ECOFFs
ECOFFs
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MIC wild type distributions and epidemiological cut-off values

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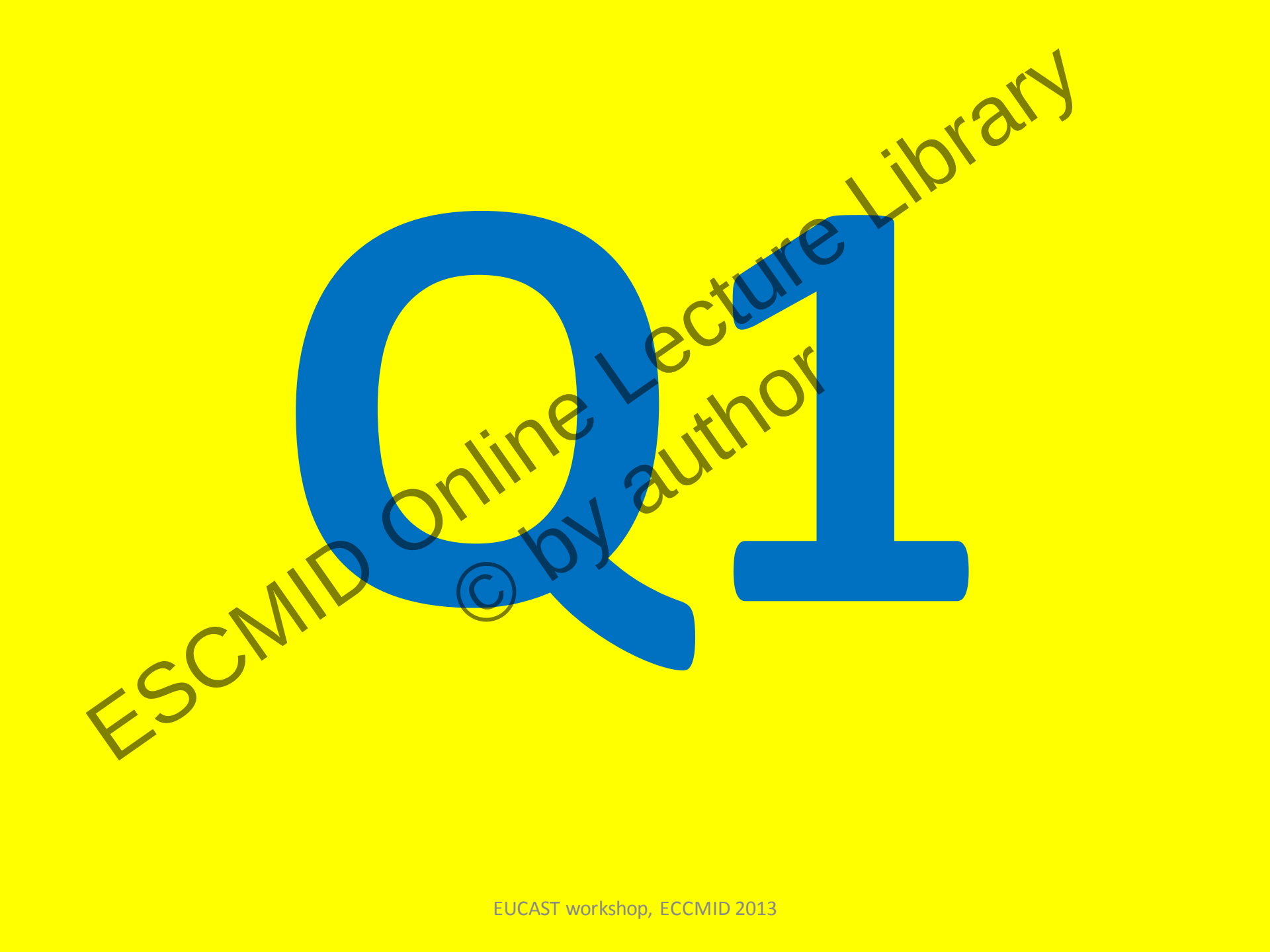
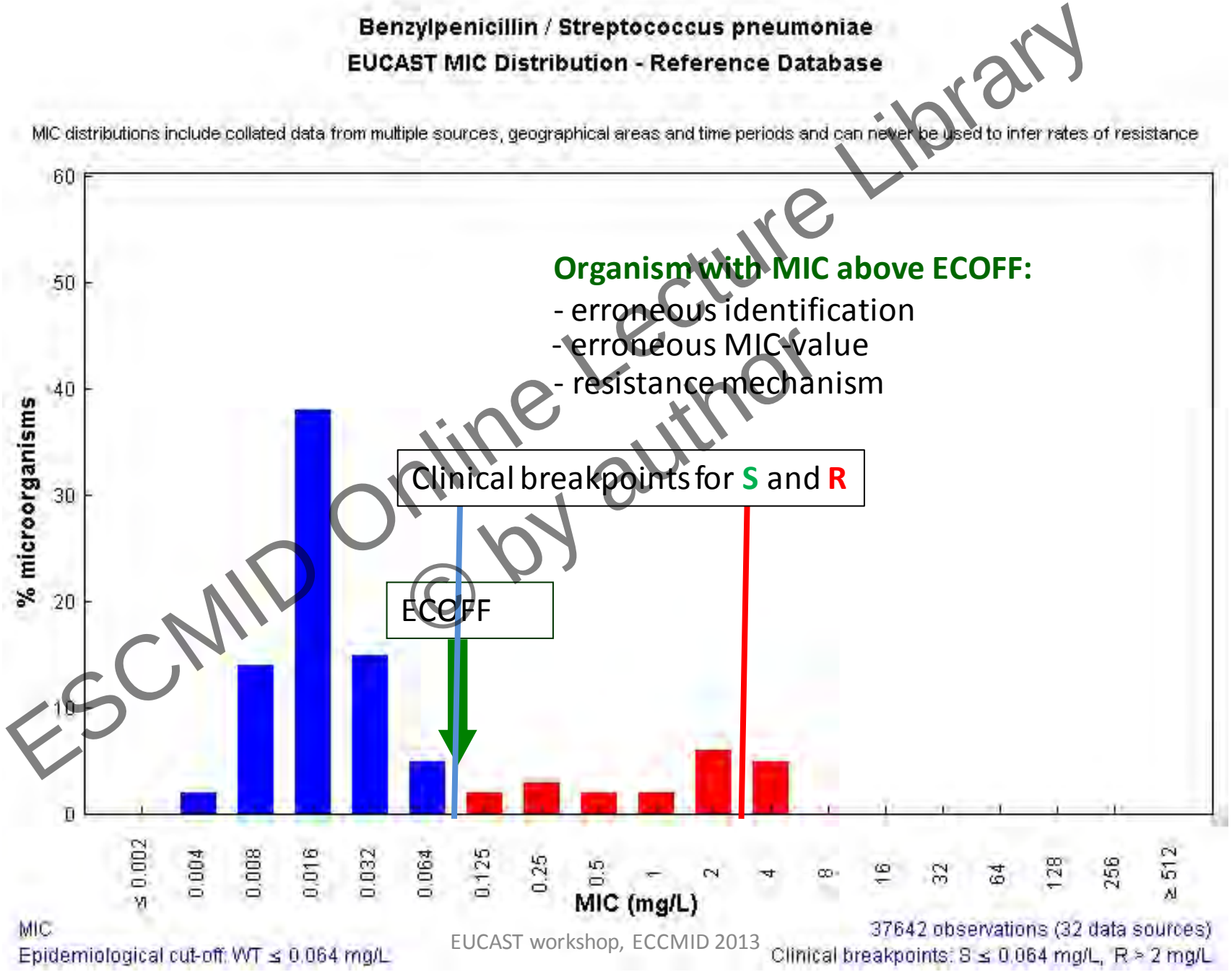




Breakpoints

Clinical breakpoints

- MIC concentrations decided by man (based on clinical outcome data, MIC distributions, accepted dosing, PK/PD-data) to distinguish treatable from non-treatable organisms.
- should not divide wild type MIC distributions of target organisms.
- may render wild type organisms Susceptible (S), Intermediate (I) or Resistant (R)
- may change with a change in circumstances (indications, new resistance mechanisms, new dosing)

Breakpoints

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 for organisms lacking phenotypically expressed resistance.
- Organisms **without** resistance mechanisms (WT) are not by default treatable and organisms **with** resistance mechanisms (NWT) are not by default resistant.
- In a species considered susceptible (S) to the agent, the ECOFF is the lowest possible S breakpoint.

Establishing ECOFFs

- **ECOFFs should only be determined on**
  - MICs determined with methods calibrated to the internationally agreed standard method for broth microdilution (ISO)
  - large numbers of MICs (n>100, ideally >1000)
  - MICs from different places (minimum 3)
  - 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

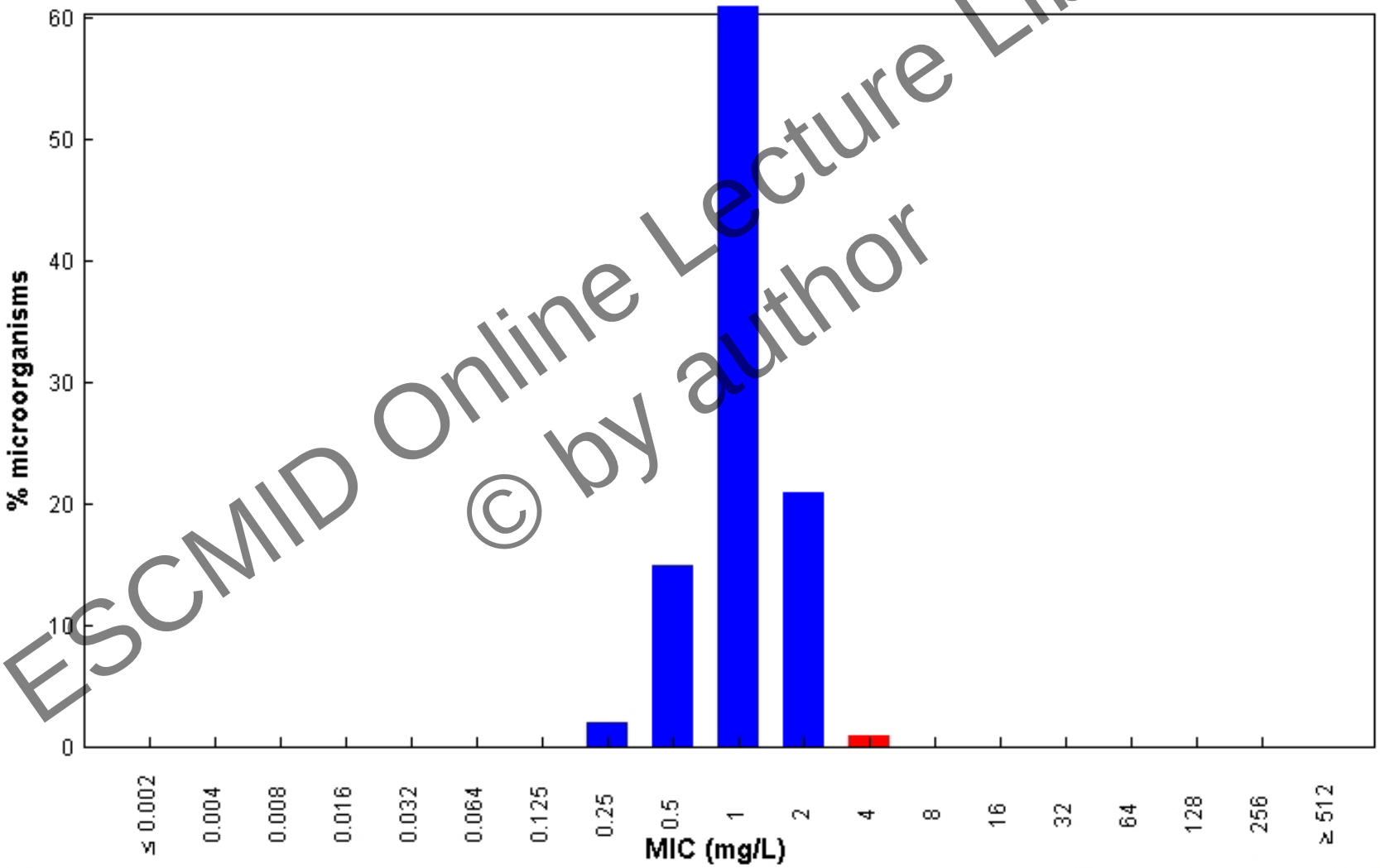
Tentative rules for aggregating MIC distributions and determine ECOFF

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		

Ciprofloxacin / Streptococcus pneumoniae

EUCAST MIC Distribution - Reference Database 2011-02-04

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



MIC

73840 observations (50 data sources)

Epidemiological cut-off: WT ≤ 2 mg/L

Clinical breakpoints: S ≤ 0.125 mg/L, R > 2 mg/L

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Home Contac

- Organization
- Clinical breakpoints
- Expert rules
- MIC - distributions and QC
- Zone diameter distributions
- EUCAST disk diffusion test
- Frequently Asked Questions (FAQ)
- Meetings
- EUCAST Presentations
- Documents
- Information for industry
- Links

Website changes

search term

MIC - distributions

MIC distributions

Link to the website with MIC distributions

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 in tables. The distributions are based on collated data from a total of close to 20000 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.

MIC QC values

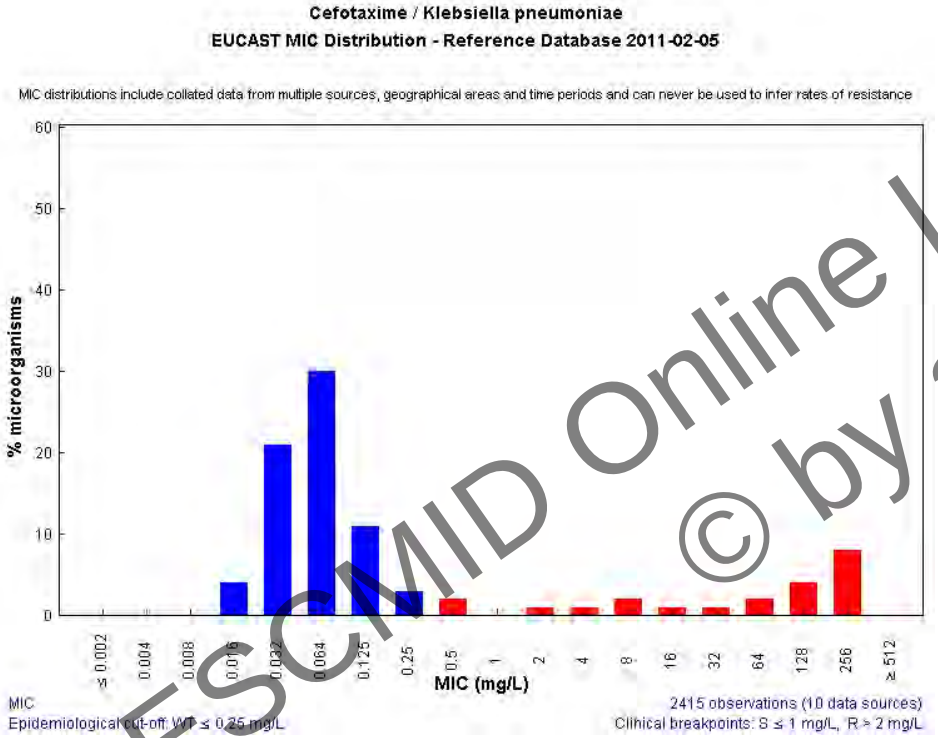
MIC QC values

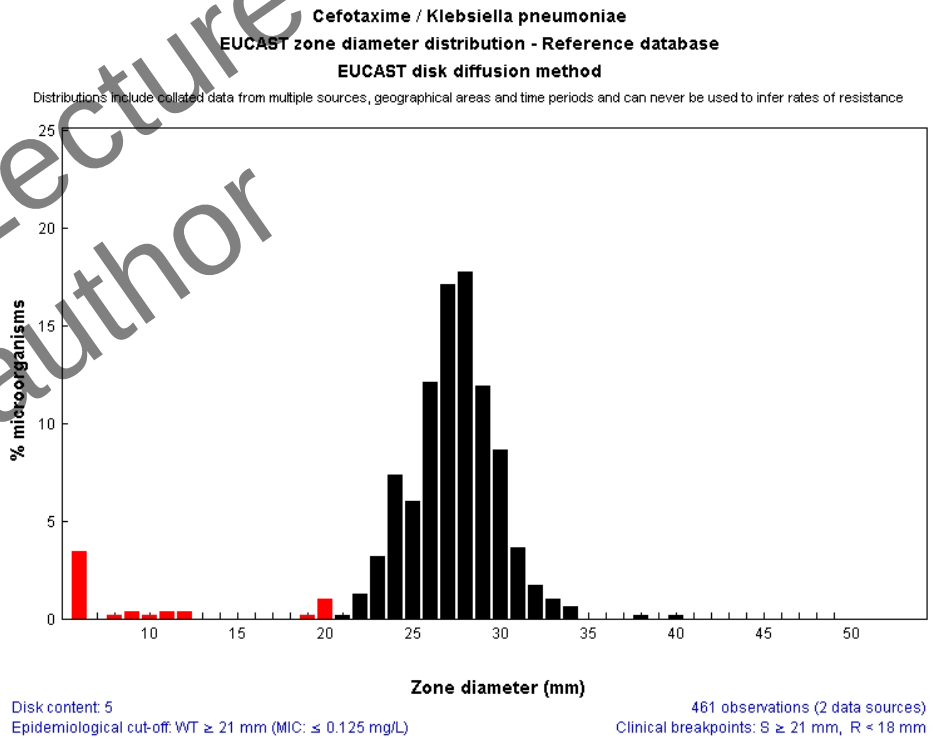
Recommend page

Internet

Distribution of MICs and inhibition zone diameters

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

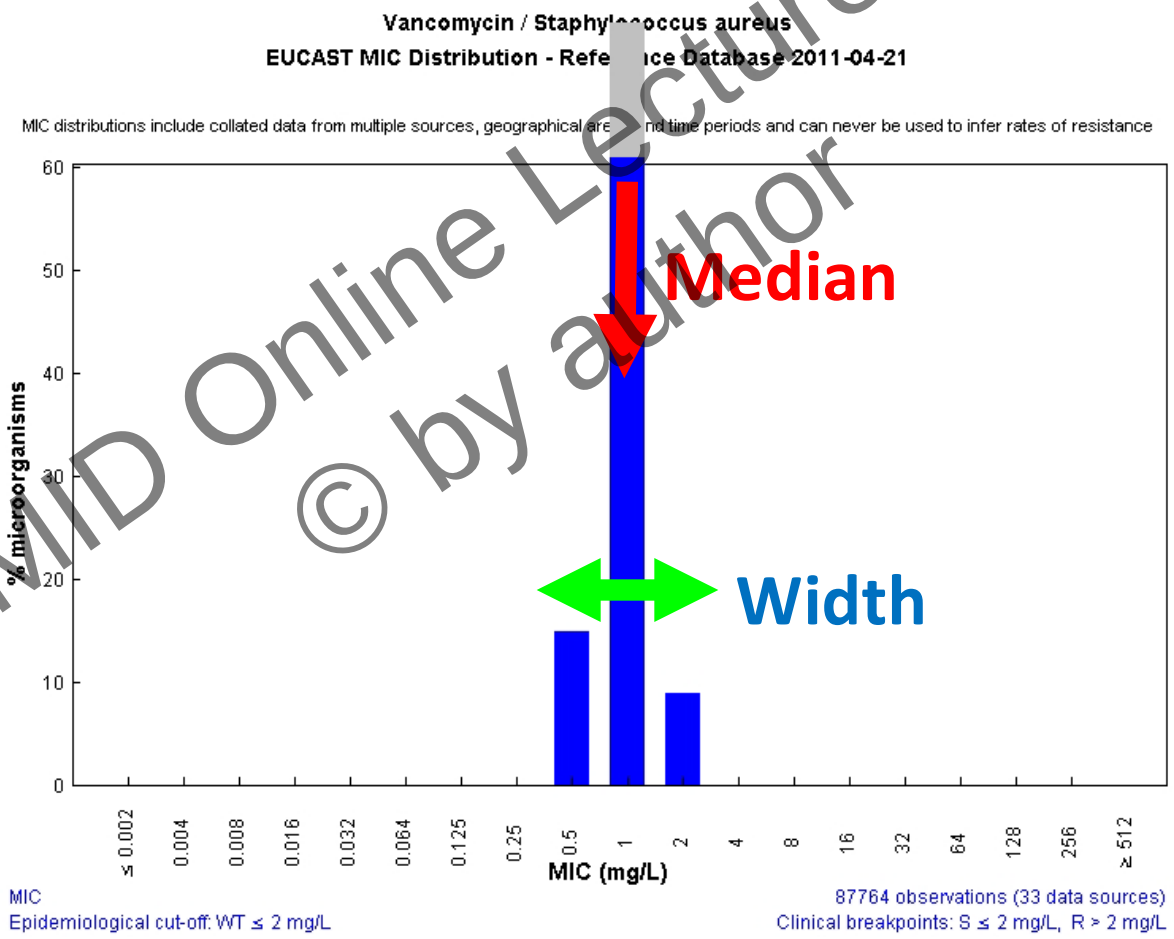




MIC distributions and ECOFFs on EUCAST website

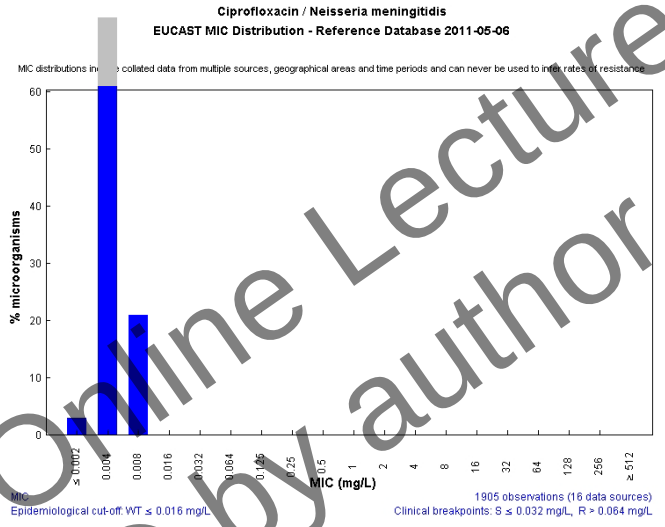
- 25 000 MIC distributions
- Up to 100 000 MIC values per distribution
- Data from many investigators (1 – 100 per distrib.)
- Data from many time periods (1950 -)
- Data from many geographical areas and projects
  (USA, Europe, Australia, Far East, South America, Sentry, Mystic, etc)
- Data of multiple 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: ECDC / ESCMID
  - Database: individual ownership of original data

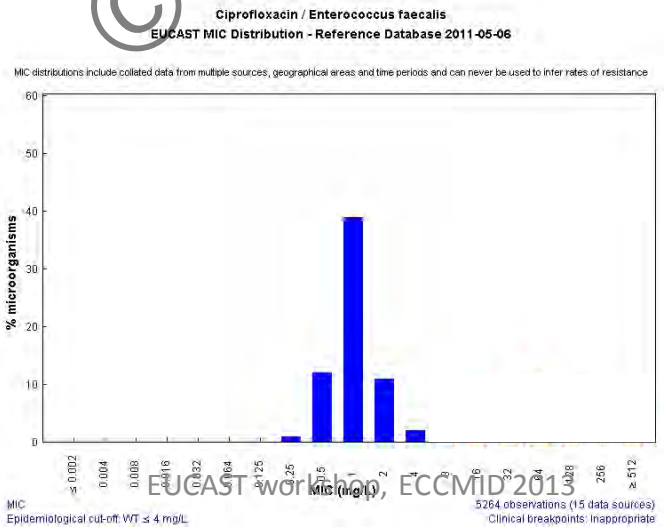
Factors influencing the median and width of WT distributions



The median of the MIC distribution:

- The inherent susceptibility of the species to the drug





The same applies to zone diameter distributions

The median of the MIC 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

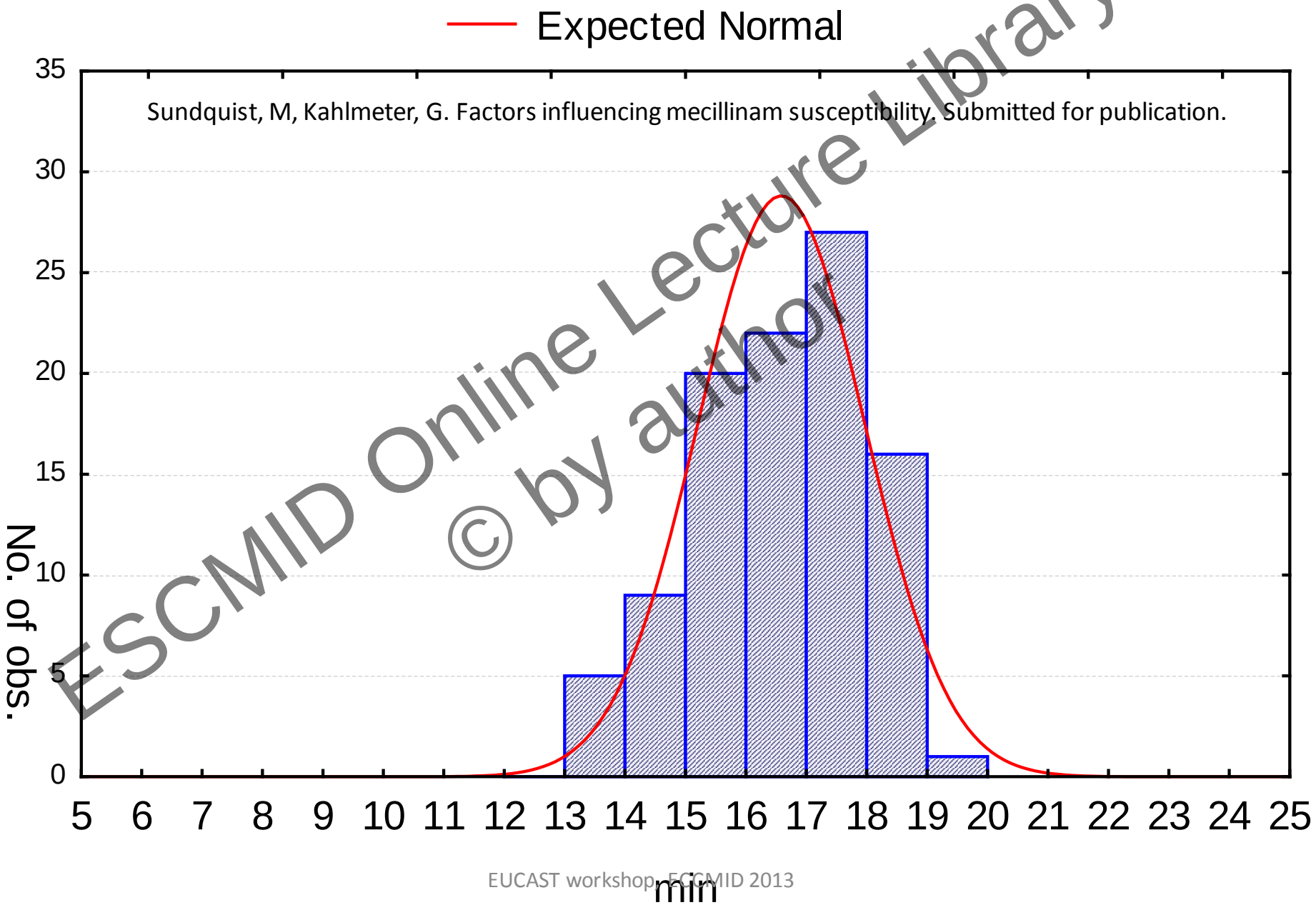
The median of the MIC (or zone diameter) distribution:

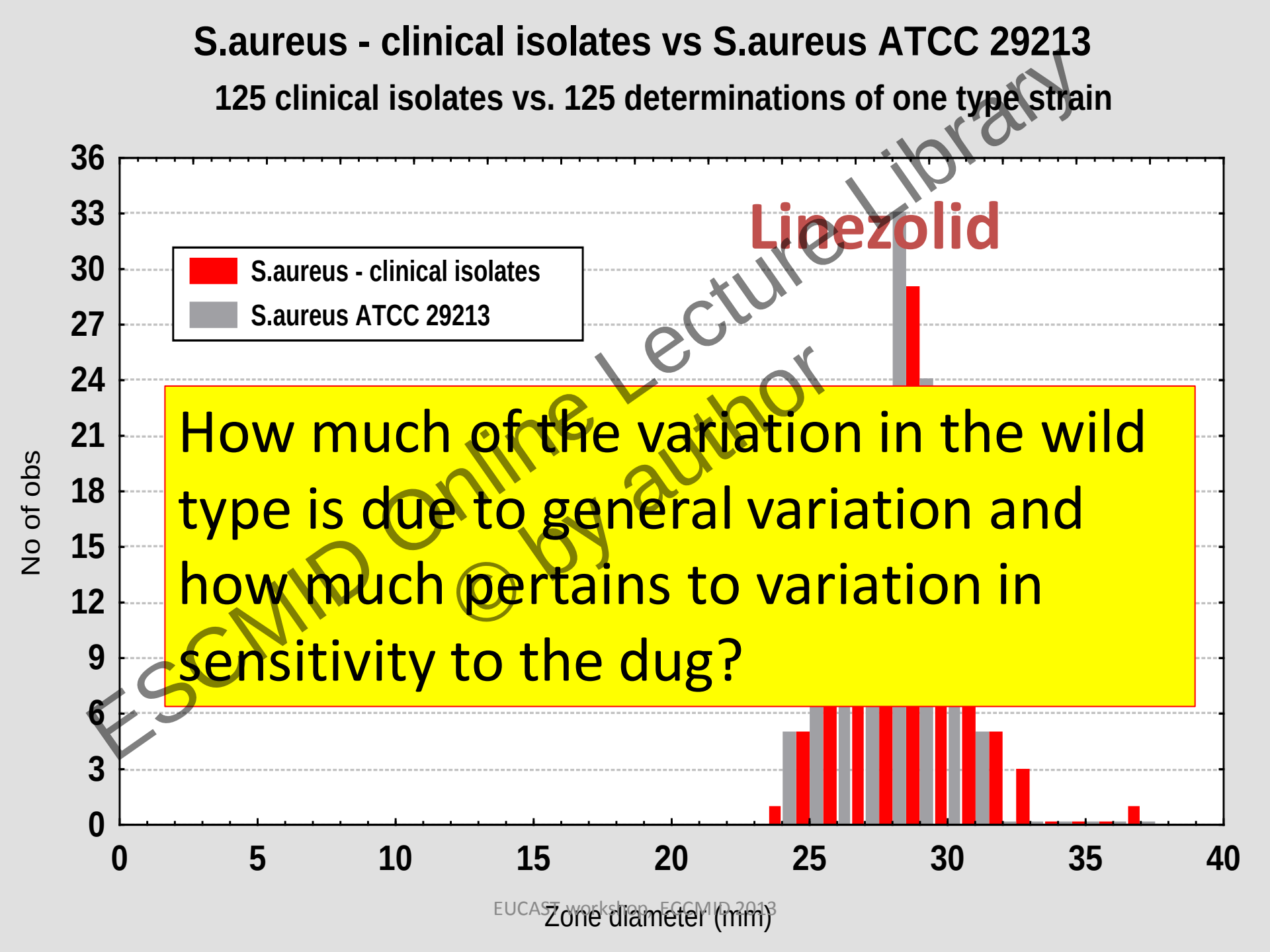
- The inherent susceptibility of the species to the drug
- Anything systematically influencing the activity of the drug
  - Medium, inoculum, pH, cations, incubation atmosphere and time,

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

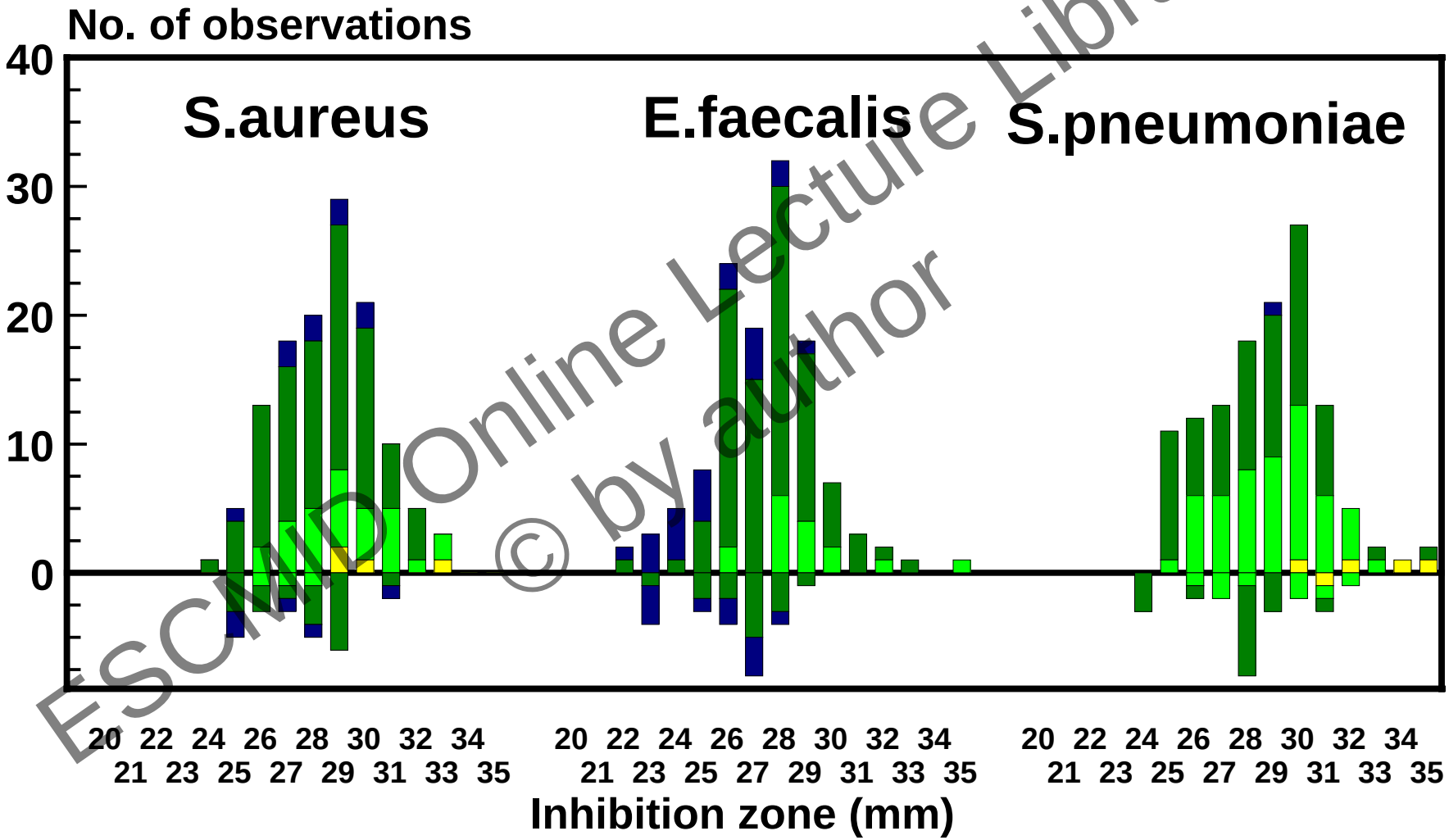
- Inherent **variation** in **susceptibility** to the drug
- Biological **variation** in **other traits** that influence the MIC
  - any biological characteristic such as generation time, nutrient dependency, atmosphere dependency etc
- Exogenous **variation** randomly influencing the activity of the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

E. coli wild type; generation times (min) (n=100)





MIC distributions in zone diameter histograms
Linezolid



Sjölund et al, CMI, 2009

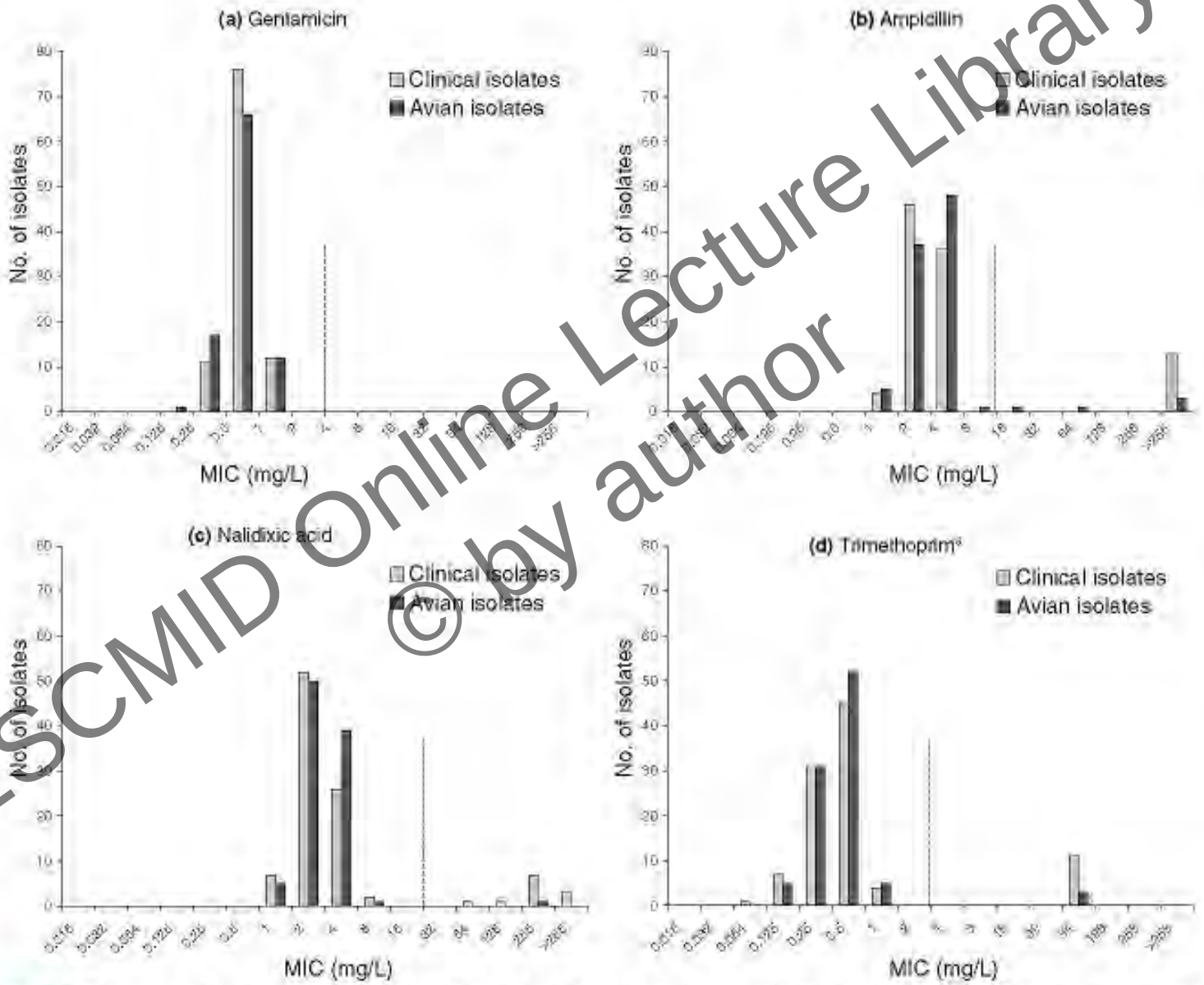
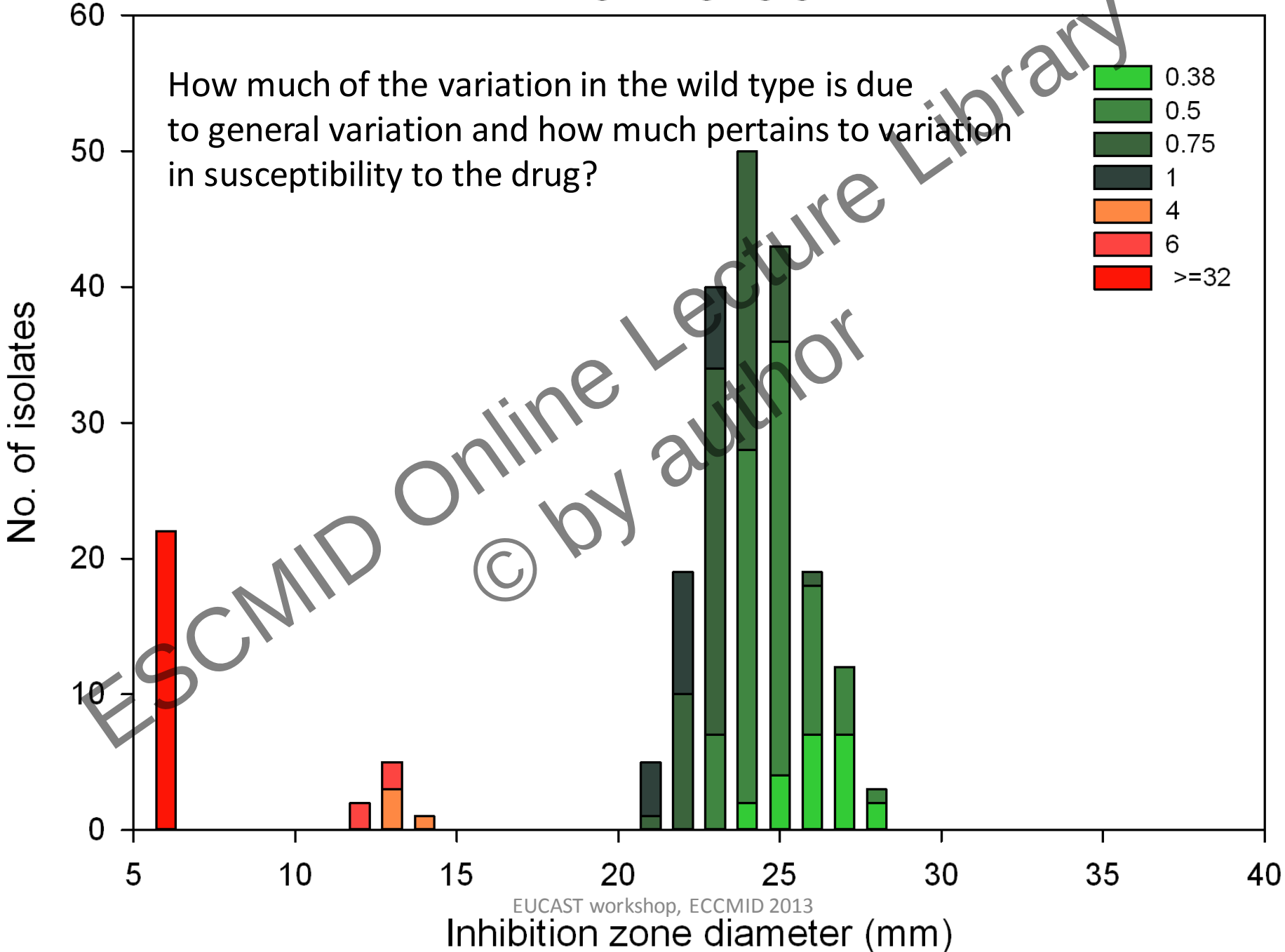


FIG. 2. MIC histograms for clinical and avian isolates. The dashed line indicates the epidemiological cut-off values (ECOFFs) for the wild-type distribution as determined by EUCAST (http://www.eucast.org). [a]Trimethoprim concentration test range: 0.016–32 mg/L.

C.difficile vs. Moxifloxacin



Methods for defining the wild type distribution (determining the ECOFF)

- The “eyeball” method (Kahlmeter)
- The 95% rule (Pfaller)
- The Normalised Resistance Interpretation (Kronvall)
- The iterative statistical method (Turnidge)
- Multimodal analysis (Meletiadis)

From John Turnidge, CLSI Workshop, Tampa, January 2013

The Normalized Resistance Interpretation

JOURNAL OF CLINICAL MICROBIOLOGY, Dec. 2010, p. 4445–4452 Vol. 48, No. 12
0095-1137/10/$12.00 doi:10.1128/JCM.01101-10

Normalized Resistance Interpretation as a Tool for Establishing Epidemiological MIC Susceptibility Breakpoints▽

Göran Kronvall*

Department of Microbiology and Tumor Biology–MTC, Clinical Microbiology, Karolinska Institutet, Karolinska University Hospital Solna, Stockholm, Sweden

- Uses an adaptation of a method originally devised for "ECOFFs" for zone diameter distributions
  - Kronvall et al., Clin Micro Infect 2003

From John Turnidge, CLSI Workshop, Tampa, January 2013

Iterative Statistical Method

ORIGINAL ARTICLE 10.1111/j.1469-0691.2006.01377.x

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

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From John Turnidge, CLSI Workshop, Tampa, January 2013

Iterative Statistical Method - COFinder

Step 1. Population Data | *CRGAT* | FLUC All

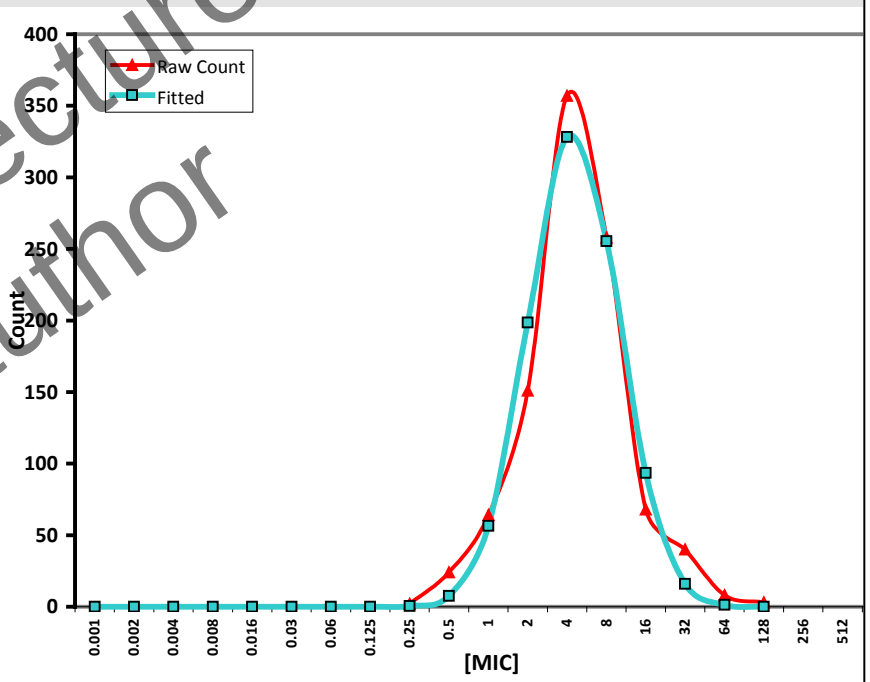
MIC	Log_2MIC	Raw Count	Cum. Count	Fitted
0.001	-10		0	0.0
0.002	-9		0	0.0
0.004	-8		0	0.0
0.008	-7		0	0.0
0.016	-6		0	0.0
0.03	-5		0	0.0
0.06	-4		0	0.0
0.125	-3		0	0.0
0.25	-2	2	2	0.5
0.5	-1	24	26	7.5
1	0	64	90	56.5
2	1	151	241	198.7
4	2	357	598	328.2
8	3	258	856	255.3
16	4	68	924	93.5
32	5	40	964	16.0
64	6	8	972	1.3
128	7	3	975	0.0
256	8		975	
512	9		975	
1024	10		975	

? Enter/paste data in this column

Modal MIC	4
Log_2MIC Mode	2
Max Log_2MIC	7
Selected Log2 Mean	1.6667 =3.17
Selected Log2 SD	1.1145

Selected CO_{WT} Values		%>
CO_{WT} 95%	16	5.2%
CO_{WT} 97.5%	16	5.2%
CO_{WT} 99%	32	1.1%
CO_{WT} 99.9%	64	0.3%

REVIEW AREA



Data from 10 laboratories

Selected CO_{WT} Values		%>
CO_{WT} 95%	16	5.2%
CO_{WT} 97.5%	16	5.2%
CO_{WT} 99%	32	1.1%
CO_{WT} 99.9%	64	0.3%

From John Turnidge, CLSI Workshop, Tampa, January 2013

”A biological approach”

- Associated resistance – an organism resistant to one agent is very likely to carry resistance to other agents.

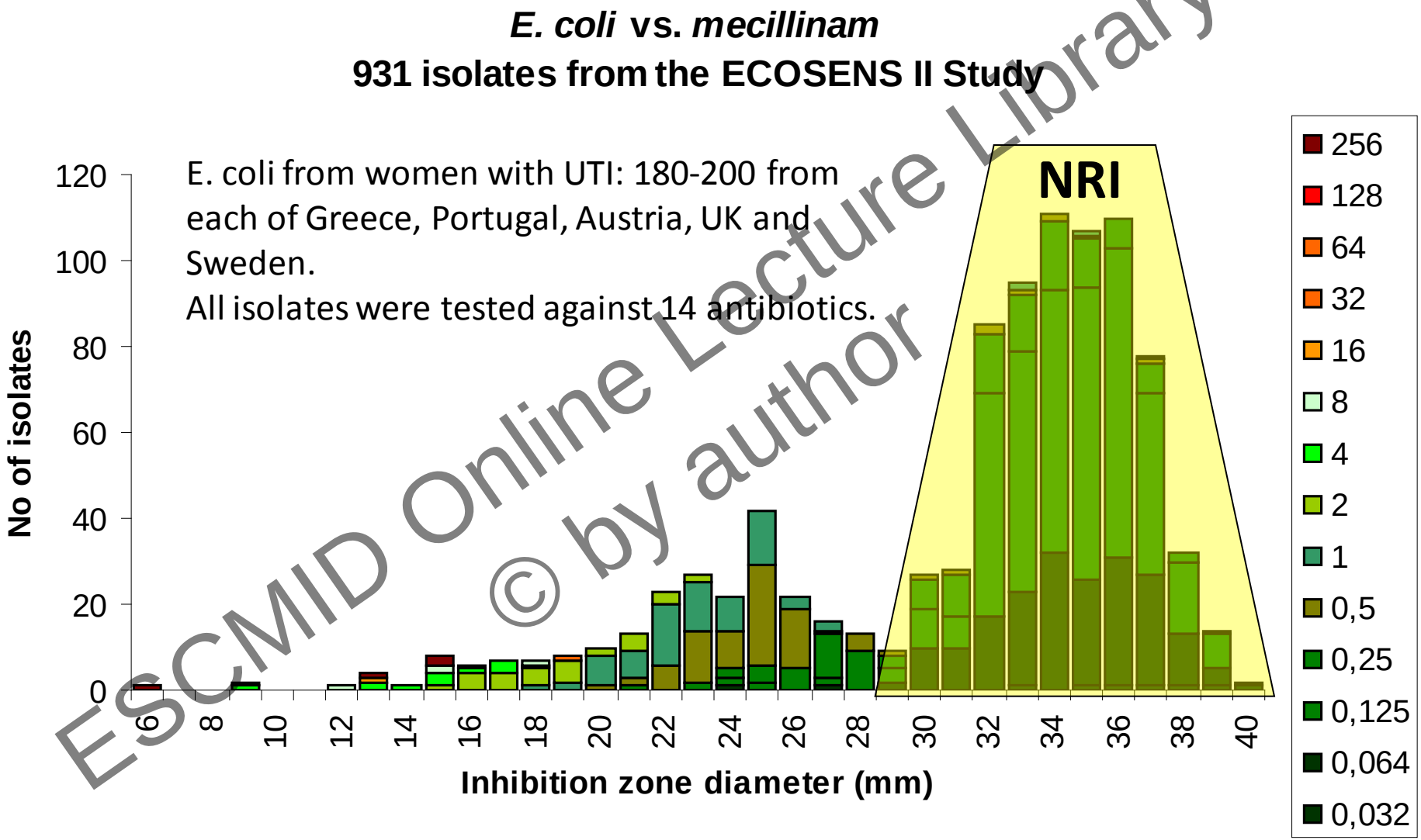
- By comparing the MIC distributions of

all isolates

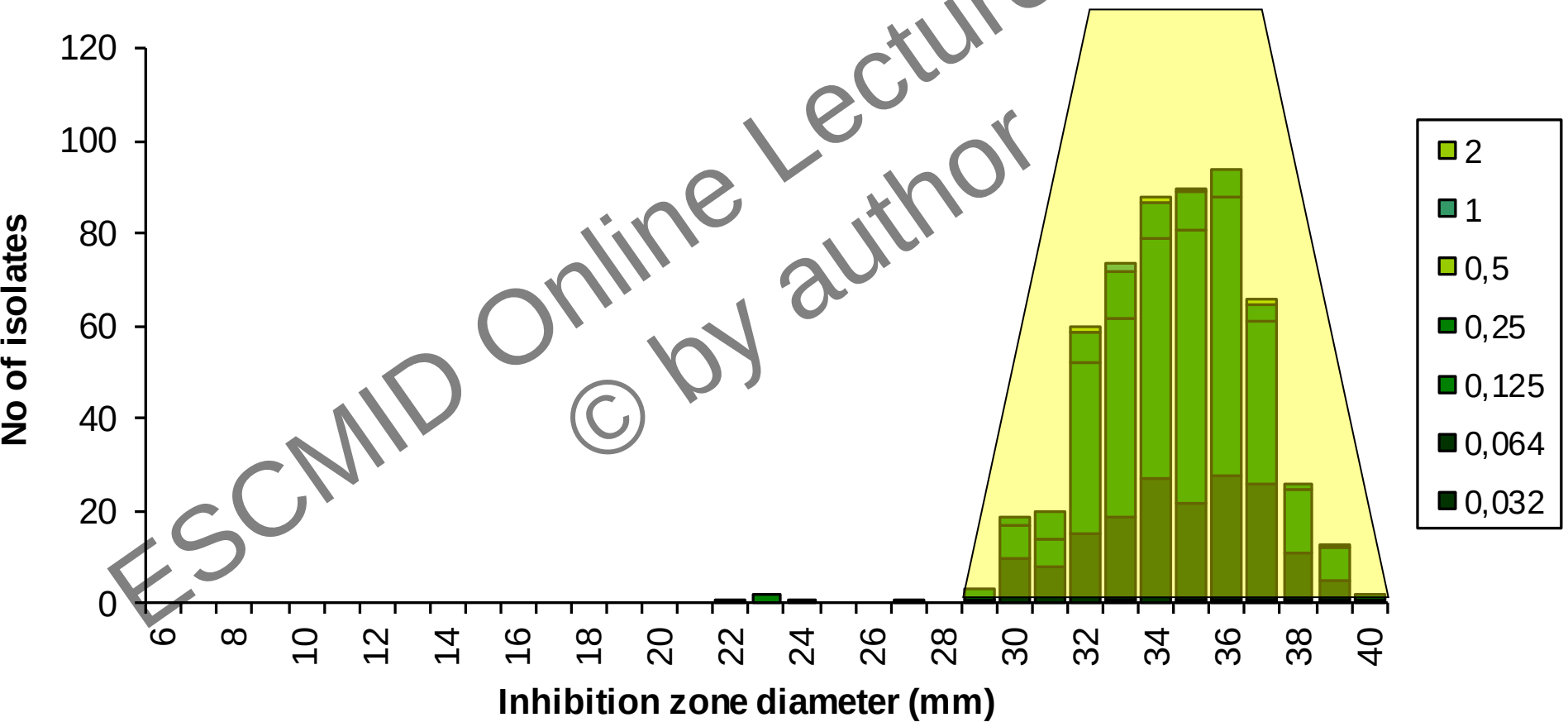
and

isolates wild type to all other agents

The original distribution with all tested organisms



The distribution when all organisms with resistance to other agents were removed.



The use of ECOFFs (1)

1. As a **tool in the determination of clinical breakpoints**
   - To avoid dividing wild type MIC distributions of target organisms
   - As a **surrogate clinical breakpoint when clinical data pertain only to wild type organisms (and** when **PK/PD data are incomplete).**

2. 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

The use of ECOFFs (2)

3. For **surveillance of antimicrobial resistance** when clinical breakpoints…
   - have not been determined
   - are not sensitive enough
   - change over time
   - differ between systems (CLSI, FDA, EUCAST etc)
   - differ between humans, cows, pigs, birds, fish and camels.

4. To **exclude resistance**
   - To exclude methicillin resistance, carbapenem resistance etc
   - food safety – in the development of functional foods

5. For **clinical susceptibility reports**?

Is it possible to report the WT/NWT status of an isolate as supplementary information to S, I and R

- *E.faecalis* with MIC 16 mg/L to gentamicin would be reported: R^{WT}
- *E.coli* with MIC 0.5 mg/L to ciprofloxacin would be reported: S^{NWT}
- *E.faecalis* with MIC 1.0 mg/L to daptomycin would be reported: IE^{WT}
- *K.pneumoniae* with MIC 1.0 mg/L (and a KPC) to meropenem would be reported: S^{NWT}