EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

What is new in 2011: Methods and breakpoints in relation to subcommittees and expert groups

Gunnar Kahlmeter, Derek Brown

Izmir, February 2011

Anaerobes subcommittee

- EUCAST Subcommittee on breakpoints in anaerobes (Arne Rodloff, Luc Dubreuil, Elizabeth Nagy)
- MIC breakpoints available in EUCAST tables
- Methods – use CLSI technical recommendations and QC until further notice
- EUCAST is looking at disk diffusion for fast growing anaerobes (*Bacteroides* spp and *Clostridium* spp)

Expert rules subcommittee

- In operation for 5 years (finishing in 2011)

  Roland Leclercq (Chair, F), Rafael Cantón (ES)
  Christian Giske (S), Peter Heisig (D)
  Patrice Nordmann (F), Gian Maria Rossolini (I)
  Trevor Winstanley (UK) (and for v1.0 D Livermore, UK)
- Produced ”EUCAST Expert Rules in AST” document v1.0 (on website) and v2.0 (May 2011)
- Background and rules v2.0 submitted for publication
- Computer program (T. Winstanley) will be made available from EUCAST website during 2011

Subcommittee on antifungal susceptibility testing (EUCAST-AFST)

- Chair: J-L Rodriguez-Tudela (ES),
  Scientific secretary: JP Donnelly (N)

- AFST Steering Committee members: MC Arendrup (DK), C Lassl-Flörl (A), W Hope (UK)

- National representatives:

  See EUCAST website

  http://www.eucast.org/organization/subcommittees/eucast_afst

EUCAST methods of MIC determination for fungi

- EUCAST Definitive Document E.DEF 7.1

  Method for the determination of broth dilution of antifungal agents for fermentative yeasts. *CMI* 2008; 14:398-405

  http://www.eucast.org/fileadmin/src/media/PDFs/4ESCMID_Library/3Publications/EUCAST_Documents/Publications/EUCAST_def_document_in_CMI_v14_MICs_yeasts.pdf

- EUCAST Definitive Document E.DEF 9.1

  Method for the determination of broth dilution minimum inhibitory concentrations of antifungal agents for conidia forming moulds
  http://www.eucast.org/fileadmin/src/media/PDFs/4ESCMID_Library/3Publications/EUCAST_Documents/Other_Documents/EUCAST_moulds_DEFINITIVE_document_V_ISO_April_08%20final.pdf

- ISO standard methods committee in progress
- Additional technical publications
  http://www.eucast.org/documents/publications_in_journals

EUCAST-AFST published breakpoints

- Published rationale documents
  http://www.eucast.org/documents/rd

Agent	Organisms	Susceptible (≤mg/L)	Resistant (>mg/L)
Fluconazole	*Candida albicans*	2	4
	Candida glabrata	IE	IE
	Candida tropicalis	2	4
	Candida krusei	-	-
	Candida parapsilosis	2	4
Voriconazole	*Candida albicans*	0.125	0.125
	Candida glabrata	IE	IE
	Candida tropicalis	0.125	0.125
	Candida krusei	IE	IE
	Candida parapsilosis	0.125	0.125

EUCAST-AFST proposed breakpoints

- Rationale documents available with consultation document from EUCAST home page www.eucast.org

Agent	Organisms	Susceptible (≤mg/L)	Resistant (>mg/L)
Amphotericin B	*Candida albicans*	1	1
	Candida glabrata	1	1
	Candida tropicalis	1	1
	Candida krusei	1	1
	Candida parapsilosis	1	1
	Candida other species	IE	IE
Posaconazole	*Candida albicans*	0.06	0.06
	Candida glabrata	IE	IE
	Candida tropicalis	0.06	0.06
	Candida krusei	IE	IE
	Candida parapsilosis	0.06	0.06
	Candida guilliermondii	IE	IE
Anidulafungin	*Candida albicans*	0.03	0.03
	Candida glabrata	0.06	0.06
	Candida tropicalis	0.06	0.06
	Candida krusei	0.06	0.06
	Candida parapsilosis	-	-
	Candida guilliermondii	-	-

Listeria monocytogenes

- MIC (and disk diffusion test)
- Project 2011 (four laboratories)

- **Antibiotics for which breakpoints are needed (bold):**
  - Benzylpenicillin (disk 1 unit)
  - **Ampicillin** (disk 2 µg)
  - **Meropenem** (disk 10 µg)
  - Moxifloxacin (disk 5 µg)
  - **Gentamicin** (disk 10 µg)
  - Vancomycin (disk 5 µg)
  - **Erythromycin** (disk 15 µg)
  - Tetracycline (disk 30 µg)
  - Linezolid (disk 10 µg)
  - **Chloramphenicol** (disk 30 µg)
  - Rifampicin (disk 5 µg)
  - Trimethoprim (disk 5 µg)
  - **Trimethoprim-sulfamethoxazole** (disk 25 µg (1.25+23.75))

- **Agents in bold are regarded as clinically important by the EUCAST Steering Committee (September 2010).**

Pasteurella multocida

- Project 2011 (2 laboratories)
- MIC and disk diffusion breakpoints
  - **Benzylpenicillin** (screen for betalactam resistance using PCG 1U)
  - **Ampicillin**
  - **Amoxicillin-clavulanic acid**
  - **Cefotaxime**
  - **Ciprofloxacin** (screen for FQ using Nalidixic acid?)
  - **Tetracycline/doxycycline**
  - **Trimethoprim-sulfamethoxazole**

Campylobacter jejuni/coli

- Project 2010 – 11 (4 laboratories)
- MIC and disk diffusion breakpoints
- Disk diffusion methodology (based on MH-F, 20-24 h incubation, Campy-environment)
  - **Ampicillin**
  - Amoxicillin-clavulanate
  - Ceftriaxone
  - Imipenem
  - Nalidixic acid
  - **Ciprofloxacin**
  - Levofloxacin
  - Enrofloxacin
  - **Erythromycin**
  - Azithromycin
  - Gentamicin
  - **Tetracycline**/doxycycline

Clostridium difficile

- Consultation with the ESCMID *C.difficile* study group (ESGCD). The following proposals are agreed between EUCAST and the study group.

Note the following:

1. There are no clinical or pharmacodynamic data on which breakpoints for *C. difficile* can be based. Breakpoints are therefore epidemiological cut-off values (ECOFFs), which distinguish the wild type from isolates with reduced susceptibility.
2. Several agents are included for epidemiological purposes only. They are inappropriate for treatment. ECOFFs have been defined when sufficient MIC distributions are available.
3. Few MIC distributions are available for some agents, so some ECOFFs are tentative. Any additional MIC distributions would be appreciated (please give method details and the source of isolates).

C. difficile – proposed epidemiological cut-off values (ECOFFs)

Agent	ECOFF (mg/L)	Comment
Metronidazole	≤2	Breakpoint based on ECOFF.
Vancomycin	≤2	Breakpoint based on ECOFF.
Fusidic acid	≤2	No clinical breakpoint. Resistance develops rapidly. Tested for epidemiological purposes only.
Moxifloxacin	≤4	No clinical breakpoint. Tested for epidemiological purposes only.
Rifampicin	≤0.004	No clinical breakpoint. Tested for epidemiological purposes only.
Tigecycline	≤0.25	No clinical breakpoint. Tested for epidemiological purposes only.
Daptomycin	≤4	No clinical breakpoint. Tested for epidemiological purposes only.

Helicobacter pylori

Note:

- Different test methods may give different results.
- There is a shortage of clinical data linking in vitro susceptibility to outcome.
- All agents are used in combination therapy so outcome data for individual agents are often difficult to assess.

Helicobacter pylori proposed breakpoints

Agent	Susceptible (mg/L)	Resistant (mg/L)	Comment
Amoxicillin	≤0.12	>0.12	The breakpoints are based on the epidemiological cut-off value (ECOFF). Isolates with higher MICs are uncommon and there is no evidence to indicate whether treatment is successful for infections caused by isolates with MICs >0.12 mg/L.
Clarithromycin	≤0.25	>0.5	These breakpoints have been clinically validated and isolates with MIC above 0.5 mg/L have a resistance mechanism (23S RNA mutation). The ECOFF is 0.25 mg/L.
Levofloxacin	≤1	>1	These breakpoints largely correlate with *gyrA* mutations (although there are no outcome data). The ECOFF is 0.5 mg/L. While ciprofloxacin test results are indicative of levofloxacin susceptibility, ciprofloxacin susceptibility should not be reported as ciprofloxacin is not effective in vivo and may mislead clinicians.
Tetracycline	≤1	>1	These breakpoints correspond to mutation in 16S RNA. Resistance is rare and there is no clinical validation. The ECOFF is 0.25 mg/L. Tetracycline susceptibility should not be used as an indicator of susceptibility to other tetracyclines as other tetracyclines are not effective in vivo.
Rifampicin	≤1	>1	Few MIC data are available. The breakpoints correspond with *rpoB* mutation. Resistance is rare and there is no clinical validation. Rifabutin is used rather than rifampicin.
Metronidazole	≤8	>8	This is the current, widely accepted breakpoint, but there is no clinical validation. The ECOFF is 4 mg/L. It is possible that different breakpoints might be appropriate for different treatment regimens.

EUCAST strategy for topical antimicrobial agents

- Some topical preparations are mixtures of antimicrobial agents
- Local concentrations may be high but there are rarely any data correlating MICs to clinical outcome – hence clinical breakpoints based on high local concentrations cannot be determined.
- There is often anecdotal evidence that an agent is effective in specific conditions in which case it can at least be assumed that wild type isolates are susceptible.
- If there is already a clinical breakpoint for the agent, this can be applied for topical preparations also.
- Otherwise the ECOFF can serve in lieu of a clinical breakpoint and/or can be used for epidemiological purposes to measure resistance development as a biological phenomenon.

Topical agents

- Topical agents?

Chloramphenicol	Tetracycline
Gentamicin	Neomycin (Framycetin)
Polymyxin B	Ofloxacin
Fusidic acid	Bacitracin

- Retapamulin

  New agent for impetigo and superficial skin infections

  ECOFF set by EUCAST as part of the marketing authorisation by EMA

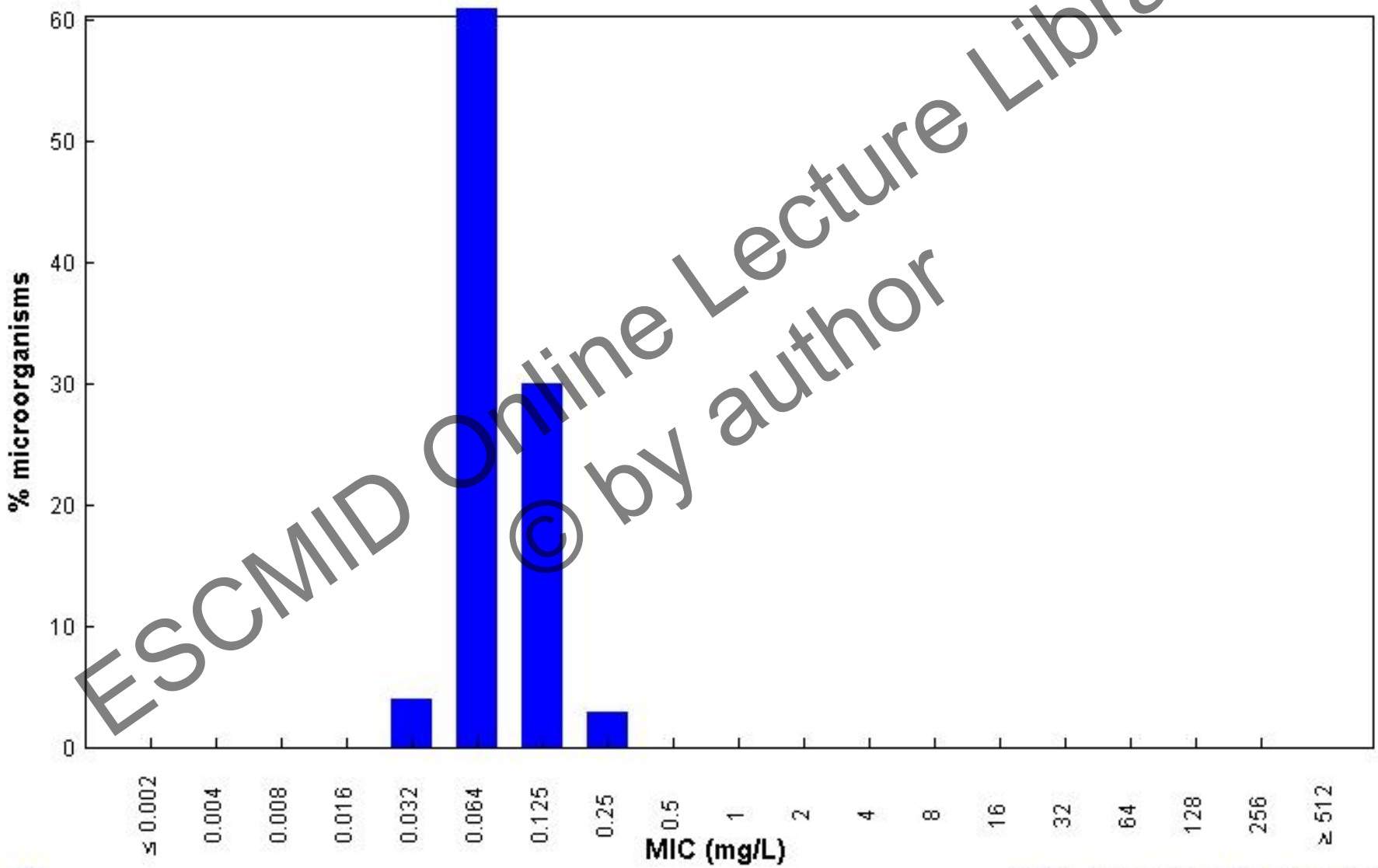
- Mupirocin

  Breakpoint set for *S. aureus* on basis of clinical data and ECOFF

Retapamulin / Staphylococcus aureus

EUCAST MIC Distribution - Reference Database 2011-02-28

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 ≤ 0.5 mg/L

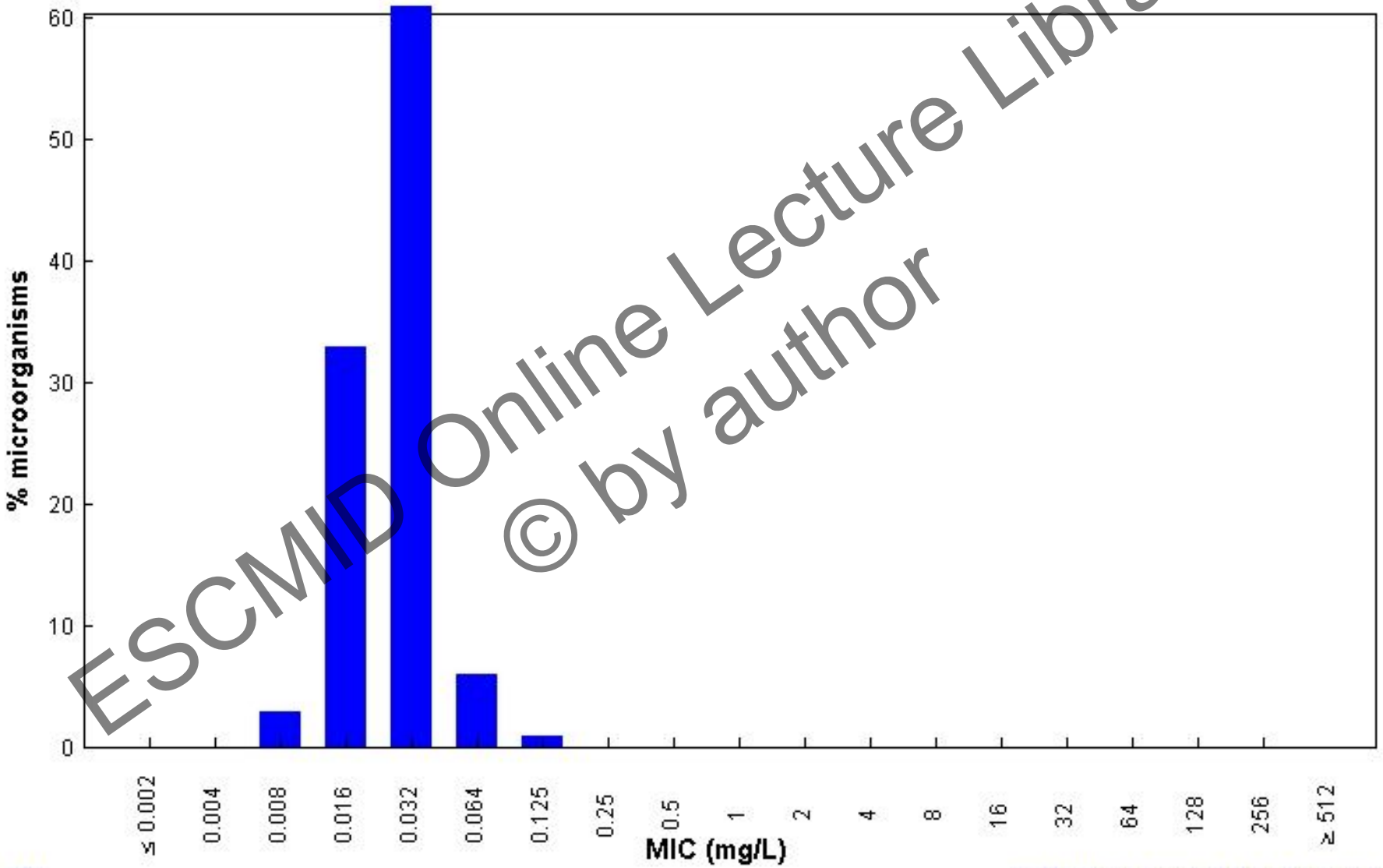
5629 observations (5 data sources)

Clinical breakpoints: S ≤ - mg/L, R > - mg/L

Retapamulin / Streptococcus pyogenes

EUCAST MIC Distribution - Reference Database 2011-02-28

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

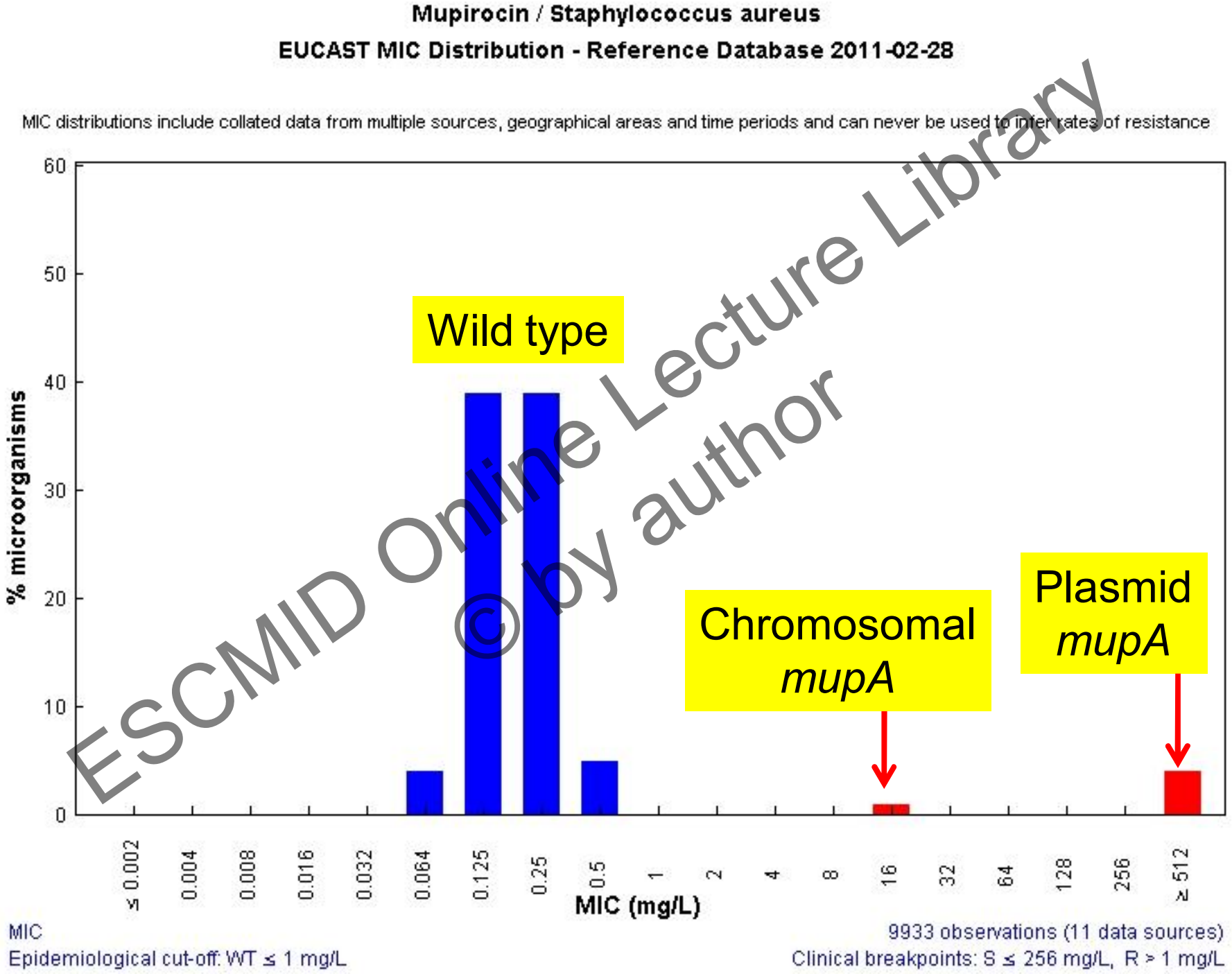


MIC

Epidemiological cut-off: WT ≤ 0.125 mg/L

2771 observations (3 data sources)

Clinical breakpoints: S ≤ - mg/L, R > - mg/L



S. aureus mupirocin breakpoints

- Clinical data indicate that for nasal colonization
  - Wild type isolates (MIC ≤1 mg/L) are cleared
  - High-level resistant isolates (MIC >256 mg/L are not cleared
  - Low-level resistant isolates (MIC 8-256 mg/L) are initially cleared but there is a high rate of "recolonization"
  - Outcome for isolates with MICs 2-4 mg/L is unknown

Susceptible MIC ≤1 mg/L	wild type
Intermediate MIC 2-256 mg/L	low-level resistant
Resistant MIC >256 gm/L	high-level resistant