



Vildtypsdistributioner, ECOFFs och brytpunkter

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NordicASTs workshop 2015

Vildtypsdistributioner och ECOFFs



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The European Committee on Antimicrobial Susceptibility Testing – EUCAST

The European Committee on Antimicrobial Susceptibility Testing - EUCAST

EUCAST is a standing committee jointly organized by ESCMID, ECDC and European national breakpoint committees. EUCAST was formed in 1997. It has been chaired by Ian Phillips (1997 - 2001), Gunnar Kahlmeter (2001 - 2012) and Rafael Canton (2012 -). Its scientific secretary is Derek Brown (1997 -). Its webmaster is Gunnar Kahlmeter (2001 -).

EUCAST deals with breakpoints and technical aspects of phenotypic in vitro antimicrobial susceptibility testing and functions as the breakpoint committee of EMA and ECDC. EUCAST does not deal with antibiotic policies, surveillance or containment of resistance or infection control. The Steering Committee is the decision making body. It is supported by a General Committee with representatives from European and other countries, FESCI and ISC. The Steering Committee also consults on EUCAST proposals with experts within the fields of infectious diseases and microbiology, pharmaceutical companies and susceptibility testing device manufacturers.

EUCAST has several subcommittees - → see page [Subcommittees](#).

Most antimicrobial MIC breakpoints in Europe have been harmonised by EUCAST. Breakpoints for new agents are set as part of the licensing process for new agents through EMA. EUCAST breakpoints are available in devices for automated susceptibility testing but with some limitations, depending on the system. A disk diffusion susceptibility test method → calibrated to EUCAST MIC breakpoints is also available.

EUCAST invites anyone with an interest in antimicrobial agents in general and antimicrobial breakpoints in particular to contact EUCAST, ESCMID or one of the National Breakpoint Committees.

Copyright

search term
QUICK NAVIGATION

EUCAST News



23 Apr 2015
EUCAST Posters at ECCMID 2015

19 Apr 2015
EUCAST breakpoints for dalbavancin, oritavancin and tedizolid released.

05 Apr 2015
Information for industry - clarification on conflicts of interest added

23 Mar 2015
Frequently Asked Questions - updated version 2015-03-23

12 Mar 2015
Sad news! Dr William A. Craig died on the 11th of March.

→ [About Newsfeeds](#)

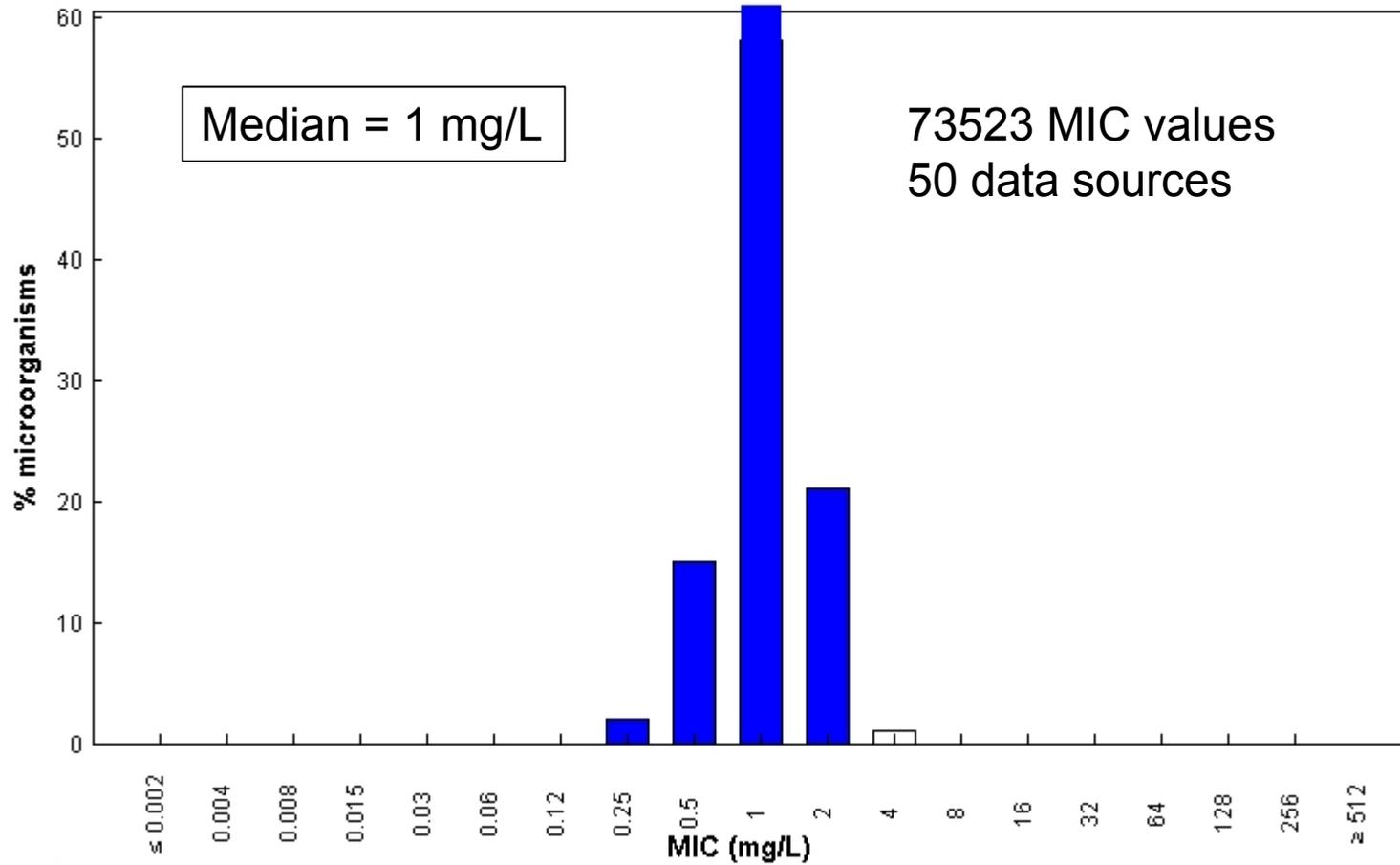


MIC distributions on EUCAST website

- 28 000 MIC distributions
- Up to 100 000 MIC values per distribution
- Data from many investigators (1 - 100 per distrib.)
- Data from many time periods (1950 -)
- Data from many geographical areas and projects
(USA, Europe, Australia, Far East, South America, Sentry, Mystic, etc)
- Data of multiple origin
(Human clinical data, Surveillance programs, Veterinarian data, Wild life, Food safety programs)

Ciprofloxacin / Streptococcus pneumoniae
International MIC Distribution - Reference Database 2015-05-07

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



MIC

Epidemiological cut-off (ECOFF): 2 mg/L

Wildtype (WT) organisms: ≤ 2 mg/L

73523 observations (50 data sources)

S. pneumoniae vs. ciprofloxacin

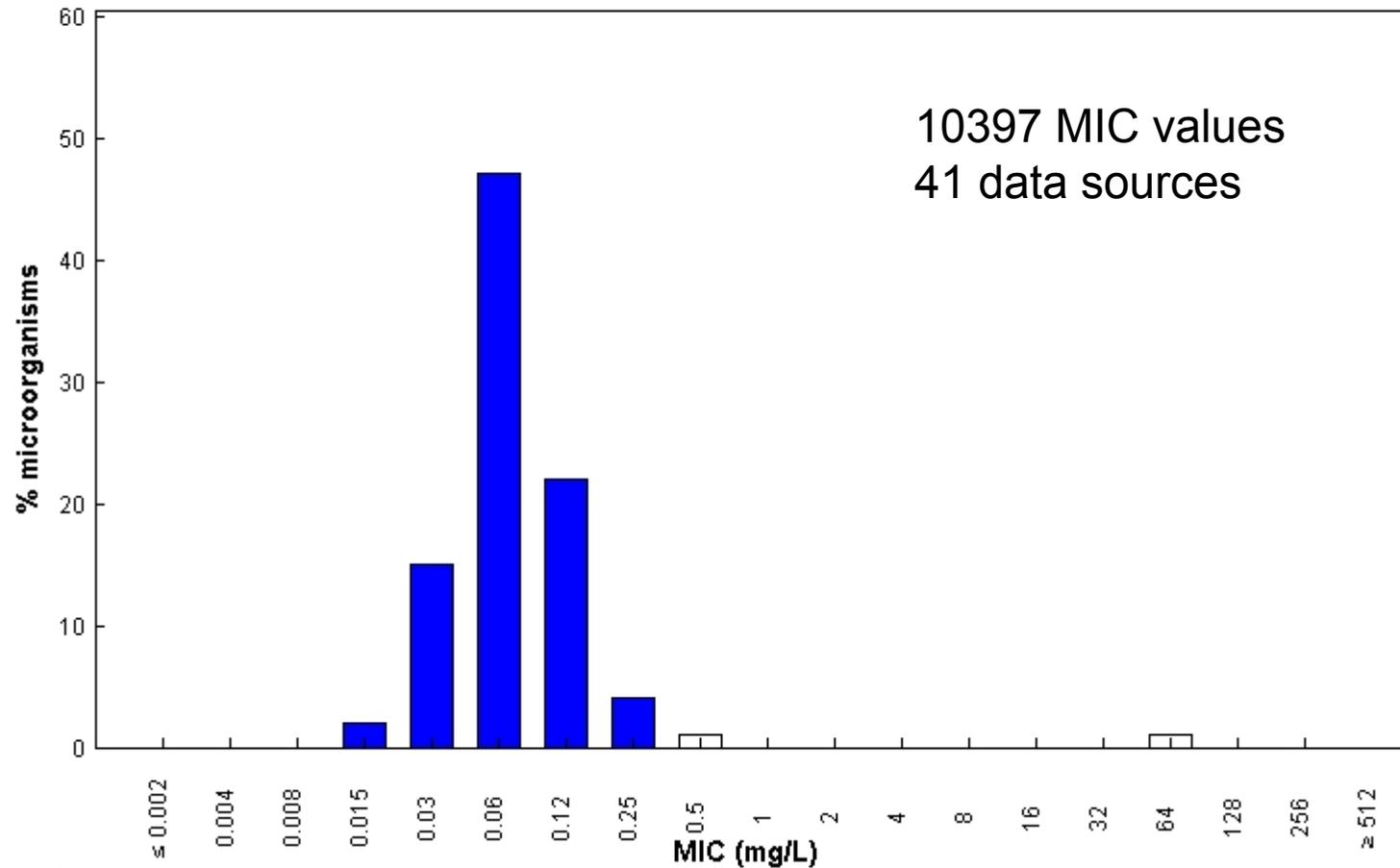
	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512
--	-------	-------	-------	-------	-------	-------	-------	------	-----	---	---	---	---	----	----	----	-----	-----	-----

S. pneumoniae vs. ciprofloxacin

	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
Ciprofloxacin	0	0	0	0	0	0	1	4	28	52	16	0	0	0	0	0	0	0	0
Ciprofloxacin	0	0	0	0	0	0	0	0	55	1191	671	101	21	2	0	2	3	0	0
Ciprofloxacin	0	0	0	0	0	0	0	4	45	363	454	119	11	0	0	0	0	0	
Ciprofloxacin	0	0	0	0	0	0	0	2	2	15	32	2	0	1	0	0	0	0	
Ciprofloxacin	0	0	0	0	0	0	3	80	256	61	11	1	1	0	0	0	0	0	
Ciprofloxacin	0	0	0	0	0	0	1	5	64	155	17	4	0	0	0	0	0	0	
Ciprofloxacin	0	0	0	0	0	0	1	4	35	130	51	3	0	0	0	0	0	0	
Ciprofloxacin	0	0	0	0	0	0	1	197	251	41	10	1	0	1	0	0	0	0	
Ciprofloxacin	0	0	0	0	0	0	1	16	125	102	28	3	0	0	0	0	0	0	
Ciprofloxacin	0	0	0	0	0	0	1	8	96	209	59	1	2	0	0	1	0	0	
Ciprofloxacin	0	0	0	0	0	0	3	20	92	69	10	3	1	0	0	0	0	0	
Ciprofloxacin	0	0	0	0	0	0	2	5	161	544	64	10	0	2	1	0	0	0	
Ciprofloxacin	0	0	0	0	6	4	4	13	245	854	379	9	6	1	1	1	0	0	
Ciprofloxacin	0	0	0	0	3	0	2	22	225	917	401	16	3	2	4	1	0	0	
Ciprofloxacin	0	0	0	0	0	1	3	9	426	933	138	11	5	2	1	0	2	0	
Ciprofloxacin	0	0	0	0	2	0	3	13	402	1193	222	19	10	0	6	0	0	0	
Ciprofloxacin	0	0	0	0	0	0	0	2	75	366	182	30	4	0	0	2	0	0	
Ciprofloxacin	0	0	0	0	0	0	0	2	36	409	186	29	2	1	1	1	0	0	
Ciprofloxacin	0	0	0	0	0	0	0	2	207	1052	225	22	2	10	0	1	0	0	
Ciprofloxacin	0	0	0	0	6	7	25	130	2195	10500	4618	144	67	0	0	0	0	0	
Ciprofloxacin	0	0	0	0	0	0	8	10	47	176	95	21	1	2	0	0	0	0	
Ciprofloxacin	0	0	0	0	0	0	0	2	302	1777	786	102	1	6	0	0	0	0	
Ciprofloxacin	0	0	0	0	0	0	2	103	335	58	11	0	1	0	0	0	0	0	
Ciprofloxacin	0	0	0	0	0	0	1	7	100	265	26	5	0	1	0	0	0	0	
Ciprofloxacin	0	0	0	0	0	1	1	4	35	130	51	3	0	0	0	0	0	0	
Ciprofloxacin	0	0	0	0	0	0	8	37	60	16	1	0	0	0	0	0	0	0	
Ciprofloxacin	0	0	0	0	0	3	20	228	280	49	11	1	1	0	0	0	0	0	
Ciprofloxacin	0	0	0	0	0	0	0	15	122	99	28	3	1	0	0	0	0	0	
Ciprofloxacin	0	0	0	0	0	0	1	10	120	331	78	2	2	0	0	0	0	0	
Ciprofloxacin	0	0	0	0	0	2	3	27	155	111	18	4	1	0	0	0	0	0	
Ciprofloxacin	0	0	0	0	0	0	0	0	50	544	149	23	2	0	1	2	1	0	
Ciprofloxacin	0	0	0	0	0	4	4	10	181	256	74	6	2	0	1	0	0	0	
Ciprofloxacin	0	0	8	13	9	8	4	34	77	210	76	9	18	1	0	0	0	3	
Ciprofloxacin	0	0	0	0	0	1	0	14	120	272	96	8	0	2	0	0	0	0	
Ciprofloxacin	0	0	0	0	0	0	0	66	85	31	2	1	4	0	0	0	0	228	
Ciprofloxacin	0	0	0	0	0	0	0	0	1	65	150	18	4	0	1	0	0	0	
Ciprofloxacin	0	0	0	0	0	0	1	2	41	99	55	11	1	0	0	0	0	0	
Ciprofloxacin	0	0	0	0	0	0	0	422	2706	13072	3987	320	68	31	82	62	0	0	

Cefotaxime / Escherichia coli
International MIC Distribution - Reference Database 2015-05-05

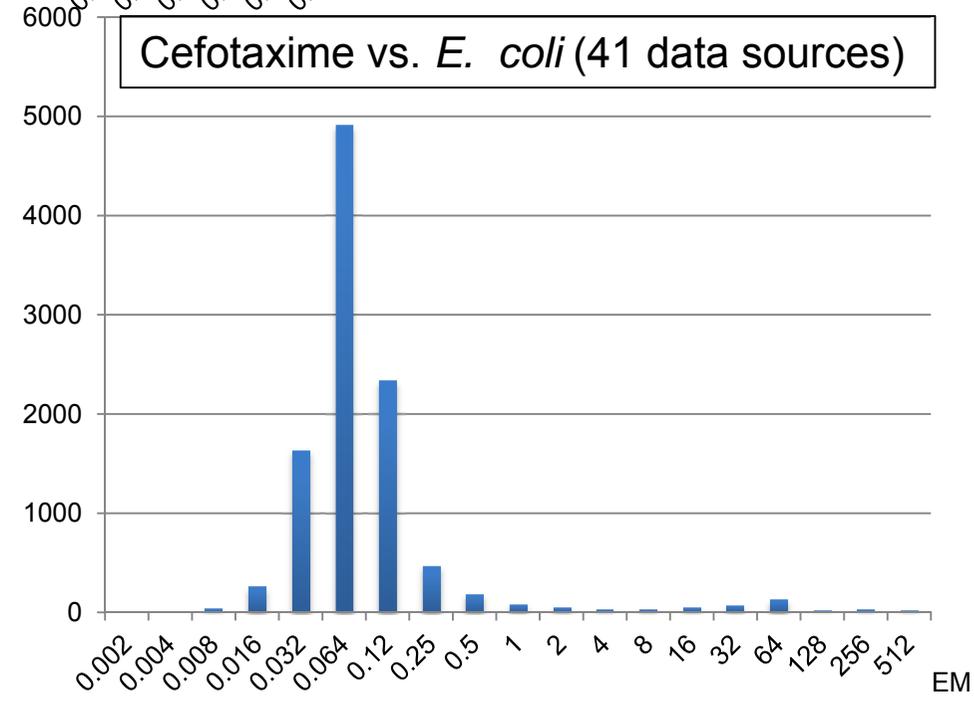
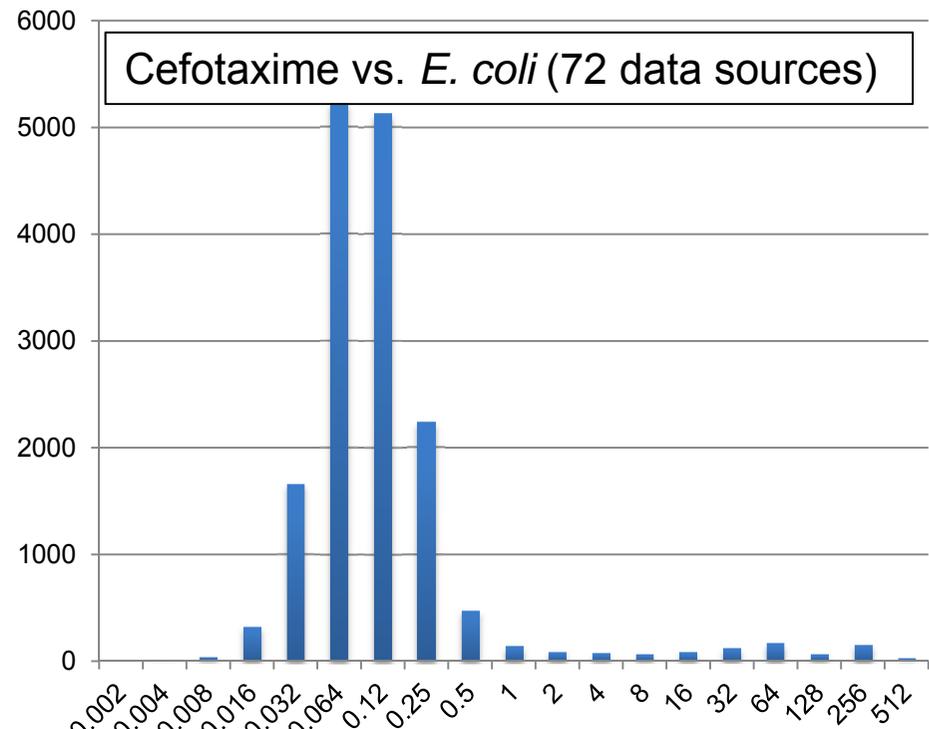
MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



MIC
Epidemiological cut-off (ECOFF): 0.25 mg/L
Wildtype (WT) organisms: ≤ 0.25 mg/L

10397 observations (41 data sources)

	0,002	0,004	0,008	0,016	0,032	0,064	0,12	0,25	0,5	1	2	4	8	126	32	64	128	256
0	0	0	0	0	0	0	0	1671	205	20	6	2	0	0	1	17	0	0
0	0	0	0	0	0	4	16	10	4	0	6	1	2	3	0	0	0	0
0	0	3	1	28	51	9	3	3	0	1	1	0	0	0	0	0	0	0
0	4	7	47	310	510	99	12	5	4	1	0	0	1	0	0	0	0	0
0	0	1	20	97	185	116	31	33	6	5	3	7	1	42	23	7	0	0
0	0	0	0	28	108	88	13	3	3	0	1	0	0	0	0	0	0	1
0	1	8	60	105	58	19	5	8	5	0	0	0	0	0	0	0	0	0
0	0	0	0	0	135	37	12	5	5	3	8	3	11	8	14	32	116	0
0	0	0	0	0	28	41	7	1	1	0	0	0	0	0	0	0	0	0
0	0	0	0	8	149	113	25	2	0	1	3	1	1	0	0	0	0	0
0	0	0	0	24	181	102	9	0	0	0	2	0	0	0	0	0	0	0
0	0	0	0	0	0	301	12	0	1	1	0	1	2	0	0	0	0	0
0	0	0	0	0	0	150	2	1	1	2	2	2	4	0	0	0	0	0
0	0	0	0	0	0	159	1	0	1	2	0	1	1	0	0	0	0	0
0	0	0	0	0	0	263	8	0	0	6	3	4	3	13	0	0	0	0
0	0	0	0	15	188	90	7	2	0	0	0	0	0	0	0	0	0	0
0	0	0	1	29	206	73	7	1	0	0	0	0	0	1	0	0	0	0
0	0	0	0	0	0	313	4	0	0	0	1	0	0	0	0	0	0	0
0	0	0	0	0	0	294	5	2	2	2	2	2	4	0	0	0	0	0
0	0	0	0	0	0	311	3	0	1	3	0	1	1	0	0	0	0	0
0	0	0	0	0	0	292	2	1	0	1	0	0	0	0	0	0	0	0
0	0	0	0	49	82	85	12	4	2	0	2	1	5	0	0	0	1	0
0	0	0	0	0	0	593	23	4	8	5	6	2	2	1	0	0	0	0
0	0	1	4	39	135	38	4	4	1	2	0	3	6	3	1	0	0	3
0	0	0	17	97	558	251	42	11	6	0	1	0	0	0	0	0	0	2
0	0	0	19	86	408	390	49	12	3	0	2	1	0	1	0	0	0	2
0	0	3	42	200	514	49	14	1	4	0	0	1	0	1	0	0	0	0
0	0	2	11	11	57	25	17	4	6	1	4	1	2	1	1	0	0	0
0	0	1	1	14	41	36	9	2	2	5	1	0	1	0	3	0	0	1
0	0	1	3	27	48	22	4	4	2	1	1	0	0	1	0	0	0	0
0	0	0	0	1	2	5	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	3	7	2	0	2	0	1	0	1	1	0	0	0	1	0
0	0	0	2	10	13	1	0	3	1	2	0	0	0	0	0	0	0	1
0	0	1	0	1	25	81	8	5	2	0	2	1	0	1	1	0	0	5
0	0	0	2	19	19	60	20	5	4	3	1	1	3	1	0	0	1	7
0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	1	0	5	2	0	0	1	0	0	0	0	0	0	0	0	1
0	0	4	3	18	20	4	5	6	1	0	1	0	1	0	0	0	0	0
0	0	0	2	9	10	8	2	3	4	1	0	1	0	0	0	1	0	0
0	0	1	0	18	24	10	3	6	1	0	0	0	0	0	0	1	0	0
0	0	0	1	2	17	5	1	0	1	0	0	1	0	0	0	0	0	0
0	0	0	0	8	19	9	4	2	1	1	0	0	0	0	0	0	0	0
0	0	0	0	13	13	10	6	1	1	1	0	0	0	0	0	1	0	0
0	0	0	1	7	18	17	2	1	0	0	0	0	0	0	0	0	0	1
0	0	1	0	7	16	9	8	1	0	0	1	0	1	0	1	0	0	1
0	0	0	0	12	11	2	7	0	1	1	1	0	0	0	0	0	0	0
0	0	0	0	4	20	9	6	1	0	1	0	0	0	0	0	0	0	1
0	0	0	0	0	3	9	2	1	0	0	0	0	0	0	0	1	2	0
0	0	0	0	4	5	1	1	0	1	0	11	0	0	0	0	0	0	0
0	0	0	0	0	1	0	0	0	0	17	0	5	0	0	0	0	0	0
0	0	0	2	28	8	4	6	0	0	1	0	0	0	0	0	0	0	0
0	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0
0	0	0	1	0	2	0	1	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	4	16	3	0	0	0	0	0	0	0	1	0	0	0	0
0	0	0	0	7	20	4	2	0	0	0	1	0	0	0	0	0	0	0
0	0	0	17	0	48	29	6	2	0	0	0	0	1	2	0	0	0	0
0	0	0	17	0	61	22	3	0	0	0	0	0	0	0	0	0	0	1
0	0	1	0	4	52	24	9	1	0	1	0	0	0	0	1	0	0	1
0	0	2	0	12	43	16	4	1	1	1	0	1	0	0	0	0	1	2
0	0	0	2	4	2	0	2	2	1	0	0	0	0	1	0	0	0	0
0	0	0	1	4	12	0	8	0	0	0	0	0	1	1	0	0	0	0
0	0	0	0	2	4	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	5	0	13	5	1	0	0	0	0	1	0	0	0	0	0	1
0	0	0	7	0	14	7	0	3	0	1	0	1	3	0	2	0	0	2
0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
0	0	0	0	2	0	1	0	1	0	0	0	0	0	0	0	0	0	0
0	0	3	5	62	113	25	8	3	1	0	3	3	5	1	0	1	0	3
0	0	0	3	18	105	71	12	4	0	1	0	1	7	4	0	8	3	3
0	0	0	26	205	816	302	76	39	17	14	5	11	10	12	97	0	0	0



EM

Why are some MIC distributions not accepted?

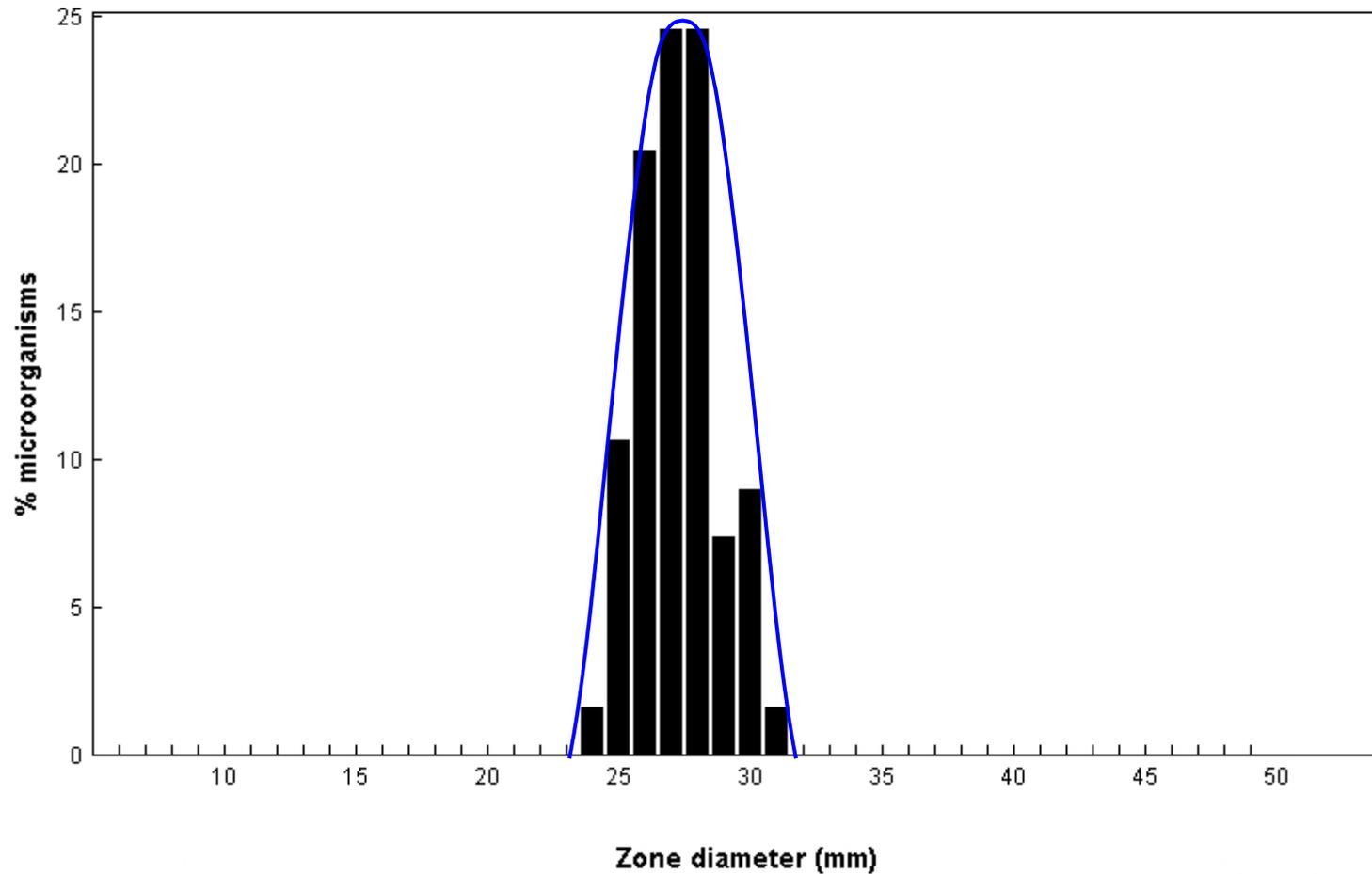
- Methodology not standardised
- Too few data points (MIC values)
- MIC testing not full scale (truncated distributions)
- MIC distribution obviously skewed

Zone diameter distributions on EUCAST website

- Data mostly from EUCAST Development Laboratory, but data from other sources are added subsequently
- Each distribution contains data using:
 - Media from at least three manufactures
 - Disks from 1 - 5 manufacturers
- Data always controlled against EUCAST QC ranges

Cefoxitin / Staphylococcus aureus ATCC 29213
EUCAST zone diameter distribution - Reference database
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

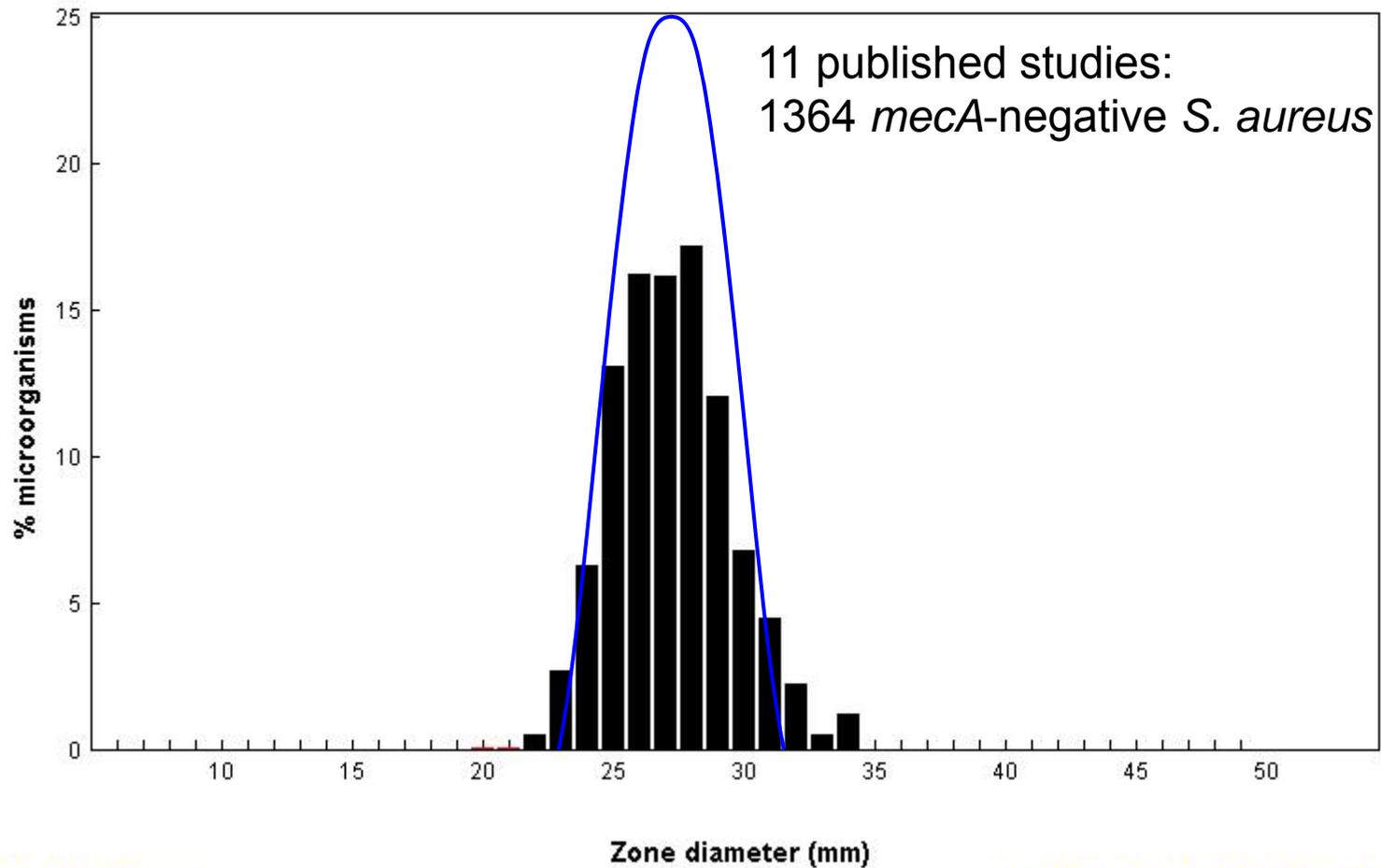


Disk content: 30
Epidemiological cut-off: WT \geq 22 mm (MIC: -)

122 observations
Clinical breakpoints: S \geq 22 mm, R $<$ 22 mm

Cefoxitin / Staphylococcus aureus MSSA
EUCAST zone diameter distributions - Reference database
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

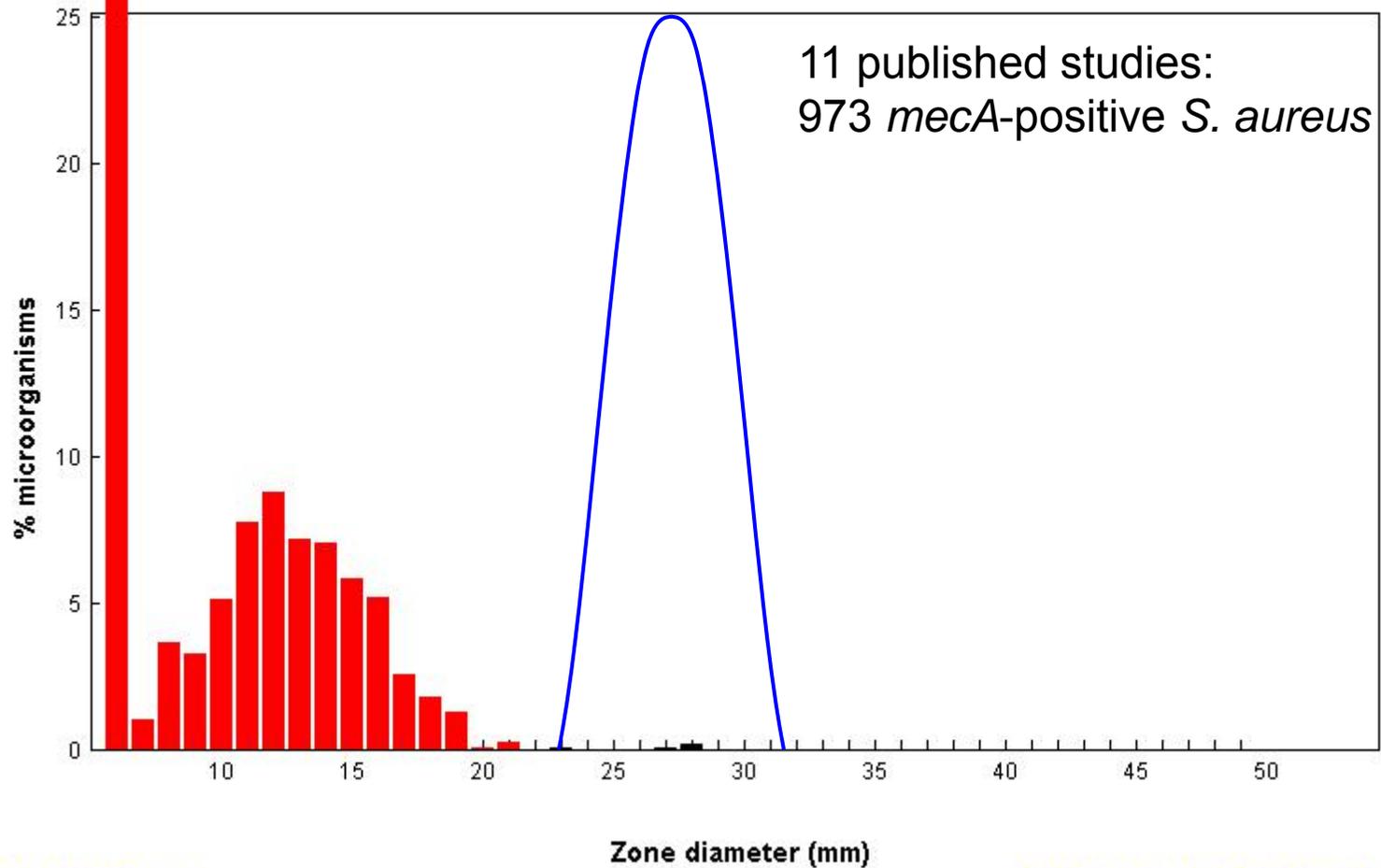


Disk content: 30
Epidemiological cut-off: WT \geq 22 mm (MIC: \leq 4 mg/L)

1364 observations (11 data sources)
Clinical breakpoints: S \geq 22 mm, R $<$ 22 mm

Cefoxitin / Staphylococcus aureus MRSA
EUCAST zone diameter distributions - Reference database
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

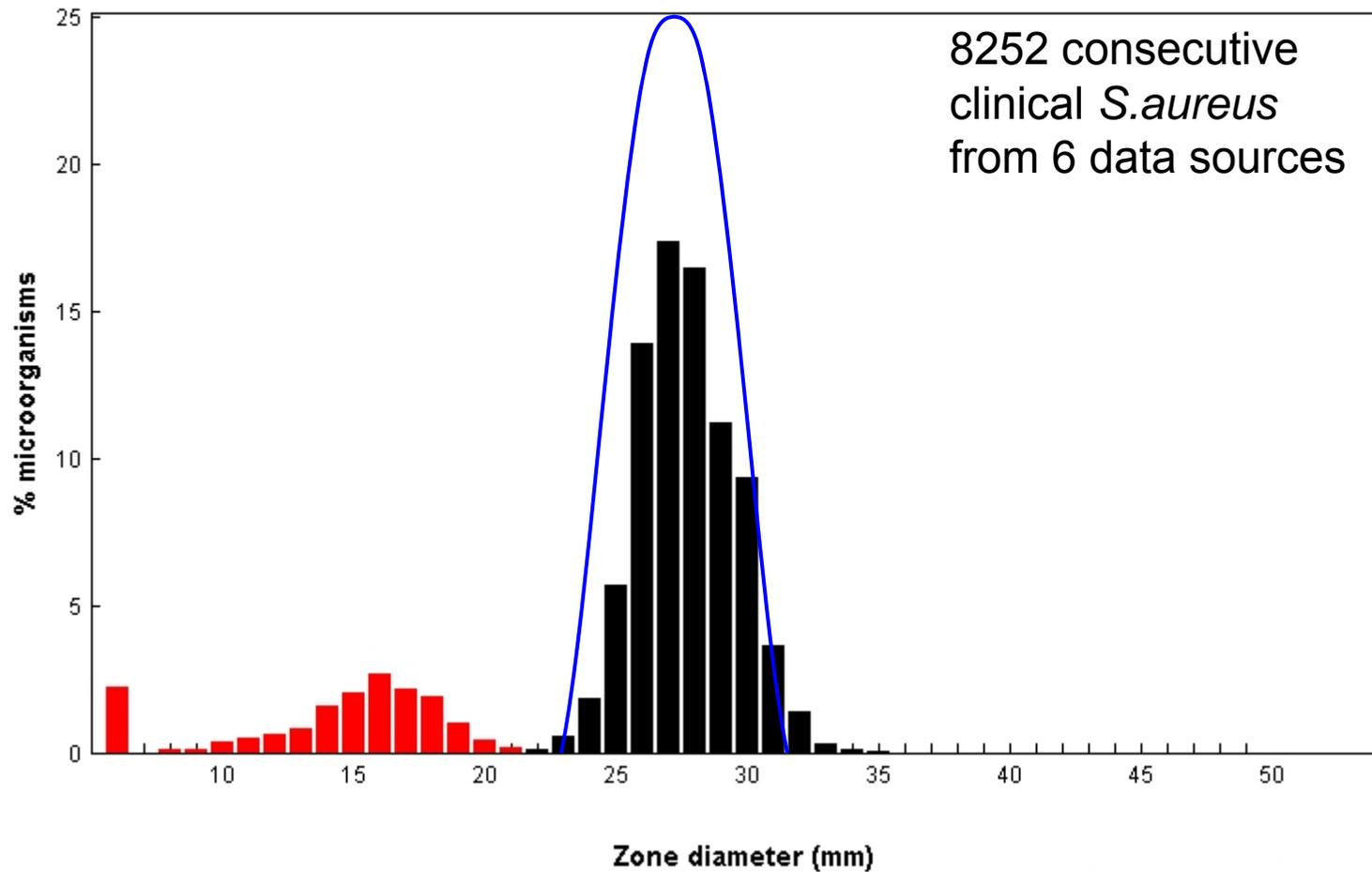


Disk content: 30
Epidemiological cut-off: WT \geq 22 mm (MIC: \leq 4 mg/L)

973 observations (11 data sources)
Clinical breakpoints: S \geq 22 mm, R $<$ 22 mm

Cefoxitin / Staphylococcus aureus
EUCAST zone diameter distribution - Reference database 2011-01-25
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: WT \geq 22 mm (MIC: \leq 4 mg/L)

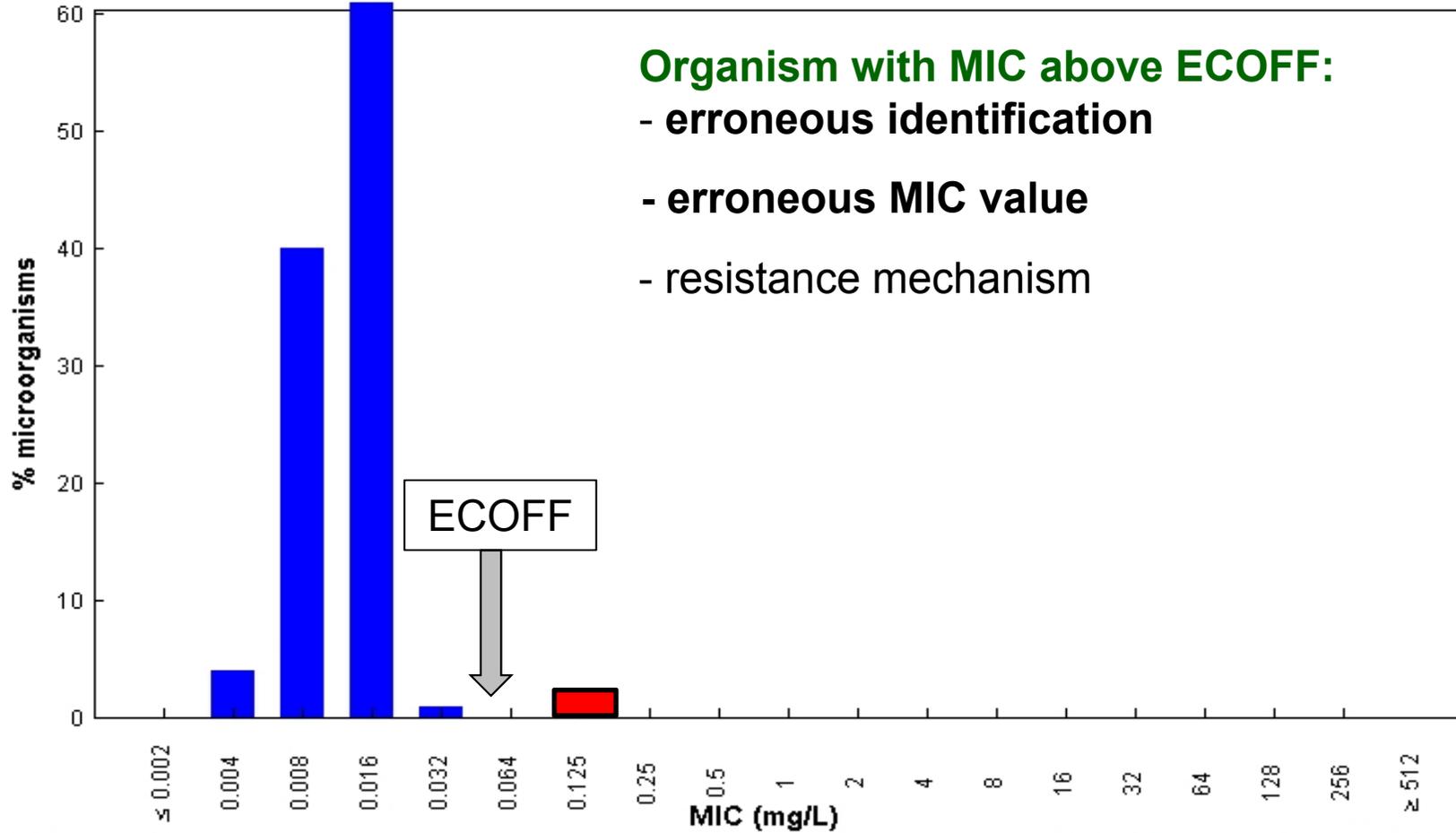
8252 observations (6 data sources)
Clinical breakpoints: S \geq 22 mm, R $<$ 22 mm

Epidemiological cut-off values ECOFFs

- Syn. Microbiological breakpoints
- For a species and a drug in a defined test system the ECOFF distinguishes between organisms **without** and **with** phenotypically expressed resistance mechanisms.
- Within a species, it is the highest MIC of organisms lacking phenotypically expressed resistance.
- Organisms **without** resistance mechanisms are not by default treatable and organisms **with** resistance mechanisms are not by default resistant.
- In a species deemed susceptible (S) to the agent, it is the lowest possible S-breakpoint.

Benzylpenicillin / *Streptococcus pyogenes*
EUCAST MIC Distribution - Reference Database

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



Organism with MIC above ECOFF:

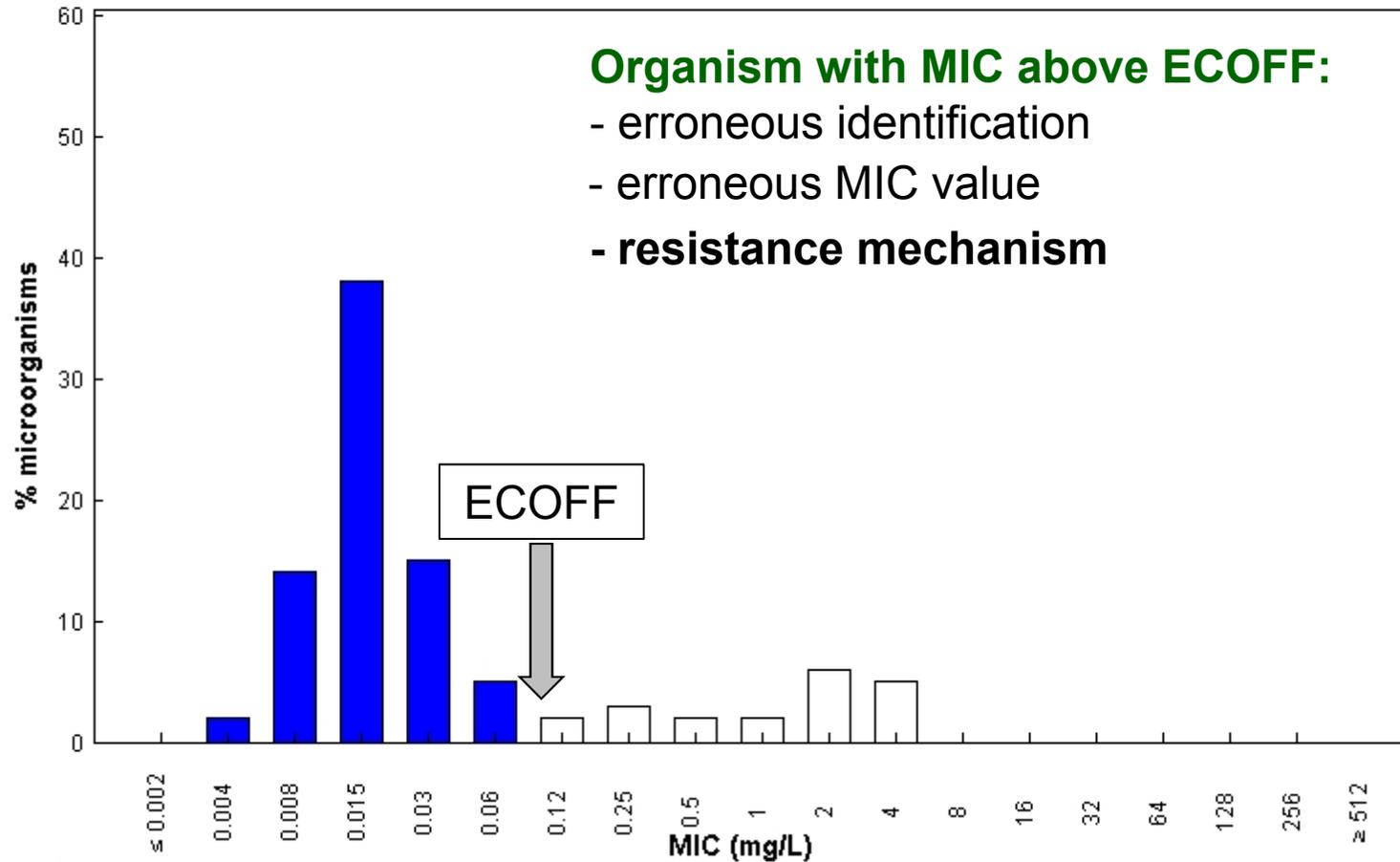
- erroneous identification
- erroneous MIC value
- resistance mechanism

MIC
 Epidemiological cut-off: WT ≤ 0.064 mg/L

3615 observations (11 data sources)
 Clinical breakpoints: S ≤ 0.25 mg/L, R > 0.25 mg/L

Benzylpenicillin / Streptococcus pneumoniae
International MIC Distribution - Reference Database 2015-05-05

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

37742 observations (33 data sources)

Establishing ECOFFs

- ECOFFs should only be determined on
 - MICs determined with methods calibrated to the internationally agreed standard method for broth micro dilution (ISO)
 - large quantities of MICs ($n > 100$, ideally > 1000)
 - MICs from many places (minimum 3 distributions)
 - MICs performed by many investigators (minimum 3, ideally 10 or more)

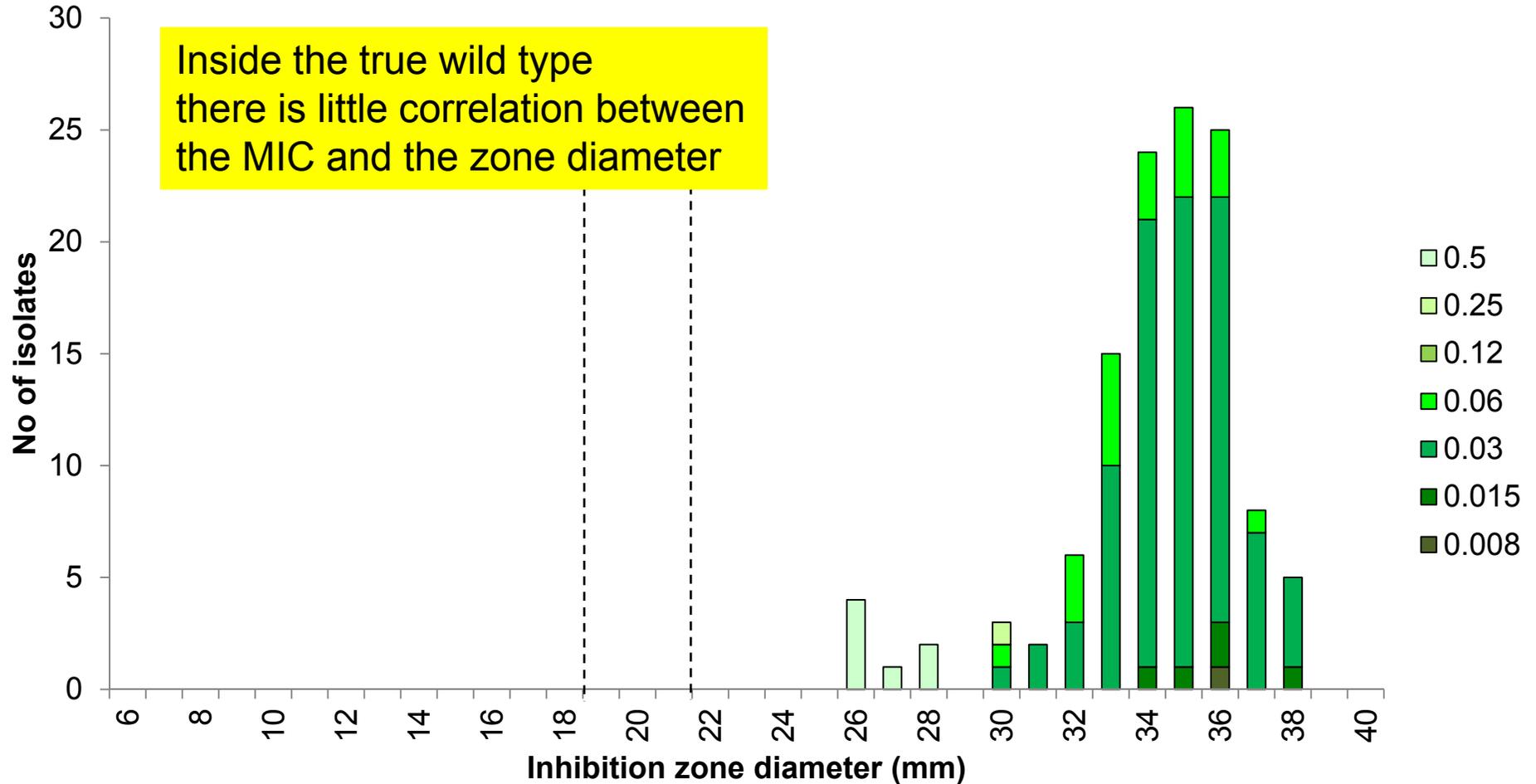
Tentative rules for aggregating MIC distributions and determine ECOFFs

MIC distributions*	Distributions which disagree**	Action (none, aggregate or aggregate and determine ECOFF)
1	0	None***
2	0	None
3	0	Aggregate 3
3	1	None
4	0	Aggregate 4 and determine ECOFF
4	1	Aggregate 3
4	>1	None
5	0	Aggregate 5 and determine ECOFF
5	1	Aggregate 4
5	>1	None
6	0	Aggregate 6 and determine ECOFF
6	1	Aggregated 5 and determine ECOFF
6	>1	Aggregate 4
7	0	Aggregate 7 and determine ECOFF
7	1	Aggregate 6 and determine ECOFF
7	2	Aggregate 5 and determine ECOFF
7	>2	None
etc		

To determine ECOFFs

- MIC distributions
 - "Graphic logical method" - evaluating shape of curve
 - Statistical methods (see Turnover et al; Kronvall et al) – evaluating shape of curve
- Zone diameter distributions
 - "Graphic logical method" – evaluating shape of curve
 - NRI statistical method (see Kronvall et al, Sjölund et al) – evaluating shape of curve
- "MIC-coloured zone diameter distribution" method
 - developed for determining zone diameter breakpoints
 - can be used to determine both MIC and zone diameter ECOFFs
- Molecular microbiological method – determine a tentative ECOFF using either of the above, and provoke it with strains with known resistance genes.

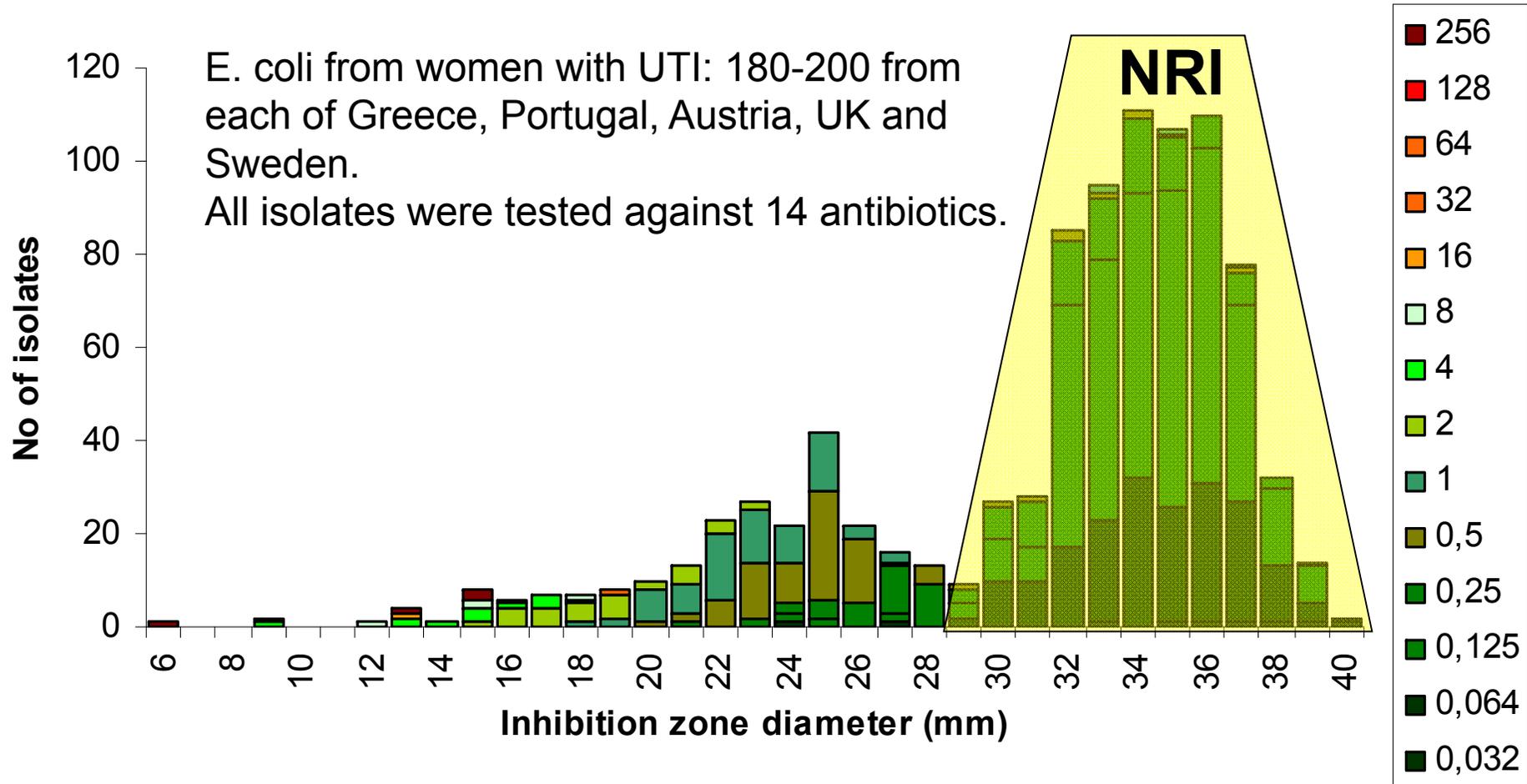
Ciprofloxacin 5 μ g vs. MIC *Yersinia enterocolitica*, 121 clinical isolates



Suggested breakpoints

MIC	$S \leq 0.5$, $R > 1$ mg/L (Enterobacteriaceae)
Zone diameter	$S \geq 22$, $R < 19$ mm (Enterobacteriaceae)

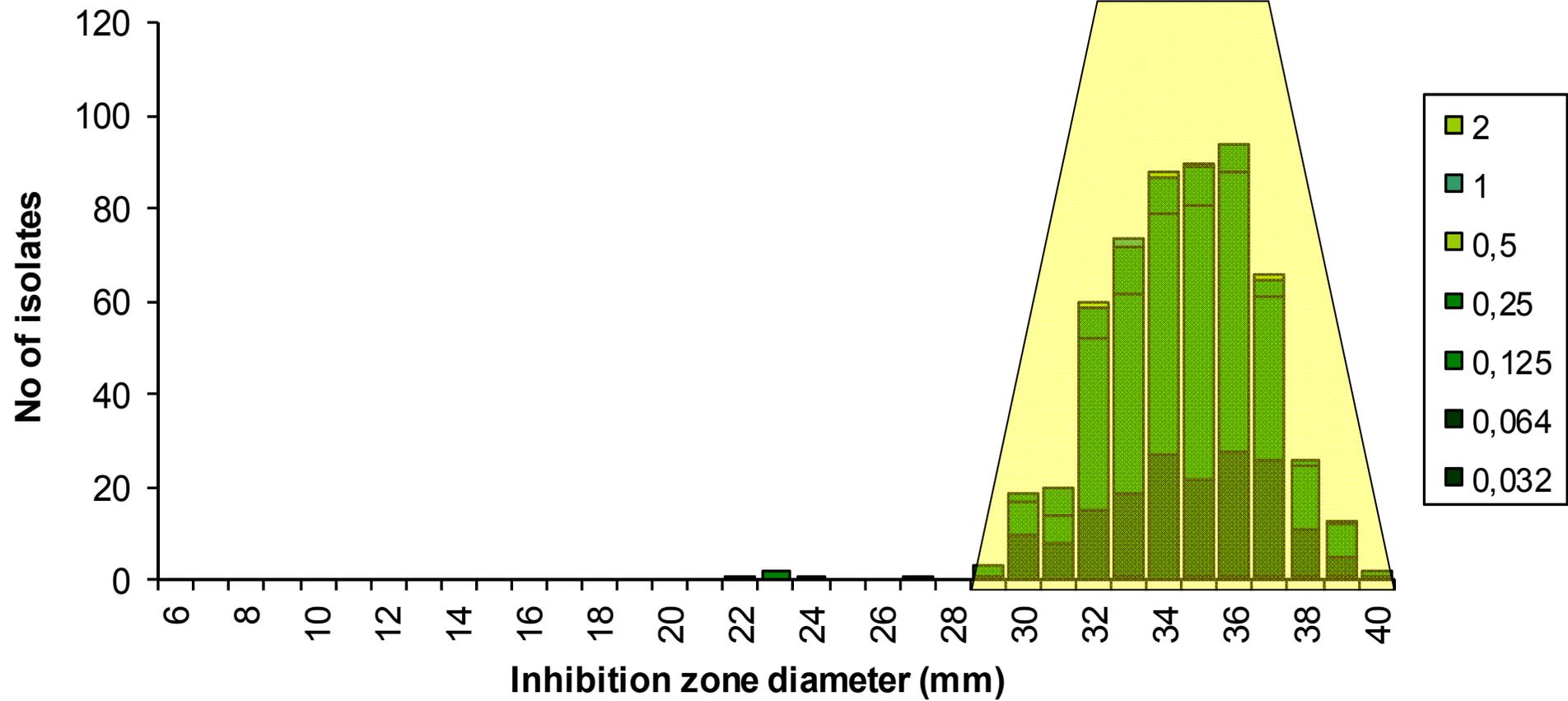
E. coli* vs. *meccillinam
931 isolates from the ECOSENS II Study



Performed on ISA

E. coli* vs. *mecillinam

560 isolates with MICs below ECOFF for all other tested agents



Performed on ISA

Frågor & diskussion

Kliniska brytpunkter

Clinical breakpoints

- MIC concentrations decided by man to distinguish treatable from non-treatable organisms
- The clinical breakpoint may render the wild type Susceptible (S), Intermediate (I) or Resistant (R) but must not divide wild type organisms

Enterobacteriaceae

EUCAST Clinical Breakpoint Table v. 5.0, valid from 2015-01-01

Disk diffusion (EUCAST standardised disk diffusion method)
Medium: Mueller-Hinton agar
Inoculum: McFarland 0.5
Incubation: Air, 35±1°C, 18±2h
Reading: Read zone edges as the point showing no growth viewed from the back of the plate against a dark background illuminated with reflected light.
Quality control: *Escherichia coli* ATCC 25922

Penicillins ¹	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)		Notes Numbers for comments on MIC breakpoints Letters for comments on disk diffusion
	S ≤	R >		S ≥	R <	
Benzylpenicillin	-	-	-	-	-	<p>1/A. Wild type Enterobacteriaceae are categorised as susceptible to aminopenicillins. Some countries prefer to categorise wild type isolates of <i>E. coli</i> and <i>P. mirabilis</i> as intermediate. When this is the case, use the MIC breakpoint S ≤ 0.5 mg/L and the corresponding zone diameter breakpoint S ≥ 50 mm. 2. For susceptibility testing purposes, the concentration of sulbactam is fixed at 4 mg/L. 3. For susceptibility testing purposes, the concentration of clavulanic acid is fixed at 2 mg/L. 4. For susceptibility testing purposes, the concentration of tazobactam is fixed at 4 mg/L. 5/D. Mecillinam (pivmecillinam) breakpoints relate to <i>E. coli</i>, <i>Klebsiella</i> spp. and <i>P. mirabilis</i> only.</p> <p>B. Ignore growth that may appear as a thin inner zone on some batches of Mueller-Hinton agars. C. Susceptibility inferred from ampicillin. E. Ignore isolated colonies within the inhibition zone for <i>E. coli</i>.</p>
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	
Phenoxyethylpenicillin	-	-	-	-	-	
Oxacillin	-	-	-	-	-	
Cloxacillin	-	-	-	-	-	
Dicloxacillin	-	-	-	-	-	
Flucloxacillin	-	-	-	-	-	
Mecillinam (uncomplicated UTI only)	8 ⁵	8 ⁵	10	15 ^{D,E}	15 ^{D,E}	

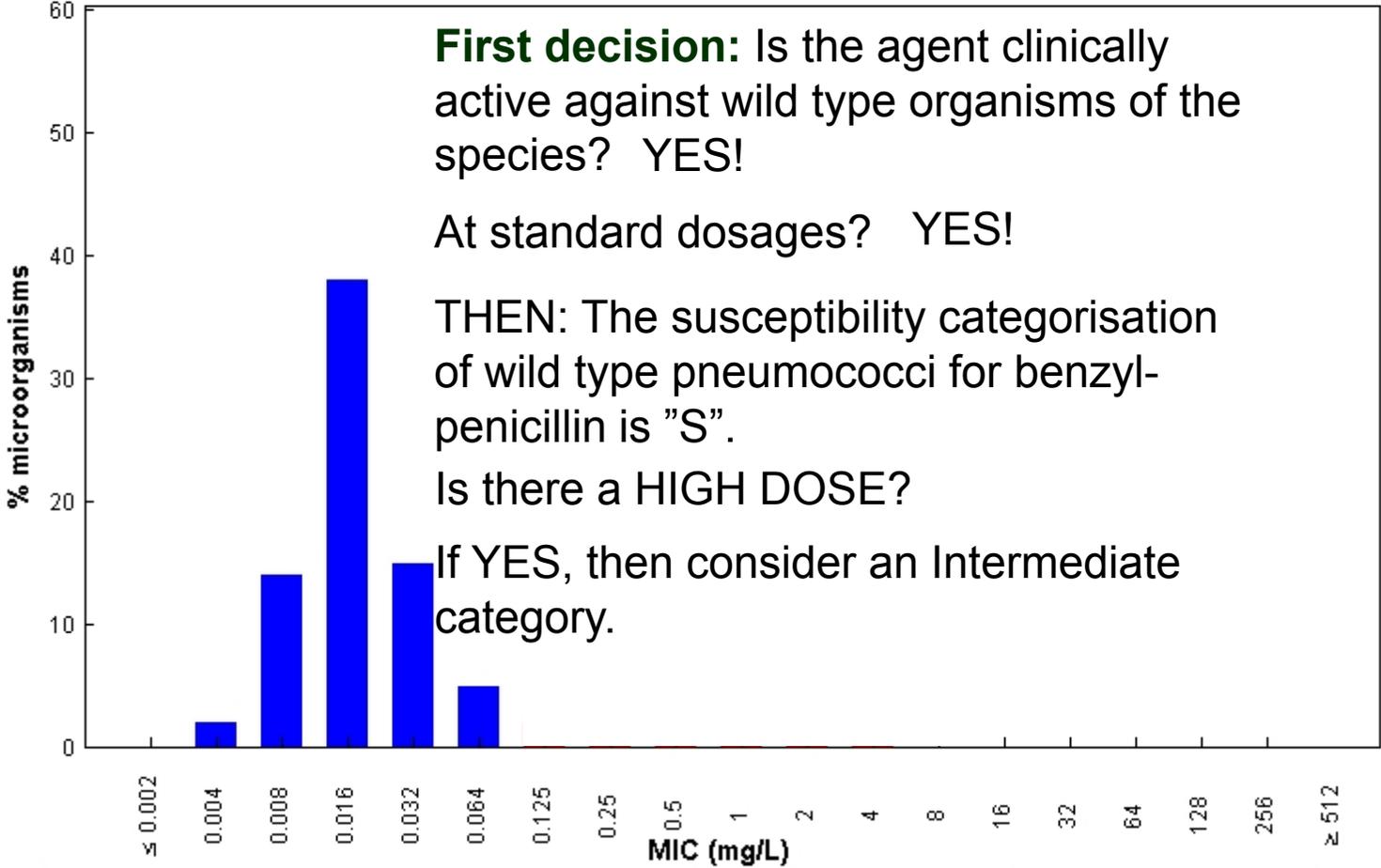
Cephalosporins ¹	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)		Notes Numbers for comments on MIC breakpoints Letters for comments on disk diffusion
	S ≤	R >		S ≥	R <	
Cefaclor	-	-	-	-	-	<p>1. The cephalosporin breakpoints for Enterobacteriaceae will detect all clinically important resistance mechanisms (including ESBL and plasmid mediated AmpC). Some isolates that produce beta-lactamases are susceptible or intermediate to 3rd or 4th generation cephalosporins with these breakpoints and should be reported as tested, i.e. the presence or absence of an ESBL does not in itself influence the categorisation of susceptibility. In many areas, ESBL detection and characterisation is recommended or mandatory for infection control purposes. 2. The cefoxitin ECOFF (8 mg/L) has a high sensitivity but poor specificity for identification of AmpC-producing Enterobacteriaceae as this agent is also affected by permeability alterations and some carbapenemases. Classical non-AmpC producers are wild type, whereas plasmid AmpC producers or chromosomal AmpC hyperproducers are non-wild type. 3/A. The breakpoint relates to a dosage of 1.5 g x 3 and to <i>E. coli</i>, <i>Klebsiella</i> spp. and <i>P. mirabilis</i> only.</p>
Cefadroxil (uncomplicated UTI only)	16	16	30	12	12	
Cefalexin (uncomplicated UTI only)	16	16	30	14	14	
Cefazolin	-	-	-	-	-	
Cefepime	1	4	30	24	21	
Cefixime (uncomplicated UTI only)	1	1	5	17	17	
Cefotaxime	1	2	5	20	17	
Cefoxitin (screen)²	NA	NA	30	19	19	
Cefpodoxime (uncomplicated UTI only)	1	1	10	21	21	
Ceftaroline	0.5	0.5	5	23	23	
Ceftazidime	1	4	10	22	19	
Ceftibuten (UTI only)	1	1	30	23	23	
Ceftobiprole	0.25	0.25	IP	IP	IP	
Ceftriaxone	1	2	30	23	20	
Cefuroxime iv	8 ³	8	30	18 ^A	18	
Cefuroxime oral (uncomplicated UTI only)	8	8	30	18	18	

The first step in setting breakpoints has always been:

- To determine if the agent is appropriate for the intended clinical indication and the target organisms?
- If "YES", then organisms belonging to the wild type distribution(s) of the target species are designated "S"
- ...in which case the lowest possible clinical breakpoint = ECOFF.

Benzylpenicillin / *Streptococcus pneumoniae*
EUCAST MIC Distribution - Reference Database

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



First decision: Is the agent clinically active against wild type organisms of the species? **YES!**

At standard dosages? **YES!**

THEN: The susceptibility categorisation of wild type pneumococci for benzylpenicillin is "S".

Is there a HIGH DOSE?

If YES, then consider an Intermediate category.

MIC
 Epidemiological cut-off: WT ≤ 0.064 mg/L

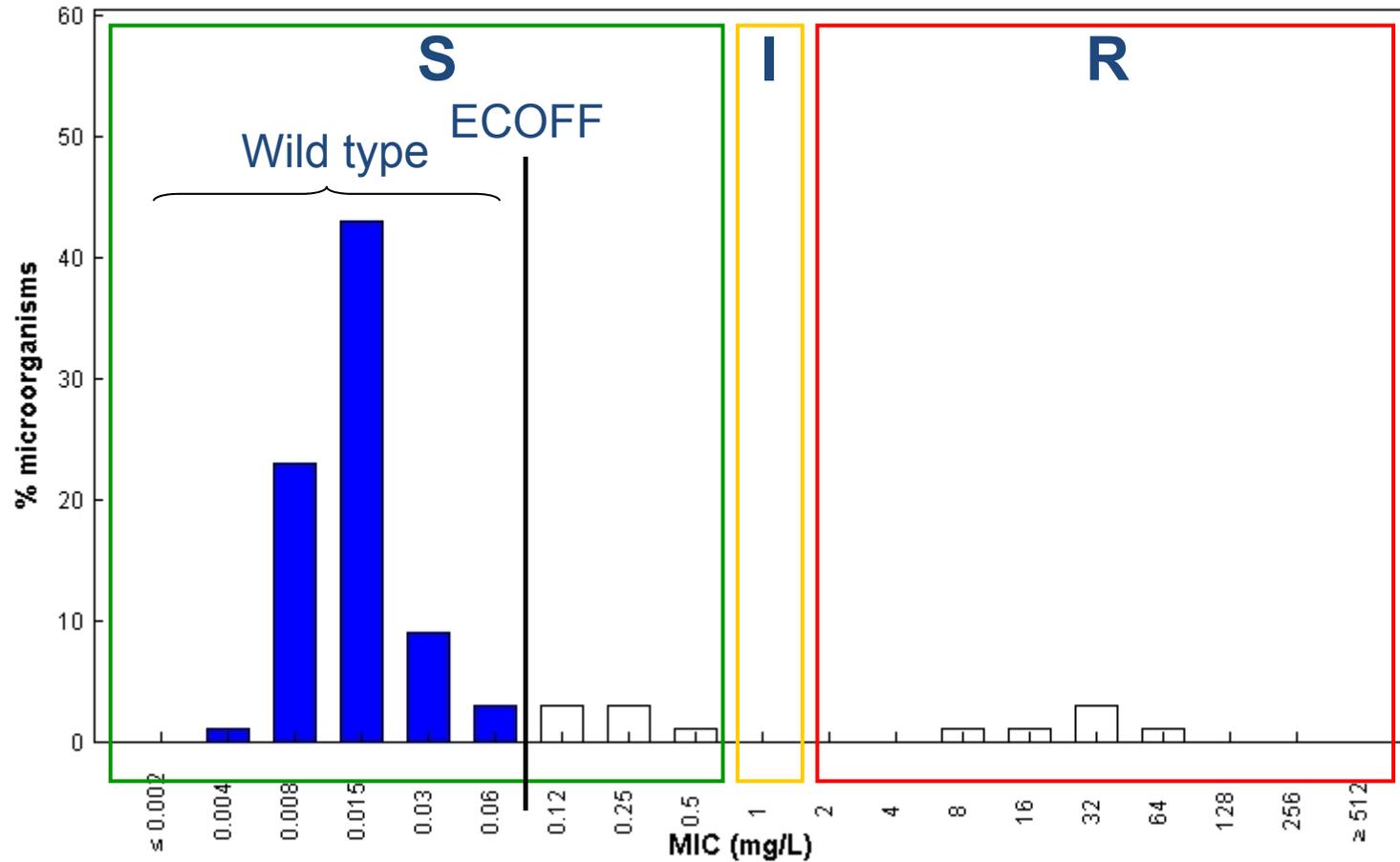
37642 observations (32 data sources)
 Clinical breakpoints: S ≤ 0.064 mg/L, R > 2 mg/L

Tools for determining **CLINICAL BREAKPOINTS**

1. Dose (or doses)
2. Target species
3. Clinical outcome on wild typ organisms of target species
4. Individual MIC-distributions for target organisms
 - breakpoints must not divide MIC-distributions of WT target species
5. Resistance mechanisms in target organisms
6. Pharmacokinetics (C_{max}, AUC, T_{1/2}, Protein binding, V_d..)
7. Pharmacodynamic properties (peak conc/MIC, AUC/MIC, TA, MCs)
8. Clinical outcome on non-wild type organisms (clinical outcome vs. MIC)
9. **Epidemiological cut off values, Pk/Pd-indices and clinical outcome data together determine the CLINICAL BREAKPOINT**

Ciprofloxacin / Escherichia coli
International MIC Distribution - Reference Database 2014-09-03

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: ≤ 0.0064 mg/L

16702 observations (55 data sources)

Examples of species/antibiotic combinations where the clinical breakpoint is much higher than the ECOFF

Antibiotic	Species	ECOFF \leq	EUCAST S \leq
Meropenem**	E.coli	0.125	2
	K.pneumoniae	0.125	2
	S. pneumoniae	0.016	2
	H. influenzae	0.25	2
Ciprofloxacin***	E. coli	0.064	0.5
	K. pneumoniae etc		
Cefotaxime	E. coli	0.25	1
Cefepime	K. pneumoniae	0.125	1
Benzylpenicillin	S. pyogenes	0.064	0.25
Ampicillin	S. pneumoniae	0.064	0.5

***Clinical Breakpoint much higher than Epidemiological Cutoff**

****And with slightly different values other carbapenems**

*****And with slightly different values other FQs**

Establishment of zone diameter breakpoints

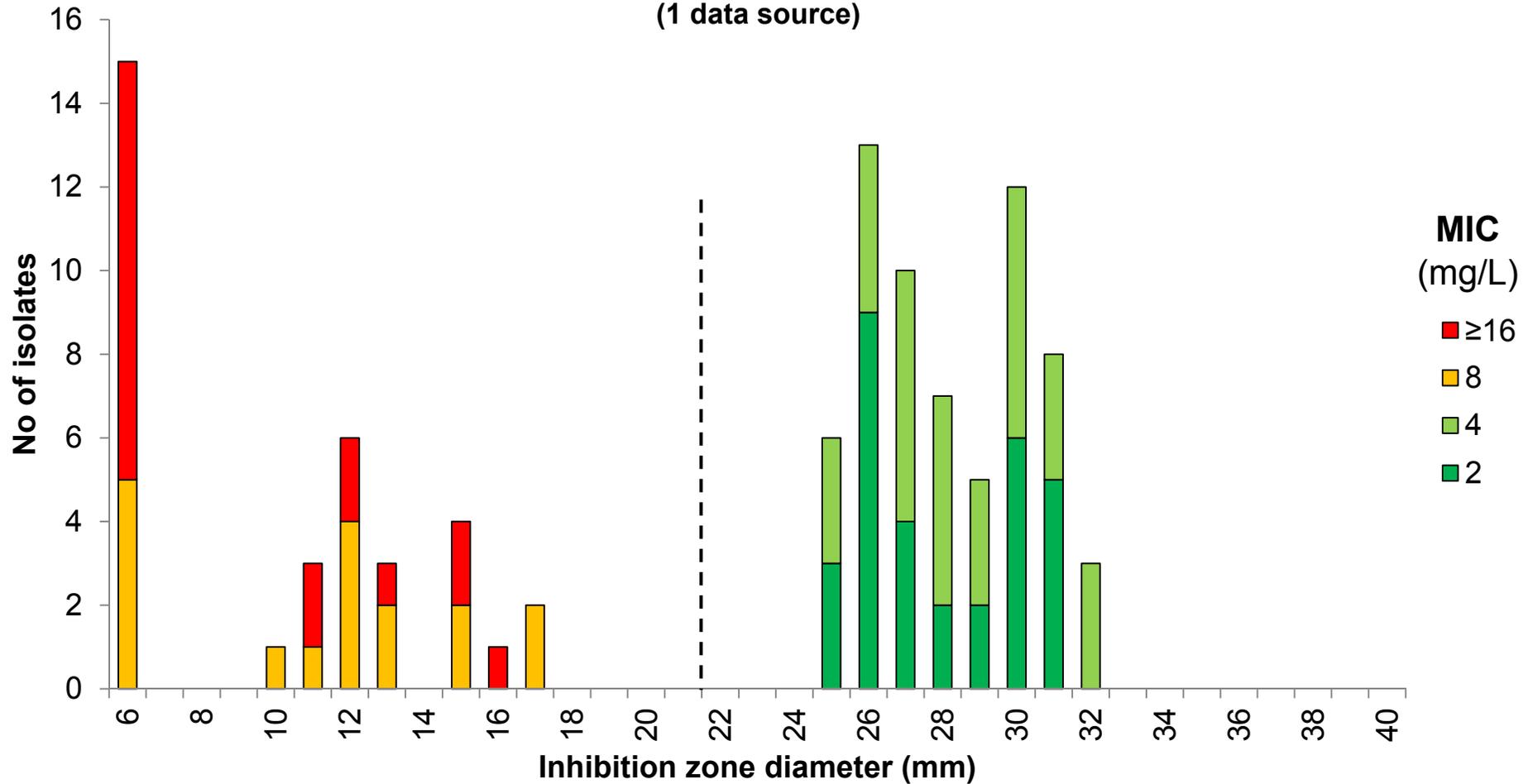
- Calibration against MIC and/or resistance mechanisms

http://www.eucast.org/ast_of_bacteria/calibration_and_validation/

Cefoxitin 30 µg vs. MIC

S. aureus, 99 clinical isolates

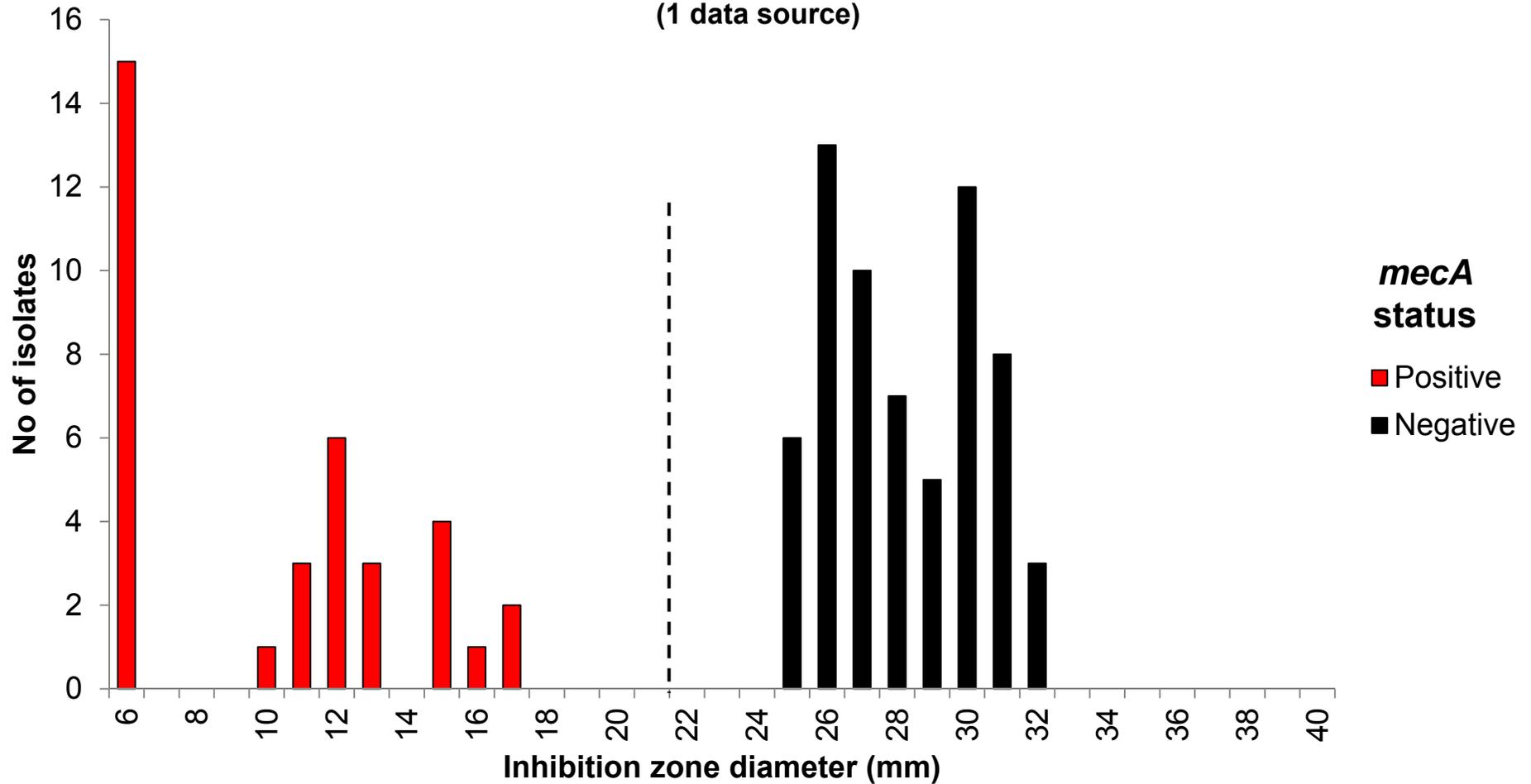
(1 data source)



Breakpoints		ECOFF
MIC (screen)	S ≤ 4, R > 4 mg/L	WT ≤ 4 mg/L
Zone diameter (screen)	S ≥ 22, R < 22 mm	

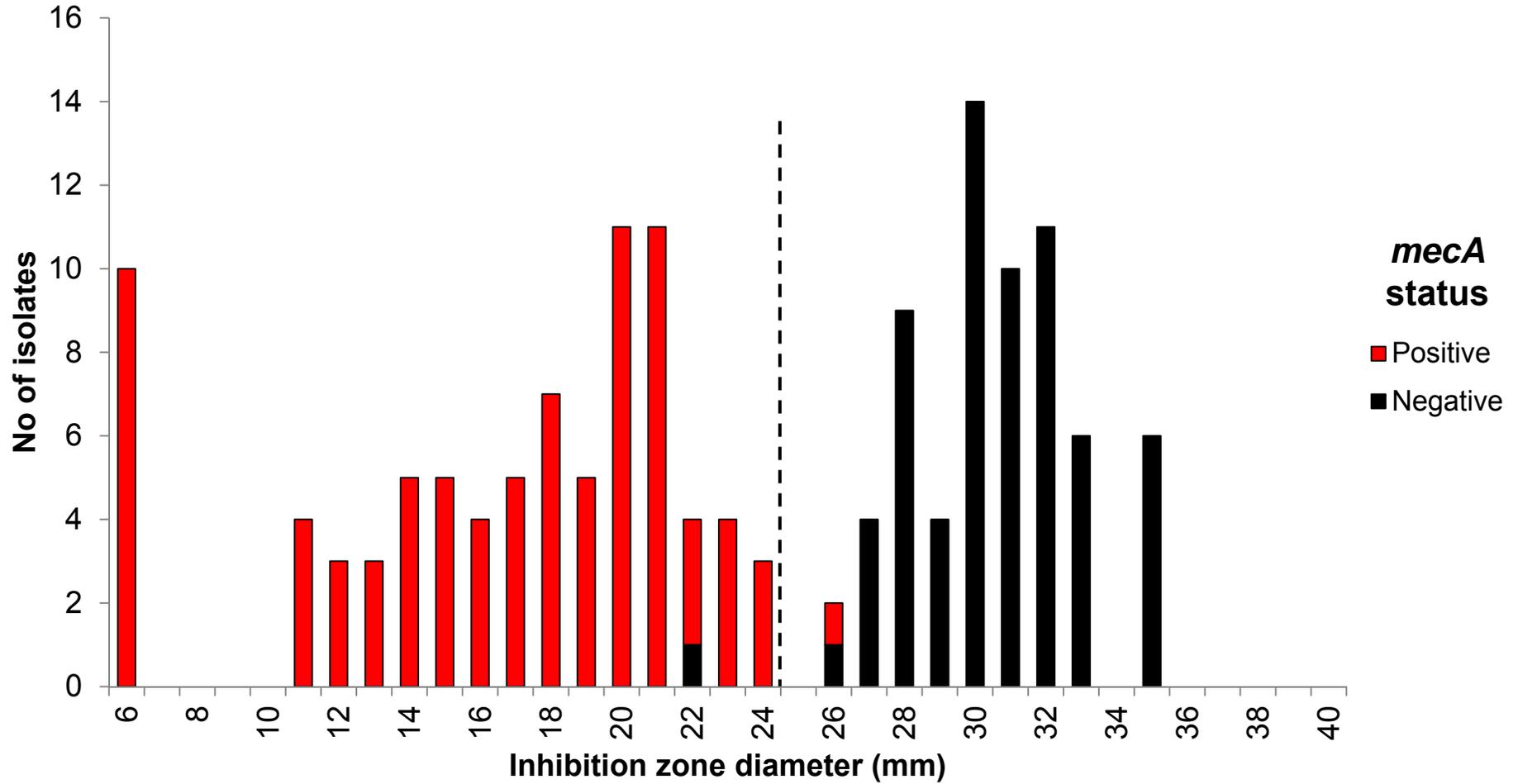
Cefoxitin 30 µg vs. *mecA* status *S. aureus*, 99 clinical isolates

(1 data source)



Breakpoints		ECOFF
MIC (screen)	S ≤ 4, R > 4 mg/L	WT ≤ 4 mg/L
Zone diameter (screen)	S ≥ 22, R < 22 mm	

Cefoxitin 30 µg vs. *mecA* status CoNS, 150 clinical isolates



Breakpoints

Zone diameter (screen) $S \geq 25$, $R < 25$ mm

Establishment of zone diameter breakpoints

- Calibration against MIC and/or resistance mechanisms

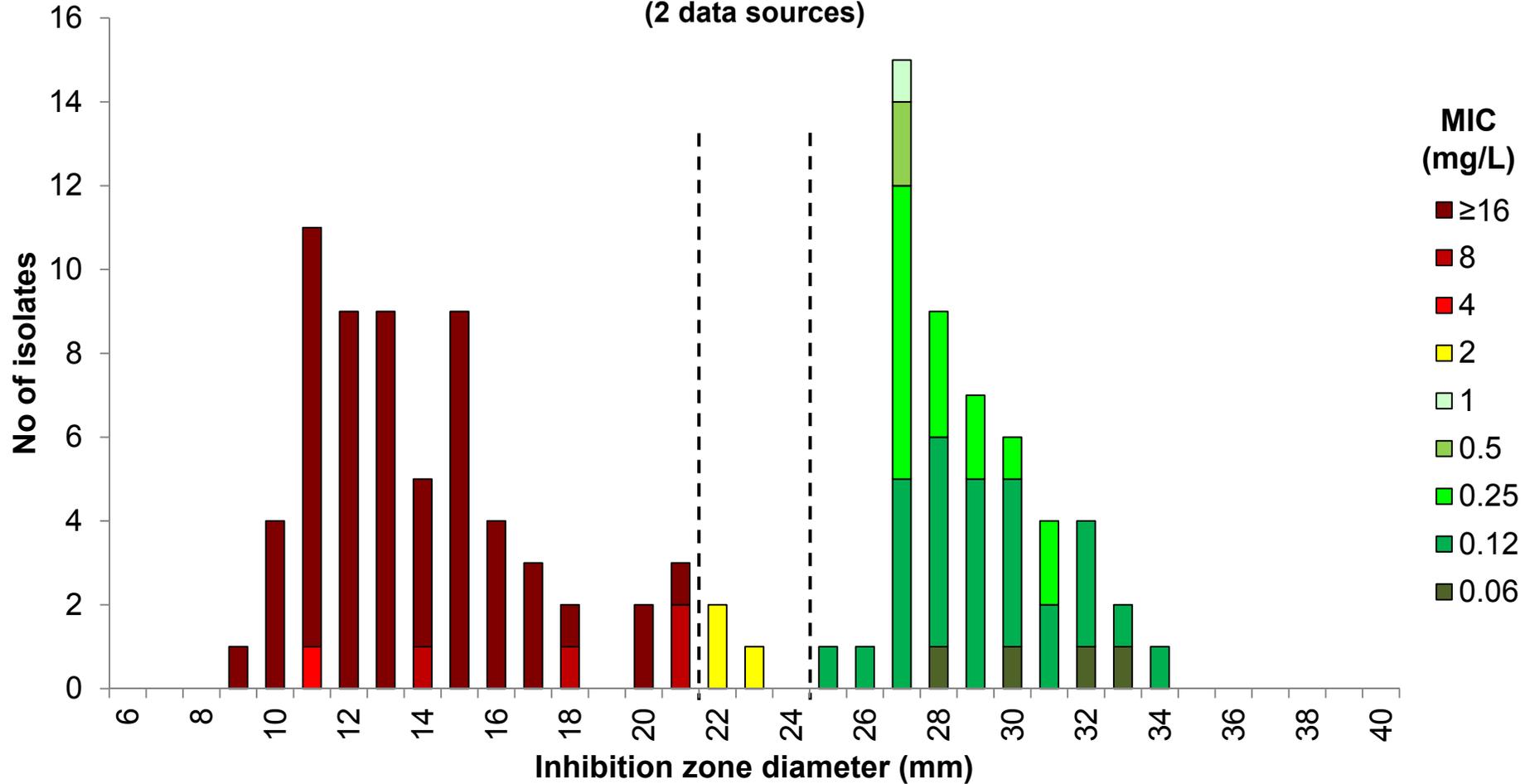
http://www.eucast.org/ast_of_bacteria/calibration_and_validation/

- Calibration of screening disks

Tetracycline 30 µg vs. MIC

S. pneumoniae, 115 clinical isolates

(2 data sources)



Breakpoints

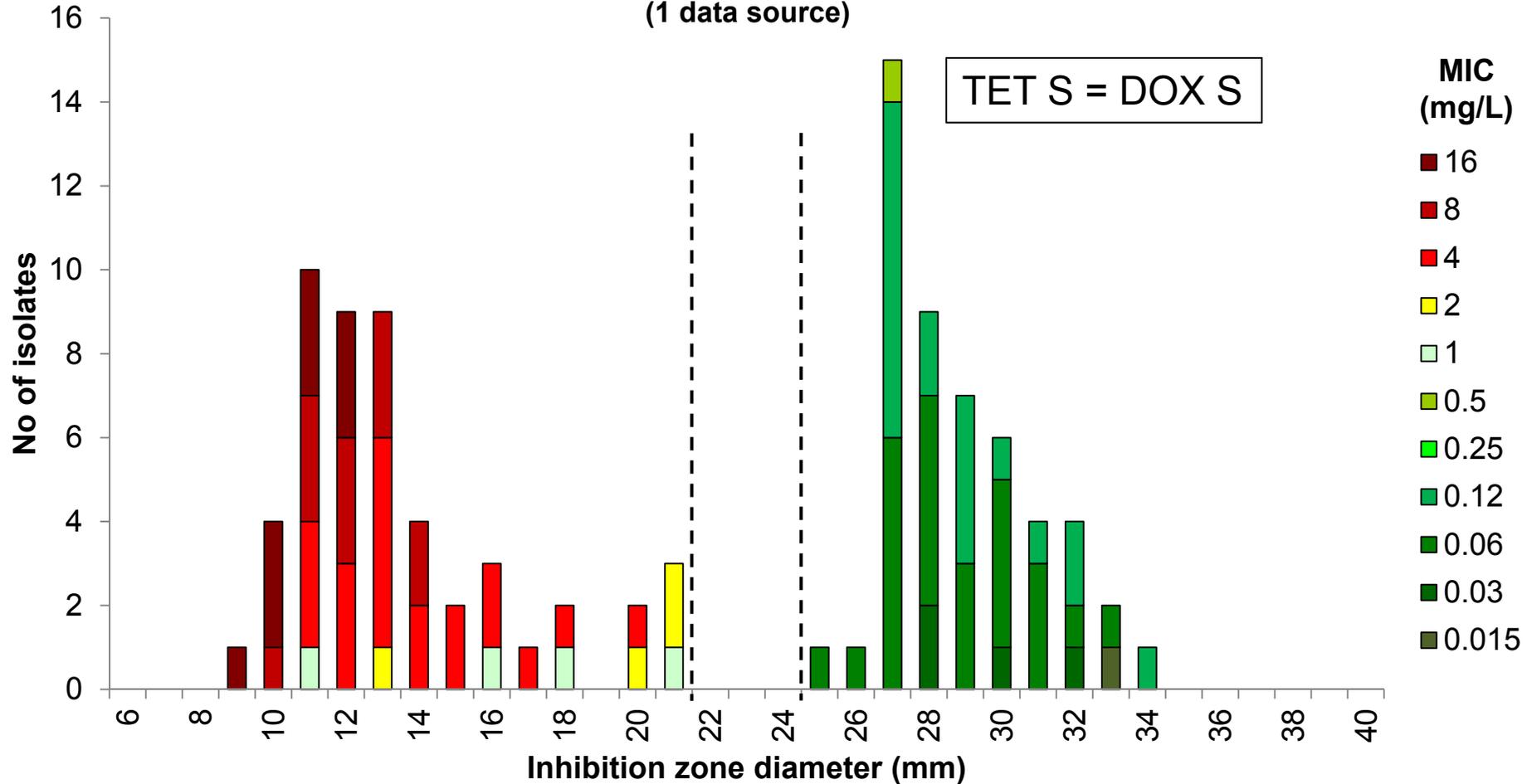
MIC $S \leq 1, R > 2$ mg/L
 Zone diameter $S \geq 25, R < 22$ mm

ECOFF

WT ≤ 1 mg/L

Tetracycline 30 µg vs. Doxycycline MIC *S. pneumoniae*, 100 clinical isolates

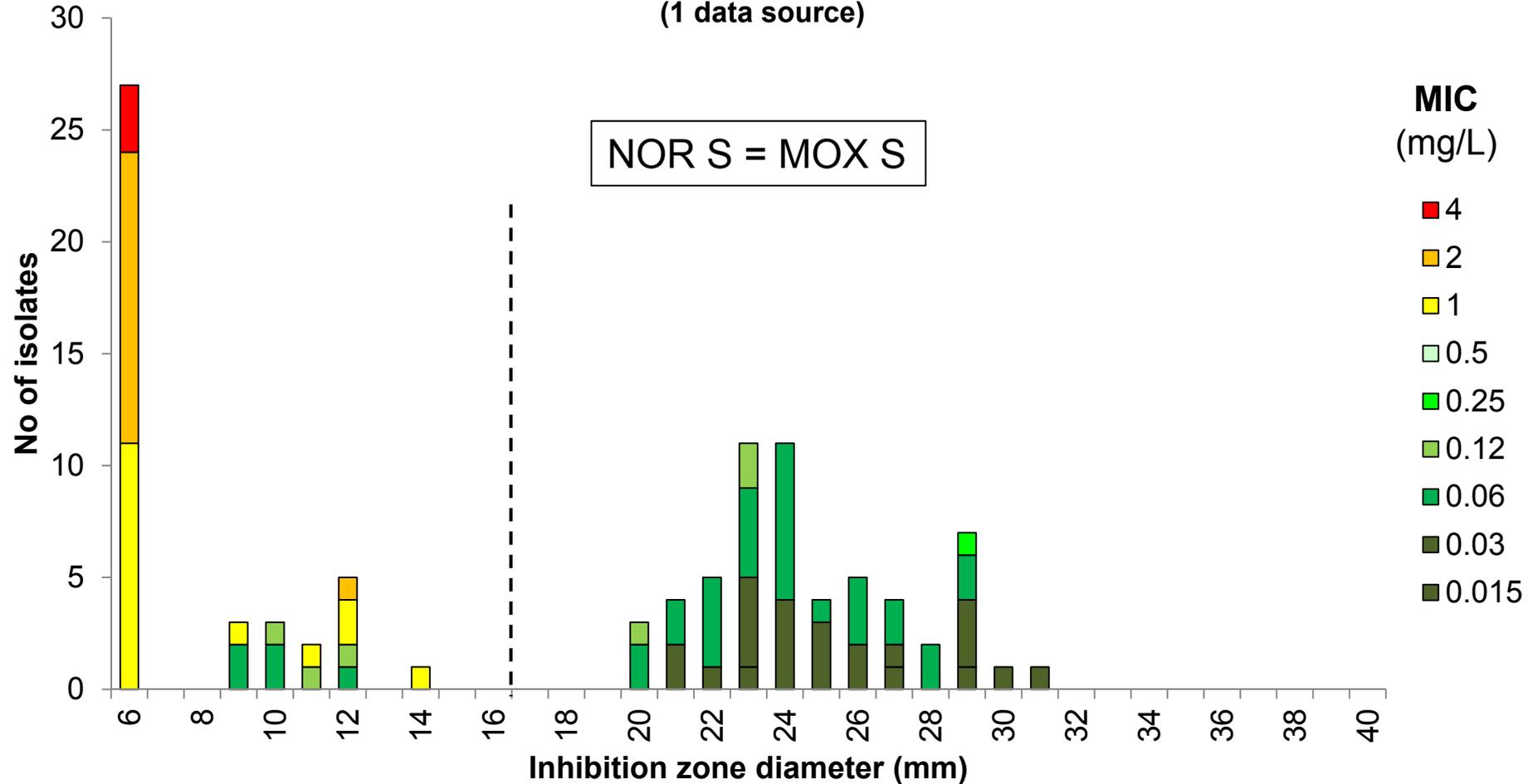
(1 data source)



Breakpoints		ECOFF
Doxycycline MIC	$S \leq 1, R > 2$ mg/L	WT ≤ 0.5 mg/L
Tetracycline zone diameter	$S \geq 25, R < 22$ mm	

Norfloxacin 10 µg vs. Moxifloxacin MIC *S. aureus*, 99 clinical isolates

(1 data source)



Breakpoints

Moxifloxacin MIC

S ≤ 0.5, R > 1 mg/L

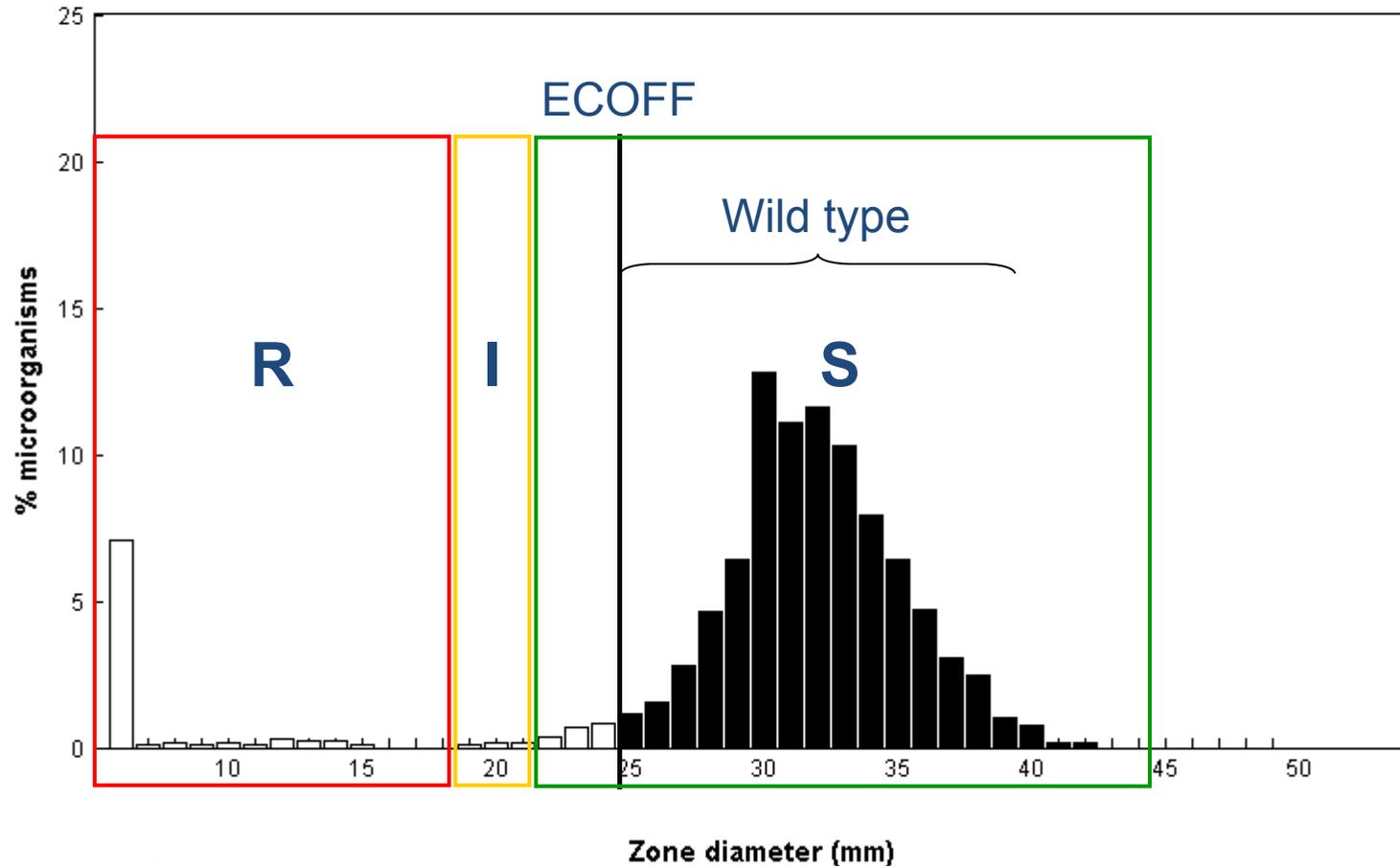
Norfloxacin zone diameter (screen) S ≥ 17 mm

ECOFF

WT ≤ 0.25 mg/L

Ciprofloxacin / Escherichia coli
International wild type zone diameter distribution - Reference database 2015-05-07
EUCAST disk diffusion method

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



Disk content: 5

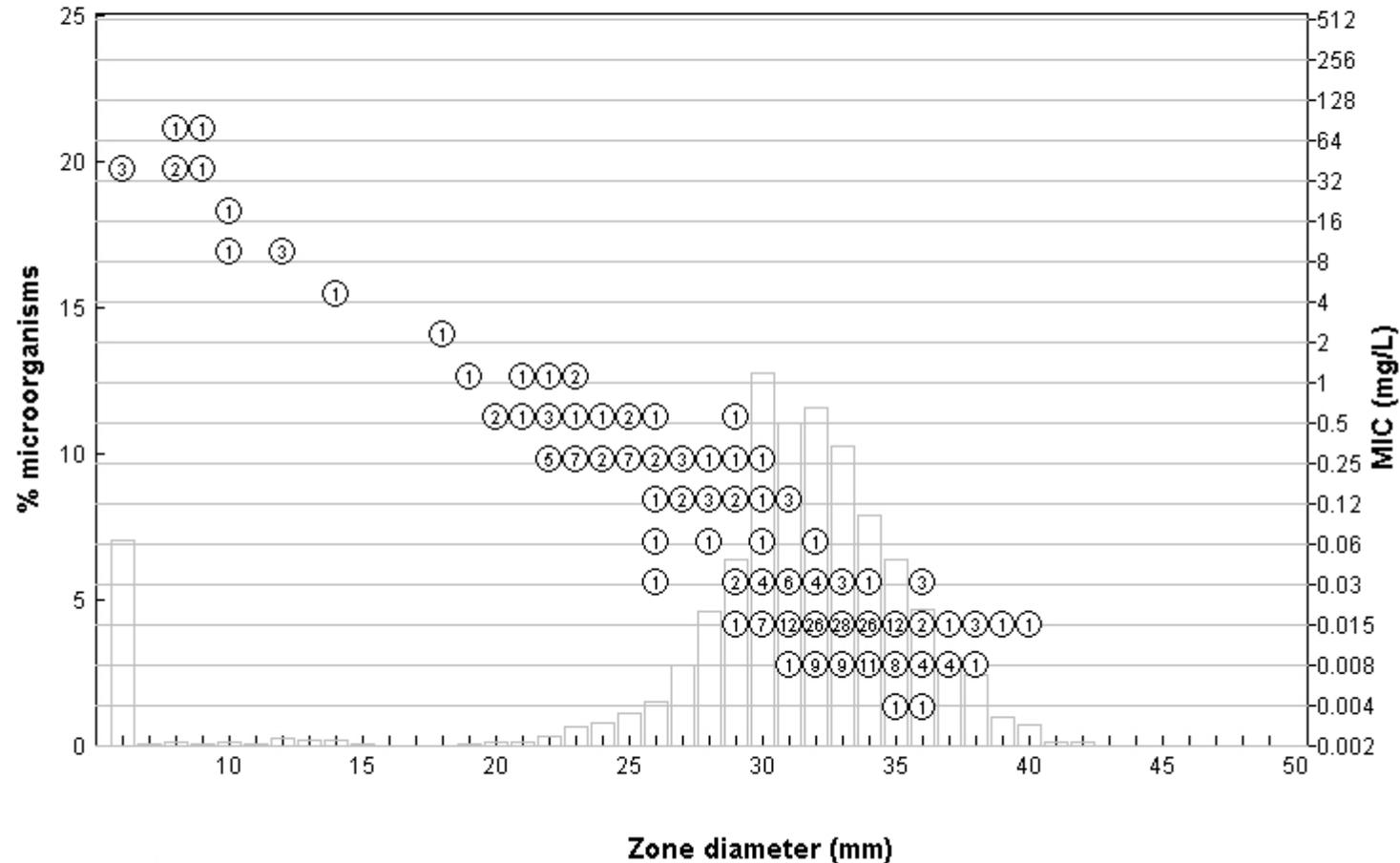
Epidemiological cut-off (ECOFF): 25 mm (MIC = 0.064 mg/L)

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

6434 observations (6 data sources)

Ciprofloxacin / Escherichia coli
International wild type zone diameter distribution - Reference database 2015-05-07
EUCAST disk diffusion method

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



Disk content: 5

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

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

6434 observations (6 data sources)

Frågor & diskussion

När och hur kan man använda ECOFFs?

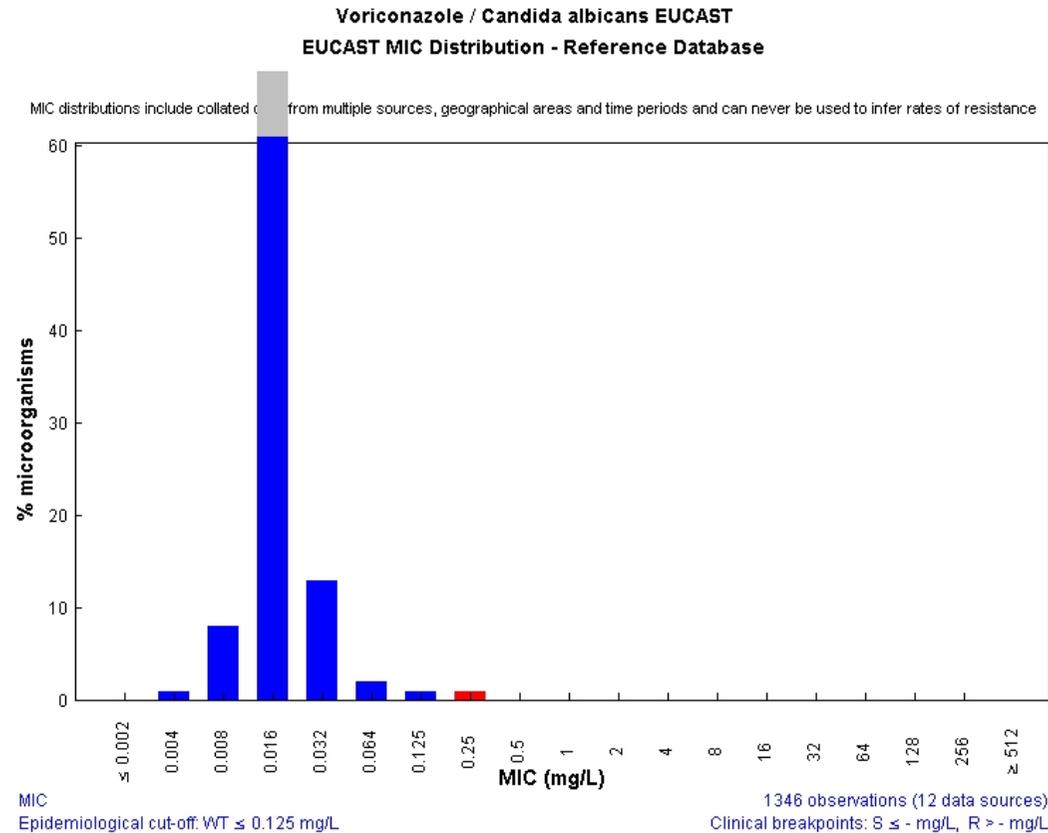
The use of ECOFFs

- As a tool in the determination of clinical breakpoints
 - To avoid dividing wild type MIC distributions of important target organisms
 - As a **surrogate clinical breakpoint** when **Pk/Pd data is incomplete and clinical data pertain only to wild type organisms**
- For **sensitive detection of (screening for) resistance**
 - oxacillin to detect all penicillin-R in *S. pneumoniae*
 - ceftiofur to detect methicillin resistance in *S. aureus*
 - benzylpenicillin to detect all betalactam resistance in *H. influenzae*
 - pefloxacin to detect quinolone resistance in *Salmonella* spp
 - meropenem to screen for KPC in Enterobacteriaceae
- For **surveillance of antimicrobial resistance** when clinical breakpoints...
 - are not sensitive enough
 - have not been determined
 - change over time
 - differ between systems (CLSI, FDA, EUCAST etc)
 - differ between humans, cows, pigs, birds, fish and camels.
- to **exclude resistance**
 - food safety – in the development of functional foods

Wild type MIC-distributions and ECOFFs for antifungal drugs as one of several tools for determining breakpoints

Principle authors:

J-L. Tudela, P. Donnelly, M. Arendrup, M. Cuenza-Estrella, C. Lass-Flörl.



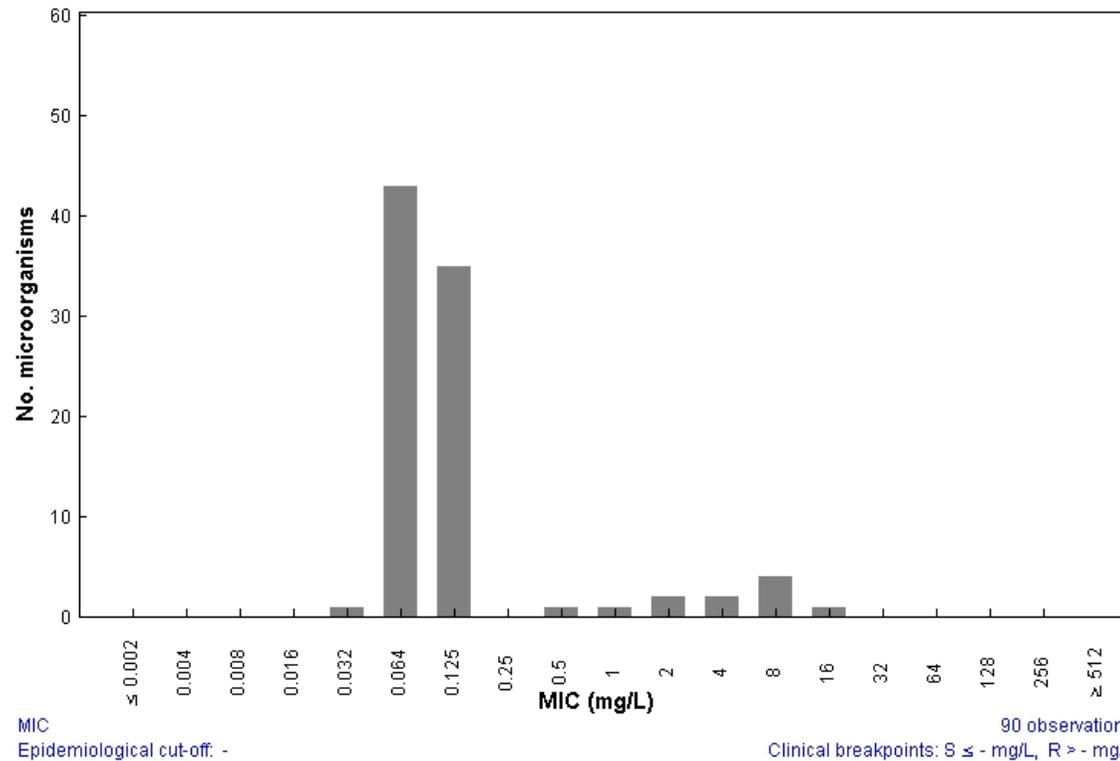
Wild-type MIC distributions and epidemiological cut-off values for antibiotics used for the treatment of *Mycobacterium tuberculosis*

Principle authors: K Ängeby, P Jurén, T Schön.

and with E Sturegård, E Chryssanthou, CG Giske, J Werngren, M Nordvall, A Johansson, G Kahlmeter, S Hoffner.

Isoniazid / *Mycobacterium tuberculosis*
EUCAST MIC Distribution - Reference Database

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



Use of ECOFF's in Resistance surveillance in animals (EU)

- As a direct of spin-off of collaboration of EU NRLs on antimicrobial resistance in animals and EUCAST, EFSA guidelines were prepared for standardized resistance surveillance



The EFSA Journal (2007), 96, 1-46. "Report including a proposal for a harmonized monitoring scheme of antimicrobial resistance in *Salmonella* in fowl (*Gallus gallus*), turkeys, and pigs and *Campylobacter jejuni* and *C. coli* in broilers"



The EFSA Journal (2008) 141: 1-44

**Report of the
Task Force on Zoonoses Data Collection
including a proposal for a harmonized monitoring
scheme of antimicrobial resistance in
Salmonella in fowl (*Gallus gallus*), turkeys, and pigs
and
Campylobacter jejuni and *C. coli* in broilers¹**

(Question N° EFSA-Q-2006-046)

Salmonella, Campylobacter

**Report from the Task Force on Zoonoses Data Collection
including guidance for harmonized monitoring and
reporting of antimicrobial resistance in commensal
Escherichia coli and *Enterococcus* spp. from food animals¹**

(Question No EFSA-Q-2007-131)

Adopted by
the Task Force on 11-12 March 2008

E. coli, enterococci

EFSA Guidelines

- Harmonized sampling strategies
- Broth microdilution according to ISO-20776-1:2006 as standard method
- List of required antibiotics to include in the tests and ECOFF's as interpretive criteria for sensitive and harmonized interpretation of surveillance results in the EU
 - see table A

	Antimicrobial	Cut-off value (mg/L)
		R>
<i>Salmonella</i>	Cefotaxime	0.5
	Nalidixic acid	16
	Ciprofloxacin	0.06
	Ampicillin	4
	Tetracycline	8
	Chloramphenicol	16
	Gentamicin	2
	Streptomycin	32
	Trimethoprim	2
	Sulphonamides	256
<i>Campylobacter jejuni</i>	Erythromycin	4
	Ciprofloxacin	1
	Tetracycline	2
	Streptomycin	2
	Gentamicin	1
<i>Campylobacter coli</i>	Erythromycin	16
	Ciprofloxacin	1
	Tetracycline	2

Officially utilizing ECOFFs

- EFSA – antimicrobial resistance surveillance in the veterinary field
- European Food Safety Project – screening for functional food microorganism candidates to exclude transferable resistance.

The image shows a screenshot of a PubMed search result page. At the top left is the PubMed.gov logo with the text "U.S. National Library of Medicine National Institutes of Health". To the right is a search bar containing "PubMed" and buttons for "Limits", "Advanced search", and "Help". Below the search bar are "Search" and "Clear" buttons. Underneath the search bar, there is a "Display Settings" link with a dropdown menu set to "Abstract" and a "Send to" link with a dropdown menu. The main text of the page is a citation for a paper: "J. Antimicrob. Chemother., 2007 May;59(5):900-12. Epub 2007 Mar 16." The title of the paper is "Antimicrobial susceptibilities of Lactobacillus, Pediococcus and Lactococcus human isolates and cultures intended for probiotic or nutritional use." The authors listed are Klare I, Konstabel C, Werner G, Huys G, Vankerckhoven V, Kahlmeter G, Hildebrandt B, Müller-Bertling S, Witte W, Goossens H. The authors' affiliation is the Robert Koch Institute, Wernigerode Branch, Wernigerode, Germany. The abstract text follows, starting with "OBJECTIVES: To determine MICs of 16 antimicrobials representing all major classes for 473 taxonomically well-characterized isolates of lactic acid bacteria (LAB) encompassing the genera Lactobacillus, Pediococcus and Lactococcus. To propose tentative epidemiological cut-off (ECOFF) values for recognizing intrinsic and acquired antimicrobial resistances in numerically dominant species. METHODS: On the basis of depositors' information, LAB were grouped in categories of probiotic, nutritional, probiotic or nutritional research, human and animal isolates and tested for their antibiotic susceptibilities by broth microdilution using LAB susceptibility test medium (LSM). Tentative ECOFFs were defined according to the recommendations of the European Committee on Antimicrobial Susceptibility Testing. Isolates showing acquired antimicrobial resistance(s) were selected for PCR-based detection of resistance gene(s) and in vitro conjugative transfer experiments. RESULTS: Tentative ECOFF values of 13 antibiotics were determined for up to 12 LAB species. Generally, LAB were susceptible to penicillin, ampicillin, ampicillin/sulbactam, quinupristin/dalfopristin, chloramphenicol and linezolid. LAB exhibited broad or partly species-dependent MIC profiles of trimethoprim, trimethoprim/sulfamethoxazole, vancomycin, teicoplanin and fusidic acid. Three probiotic Lactobacillus strains were highly resistant to streptomycin. Although erythromycin, clindamycin and oxetetracycline possessed high antimicrobial activities, 17 Lactobacillus isolates were resistant to one or more of these antibiotics. Eight of them, including six probiotic and nutritional cultures, possessed erm(B) and/or tet(M), tet(M) or unidentified members of the tet(M) group. In vitro intra- and interspecies filter-mating experiments failed to show transfer of resistance determinants. CONCLUSIONS: Finding of acquired resistance genes in isolates intended for probiotic or nutritional use highlights the importance of antimicrobial susceptibility testing in documenting the safety of commercial LAB." Below the abstract is the PMID: 17369270 [PubMed - indexed for MEDLINE]. At the bottom, there are two links: "+ Publication Types, MeSH Terms, Substances" and "+ LinkOut - more resources".

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J. Antimicrob. Chemother., 2007 May;59(5):900-12. Epub 2007 Mar 16.

Antimicrobial susceptibilities of Lactobacillus, Pediococcus and Lactococcus human isolates and cultures intended for probiotic or nutritional use.

Klare I, Konstabel C, Werner G, Huys G, Vankerckhoven V, Kahlmeter G, Hildebrandt B, Müller-Bertling S, Witte W, Goossens H.
Robert Koch Institute, Wernigerode Branch, Wernigerode, Germany. i.klare@rki.de

OBJECTIVES: To determine MICs of 16 antimicrobials representing all major classes for 473 taxonomically well-characterized isolates of lactic acid bacteria (LAB) encompassing the genera Lactobacillus, Pediococcus and Lactococcus. To propose tentative epidemiological cut-off (ECOFF) values for recognizing intrinsic and acquired antimicrobial resistances in numerically dominant species. METHODS: On the basis of depositors' information, LAB were grouped in categories of probiotic, nutritional, probiotic or nutritional research, human and animal isolates and tested for their antibiotic susceptibilities by broth microdilution using LAB susceptibility test medium (LSM). Tentative ECOFFs were defined according to the recommendations of the European Committee on Antimicrobial Susceptibility Testing. Isolates showing acquired antimicrobial resistance(s) were selected for PCR-based detection of resistance gene(s) and in vitro conjugative transfer experiments. RESULTS: Tentative ECOFF values of 13 antibiotics were determined for up to 12 LAB species. Generally, LAB were susceptible to penicillin, ampicillin, ampicillin/sulbactam, quinupristin/dalfopristin, chloramphenicol and linezolid. LAB exhibited broad or partly species-dependent MIC profiles of trimethoprim, trimethoprim/sulfamethoxazole, vancomycin, teicoplanin and fusidic acid. Three probiotic Lactobacillus strains were highly resistant to streptomycin. Although erythromycin, clindamycin and oxetetracycline possessed high antimicrobial activities, 17 Lactobacillus isolates were resistant to one or more of these antibiotics. Eight of them, including six probiotic and nutritional cultures, possessed erm(B) and/or tet(M), tet(M) or unidentified members of the tet(M) group. In vitro intra- and interspecies filter-mating experiments failed to show transfer of resistance determinants. CONCLUSIONS: Finding of acquired resistance genes in isolates intended for probiotic or nutritional use highlights the importance of antimicrobial susceptibility testing in documenting the safety of commercial LAB.

PMID: 17369270 [PubMed - indexed for MEDLINE]

+ Publication Types, MeSH Terms, Substances

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0095-1137/10/\$12.00+0 doi:10.1128/JCM.01590-09

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Wild-Type MIC Distributions and Epidemiological Cutoff Values for the Echinocandins and *Candida* spp. ▾

M. A. Pfaller,^{1*} L. Boyken,¹ R. J. Hollis,¹ J. Kroeger,¹ S. A. Messer,¹ S. Tendolkar,¹ R. N. Jones,^{3,4} J. Turnidge,⁵ and D. J. Diekema^{1,2}

Departments of Pathology,¹ Medicine, University of Iowa Carver College of Medicine, Iowa City, Iowa,² JMI Laboratories, North Liberty, Iowa,³ Tufts University School of Medicine, Boston, Massachusetts,⁴ Division of Laboratory Medicine, Women's and Children's Hospital, North Adelaide, South Australia, Australia⁵

Received 17 August 2009/ Returned for modification 7 October 2009/ Accepted 13 October 2009

We tested a global collection of *Candida* sp. strains against anidulafungin, caspofungin, and micafungin, using CLSI M27-A3 broth microdilution (BMD) methods, in order to define wild-type (WT) populations and epidemiological cutoff values (ECVs). From 2003 to 2007, 8,271 isolates of *Candida* spp. (4,283 *C. albicans*, 1,236 *C. glabrata*, 1,238 *C. parapsilosis*, 996 *C. tropicalis*, 270 *C. krusei*, 99 *C. lusitanae*, 88 *C. guilliermondii*, and 61 *C. kefyr* isolates)

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Genotyping using whole-genome sequencing is a realistic alternative to surveillance based on phenotypic antimicrobial susceptibility testing

Ea Zankari^{1,2}, Henrik Hasman¹, Rolf Sommer Kaas^{1,2}, Anne Mette Seyfarth¹, Yvonne Agersø¹, Ole Lund², Mette Voldby Larsen² and Frank M. Aarestrup^{1*}

- 43 plasmid borne genes (AG, Bla, MLS, CAT, Sul, Tet, Tmp, vanA) were identified with WGS.
- 482/3051 (16%) isolates exhibited one or more R-genes.
- The detection/identification of the NWT using WGS was compared with the detection of NWT using the EUCAST ECOFFs: 99.7% agreement.