



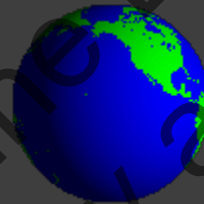
EUCAST

EUROPEAN COMMITTEE
ON ANTIMICROBIAL
SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

The European Committee on Antimicrobial Susceptibility Testing

June 2011



Gunnar Kahlmeter

Chairman of EUCAST



ESCMID

EUROPEAN SOCIETY
OF CLINICAL MICROBIOLOGY
AND INFECTIOUS DISEASES



Antimicrobial susceptibility testing of bacteria and fungi

- **To choose appropriate therapy and predict clinical outcome in individual patients**
- **As a basis for empiric therapy**
- **Screening for organisms with exceptional resistance (MRSA, VRE, ESBL, KPC, NDM etc)**
 - to prevent dissemination in Health Care and community
- **To determine the rate of resistance development**
 - To evaluate the appropriateness of empiric therapy
 - To predict resistance development
 - To form strategies to counteract antimicrobial resistance and to measure the success

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....
- **Predicts resistance, not sensitivity**
- **Not quantifiable**

- **By deduction** – “expert rules”

- If mecA-positive then report betalactam antibiotics R;
If ESBL-positive, then report betalactam antibiotics R – or maybe not!?
- If erythromycin-resistant, then report roxithro- and clarithromycin R;
- **Some rules predict susceptibility, others resistance.**
- **Rules change over time**
- **Not quantifiable**

EUCAST was formed in 1996 and reformed in 2001.

| Committee | Country | Disk Diffusion test? |
|--|---------|----------------------|
| EUCAST  | Europe | Yes |
| CLSI  | USA | Yes |

*EUCAST is now an umbrella for national breakpoint committees BSAC, CA-SFM, CRG, DIN, NWGA & SRGA.



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



EUCAST General Committee
All European Countries + ISC/FESCI

EUCAST Steering Committee
BSAC, CA-SFM, CRG, DIN, NWGA, SRGA
And 2 reps from the General Committee*



Subcommittees
Antifungals
Anaerobes
Expert Rules

Expert groups
Neisseria
Helicobacter
C.difficile
etc...

*Currently: Estonia and Austria



**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.
- Clinical breakpoints
- Rationale for decisions not published.
- Documents for sale

EUCAST and CLSI breakpoints are different

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

[Organization](#)

[Clinical breakpoints](#)

[Expert rules](#)

[MIC distributions](#)

[Zone diameter distributions](#)

[EUCAST disk diffusion test](#)

[Meetings](#)

[EUCAST Presentations](#)

[Documents](#)

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search term [Search](#)
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

www.eucast.org

ISC. The Steering Committee also consults experts within the fields of Infectious Diseases and Microbiology, pharmaceutical companies and susceptibility testing device manufacturers on EUCAST proposals.

EUCAST has subcommittees on antifungal susceptibility testing, expert rules for antimicrobial susceptibility testing, and antimicrobial susceptibility testing of anaerobes.

Most antimicrobial MIC breakpoints in Europe have been harmonised by EUCAST by 2009. Breakpoints for new agents are set as part of the licensing process for new agents through EMEA. EUCAST breakpoints will be available in devices for automated susceptibility testing during 2009 and 2010. A disk diffusion test calibrated to EUCAST MIC breakpoints was launched at the end of 2009.

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.

Mupirocin breakpoint consultation - deadline for comments 22 March 2010.


New rationale Documents from EUCAST.

 [metronidazole](#)

EUCAST presentation now available



This presentation gives an overview of EUCAST and its activities.

 [download](#)

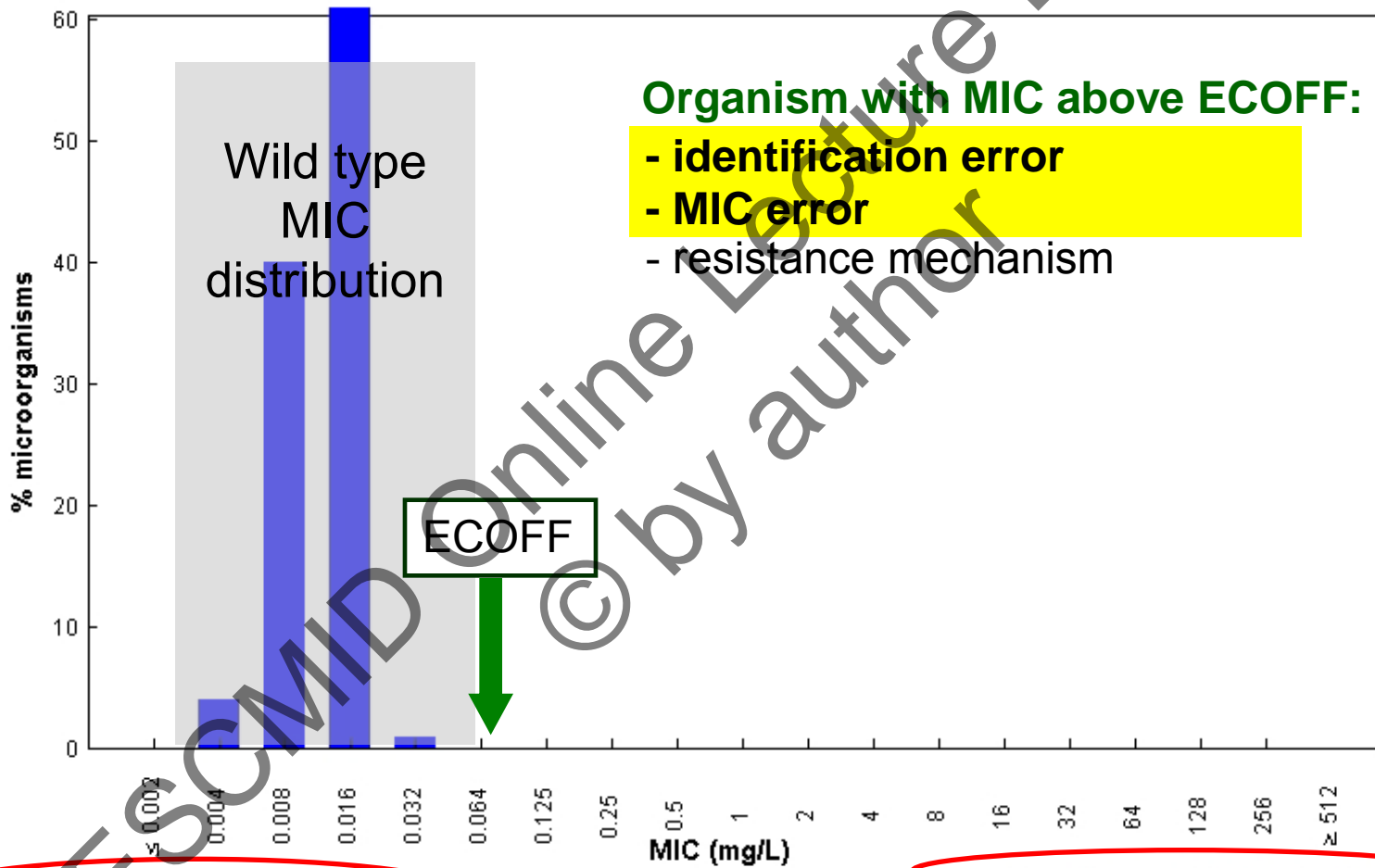
 **ESCMID** EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES


European Medicines Agency


ecdc

Benzylopicillin / *Streptococcus pyogenes*
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

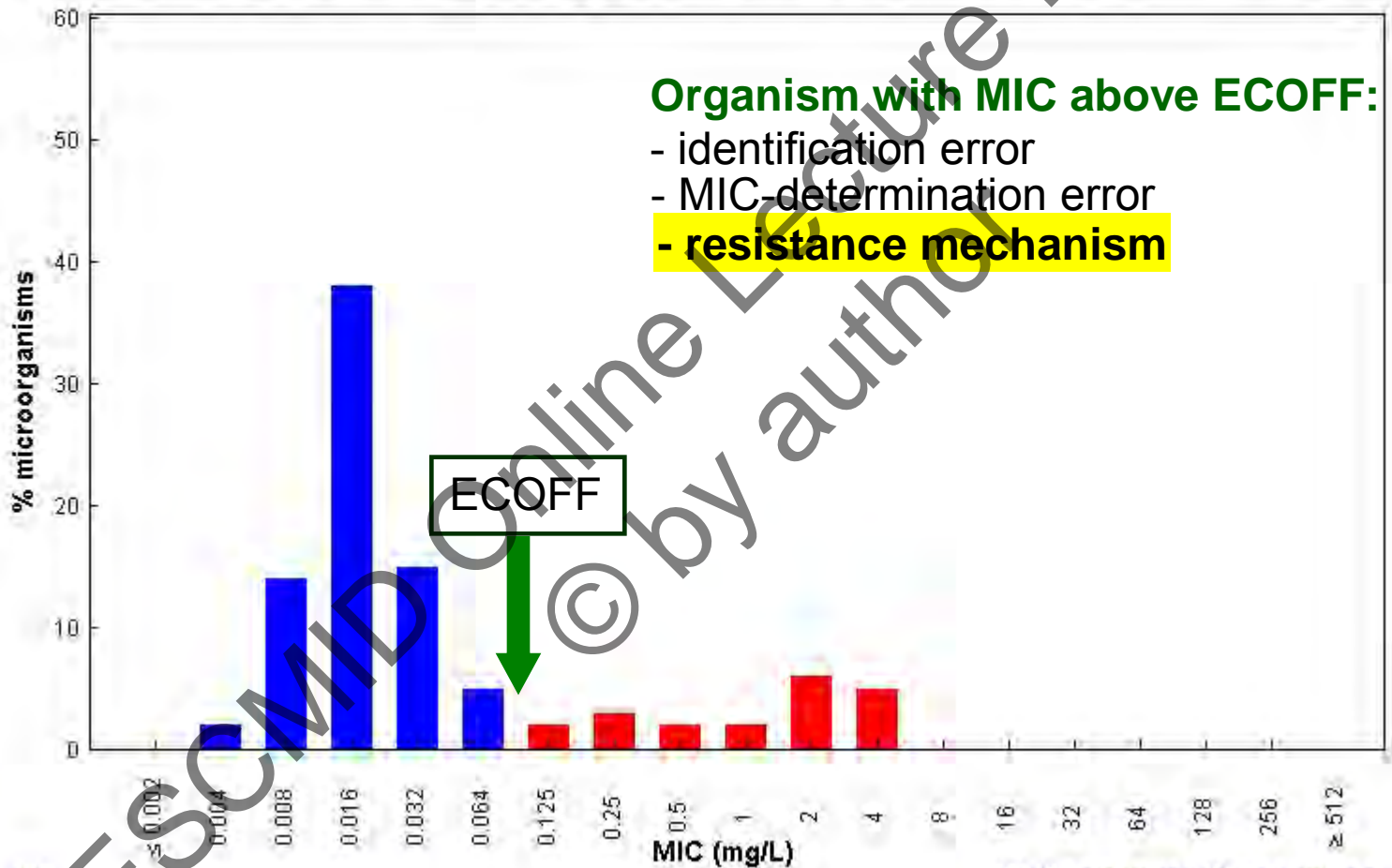


MIC Epidemiological cut-off: WT ≤ 0.064 mg/L

3615 observations (11 data sources)
Clinical breakpoints: S ≤ 0.25 mg/L, R > 0.25 mg/L

Benzylpenicillin / Streptococcus pneumoniae
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

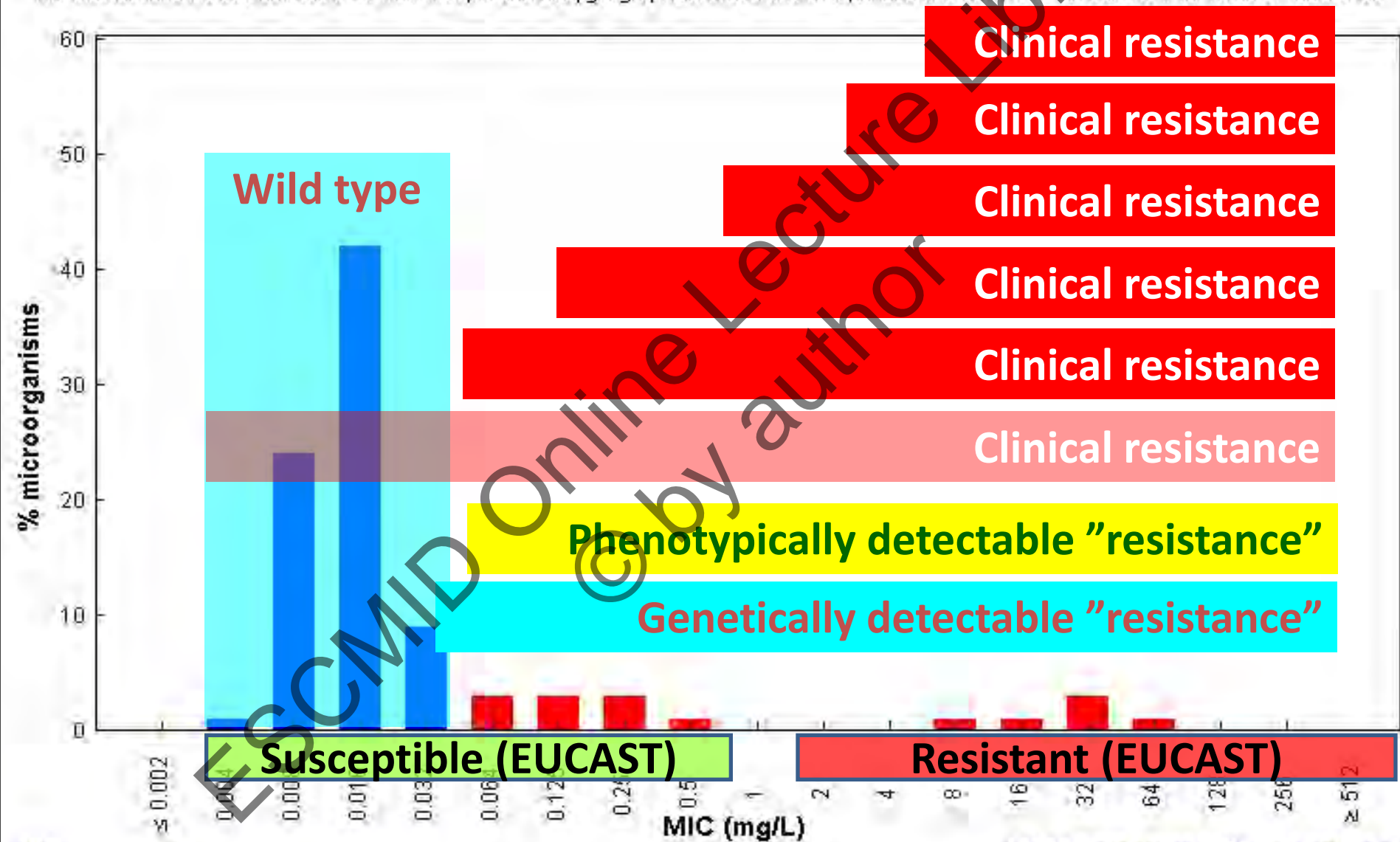


MIC Epidemiological cut-off: WT ≤ 0.064 mg/L

37642 observations (32 data sources)
Clinical breakpoints: S ≤ 0.064 mg/L, R > 2 mg/L

Ciprofloxacin / Escherichia coli
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 ≤ 0.032 mg/L

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

Tools for determining **CLINICAL BREAKPOINTS**

1. Dose or doses
2. Target organisms
3. Individual MIC-distributions for target organisms
 - breakpoints must not divide MIC-distributions of WT target organisms
4. Resistance mechanisms in target organisms
5. Clinical indications
6. Pharmacokinetics (C_{max}, AUC, T_{1/2}, Protein binding, V_d..)
7. Pharmacodynamic properties (peak conc/MIC, AUC/MIC, TA, MCs)
8. Clinical outcome (clinical outcome vs. MIC)
9. Epidemiological cutoffs, Pk/Pd-breakpoints and clinical data together determine the **CLINICAL BREAKPOINT**

In 2011, the most important difference between CLSI and EUCAST is that EUCAST has completed a full review of all breakpoints.

- EUCAST: Breakpoints must be reviewed at intervals
 - Extension of indications
 - Extension of target organisms
 - New resistance mechanisms
 - New drug in class
 - New clinical experience
 - New dosing or administration
 - Time

Recently reviewed/revised breakpoints

EUCAST and CLSI

- **3rd gen cephalosporins vs. Enterobacteriaceae**

- Cefotaxime & ceftriaxone: both 1/2 mg/L
- Ceftazidim: EUCAST 1/4 vs. CLSI 4/8 mg/L
- Cefepime: EUCAST 1/4 vs. CLSI 8/8 mg/L

- **Carbapenems vs. Enterobacteriaceae**

- CLSI: 1 dilution step lower – inflated variance

- **Vancomycin vs. Staphylococcus aureus**

- EUCAST from $S \leq 4$, $R > 8$ mg/L to $S \leq 2$, $R > 2$ mg/L*
- CLSI from $S \leq 8$, $R \geq 32$ mg/L to $S \leq 2$, $R \geq 16$ mg/L**

*EUCAST: "impaired response may be seen already at MIC 2 mg/L"

**CLSI: impaired response at 4 and 8 and during prolonged treatment.

EUCAST and the review process

Reviewed 2002 – 2009:

- Aminoglycosides
- Carbapenems & aztreonam (2nd review)
- Cephalosporins iv (2nd review)
- Cephalosporins oral
- Fluoroquinolones
- Glycopeptides (2nd review)
- Macrolides and lincosamines
- Miscellaneous antimicrobials
- Penicillins
- Tetracyclines

- Antifungal drugs
 - fluconazole, voriconazole, posaconazole
 - anidulafungin, amfotericin B

Topical agents:

Mupirocin (LLR/HLR)
Retapamulin (ECOFF)

Drugs being addressed:

Cefalothin (ECOFF)
Cefazoline (ECOFF)
Cefoperazone (ECOFF)
Sulbactam (alone)
Kanamycin
Streptomycin
Josamycin
Spiramycin
....

**Lack of data for
older drugs!**

EUCAST

- breakpoints for new drugs with EMA

- Daptomycin ✓
- Tigecycline ✓
- Doripenem ✓
- Glycopeptides (two ongoing)
- Cefalosporine (ongoing)

- Anti-Tb (to be started)
- Cefalosporine
- Fluoroquinolone (withdrawn)
- Diaminopyrimidine (withdrawn)

- Extensions of indications (currently none)

Miscellaneous organisms

Consultation with expert groups on breakpoints and methods

- *Neisseria meningitidis* (review) - 2011
- *Moraxella catarrhalis* (revised) - 2011
- *Helicobacter pylori* (finalized) - 2011
- *Clostridium difficile* (finalized) - 2011
- *Campylobacter* (ongoing) - 2011
- *Listeria monocytogenes* (ongoing) - 2011
- *Pasteurella multocida* (ongoing) - 2011
- *Burkholderia cepacia* (started) - 2012
- *Corynebacteria* (started) - 2012
- ...

EUCAST subcommittees

- **Expert rules and interpretive reading**

- Major revision (v 2.0) available 2011
- Published in CMI during 2011
- Software for expert rules 2011



- **Antifungal susceptibility testing**

- 5 antifungals RDs and breakpoints in 2011: fluconazole, voriconazole, posaconazole, anidulafungin and amfotericin B.

- **Anaerobe susceptibility testing**

- Finalised: drugs in need of breakpoints defined; breakpoints determined
- Ongoing: Methodological development

EUCAST expert rules

v2.0 (2011)

- **Intrinsic resistance – assumes resistance!**
- **Exceptional phenotypes – “Don’t believe it if you see one!”**
 - Exceptional resistance (ex. Penicillin resistance in *S. pyogenes*)
 - Exceptional susceptibility (ex. Ampicillin susceptibility in *K. pneumoniae*)
- **Interpretive reading (Rules): IF - THEN**
 - If *mecA*-positive, then report all betalactam antibiotics R (or maybe not!?)
 - If ESBL-positive, then report betalactam antibiotics R (no longer valid!)

Expert rules are useful but unreliable!

EUCAST expert rules

Intrinsic resistances affecting β -lactams

| Rule no. | Bacterial species | PEN G | AMP | AMOX /CLAV | TIC | CFZ | FOX | CFM | CXM | Mechanisms of resistance |
|----------|--------------------------------|-------|-----|------------|-----|-----|-----|-----|-----|--------------------------|
| 1.1 | All Enterobacteriaceae | R | | | | | | | | Impermeability |
| 1.2 | <i>Citrobacter koseri</i> | R | R | | R | | | | | Class A Bla |
| 1.3 | <i>Citrobacter freundii</i> | R | R | R | | R | R | | | Class C Bla (AmpC) |
| 1.4 | <i>Enterobacter cloacae</i> | R | R | R | | R | R | | | Class C Bla (AmpC) |
| 1.5 | <i>Enterobacter aerogenes</i> | R | R | R | | R | R | | | Class C Bla (AmpC) |
| 1.6 | <i>Escherichia hermannii</i> | R | R | | R | | | | | Class A Bla |
| 1.7 | <i>Hafnia alvei</i> | R | R | R | | R | R | | | Class C Bla (AmpC) |
| 1.8 | <i>Klebsiella</i> spp. | R | R | | R | | | | | Class A Bla (SHV-1, K1) |
| 1.9 | <i>Morganella morganii</i> | R | R | R | | R | | | | Class C Bla (AmpC) |
| 1.11 | <i>Proteus vulgaris</i> | R | R | | | R | | R | R | Class A Bla (CumA) |
| 1.12 | <i>Proteus penneri</i> | R | R | | | R | | R | R | Class A Bla (HugA) |
| 1.13 | <i>Providencia rettgeri</i> | R | R | R | | R | | | | Class C Bla (AmpC) |
| 1.14 | <i>Providencia stuartii</i> | R | R | R | | R | | | | Class C Bla (AmpC) |
| 1.16 | <i>Serratia marcescens</i> | R | R | R | | R | | R | R | Class C Bla (AmpC) |
| 1.17 | <i>Yersinia enterocolitica</i> | R | R | R | R | R | R | R | R | Class A Bla (Yent) |

Disk diffusion methods

EUCAST vs. CLSI

- Both methods are based on Mueller-Hinton agar, but there are differences in:
 - Disks
 - Several disk contents are lower in EUCAST
 - EUCAST has two media instead of three
 - Medium for fastidious organisms: MH-F
 - Incubation time
 - EUCAST: 16-20 h for all organisms
 - CLSI: 16-18 or 20-24 h

EUCAST susceptibility testing media

- **MH**

- **Mueller-Hinton agar**

- Enterobacteriaceae

- *Acinetobacter* spp.

- *Pseudomonas* spp.

- *Staphylococcus* spp.

- *Enterococcus* spp.



- **MH-F**

- **Mueller-Hinton agar with 5% horse blood and 20 mg/L β -NAD**

- *Haemophilus influenzae*

- *Moraxella catarrhalis*

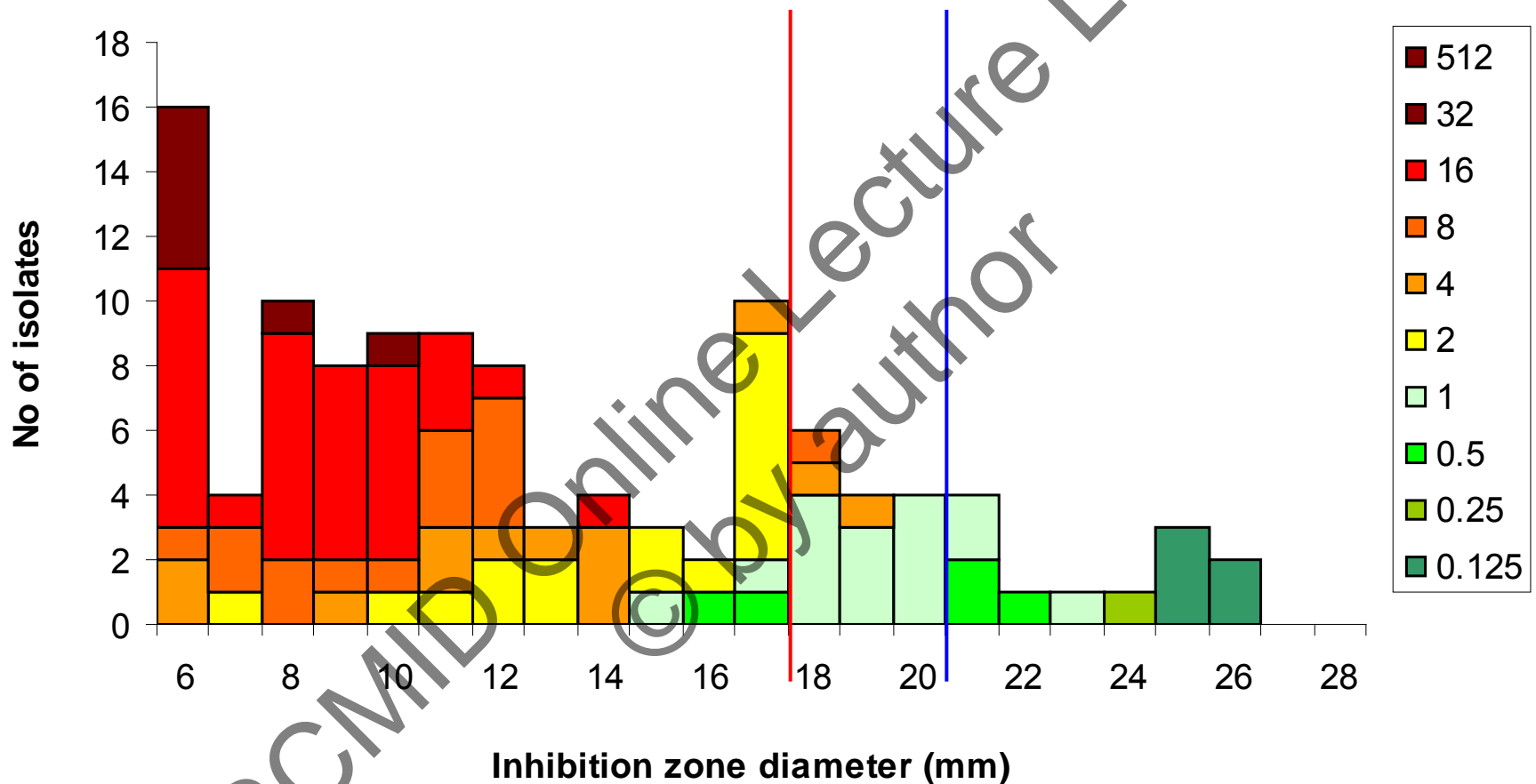
- *Streptococcus pneumoniae*,

- Streptococci

- *Campylobacter*, *Listeria*, *Corynebacterium*, *Pasteurella*

E coli /Cefotaxime 5 ug

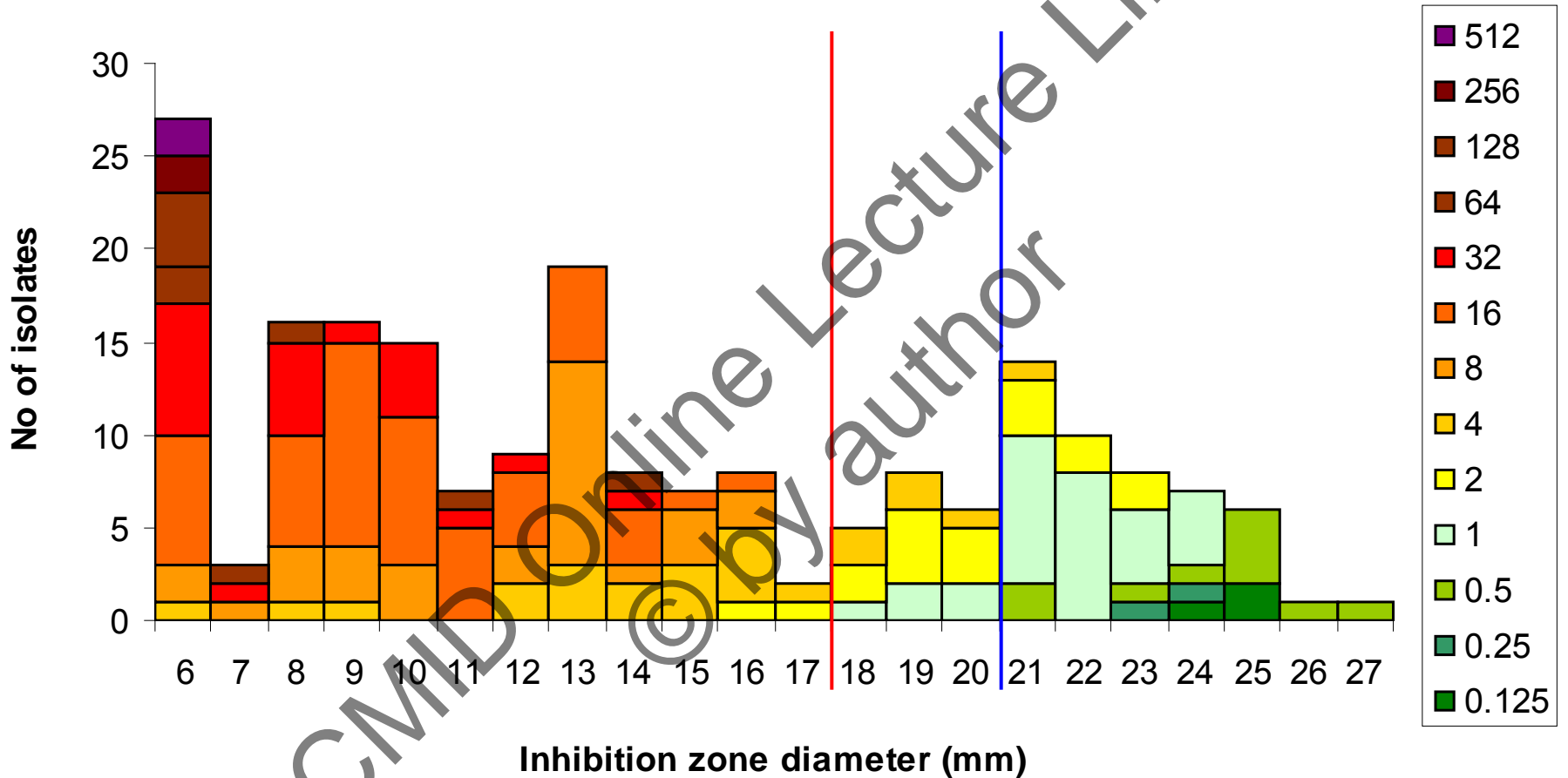
112 non-consecutive isolates chose because of resistance



| Breakpoints | S | R |
|---------------|-----------|--------|
| MIC | ≤ 1 | > 2 |
| Zone diameter | ≥ 21 | < 18 |

E. coli /Ceftazidime 10 ug

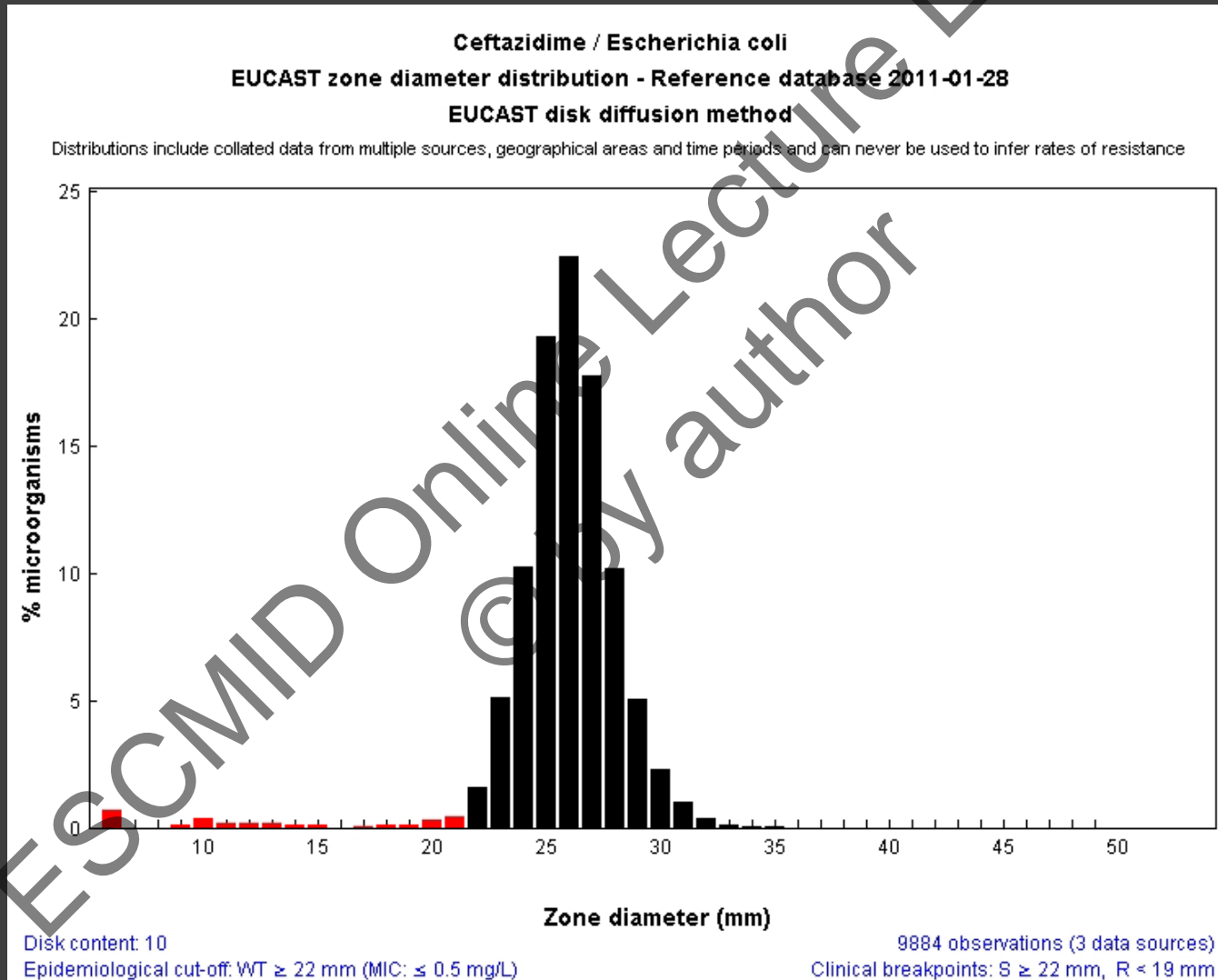
203 non-consecutive isolates chosen because of resistance



| Breakpoints | S | R |
|---------------|-----------|--------|
| MIC | ≤ 1 | > 4 |
| Zone diameter | ≥ 21 | < 18 |

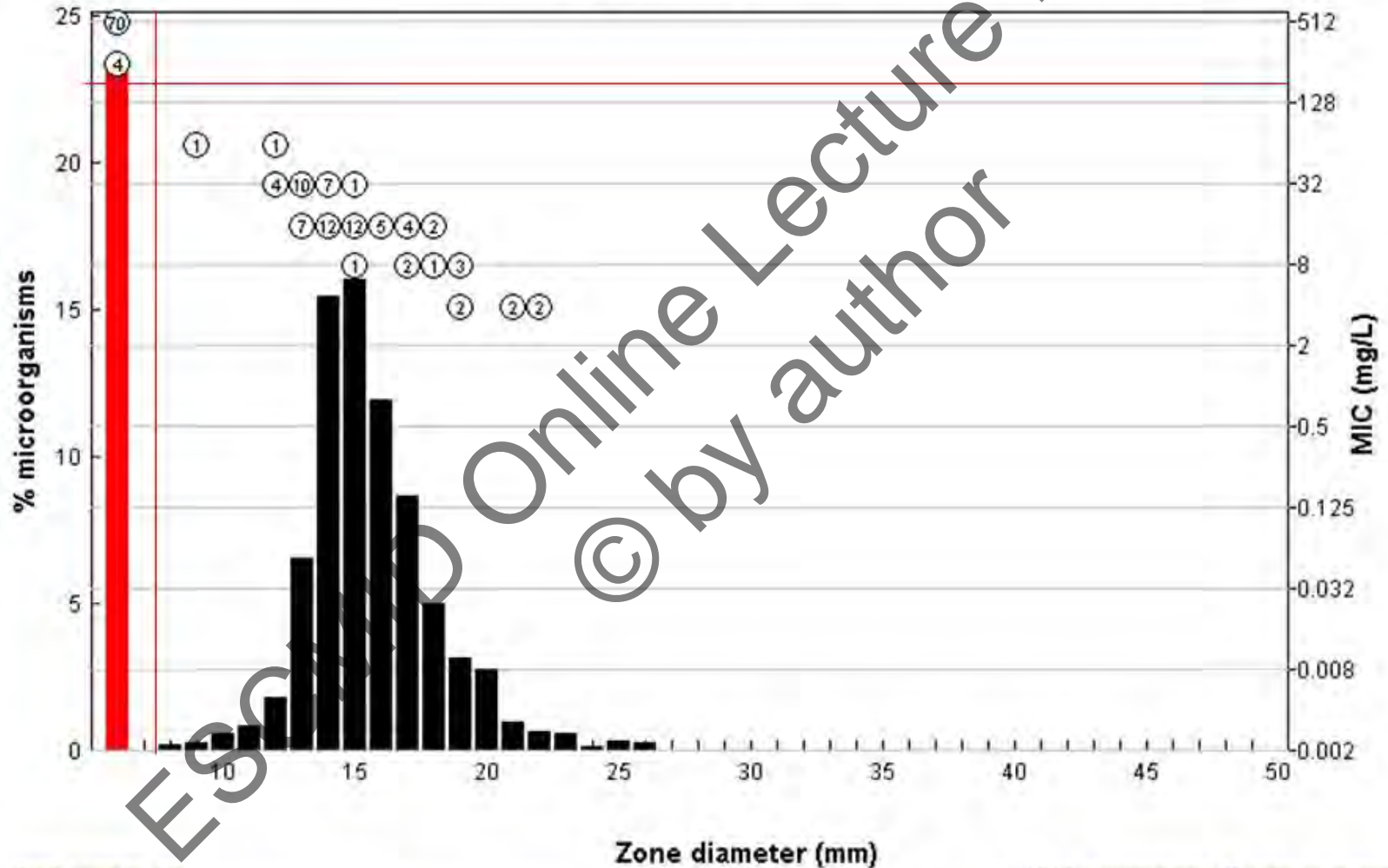
New breakpoints

Inhibition zone diameter distributions on EUCAST website



Gentamicin / Enterococcus faecalis
EUCAST zone diameter distribution - Reference database 2011-02-26
EUCAST disk diffusion method

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

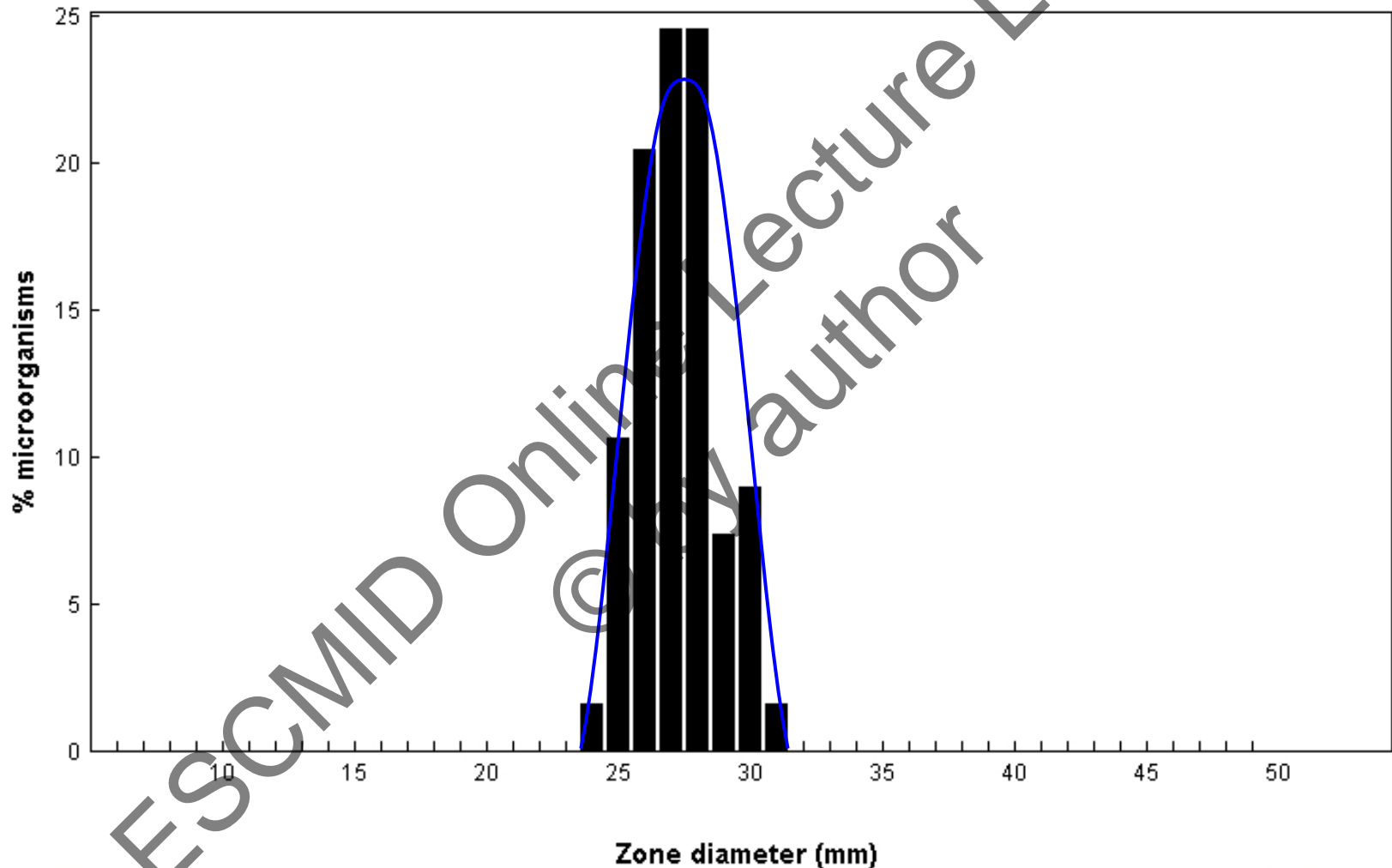


Disk content: 30
 Epidemiological cut-off: WT \geq 8 mm (MIC: \leq 32 mg/L)

1718 observations (2 data sources)
 Clinical breakpoints: Inappropriate

Cefoxitin / Staphylococcus aureus ATCC 29213
EUCAST zone diameter distribution - Reference database
EUCAST disk diffusion method

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



Disk content: 30

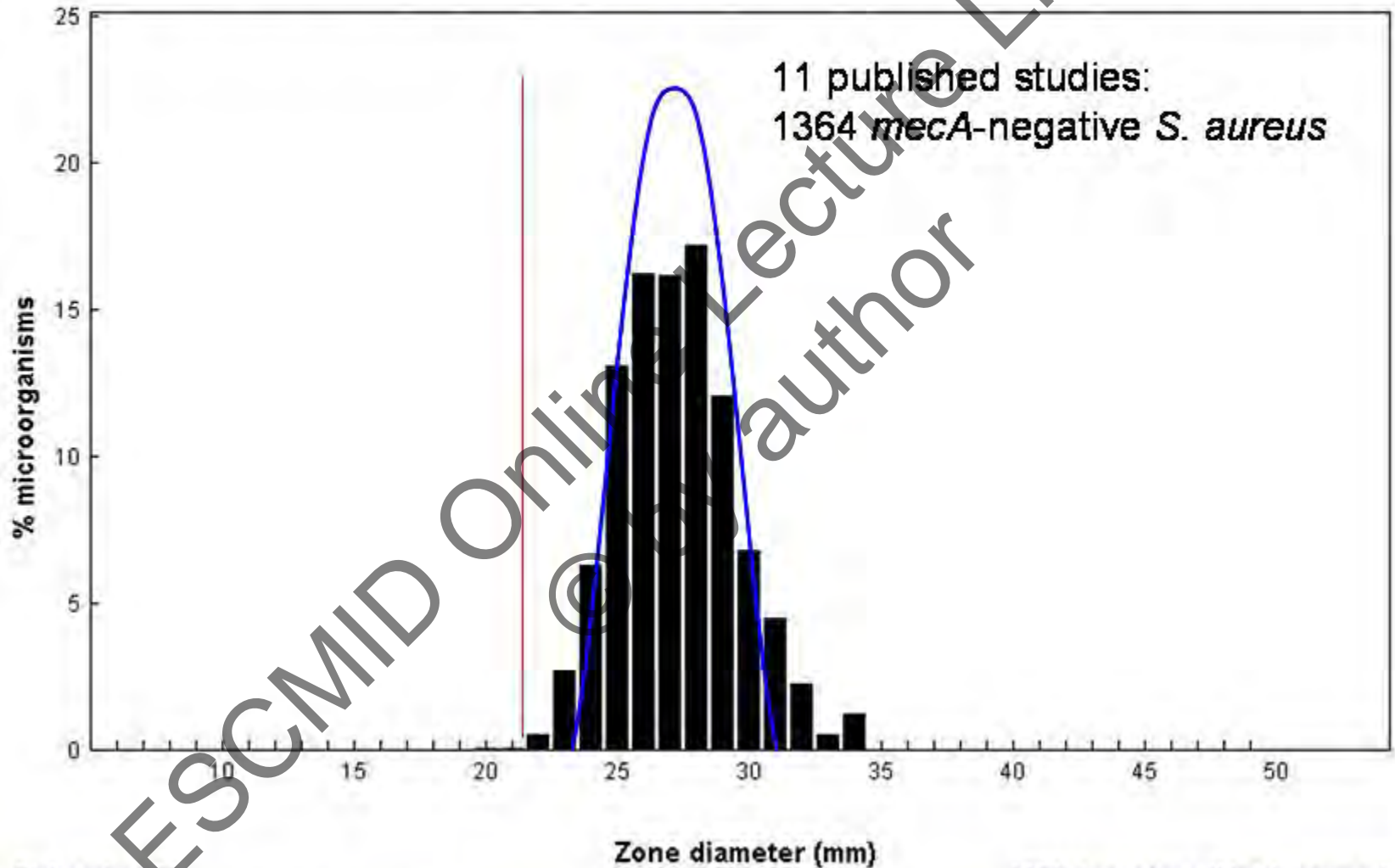
Epidemiological cut-off: WT \geq 22 mm (MIC: -)

122 observations

Clinical breakpoints: S \geq 22 mm, R < 22 mm

Cefoxitin / Staphylococcus aureus MSSA
EUCAST zone diameter distributions - Reference database
EUCAST disk diffusion method

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

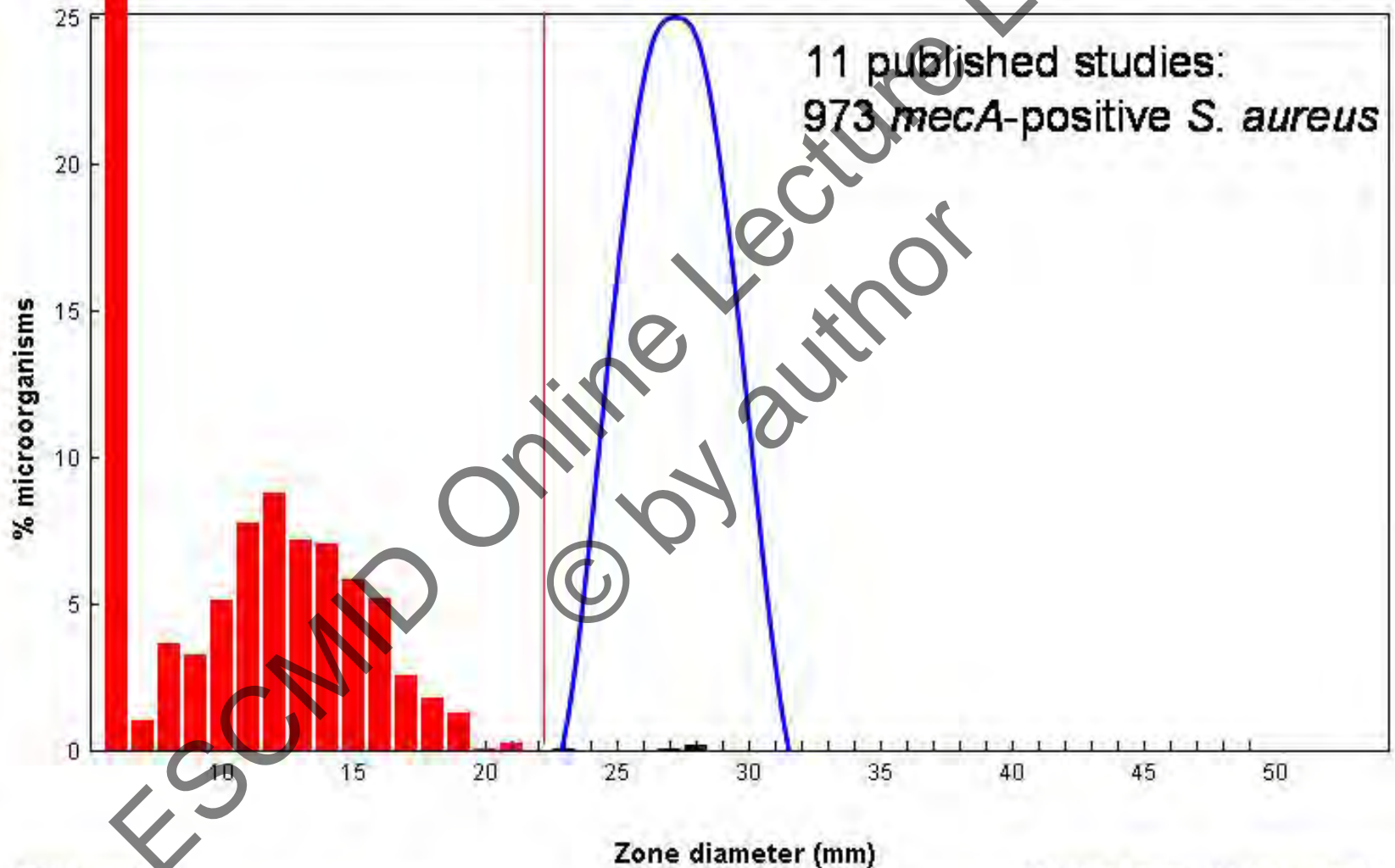


Disk content: 30
Epidemiological cut-off: WT \geq 22 mm (MIC: \leq 4 mg/L)

1364 observations (11 data sources)
Clinical breakpoints: S \geq 22 mm, R $<$ 22 mm

Cefoxitin / Staphylococcus aureus MRSA
EUCAST zone diameter distributions - Reference database
EUCAST disk diffusion method

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

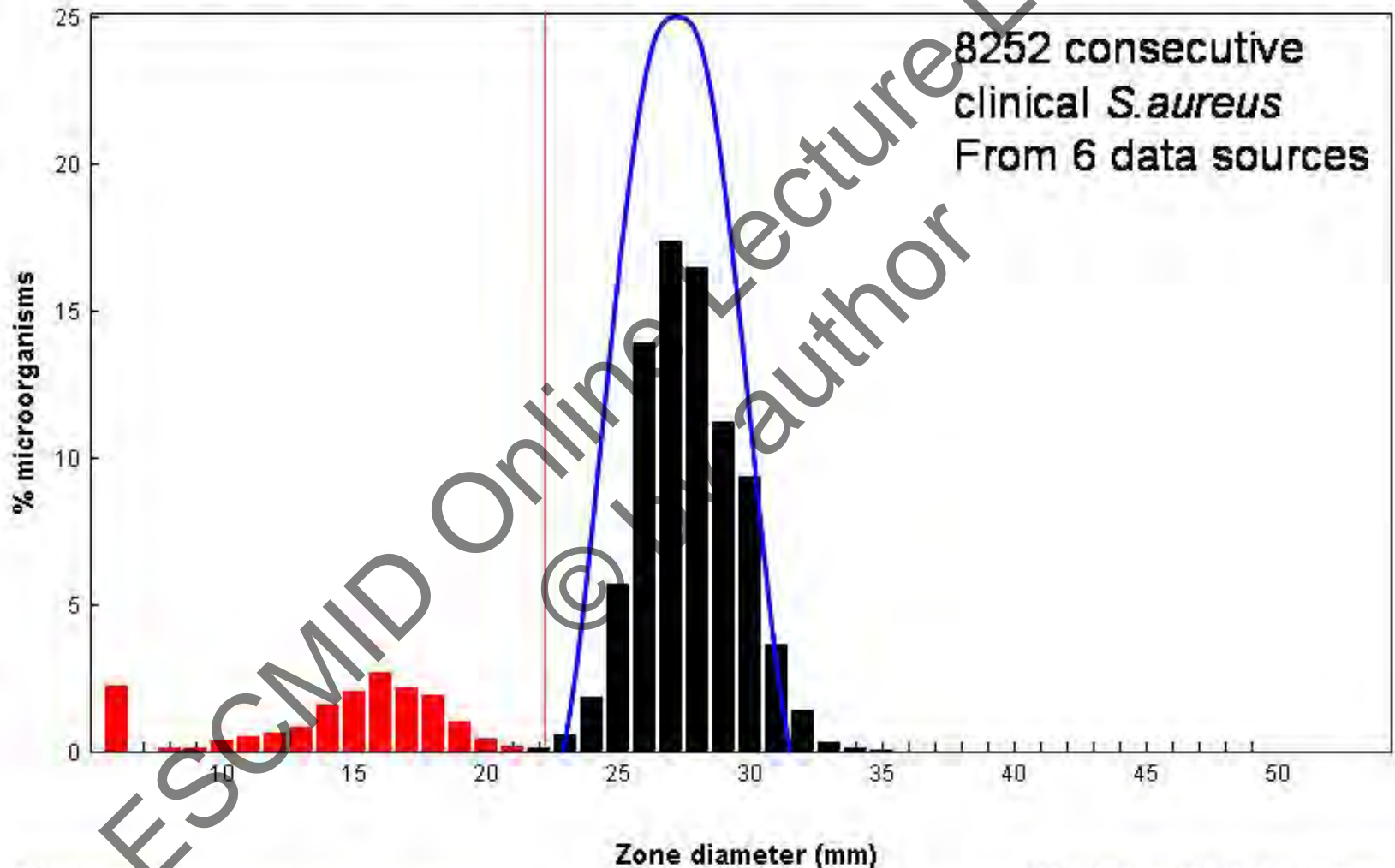


Disk content: 30
Epidemiological cut-off: WT \geq 22 mm (MIC: \leq 4 mg/L)

973 observations (11 data sources)
Clinical breakpoints: S \geq 22 mm, R $<$ 22 mm

Cefoxitin / *Staphylococcus aureus*
EUCAST zone diameter distribution - Reference database 2011-01-25
EUCAST disk diffusion method

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



Disk content: 30
Epidemiological cut-off: WT ≥ 22 mm (MIC: ≤ 4 mg/L)

8252 observations (6 data sources)
Clinical breakpoints: S ≥ 22 mm, R < 22 mm

EUCAST breakpoint table

| | A | B | C | D | E | F | G | H |
|----|------------------------------------|-----------------------|-----|---------------------|----------------------|-----|--|---|
| 44 | | | | | | | | |
| 45 | Carbapenems | MIC breakpoint | | Disk content | Zone diameter | | Notes | |
| 46 | | S ≤ | R > | | S ≥ | R < | Numbers for comments on MIC breakpoints | |
| 47 | | | | | | | | |
| 48 | Doripenem | 1 | 4 | 10 | 24 | 18 | | |
| 49 | Ertapenem | 0.5 | 1 | 10 | 25 | 22 | | |
| 50 | Imipenem ¹ | 2 | 8 | 10 | 21 | 15 | 1. <i>Proteus</i> and <i>Morganella</i> species are considered poor targets for imipenem. | |
| 51 | Meropenem | 2 | 8 | 10 | 22 | 16 | | |
| 52 | | | | | | | | |
| 53 | | | | | | | | |
| 54 | Monobactams | MIC breakpoint | | Disk content | Zone diameter | | Notes | |
| 55 | | S ≤ | R > | | S ≥ | R < | Numbers for comments on MIC breakpoints | |
| 56 | | | | | | | | |
| 57 | Aztreonam ¹ | 1 | 8 | 30 | 25 | 21 | 1. The aztreonam breakpoints for Enterobacteriaceae will detect resistance mediated by most ESBLs and other clinically important beta-lactamases in Enterobacteriaceae. However, some strains that produce ESBLs appear to be susceptible on control purposes laboratories | |
| 58 | | | | | | | | |
| 59 | | | | | | | | |
| 60 | Fluoroquinolones | | | | | | | |
| 61 | | | | | | | | |
| 62 | | | | | | | | |
| 63 | Ciprofloxacin ¹ | | | | | | response in systemic infections (mg/L). The available data relate to <i>Salmonella</i> species. | |
| 64 | Levofloxacin | | | | | | | |
| 65 | Moxifloxacin | | | | | | | |
| 66 | Halidixic acid (screen) | | | | | | Enterobacteriaceae. The zone diameter for <i>Salmonella</i> spp. are resistant report the agent in question. | |
| 67 | Fluoroquinolones | | | | | | | |
| 68 | Fluoroquinolones | | | | | | | |
| 69 | Fluoroquinolones | | | | | | | |
| 70 | Fluoroquinolones | | | | | | | |
| 71 | Aminoglycosides¹ | | | | | | | |
| 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 content | Zone diameter | | Notes | |
| 81 | | S ≤ | R > | | 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

EUCAST breakpoint table terminology

| | | | | |
|----------------------|---|---|---|--|
| MIC | S _≤ , R _{>} | EUCAST S _≤ 1, R _{>} 2 mg/L | = | CLSI S _≤ 1, R _≥ 4 mg/L |
| Zone diameter | S _≥ , R _{<} | EUCAST S _≥ 21, R _{<} 18 mm | = | CLSI S _≥ 21, R _≤ 17 mm |
| - | Susceptibility testing not recommended as the species is a poor target for therapy with the drug (Report as R without testing, or don't report) | | | |
| IE | Insufficient evidence to set a breakpoint (MIC values with comment but no categorical interpretation can be reported) | | | |
| NA | Not Applicable (mostly used for disk screening tests when they are not applicable to particular organisms, eg, nalidixic acid screen and <i>Pseudomonas</i> spp.) | | | |
| IP | In preparation (Breakpoints will be established) | | | |

Automated systems for AST

Phoenix, BD

- EUCAST breakpoints in 2009
- Evaluations (3): 2009 – 2010
- EUCAST panels/cards
- Several bugs and drugs are missing

Vitek2, BM

- EUCAST breakpoints in 2010 but in need of major software update 2011 (April – June)
- Cards containing mixture of breakpoints
- Problems with concept “EUCAST breakpoints”
- Evaluations ongoing
- Several bugs and drugs are missing

Microscan, Siemens

- EUCAST breakpoints 2010
- Launch April 2010
- no known evaluation
- Breakpoints panels and concept declared
- Several bugs and drugs are missing





EUCAST

EUROPEAN COMMITTEE
ON ANTIMICROBIAL
SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

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