Better Training for Safer Food

Initiative

Antimicrobial Resistance One Health approach

BREAKPOINT-CUT OFF VALUES: DECISIONS TAKEN UPON THE RESULTS

BTSF

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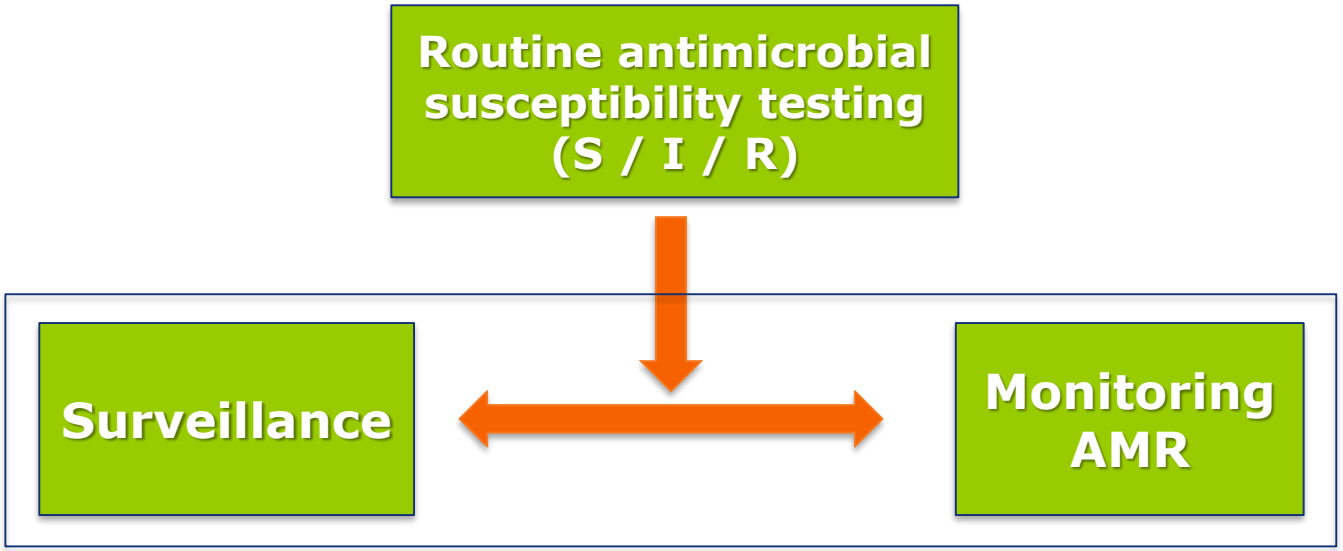
Food safety

Malaga, Spain – 25-28 November 2019


Routine antimicrobial susceptibility testing (S / I / R)
Surveillance
Monitoring AMR

Do we need MIC values in surveillance programs for Public Health?

THE ROLE OF THE MIC VALUE:
Not just a number!

INTERNATIONAL STANDARD **ISO 20776-1**

First edition
2006-11-15

Clinical laboratory testing and *in vitro* diagnostic test systems — Susceptibility testing of infectious agents and evaluation of performance of antimicrobial susceptibility test devices —

Part 1:
Reference method for testing the *in vitro* activity of antimicrobial agents against rapidly growing aerobic bacteria involved in infectious diseases

MIC

- **Microbiological data based in MIC values**
- **PK/PD analysis using MIC values as PD**
- **Clinical outcome correlation with MIC values**

Clinical categories and ECOFFs

Setting MIC clinical breakpoints and ECOFFs

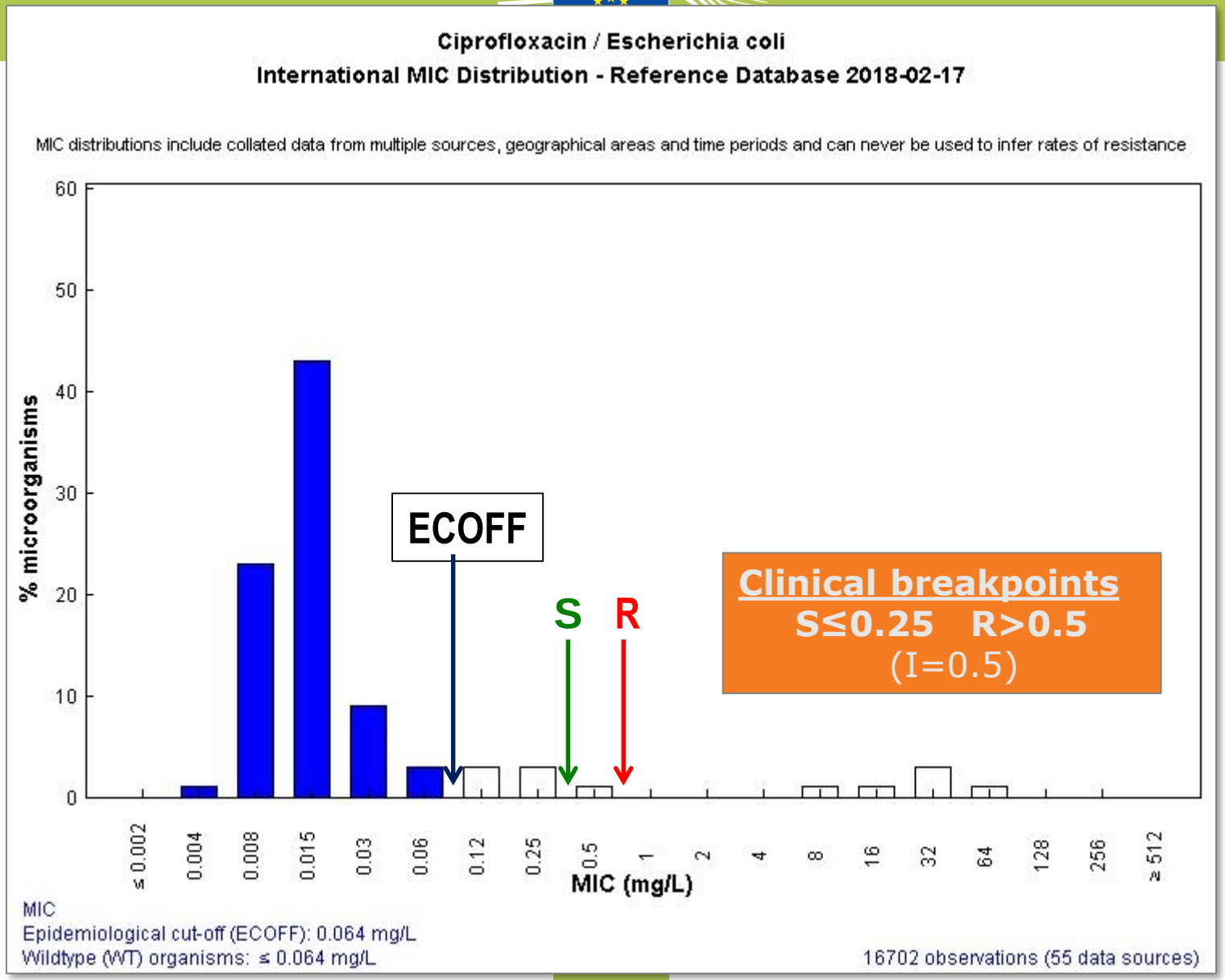
MIC distribution data

- **Methodology**. different processes using a variety of methods
- **Source.** Databases fed by a wide variety of sources
  - Breakpoint committees
  - Individual researchers, human (mainly) and veterinary medicine
  - Surveillance AMR programs programmes in humans and animals
  - EUCAST development projects
  - Food safety projects (EFSA)
  - Environmental studies

ECOFF: ***the highest MIC for organisms devoid of phenotypically detectable acquired resistance mechanisms.***

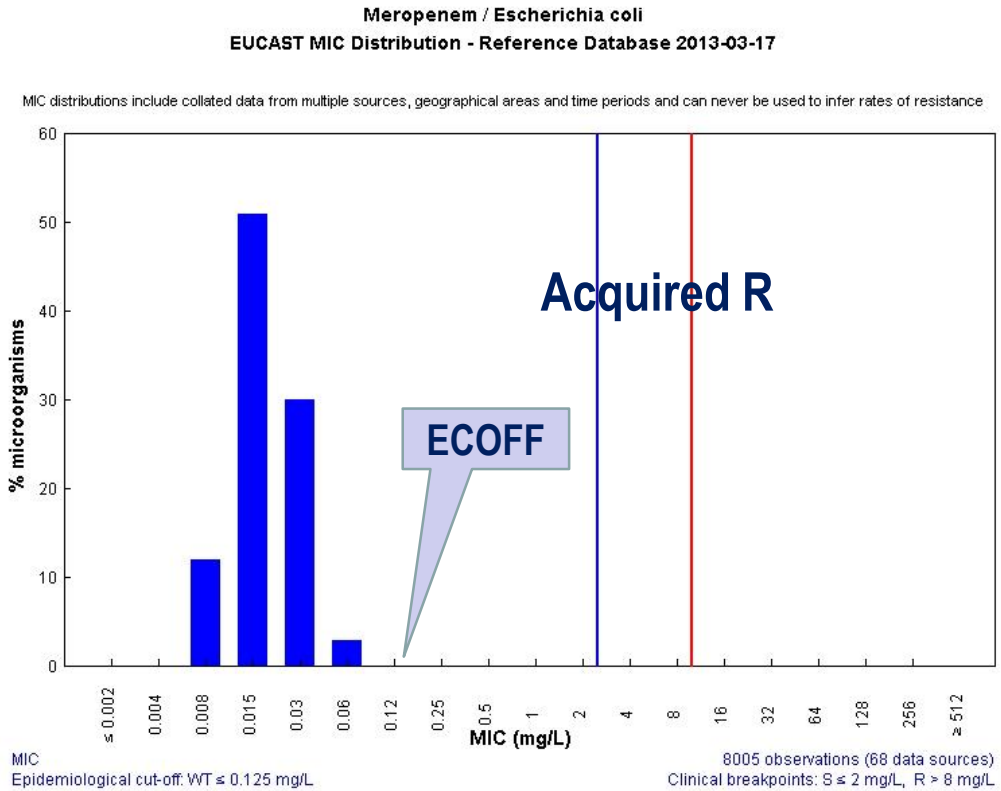
It defines the upper end of the wild-type MIC distribution for a given microbial species and antimicrobial agent.

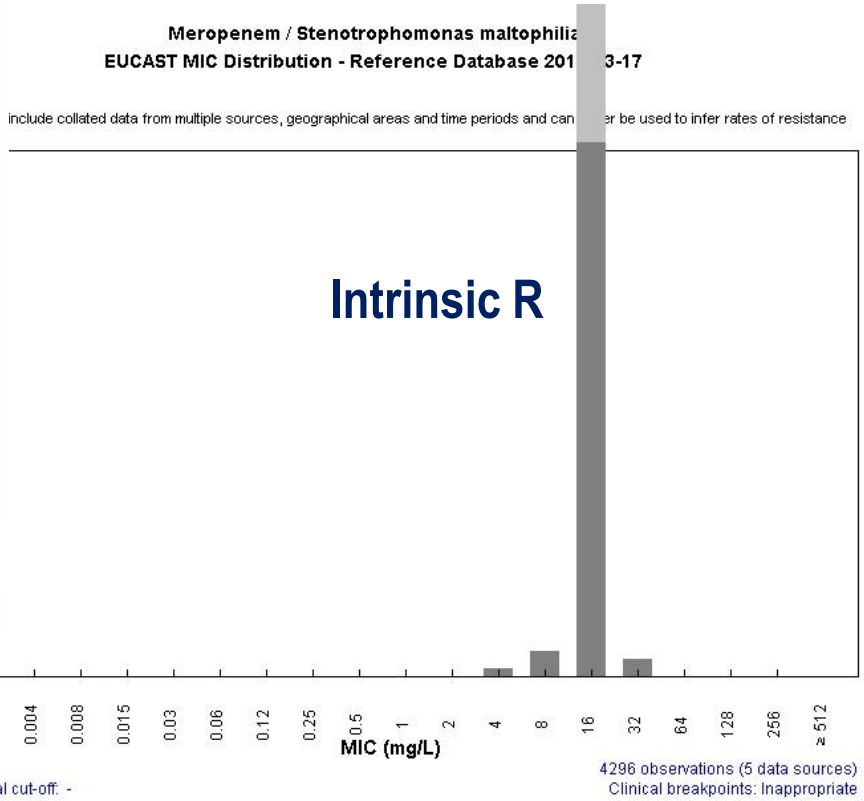
It allows comparing rates of acquired resistance when clinical breakpoints differ (e.g. between organisations, between humans and animals), change over time or have not been set



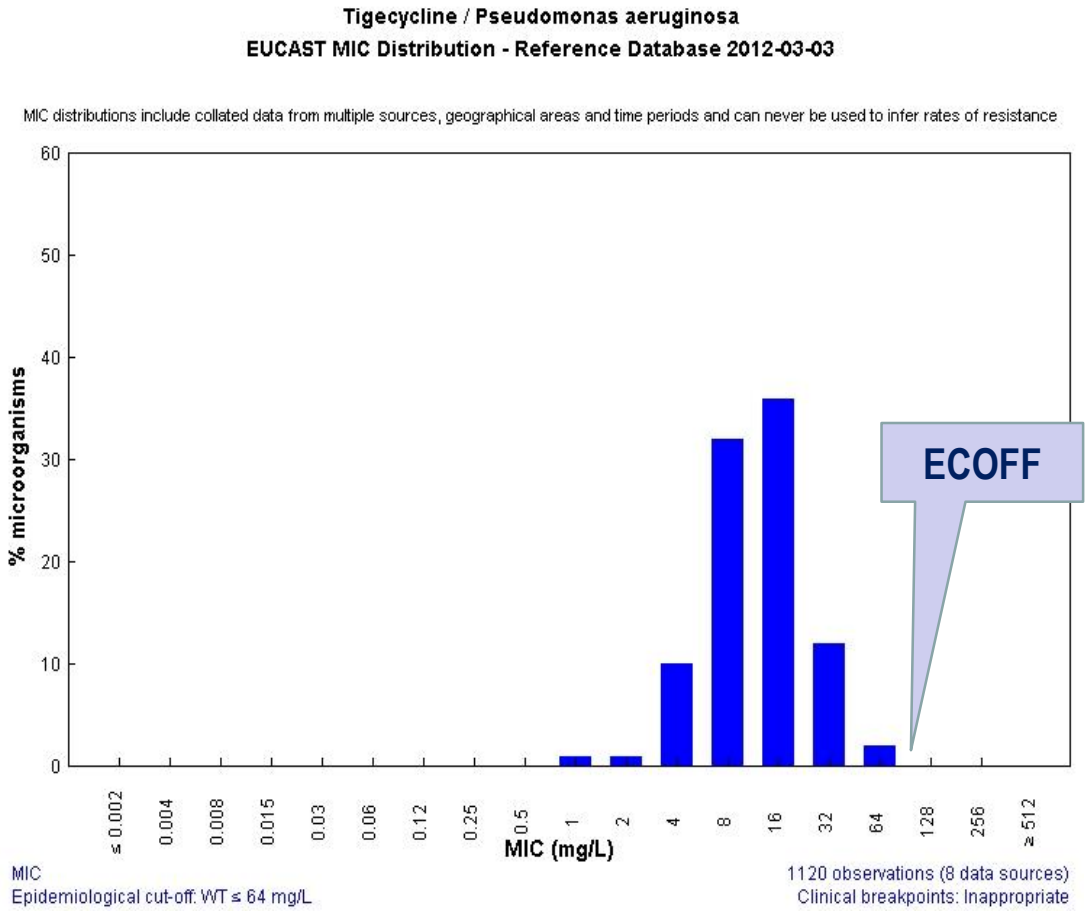
https://mic.eucast.org/Eucast2/

EUCAST, ECOFFs and intrinsic resistance





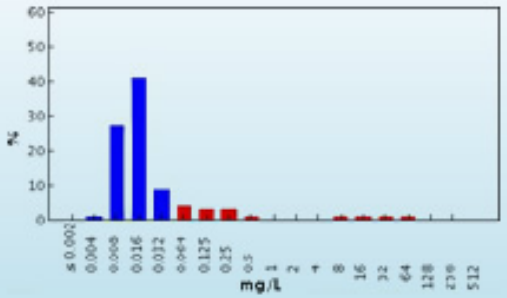
EUCAST, ECOFFs and intrinsic resistance



MIC distributions

- Organization
- EUCAST News
- Clinical breakpoints
- Expert rules
- Resistance mechanisms
- **MIC distributions ECOFFs**
- Zone distributions ECOFFs
- AST of bacteria
- AST of fungi
- AST of veterinary pathogens
- Frequently Asked Questions (FAQ)
- Meetings
- EUCAST Presentations
- Documents
- Translations
- Information for industry
- Links
- Contacts

Ciprofloxacin/Escherichia coli
Anitmicrobial wild type distributions of microorganisms – references database EUCAST



MIC distributions and ECOFFs

Link to the website with MIC distributions and ECOFFs

The website gives MIC distributions (and since 2010 inhibition zone diameter distributions generated with the new EUCAST disk diffusion method) for a wide range of organisms and antimicrobial agents, including antifungals.

The distributions are based on collated data from a total of more than 24000 MIC distributions from worldwide sources. The distributions include MICs from national and international studies such as resistance surveillance programs (Alexander, BSAC, ECO-SENS, MYSTIC, NORM and SENTRY), as well as MIC distributions from published articles, the pharmaceutical industry, veterinary programmes and individual laboratories. Histograms display wild type organisms, together with EUCAST clinical breakpoints and epidemiological cut-off values (ECOFFs). The distributions should **never be referred to in any epidemiological context** since data from many time periods and many countries have been aggregated.

Contributions of MIC and/or Zone diameter distributions can be made using the following Excel file templates:

- MIC distributions organised by agent or species
- Zone diameter distributions organised by agent or species

Please send the completed file to Erika.Matuschek[at]ltkronoberg.se

http://www.eucast.org

European Commission

MIC distributions and ECOFFs

http://www.eucast.org

Distribución de CMIs y ECOFFs

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

Antimicrobial wild type distributions of microorganisms

Search

Method: (•) MIC ( ) Disk diffusion

Antimicrobial: Antimicrobial... Species: Pseudomonas aeruginosa

Species: **Pseudomonas aeruginosa** (Method: **MIC**)

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

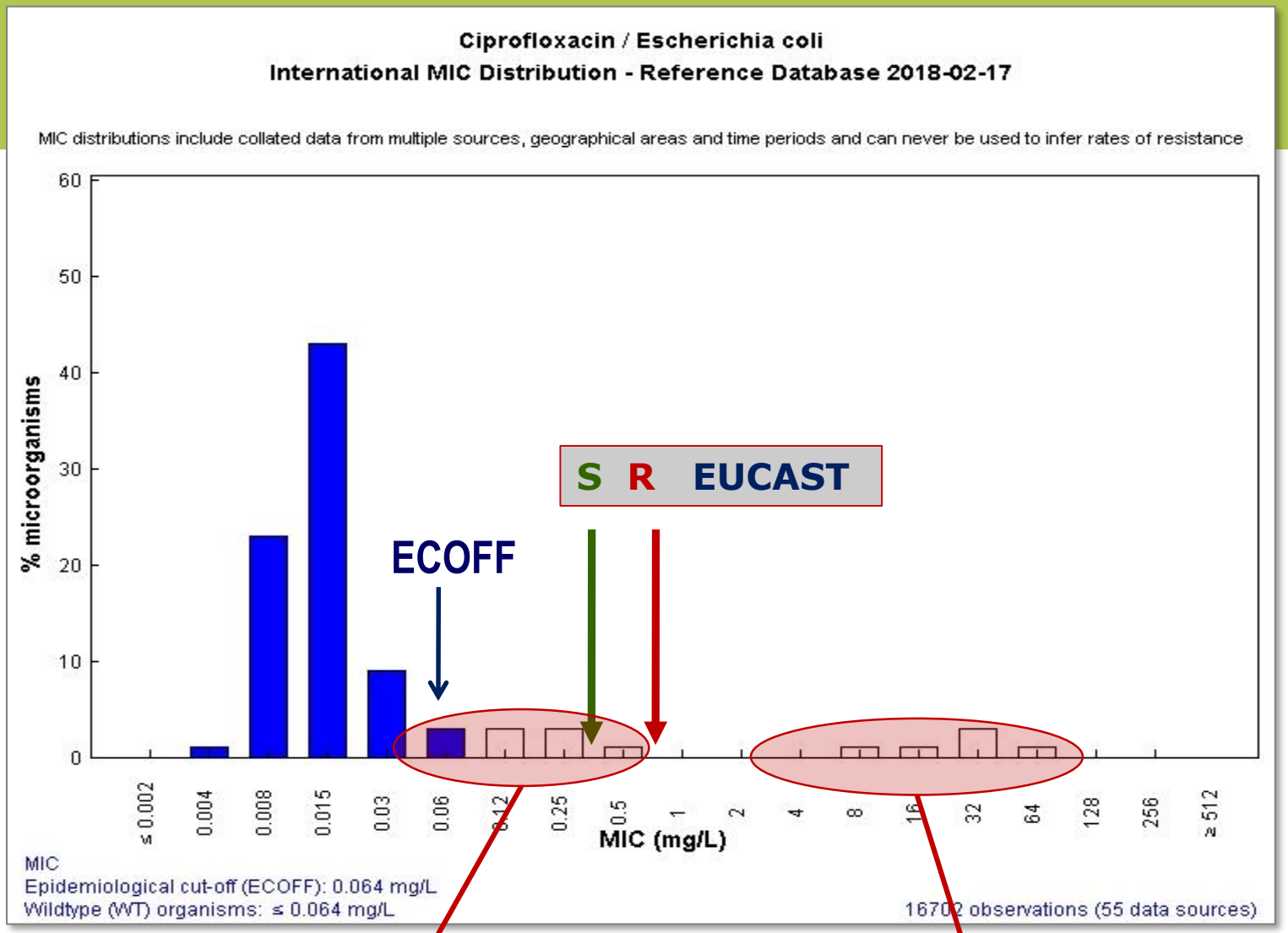
	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
Amikacin	0	0	0	0	0	0	0	93	369	963	5440	6280	2974	997	104	152	19	5	0	16.0
Ampicillin-sulbactam (ratio)	0	0	0	0	0	0	0	1	21	3	5	7	16	24	80	3468	0	0	0	ND
Aztreonam	0	0	0	0	1	2	6	8	62	87	510	1244	509	430	229	61	41	1	0	16.0
Cefepime	0	0	0	1	1	1	99	152	793	3787	10519	7295	6110	4438	3779	113	38	12	0	8.0
Cefotaxime	0	0	0	0	2	3	2	2	10	13	21	93	412	419	274	155	79	14	0	32.0
Cefpirome	0	0	0	0	0	0	0	1	9	135	262	154	77	38	16	6	6	0	0	ND
Cefpodoxime	0	0	0	0	0	0	8	0	3	1	0	0	1	2	2	7	414	0	0	ND
Ceftazidime	0	0	0	1	4	8	31	292	966	5975	12322	6271	2738	1712	815	751	167	117	106	8.0
Ceftobiprole	0	0	0	1	4	11	11	67	446	2209	2134	1437	1373	1435	98	168	0	0	0	ND
Ceftriaxone	0	0	0	0	0	0	0	79	135	239	374	868	2008	2961	4489	21738	9	11	0	ND
Ciprofloxacin	0	0	19	42	535	3046	9340	4559	3234	1882	1501	876	928	516	499	720	137	28	105	0.5
Clinafloxacin	0	0	0	0	12	36	147	336	165	104	51	36	27	0	0	0	0	0	104	ND
Colistin	0	0	0	0	1	5	18	100	913	1818	1146	112	25	45	6	1	12	0	6	4.0
Doripenem	0	0	0	9	80	587	1667	2194	2196	1439	795	878	662	596	45	7	0	0	0	1.0
Ertapenem	0	0	1	2	2	1	21	21	72	178	304	319	286	267	208	218	104	0	105	ND

http://www.eucast.org

Do we need MIC values in surveillance programs for Public Health?

THE ROLE OF THE MIC VALUE: Not just a number!

- More information can be obtained with MICs than when only use clinical breakpoints
- Breakpoints can be modified by different committees over time (resistance rates can be reinterpreted when MICs are available)
- MICs explain differences between different breakpoints
- Clinical breakpoints might be ineffective to detect resistance mechanisms and MICs are useful for this purpose
- MICs can simplify complex resistance mechanisms
- MICs are relevant when using molecular methods for surveillance



Low level R mechanism (*qnr, qyrA* single mutants)

High level R mechanism (*qyrA, parC* double mutants)

https://mic.eucast.org/Eucast2/

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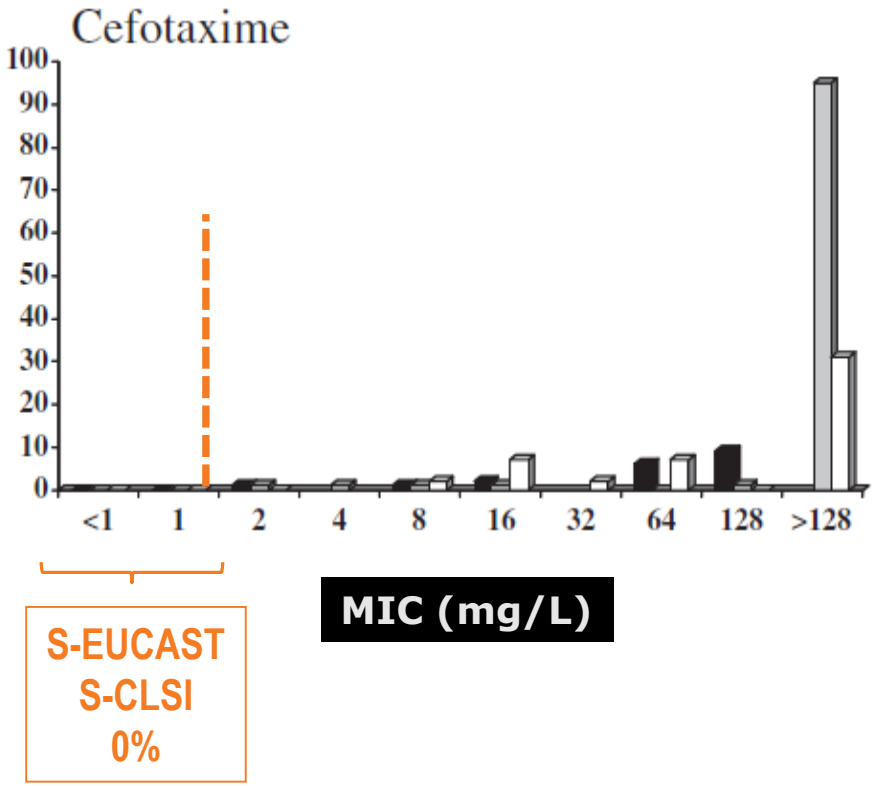
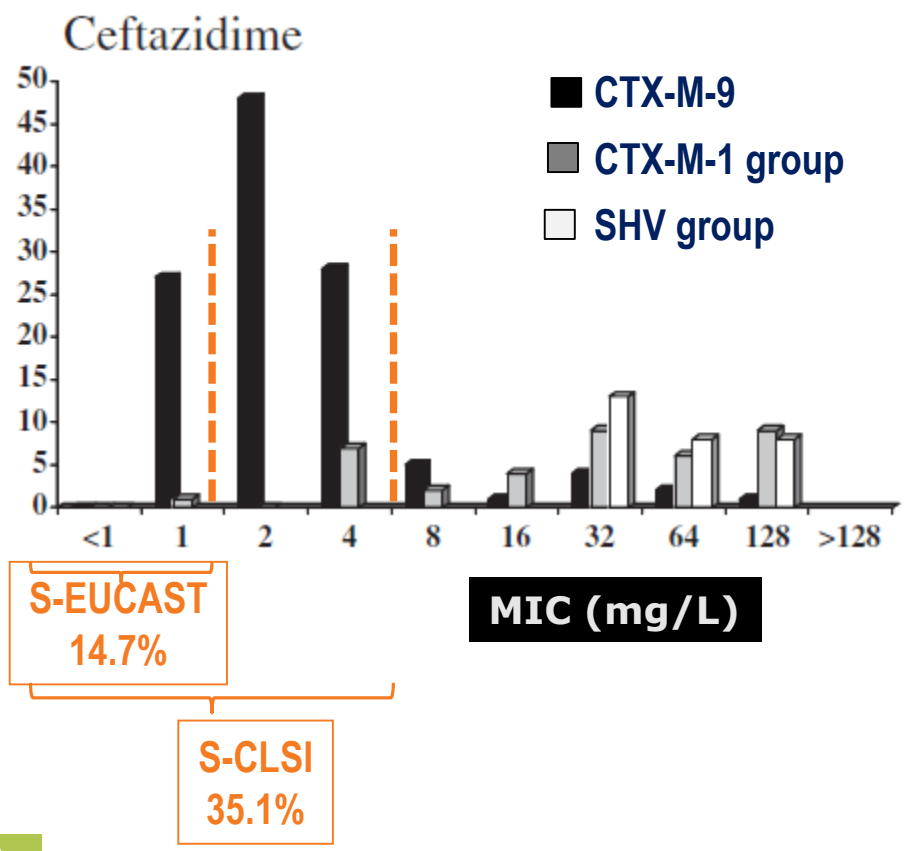
Cephalosporin breakpoints and Enterobacteriaceae

- Impact of CLSI & EUCAST breakpoints in ESBL-*E. coli* blood isolates





Rodriguez-Baño et al. CMI 2012; 18:894-900

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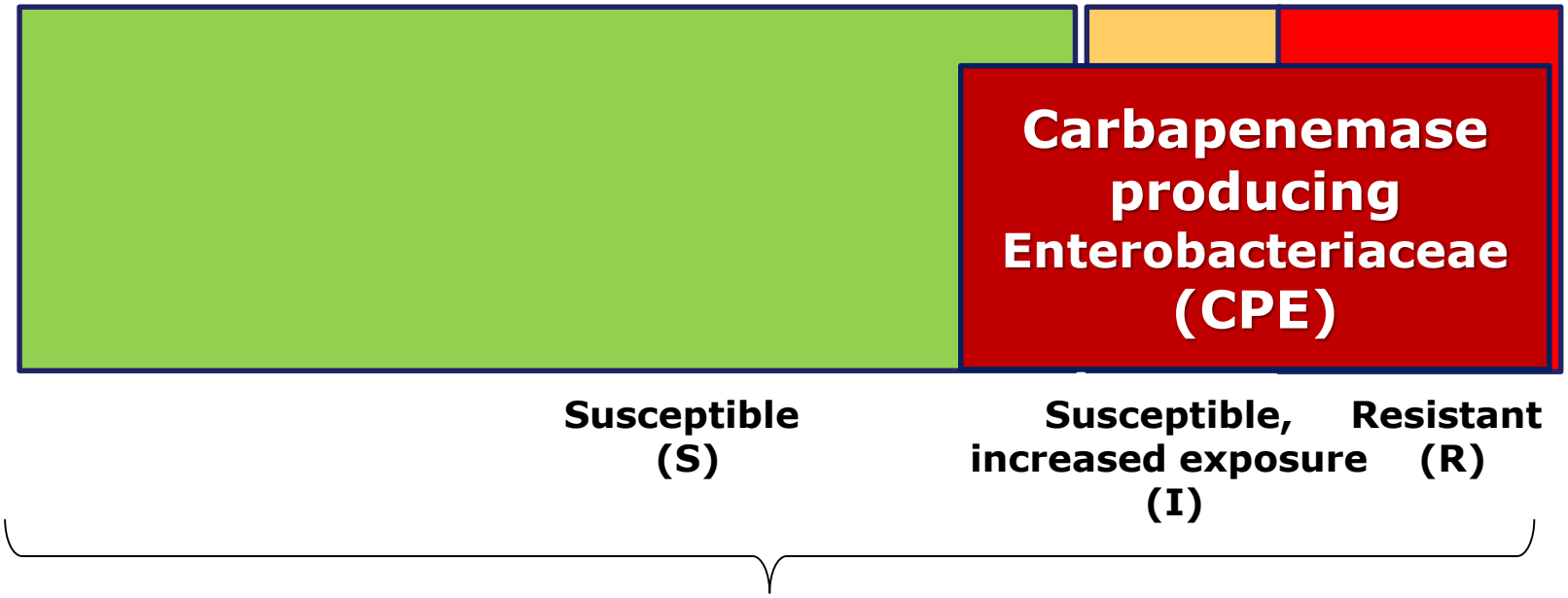
Clinical breakpoints and detection of resistance

- Most carbapenemase producing Enterobacteriaceae are considered resistant (R) to carbapenems but can be also susceptible (S) or intermediate (I)



European Commission

Guidelines for detection of resistance mechanisms and specific resistances of clinical and/or epidemiological importance

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

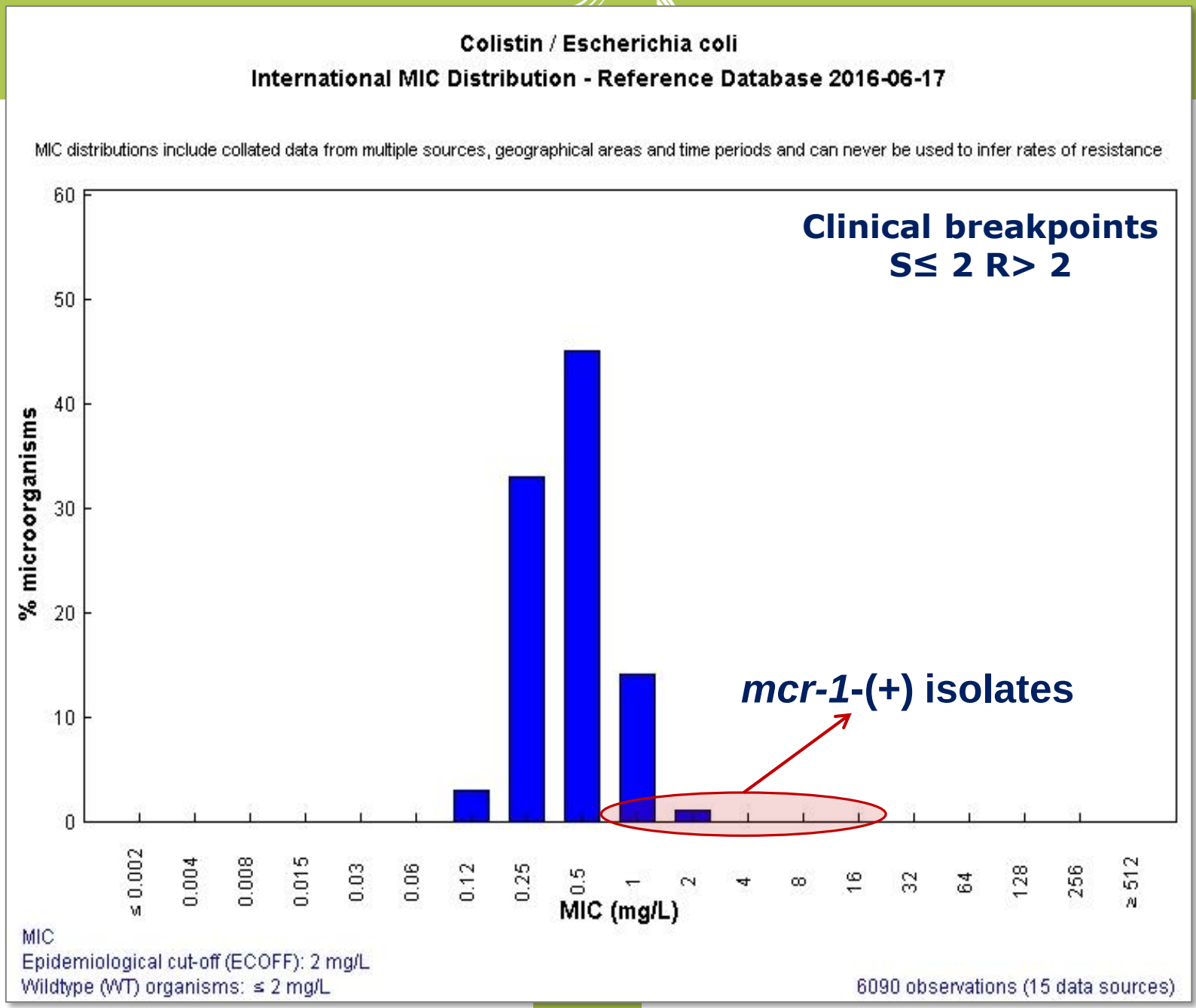
Clinical breakpoints and screening cut-off values for carbapenemase-producing Enterobacteriaceae

Carbapenem	MIC (mg/L)		Disk diffusion zone diameter (mm)	
	S/I breakpoint	Screening cut-off	S/I breakpoint	Screening cut-off
Meropenem[1]	≤2	>0.125	≥22	<25[2]
Imipenem	≤2	>1	≥22	<23
Ertapenem[3]	≤0.5	>0.125	≥25	<25

[1]Best balance of sensitivity and specificity.

[2]In rare cases OXA-48-producers have zone diameters of 24-26 mm, so 27 mm may be used as a screening cut-off during outbreaks, but with significant reduction in specificity.

[3]High sensitivity, but low specificity and therefore not recommended.

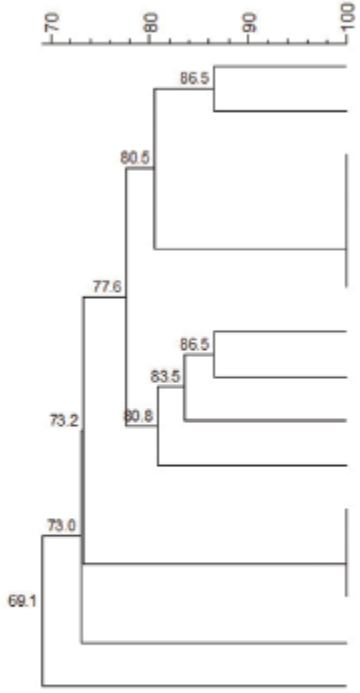

Colistin / Escherichia coli
International MIC Distribution - Reference Database 2016-06-17
MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance
Clinical breakpoints
S≤ 2 R> 2
mcr-1-(+) isolates
% microorganisms
60
50
40
30
20
10
0
≤ 0.002
0.004
0.008
0.015
0.03
0.06
0.12
0.25
0.5
1
2
4
8
16
32
64
128
256
≥ 512
MIC (mg/L)
MIC
Epidemiological cut-off (ECOFF): 2 mg/L
Wildtype (WT) organisms: ≤ 2 mg/L
6090 observations (15 data sources)

RAPID COMMUNICATIONS

Silent dissemination of colistin-resistant *Escherichia coli* in South America could contribute to the global spread of the *mcr-1* gene

Eurosurveillance; 28 April 2016

MR Fernandes [1], Q Moura [2], L Sartori [1], KC Silva [3], MP Cunha [3], F Esposito [1], R Lopes [2], LK Otutumi [4], DD Gonçalves [4], M Dropa [5], MH Matté [5], DF Monte [6], M Landgraf [6], GR Francisco [7], MF Bueno [7], D de Oliveira Garcia [7], T Knöbl [3], AM Moreno [3], N Lincopan [1]



Isolate	Source	Year	State[b]	Resistance profile (Kirby – Bauer)[c]	Colistin MIC (mg/L)[d]	β-lactamase	Phylogroup	PFGE cluster[e]
5.3	Chicken	2013	PR	CRO, CTX, CTF, CPM, TET	8	CTX-M-1	A	A
662	Chicken	2013	SP	–	8	–	A	B
12.3	Chicken	2013	PR	CRO, CTX, TET	16	CTX-M-8	A	C
12.6	Chicken	2013	PR	–	8	–	A	C
6.3	Chicken	2013	PR	CRO, CTX	8	CTX-M-8	A	C
9.6	Chicken	2013	PR	CRO, CTX, CTF, CPM, ENO	8	CTX-M-8	A	C
2.6	Chicken	2013	PR	CRO, CTX, TET	8	CTX-M-15	A	D
3.6	Chicken	2013	PR	TET	8	–	B1	E
5.5	Chicken	2013	PR	CRO, CTX, CTF, CPM, TET	8	CTX-M-15	A	F
146	Swine	2012	SC	AMC, FOX, CLO, SXT, TET	1	CMY-2	A	G
11.3	Chicken	2013	PR	CRO, CTX, CTF, CPM, CIP, ENO	8	CTX-M-8	B1	H
11.8	Chicken	2013	PR	CRO, CTX, CTF, CPM, CIP, ENO	8	CTX-M-8	B1	H
9.3	Chicken	2013	PR	CRO, CTX, CPM, CIP, ENO	8	CTX-M-8	B1	H
96	Chicken	2013	MG					
5.2.1	Chicken	2013	PR					
171	Swine	2012	MG					

mcr-1 gene can be also present in colistin-susceptible *E. coli* isolates

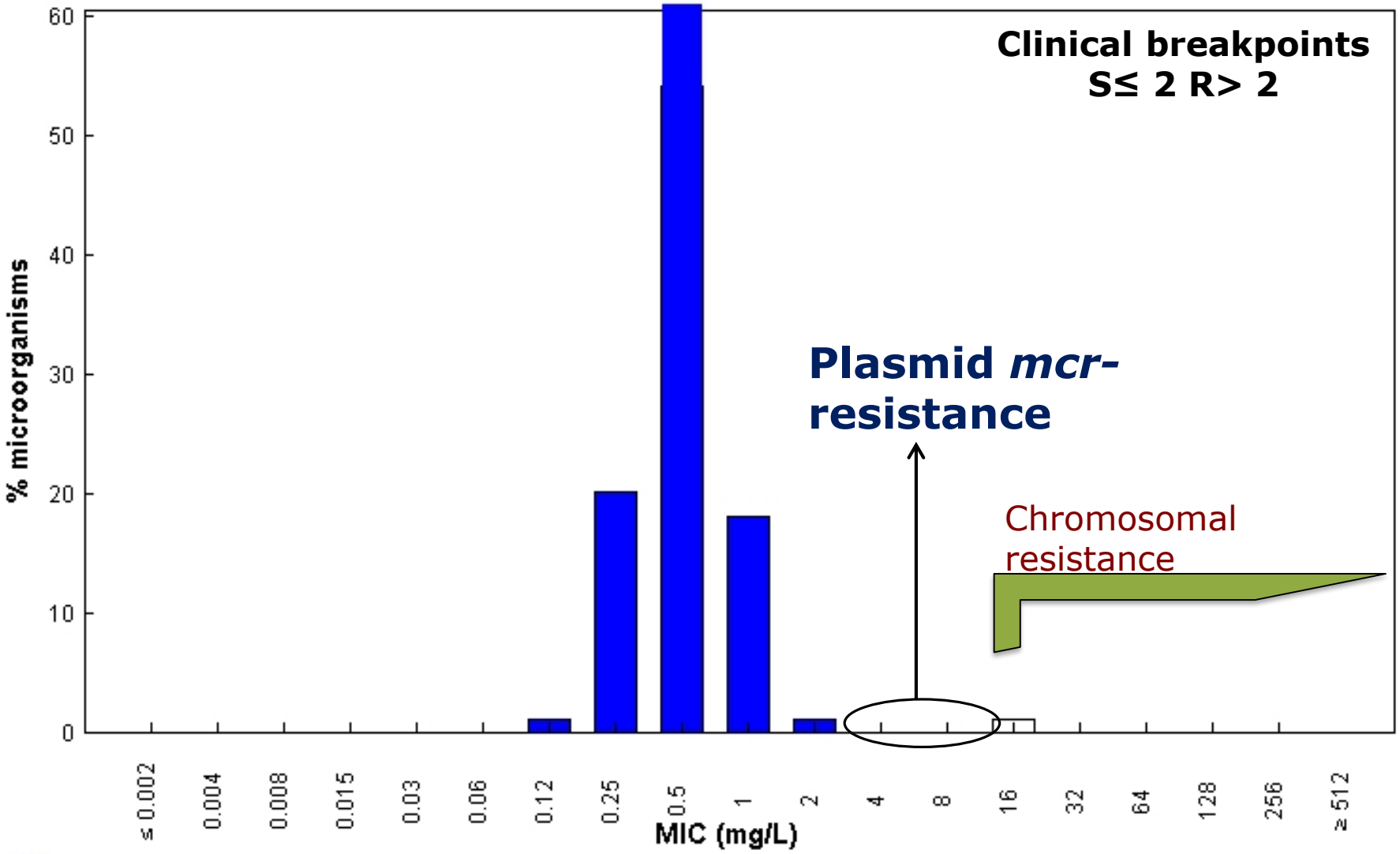
MIC: minimum inhibitory concentration; nt: non typeable by PFGE.

GenBank accession number for mcr-1 genes identified in this study: KU750813, KU928239–42, KU935441–9, KX01152–1.

Colistin / Klebsiella pneumoniae

International MIC Distribution - Reference Database 2017-12-10

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

2237 observations (10 data sources)

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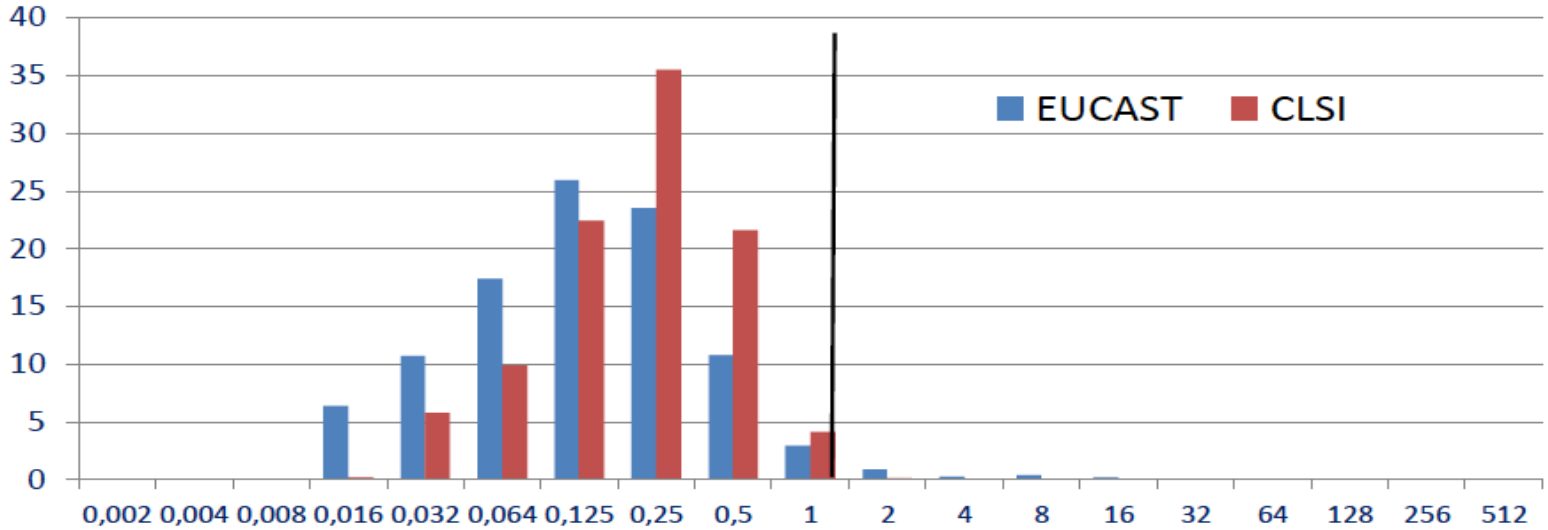
Neisseria gonorrhoeae and azithromycin

CLSI and EUCAST data base



Criteria	Breakpoint		ECV - ECOFF	
	CLSI	EUCAST	CLSI	EUCAST
S	-	≤ 0.25	≤1	≤1
I	-	0.5		
R	-*	> 0.5		

* NWT: 2 mg/L

Kirkcaldy *el al*. Antimicrob Agents Chemother 2015; 59: 998-1003 CLSI M100-S27
www.eucast.org

Neisseria gonorrhoeae and azithromycin

Resistance mechanisms

- Different levels of resistance caused by different resistance mechanisms

High level resistance (MICs ≥256 mg/L)

- 23S rRNA gene mutations (A2059G) (3 or 4 of the 4 alleles)

Low to moderate level (MICs 2-32 mg/L)

- 23S rRNA gene mutations (C2611T) (3 or 4 of the 4 alleles)
- 23S rRNA methylases *(ermA, ermB, ermC, and ermF)*
- Eflux pumps:
  - MtrCDE overexpression (35A deletion in the promoter of *mtrR* repressor)
  - MtrR A39T and G45D mutations
  - MacAB
  - *mef*
- mutations in the ribosomal genes: *rplD, rplV*

- Presence of different resistance mechanisms

Chisholm *et al*. AAC. 2010; 54: 3812–6
Demczuk *et al*. JCM. 2016; 54: 1304-13
Kirkcaldy *el al*. AAC 2015; 59: 998-1003

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Clinical Microbiology and Infection 23 (2017) 2–22

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Review

The role of whole genome sequencing in antimicrobial susceptibility testing of bacteria: report from the EUCAST Subcommittee

M.J. Ellington [1, †], O. Ekelund [2, †], F.M. Aarestrup [3], R. Canton [4], M. Doumith [1], C. Giske [5], H. Grundman [6], H. Hasman [7], M.T.G. Holden [8], K.L. Hopkins [1], J. Iredell [9], G. Kahlmeter [2], C.U. Köser [10], A. MacGowan [11], D. Mevius [12, 13], M. Mulvey [14], T. Naas [15], T. Peto [16], J.-M. Rolain [17], Ø. Samuelsen [18], N. Woodford [1, *]

…**the MIC**… reflects more than gene presence / absence; … multiple and complex interplays between different systems including cellular permeability, influx/efflux, target availability and binding as well as enzymatic expression levels and activities.

… the primary AST comparator for WGS-based prediction should be the **ECOFF**, wherever possible, in order to assess WGS--inferred 'antibiograms' (based on gene positivity) against phenotypically-defined categories of wild-type or non-wild-type.

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Food safety