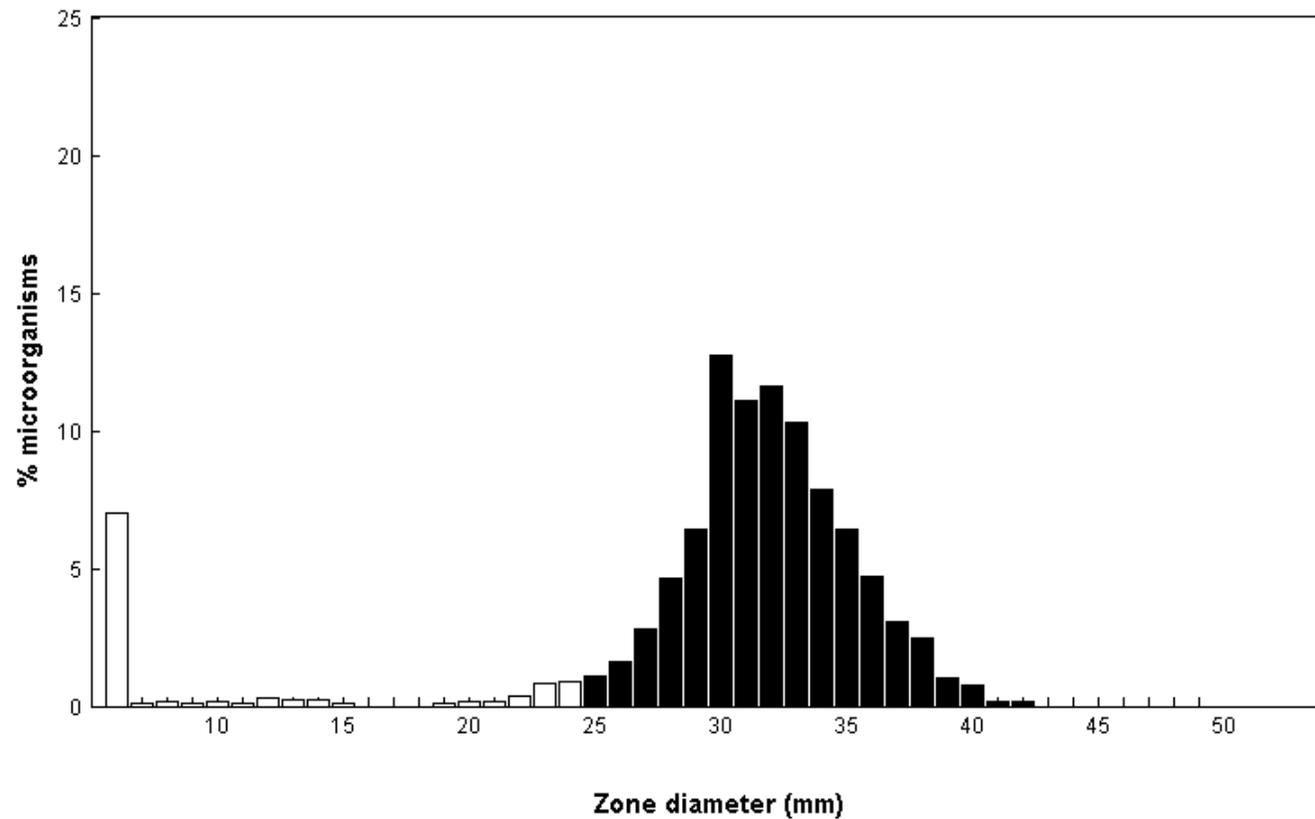
- In an MIC-test based on two-fold dilutions of the agent, the variation is often 1 dilution step around the “mean” (not the true) value.
- the more systems involved
 - Broth micro dilution
 - Agar dilution
 - Gradient tests
 - Automated MIC-determination machines etc
- the more people involved,
- the more labs involved etc

Disk diffusion

- In a disk diffusion test, the variation in zone diameters in a standard laboratory is well known.
- Daily internal QC with registration of zone diameters not only checks that today's results are within spec but also yields overall MEAN and SD
- A typical result over time:

Ciprofloxacin / Escherichia coli
International wild type zone diameter distribution - Reference database 2016-03-26
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

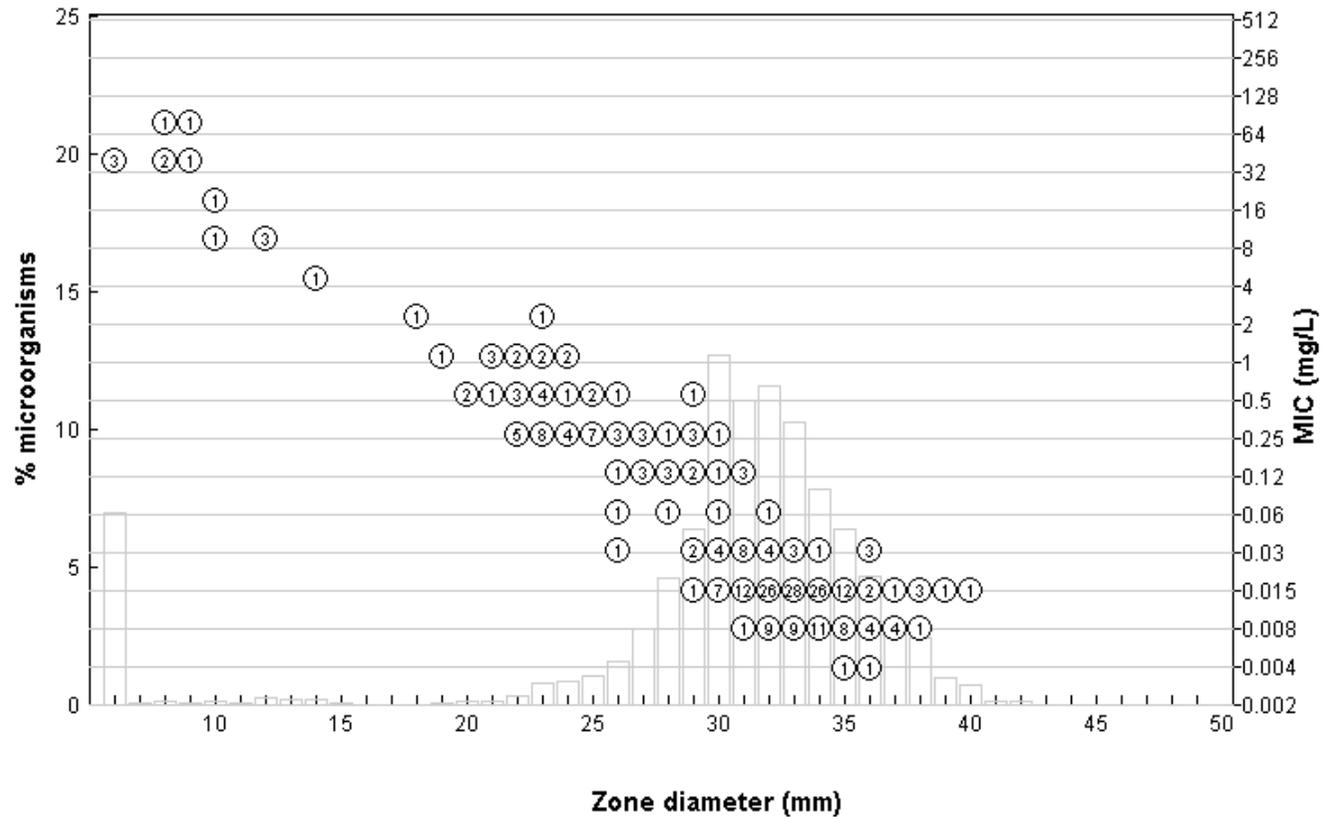
Epidemiological cut-off (ECOFF): 25 mm (MIC = 0.064 mg/L)

Wildtype (WT) organisms: ≥ 25 mm (MIC = 0.064 mg/L)

6449 observations (7 data sources)

Ciprofloxacin / Escherichia coli
International wild type zone diameter distribution - Reference database 2016-03-26
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)

6449 observations (7 data sources)

The following breakpoints with intermediate category have only one dose

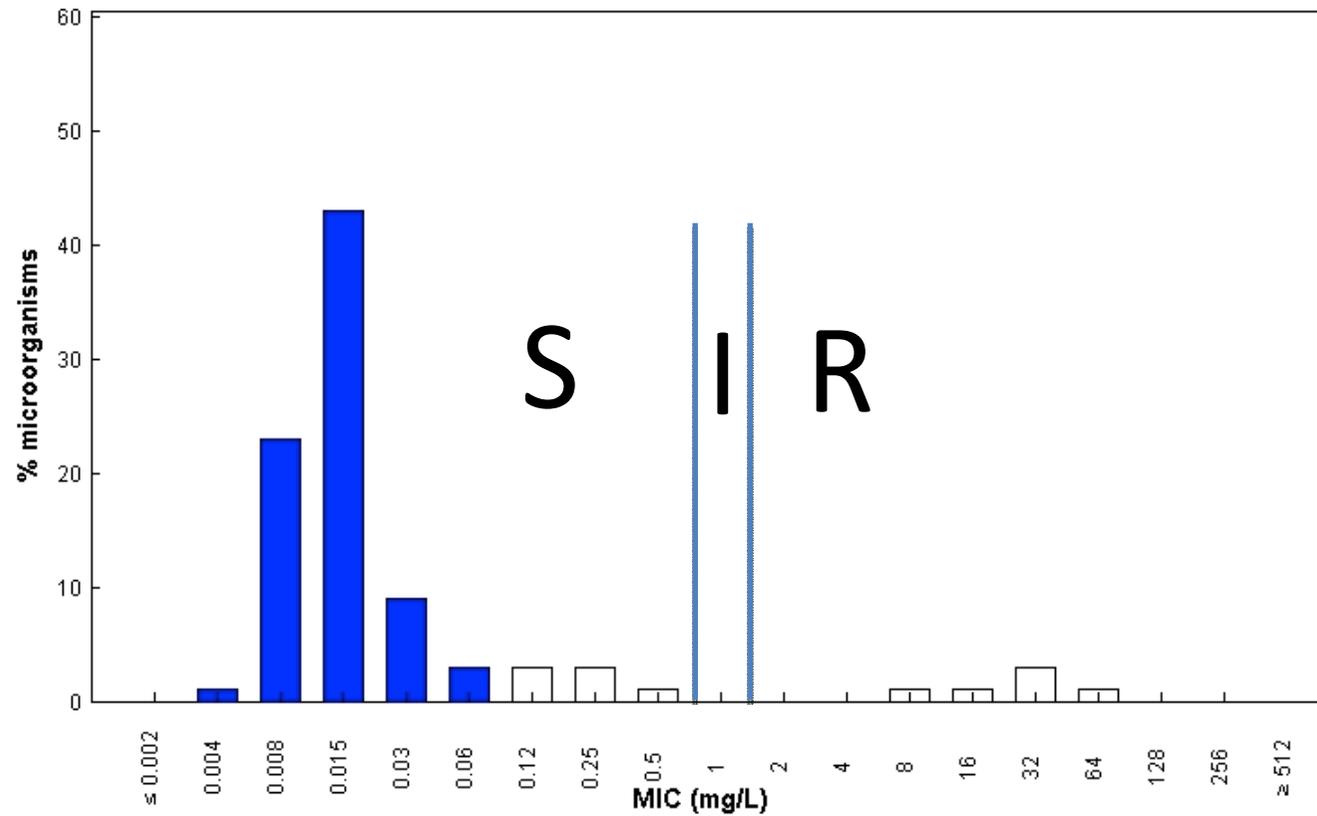
Species	Agent	Problem
Enterobacteriaceae	Ertapenem	Intermediate category (0.5/1), only one dose
Enterobacteriaceae	Genta-, Tobra- and Netilmicin.	Intermediate category (2/4), only one dose It could be argued that these represent agents which concentrate significantly in urine.
Enterobacteriaceae + Pseudomonas + Acinetobacter + Staphylococci	Amikacin	Intermediate category, only one dose. It could be argued that these represent agents which concentrate significantly in urine.
Enterobacteriaceae	Tigecycline	Intermediate category (1/2), only one dose
Staphylococci	Clindamycin	
Enterococci	Tigecycline	Intermediate category (0.25/0.5), only one dose
Streptococci	Macrolides	

Breakpoint table comment: High dose

Item	Breakpoint	
Pseudomonas/Piperacillin	16	WT susceptible, breakpoint higher than PK/PD
Pseudomonas/Cefepime	8	WT susceptible, breakpoint higher than PK/PD
Pseudomonas/Ceftazidime	8	WT susceptible, breakpoint higher than PK/PD
Pseudomonas/Aztreonam	1/16	No S, all WT Intermediate
Pseudomonas/Doripemen	1	WT susceptible, breakpoint higher than PK/PD
Pseudomonas/Imipenem	4	WT susceptible, breakpoint higher than PK/PD
Staphylococcus/ciprofloxacin	1	WT susceptible, breakpoint higher than PK/PD

Ciprofloxacin / Escherichia coli
International MIC Distribution - Reference Database 2016-03-26

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

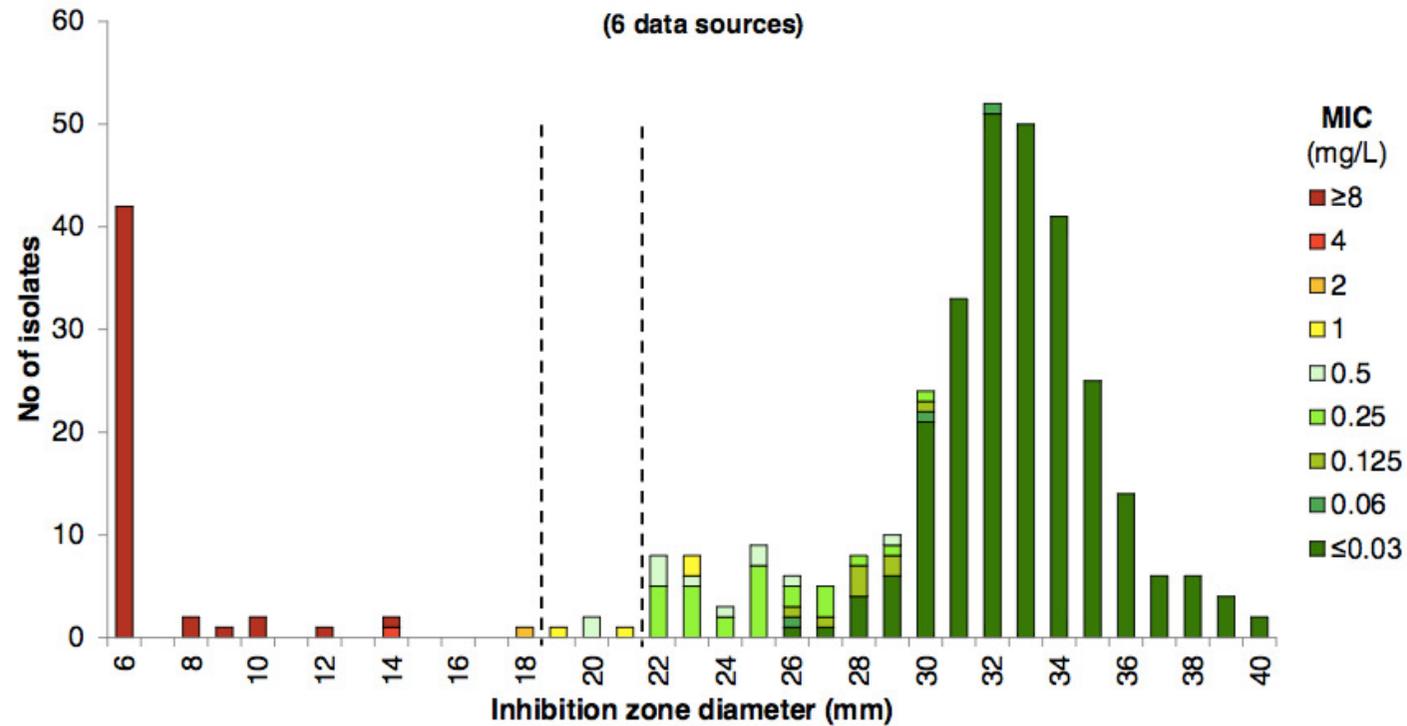


MIC
Epidemiological cut-off (ECOFF): 0.064 mg/L
Wildtype (WT) organisms: ≤ 0.064 mg/L

16702 observations (55 data sources)

Ciprofloxacin 5 µg vs. MIC *E. coli*, 369 clinical isolates

(6 data sources)



Breakpoints

MIC S≤0.5, R>1 mg/L
Zone diameter S≥22, R<19 mm

ECOFF

0.06 mg/L

EUCAST breakpoints are set to avoid cutting into wild type distributions of target microorganisms

Wild type distribution where breakpoints used to divide:

- Haemophilus influenzae vs. erythromycin
- Streptococcus pneumoniae vs ciprofloxacin
 - Pseudomonas vs. aztreonam
 - ...

The EUCAST AST system

Microorganisms are categorized as S, I or R by applying breakpoints in a defined phenotypic test system.

Disk diffusion correlates (inhibition zone breakpoints) are determined on large collections of organisms (wild type + clinical isolates with defined and varied resistance mechanisms).

The EUCAST AST system

Clinical breakpoints are presented as

$S \leq x \text{ mg/L}; I > x, \leq y \text{ mg/L}; R > y \text{ mg/L}$
(CLSI $R > z \text{ mg/L}$)

The EUCAST AST system

- Clinical breakpoints are subject to review and revision when circumstances change.

The change may be in

- **Indications – clinical**
- **Indications – target species**
- **Resistance mechanisms**
- **Dosing**
- **Routes of administration**

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 ^I	7 ^{II}	17 ^{III}	23 ^I	13 ^{II}

^I5 of these (all betalactam agents) were more than 1 dilution wide.

^{II}1 of these (betalactam) were more than 1 dilution wide.

^{III}2 of these (mupirocin, rifampicin) were more than 1 dilution wide.

CLSI Intermediate category

	Entero- bacteriaceae	Pseudo- monas	Staphylo- cocci	S.pneu- moniae	Haemo- philus
No of numerical breakpoints	75	22	43	41	45
WITHOUT Intermediate	17	0	10	5	14
WITH Intermediate	58 ^I	22 ^{II}	33 ^{III}	36 ^{IV}	31 ^V

^I5 of these (all betalactam agents) were more than 1 dilution wide.

^{II}3 of these (betalactam) were more than 1 dilution wide.

^{III}2 of these (vancomycin, erythromycin) were more than 1 dilution wide.

^{IV}3 of these (benzylpenicillin, imipenem and trimsulfa) were more than 1 dilution wide

^V1 of these (trimsulfa) was more than 1 dilution step wide.