How do breakpoints relate to clinical every day life?

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Antimicrobial susceptibility testing of bacteria and fungi

- **To choose appropriate therapy and predict clinical outcome in individual patients**
- **To obtain a basis for empiric therapy**
- **To screen for organisms with exceptional (spectacular) resistance (MRSA, VRE, ESBL, KPC, NDM, MDRTB etc)**
  - **Public health: to prevent dissemination in health care and community**
- **To determine the rate of resistance development**
  - To understand and predict resistance development
  - To form strategies to counteract antimicrobial resistance development and to measure success and failures of strategies

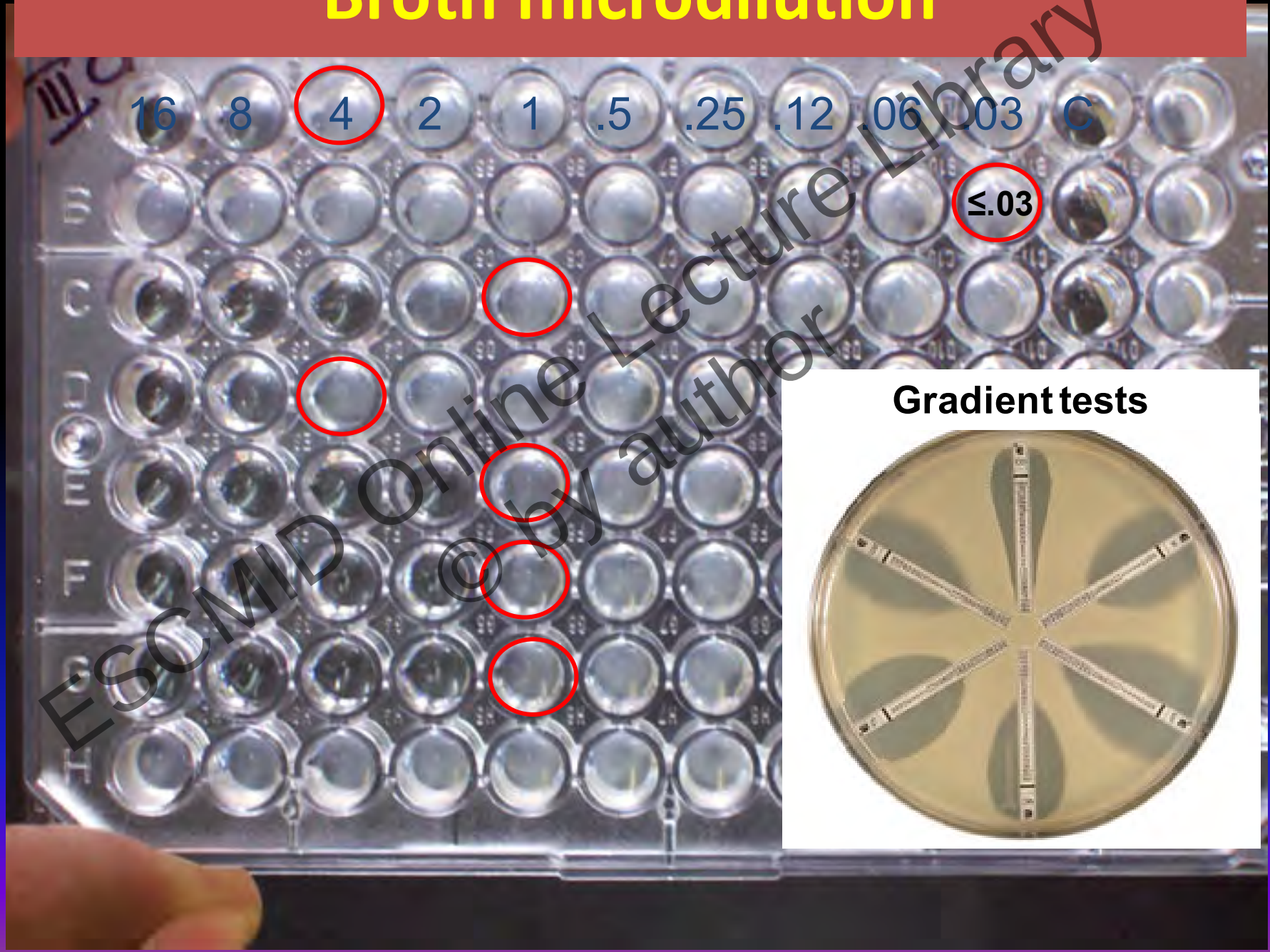
Methods for susceptibility testing

- **Phenotypic test methods**
  based on **antimicrobial activity (MIC)** and **breakpoints**
  - MIC, disk diffusion, automated systems like Phoenix, Vitek2, Microscan
  - **Predicts susceptibility and resistance**
  - **Quantifiable**
- **Genotypic test methods**
  based on the detection of a **resistance gene** or its **product**
  - mecA, vanA, vanB, ….PBP2, … betalactamase detection (enzyme detection, Maldi Tof)
  - **Predicts resistance, not sensitivity**
  - **Not quantifiable**
  - **Useful for epidemiological purposes**
- **By deduction** – ”expert rules”
  - If MRSA then report all betalactam antibiotics R – or soon not?
    If ESBL-positive, then report betalactam antibiotics R – but not any longer!
    If erythromycin-resistant, then report all macrolide antibiotics as R;
  - **Some rules predict susceptibility, others resistance.**
  - **Unreliable!**
  - **Not quantifiable!**

Phenotypic susceptibility testing are based on

MIC

Broth microdilution



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

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QUICK NAVIGATION

The European Committee on Antimicrobial Susceptibility Testing - EUCAST

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

EUCAST has a subcommittee on antifungal susceptibility testing. Subcommittees on expert rules for antimicrobial susceptibility testing and antimicrobial susceptibility testing of anaerobes have completed their tasks and have been disbanded.

Most antimicrobial MIC breakpoints in Europe have been harmonised by

EUCAST News

17 Jan 2012
Posaconazole vs. Aspergillus breakpoints and RD

12 Jan 2012
Amphotericin and itraconazole aspergillus breakpoints and RDs

31 Dec 2011
EUCAST AFST Subcommittee distributes for consultation.

24 Dec 2011
EUCAST Breakpoint Tables v 2.0

Vancomycin MICs in S. aureus
Median MIC of each population in yellow

	0	0	0.01	0.02	0.03	0.06	0.13	0.3	0.5	1	2	4	8	16	32	64	128	256	512
Staphylococcus aureus																0	0	0	0
Staphylococcus aureus																0	0	0	0
Staphylococcus aureus																0	0	0	0
Staphylococcus aureus																0	0	0	0
Staphylococcus aureus	0	0	0	0	0	0	1	2	316	82	0	0	0	0	0	0	0	0	0
Staphyloc																		0	0
Staphyloc																		0	0
Staphyloc																		0	0
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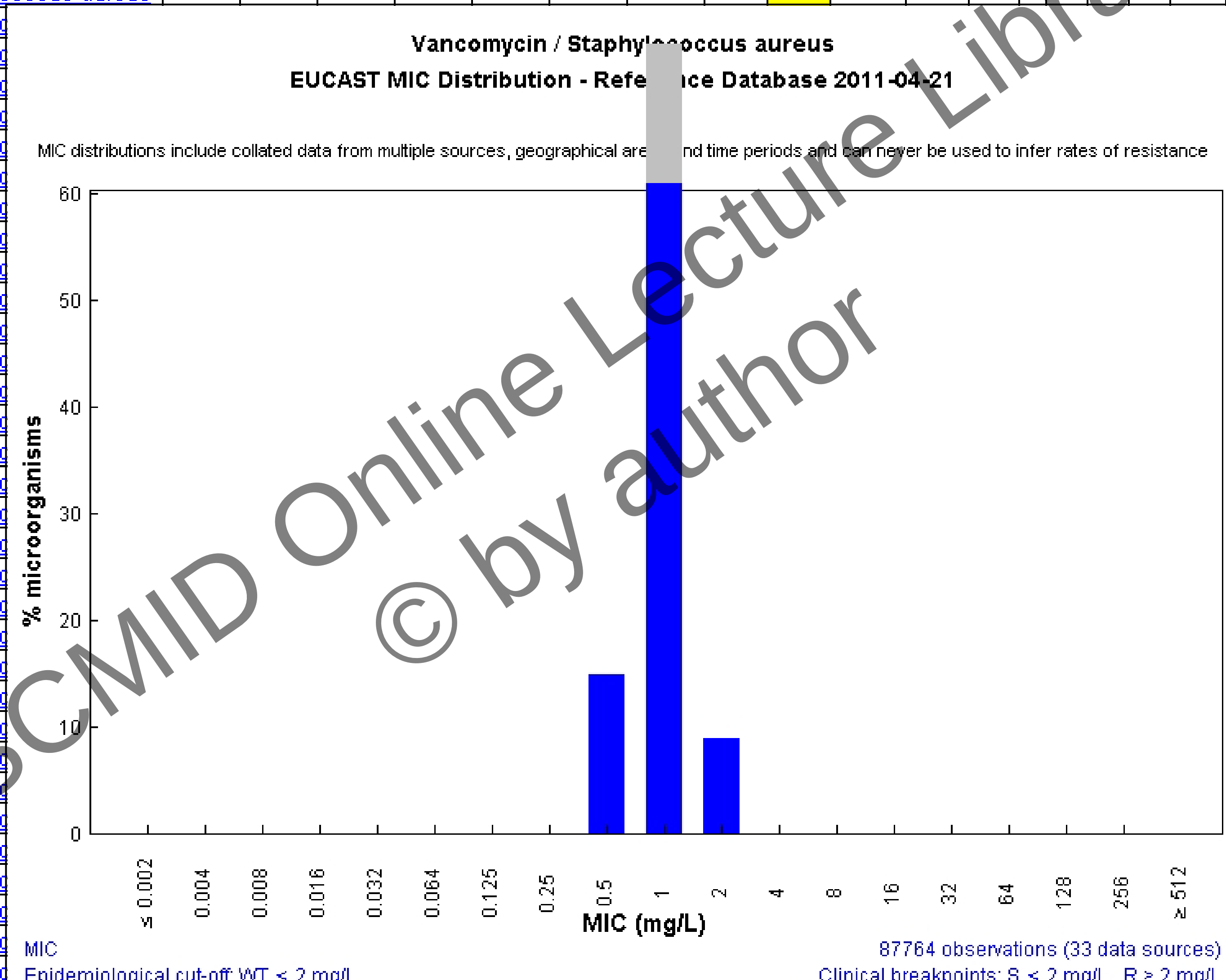
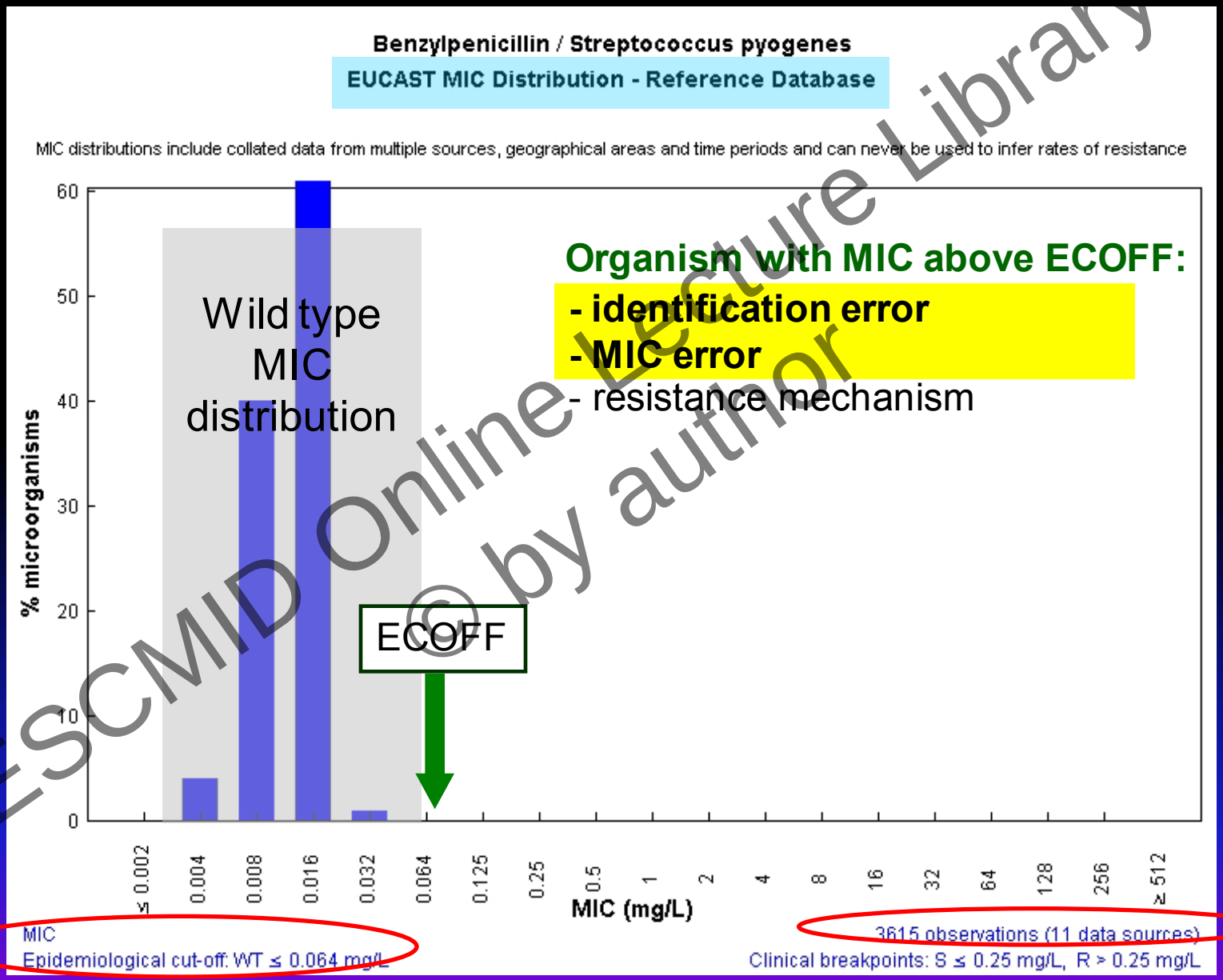
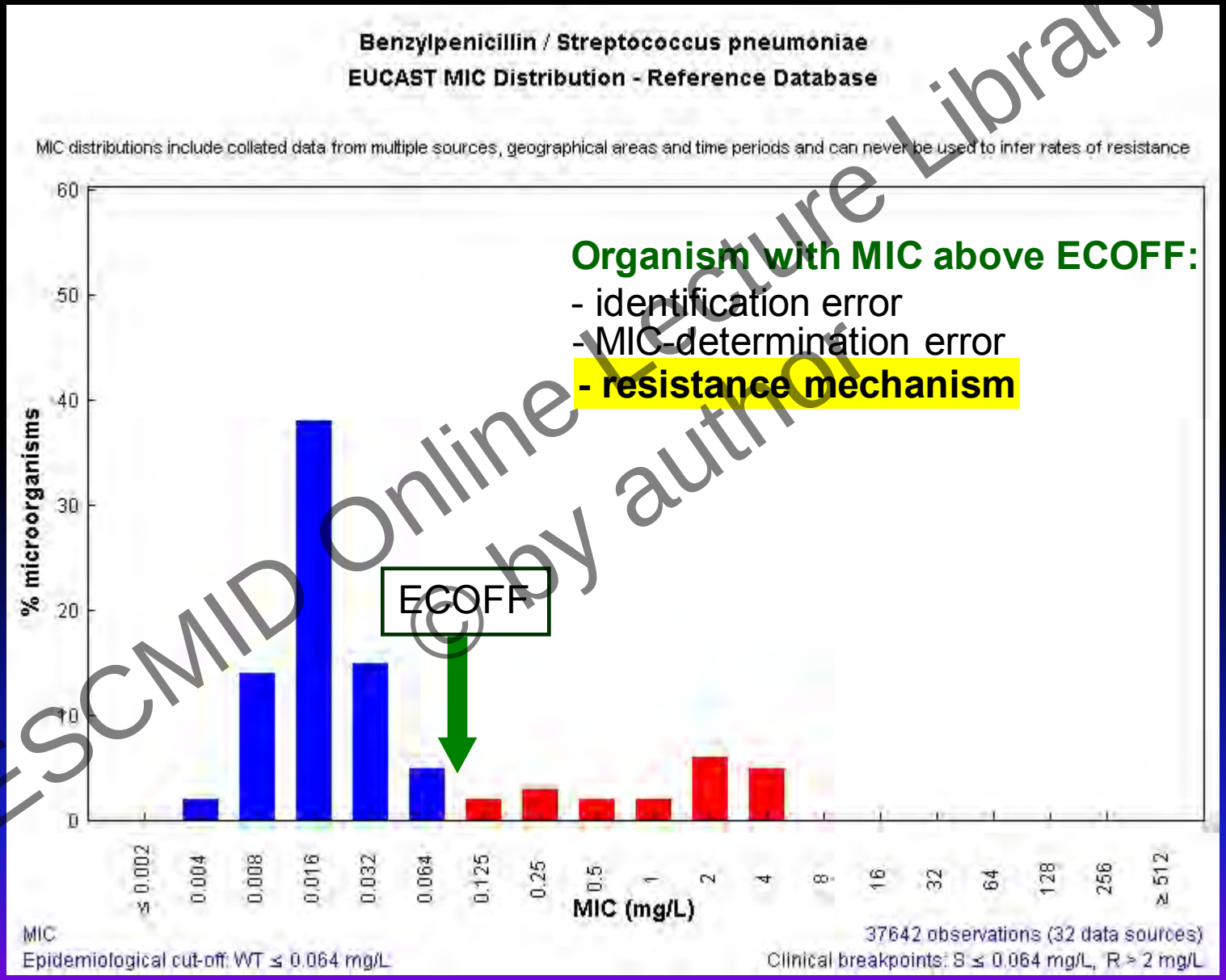
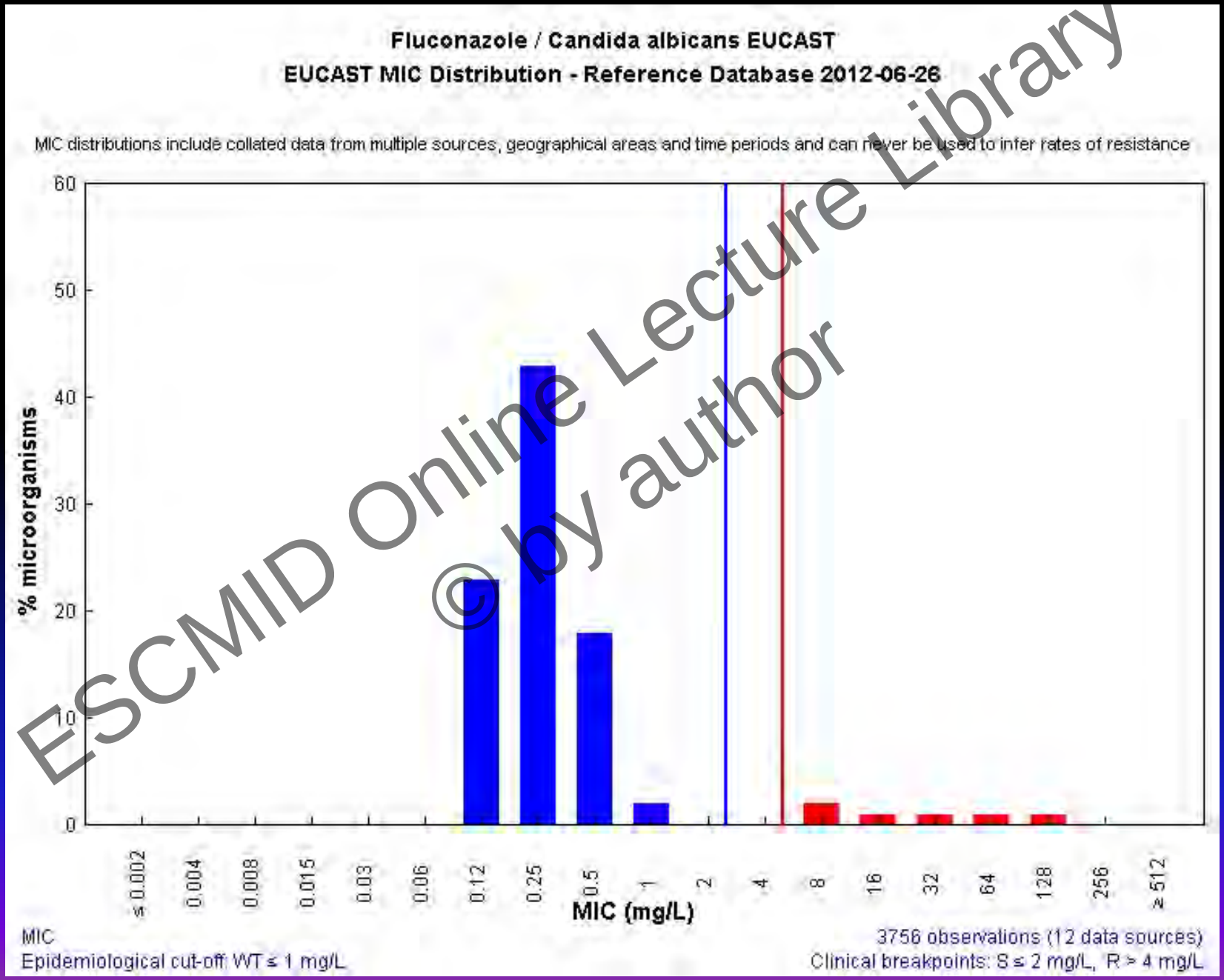
Staphyloc																		0	0
Staphylococcus aureus I	0	0	0	0	0	0	0	0	0	26	100	0	0	0	0	0	0	0	0
Staphylococcus aureus I	0	0	0	0	0	0	0	0	0	82	75	0	0	0	0	0	0	0	0
Staphylococcus aureus I	0	0	0	0	0	0	0	0	0	100	55	0	0	0	0	0	0	0	0
Staphylococcus aureus I	0	0	0	0	0	0	0	0	0	17	116	0	0	0	0	0	0	0	0





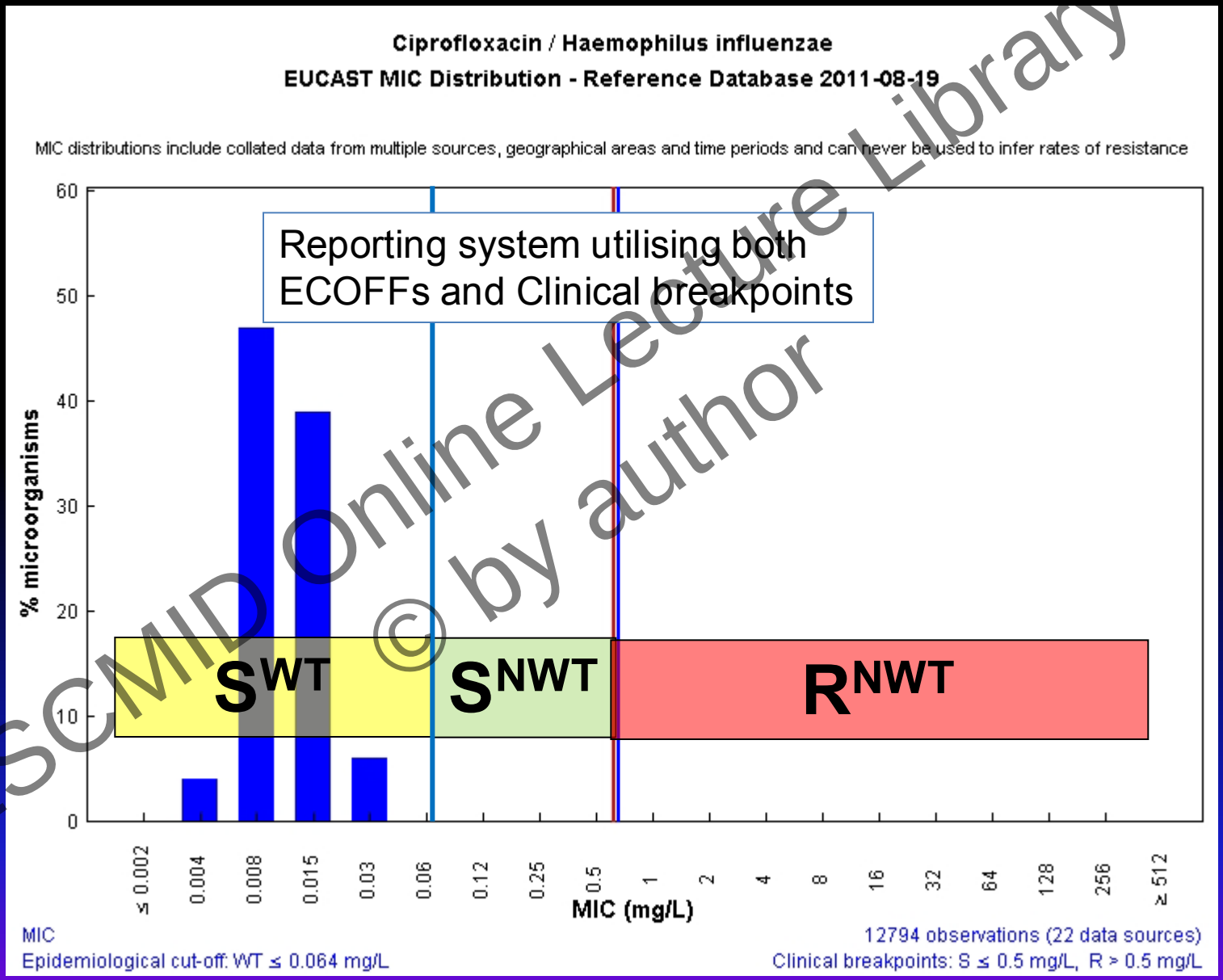


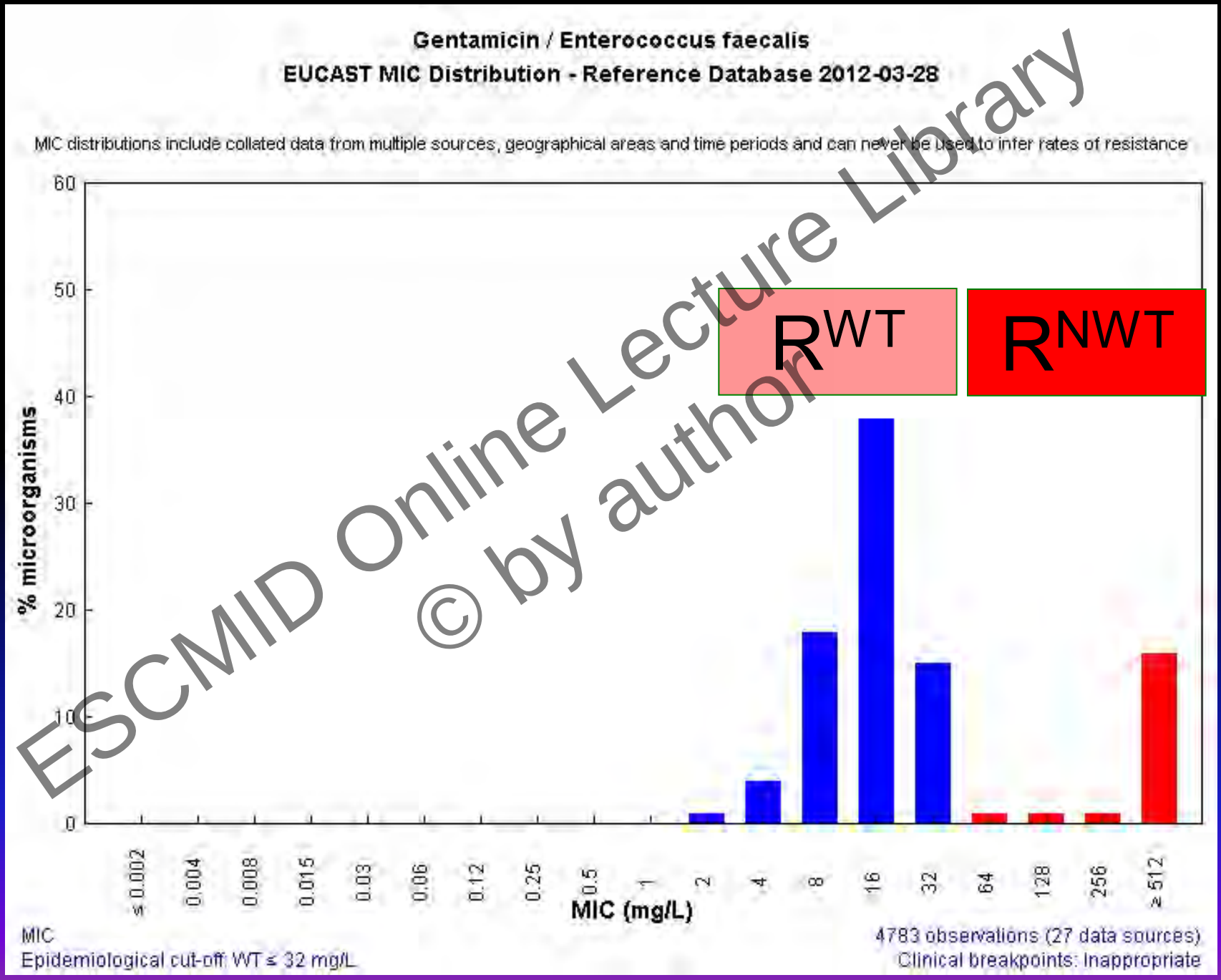


EUCAST MIC distributions
WT, NWT and ECOFF

- The **ECOFF** is the breakpoint which provides the most sensitive measure of resistance. It does not change over time, origin of the isolates or with geography.
  It is tied to the agent, the species and a standardised method.

- **Be prepared to ask (as a clinician) or answer (as the microbiologist) ”if the isolate is wild type or non-wild type to the relevant drug”.**





Clinical breakpoints

are determined by

- breakpoint committees (EUCAST, CLSI)

- by medicines agencies (FDA, EMA, national medicines agencies) as part of the regulatory process

EUCAST was formed in 1996 and reformed in 2001.

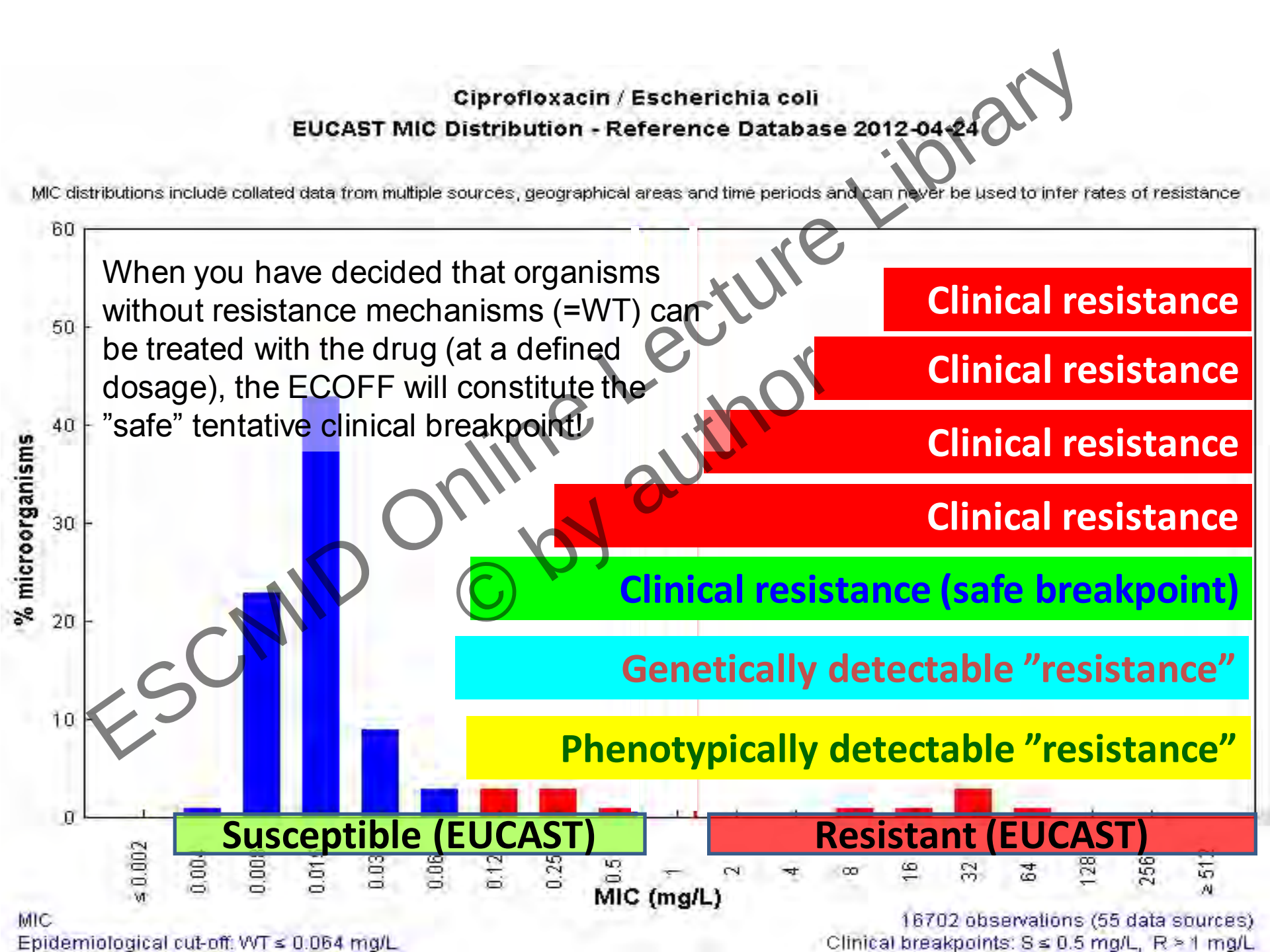
Committee	Country	Regulatory agreement
EUCAST [1]	Europe	Yes[1]
CLSI	USA	No
FDA[2]	USA	As part of the regulatory process

[1]EUCAST is the umbrella for national breakpoint committees in Europe: BSAC, CA-SFM, CRG, (DIN), NWGA & SRGA and is the breakpoint committee of EMA.

[2]FDA has no committee; breakpoints are suggested by company and evaluated by individual rapporteurs as part of approval process.

Tools needed for determining **CLINICAL BREAKPOINTS**

1. Dose or doses
2. Clinical indications
3. Target organisms
4. Individual MIC-distributions for target organisms
   - breakpoints must not divide MIC-distributions of WT target organisms
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 (clinical outcome vs. MIC)
9. Epidemiological cutoff values, Pk/Pd-indices and clinical data together determine the **CLINICAL BREAKPOINT**

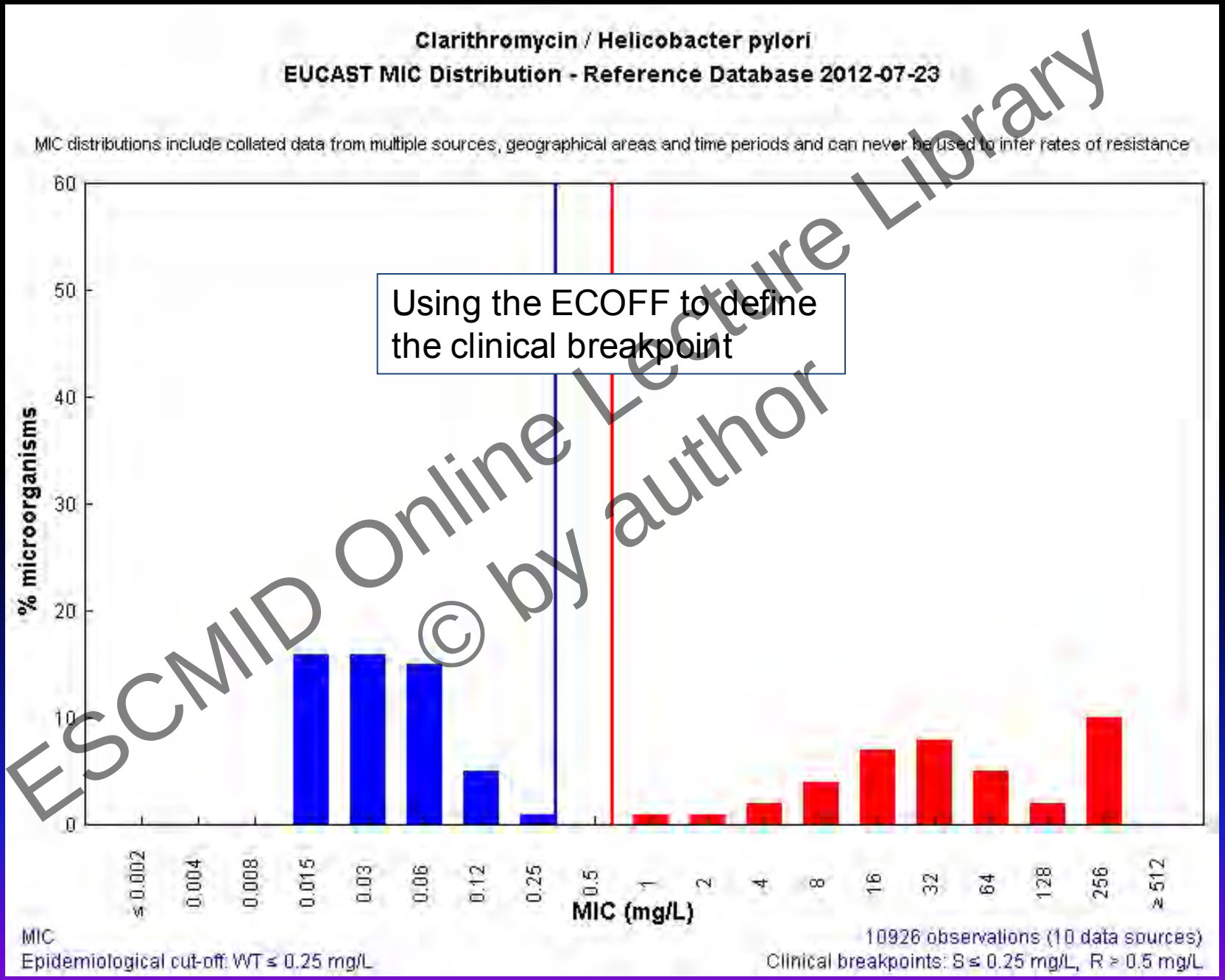


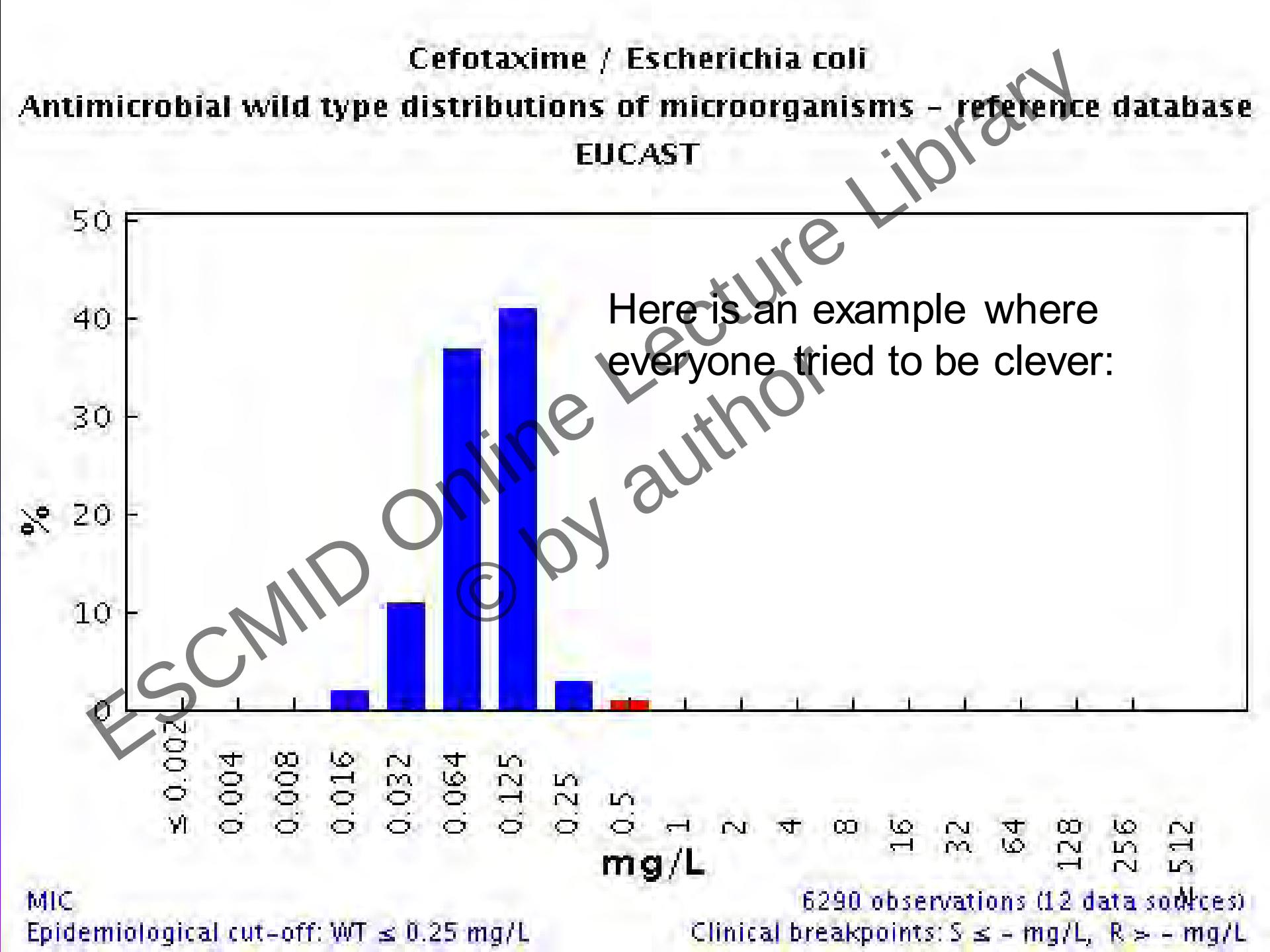
Clinical breakpoints from EUCAST

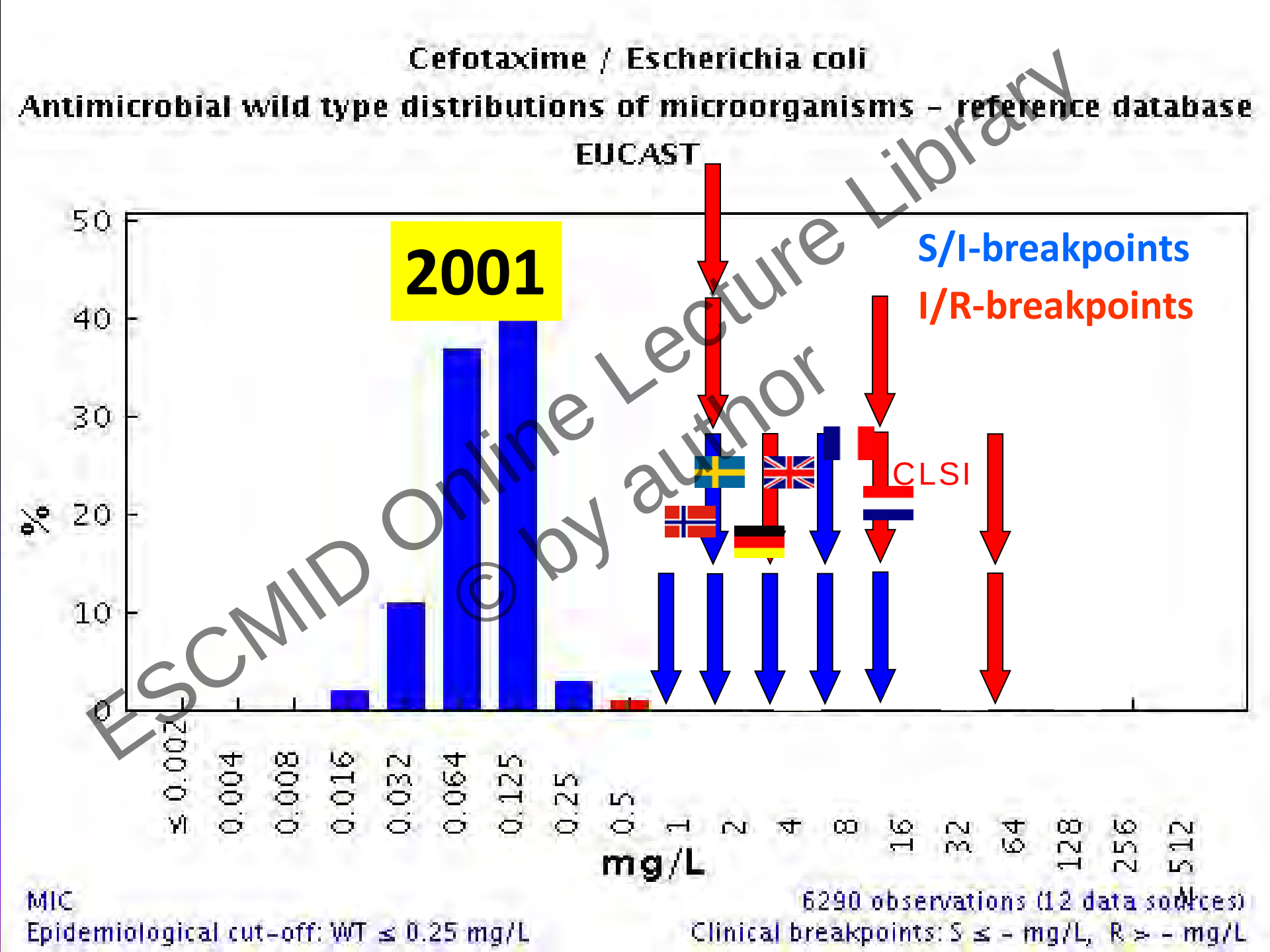
- synthesis of the ECOFF, the Pk/Pd-cut off and the clinical cut-off, sometimes they point to the same value, sometime one needs to adjust one or several dilutions.

- The ECOFF is always available, but either or both of the other two may not be!
  When this is the case, a "tentative clinical breakpoint", based on (a) the evidence that the drug is successful against wild type isolates and (b) the ECOFF, may be decided on.

  Here is one example:

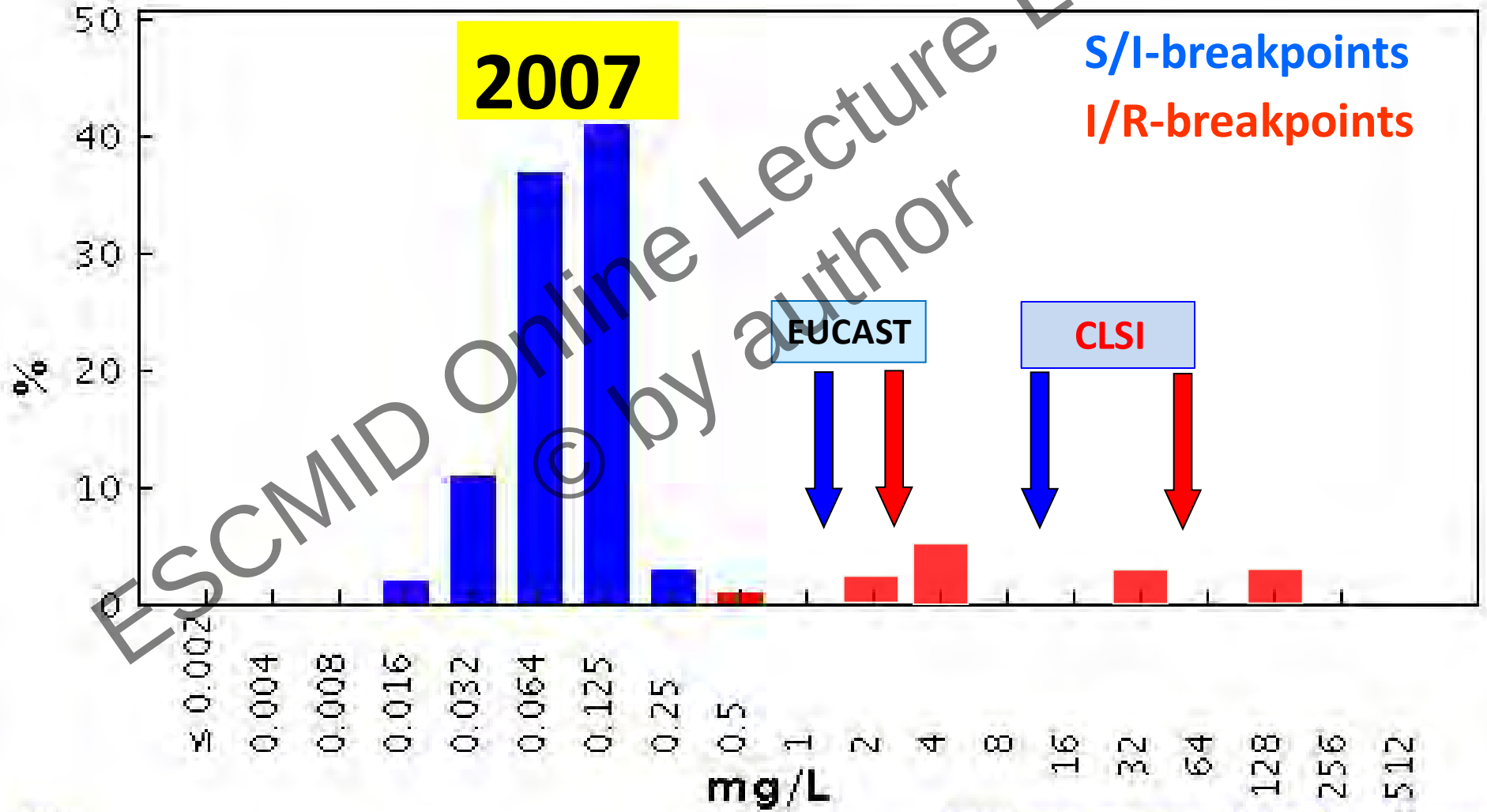






Cefotaxime / Escherichia coli

Antimicrobial wild type distributions of microorganisms – reference database EUCAST



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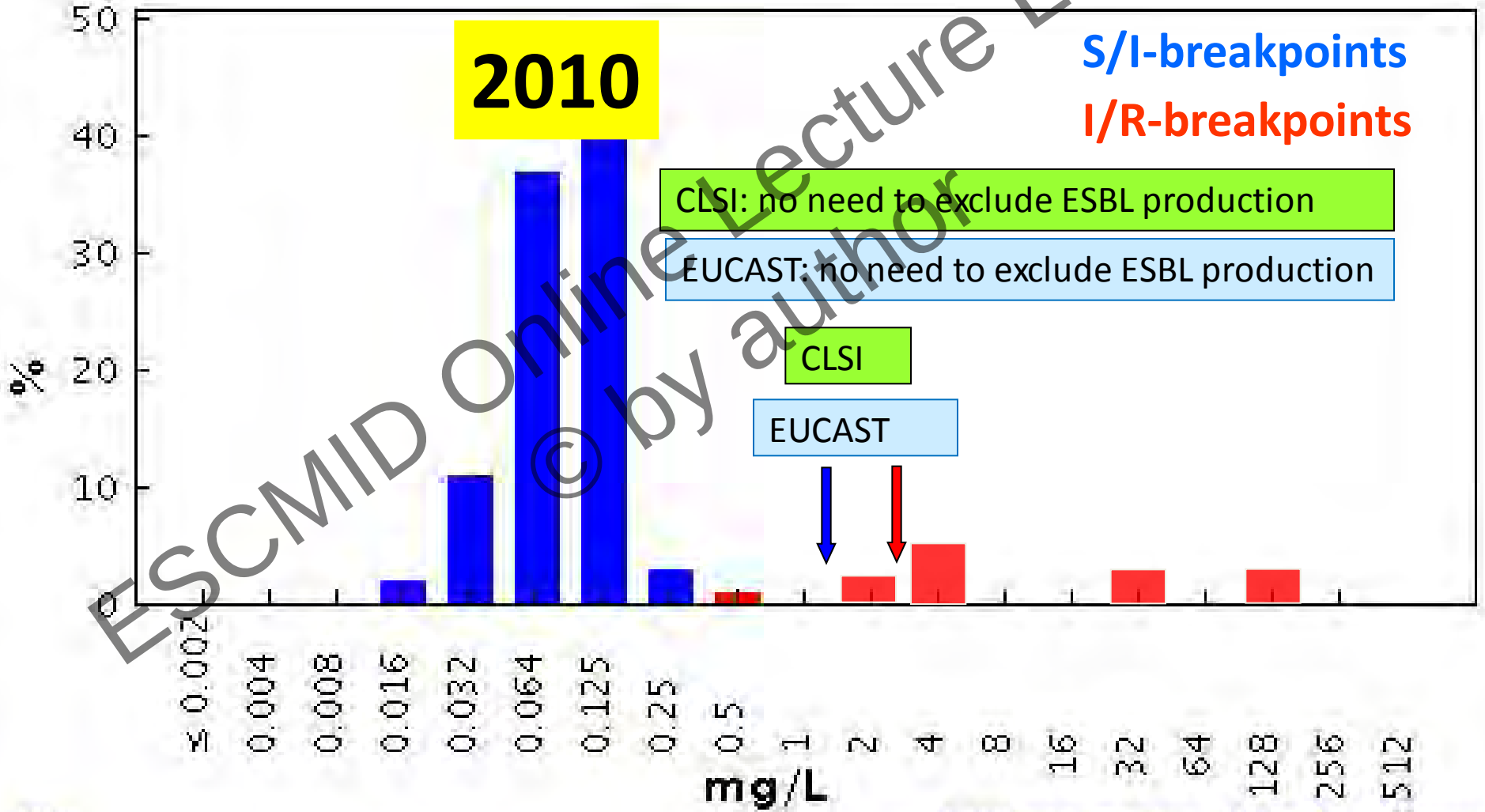
Antimicrobial wild type distributions of microorganisms – reference database EUCAST




R R I S
R S A S
B I S
R I S S R
ESCMID Online Lecture
© by author

Susceptible (S)

- A micro-organism is defined as susceptible by a level of antmicrobial activity associated with a high likelihood of therapeutic success.
- A micro-organism is categorized as susceptible by applying the appropriate breakpoint in a defined phenotypic test system.
- Note: This breakpoint may be altered with legitimate changes in circumstances

Intermediate (I)

- A micro-organism is defined as intermediate by a level of antimicrobial activity associated with indetermiate therapeutic effect.

- A micro-organism is categorized as intermediate by applying the appropriate breakpoints in a defined phenotypic test system.

- Note: This breakpoints may be altered with legitimate changes in circumstances.

Resistant (R)

- A micro-organism is defined as resistant by a level of antimicrobial activity associated with a high likelihood of therapeutic failure.

- A micro-organism is categorized as resistant by applying the appropriate breakpoint in a defined phenotypic test system.

- Note: This breakpoint may be altered with legitimate changes in circumstances**Resistant (R)**

Breakpoints can fail in several ways!

- Fail to predict failure (undercall resistance)
  - CLSI piperacillintazobactam breakpoints in Pseudomonas
  - Imipenem breakpoints in MRSA
- Fail to predict success (overcall resistance)
  - Penicillin breakpoints in *S.pneumoniae* in pneumonia
- Generally fail to be useful (lack of correlation with either success or failure)
  - CLSI Erythromycin breakpoints in H.influenzae (dividing a WT population in three SIR-categories)

Breakpoints that failed to predict failures!

- Chloramphenicol in H.influenzae (70ies)
  - Lower breakpoint for H.influenze from 8 to 2 mg/L
- Carbapenem in MRSA (80ies)
  - Breakpoints removed, expert rule, ”test for MRSA”
- Cephalosporin in Enterobacteriaceae (1980 – 2010)
  1. Breakpoints only valid if ESBL excluded
  2. Later, lower breakpoint and report as tested
- Erythromycin in *S.pneumoniae*
  - Lower breakpoint
- Piperacillintazobactam in Pseudomonas (1990 – 2010)
  - Lower breakpoint from 64 to 16 mg/L
- Ciprofloxacin in systemic Salmonella infections (2005)
  - Lower ciprofloxacin breakpoint in Salmonella
- Vancomycin in *S.aureus* (2005)
  - See next slide

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

ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

ESCMID
EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

National Breakpoint Committees
F, N, NL, S, UK,

EUCAST General Committee
All European Countries

EUCAST Steering Committee
BSAC, CA-SFM, CRG, NWGA, SRGA
And 3 reps from the General Committee*

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Subcommittees
Antifungals
(Expert Rules)
Resistance mechanisms

Expert groups

*Currently: Austria, Denmark and Spain

Area Committee - microbiology

Area Committee - chemistry

Area Committee - hematology

Subcommittee on Antimicrobial Susceptibility Testing

Subcommittee on Antifungal Susceptibility Testing

Subcommittee on …

12 voting members (industry, profession)*

12 advisors (industry, profession, CDC, FDA)

*Chairmen from industry and profession on rotation

EUCAST and CLSI are different

EUCAST

- Profession together with regulatory authorities
- Funded by ESCMID, ECDC and national breakpoint committees.
- Industry consultative role.
- Decision by consensus.
- Five meetings per year.
- EUCAST=EMEA brpt committee.
- Clinical breakpoints and ECOFFs
- Rationale for decisions published
- Documents free of charge (on web)

CLSI

- Industry, the profession, advisory regulators.
- Funded by industry and sales of output.
- Industry part of decision process
- Decision by vote.
- Two meetings per year.
- CLSI technical standing with FDA but breakpoints not accepted by FDA.
- Clinical breakpoints
- Rationale for decisions not published.
- Documents for sale

EUCAST and CLSI breakpoints are different

	Antibiotics	Identical breakpoints		
	compared	S and R	Only S	Only R
Enterobacteriaceae	33	3	4	3
Pseudomonas spp.	16	1	5	2
Acinetobacter spp.	10	1	4	2
Staphylococcus spp.	27	4	6	2
Enterococcus spp.	6	0	2	3
Strept A, B, C and G	13	2	2	2
S. pneumoniae	24	3	2	5
Other streptococci	9	0	0	2
Haemophilus spp.	25	0	3	0

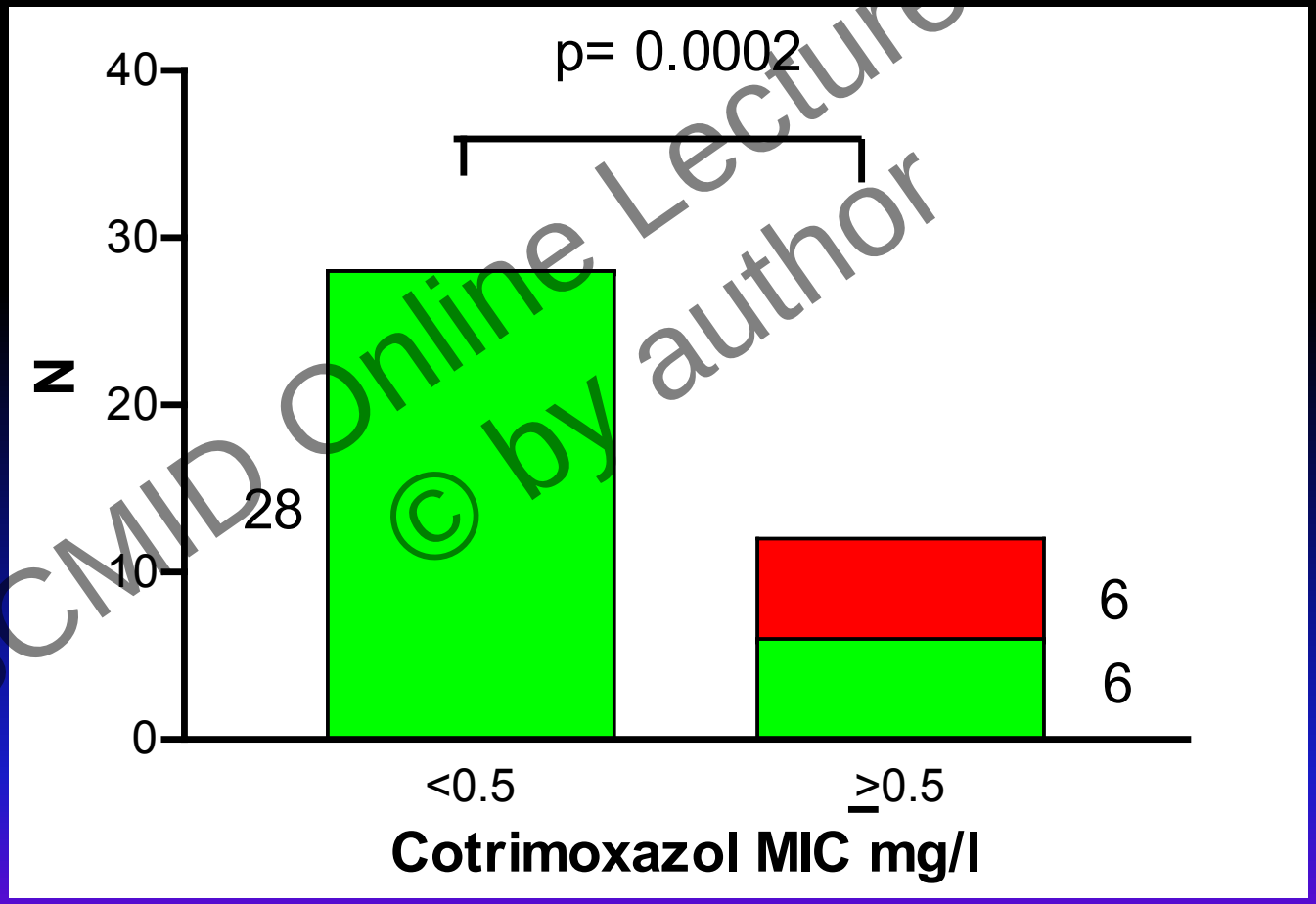
The significance of vancomycin breakpoints

	MIC mg/L	N=		Reference
S. aureus bacteremia	≤ 2 ≥ 4	42 21	12 % mortality 63 % mortality	Fridkin et al, 2003, CID; 36: 429
S. aureus bacteremia	≤ 0.5 1-2	87	44 % failure 90.5 % failure	Sakoulas et al, 2004, JCM; 42: 2398
S. aureus bacteremia	AUC/PAP ≤0.9 vancomycin MIC 0.5-2mg/L AUC/PAP >0.9 vancomycin MIC 2-4mg/L	5 48	MIC 2-4mg/L had longer bacteraemia, more fever days but equivalent mortality at end of therapy	Charles et al, 2004, CID; 38: 448
S. aureus bacteremia	< 2 > 2	79	15% failure 38% failure	Hidayat et al, 2006, Arch Intern Med; 166: 2138
S. aureus bacteremia	≥2	414	MIC ≥ 2 predicted mortality (OR 6.4)	Soriano et al, 2008, CID; 46: 193
Nosocomial MRSA infections	0.5–1 1.5–2	40 39	15 (10 % mortality) 38 (24 % mortality)	Hidayat *et al* (2006)

Vancomycin breakpoints for Staphylococci were recently revised by both CLSI and EUCAST

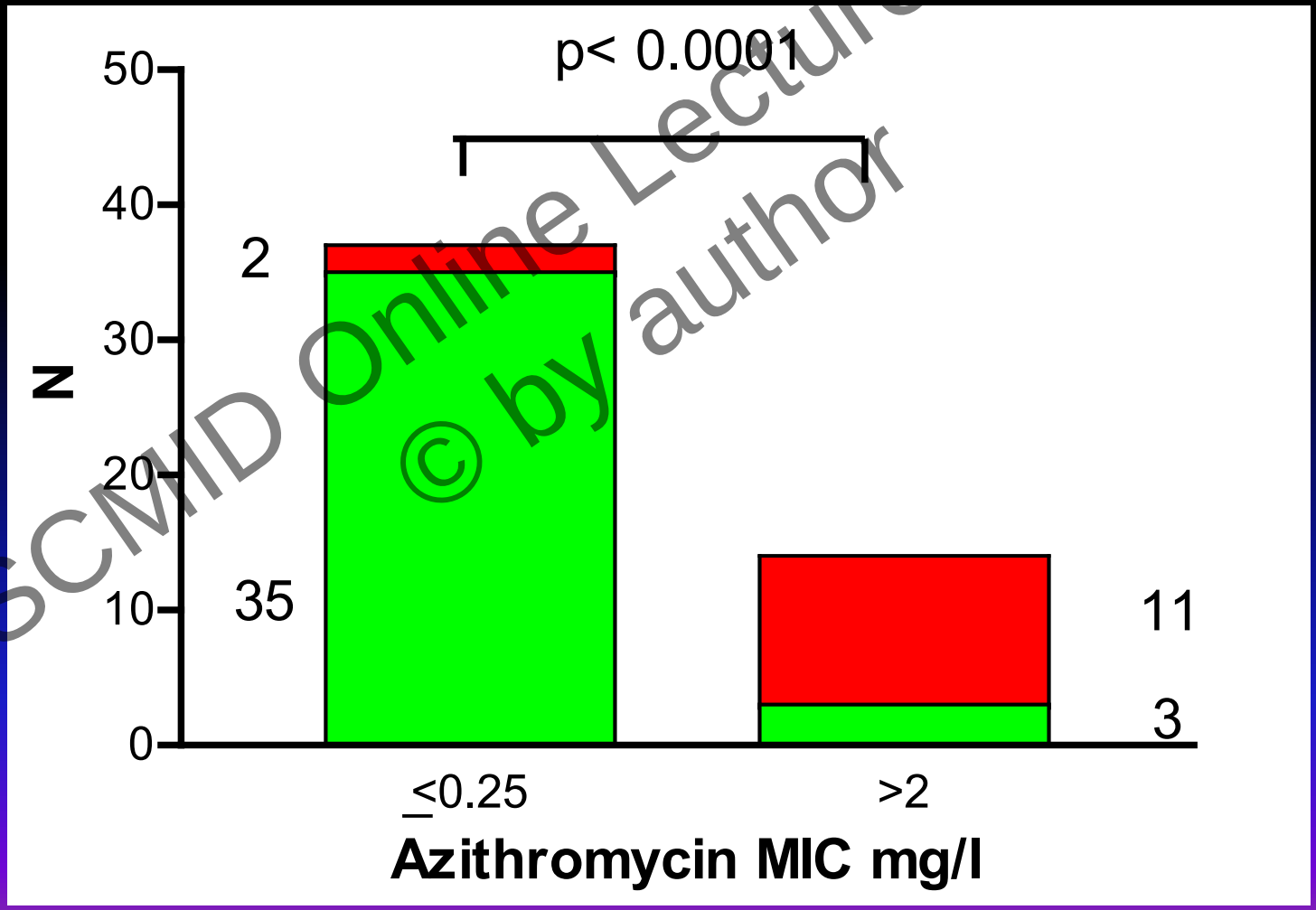
Trimethoprimsulfamethoxazole an *H. influenzae*
Bacteriological failure in AOM

Based on data from Leiberman et al, PIDJ 2001



Azithromycin and *S. pneumoniae*
Bacteriological failure in AOM

Based on data from Dagan et al, PIDJ 2000; AAC 2000, IJID 2003



EUCAST - breakpoints for new drugs with EMA

- Daptomycin √
- Tigecycline √
- Doripenem √
- Telavancin √
- Glycopeptides (one ongoing)
- Cefalosporines (activity against MRSA – two agents ongoing)
- Anti-Mtb (two agents - ongoing)

- Glycopeptide (withdrawn)
- Fluoroquinolone (withdrawn)
- Diaminopyrimidine (withdrawn)

- Extensions of indications (currently none)

EMA = European Medicines Agency

Miscellaneous organisms

Consultation with expert groups on breakpoints and methods

- Neisseria meningitidis (review) - 2012
- Moraxella catarrhalis (finalized) - 2011
- Helicobacter pylori (finalized) - 2011
- Clostridium difficile (finalized) - 2011
- Listeria monocytogenes (finalized) - 2011
- Campylobacter (on consultation) - 2012
- Pasteurella multocida (on consultation) - 2012
- Corynebacteria (ongoing) - 2012
- Yersinia (ongoing) - 2012
- Burkholderia cepacia (started) - 2012
- …

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EUCAST has a subcommittee on antifungal susceptibility testing and on methods for detection of resistance mechanisms of clinical and/or epidemiological importance.

Subcommittees on expert rules for antimicrobial susceptibility testing and antimicrobial susceptibility testing of anaerobes have completed their tasks and have been disbanded.

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

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

EUCAST News

18 Jun 2012
Media preparation v 2.0 - new German translation

12 Jun 2012
Voriconazole and Aspergillus spp v 1.0 - rationale document now available

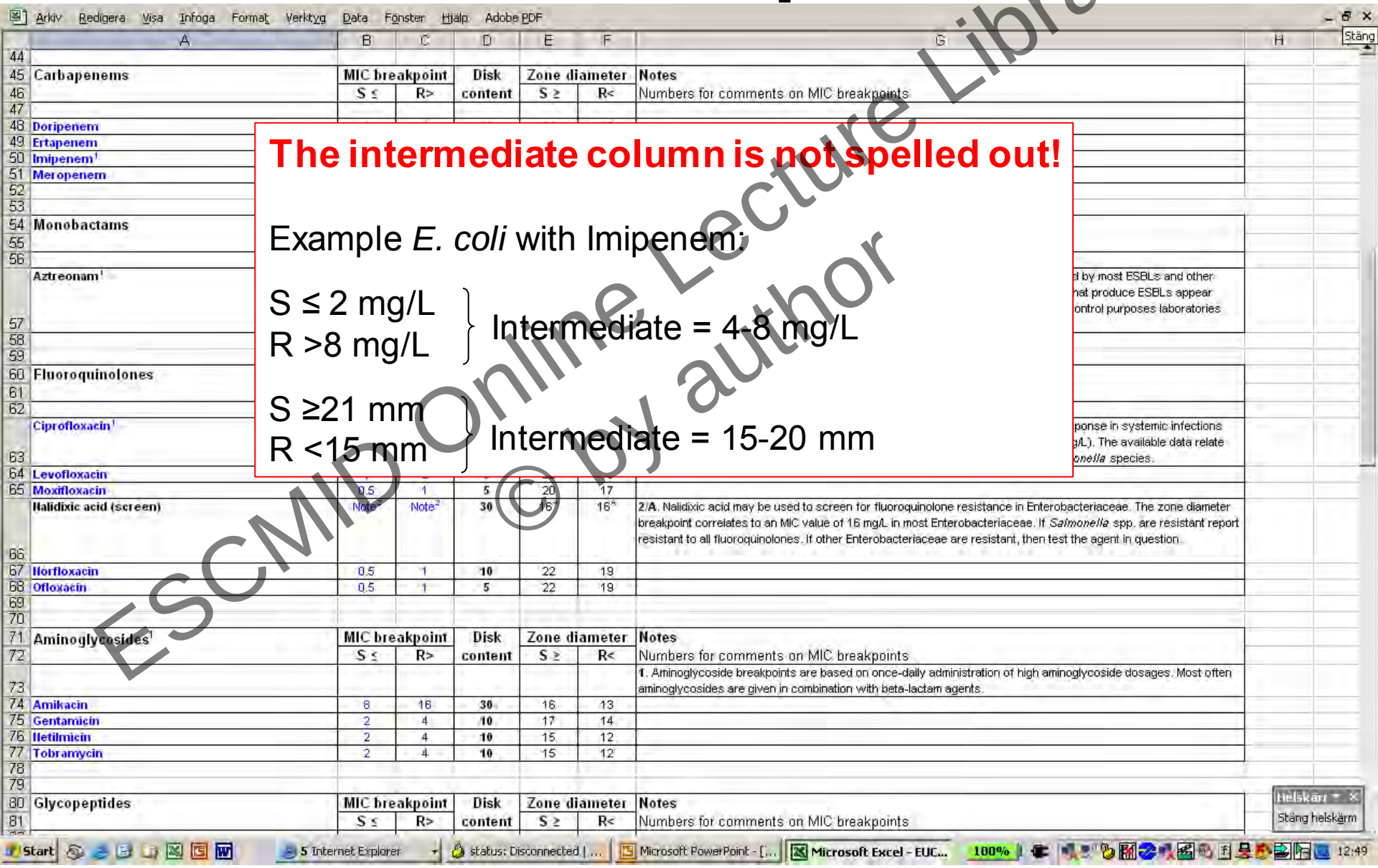
05 Jun 2012
French translations of EUCAST documents

28 May 2012
Media preparation - update with broth for fastidious organisms

09 May 2012
Amoxicillin-clavulanate and Enterobacteriaceae from urinary tract infections

About Newsfeeds

EUCAST breakpoint table



	A	B	C	D	E	F	G	H
44								
45	Carbapenems	MIC breakpoint		Disk	Zone diameter		Notes	
46		S ≤	R>	content	S ≥	R<	Numbers for comments on MIC breakpoints	
47								
48	Doripenem							
49	Ertapenem							
50	Imipenem[1]							
51	Meropenem							
52								
53								
54	Monobactams							
55								
56								
57	Aztreonam[1]						d by most ESBLs and other hat produce ESBLs appear ontrol purposes laboratories	
58								
59								
60	Fluoroquinolones							
61								
62								
63	Ciprofloxacin[1]						ponse in systemic infections g/L). The available data relate *onella* species.	
64	Levofloxacin							
65	Moxifloxacin	0.5	1	5	20	17		
66	Nalidixic acid (screen)	Note[2]	Note[2]	30	16*	16*	2/A. Nalidixic acid may be used to screen for fluoroquinolone resistance in Enterobacteriaceae. The zone diameter breakpoint correlates to an MIC value of 16 mg/L in most Enterobacteriaceae. If *Salmonella* spp. are resistant report resistant to all fluoroquinolones. If other Enterobacteriaceae are resistant, then test the agent in question.	
67	Norfloxacin	0.5	1	10	22	19		
68	Ofloxacin	0.5	1	5	22	19		
69								
70								
71	Aminoglycosides[1]	MIC breakpoint		Disk	Zone diameter		Notes	
72		S ≤	R>	content	S ≥	R<	Numbers for comments on MIC breakpoints	
73							1. Aminoglycoside breakpoints are based on once-daily administration of high aminoglycoside dosages. Most often aminoglycosides are given in combination with beta-lactam agents.	
74	Amikacin	8	16	30	16	13		
75	Gentamicin	2	4	10	17	14		
76	Netilmicin	2	4	10	15	12		
77	Tobramycin	2	4	10	15	12		
78								
79								
80	Glycopeptides	MIC breakpoint		Disk	Zone diameter		Notes	
81		S ≤	R>	content	S ≥	R<	Numbers for comments on MIC breakpoints	

The intermediate column is not spelled out!

Example *E. coli* with Imipenem:

S ≤ 2 mg/L
R >8 mg/L
} Intermediate = 4-8 mg/L

S ≥21 mm
R <15 mm
} Intermediate = 15-20 mm

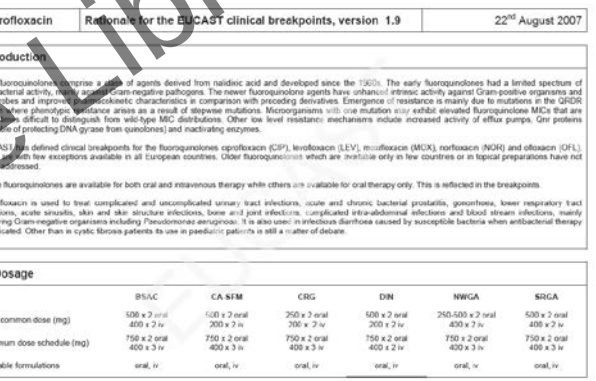
Links in EUCAST breakpoint table

Click on antibiotic for **Rationale Document**

Click on MIC breakpoint for **MIC distributions**

Click on zone breakpoint for **zone diameter distributions**

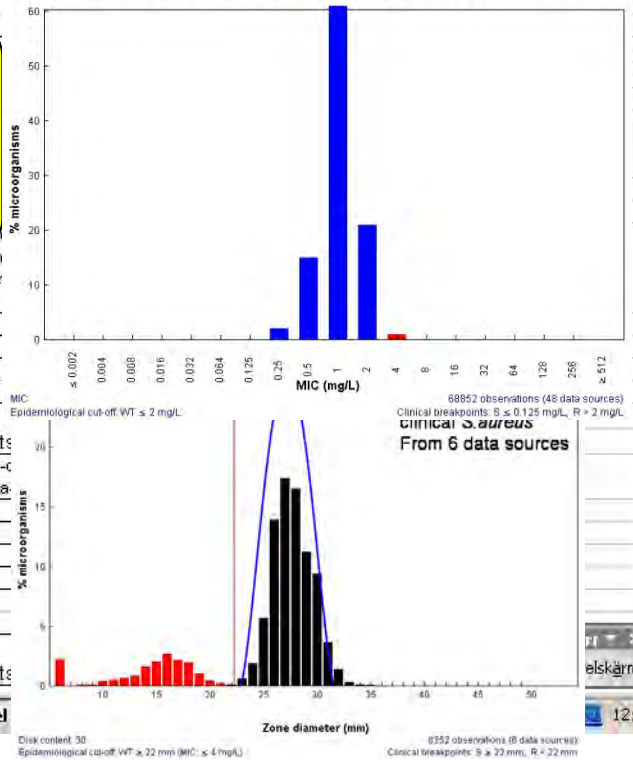
	Carbapenems	MIC breakpoint S ≤	MIC breakpoint R>	Disk content	Zone diameter S ≥	Zone diameter R<	Notes
48	Doripenem						
49	Ertapenem						
50	Imipenem[1]						
51	Meropenem						
54	**Monobactams**	**MIC breakpoint**		**Disk**	**Zone diameter**		**Notes**
55		S ≤	R>	content	S ≥	R<	Numbers for comments on MI
57	Aztreonam[1]	1	8	30	25	21	1. The aztreonam breakpoints for En clinically important beta-lactamases susceptible or intermediate with the may want to use a test which speci
60	**Fluoroquinolones**	**MIC breakpoint**		**Dis**			
61		S ≤	R>				
63	Ciprofloxacin[1]	0.5		5			
64	Levofloxacin	1	2	5			
65	Moxifloxacin	0.5	1	5			
66	Nalidixic acid (screen)	Note[2]	Note[2]	30			resistant to all fluoroquinolones. If other Enterobac
67	Norfloxacin	0.5	1	10	22	19	
68	Ofloxacin	0.5	1	5	22	19	
71	**Aminoglycosides**[1]	**MIC breakpoint**		**Disk**		**iameter**	**Notes**
72		S ≤	R>	conten		R<	Numbers for comments on MIC breakpoints
73							1. Aminoglycoside breakpoints are based on once-d aminoglycosides are given in combination with beta
74	Amikacin	8	16			13	
75	Gentamicin	2					
76	Netilmicin	2					
77	Tobramycin	2					
80	**Glycopeptides**	**MIC bre**					
81		S ≤					


Ciprofloxacin | Rationale for the EUCAST clinical breakpoints, version 1.9 | 22nd August 2007

Introduction

1. Dosage

	BSAC	CA-SFM	CRG	DIN	NWGA	SRGA
Most common dose (mg)	500 x 2 oral 400 x 2 iv	500 x 2 oral 200 x 2 iv	250 x 2 oral 200 x 2 iv	500 x 2 oral 200 x 2 iv	250-500 x 2 oral 400 x 2 iv	500 x 2 oral 400 x 2 iv
Maximum dose schedule (mg)	750 x 2 oral 400 x 3 iv	750 x 2 oral 400 x 3 iv	750 x 2 oral 400 x 3 iv	750 x 2 oral 400 x 2 iv	750 x 2 oral 400 x 3 iv	750 x 2 oral 400 x 3 iv
Available formulations	oral, iv	oral, iv	oral, iv	oral, iv	oral, iv	oral, iv



Thank you!

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