



EUCAST

EUROPEAN COMMITTEE
ON ANTIMICROBIAL
SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases



CLINICAL AND
LABORATORY
STANDARDS
INSTITUTE®

www.EUCAST.org

www.CLSI.org

Breakpoints EUCAST or CLSI?

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EUCAST and CLSI

EUCAST	CLSI
Established 1998 (National Committees formed in 1970s-80s)	Established 1970s Formerly NCCLS (National Committee for Clinical Laboratory Standards)
Susceptibility testing is sole remit	Remit covers all aspects of laboratory medicine. <p style="text-align: center;">CLSI ↓ Area Committee Microbiology ↓ Subcommittee on Antimicrobial Susceptibility testing</p>

EUCAST and CLSI

Organisation

EUCAST	CLSI
<p>Steering Committee (11) with representatives of European breakpoint committees and three representatives of other countries (plus two observers)</p> <p>5-6 meetings per year</p>	<p>Voting committee (12) with representatives of the profession and industry</p> <p>12 “observers” (profession, industry, FDA, CDC, EUCAST)</p> <p>2 meetings per year</p>
<p>General committee with representatives of all European (and some non-European) countries, FESCI & ISC.</p> <p>Consultation and one open meeting per year</p>	<p>Open membership by subscription</p>
<p>Industry consultative role</p>	<p>Industry part of decision process</p>

EUCAST and CLSI

Relationship to regulatory authorities

EUCAST	CLSI
EUCAST sets breakpoints for European Medicines Agency (EMA) Advises ECDC and EFSA	United States Food and Drug Administration (FDA) sets official breakpoints CLSI sets breakpoints for new agents if requested by the company.
EUCAST breakpoints in EMA Specifications of Product Characteristics (SmPCs)	FDA breakpoints in US SmPCs.
EMA Standard Operating Procedure defines relationship with EUCAST	

EUCAST and CLSI

Breakpoint setting for new agents

EUCAST	CLSI
In parallel with submission to EMA for product licence	In addition to FDA if requested by the company (cannot suggest anything different from FDA for 2 years)
Closed presentation to Steering Committee (SC) by company	Open presentation to CLSI by the company
Discussion process involving the SC, EMA, National Breakpoint Committees and the company over several weeks	Discussion following the presentation
Consensus decision on breakpoints by SC	Voting committee vote following discussion

EUCAST and CLSI

Review of breakpoints for existing agents

EUCAST	CLSI
Review and harmonisation of breakpoints for all the most widely used agents in Europe completed	Few changes to breakpoints, e.g cephalosporins, carbapenems and for Enterobacteriaceae, piperacillin-tazobactam for <i>P. aeruginosa</i> , vancomycin for <i>S. aureus</i> . (official FDA breakpoints unchanged)

EUCAST and CLSI Funding

EUCAST	CLSI
Contract with ECDC	Subscriptions of members
ESCMID	Sale of documents
National Breakpoint Committees	Government grant to support distribution of documents to developing countries

EUCAST and CLSI Documents

EUCAST	CLSI
Clinical breakpoints	Clinical breakpoints
Rationale documents (RDs) giving breakpoint background	
Method guidelines	Method guidelines
Comprehensive expert rules with supporting explanations and references	Some expert rules included in breakpoint tables
Documents free	Documents for sale

EUCAST and CLSI

Website resources

EUCAST

CLSI

<http://www.EUCAST.org>

All EUCAST documents

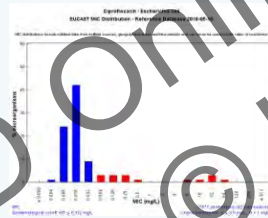
<http://www.CLSI.org>

All CLSI documents

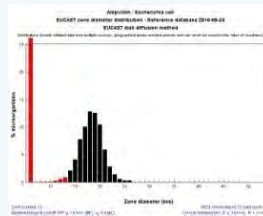
<http://mic.eucast.org/Eucast2>

MIC and zone diameter distributions

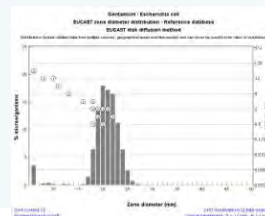
MIC distributions



Zone diameter distributions



MIC-zone diameter correlations



EUCAST and CLSI Breakpoint expression

EUCAST	CLSI
Susceptible $\leq x$ mg/L Resistant $> y$ mg/L	Susceptible $\leq x$ μ g/mL Resistant $\geq y$ μ g/mL
e.g. Enterobacteriaceae with cefotaxime Susceptible ≤ 1 mg/L Resistant > 2 mg/L	Susceptible ≤ 1 μ g/mL Intermediate 2 mg/L Resistant ≥ 4 μ g/mL
Intermediate inferred	Intermediate spelt out

Why are breakpoints different?

- Wild-type bacteria are identical worldwide
(the prevalence of acquired resistance may differ)
- Dosage regimens similar in most countries
- Pharmacokinetics differ more within ethnic groups (age, weight etc) than between them
- **Breakpoints should be the same...**

But breakpoints setting is not an exact science...

Breakpoints are based on:

- Microbiological data
- Pharmacokinetics
- Pharmacodynamics
- Clinical outcome related to MIC

Different weighting → Different breakpoints

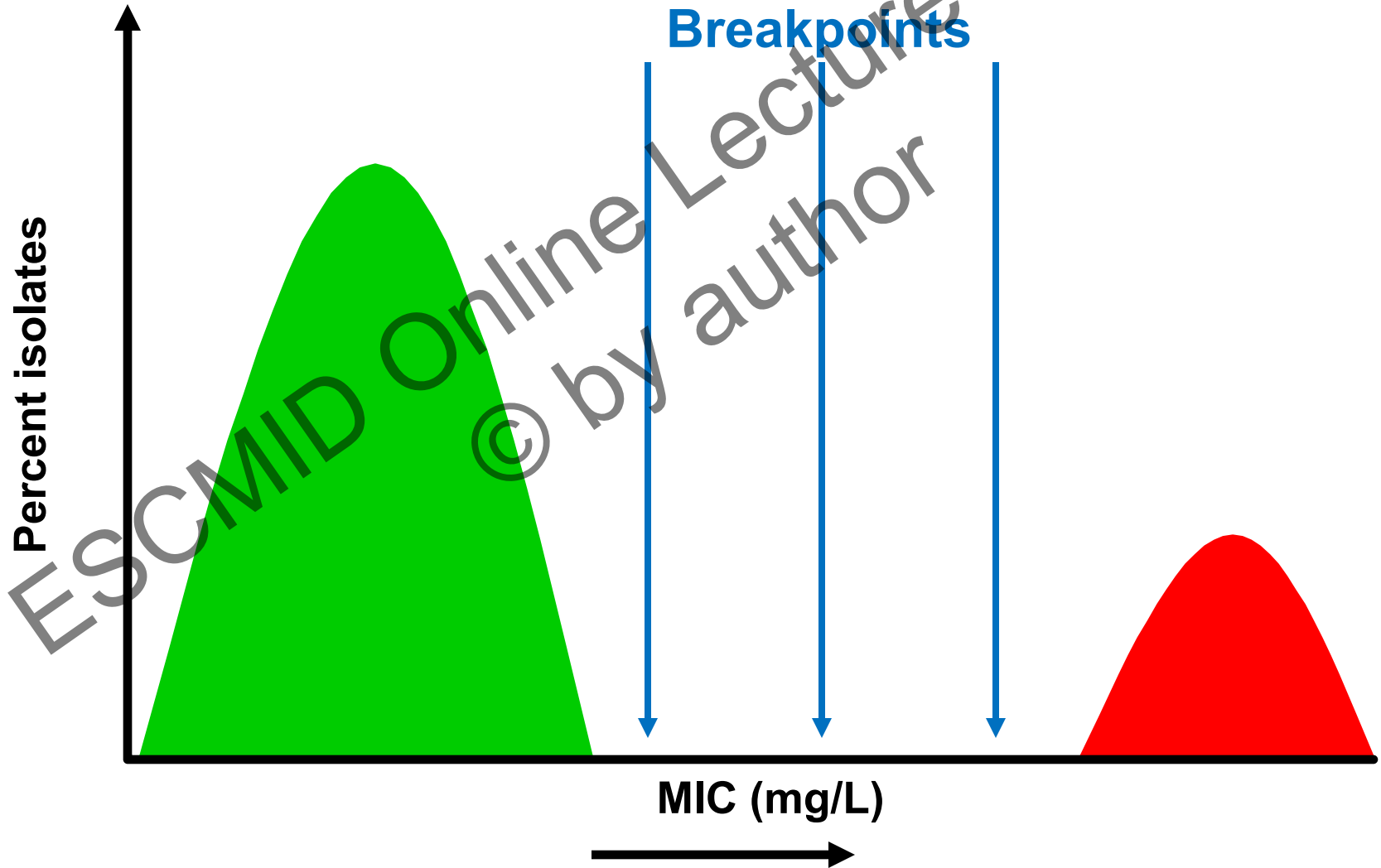
Implications of differences between EUCAST and CLSI breakpoints

Resistance rates may be different despite no difference in MIC distribution

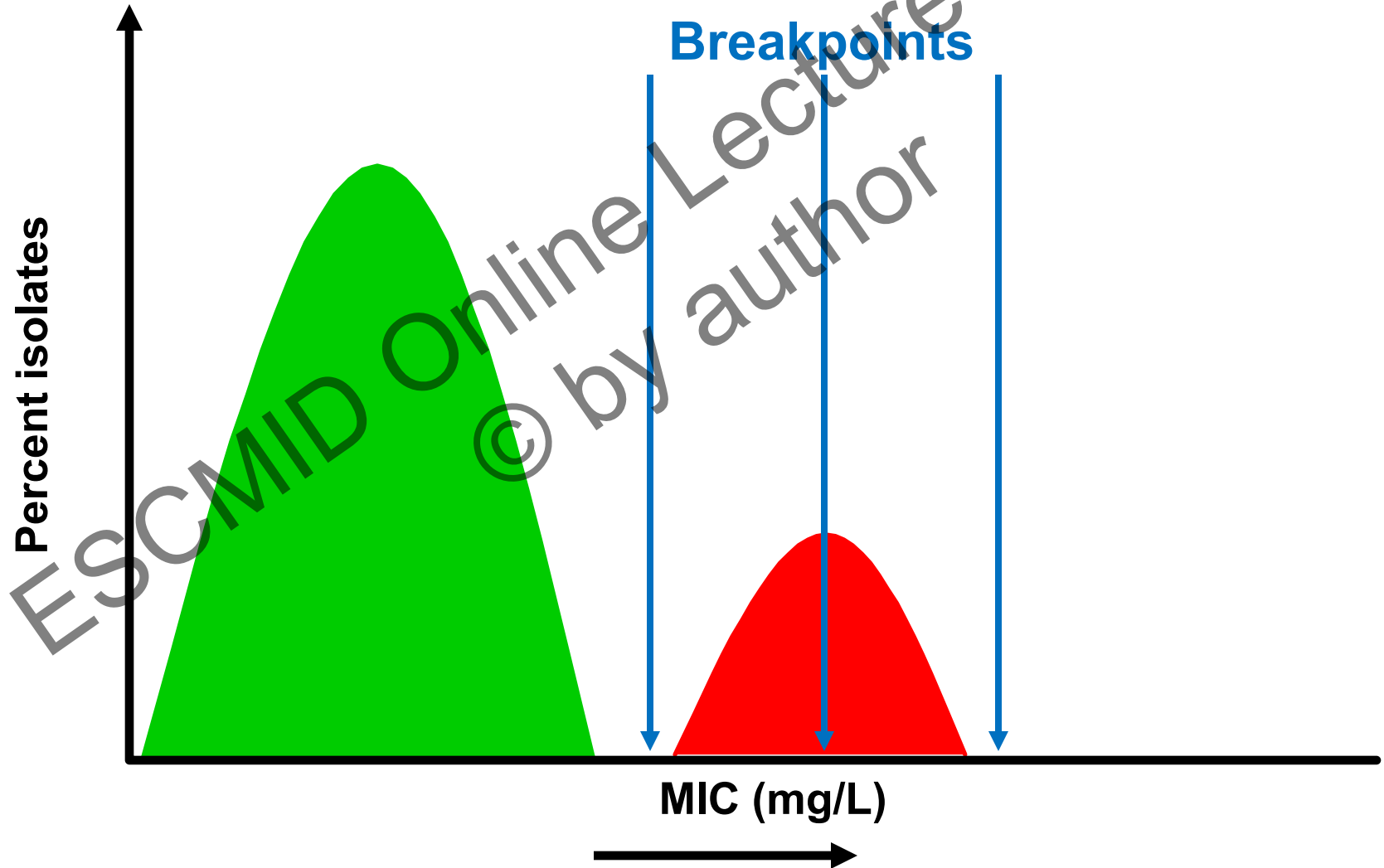
Implications for:

- Guidance on appropriate therapy
- Comparing surveillance data from different studies
- Changing guidelines used

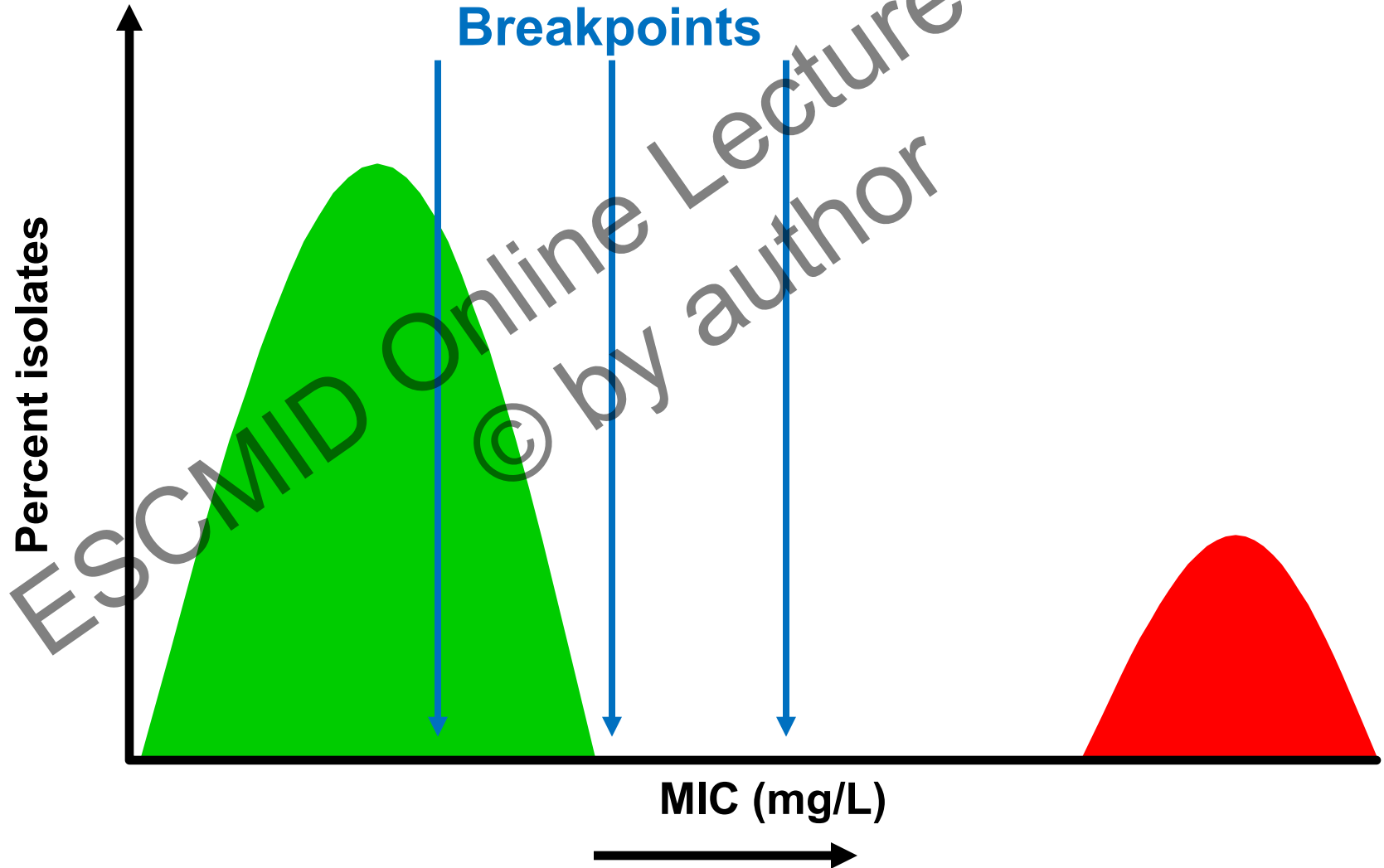
Differences in breakpoints but no effect on resistance rates



Differences in breakpoints affecting resistance rates



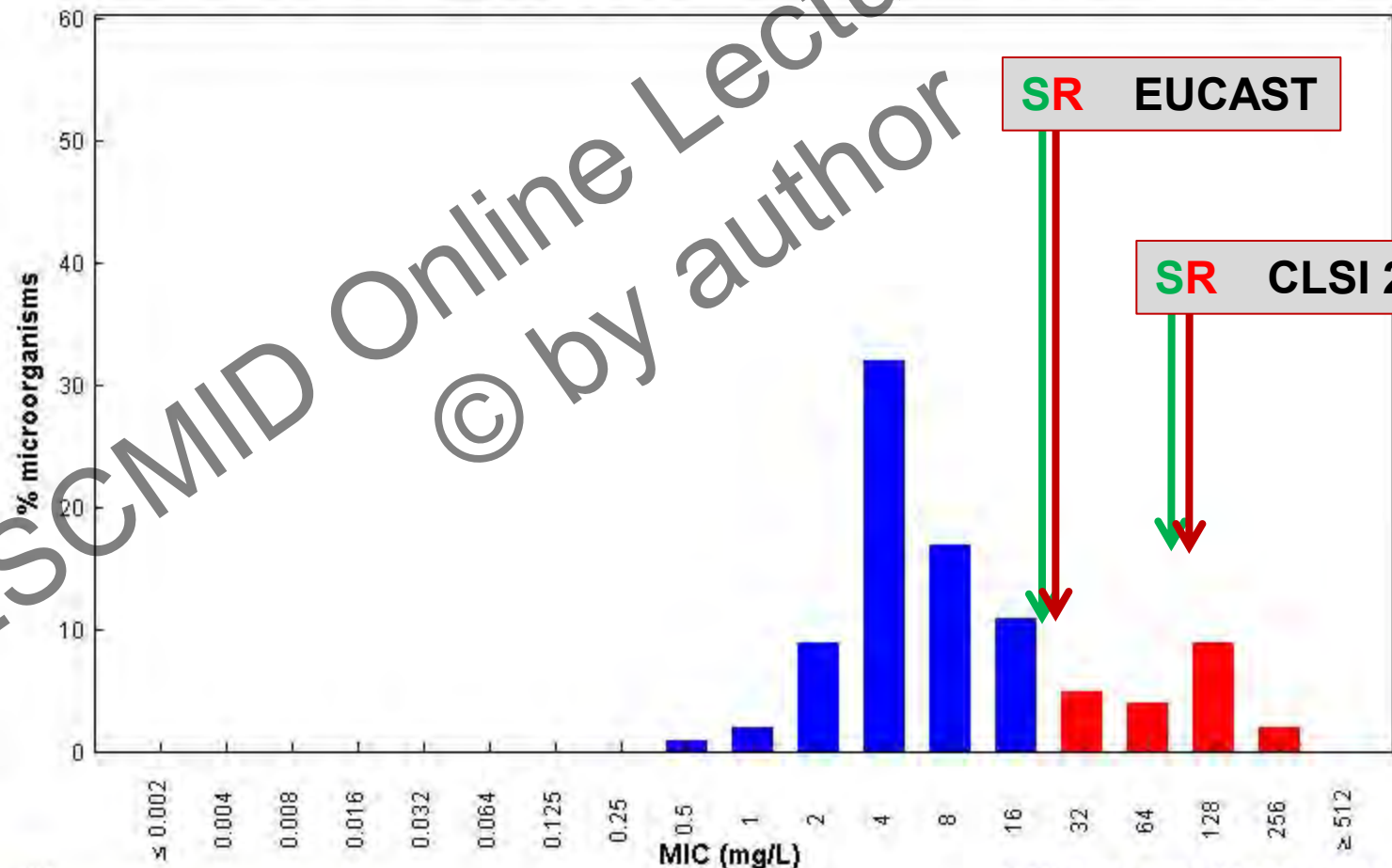
Differences in breakpoints affecting resistance rates



MIC distributions allow effects of different breakpoints to be assessed

Piperacillin-tazobactam / *Pseudomonas aeruginosa*
EUCAST MIC Distribution - Reference Database

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



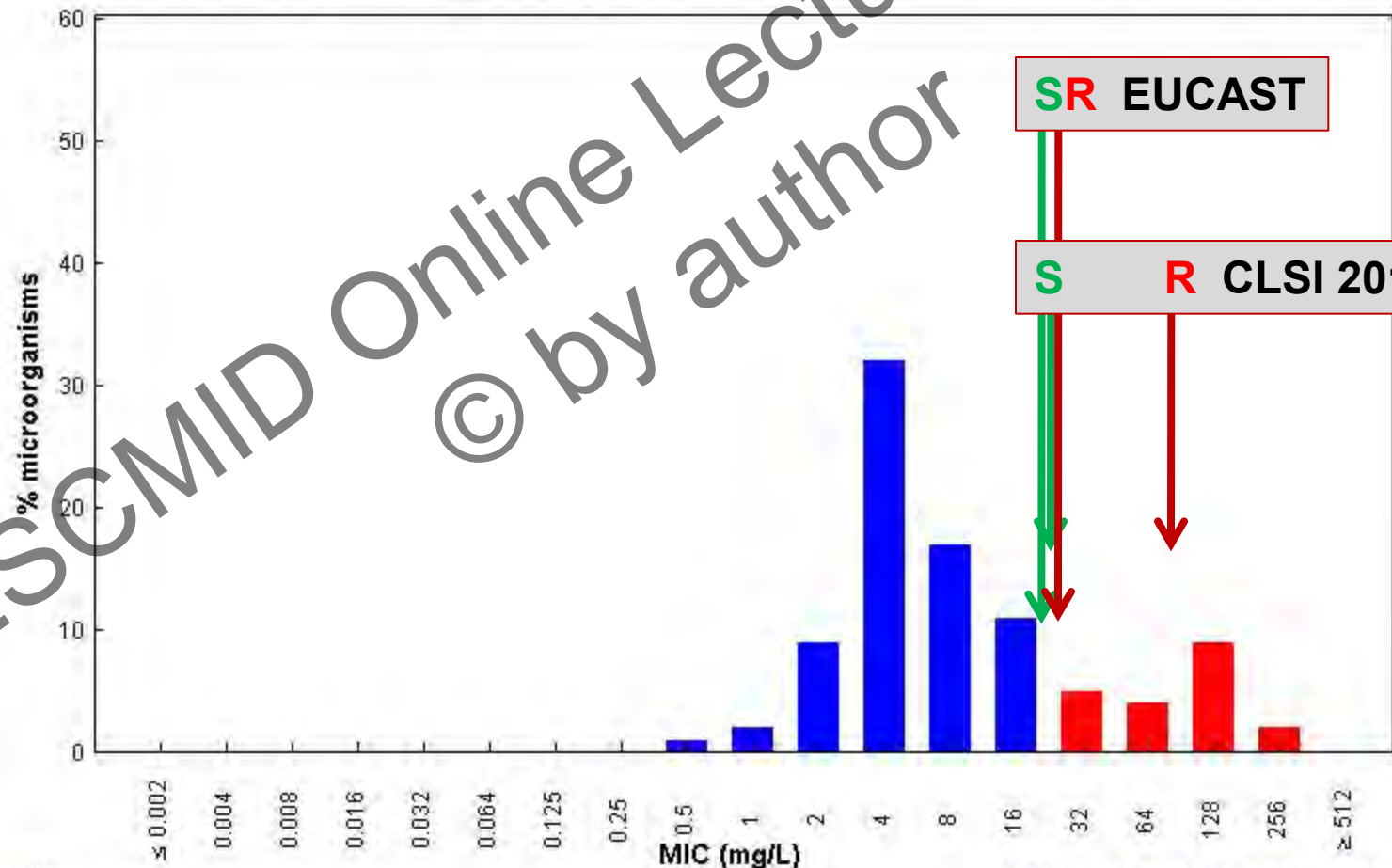
MIC
Epidemiological cut-off: WT ≤ 16 mg/L

31500 observations (68 data sources)
Clinical breakpoints: S ≤ 16 mg/L, R > 16 mg/L

MIC distributions allow effects of different breakpoints to be assessed

Piperacillin-tazobactam / *Pseudomonas aeruginosa*
EUCAST MIC Distribution - Reference Database

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MIC
Epidemiological cut-off: WT ≤ 16 mg/L

31500 observations (68 data sources)
Clinical breakpoints: S ≤ 16 mg/L, R > 16 mg/L

EUCAST and CLSI breakpoints

Microorganisms	Number of Breakpoints	Same breakpoints for		
		S and R	S	R
Enterobacteriaceae	35	3	8	1
<i>Pseudomonas</i>	17	0	9	2
<i>Acinetobacter</i>	10	1	3	2
<i>Staphylococcus</i>	27	5	6	1
<i>Enterococcus</i>	8	0	2	3
Streptococcus A,B,C,G	12	2	2	2
<i>S. pneumoniae</i>	26	4	4	5
<i>H. influenzae</i>	24	0	3	0

Enterobacteriaceae

EUCAST and CLSI breakpoints

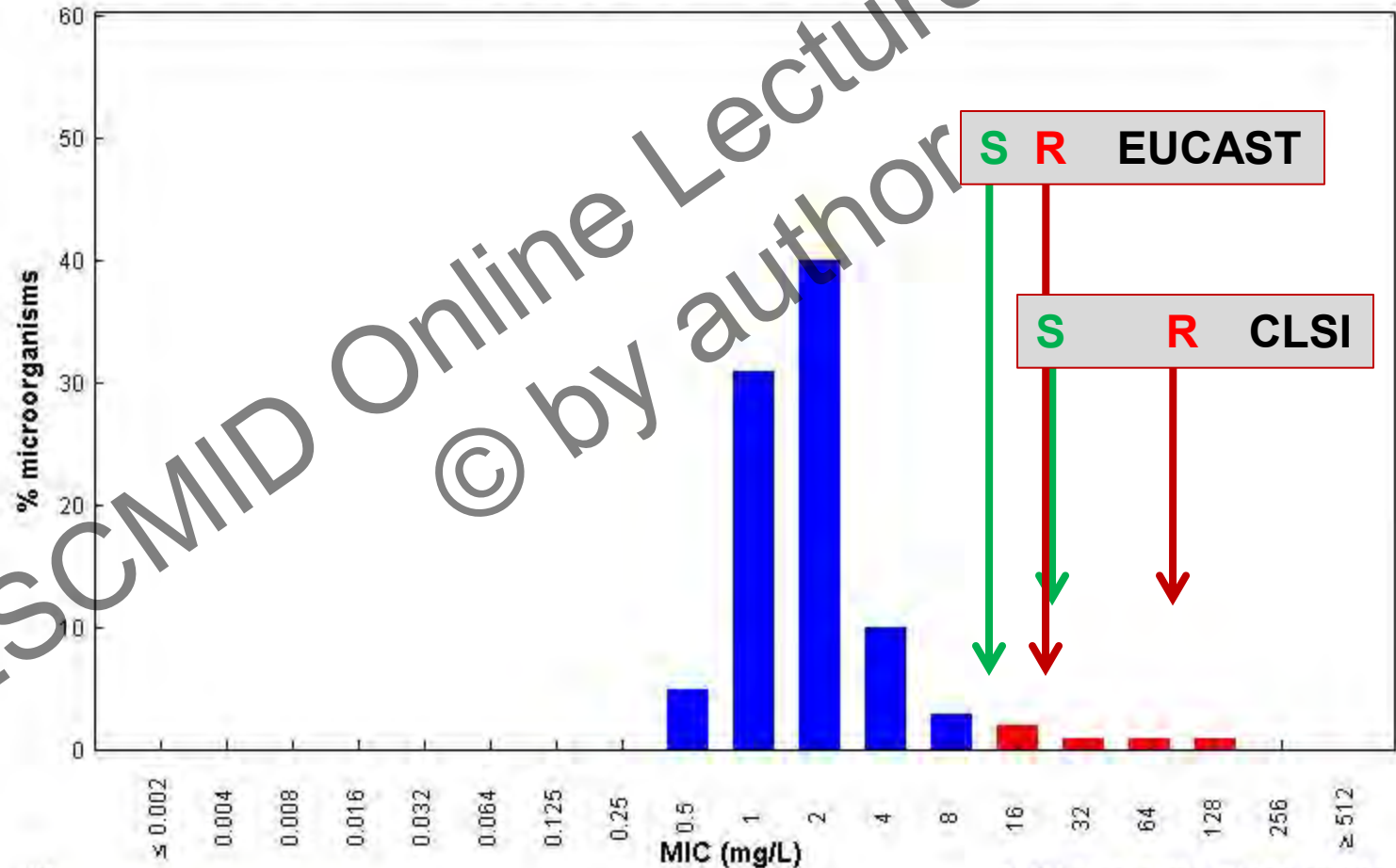
(CLSI adjusted to EUCAST format)

Antimicrobial agent	EUCAST S≤/R> (mg/L)	CLSI S≤/R> (mg/L)
Ampicillin	8 / 8	8 / 16
Amoxicillin	8 / 8	- / -
Ceftazidime	1 / 4	4 / 8
Cefotaxime	1 / 2	1 / 2
Ceftriaxone	1 / 2	1 / 2
Imipenem	2 / 8	1 / 4
Meropenem	2 / 8	1 / 4
Piperacillin-tazobactam	8 / 16	16 / 64
Ciprofloxacin	0.5 / 1	1 / 2
Gentamicin	2 / 4	4 / 8
Amikacin	8 / 16	16 / 32
Tobramycin	2 / 4	4 / 8

Pip-tazo breakpoints for *E. coli*

Piperacillin-tazobactam / *Escherichia coli*
EUCAST MIC Distribution - Reference Database 2010-05-13

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



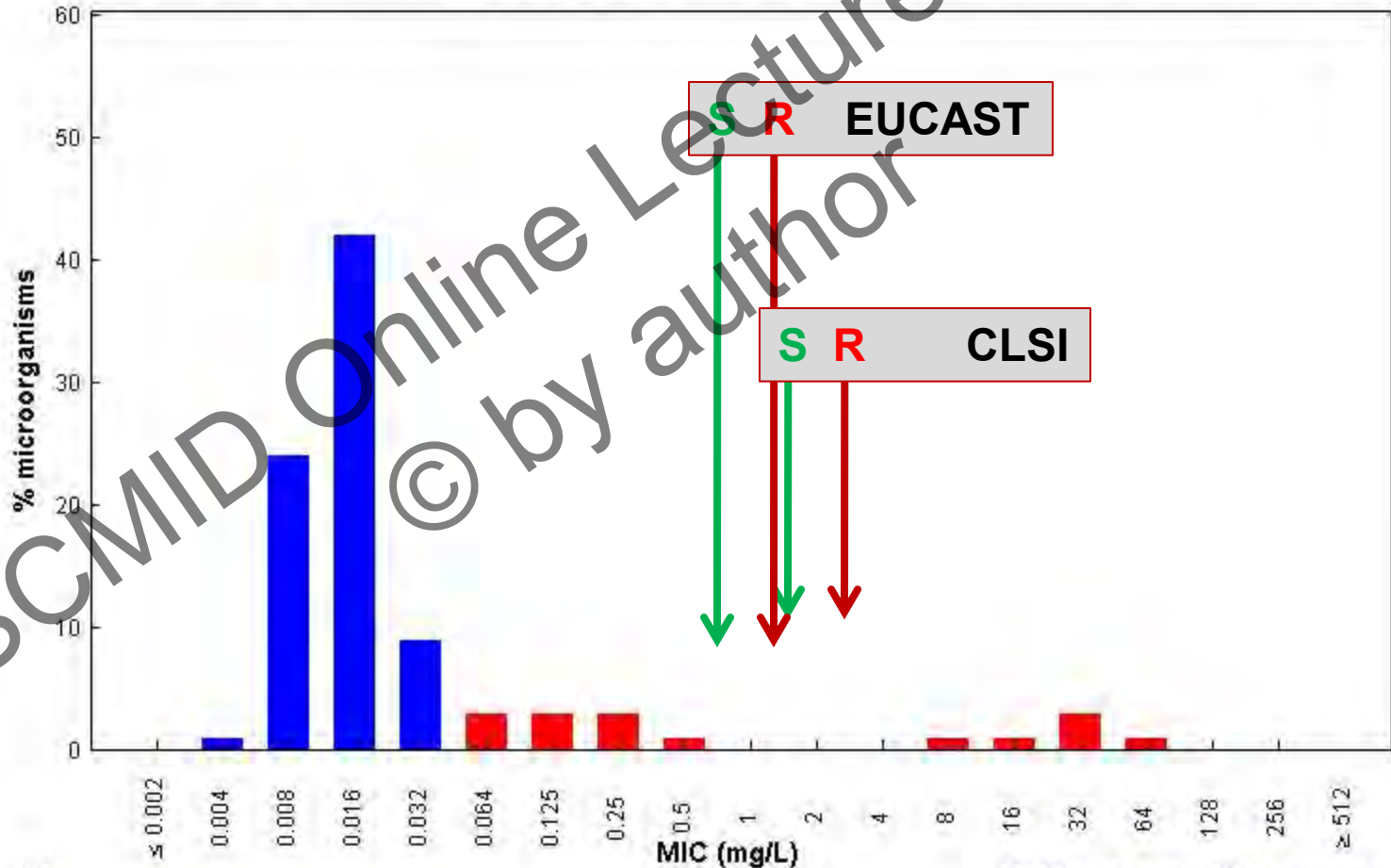
MIC
Epidemiological cut-off: WT ≤ 8 mg/L

51561 observations (79 data sources)
Clinical breakpoints: S ≤ 8 mg/L, R > 16 mg/L

Ciprofloxacin breakpoints for *E. coli*

Ciprofloxacin / Escherichia coli
EUCAST MIC Distribution - Reference Database 2010-05-10

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: WT ≤ 0.032 mg/L

17877 observations (82 data sources)
Clinical breakpoints: S ≤ 0.5 mg/L, R ≥ 1 mg/L

Pseudomonas aeruginosa

EUCAST and CLSI breakpoints

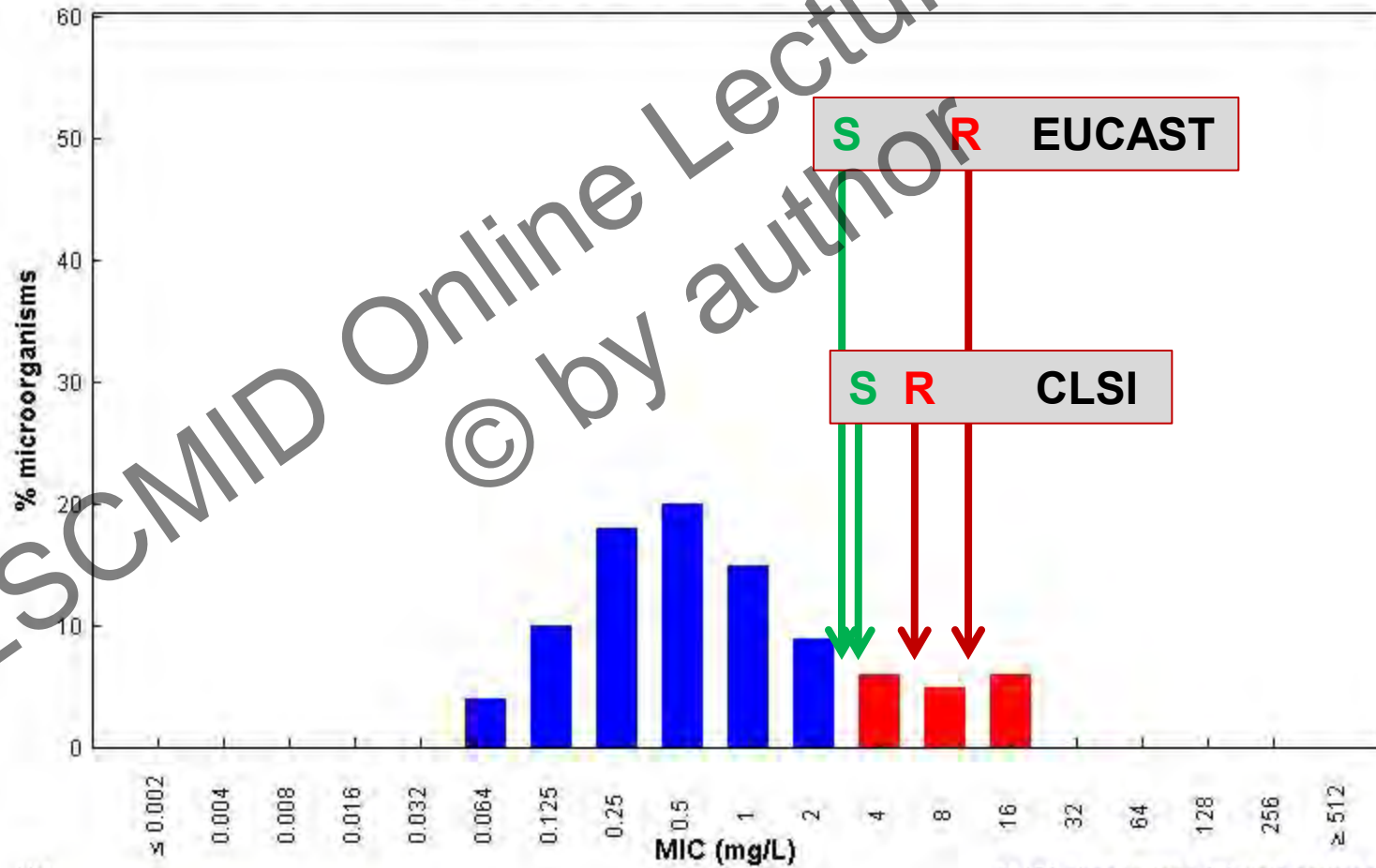
(CLSI adjusted to EUCAST format)

Antimicrobial	EUCAST S≤/R> (mg/L)	CLSI S≤/R> (mg/L)
Ceftazidime	8 / 8	8 / 16
Imipenem	4 / 8	2 / 4
Meropenem	2 / 8	2 / 4
Piperacillin-tazobactam	16 / 16	16 / 64
Ciprofloxacin	0.5 / 1	1 / 2
Gentamicin	4 / 4	4 / 8
Amikacin	8 / 16	16 / 32
Tobramycin	4 / 4	4 / 8

Meropenem breakpoints for *P. aeruginosa*

Meropenem / *Pseudomonas aeruginosa*
EUCAST MIC Distribution - Reference Database 2010-05-10

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: WT ≤ 2 mg/L

57470 observations (72 data sources)
Clinical breakpoints: S ≤ 2 mg/L, R > 8 mg/L

Staphylococcus aureus

EUCAST and CLSI breakpoints

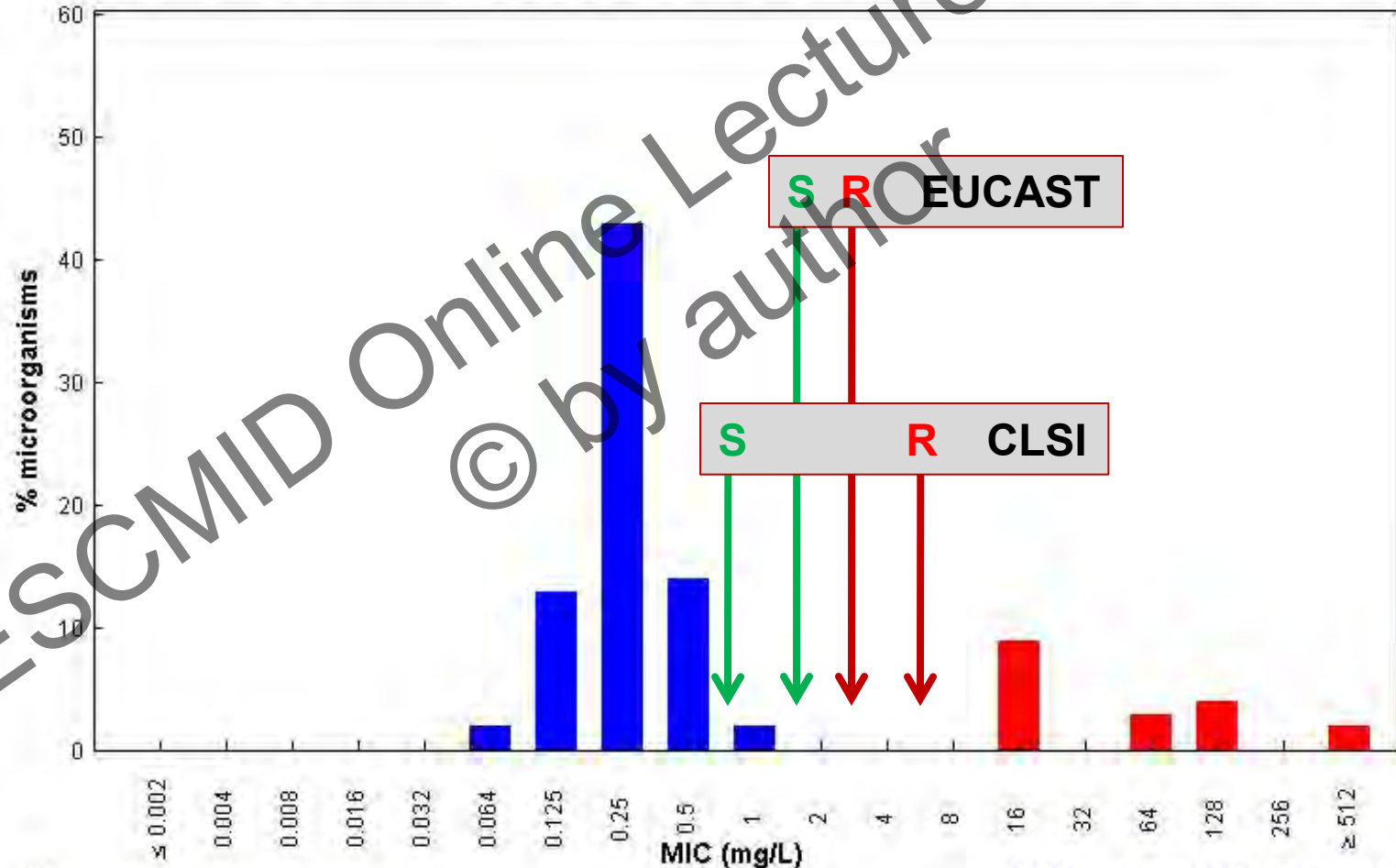
(CLSI adjusted to EUCAST format)

Antimicrobial	EUCAST S≤/R> (mg/L)	CLSI S≤/R> (mg/L)
Penicillin	0.12 / 0.12	0.12 / 0.12
Oxacillin	2 / 2 (in note)	2 / 2
Cefoxitin	4 / 4 (in note)	4 / 4
Ciprofloxacin	1 / 1	1 / 2
Vancomycin	2 / 2	2 / 8
Teicoplanin	2 / 2	8 / 16
Erythromycin	1 / 2	0.5 / 4
Gentamicin	1 / 1	4 / 8
Tetracycline	1 / 2	4 / 8
Fusidic acid	1 / 1	- / -
Rifampicin	0.06 / 0.5	1 / 2

Erythromycin breakpoints for *S. aureus*

Erythromycin / *Staphylococcus aureus* EUCAST MIC Distribution - Reference Database

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



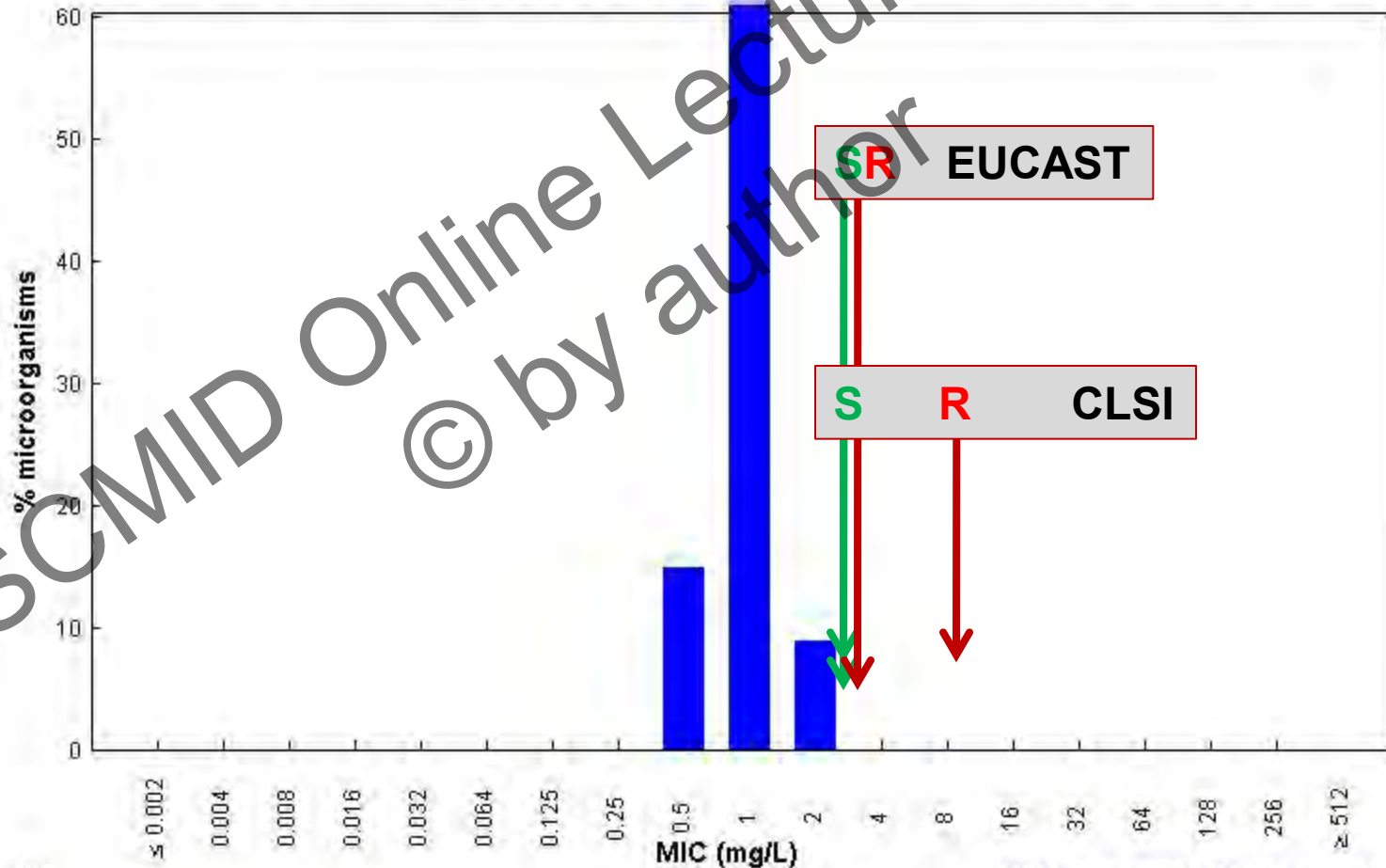
MIC
Epidemiological cut-off: WT ≤ 1 mg/L

36038 observations (26 data sources)
Clinical breakpoints: S ≤ 1 mg/L, R > 2 mg/L

Vancomycin breakpoints for *S. aureus*

Vancomycin / *Staphylococcus aureus* EUCAST MIC Distribution - Reference Database

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: WT ≤ 2 mg/L

87764 observations (33 data sources)
Clinical breakpoints: S ≤ 2 mg/L, R > 2 mg/L

Enterococcus spp

EUCAST and CLSI breakpoints

(CLSI adjusted to EUCAST format)

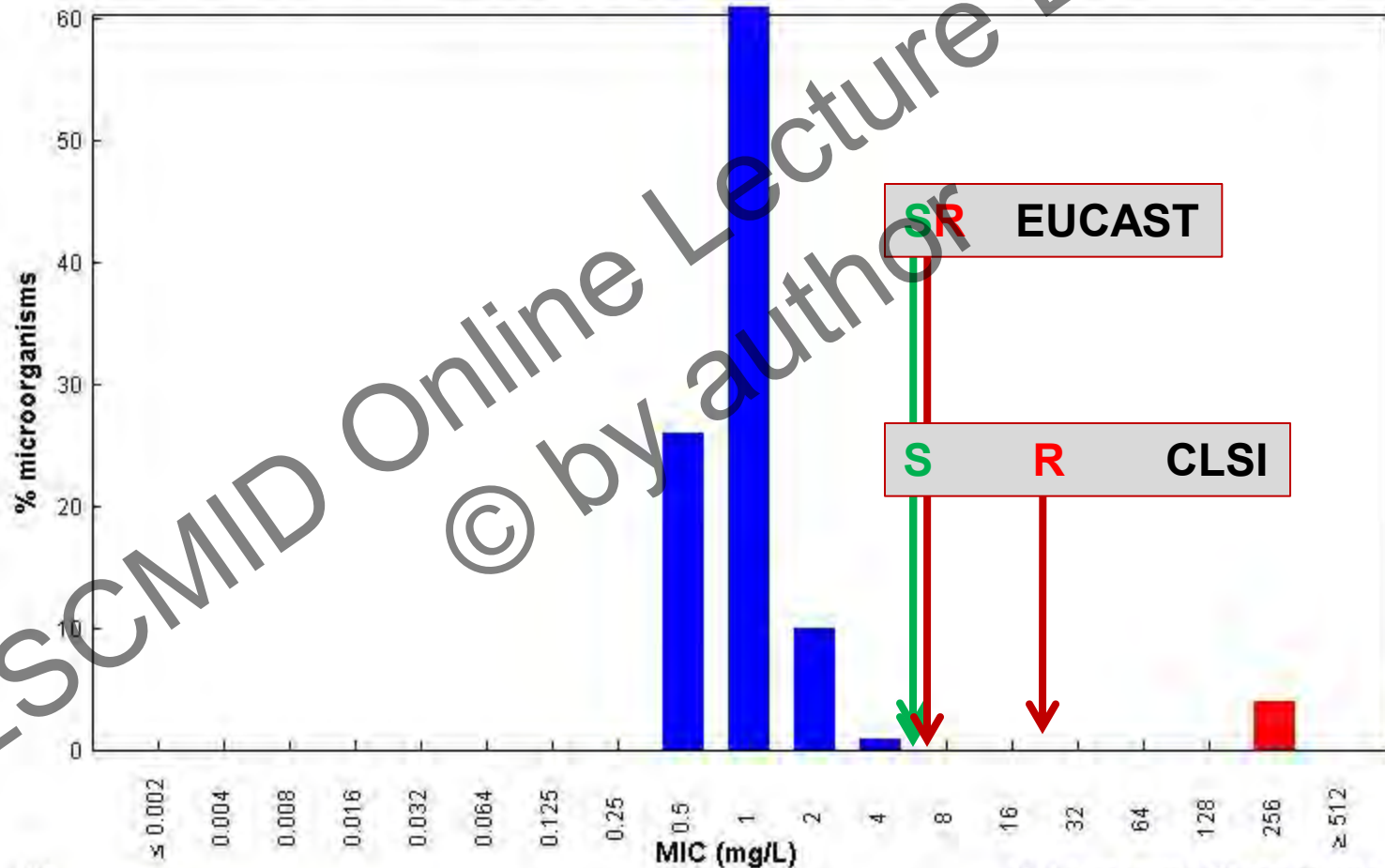
Antimicrobial	EUCAST S≤/R> (mg/L)	CLSI S≤/R> (mg/L)
Ampicillin	4 / 8	8 / 8
Amoxicillin	4 / 8	- / -
Vancomycin	4 / 4	4 / 16
Teicoplanin	2 / 2	8 / 16
Gentamicin (High Level)	128 / 128	500 / 500

Vancomycin breakpoints for *E. faecium*

Vancomycin / *Enterococcus faecium*

EUCAST MIC Distribution - Reference Database 2010-09-24

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: WT ≤ 4 mg/L

4241 observations (20 data sources)
Clinical breakpoints: S ≤ 4 mg/L, R > 4 mg/L

Conclusions

- There are significant differences between EUCAST and CLSI in organisation, funding, relationship to regulatory authorities and decision making
- Differences in breakpoints between CLSI and EUCAST probably have small effects on resistance rates for most organism-agent combinations but some differences are more significant
- In recent years EUCAST has reviewed breakpoints for all commonly used agents