ECOFF

MIC wild type distributions and epidemiological cut-off values

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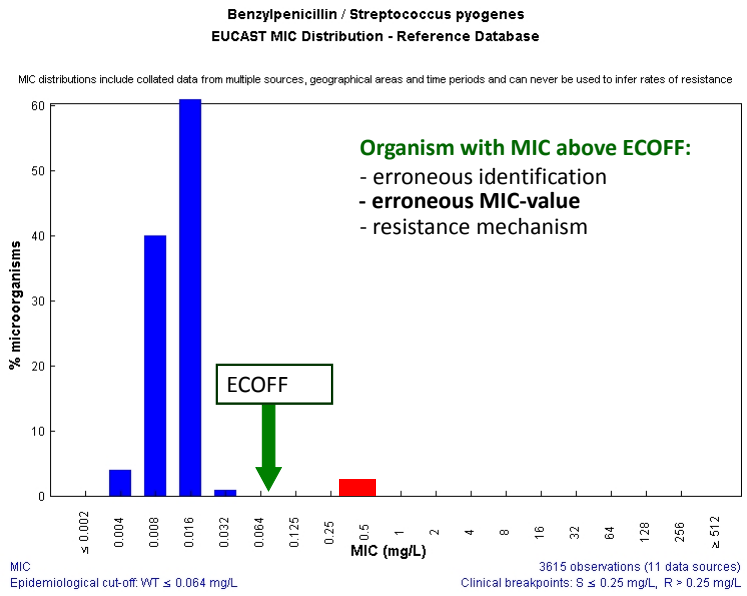
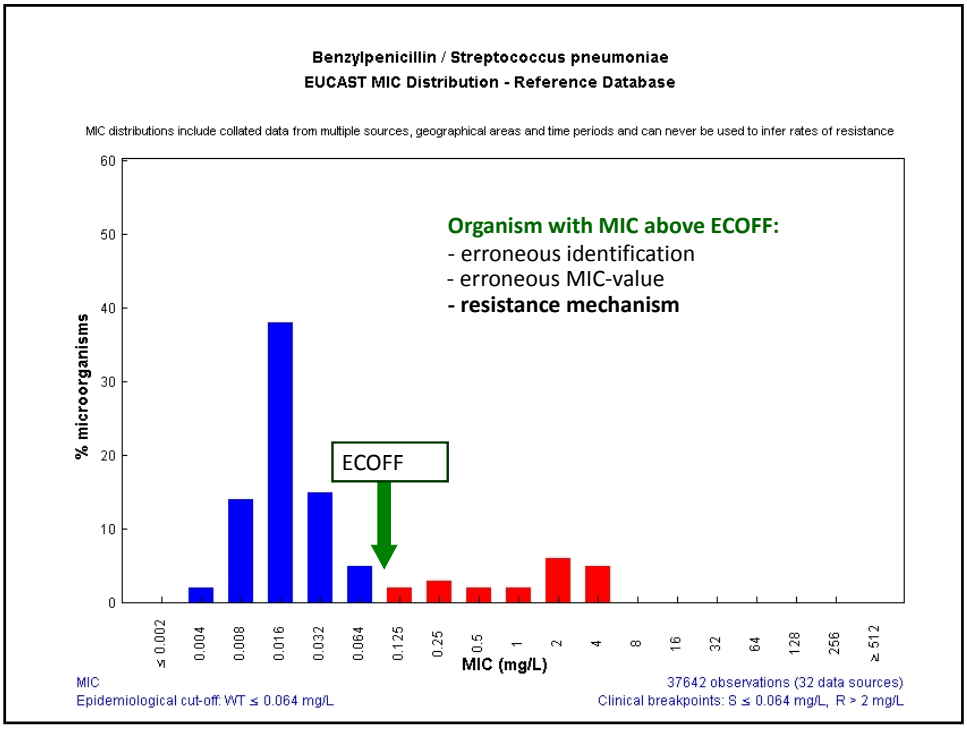




Breakpoints

- The ECOFF
  - The ECOFF distinguishes between organisms **without** and **with** phenotypically expressed resistance mechanisms for a species and a drug in a defined test system.
  - 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.
- The Clinical breakpoint
  - 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.

Establishing ECOFFs

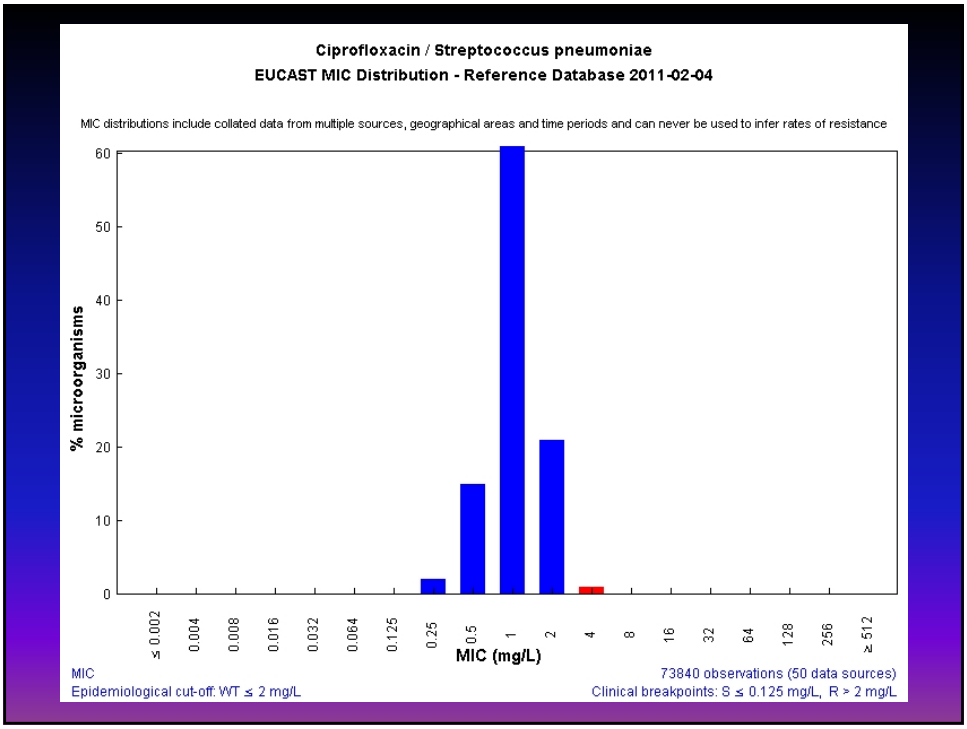
- ECOFFs should only be determined on
  - MICs determined with methods calibrated to the internationally agreed standard method for broth micro dilution (ISO)
  - large quantities of MICs (n>100, ideally >1000)
  - MICs from many places (minimum 3 distributions)
  - MICs performed by many investigators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

S.pneumoniae vs ciprofloxacin

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

Tentative rules for aggregating MIC distributions and determine ECOFF

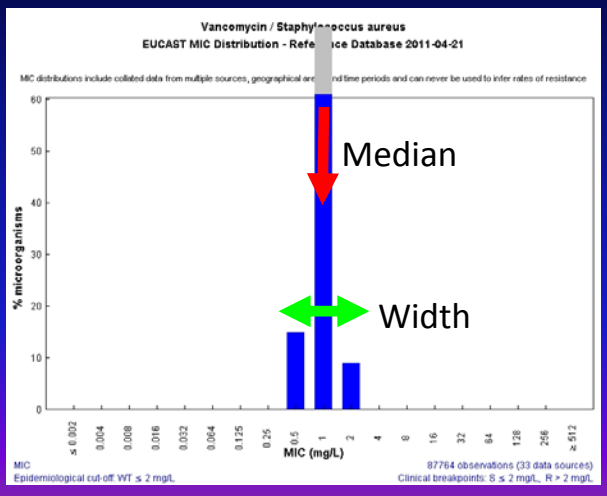
MIC distributions*	Distributions which disagree**	Action (none, aggregate or aggregate and determine ECOFF)
1	0	None***
2	0	None
3	0	Aggregate 3
3	1	None
4	0	Aggregate 4 and determine ECOFF
4	1	Aggregate 3
4	>1	None
5	0	Aggregate 5 and determine ECOFF
5	1	Aggregate 4
5	>1	None
6	0	Aggregate 6 and determine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



The use of ECOFFs

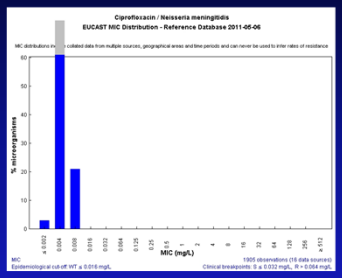
- As a tool in the determination of clinical breakpoints
  - To avoid dividing wild type MIC distributions of important target organisms
  - As a **surrogate clinical breakpoint** when **Pk/Pd data is incomplete and clinical data pertain only to wild type organisms**
- For **sensitive detection of (screening for) resistance**
  - oxacillin to detect all penicillin-R in *S. pneumoniae*
  - cefoxitin 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

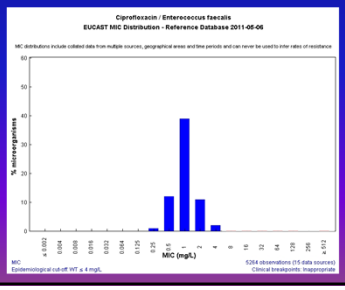
Factors influencing the median and width of WT distributions



The median of the MIC (or zone diameter) distribution:

- The inherent susceptibility of the species to the drug





The median of the MIC (or zone diameter) distribution:

- The inherent susceptibility of the species to the drug
- Anything systematically influencing the activity of the drug:

Medium – variation in MICs depending on medium

Inoculum – increasing MICs with higher inocula

Incubation – increasing MICs with longer incubation

Atmosphere – affects the activity of some drugs

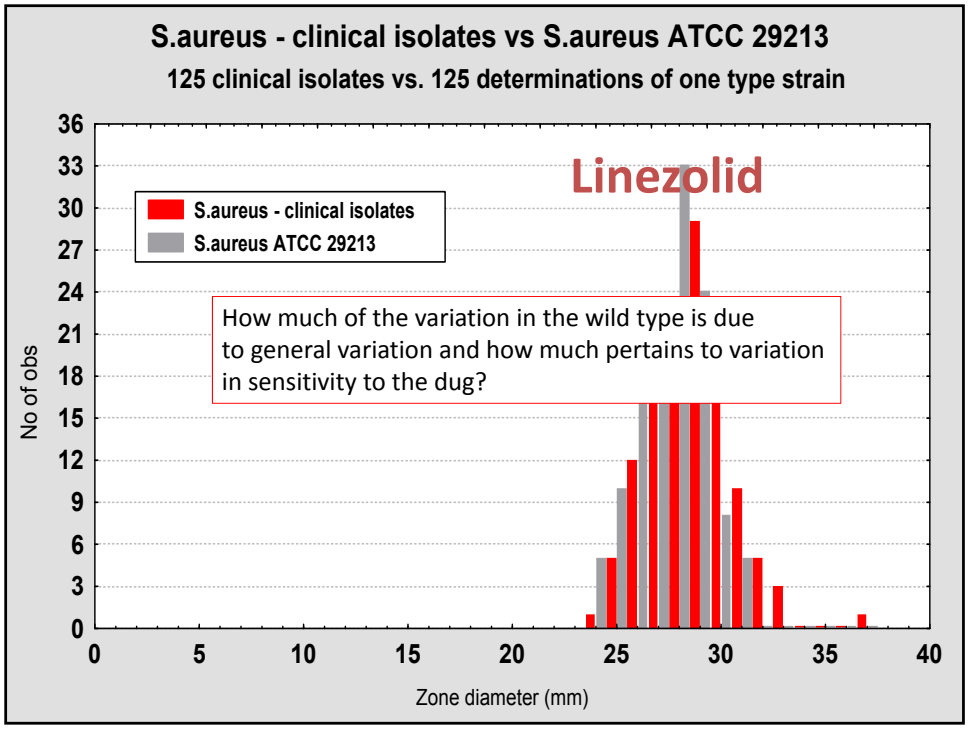
pH – some drugs are more active at high pH, others at low

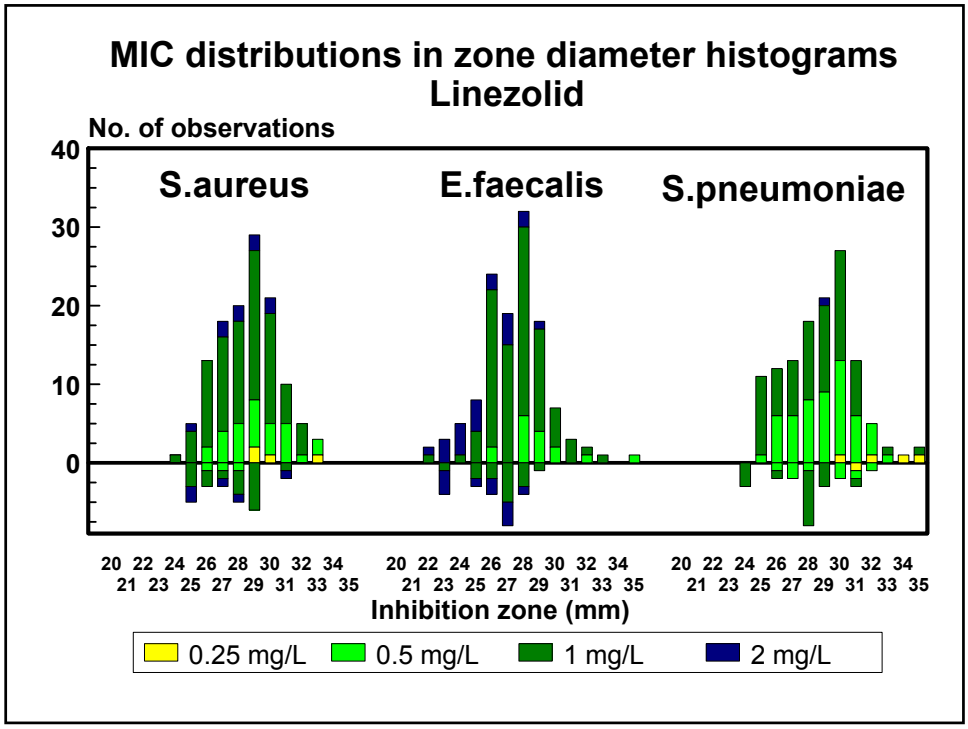
The median of the MIC (or zone diameter) distribution:

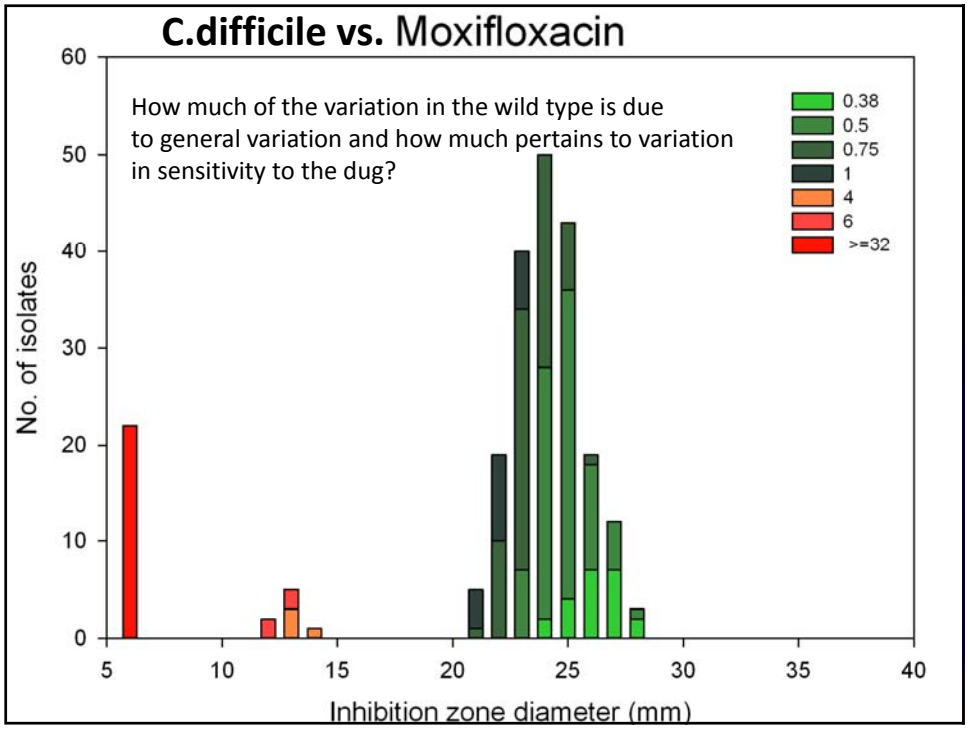
- The inherent susceptibility of the species to the drug
- Anything systematically influencing the activity of the drug
  - Medium, inoculum, pH, cations, incubation atmosphere and time,

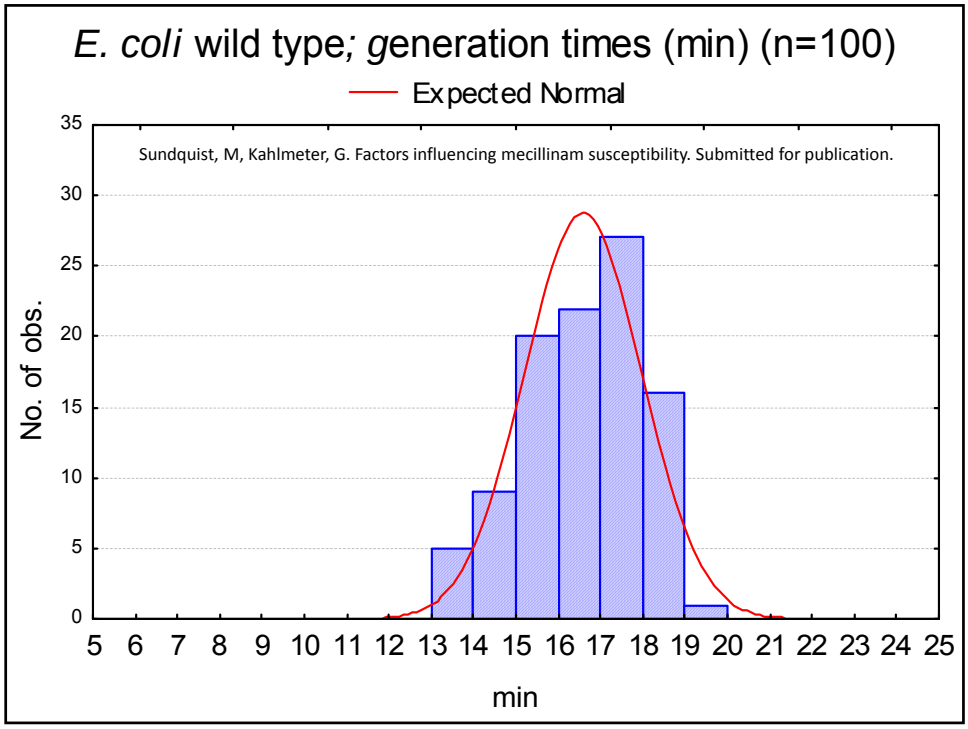
The width of the MIC (or zone diameter) distribution:

- Inherent **variation** in **susceptibility** to the drug
- Biological **variation** in **other traits** that influence the MIC
  - any biological characteristic such as generation time, nutrient dependency, atmosphere dependency etc
- Exogenous **variation** randomly influencing the activity of the drug
  - pH, cations, incubation atmosphere and time, etc
- **Variation** in reading (between days, between readers, between systems)
- The stability of the molecule
- …



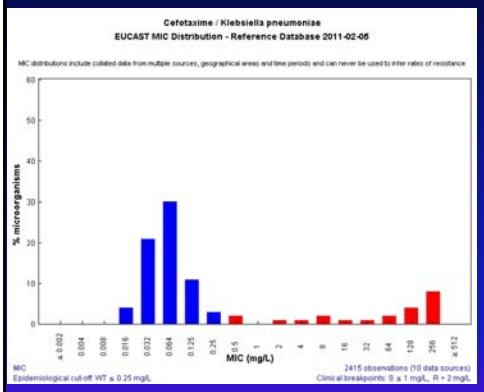

MIC distributions in zone diameter histograms
Linezolid
No. of observations
40
30
20
10
0
S.aureus
E.faecalis
S.pneumoniae
20 22 24 26 28 30 32 34
21 23 25 27 29 31 33 35
Inhibition zone (mm)
0.25 mg/L
0.5 mg/L
1 mg/L
2 mg/L

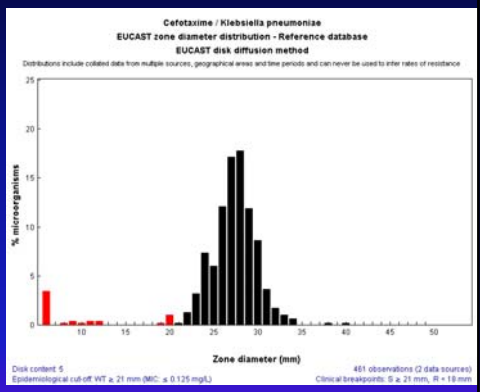

C.difficile vs. Moxifloxacin
How much of the variation in the wild type is due to general variation and how much pertains to variation in sensitivity to the dug?
0.38
0.5
0.75
1
4
6
>=32
No. of isolates
60
50
40
30
20
10
0
5
10
15
20
25
30
35
40
Inhibition zone diameter (mm)

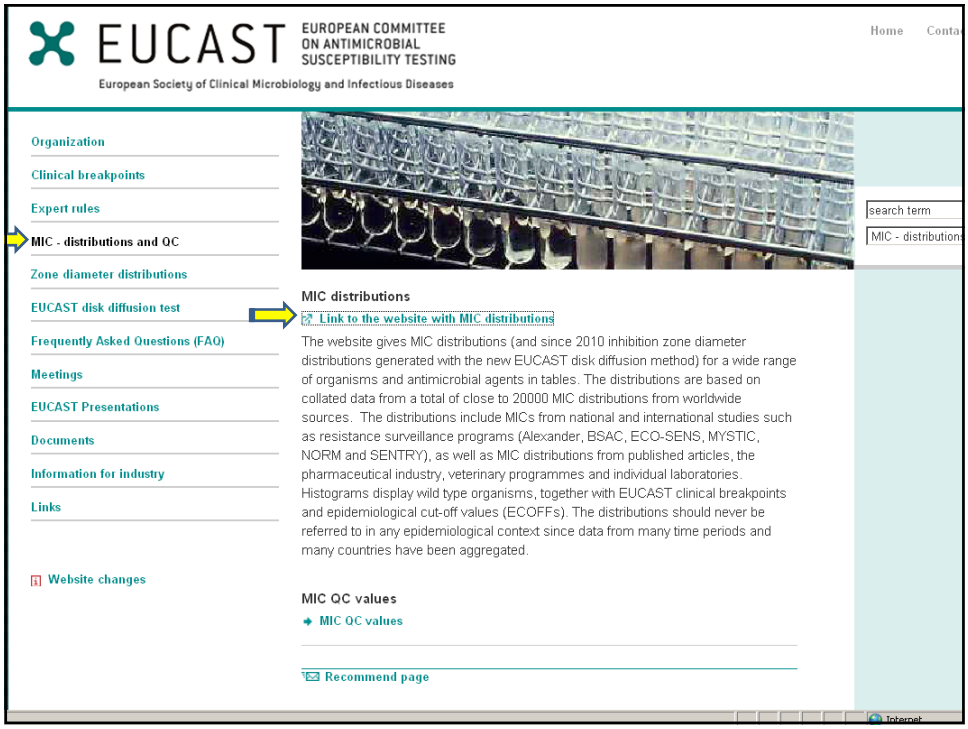


Distribution of MICs and inhibition zone diameters

Defined by agent, species and test systems are freely available on the internet (www.eucast.org)

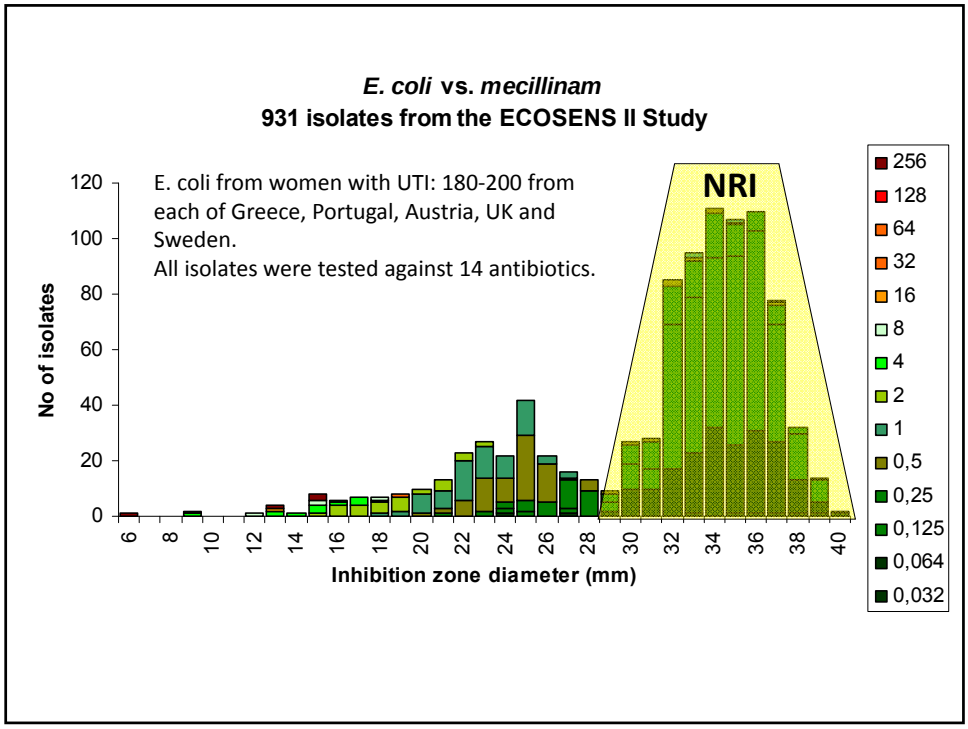


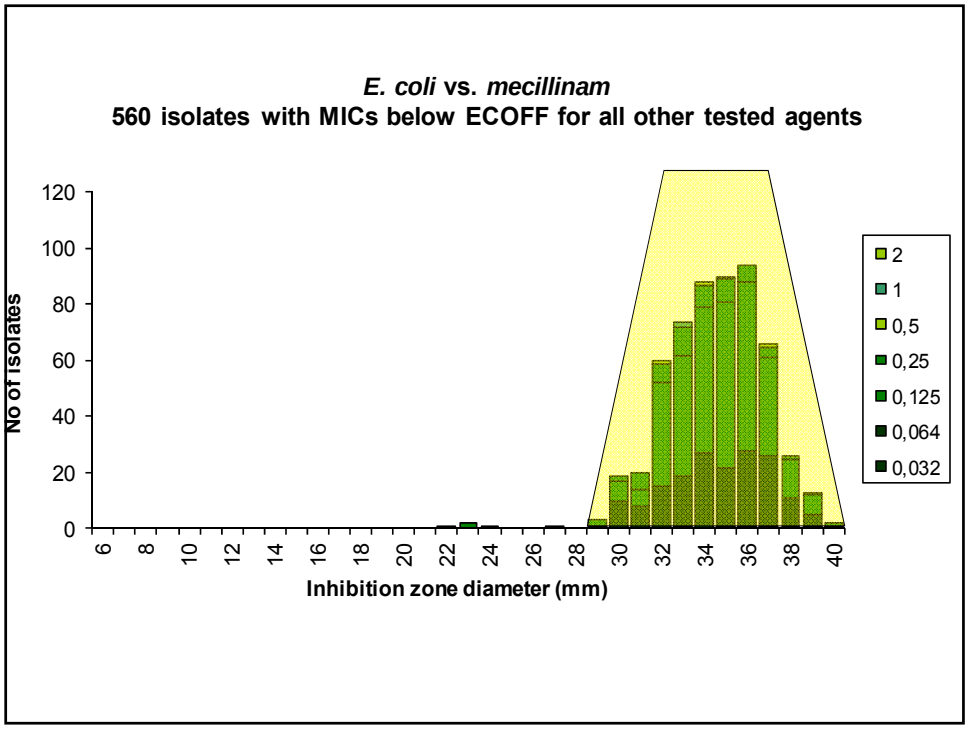




MIC distributions and ECOFFs on EUCAST website

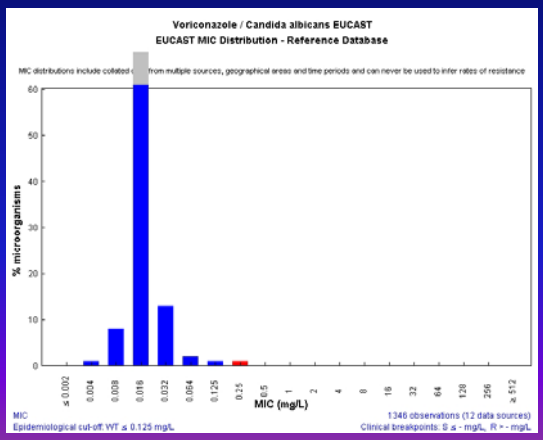
- 25 000 MIC distributions
- Up to 100 000 MIC-values per distribution
- Data from many investigators (1 – 100 per distrib.)
- Data from many time periods (1950 -)
- Data from many geographical areas and projects
  (USA, Europe, Australia, Far East, South America, Sentry, Mystic, etc)
- Data of multiple origin
  (Human clinical data, Surveillance programs, Veterinarian data, Wild life, Food safety programs)
- Database secure on three servers in different parts of Dusseldorf under the official responsibility of EUCAST and ESCMID.
- Ownership:
  - Software and administration: ESCMID/EUCAST
  - Database: individual ownership of original data


E. coli vs. *mecillinam*
931 isolates from the ECOSENS II Study
E. coli from women with UTI: 180-200 from each of Greece, Portugal, Austria, UK and Sweden.
All isolates were tested against 14 antibiotics.
NRI
No of isolates
Inhibition zone diameter (mm)
256
128
64
32
16
8
4
2
1
0,5
0,25
0,125
0,064
0,032


E. coli vs. *mecillinam*
560 isolates with MICs below ECOFF for all other tested agents
No of isolates
Inhibition zone diameter (mm)
2
1
0,5
0,25
0,125
0,064
0,032

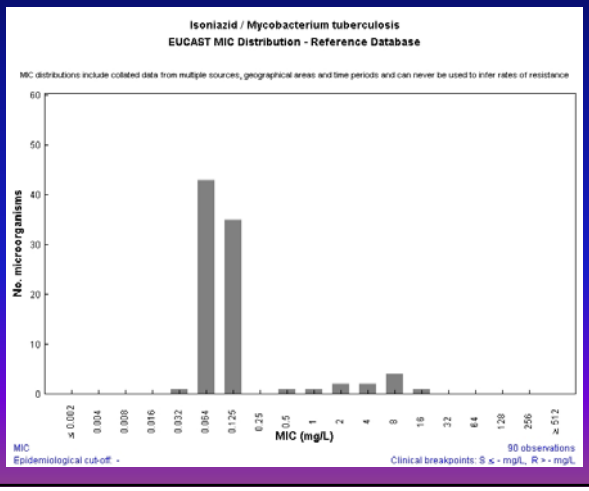
Wild type MIC-distributions and ECOFFs for antifungal drugs as one of several tools for determining breakpoints

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*

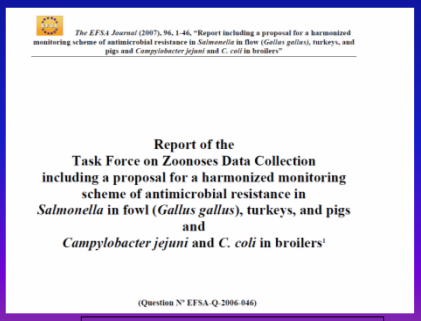
Principle authors: K Ängeby, P Jurén, T Schön.
and with E Sturegård, E Chryssanthou, CG Giske, J Werngren, M Nordvall, A Johansson, G Kahlmeter, S Hoffner.



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

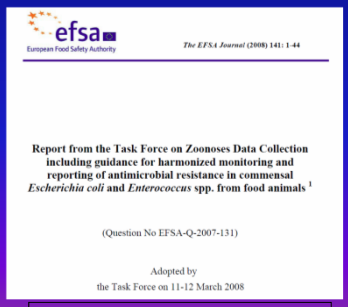


The EFSA Journal (2007), 96, 1-46, "Report including a proposal for a harmonized monitoring scheme of antimicrobial resistance in *Salmonella* in fowl (*Gallus gallus*), turkeys, and pigs and *Campylobacter jejuni* and *C. coli* in broilers"

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 broilers[1]

(Question N° EFSA-Q-2006-046)

Salmonella, Campylobacter



efsa European Food Safety Authority

The EFSA Journal (2008) 141: 1-44

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 animals [1]

(Question No EFSA-Q-2007-131)

Adopted by the Task Force on 11-12 March 2008

E. coli, enterococci

EFSA Guidelines

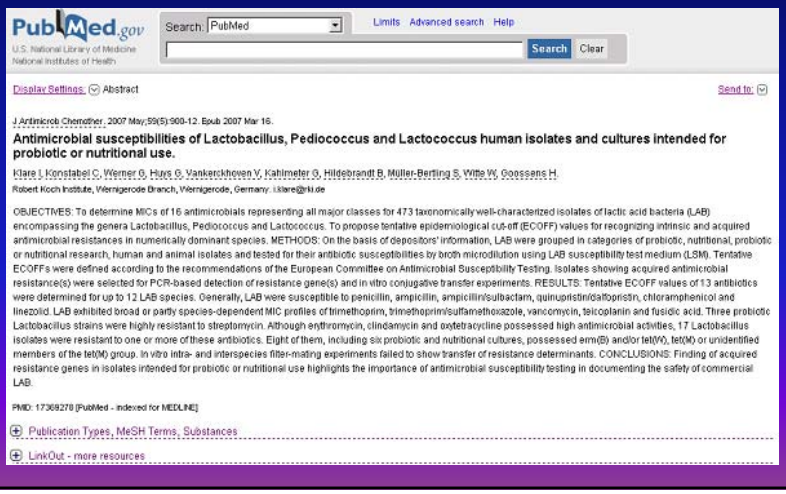
- Harmonized sampling strategies
- Broth microdilution according to ISO-20776-1:2006 as standard method
- List of required antibiotics to include in the tests and ECOFF's as interpretive criteria for sensitive and harmonized interpretation of surveillance results in the EU
  - see table A

Table A. Antimicrobials to be included in the antimicrobial resistance monitoring for each zoonotic agent and the cut-off value for each antimicrobial to be used to determine susceptibility.

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



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J Antimicrob Chemother. 2007 May;59(5):909-12. 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, Muller-Bertling S, Witte W, Goossens H.

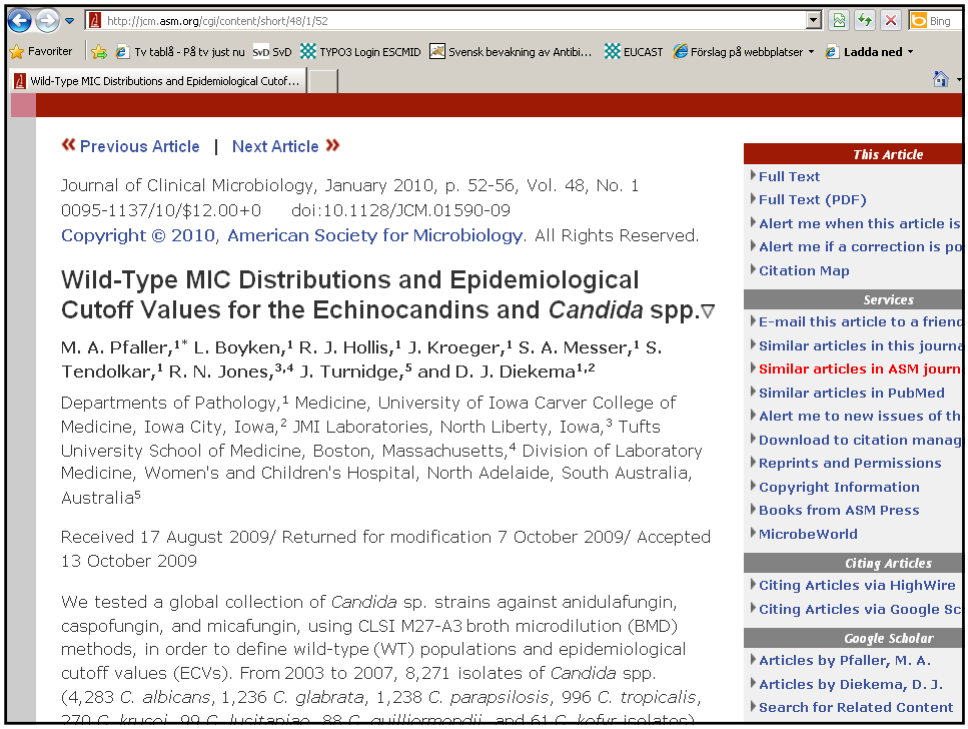
Robert Koch Institute, Wernigerode Branch, Wernigerode, Germany. iklare@rki.de

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 oxytetracycline 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(W), 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: 17369278 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances

LinkOut - more resources



http://jcm.asm.org/cgi/content/short/48/1/52

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Wild-Type MIC Distributions and Epidemiological Cutof...

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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.▽

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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. lusitaniae*, 88 *C. guilliermondii*, and 61 *C. kefyr* isolates)

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ECOFFs in lieu of Clinical Breakpoints

Gunnar Kahlmeter

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Can ECOFFs be used in lieu of clincal breakpoints?

- Never by default
- Yes, after consideration

The ECOFF

- The ECOFF distinguishes between organisms **without** and **with** phenotypically expressed resistance mechanisms.
- Organisms **without** resistance mechanisms are not by default treatable and organisms **with** resistance mechanisms are not by default resistant.
- The wild type may be deemed ”susceptible”, ”intermediate” or ”resistant” by the clinical breakpoint.

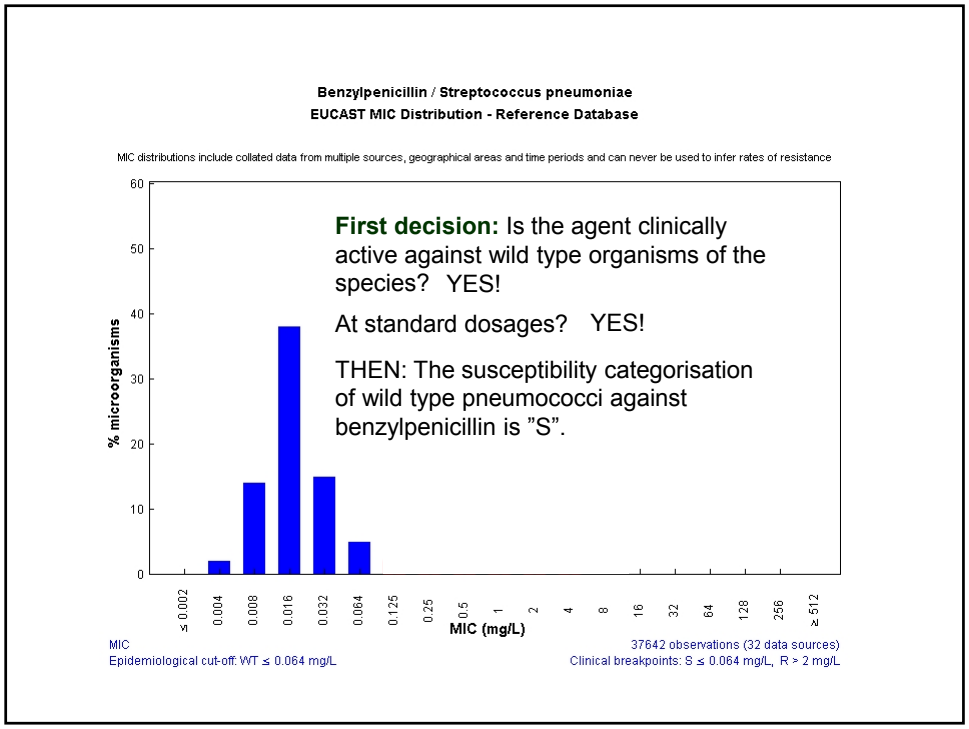
- **Thus, the ECOFF can never automatically replace a clinical breakpoint.**

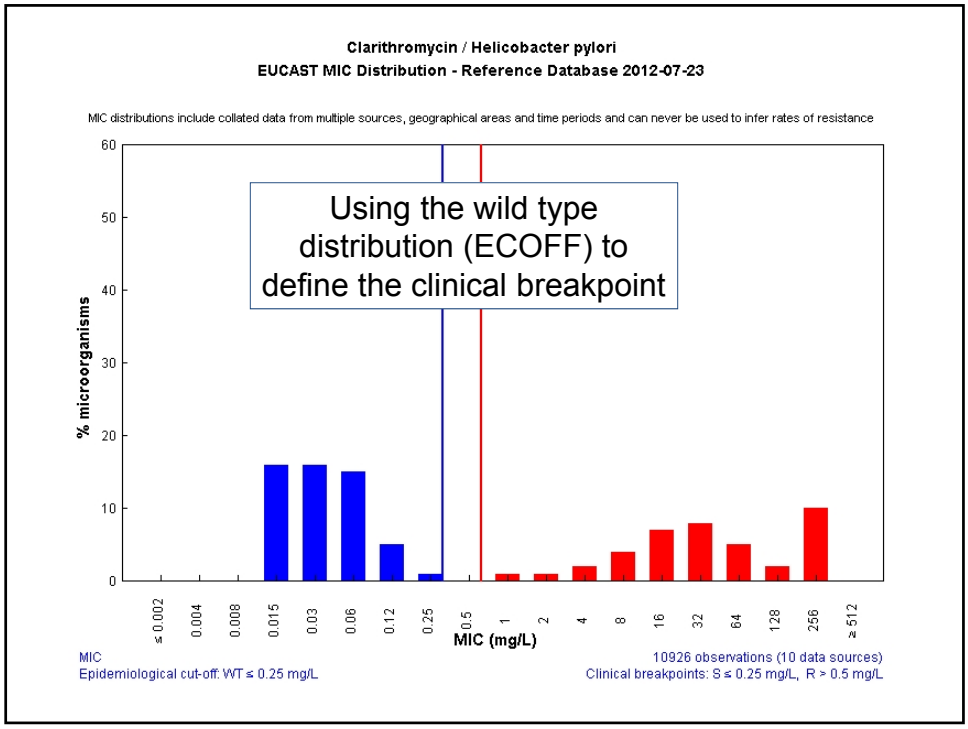
When should the ECOFF be considered in lieu of a formal clinical breakpoint

- When clinical data support the use of the agent for an approved indication and wild type organisms of one or several species.
- When there is a lack of convincing Pk/Pd data
- When there is a lack of data to support the use of the agent for infections with organisms with resistance mechanisms (MICs above the ECOFF).

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 must be designated ”S”
- …in which case the lowest possible clinical breakpoint = ECOFF.

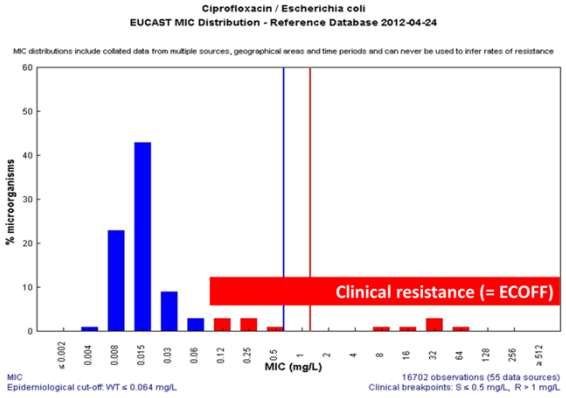




Ciprofloxacin

CLINICAL BREAKPOINTS

1. Dose c
2. Clinica UTI
3. Target irabilis …
4. ECOFF



When this is known - you know everything you need to set a breakpoint at S≤0.064 mg/L, R>0.064 mg/L.
If you want to set it above the ECOFF, you need more information.

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 (Cmax, AUC, T½, Protein binding, Vd..)
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

Species/antibiotic combinations where CBP = ECOFF*

Antibiotic	Species	ECOFF WT≤	CBP S≤
Ampicillin	*E.coli*	8	8
Ciprofloxacin	*Salmonella spp*	0.06	0.06
Ciprofloxacin	*S. aureus*	1	1
Cefoxitin	*S. aureus*	2	2
Vancomycin*	*S. aureus*	2	2
Gentamicin	*E.coli*	2	2
Chloramphenicol	*H. influenzae*	1	1
Meropenem	*P. aeruginosa*	2	2
Trimethoprim	*E. coli*	2	2
Piperacillin	*P. aeruginosa*	16	16
Levofloxacin	*S. pneumoniae*	2	2
Erythromycin	*S. pneumoniae*	0.25	0.25

*Clinical Break Point = Epidemiological Cutoff

Examples of species/antibiotic combinations where CBP >> ECOFF*

Antibiotic	Species	ECOFF≤	EUCAST S≤
Meropenem**	E.coli K.pneumoniae	0.125 0.125	2 (1) 2 (1)
	S. pneumoniae	0.016	2
	H. influenzae	0.25	2
Ciprofloxacin***	E. coli K. pneumoniae etc	0.064	0.5
Cefotaxime	E. coli	0.25	1
Cefepime	K. pneumoniae	0.125	1 (8)
Benzylpenicillin	S. pyogenes	0.064	0.25
Ampicillin	S. pneumoniae	0.064	0.5

*Clinical Break Point much higher than Epidemiological Cutoff

**And with slightly different values other carbapenems

***And with slightly different values other FQs

The End

…but hopefully lots of discussion