MIC directed therapy: why, when and what are the pitfalls?

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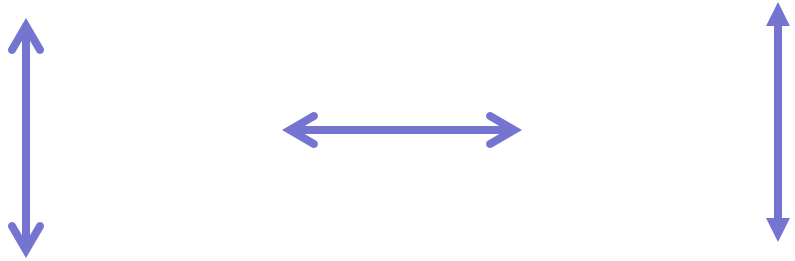
Disclosures

None

Antimicrobial therapy in general

Efficacy of the drug



Potency of a drug
(MIC)

Exposure to the bug
In vivo
(PK)

PK/PD indices

- The MIC in included in the indices:
  - %*f*T>MIC
  - AUC/MIC

The reference method

European Committee for Standardization
Comité Européen de Normalisation
Europäisches Komitee für Normung

↓

International Organization for Standardization

2003 20 june DIN Berlin
CEN TC140/WG10

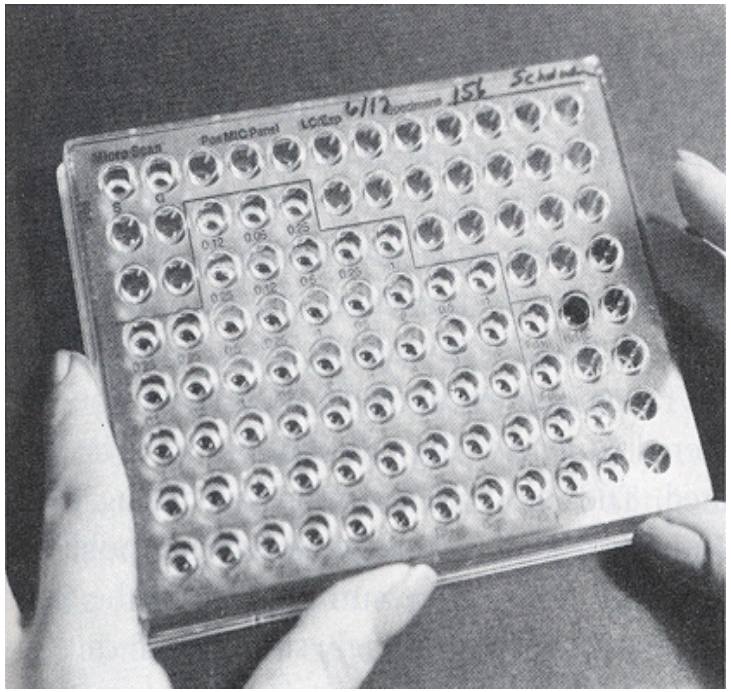
2004 22 april DIN Berlin
Combined meeting with
ISO ISO/TC 212 WG4
Vienna Agreement

2005 Vote on first draft and comments by all Member Countries

2006 Final version 27 October 2006,
8th CEN, 6th ISO meeting
ISO 20776-1

2007 Final version validation ISO 20776-2.

Minimum inhibitory concentration (MIC)



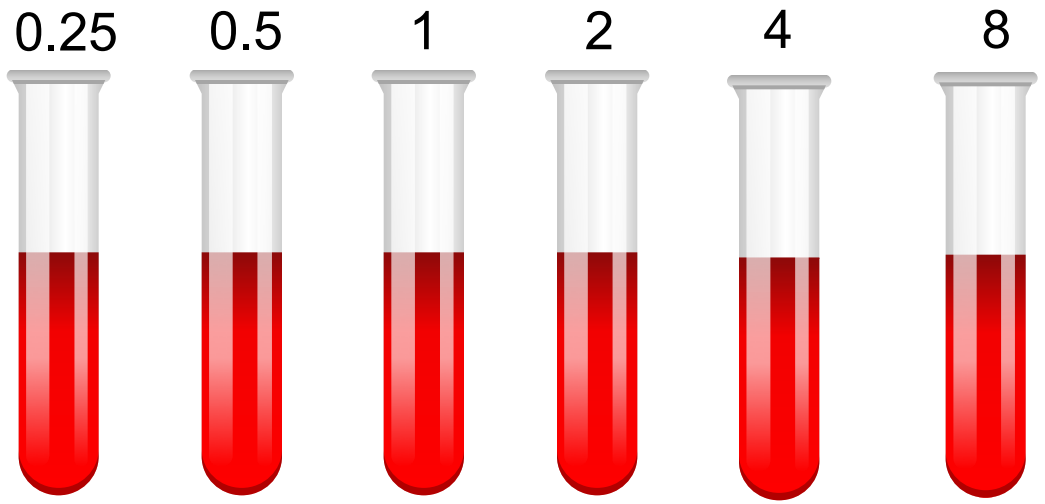
The reference method: microdilution

Measure of potency of the antibacterial effect

Minimum inhibitory concentration (MIC)

2-fold increasing antibiotic concentrations in mg/L in Mueller Hinton

Zoom in at the wells



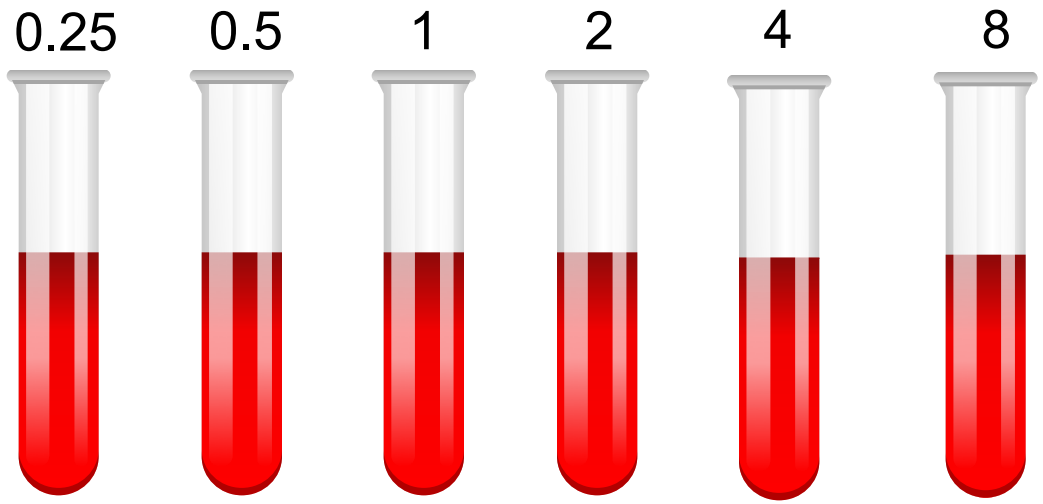
0.1ml suspension

Bacterial suspension: Inoculum 5 (2-8) .10E5 cfu/ml

Minimum inhibitory concentration (MIC)

2-fold increasing antibiotic concentrations in mg/L in Mueller Hinton

Bacterial suspension: Inoculum 5 (2-8) .10E5 cfu/ml

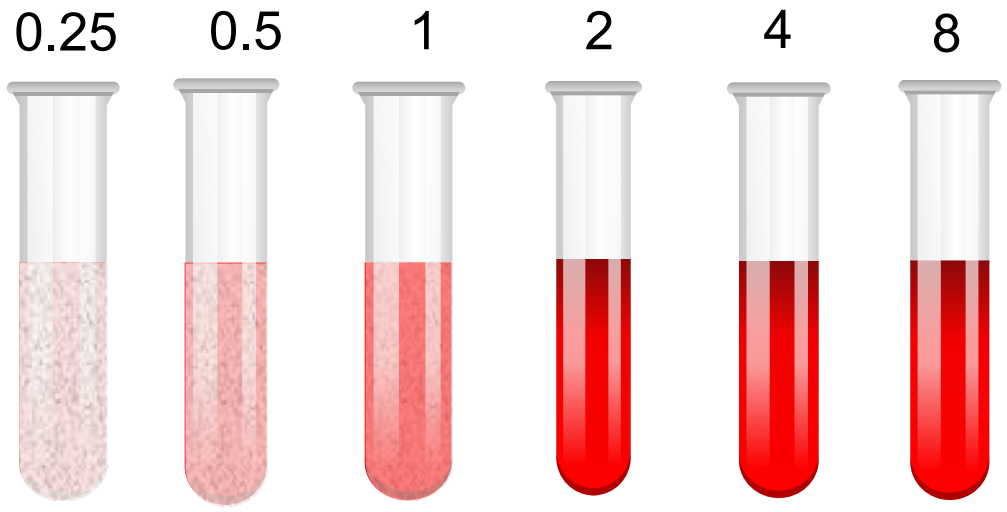


Incubate 36 +/- 1º C
18 +/- 2 hours

Minimum inhibitory concentration (MIC)

2-fold increasing antibiotic concentrations in mg/L in Mueller Hinton

Bacterial suspension: Inoculum 5 (2-8) .10E5 cfu/ml

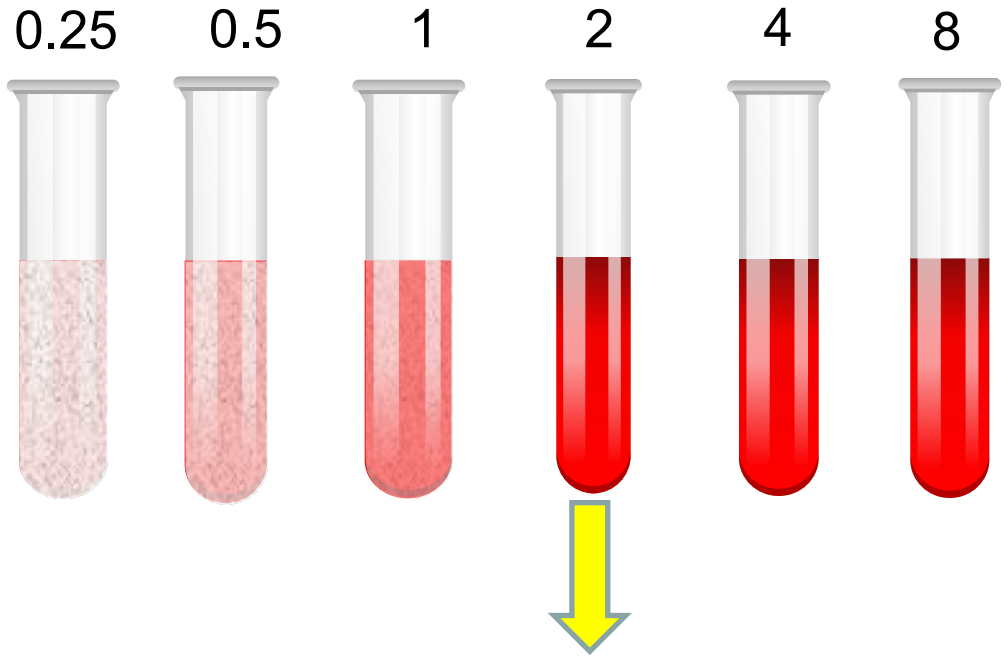


MIC= 2 mg/L

After inbubation: MIC= Lowest concentration with no **visible** growth

Minimum inhibitory concentration (MIC)

MIC= Lowest concentration with no **visible** growth



MIC= 2 mg/L

Number of bacteria in this tube varies between 0-10^8 CFU/ml

What happened in the tubes?

Bacterial growth
Bacterial kill
Continuous process over time

MIC= 2 mg/L

Growth Kill

$$\frac{dN}{dt} = \{\lambda \bullet (1 - \frac{N}{N_{max}}) - \varepsilon \bullet \frac{C^{\gamma}}{C^{\gamma} + EC_{50}^{\gamma}}\} \bullet N \quad (1)$$

Growth rate Max kill rate

MIC is the result of these processes over time

Mouton et al 1997

“The” MIC

Does NOT Quantify bacterial growth

Does NOT Quantify bacterial kill

It is the result of these biological processes over time

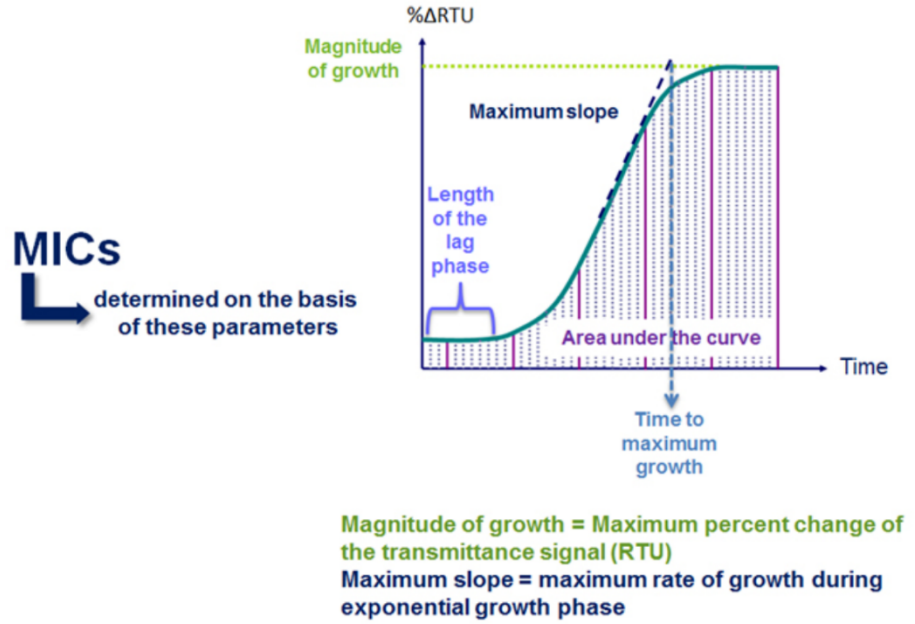
High variability and is not very reproducible

The use of other methods

- All methods need to be validated versus the reference method

Vitek 2 system, BioMérieux

- algoritm based on a few measurements.
- Not 2-fold dilution.
- Totally different approach
- repetitive turbidimetric monitoring of bacterial growth during an abbreviated incubation period.

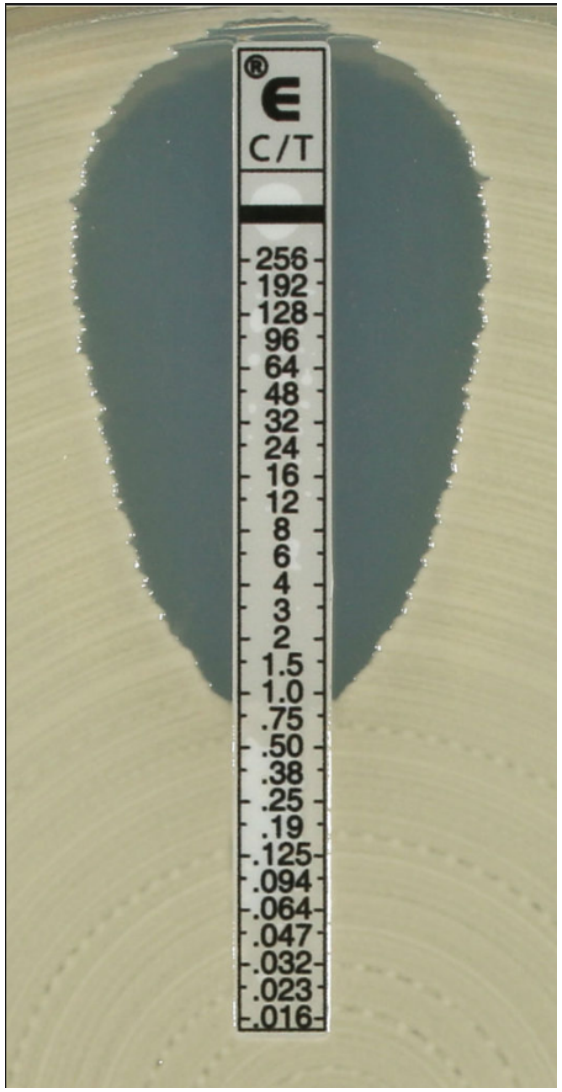


Phoenix system, BD

* 2-fold dilution,
* micro-dilution,
* growth or no-growth (turbidometric and colorimetric (oxidation-reduction indicator) growth detection).

* different inoculum from the reference method

Gradiënt-tests



- Increasing concentration on the strip
- Antibiotic diffuses into the agar

Ceftolozane/Tazobactam (C/T 256)

Figure: BioMérieux website

Disc diffusion

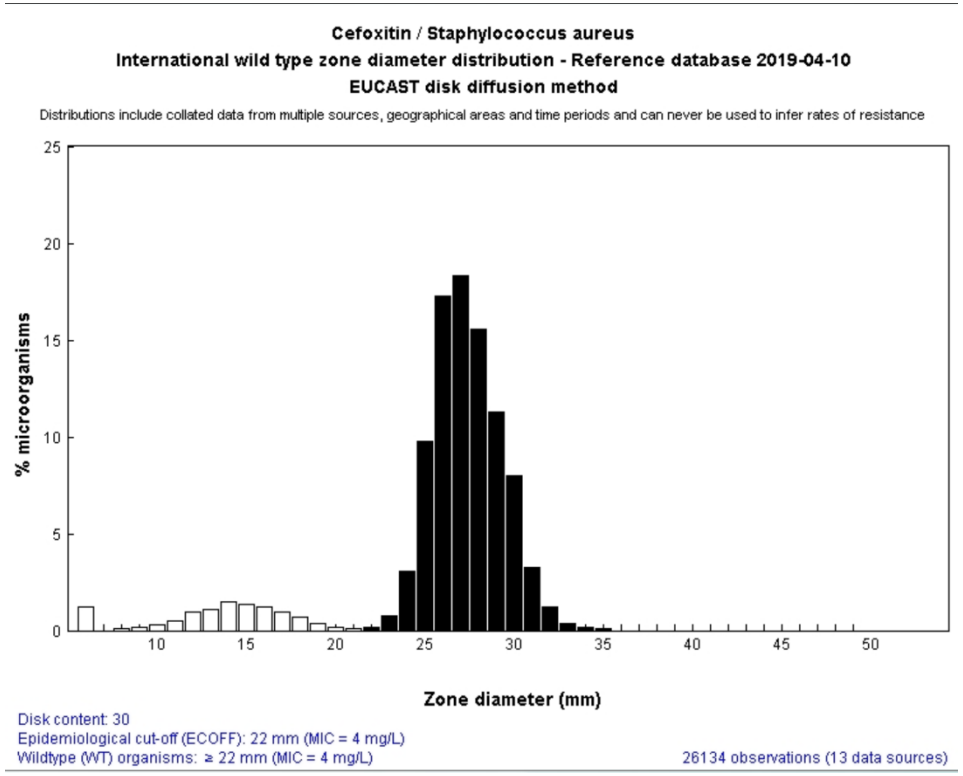
- Do not result in a value in mg/L, but in mm of the zone.

Figure: Thermo Fisher Scientific

Variation in measurements

- Biological variation within one strain
- between-strain variation
- between-laboratory variation
  - Materials
  - people

Disc diffusion *S aureus* and cefoxitin

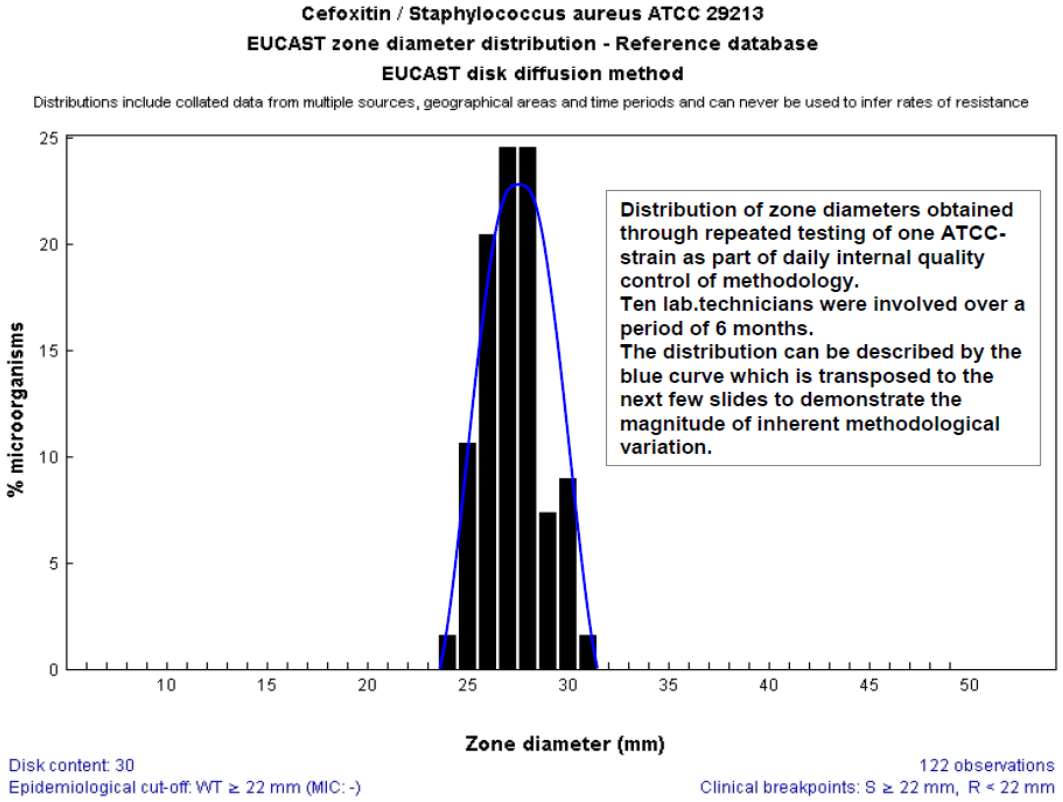


Different areas
~26000 observations (strains)
13 sources (different labs)
Different time periods
Susceptible strains: 22-35mm

Variation in measurements

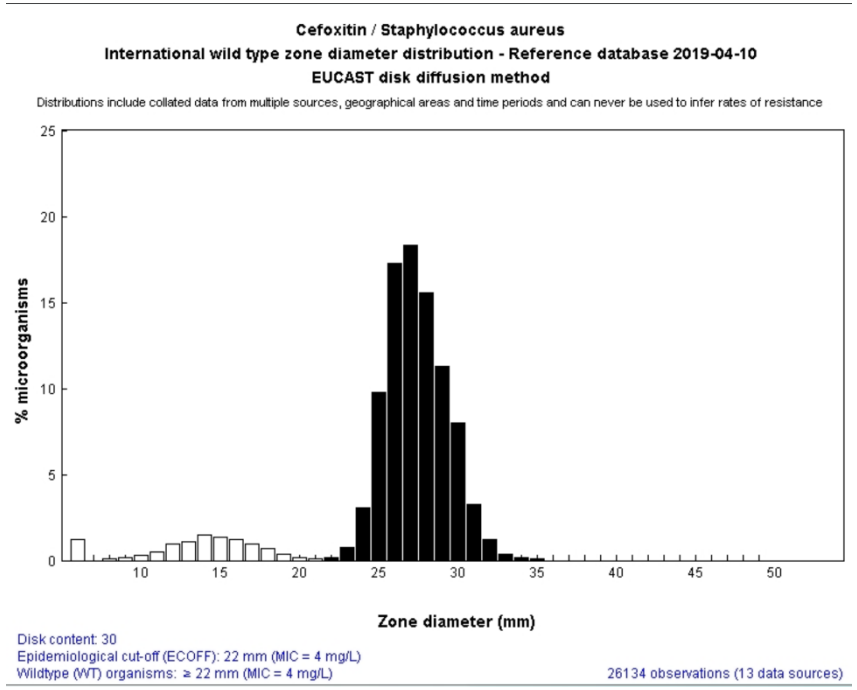
- Biological variation within one strain
- ~~between-strain variation~~
- ~~between-laboratory variation~~

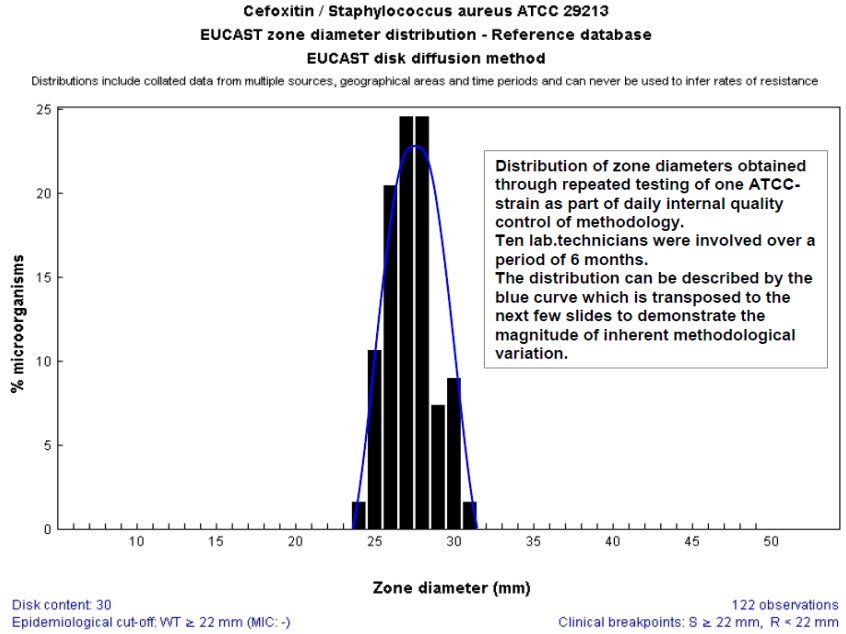
S aureus ATCC 29213 in 1 laboratory



1 strain
122 measurements
6 months
10 labtechnicians
Zones between 24-31 mm

Compare the two distributions





~26000 strains

1 strain
122 measurements

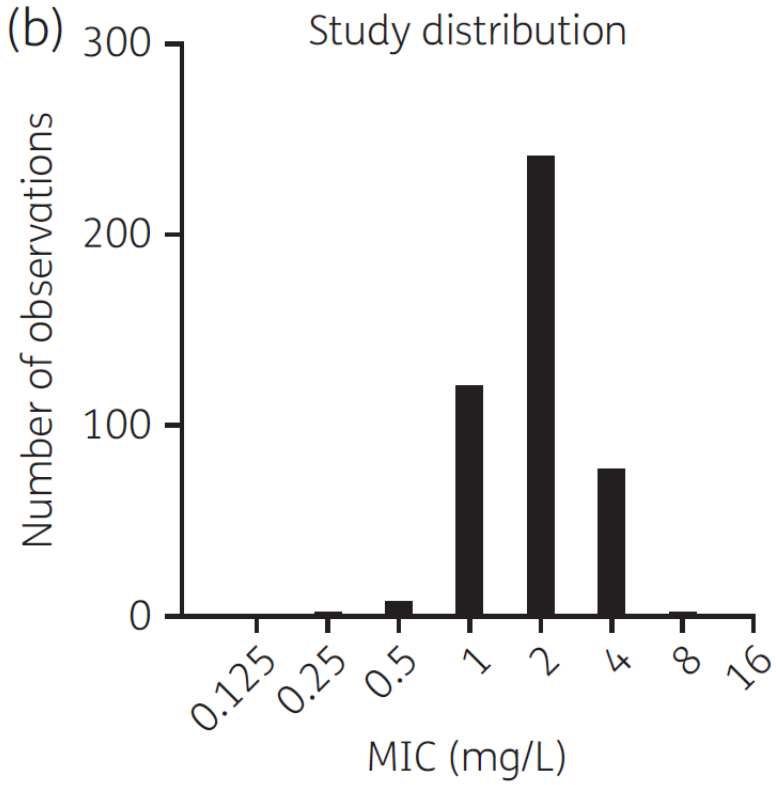
Second example on the variability

S aureus and linezolid MIC determined by gradienttest (Etest®)

Analysis:
22 different strains
5 different laboratories
Sent in quadruplicate (blind fashion)
440 observations

Mouton, 2018, p2374

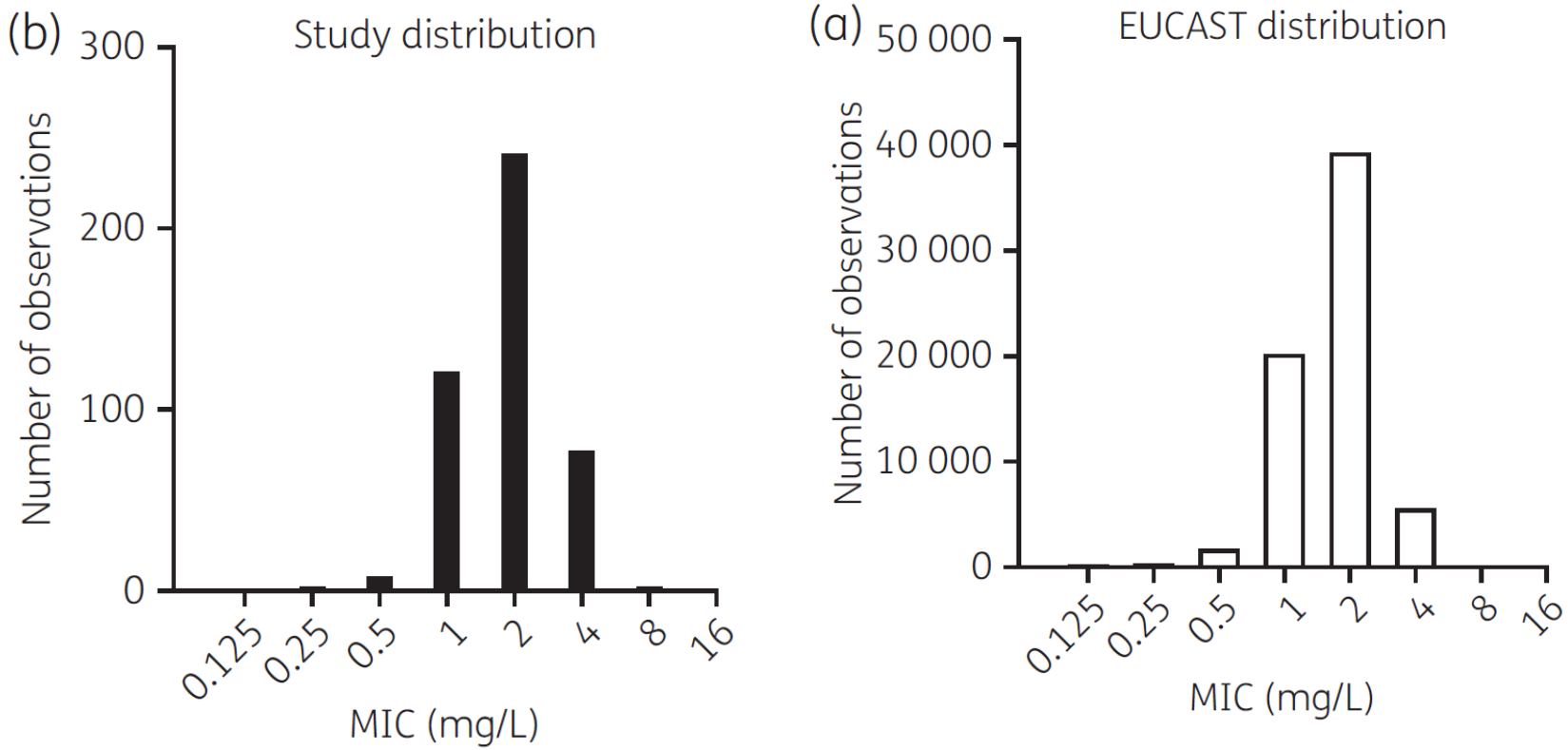
MIC-distribution of the strains



440 observations in 5 labs
→ 20 observations per strain

Mouton, 2018, p2374

MIC-distribution of the strains



440 observations in 5 labs
→ 20 observations per strain

Mouton, 2018, p2374

Linezolid and *S. aureus*

Source of the variation

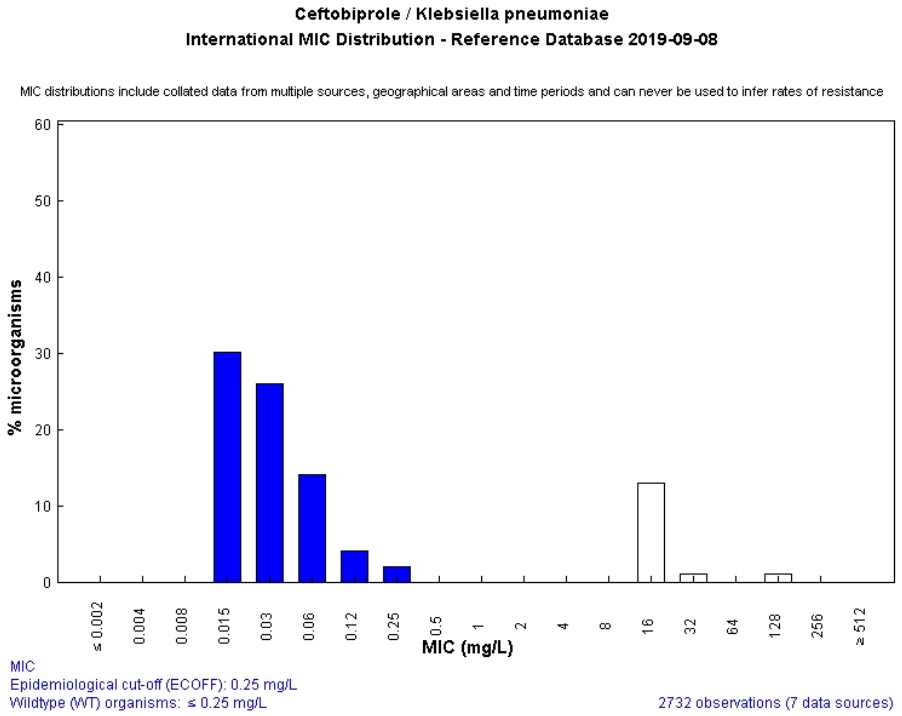
		Sum of squares (% of total error)					
	Observations (n)	total variation	strain variation	laboratory variation	Explained	R^2	Unexplained assay variation
Total	440	227.82 (100%)	109.22 (47.9%)	23.57 (10.3%)	132.79 (58.3%)	0.58	95.03 (41.7%)

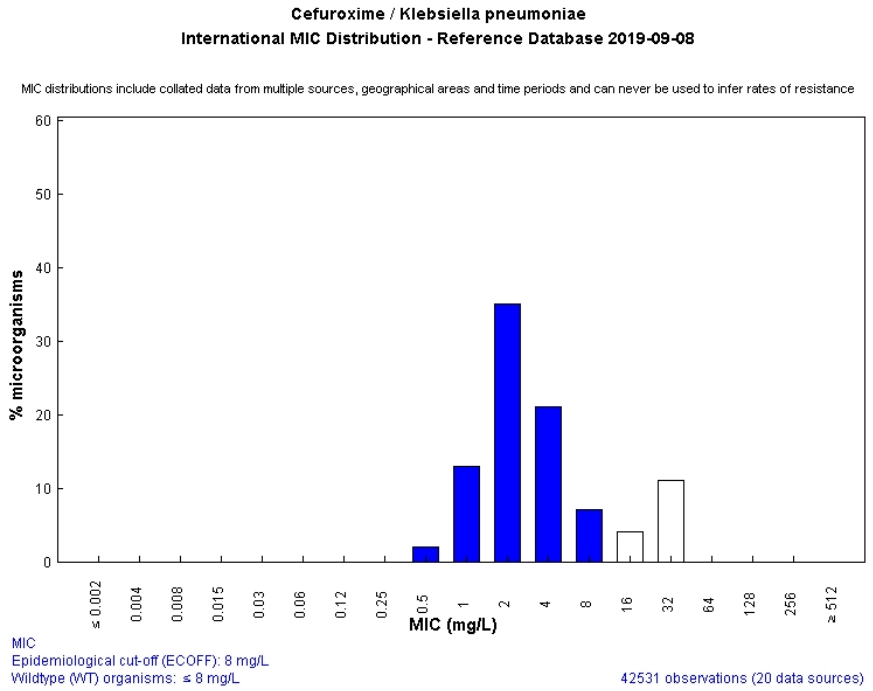
So, “the” MIC does not exists in the routine lab

Mouton, 2018, p2374

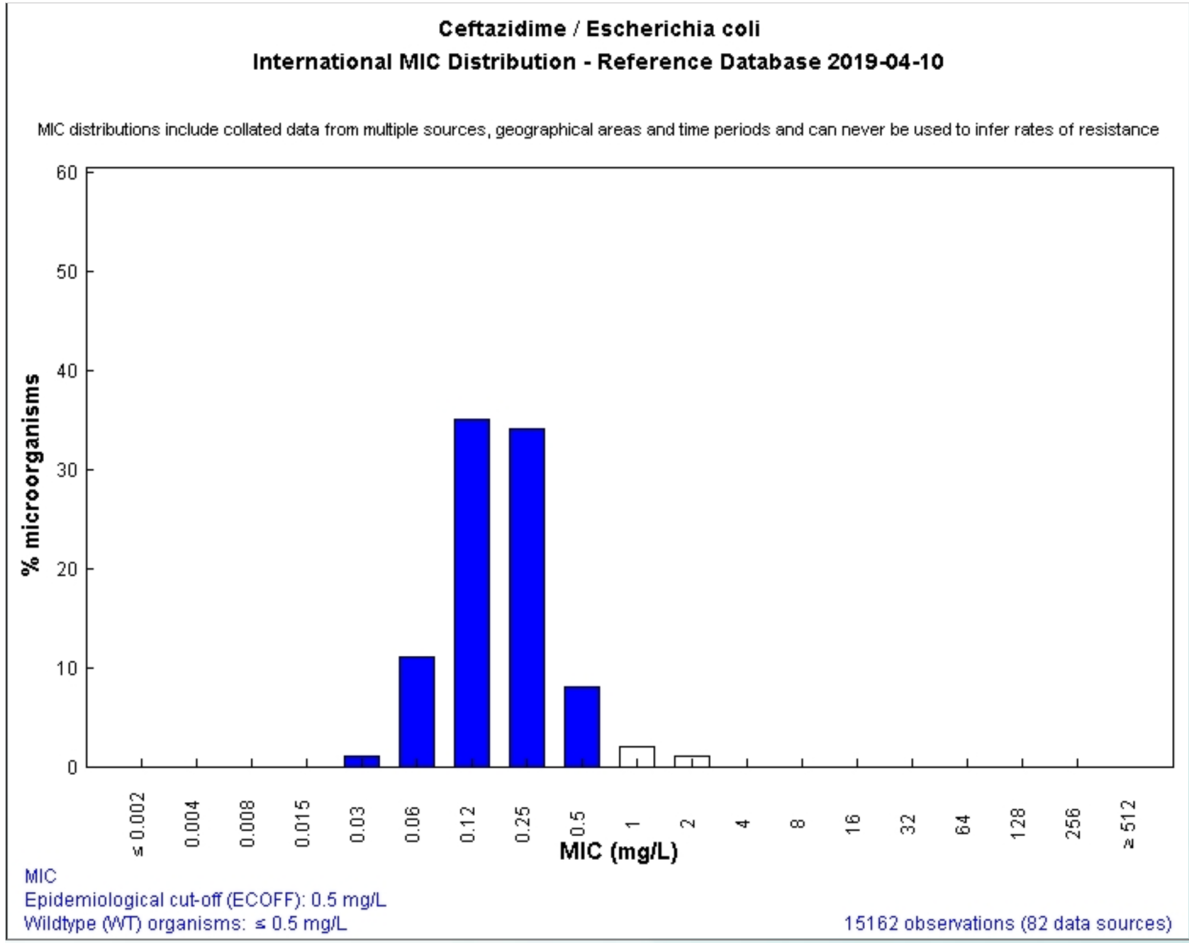
Wild-type distribution

- Distribution of MICs for micro-organisms without resistance mechanisms
- www.eucast.org





Epidemiological cut-off (ECOFF)



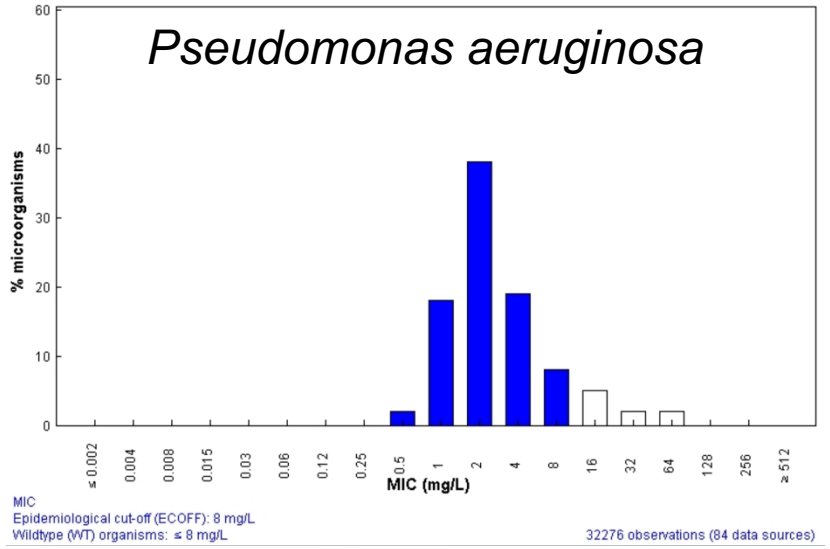
ECOFF: 0.5 mg/L

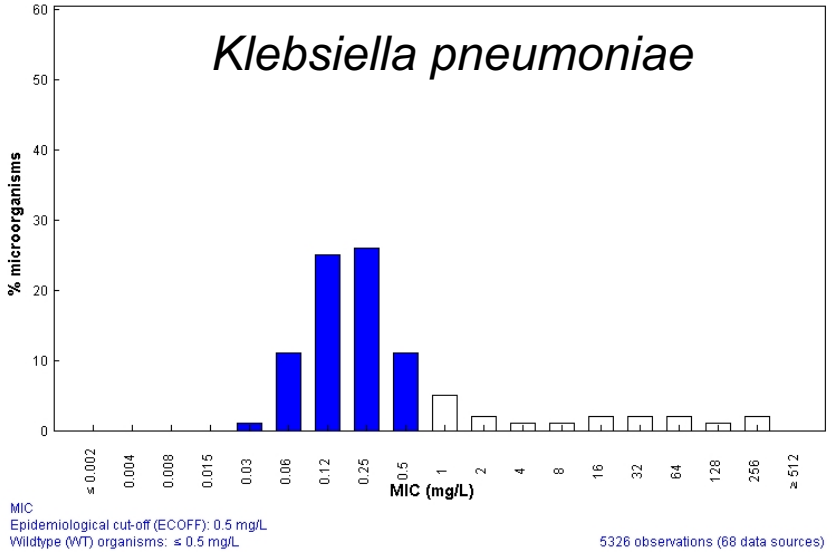
Ceftazidime and *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*

- MIC

	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
Klebsiella pneumoniae	0	0	10	9	89	592	1346	1425	611	281	145	88	104	113	146	136	92	112	27	0.5
Klebsiella spp	0	0	0	15	125	343	351	158	71	43	13	3	3	0	2	0	1	0	0	0.5
Moraxella catarrhalis	0	0	0	6	27	28	10	7	1	1	0	0	0	0	0	0	0	0	0	ND
Morganella morganii	0	2	5	18	67	64	48	38	34	15	12	10	7	19	4	3	0	1	0	0.25
Neisseria gonorrhoeae	0	2	3	12	16	5	0	0	0	0	0	0	0	0	0	0	0	0	0	ND
Proteus mirabilis	0	0	6	86	517	461	92	50	37	30	10	9	2	4	2	2	0	3	0	0.125
Proteus vulgaris	0	0	0	10	52	82	12	2	6	1	1	1	1	1	0	0	0	0	0	0.125
Providencia spp	0	0	0	0	1	9	28	43	6	2	0	4	0	0	0	0	0	0	0	0.5
Providencia stuartii	0	0	0	0	1	1	1	6	4	2	8	6	2	3	1	1	0	1	0	0.5
Pseudomonas aeruginosa	0	0	0	1	4	8	31	292	966	5975	12322	6271	2738	1712	815	751	167	117	106	8.0

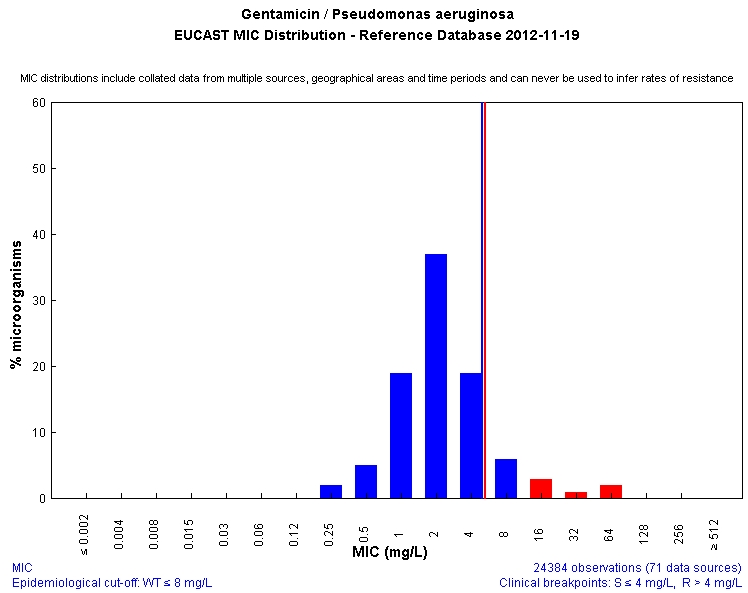
MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance





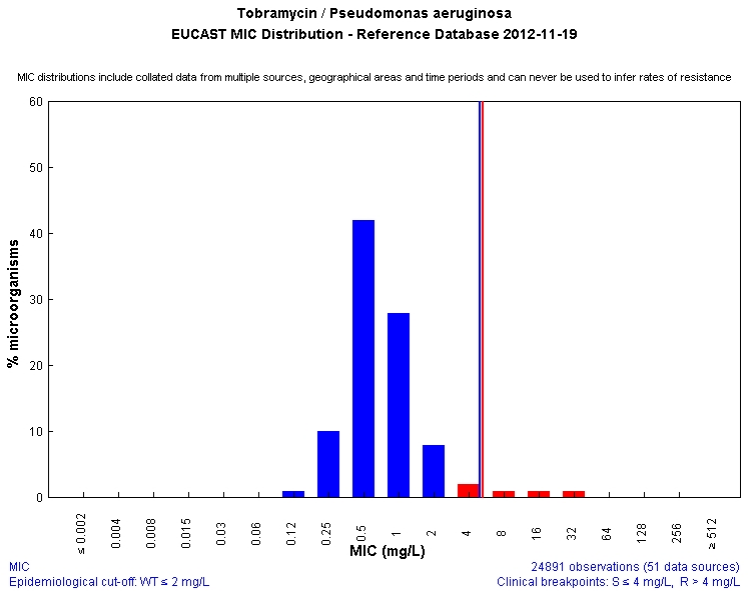
Wild-type distributions

Gentamicin



ECOFF 8 mg/L

Tobramycin



ECOFF 2 mg/L

Pharmacokinetic profile is very similar
PK/PD targets similar

Dosing based on an individual MIC?

NO!

Literature….. example

Int J Antimicrob Agents. 2019 Mar 6. pii: S0924-8579(19)30054-8. doi: 10.1016/j.ijantimicag.2019.03.002. [Epub ahead of print]

Be careful about MICs to amoxicillin for patients with Streptococci-related infective endocarditis.

Pilmis B[1], Lourtet-Hascoët J[2], Barraud O[3], Piau C[4], Isnard C[5], Hery-Arnaud G[6], Amara M[7], Merens A[8], Farfour E[9], Thomas E[10], Jacquier H[11], Zahar JR[12], Bonnet E[13], Le Monnier A[2], Cattoir V[4], Corvec S[10], Boutoille D[14], Péan de Ponfilly G[11], Reissier S[5]; GMC Study Group.

In multivariate analysis, the only factor associated with in-hospital mortality was MIC for amoxicillin between 0.25 and 2mg/L (p=0.04; OR= 2.23 [1.03-4.88]) whereas protective factor was performance of cardiac surgery for IE (p=0.001, OR = 0.23 [0.1-0.56]).

- Population level, not individual level

Conclusion MIC determination and dosing

- Considerable amount of variation
- The only conclusion that can be drawn is, whether the bacteria is within the wild-type distribution or not.
- Do not use such values in individual patient care

Table 1. Suggested interpretation of the MIC for target attainment under various conditions

MIC found	Interpretation for target attainment
Within WT, ≤ECOFF	ECOFF
>ECOFF	MIC + two 2-fold dilutions[a]

[a]Number of dilutions could be higher or lower than two depending on the proficiency of the lab and the drug–species distribution.

Mouton, 2018, p564

Example TDM for sepsis with *Klebsiella pneumoniae*

- Local lab results reports S for ceftazidime
  - Hopefully the lab does not report a value, such as 0.125mg/L
  - You know that the MIC is maximum 0.5 mg/L

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Pseudomonas aeruginosa	0	0	0	1	4	8	31	292	966	5975	12322	6271	2738	1712	815	751	167	117	106	8.0

  - Target value for TDM will be MIC of 0.5 mg/L