- Wild type MIC (and zone diameter) distributions
- ECOFFs (vs. clinical breakpoints)

- The EUCAST international MIC distribution database

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EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

The MIC is a relative value and will vary with the ”system”

- Medium
- pH
- Cation concentration
- Inoculum
- Atmosphere
- Growth characteristics and ability
- Incubation time
- ……..

We go to great lengths to achieve reproducibility – but the MIC value is still only a relative value.

INTERNATIONAL STANDARD

ISO 20776-1

Second edition
2019-06

Susceptibility testing of infectious agents and evaluation of performance of antimicrobial susceptibility test devices —

Part 1:
Broth micro-dilution reference method for testing the in vitro activity of antimicrobial agents against rapidly growing aerobic bacteria involved in infectious diseases

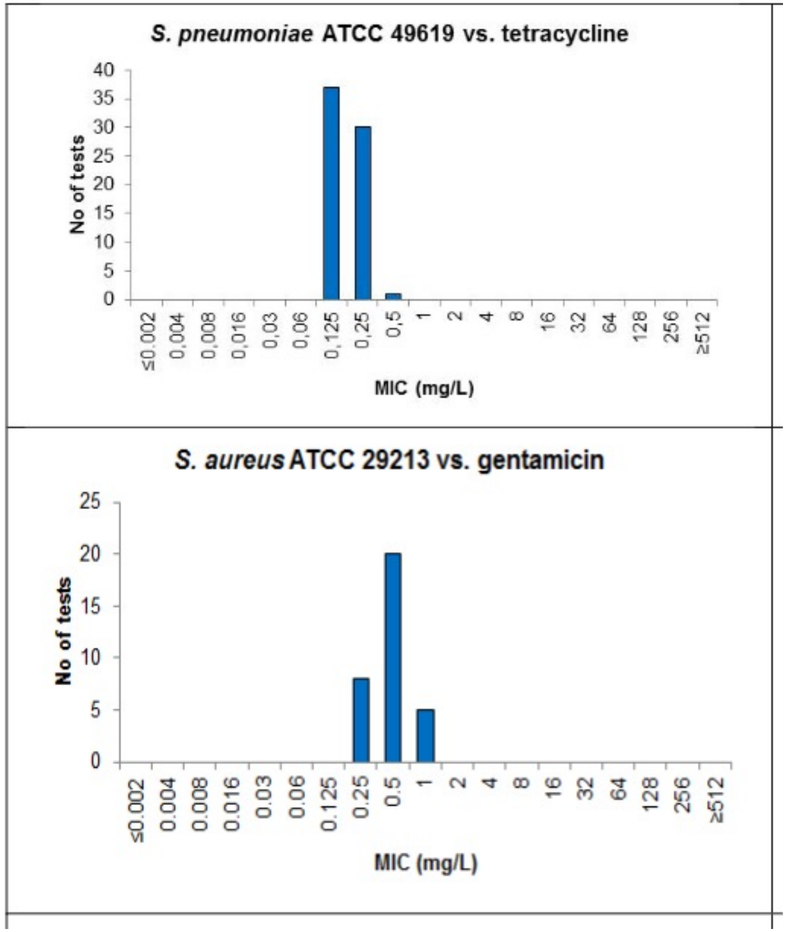
If

- you stick to the methodology,
- buy the best material,
- educate and train yourself and staff,
- avoid common pitfalls and
- practice, practice, practice

– the testing of one and the same isolate and the testing of many isolates will generate MIC distributions like these:

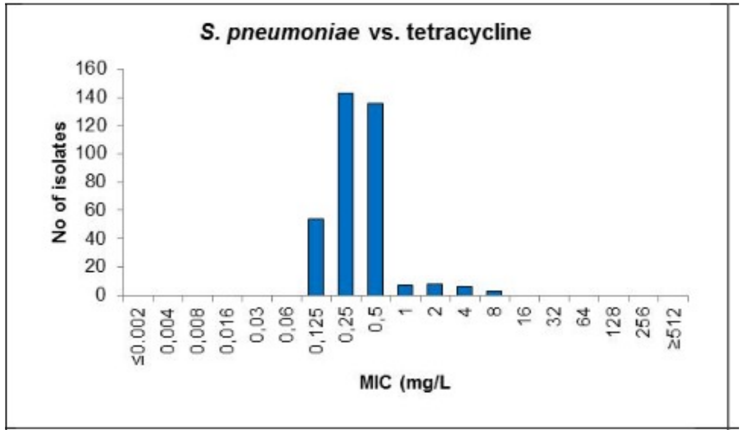
MIC – reproducibility of the MIC and defining a wild type

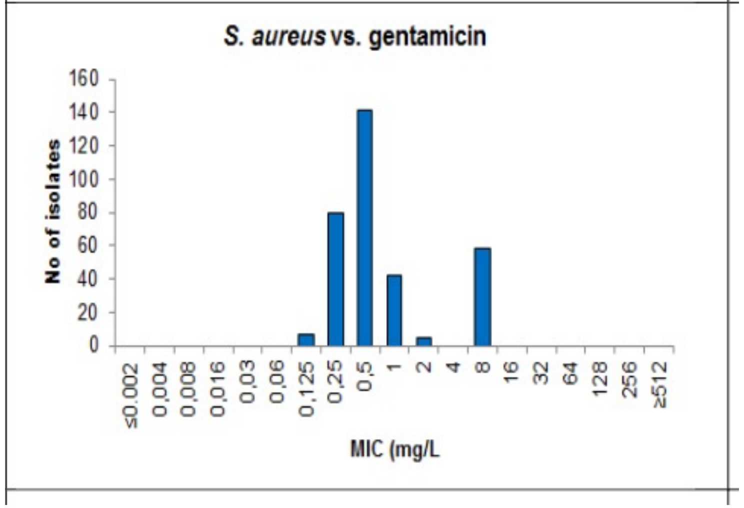
Repeat MIC testing of one strain (one lab, reference BMD)



MIC – reproducibility of the MIC and defining a wild type

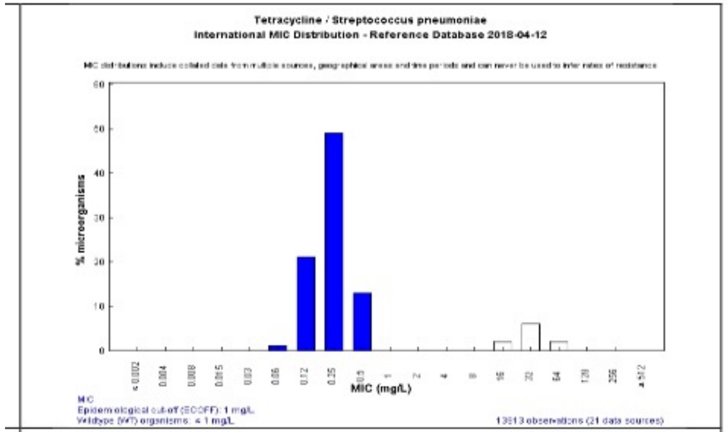
MIC testing of consecutive clinical isolates (one lab, reference BMD)

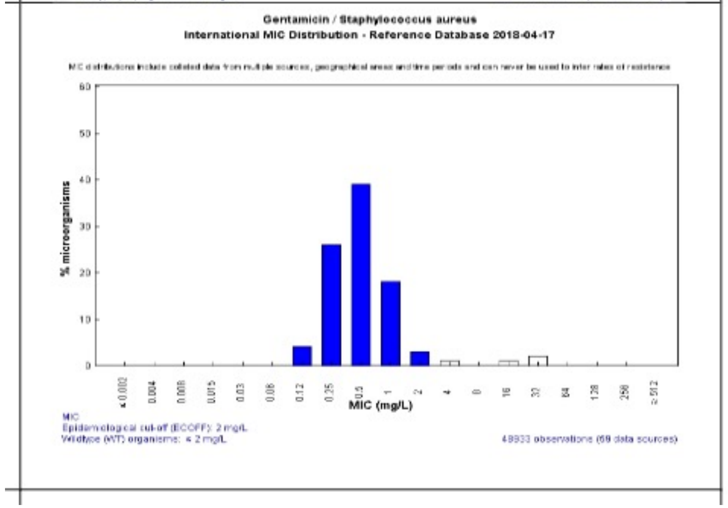




MIC – reproducibility of the MIC and defining a wild type

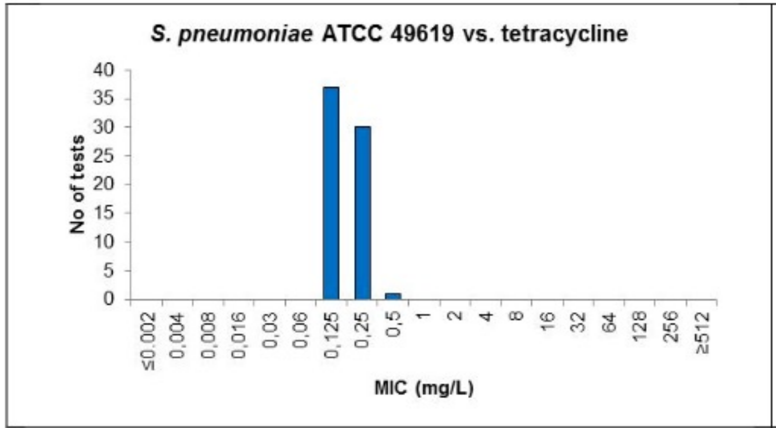
MIC testing of clinical isolates, many investigators.

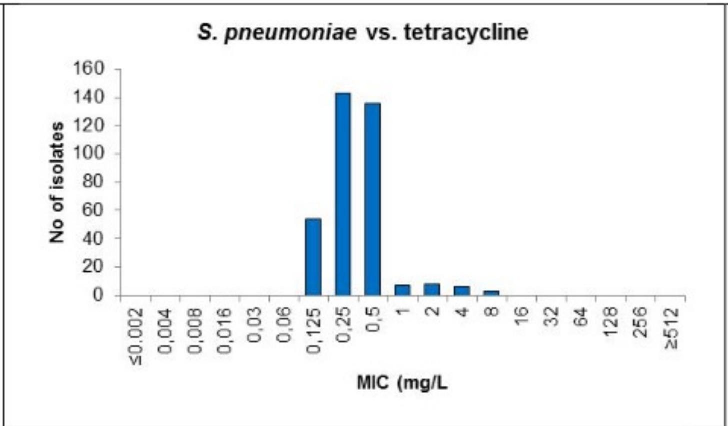


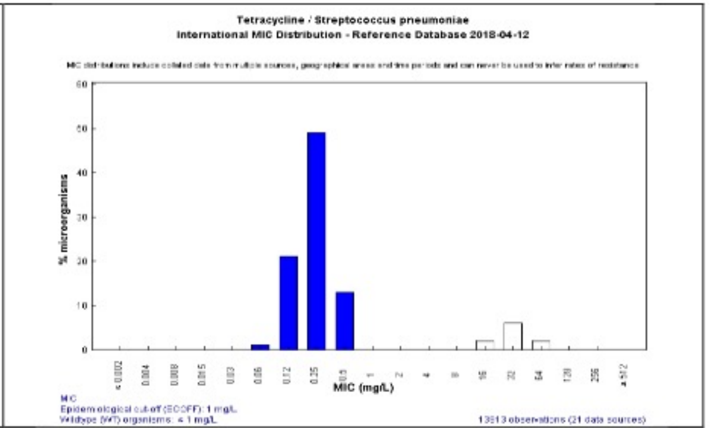


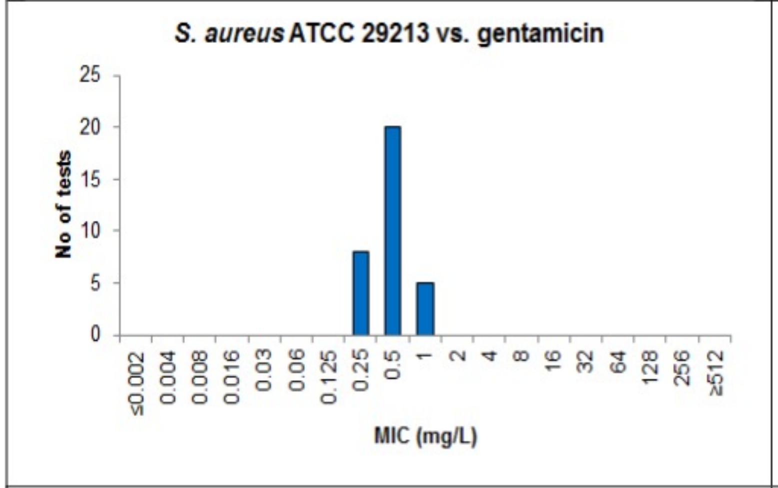
MIC – reproducibility of the MIC and defining a wild type

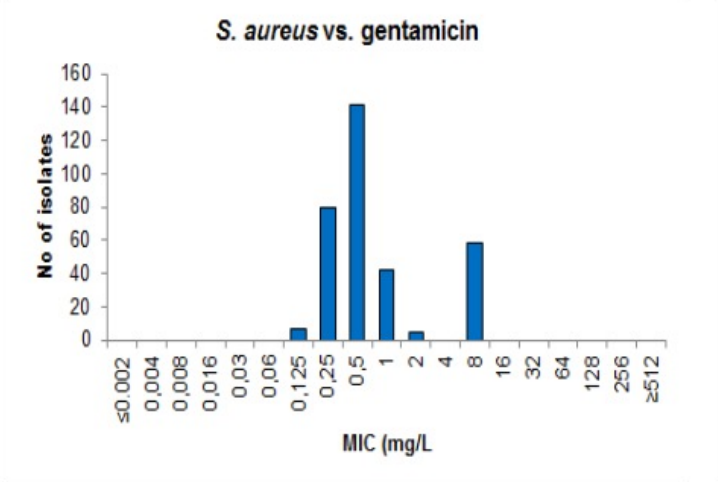
Repeat MIC testing of one strain (one lab, reference BMD)	MIC testing of consecutive clinical isolates (one lab, reference BMD)	MIC testing of clinical isolates, many investigators.

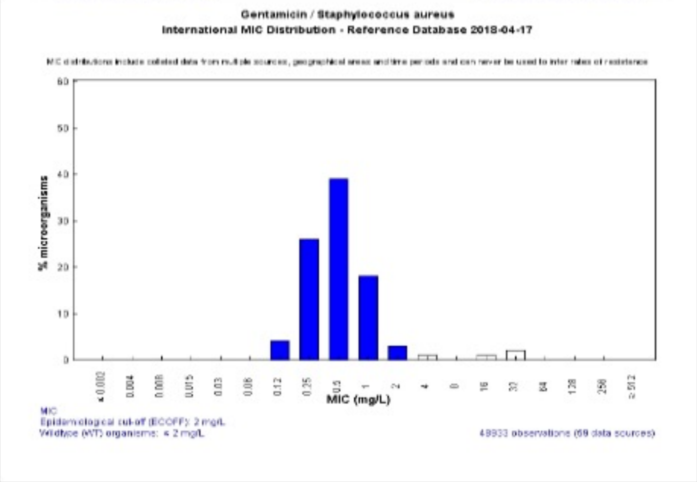






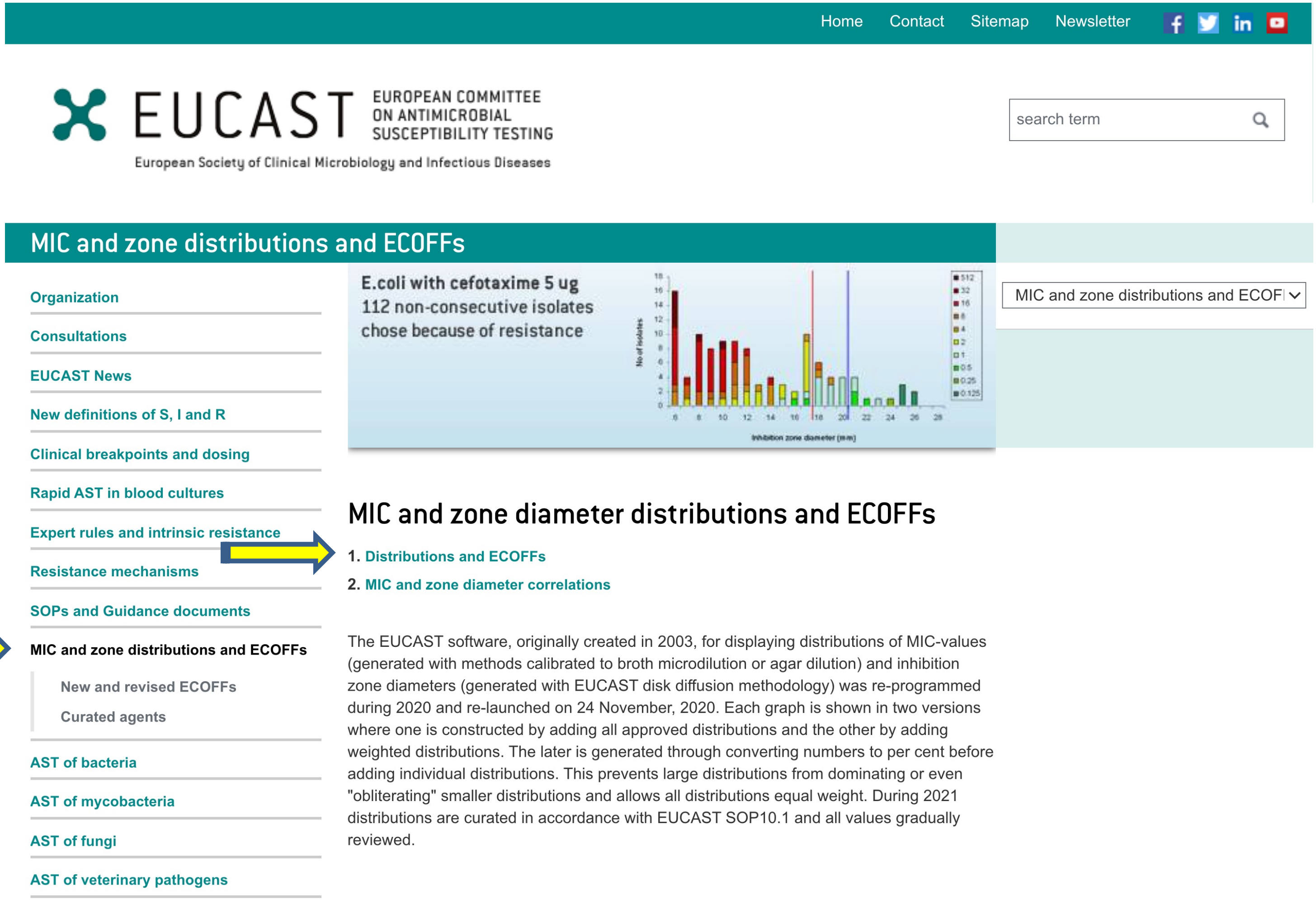






For >20 years EUCAST has systematically gathered MIC (and zone diameter) distributions and made them publicly and freely available

https://mic.eucast.org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search term

MIC and zone distributions and ECOFFs

MIC and zone distributions and ECOFFs

- Organization
- Consultations
- EUCAST News
- New definitions of S, I and R
- Clinical breakpoints and dosing
- Rapid AST in blood cultures
- Expert rules and intrinsic resistance
- Resistance mechanisms
- SOPs and Guidance documents
- MIC and zone distributions and ECOFFs
  - New and revised ECOFFs
  - Curated agents
- AST of bacteria
- AST of mycobacteria
- AST of fungi
- AST of veterinary pathogens

MIC and zone diameter distributions and ECOFFs

1. Distributions and ECOFFs
2. MIC and zone diameter correlations

The EUCAST software, originally created in 2003, for displaying distributions of MIC-values (generated with methods calibrated to broth microdilution or agar dilution) and inhibition zone diameters (generated with EUCAST disk diffusion methodology) was re-programmed during 2020 and re-launched on 24 November, 2020. Each graph is shown in two versions where one is constructed by adding all approved distributions and the other by adding weighted distributions. The later is generated through converting numbers to per cent before adding individual distributions. This prevents large distributions from dominating or even "obliterating" smaller distributions and allows all distributions equal weight. During 2021 distributions are curated in accordance with EUCAST SOP10.1 and all values gradually reviewed.

EUCAST open website for MIC and Zone diameter distributions and ECOFFs was created (https://mic.eucast.org)

MIC EUCAST

Login

Antimicrobial wild type distributions of microorganisms

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

Search database

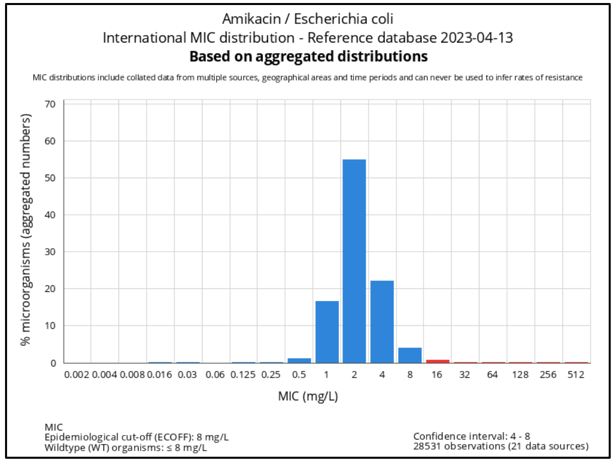
MIC and Inhibition zone diameter distributions of microorganisms without and with phenotypically evident resistance mechanisms

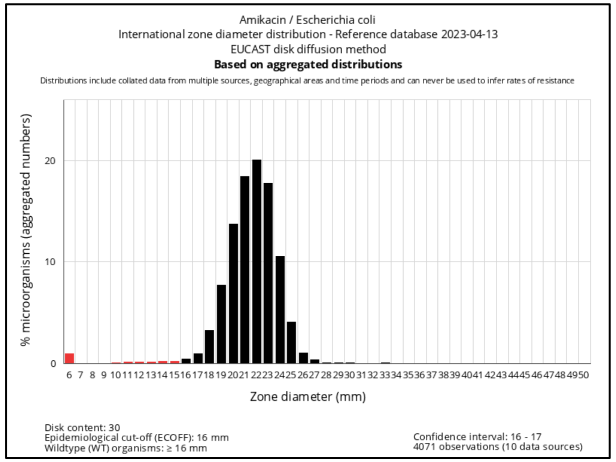
MIC and inhibition zone diameter distributions

The database of MIC and zone diameter distributions was created by Gunnar Kahlmeter for EUCAST from 2002 and onwards. More data is regularly added and all data is curated by Gunnar Kahlmeter and John Turnidge, EUCAST. Distributions are shown as "aggregated distributions" and as "aggregated weighted distributions". For aggregated distributions all accepted distributions (as defined in SOP 10) were added to form one common distribution. For aggregated weighted distributions each individual distribution was converted to contribute equally to the common aggregated distribution. In this way large distributions are prevented from drowning out smaller distributions.

For additional information on “Wild type distributions and ECOFFs”, see Gunnar Kahlmeter & John Turnidge. How to: ECOFFs-the why, the how, and the don'ts of EUCAST epidemiological cutoff values. Clinical Microbiology and Infection 2022 Jul;28(7):952-954. DOI: 10.1016/j.cmi.2022.02.024

Gunnar Kahlmeter & John Turnidge. Wild-type distributions of minimum inhibitory concentrations and epidemiological cut-off values-laboratory and clinical utility. Clinical Microbiology Reviews 2023. DOI: 10.1128/cmr.00100-22





Antimicrobial wild type distributions of microorganisms

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

Search database

Method ● MIC ○ Disk diffusion

Antimicrobial

Cefotaxime

Species

Species...

Elements per page 50

MIC distributions for Cefotaxime, 2024-09-01

Antimicrobial: Cefotaxime (Method: MIC)

	0.002	0.004	0.008	0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	Distributions	Observations	(T)ECOFF	Confidence interval
Acinetobacter baumannii	0	0	0	0	1	0	0	24	4	7	20	72	289	338	127	55	6	88	5	6	1036	64	16 - 512
Citrobacter freundii	0	0	0	1	3	6	47	6	6	3	4	5	3	21	21	7	1	0	0	4	134	(0.5)	0.06 - 2
Citrobacter koseri	0	0	0	0	3	4	3	1	1	2	1	0	0	0	0	1	0	0	0	1	16	ID	
Clostridioides difficile	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	30	139	47	24	1	243	ID	
Corynebacterium diphtheriae	0	0	0	0	0	0	0	0	1	31	166	2	0	0	0	0	0	0	0	2	200	ID	
Corynebacterium ulcerans	0	0	0	0	0	0	0	0	11	175	14	0	0	0	0	0	0	0	0	2	200	ID	
Enterobacter agglomerans	0	0	0	2	4	27	17	2	0	0	2	0	0	0	0	0	0	0	0	1	54	ID	
Enterobacter cloacae	1	2	10	43	137	222	386	341	222	83	54	54	68	101	162	169	78	76	23	28	2232	1	0.25 - 2
Escherichia coli	0	5	37	303	1618	4952	2362	470	189	80	49	47	38	52	71	131	24	31	28	44	10487	0.25	0.125 - 0.25
Escherichia coli ATCC 25922	0	0	0	0	0	33	67	0	0	0	0	0	0	0	0	0	0	0	0	2	100	ID	
Escherichia coli NCTC 13846	0	0	0	0	0	0	0	23	44	0	0	0	0	0	0	0	0	0	0	2	67	ID	
Francisella tularensis	0	0	0	0	1	2	3	4	3	11	5	2	0	0	0	1	0	0	0	1	32	-	
Haemophilus influenzae	42	339	3226	5616	2338	752	136	31	25	12	0	1	0	0	0	0	0	0	0	18	12518	0.06	0.016 - 0.125
Haemophilus influenzae ATCC 49247	0	0	0	0	0	0	21	57	0	0	0	0	0	0	0	0	0	0	0	2	78	ID	
Kingella kingae	0	0	0	53	143	6	0	0	0	0	0	0	0	0	0	0	0	0	0	1	202	ID	

Antimicrobial wild type distributions of microorganisms

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

Search database

Method ○ MIC ◉ **Disk diffusion**

Antimicrobial: Cefotaxime

Species: Species...

Disk content: Disk content...

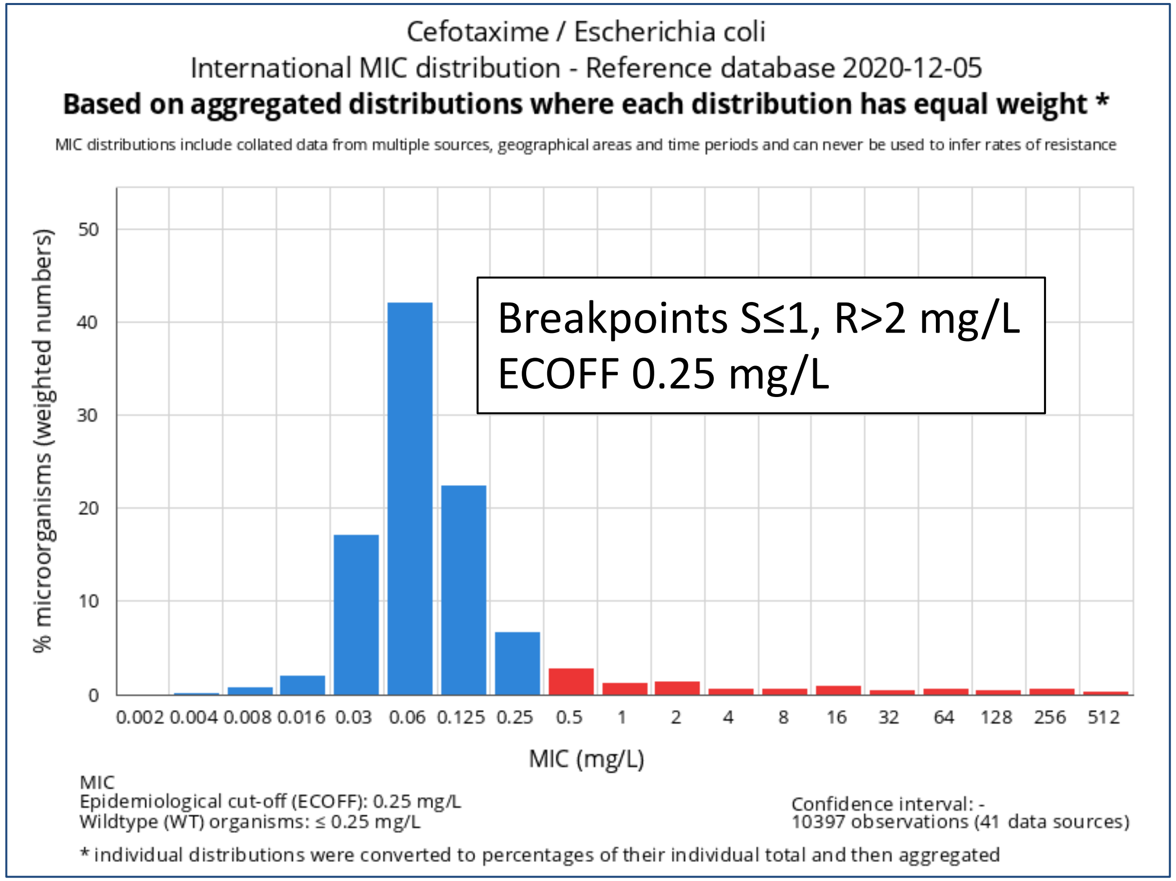
Elements per page 50

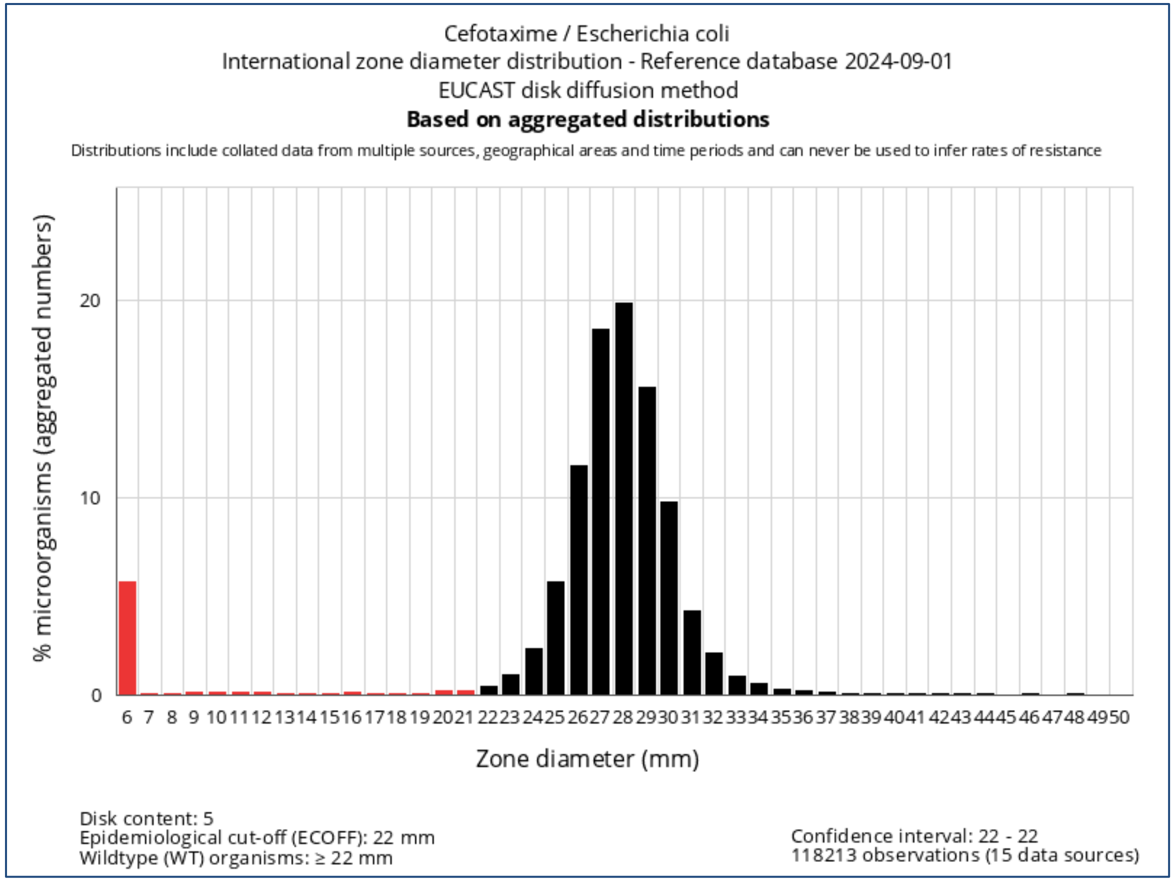
Disk diffusion distributions for Cefotaxime, 2024-09-01

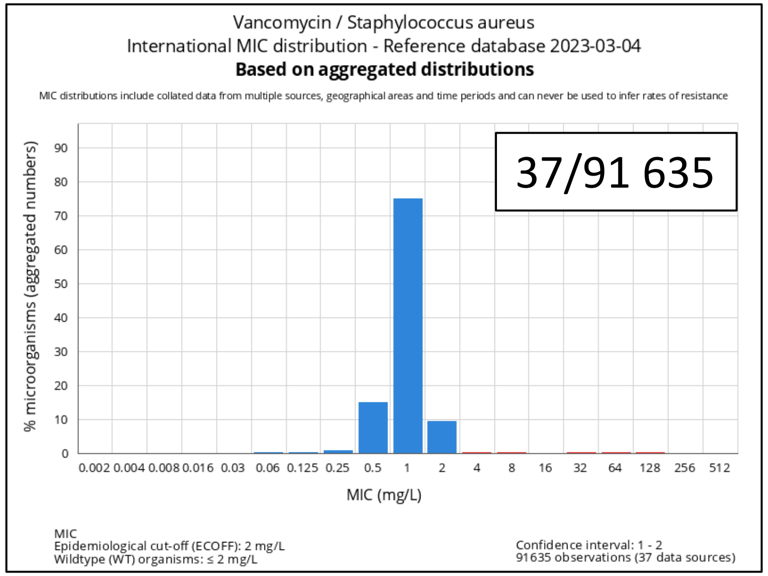
Antimicrobial: Cefotaxime (Method: Disk diffusion)

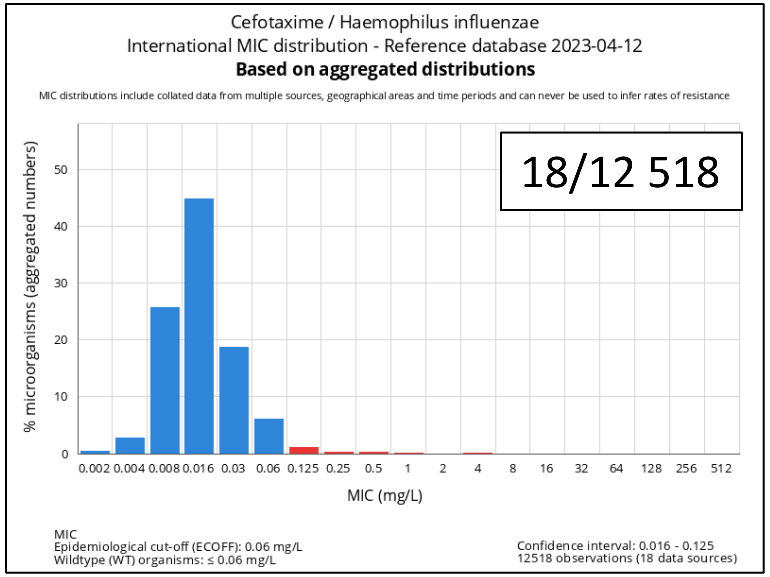
	Disk content	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Aerococcus urinae	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	4	7	7	0
Citrobacter freundii	5	207	0	0	1	4	1	2	2	2	4	2	3	3	2	11	19	41	107	162	246	332	257	113
Citrobacter koseri	5	3	0	0	0	0	0	0	0	2	0	2	0	0	1	5	7	23	42	60	121	133	238	287
Corynebacterium diphtheriae	5	0	0	0	1	0	0	1	0	2	6	4	14	27	52	46	28	11	3	3	1	0	0	1
Corynebacterium ulcerans	5	0	0	0	0	0	0	0	0	0	0	0	0	0	3	12	22	72	52	26	11	1	0	1
Enterobacter cloacae	5	450	0	2	5	12	7	12	7	12	11	10	15	30	36	89	123	195	336	493	522	452	326	142
Escherichia coli	5	6729	23	76	124	109	101	109	67	73	65	103	70	79	66	182	221	510	1210	2750	6708	13686	21867	23404
Haemophilus influenzae	5	0	0	0	0	0	0	0	0	0	0	6	5	10	25	28	22	19	14	10	21	13	210	351
Haemophilus influenzae ATCC 49766	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	11
Kingella kingae	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
Klebsiella aerogenes	5	160	0	5	12	7	9	5	5	5	8	5	8	5	6	15	21	32	71	129	196	250	203	118
Klebsiella oxytoca	5	32	1	0	1	0	3	3	1	2	12	18	22	30	15	24	20	31	62	113	196	388	631	894
Klebsiella pneumoniae	5	914	1	3	13	18	19	24	14	13	22	26	14	15	14	47	73	123	252	519	973	1690	2326	2239
Morganella morganii	5	15	0	1	1	3	7	7	3	8	8	5	6	4	4	9	7	14	8	7	23	47	74	113

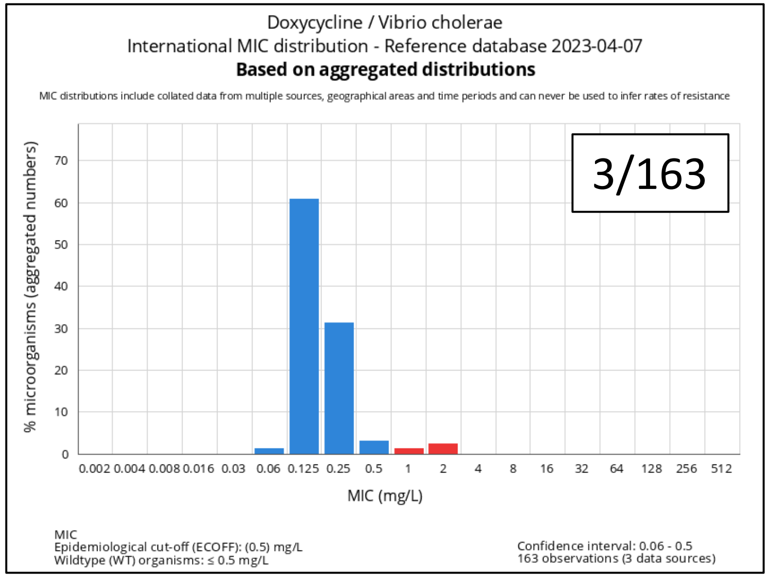
	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	Distributions	Observations	(T)ECOFF	Confidence interval
Aerococcus urinae	7	8	6	7	4	11	10	3	1	2	0	0	0	0	1	0	0	1	0	0	0	0	1	81	-	ID
Citrobacter freundii	50	31	8	4	6	0	1	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	13	1623	21	20 - 21
Citrobacter koseri	219	147	63	31	6	2	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	10	1397	22	22 - 23
Corynebacterium diphtheriae	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	200	-	ID
Corynebacterium ulcerans	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	200	((19))	ID
Enterobacter cloacae	71	52	21	19	9	5	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	13	3466	18	18 - 19
Escherichia coli	18413	11510	4997	2441	1127	632	343	184	99	44	33	29	4	13	1	6	0	3	0	2	0	0	15	118213	22	22 - 22
Haemophilus influenzae	398	481	473	453	359	268	184	118	78	44	26	16	9	1	6	2	2	2	0	2	1	1	5	3658	20	22 - 22
Haemophilus influenzae ATCC 49766	199	491	745	976	872	597	363	109	34	8	1	0	0	0	0	0	0	0	0	0	0	0	26	4409	-	
Kingella kingae	1	1	2	13	7	12	15	26	25	17	16	10	2	4	4	1	1	0	0	1	0	0	1	159	-	ID
Klebsiella aerogenes	57	34	13	5	2	4	1	2	0	2	0	1	0	0	0	0	0	0	0	0	0	0	10	1396	21	20 - 21
Klebsiella oxytoca	894	747	426	203	82	31	11	11	2	2	2	1	0	0	0	0	0	0	0	0	0	0	13	4911	23	22 - 23
Klebsiella pneumoniae	1557	936	420	234	117	60	36	21	9	6	3	8	1	1	0	1	0	0	0	0	0	0	13	12762	21	21 - 22
Morganella morganii	137	131	73	50	25	10	5	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	10	807	24	23 - 24

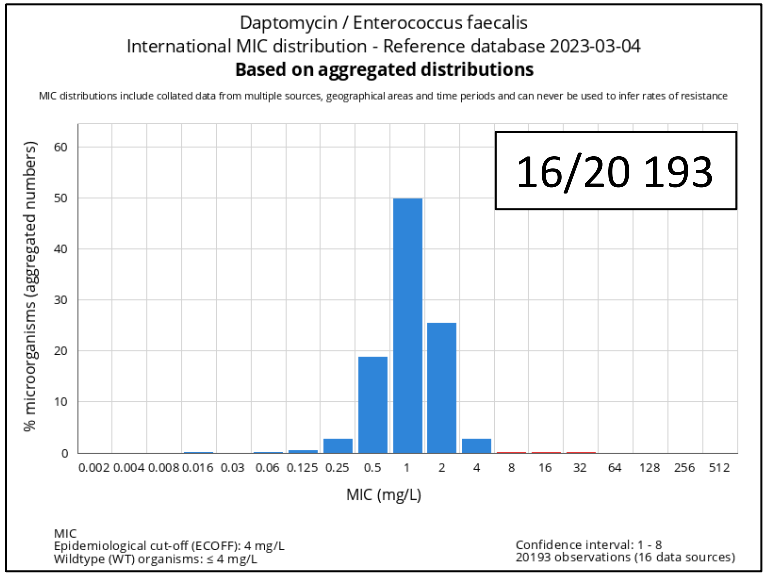

Cefotaxime / Escherichia coli
International MIC distribution - Reference database 2020-12-05
Based on aggregated distributions where each distribution has equal weight *
MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance
Breakpoints S≤1, R>2 mg/L
ECOFF 0.25 mg/L
% microorganisms (weighted numbers)
0
10
20
30
40
50
0.002 0.004 0.008 0.016 0.03 0.06 0.125 0.25 0.5 1 2 4 8 16 32 64 128 256 512
MIC (mg/L)
MIC
Epidemiological cut-off (ECOFF): 0.25 mg/L
Wildtype (WT) organisms: ≤ 0.25 mg/L
Confidence interval: -
10397 observations (41 data sources)
* individual distributions were converted to percentages of their individual total and then aggregated

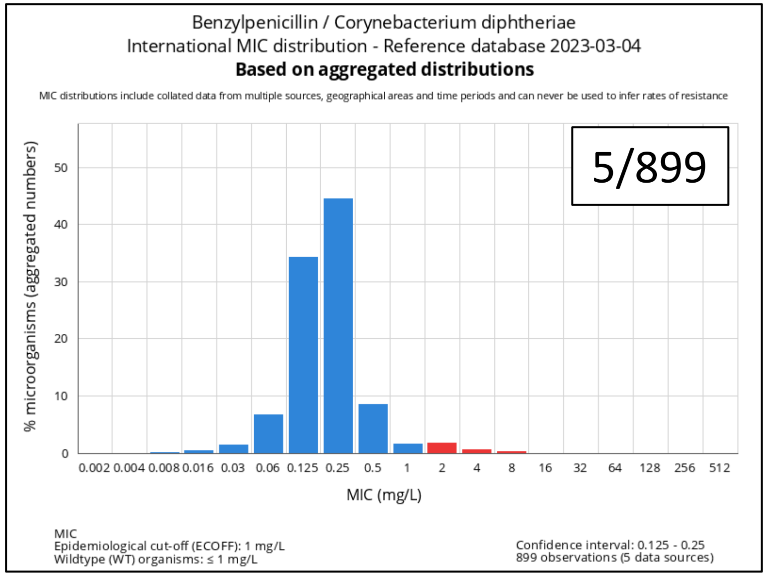

Cefotaxime / Escherichia coli
International zone diameter distribution - Reference database 2024-09-01
EUCAST disk diffusion method
Based on aggregated distributions
Distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance
% microorganisms (aggregated numbers)
0
10
20
6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50
Zone diameter (mm)
Disk content: 5
Epidemiological cut-off (ECOFF): 22 mm
Wildtype (WT) organisms: ≥ 22 mm
Confidence interval: 22 - 22
118213 observations (15 data sources)

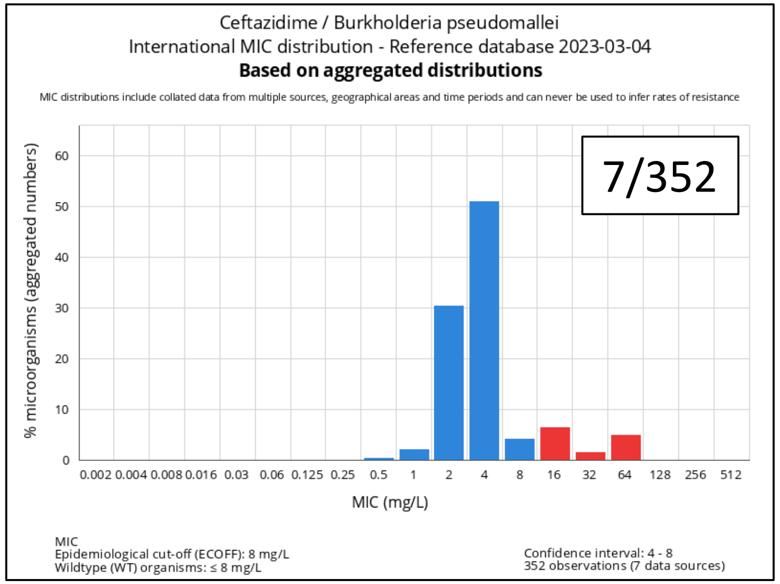












Wild type distributions are stereotype in appearance!

Commonly asked questions:

How are ECOFFs determined and who decides?

What is the relationship between ECOFFs and clinical breakpoints?

How often are clinical breakpoints and ECOFFs the same?

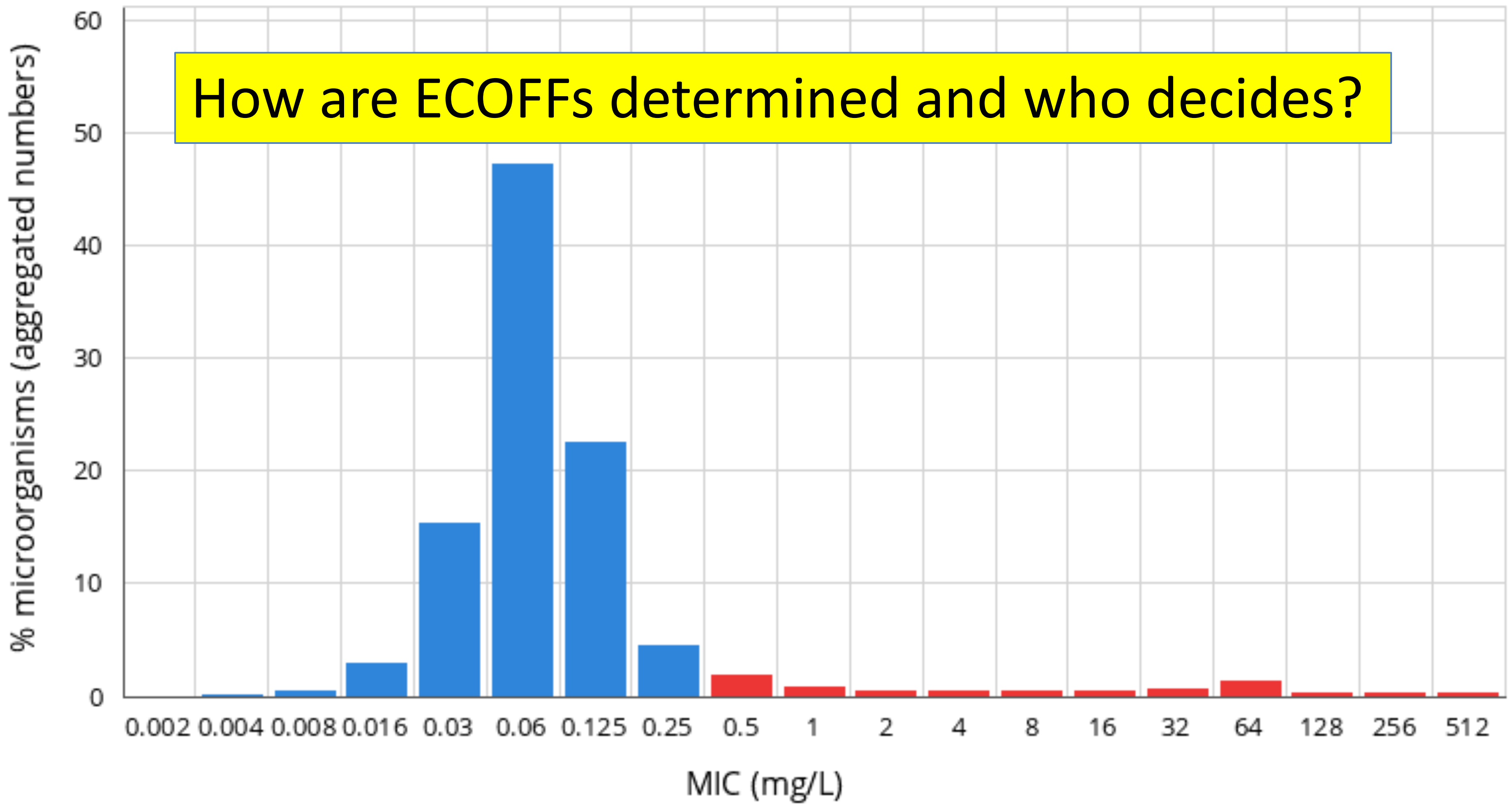
How ECOFFs are determined

- ECOFF requires five acceptable distributions
- TECOFF requires three acceptable distributions
- In the beginning ECOFFs were set using the ”Eye-ball method”
- Later a statistical program (ECOFFinder) to assist was created (J Turnidge).

- Today ECOFFs are
  - Set jointly by the curators of the database
  - Statistical analysis AND a visual inspection
  - Regular review and revision (when data is added)
  - Open invitation for colleagues to (a) submit distributions and (b) be part of the ECOFF setting process and (c) to question the correctness of an ECOFF.

Cefotaxime / Escherichia coli
International MIC distribution - Reference database 2023-03-20
Based on aggregated distributions

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

Confidence interval: 0.125 - 0.25
10487 observations (44 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	1671	205	20	6	2	0	0	1	17	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	4	7	47	310	510	99	12	5	4	1	0	0	1	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	28	108	88	13	3	3	0	1	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	135	37	12	5	5	3	8	3	11	8	14	32	116
0	0	0	0	0	28	41	7	1	1	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	24	181	102	9	0	0	0	2	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	150	2	1	1	2	2	2	4	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	263	8	0	0	6	3	4	3	13	0	0	0
0	0	0	0	15	188	90	7	2	0	0	0	0	0	0	0	0	0
0	0	0	1	29	206	73	7	1	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	294	5	2	2	2	2	2	4	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	292	2	1	0	1	0	0	0	0	0	0	0
0	0	0	0	49	82	85	12	4	2	0	2	1	5	0	0	1	0
0	0	0	0	0	0	593	23	4	8	5	6	2	2	1	0	0	0
0	0	1	4	39	135	38	4	4	1	2	0	3	6	3	1	0	3
0	0	0	17	97	558	251	42	11	6	0	1	0	0	0	0	0	2
0	0	0	19	86	408	390	49	12	3	0	2	1	0	1	0	0	2
0	0	3	42	200	514	49	14	1	4	0	0	1	0	1	0	0	0
0	0	2	1	11	57	25	17	4	6	1	4	1	2	1	1	0	0
0	0	1	1	14	41	36	9	2	2	5	1	0	1	0	3	0	1
0	0	1	3	27	48	22	4	4	2	1	1	0	0	1	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	3	7	2	0	2	0	1	0	1	1	0	0	1	0
0	0	0	2	10	13	1	0	3	1	2	0	0	0	0	0	0	1
0	0	1	0	1	25	81	8	5	2	0	2	1	0	1	1	0	5
0	0	0	2	19	19	60	20	5	4	3	1	1	3	1	0	1	7
0	0	0	0	0	0	1	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	1	0
0	0	4	3	18	20	4	5	6	1	0	1	0	1	0	0	0	0
0	0	0	2	9	10	8	2	3	4	1	0	1	0	0	1	0	0
0	0	1	0	18	24	10	3	6	1	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	8	19	9	4	2	1	1	0	0	0	0	0	0	0
0	0	0	0	13	13	10	6	1	1	1	0	0	0	0	1	0	0
0	0	0	1	7	18	17	2	1	0	0	0	0	0	0	0	1	0
0	0	1	0	7	16	9	8	1	0	0	1	0	1	0	1	0	1
0	0	0	0	12	11	2	7	0	1	1	1	0	0	0	0	0	0
0	0	0	0	4	20	9	6	1	0	1	0	0	0	0	0	1	1
0	0	0	0	0	3	9	2	1	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	1	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	2	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	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	4	16	3	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	17	0	48	29	6	2	0	0	0	0	1	2	0	0	0
0	0	0	17	0	61	22	3	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	1
0	0	2	0	12	43	16	4	1	1	1	0	1	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	1	4	12	0	8	0	0	0	0	0	1	1	0	0	0
0	0	0	0	2	4	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	1	0
0	0	0	7	0	14	7	0	3	0	1	0	1	3	0	2	0	2
0	0	0	0	0	1	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	3	5	62	113	25	8	3	1	0	3	3	5	1	0	1	3
0	0	0	3	18	105	71	12	4	0	1	0	1	7	4	0	8	3

Some MIC distributions are not accepted?

This table consists of 72 MIC distributions for cefotaxime on *E. coli*.

31 were rejected.
41 were accepted.

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	1671	205	20	6	2	0	0	1	17	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	4	7	47	310	510	99	12	5	4	1	0	0	1	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	28	108	88	13	3	3	0	1	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	135	37	12	5	5	3	8	3	11	8	14	32	116
0	0	0	0	0	28	41	7	1	1	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	24	181	102	9	0	0	0	2	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	150	2	1	1	2	2	2	4	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	263	8	0	0	6	3	4	3	13	0	0	0
0	0	0	0	15	188	90	7	2	0	0	0	0	0	0	0	0	0
0	0	0	1	29	206	73	7	1	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	294	5	2	2	2	2	2	4	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	292	2	1	0	1	0	0	0	0	0	0	0
0	0	0	0	49	82	85	12	4	2	0	2	1	5	0	0	1	0
0	0	0	0	0	0	593	23	4	8	5	6	2	2	1	0	0	0
0	0	1	4	39	135	38	4	4	1	2	0	3	6	3	1	0	3
0	0	0	17	97	558	251	42	11	6	0	1	0	0	0	0	0	2
0	0	0	19	86	408	390	49	12	3	0	2	1	0	1	0	0	2
0	0	3	42	200	514	49	14	1	4	0	0	1	0	1	0	0	0
0	0	2	1	11	57	25	17	4	6	1	4	1	2	1	1	0	0
0	0	1	1	14	41	36	9	2	2	5	1	0	1	0	3	0	1
0	0	1	3	27	48	22	4	4	2	1	1	0	0	1	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	3	7	2	0	2	0	1	0	1	1	0	0	1	0
0	0	0	2	10	13	1	0	3	1	2	0	0	0	0	0	0	1
0	0	1	0	1	25	81	8	5	2	0	2	1	0	1	1	0	5
0	0	0	2	19	19	60	20	5	4	3	1	1	3	1	0	1	7
0	0	0	0	0	0	1	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	1	0
0	0	4	3	18	20	4	5	6	1	0	1	0	1	0	0	0	0
0	0	0	2	9	10	8	2	3	4	1	0	1	0	0	1	0	0
0	0	1	0	18	24	10	3	6	1	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	8	19	9	4	2	1	1	0	0	0	0	0	0	0
0	0	0	0	13	13	10	6	1	1	1	0	0	0	0	1	0	0
0	0	0	1	7	18	17	2	1	0	0	0	0	0	0	0	1	0
0	0	1	0	7	16	9	8	1	0	0	1	0	1	0	1	0	1
0	0	0	0	12	11	2	7	0	1	1	1	0	0	0	0	0	0
0	0	0	0	4	20	9	6	1	0	1	0	0	0	0	0	1	1
0	0	0	0	0	3	9	2	1	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	1	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	2	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	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	4	16	3	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	17	0	48	29	6	2	0	0	0	0	1	2	0	0	0
0	0	0	17	0	61	22	3	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	1
0	0	2	0	12	43	16	4	1	1	1	0	1	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	1	4	12	0	8	0	0	0	0	0	1	1	0	0	0
0	0	0	0	2	4	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	1	0
0	0	0	7	0	14	7	0	3	0	1	0	1	3	0	2	0	2
0	0	0	0	0	1	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	3	5	62	113	25	8	3	1	0	3	3	5	1	0	1	3
0	0	0	3	18	105	71	12	4	0	1	0	1	7	4	0	8	3
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

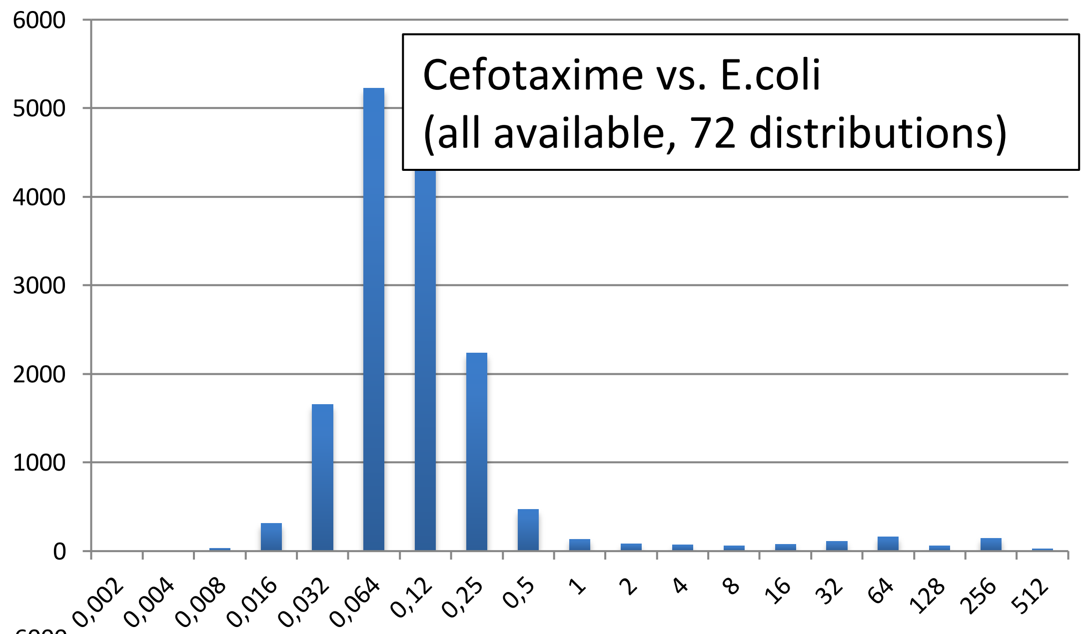
Taking the rules to the cefotaxime distributions?

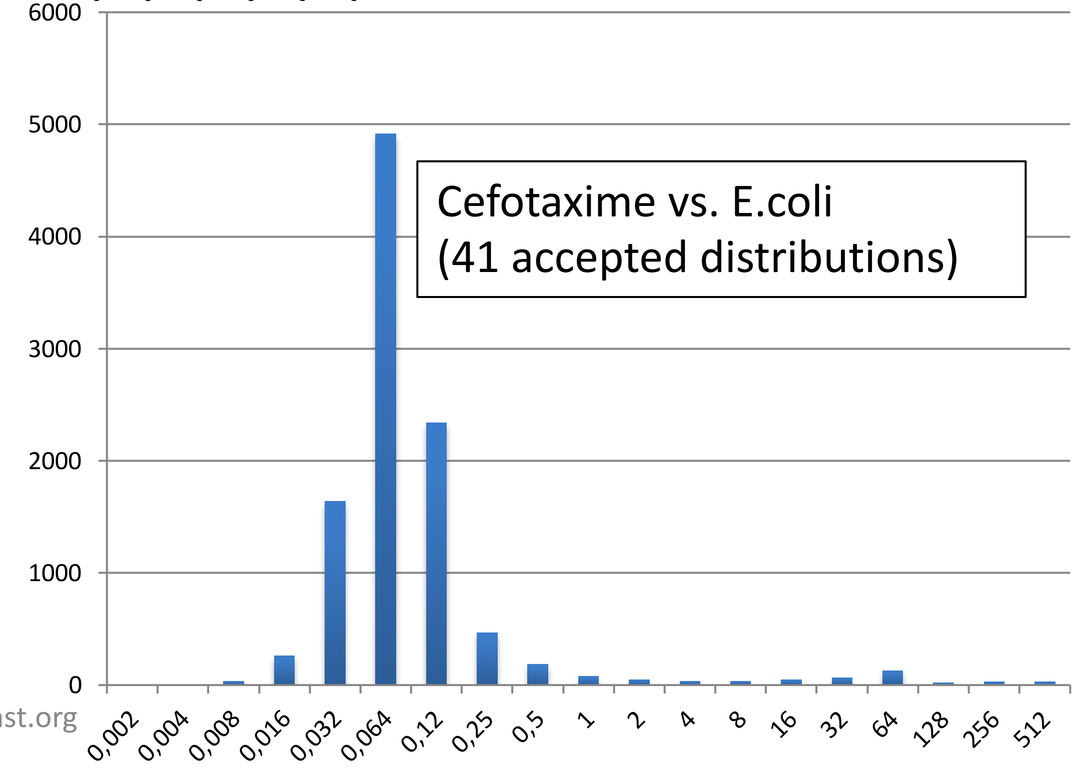
Excluded distributions are marked grey.

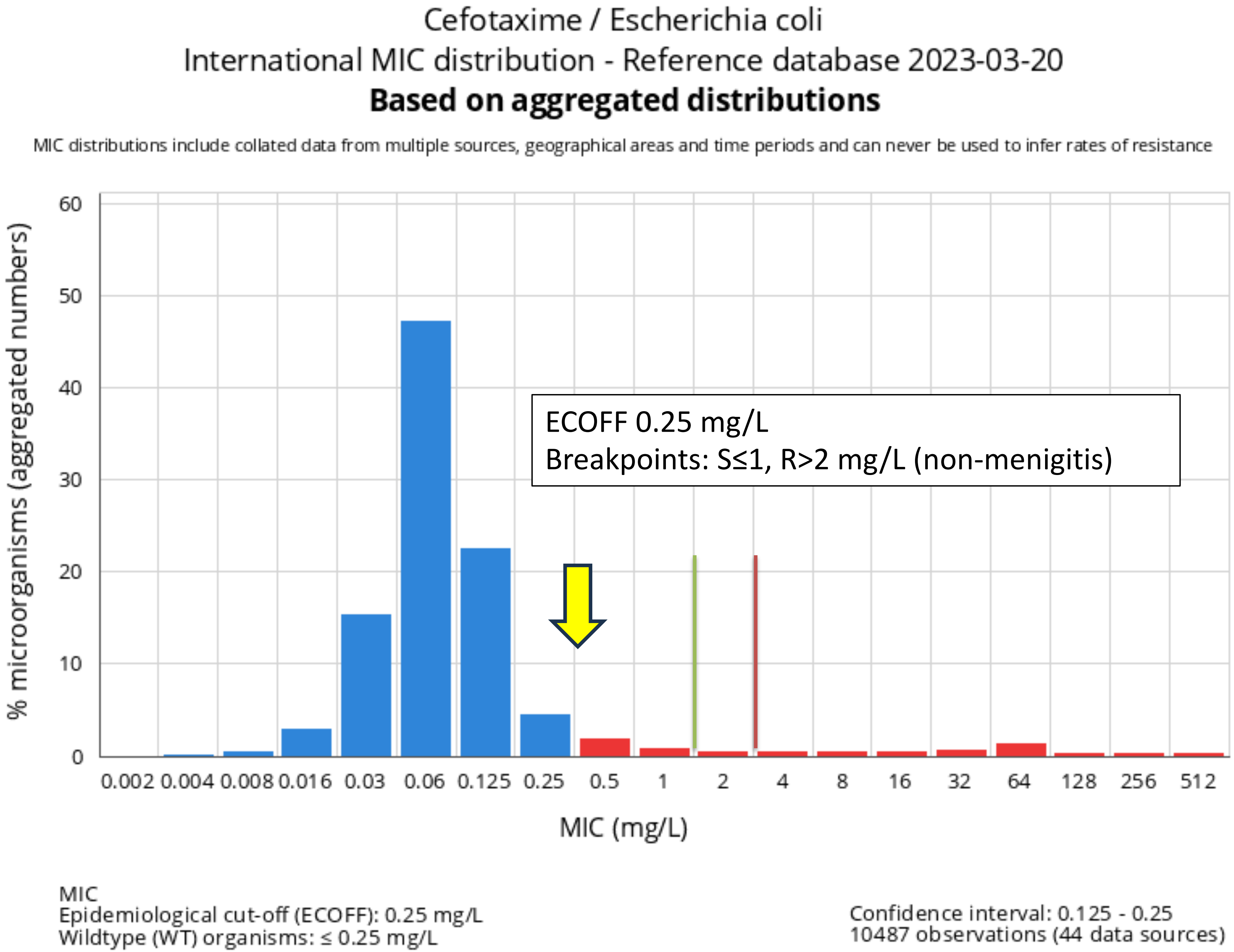
Accepted distributions:
AST method accepted
Full concentration series – no truncation
Sufficient number of isolates to permit identification of WT
Data to permit ECOFF calculation of individual distributions

ECOFF – the mean of ECOFFs of 5 or more accepted distributions.

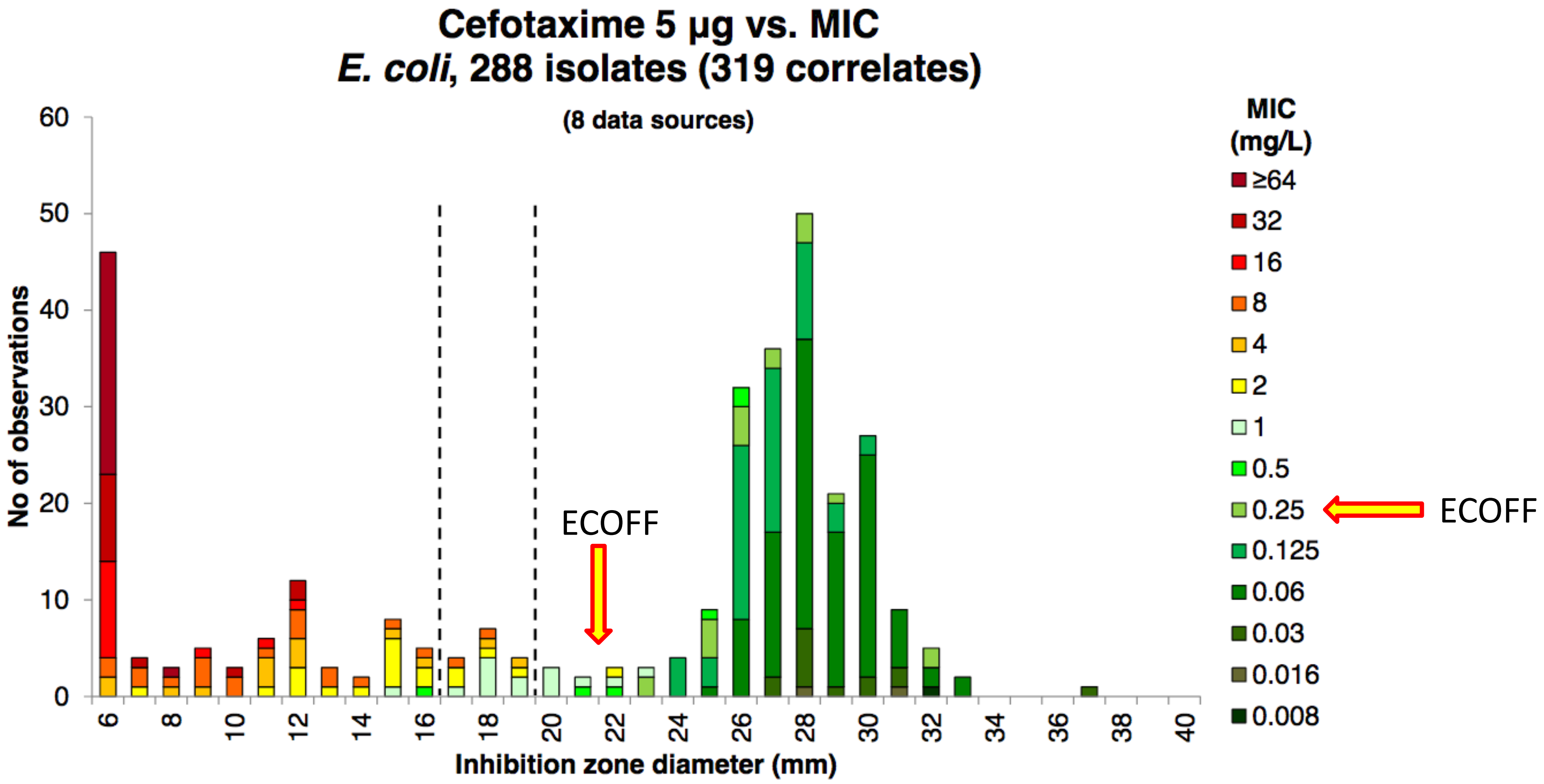
0,002	0,004	0,008	0,016	0,032	0,064	0,12	0,25	0,5	1	2	4	8	126	32	64	128	256
0	0	0	0	0	0	0	1671	205	20	6	2	0	0	1	17	0	0
0	0	0	0	0	4	16	10	4	0	6	1	2	3	0	0	0	0
0	0	3	1	28	51	9	3	3	0	1	1	0	0	0	0	0	0
0	4	7	47	310	510	99	12	5	4	1	0	0	1	0	0	0	0
0	0	1	20	97	185	116	31	33	6	5	3	7	1	42	23	7	0
0	0	0	0	28	108	88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



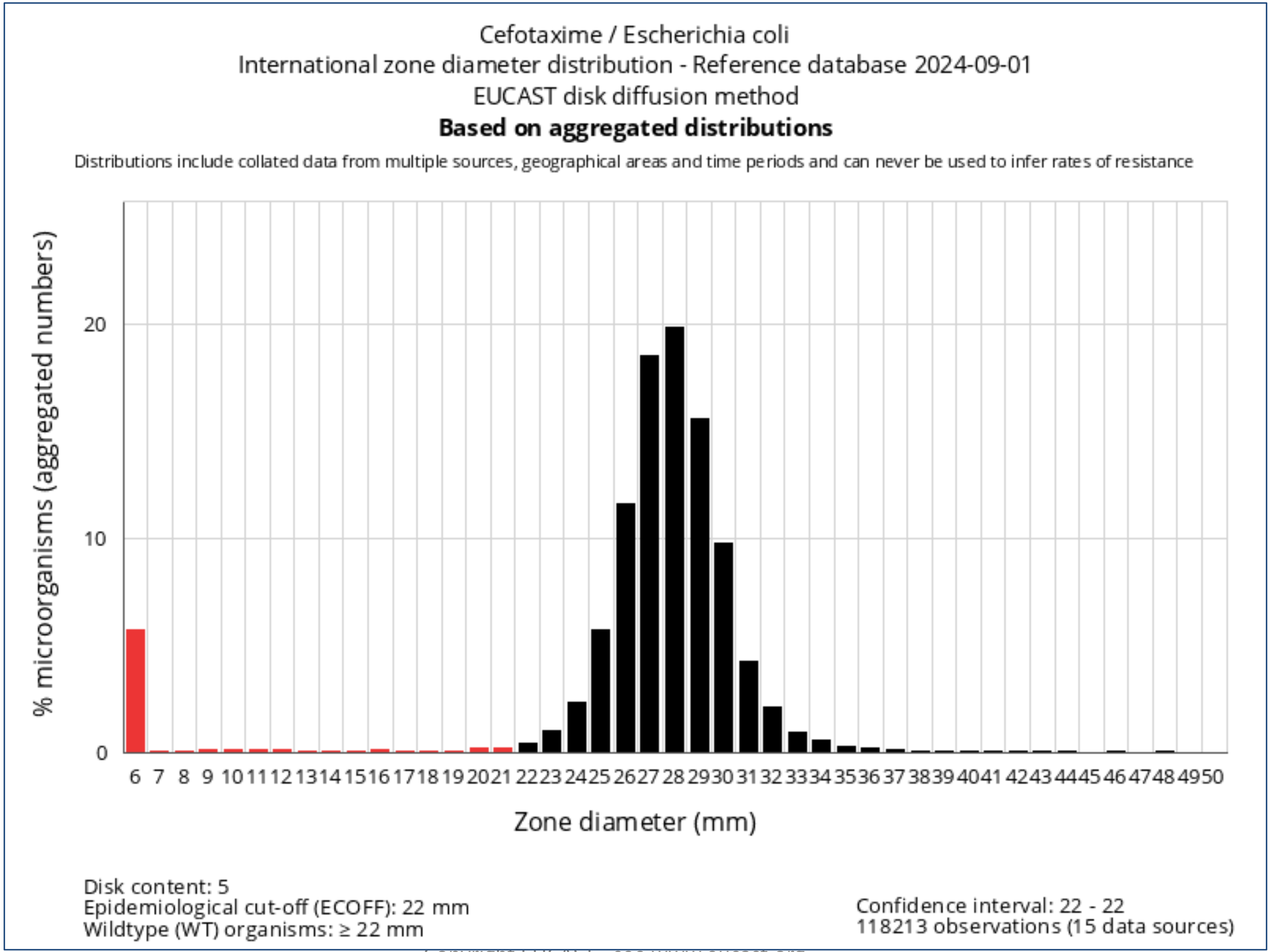



Cefotaxime / Escherichia coli
International MIC distribution - Reference database 2023-03-20
Based on aggregated distributions
MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance
% microorganisms (aggregated numbers)
60
50
40
30
20
10
0
0.002
0.004
0.008
0.016
0.03
0.06
0.125
0.25
0.5
1
2
4
8
16
32
64
128
256
512
MIC (mg/L)
ECOFF 0.25 mg/L
Breakpoints: S≤1, R>2 mg/L (non-menigitis)
MIC
Epidemiological cut-off (ECOFF): 0.25 mg/L
Wildtype (WT) organisms: ≤ 0.25 mg/L
Confidence interval: 0.125 - 0.25
10487 observations (44 data sources)

Checking the validity of MIC ECOFFs using zone diameter distributions.



Breakpoints		ECOFF
MIC	S≤1, R>2 mg/L	0.25 mg/L
Zone diameter	S≥20, R<17 mm	


Cefotaxime / Escherichia coli
International zone diameter distribution - Reference database 2024-09-01
EUCAST disk diffusion method
Based on aggregated distributions
Distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance
% microorganisms (aggregated numbers)
0
10
20
6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50
Zone diameter (mm)
Disk content: 5
Epidemiological cut-off (ECOFF): 22 mm
Wildtype (WT) organisms: ≥ 22 mm
Confidence interval: 22 - 22
118213 observations (15 data sources)

Commonly asked questions:

How are ECOFFs determined and who decides?

What is the relationship between ECOFFs and clinical breakpoints?

How often are clinical breakpoints and ECOFFs the same?

ECOFFs and Clinical breakpoints

- There is no automatic relationship between the ECOFF and a clinical breakpoint
  - The clinical breakpoint can be the same, higher than or below the ECOFF
    - Benzylpenicillin and *Streptococcus pneumoniae* – higher
    - Vancomycin and *Staphylococcus aureus* - the same
    - Gentamicin and Enterococcus species (wild type isolates R)
- Clinical breakpoints should not divide wild type distributions
  - It does not make biological sense since the MIC distribution primarily represents technical variation
  - It will not permit good reproducibility of results in the wild type

Commonly asked questions:

How are ECOFFs determined and who decides?

What is the relationship between ECOFFs and clinical breakpoints?

How often are clinical breakpoints and ECOFFs the same?

Clinical breakpoints = ECOFFs

Species	Agent	ECOFF	Breakpoint
Enterobacterales	Ampicillin, amoxicillin +/-inhibitor	8	8/8
	Piperacillin +/-inhibitor	8	8/8
	Cefadroxil, cefalexin	16	16/16
	Ciprofloxacin	0.12 - 0.25	0.25/0.5
	Gentamicin, tobramycin, netilmicin	2	2/2
	Amikacin	8	8/16
	Tigecycline	0.5 - 1	0.5/0.5
	Colistin	2	2/2
	Fosfomycin (E. coli)	8	4/4
	Nitrofurantoin (E. coli)	64	64/64
	Nitroxoline	16	16/16

Clinical breakpoints = ECOFFs

Species	Agent	ECOFF	Breakpoint
Ps. aeruginosa	Piperacillintazobactam	16	0.001/16
	Cefepime	8	0.001/8
	Ceftazidime, Ceftazidime-avibactam	8 (8)	0.001/8 8/8
	Ceftolozane-tazobactam	4	4/4
	Ciprofloxacin	0.5	0.001/0.5
	Meropenem	2	2/8
	Gentamicin Tobramycin	8 2	- 2/2
	Colistin	4	4/4

Clinical breakpoints = ECOFFs

Species	Agent	ECOFF	Breakpoint
Staphylococcus aureus	Benzylpenicillin	0.12 or 0.064	0.12/0.12
	Ciprofloxacin Moxifloxacin	1 0.25	0.001/1 0.25/0.25
	Amikacin,	16	16/16
	Gentamicin, tobramycin	2	2/2
	Vancomycin	2	2/2
	Macrolides	1	1/2
	Tetracycline	1	1/2
	Linezolid	4	4/4
	Tedizolid	0.5	0.5/0.5
	Chloramphenicol	8	8/8
	Daptomycin	1	1/1
	Nitrofurantoin	64	64/64
	Rifampicin	0.06	0.06/0.06
	Trimethoprim, Trimsulfa		2/4

Clinical breakpoints > ECOFFs

Species	Agent	ECOFF	Breakpoint
Enterobacterales	Pivmecillinam	1	8/8
	Cefotaxime	0.25	1/2
	Ceftriaxone	0.12	1/ 2
	Ceftazidime	0.5	1/4
	Ceftazidime-avibactam	0.5	8/8
	Cefepime	0.12	1/4
	Imipenem	0.5 - 1	2/4
	Meropenem	0.12	2/8
Ps. aeruginosa	--	--	--
Staphylococcus	Ceftaroline, general	0.5	1 / 1
	Ceftobiprole	1	2 / 2

Beta-lactam agents hav low toxicity and a wide dose span

More information on wild type distributions and ECOFFs

- https://mic.eucast.org
- EUCAST SOP10.2

> Clin Microbiol Infect. 2006 Jun;12(6):501-3. doi: 10.1111/j.1469-0691.2006.01454.x.

European Committee on Antimicrobial Susceptibility Testing (EUCAST) Technical Notes on antimicrobial susceptibility testing

G Kahlmeter [1], D F J Brown, F W Goldstein, A P MacGowan, J W Mouton, I Odenholt, A Rodloff, C-J Soussy, M Steinbakk, F Soriano, O Stetsiouk

> Antimicrob Agents Chemother. 2009 Apr;53(4):1628-9. doi: 10.1128/AAC.01624-08. Epub 2009 Feb 2.

Breakpoints for susceptibility testing should not divide wild-type distributions of important target species

Maiken Cavling Arendrup [1], Gunnar Kahlmeter, Juan Luis Rodriguez-Tudela, J Peter Donnelly

Review > Clin Microbiol Rev. 2023 Dec 20;36(4):e0010022. doi: 10.1128/cmr.00100-22. Epub 2023 Dec 1.

Wild-type distributions of minimum inhibitory concentrations and epidemiological cut-off values-laboratory and clinical utility

Gunnar Kahlmeter [1 2 3], John Turnidge [4 5]

Affiliations + expand

PMID: 38038445 PMCID: PMC10732016 DOI: 10.1128/cmr.00100-22

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Turnidge J. • Kahlmeter G. • Kronvall G.

Statistical characterisation of bacterial wild-type MIC value distributions and the determination of epidemiological cut-off values.

Clin Microbiol Infect. 2006; **12**: 418-425

Review > J Antimicrob Chemother. 2015 Sep;70(9):2427-39. doi: 10.1093/jac/dkv145. Epub 2015 Jun 18.

The 2014 Garrod Lecture: EUCAST - are we heading towards international agreement?

Gunnar Kahlmeter [1]

Affiliations + expand

PMID: 26089441 DOI: 10.1093/jac/dkv145

Review > Clin Microbiol Infect. 2022 Jul;28(7):952-954. doi: 10.1016/j.cmi.2022.02.024. Epub 2022 Feb 24.

How to: ECOFFs-the why, the how, and the don'ts of EUCAST epidemiological cutoff values

Gunnar Kahlmeter [1], John Turnidge [2]

Review > Clin Microbiol Rev. 2023 Dec 20;36(4):e0010022. doi: 10.1128/cmr.00100-22.
Epub 2023 Dec 1.

Wild-type distributions of minimum inhibitory concentrations and epidemiological cut-off values-laboratory and clinical utility

Gunnar Kahlmeter [1] [2] [3], John Turnidge [4] [5]

Affiliations + expand

PMID: 38038445 PMCID: PMC10732016 DOI: 10.1128/cmr.00100-22

MIC distributions and ECOFFs on EUCAST website

- >40 000 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, Pharma company development programmes, Veterinarian, Wild life, Food safety programs)
- EUCAST coined the expressions
  - ”Wild type MIC distributions”
  - ”Epidemiological cut-off values (ECOFF)”.
- 25 000 hits per month
- Ownership: ESCMID and contributors

ECOFF is always the same irrespective of when (in time), where (geographical origin), and from whom (humans, animals) the organisms are obtained.

1. The usefulness of MIC wild type distributions and ECOFFs

- A reference
  - A wild-type distribution agreed by many investigators will serve as a reference of agent activity against a defined species.
- A tool in the determination of clinical breakpoints
  - When determining clinical breakpoints, the sequence of the discussion is: (a) identify what is “normal” (the wild type for the species and agent), (b) agree that the wild type is or is not a suitable target for treatment with the agent (if so, the wild type should be categorised S or I), c) discuss whether there is evidence to allow a higher breakpoint than the ECOFF. EUCAST requires that clinical breakpoints should not be set to split wild-type distributions
- As a tool to exclude resistance.
  - The ECOFF provides the most sensitive phenotypic measurement with which to identify and exclude resistance. This is of interest for resistance screening purposes and is often used by EUCAST. Next slide.

2. The usefulness of MIC wild type distributions and ECOFFs

- For surveillance of resistance development
  - Clinical breakpoints are in many ways unsuitable for determination and surveillance of resistance rates.
    - Not sensitive enough; resistance may go undetected
    - Change over time – clinical breakpoints are reviewed and revised at intervals
    - Differ between organisations
- For local, national, and international comparisons
  - Comparison of WT and NWT (via ECOFFs) is largely independent of origin of isolates (in time, geographically and the animal species), methods (as long as non-truncated MIC or disk diffusion) and of course clinical breakpoints.
- In lieu of clinical breakpoints
  - The wild type is not automatically susceptible; some wild type organisms are clinically resistant (*Enterococcus* spp vs. Aminoglycosides; *K.pneumoniae* vs. Ampicillin/amoxicillin).
  - If there is a well-founded clinical experience to successfully use a specific agent and dose for an infection with a specific organism, the ECOFF may be used in lieu of a clinical breakpoint.

3. The usefulness of MIC wild type distributions and ECOFFs

- In therapeutic drug monitoring
  - in therapeutic drug monitoring and dosage adjustment in seriously ill patients, a practice is developing where drug exposure is compared to a measurement of the MIC of the infecting pathogen.

    This is used to estimate whether the patient is receiving sufficient exposure (dosage) to ensure that PK-PD targets are reached.

    Since a single MIC measurement cannot be relied upon (due to the intrinsic variation in assays), it is better to determine whether or not the isolate is WT or NWT for the agent in question, identify the ECOFF and to add one or two dilutions and to then aim for a PK-PD higher than this value.

    This approach guarantees that assay variation has been accounted for, and ensures the highest margin for efficacy should dosage adjustment be required