# Towards Rational International Antibiotic Breakpoints: Actions from the European Committee on Antimicrobial Susceptibility Testing (EUCAST)

**A report to ISC**

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**representative of ISC to EUCAST**

**and based on an official presentation of EUCAST**

**prepared by G. Khalmeter & J. Mouton**

Manila, Philippines
June 4th, 2005

# What was the problem ?

- Europe has a number of different breakpoints-setting authorities … and, therefore (?) different breakpoints …

- NCCLS-defined breakpoints are not (always) rational and realistic, and, in any case, are linked to the US situation

# One simple example …

| cefotaxime vs. *E.coli* | | S≤ / R |
|---|---|---|
| BSAC | United Kingdom | 2 / ≥4 |
| CA-SFM | France | 4 / >32 |
| CRG | The Netherlands | 4 / >16 |
| DIN | Germany | 2 / ≥16 |
| NWGA | Norway | 1 / ≥32 |
| SRGA | Sweden | 0.5 / ≥2 |
| | | |
| NCCLS | U.S.A. | 8 / ≥64 |

**Yet, breakpoints are used everyday by clinical microbiology laboratories to advise clinicians about useful antibiotics against the bacteria they are after …**

# What is EUCAST ?

## European Committee on Antimicrobial Susceptibility Testing

- formed in 1997
- convened by
  - European Society for Clinical Microbiology and Infectious Diseases (ESCMID)
  - National Breakpoint Committees in Europe
- financed by
  - ESCMID
  - National Breakpoint Committees in Europe
  - DG-SANCO of the European Union (3 year grant from May 2004)

# Main objectives of EUCAST

- **In Europe**
  - to set **common breakpoints** for **surveillance of antimicrobial resistance**;
  - to **harmonise clinical breakpoints** for existing and new antimicrobial drugs;
  - to promote **standardisation of methods**;
  - to **collaborate** with groups concerned with antimicrobial susceptibility testing and/or the epidemiology of antimicrobial resistance;
  - to **advise European Union Institutions** on the technology and interpretation of antimicrobial susceptibility testing;
- **In the world**
  - to **work with** other active groups (eg CLSI [formerly NCCLS] ) to achieve international consensus on susceptibility testing;

# EUCAST definitions of epidemiological cut off values

**Wild type (WT)**

- a microorganism is defined as wild type (WT) for a species by the absence of acquired and mutational resistance mechanisms to the drug in question.
- a microorganism is categorized as wild type (WT) for a species by applying the appropriate cut-off value in a defined phenotypic test system.
- wild type microorganisms may or may not respond clinically to antimicrobial treatment.

**Microbiological resistance - non-wild type (NWT)**

- a microorganism is defined as non-wild type (NWT) for a species by the presence of an acquired or mutational resistance mechanism to the drug in question.
- a microorganism is categorized as non-wild type (NWT) for a species by applying the appropriate cut-off value in a defined phenotypic test system.
- non-wild type microorganisms may or may not respond clinically to antimicrobial treatment.

**Epidemiological cut-off values will not be altered by changing circumstances.**

Menu Deconnecter

## Distribution des CMI vs. Phenotypes sauvages

http://www.eucast.org

Recherche

Méthode: CMI Methode de diffusion

Éléments par page: 15

Antimicrobien: Ciprofloxacin Espèce: Espèce...

**Specify the drug or the bug (never both) - after a few seconds a table of MIC-distributions is shown. Click on any species in the left hand column to display the data as a bar chart, with EUCAST epidemiological cut-off values and harmonised European clinical breakpoints.**

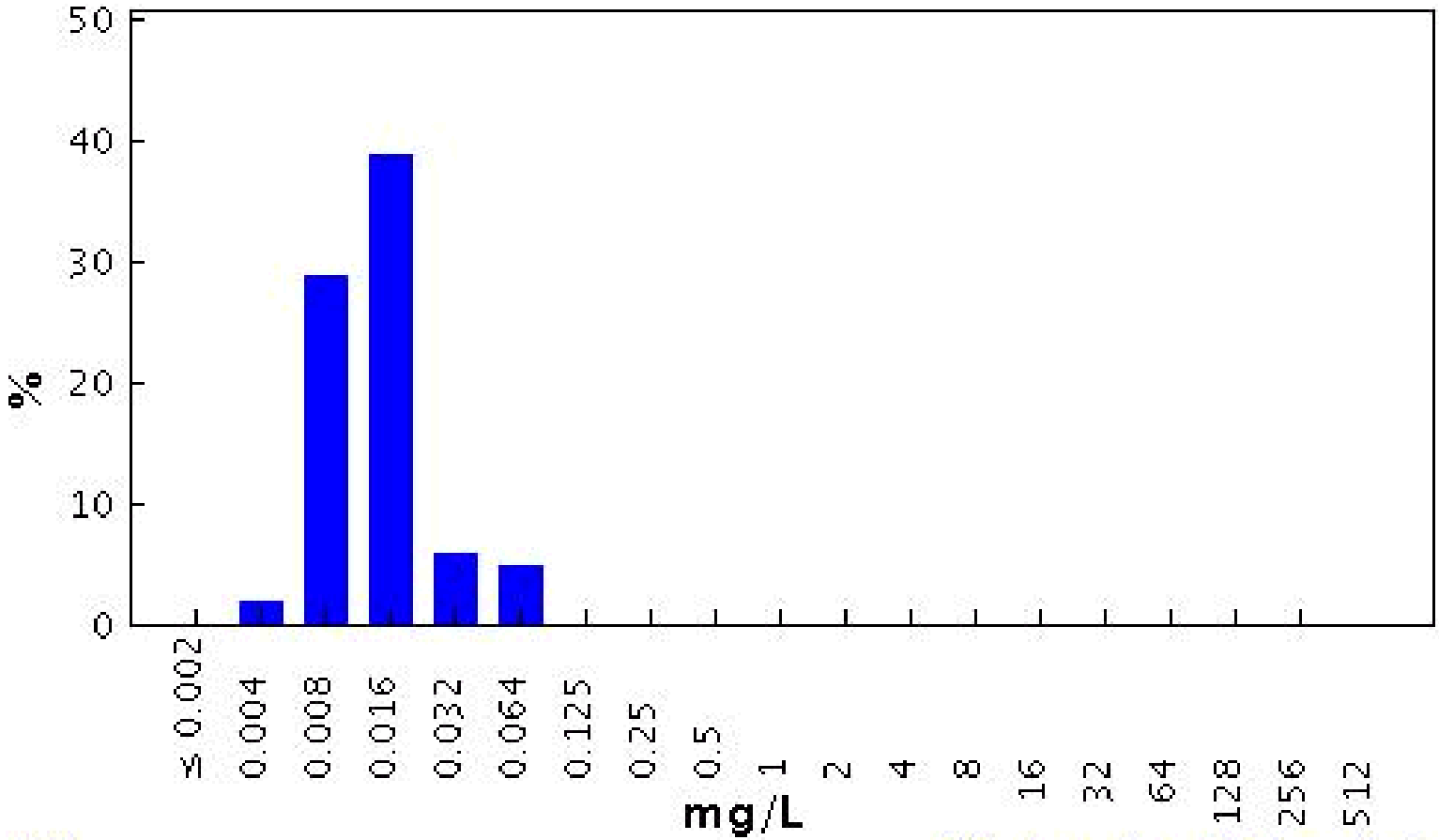
| Antimicrobien: | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Acinetobacte | | | | | | | | | | | | | | | | | | | |
| Bacteroides f | | | | | | | | | | | | | | | | | | | |
| Burkholderia | | | | | | | | | | | | | | | | | | | |
| Campylobact | | | | | | | | | | | | | | | | | | | |
| Campylobact | | | | | | | | | | | | | | | | | | | |
| Citrobacter s | | | | | | | | | | | | | | | | | | | |
| Coagulase negative staphylococci | 0 | 0 | 0 | 0 | 5 | 0 | 7 | 13 | 13 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Enterobacter species | 0 | 14 | 30 | 132 | 110 | 27 | 15 | 9 | 11 | 5 | 8 | 4 | 5 | 6 | 0 | 8 | 0 | 0 | 0 |
| Enterococcus faecalis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 8 | 9 | 25 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Enterococcus faecium | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 10 | 19 | 35 | 68 | 37 | 21 | 3 | 3 | 0 | 0 | 0 | 0 |
| Escherichia coli | 11 | 158 | 1469 | 2032 | 147 | 52 | 116 | 81 | 31 | 19 | 8 | 47 | 85 | 62 | 60 | 32 | 5 | 0 | 0 |
| Haemophilus influenzae | 6 | 47 | 258 | 674 | 367 | 46 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Haemophilus parainfluenzae | 0 | 0 | 74 | 111 | 18 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Klebsiella pneumonia | 0 | 2 | 38 | 217 | 295 | 79 | 30 | 31 | 17 | 8 | 1 | 2 | 0 | 7 | 7 | 1 | 2 | 0 | 0 |
| Klebsiella spp | 0 | 12 | 20 | 86 | 888 | 126 | 76 | 39 | 27 | 29 | 11 | 18 | 17 | 0 | 0 | 0 | 0 | 0 | 0 |

Ac-Le Le-St St-

Retourner

## Ciprofloxacin / Escherichia coli

### Antimicrobial wild type distributions of microorganisms - reference database EUCAST




MIC

6423 observations (9 data sources)

Epidemiological cut-off: WT ≤ 0.064 mg/L

Clinical breakpoints: S ≤ 0.5 mg/L, R > 1 mg/L

# EUCAST wild type MIC distributions and epidemiological cut-off values – the concept

**JAC 2003; 52: 145-148**

- Software was created to receive and display large volumes of MIC data for bacteria and fungi over the Internet. It is freely available at **http://www.eucast.org**.
- Tables and graphs show the part of the MIC distribution which, when EUCAST defines the ”epdemiological cut-off value”, is defined as the ”wild type distribution”.
- The **epidemiological cut-off value** separating microorganisms without (wild type) and with acquired or mutational resistance (non-wild type) and **clinical breakpoints** are, if defined, shown on the bottom line of the graph.
- The epidemiological cut-off value is shown as WT$\leq$ x mg/L.

# EUCAST wild type MIC distributions and epidemiological cut-off values – methods and data

## Origin of MIC data

Each distribution is comprised of aggregated MIC data including individual MIC distributions from

- publications in international journals
- breakpoint committees
- antimicrobial surveillance systems such as EARSS, SENTRY, the Alexander Project
- pharmaceutical companies and susceptibility testing device manufacturers.

Although different methods may be used, results rarely vary by more than one doubling dilution step. In this way the aggregated EUCAST MIC distributions contain the random variation between different investigators and the systematic variation seen between different methods.

# EUCAST wild type MIC distributions – how to contribute data

**Everyone is invited to contribute data**

All who have full-range MIC data for bacteria or fungi are invited to contribute data as long as MICs are determined with an accepted standardised method, which should be named. Once entered on the database the data will not be identifiable as separate distributions but will help build the aggregate reference distributions. The biologically resistant (non-wild type) part of the distribution will be seen only by the EUCAST Steering Committee.

**Submitting data to the EUCAST database does not interfere with publication of data.**

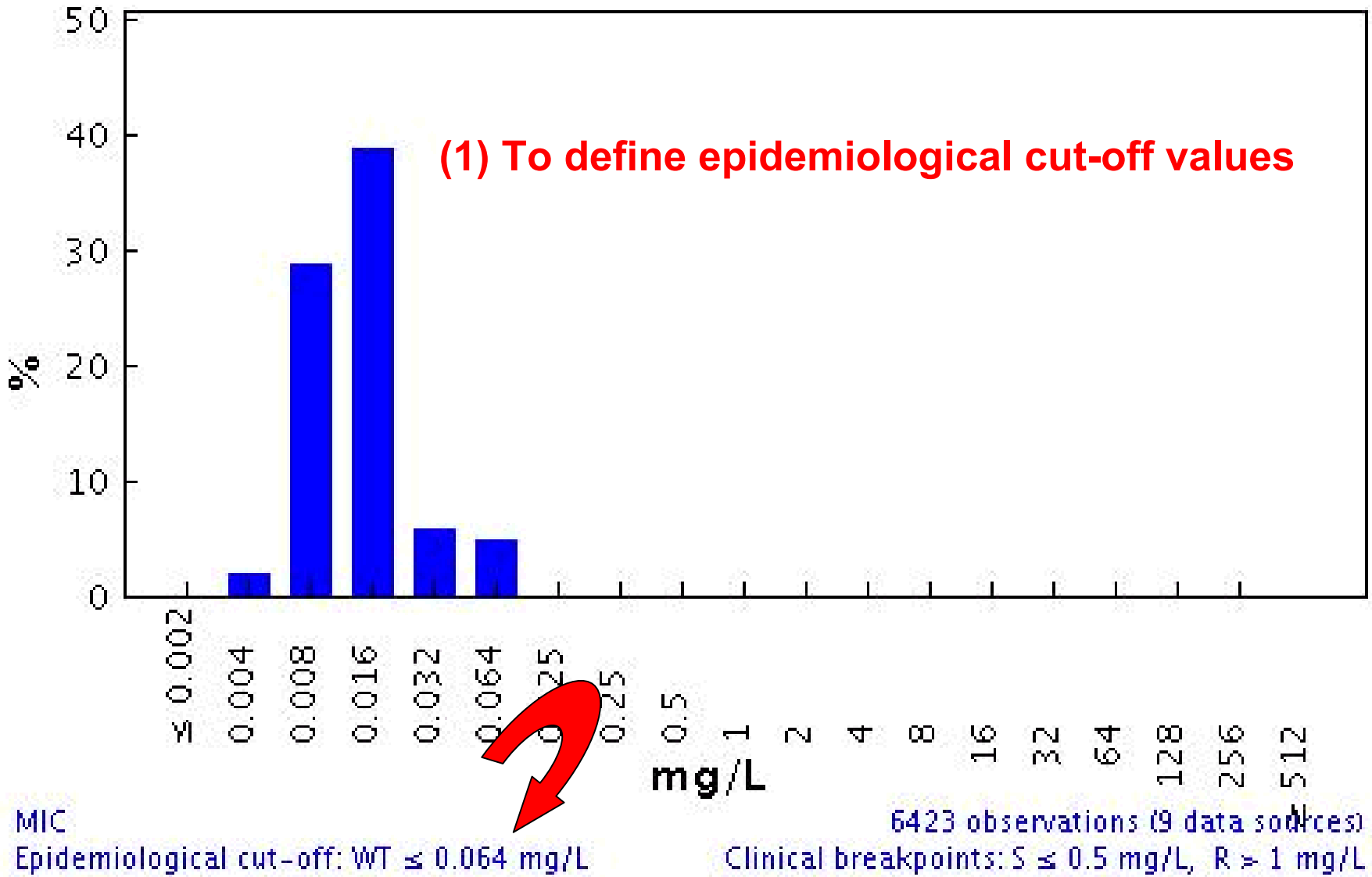
**Where can I get more information?**

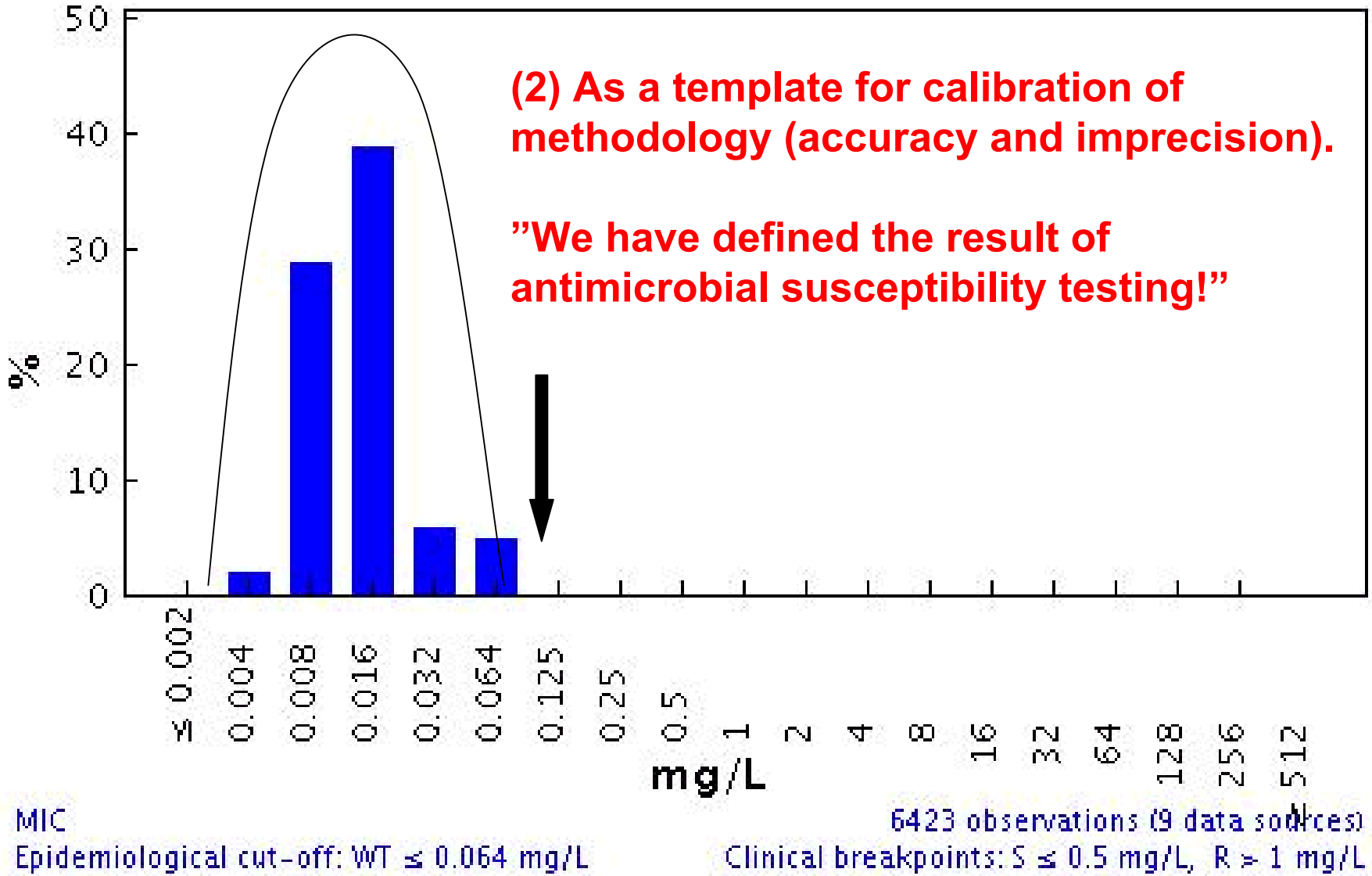
Contact EUCAST – email addresses and information can be obtained through the EUCAST website at **http://www.eucast.org**

# Use of EUCAST wild type MIC distributions

**The wild type MIC distributions provide**

1. reference material for **epidemiological cut-off values** for antimicrobial resistance surveillance
2. an international reference for **calibration of antimicrobial susceptibility testing methods**
3. reference **MIC ranges of wild type organisms** for a wide spectrum of species and antimicrobials
4. reference material for committees involved in decisions on **clinical breakpoints**


Ciprofloxacin / Escherichia coli
Antimicrobial wild type distributions of microorganisms - reference database
EUCAST
(1) To define epidemiological cut-off values
%
50
40
30
20
10
0
≤ 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
mg/L
MIC
Epidemiological cut-off: WT ≤ 0.064 mg/L
6423 observations (9 data sources)
Clinical breakpoints: S ≤ 0.5 mg/L, R > 1 mg/L


Ciprofloxacin / Escherichia coli
Antimicrobial wild type distributions of microorganisms - reference database
EUCAST
(2) As a template for calibration of methodology (accuracy and imprecision).
”We have defined the result of antimicrobial susceptibility testing!”
%
50
40
30
20
10
0
≤ 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
mg/L
MIC
Epidemiological cut-off: WT ≤ 0.064 mg/L
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# EUCAST definitions of clinical breakpoints

**Clinically Susceptible (S)**

- level of antimicrobial activity associated with a high likelihood of therapeutic success

**Clinically Intermediate (I)**

- level of antimicrobial activity associated with indeterminate therapeutic effect

**Clinically Resistant (R)**

- level of antimicrobial activity associated with a high likelihood of therapeutic failure.

a microorganism is categorized as S, I or R by applying the appropriate breakpoint in a defined phenotypic test system

**Clinical breakpoints may be altered with legitimate changes in circumstances**

**Clinical breakpoints are presented as S≤ x mg/L ; I >x, ≤ y mg/L ; R >y mg/L**

# EUCAST procedure for setting breakpoints

The next slides describe the EUCAST procedure for harmonising European breakpoints and reach rational values.

# 1. Data on dosing, formulations, clinical indications and target organisms are reviewed and differences which might influence breakpoints are highlighted

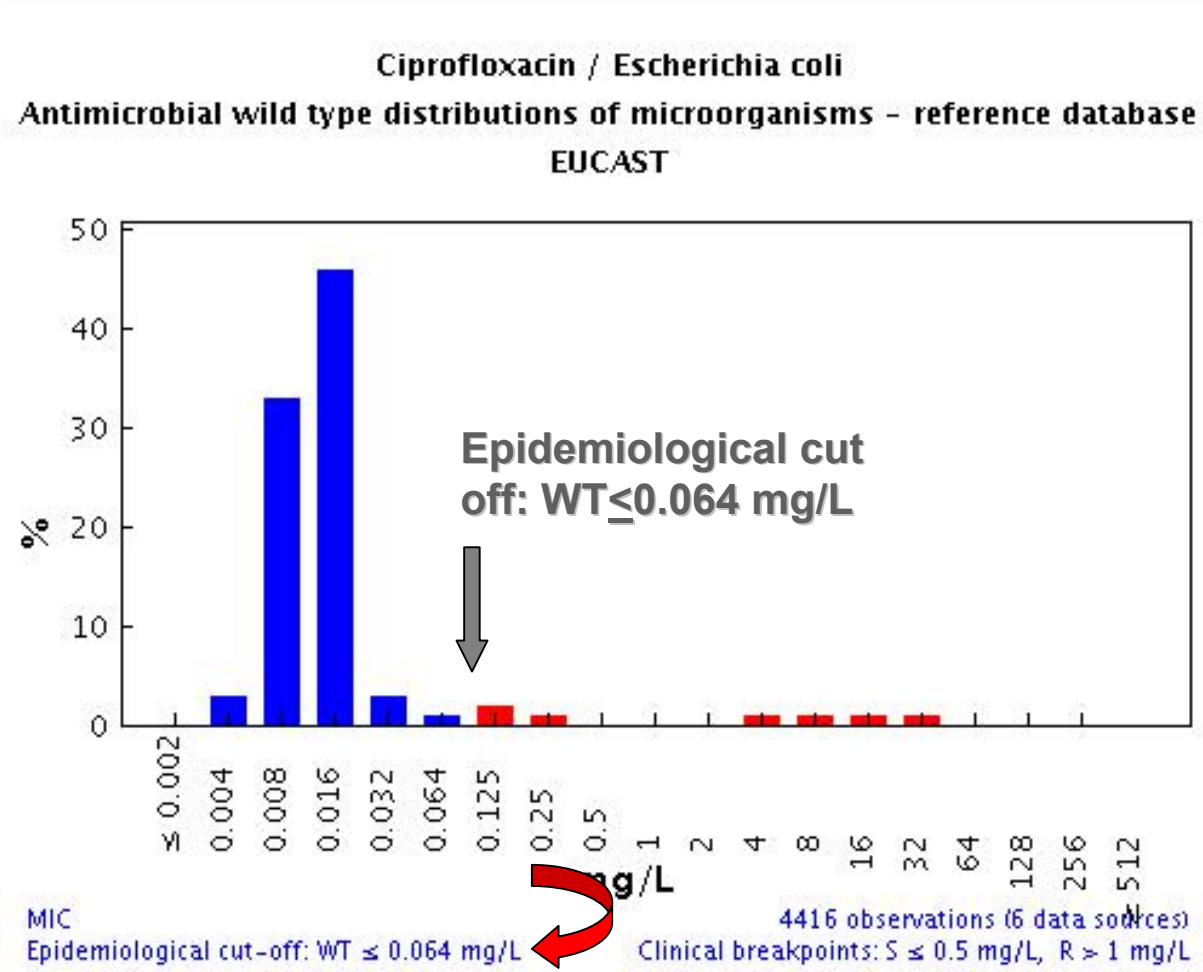
| Dosage | National breakpoint committees | | | | | | |
|---|---|---|---|---|---|---|---|
| **Most common dose** | 500 x 2 oral<br>400 x 2 iv | 500 x 2 oral<br>200 x 2 iv | 250 x 2 oral<br>200 x iv | 500 x 2 oral<br>200 x 2 iv | 200-400 x 2 oral<br>400 x 2 iv | 500 x 2 oral<br>400 x 2 iv | |
| **Maximum dose schedule** | 750 x 2 oral<br>400 x 3 iv | 750 x 2 oral<br>400 x 3 iv | 750 x 2 oral<br>400 x 3 iv | 750 x 2 oral<br>400 x 2 iv | data pending | 750 x 2 oral<br>400 x 3 iv | |
| **Available formulations** | oral, iv | oral, iv | oral, iv | oral, iv | oral, iv | oral, iv | |

**Clinical data**

There is clinical evidence for ciprofloxacin to indicate a poor response in systemic infections caused by *Salmonellae* with low-level fluoroquinolone resistance (MIC>0.064 mg/L) EUCAST has suggested that the epidemiological cut off value (S≤0.064/R>0.064 mg/L) be used in Salmonellae systemic infections. These strains are best found using a nalidixic acid 30 µg screen disc in routine susceptibility testing.

There is agreement in EUCAST that ciprofloxacin activity against Enterococci and Streptococci, including S.pneumoniae, is insufficient to categorize wild type bacteria “susceptible”.

## 2. Multiple MIC-distributions are collected, the wild type MIC distribution is defined and tentative epidemiological cut-off values determined (WT ≤X mg/L)



# 3. Existing national clinical breakpoints are compared

**Ciprofloxacin** was used in this example:

| **Breakpoints prior to harmonisation (mg/L) S≤ R>** | | | | | | | |
|---|---|---|---|---|---|---|---|
| | **BSAC** | **CA-SFM** | **CRG** | **DIN** | **NWGA** | **SRGA** | **NCCLS** |
| **General breakpoints** | **ND** | **1/2** | **1/2** | **1/2** | **0.125/2** | **1/2** | |
| **Species related breakpoints** | | **not yet** | | **no** | | | |
| Enterobacteriaceae | **1/1** | | | | **0.12/2** | **0.12/1** | **1/2** |
| *Pseudomonas* spp. | **1/4** | | | | **ND** | **1/1** | **1/2** |
| *Acinetobacter* spp. | | | | | | **1/1** | **1/2** |
| Staphylococci | **1/1** | | | | **0.12/2** | **0.06/2** | **1/2** |
| Streptococci | **1/1** | **excluded** | | | **0.12/2** | **0.12/2** | **excl** |
| *S. pneumoniae* | **2/2 (I)*** | **excluded** | | | **0.12/2 (I)*** | **0.12/2 (I)*** | **excl** |
| Enterococci | **excluded** | **excluded** | | | **0.12/2** | **0.12/2** | **1/2** |
| *Haemophilus/Moraxella* spp. | **1/1** | | | | **0.12/0.5** | **0.12/0.25** | **1/-** |
| Corynebacteria | | | | | | **excl** | |
| *N. Meningitidis* | **1/1** | | | | **0.06/0.12** | **0.03/0.25** | |
| *N. Gonorrhoeae* | **0.06/-** | | **0.06/1** | | **0.06/0.12** | **0.06/0.25** | **0.06/0.5** |
| *P. Multocida* | **ND** | | | | **ND** | **0.12/0.25** | |
| Anaerobes | **excluded** | | | | **ND** | **excluded** | |
| *Campylobacter* spp. | **1/1** | | | | | | |
| *Helicobacter pylori* | **2/2** | **no** | **no** | | **no** | **no** | |

## 4. Pharmacokinetic data are collected and evaluated

Pharmacokinetic data are collected from various sources, particularly data from patients. If the data allow it and if necessary, population pharmacokinetic models are developed.

These are necessary for pk/pd analyses, including Monte Carlo simulations

## 5. Pharmacodynamic data are evaluated

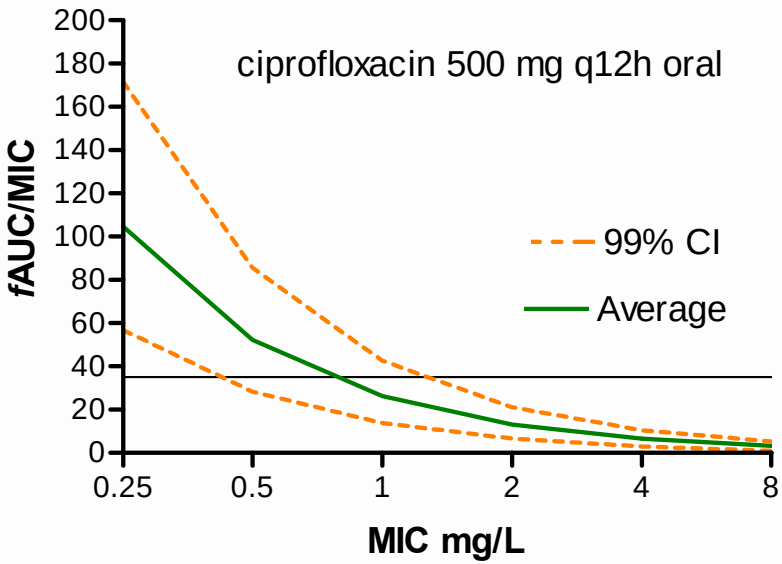
The PK/PD index value resulting in optimal outcome is determined from:

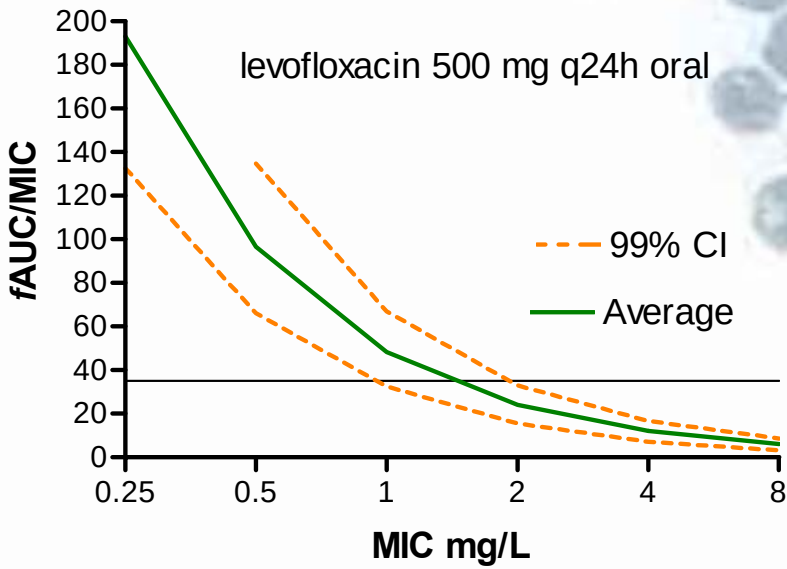
- in vitro data
- animal studies
- clinical trials

The efficacy of the drugs is assessed quantitatively.

Relationships between concentration time profiles and emergence of resistance are evaluated

## Monte Carlo simulations are performed and a PK/PD breakpoint calculated based on conventional dosing regimens




S = 0.5 mg/L

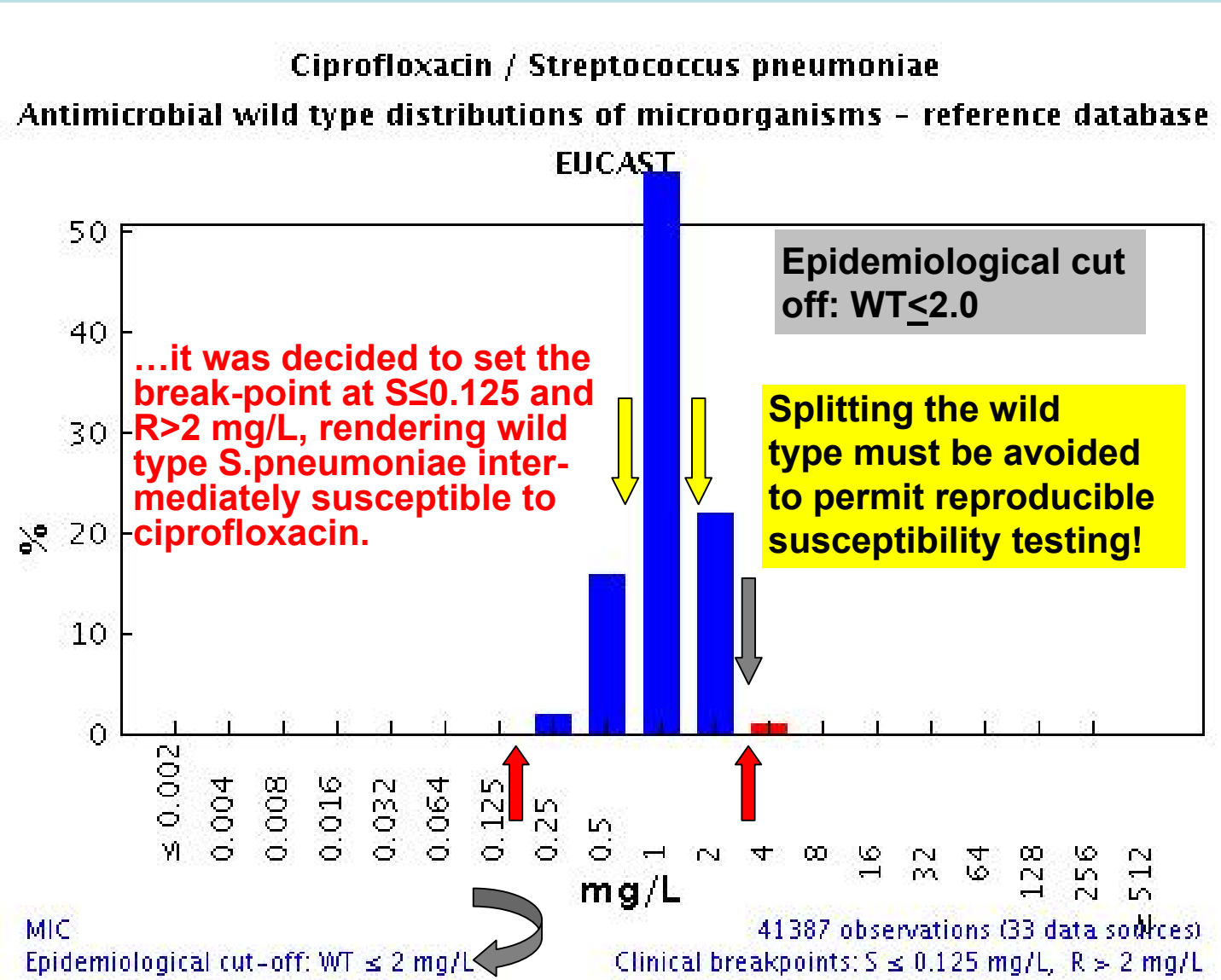
Pk/Pd

S = 1 mg/L

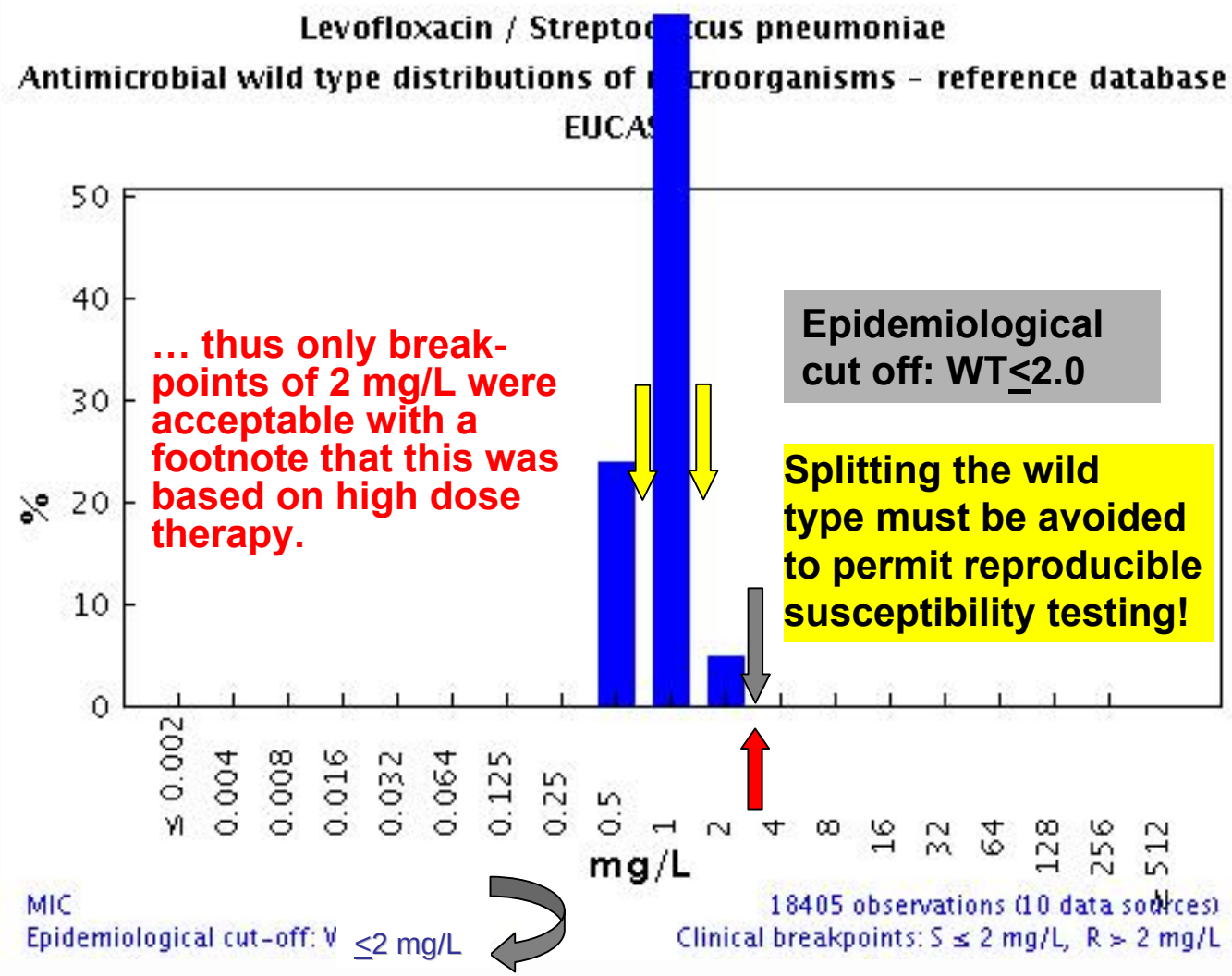
**5. Clinical data relating outcome to MIC-values, wildtype and resistance mechanisms are assessed in relation to the tentative breakpoint**

”Minimum requirement for S-category” is that the highest MIC value of the wild type MIC-distribution is consistent with the MIC derived from the PK/PD index needed for optimal efficacy based on free drug”.

# 6a. Pk/Pd breakpoints are checked against target species wild type MIC distributions to avoid splitting the wild type to obtain tentative breakpoints - example ciprofloxacin



# 6b. Pk/Pd breakpoints are checked against target species wild type MIC distributions to avoid splitting the wild type to obtain tentative breakpoints - example levofloxacin



7. Tentative breakpoints by the EUCAST Steering Committee are referred to the national breakpoint committees for comments.
When steering committee and national committees agree the tentative breakpoints are subjected to the EUCAST consultation process:

8. Consultation process on tentative breakpoints:

- EUCAST general committee
- Expert committees (Neisseria, Anaerobes, others)
- pharmaceutical industry, AST device manufacturers
- others via EUCAST website

9 . Rationale document prepared and published on website

# Aminoglycosides - EUCAST clinical MIC breakpoints 23 november 2004

| Aminoglycosides[1] | Species-related breakpoints (S≤/R>) | | | | | | | | | | | Non-species related breakpoints[5] S≤/R> |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Enterobac-teriaceae* | *Pseudo-monas*[2] | *Acineto-bacter*[2] | *Staphylo-coccus* | *Entero-coccus*[3] | *Strepto-coccus A,B,C,G* | *S.pneu-moniae* | *H.influenzae M.catarrhalis* | *N.gonorr-hoeae* | *N.mening-itidis* | *Gram-negative anaerobes* | |
| Amikacin | 8/16 | 8/16 | 8/16 | 8/16[4] | -- | -- | -- | IE | -- | -- | -- | 8/16 |
| Gentamicin | 2/4 | 4/4 | 4/4 | 1/1 | -- | -- | -- | IE | -- | -- | -- | 2/4 |
| Netilmicin | 2/4 | 4/4 | 4/4 | 1/1 | -- | -- | -- | IE | -- | -- | -- | 2/4 |
| Tobramycin | 2/4 | 4/4 | 4/4 | 1/1 | -- | -- | -- | IE | -- | -- | -- | 2/4 |

1. The aminoglycoside breakpoints are based on modern once-daily administration of high aminoglycoside dosages. Most often aminoglycosides are given in combination with beta-lactam agents. For unlisted aminoglycosides refer to breakpoints determined by national breakpoint committees.
2. The S/I breakpoint has been increased from 2 to 4 mg/L for agents other than amikacin to avoid dividing the wild type MIC distribution. Thus there is no intermediate category for *Pseudomonas* species and *Acinetobacter* species.
3. *Enterococcus* spp - aminoglycoside monotherapy is ineffective against enterococci. There is synergism between aminoglycosides and betalactams in enterococci without acquired resistance mechanisms. There is no synergistic effect in enterococci with high level aminoglycoside resistance, i.e with gentamicin MIC>128 mg/L.
4. Resistance to amikacin and kanamycin is most reliably determined using kanamycin as test substance.
5. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or **IE** in the table).

**--** = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
**IE** = There is insufficient evidence that the species in question is a good target for therapy with the drug.

*Breakpoints finalised at EUCAST Steering committee meeting 2004 April 30 and updated 22 November 2004*

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*EUCAST 2003 (The European Committee on Antimicrobial Susceptibility Testing)*
*Updated 2004-11-23, G Kahlmeter*

# Oxazolidinones - EUCAST clinical MIC breakpoints 30 april 2004

| Oxazolidinone | Species-related breakpoints (S≤/R>) | | | | | | | | | | | Non-species related breakpoints[2] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Enterobacteriaceae* | *Pseudomonas* | *Acinetobacter* | *Staphylococcus*[1] | *Enterococcus*[1] | *Streptococcus A,B,C,G* | *S.pneumoniae* | *H.influenzae M.catarrhalis* | *N.gonorrhoeae* | *N.meningitidis* | *Gram-negative anaerobes* | |
| Linezolid | -- | -- | -- | 4/4 | 4/4 | 2/4 | 2/4 | -- | -- | -- | -- | 2/4 |

1. The S/I-breakpoint has been increased from 2.0 to 4.0 mg/L to avoid dividing wild type MIC-distributions. Hence there is no intermediate category.

2. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or **IE** in the table).

**--** = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
**IE** = There is insufficient evidence that the species in question is a good target for therapy with the drug.

*Breakpoints finalised at EUCAST Steering committee meeting 2004 April 30.*

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*EUCAST 2003 (The European Committee on Antimicrobial Susceptibility Testing)*
*Updated 2004-11-23, G Kahlmeter*

# How to implement EUCAST breakpoints

- The national breakpoint committees have committed themselves to implementing EUCAST breakpoints – which means that anyone using the one of the European national systems will gradually adhere to the European breakpoint system

- Breakpoints as presented in EUCAST tables can be directly applied to MIC distributions (local and national surveillance, EARSS, etc)

- Systems for automated susceptibility testing can be set up with EUCAST MIC breakpoints.

- Through an agreement between EMEA, EFPIA and EUCAST new antimicrobials will be given breakpoints through EUCAST as part of the registration process. The SPC for these drugs will contain only EUCAST breakpoints.

# Collaboration between EUCAST and the Clinical Laboratory Standards Institute (CLSI; formerly NCCLS)

Ongoing …

- Cephalosporin breakpoints for Enterobacteriaceae
- Carbapenems and Monobactams (!?)

**CEN and ISO (EUCAST and CLSI) – international reference method for determination of MICs for non-fastidious bacteria.**

# EUCAST presentation at CLSI (January 2005, Tampa, Fla)

# EUCAST presentation at ICC (June 4th, 2005, Manila, Philippines

# EUCAST websites are found at

# www.eucast.org

The EUCAST websites are accessed via **www.eucast.org**

This is a section of the official ESCMID website giving details of all EUCAST activities including

- constitution
- organisation
- committee member lists
- meetings
- EUCAST documents
- clinical MIC breakpoint tables
- MIC distributions for wild type bacteria and fungi
- epidemiological MIC cut-off values

# EUCAST publications


1. European Committee on Antimicrobial Susceptibility Testing. (2000). Terminology relating to methods for the determination of susceptibility of bacteria to antimicrobial agents. EUCAST Definitive Document E.Def 1.2. *Clinical Microbiology and Infection* 6, 503-8.
2. European Committee on Antimicrobial Susceptibility Testing. (2000). Determination of antimicrobial susceptibility test breakpoints. EUCAST Definitive Document E.Def 2.1. *Clinical Microbiology and Infection* 6, 570-2.
3. European Committee on Antimicrobial Susceptibility Testing. (2000). Determination of minimum inhibitory concentrations (MICs) of antibacterial agents by agar dilution. EUCAST Definitive Document E.Def 3.1. *Clinical Microbiology and Infection* 6, 509-15.
4. European Committee on Antimicrobial Susceptibility Testing. (2001). Linezolid breakpoints. EUCAST Definitive Document E.Def 4.1. *Clinical Microbiology and Infection* 7, 283-4.
5. European Committee on Antimicrobial Susceptibility Testing. (2003). Determination of minimum inhibitory concentrations (MICs) of antibacterial agents by broth microdilution. EUCAST Discussion Document E.Def 5.1. *Clinical Microbiology and Infection* 9 (issue 7 insert) 1-10.
6. Ridgway, G.L., Bébéar, C., Bébéar, C.M, *et al*. (2001). Antimicrobial susceptibility testing of intracellular and cell-associated pathogens. EUCAST Discussion Document E.Dis 6.1. *Clinical Microbiology and Infection* 7 (issue 12 insert),1-10.
7. Rodriguez-Tudela, J.L., Barchiesi, F., Bille, J. *et al*. (2003). Determination of minimum inhibitory concentrations by broth microdilution of fermentative yeasts. EUCAST Discussion Document E.Dis 7.1. *Clinical Microbiology and Infection* 9 (issue 8 insert), 1-8.
8. Drobniewski, F. (2002). Antimicrobial susceptibility testing of *Mycobacterium* tuberculosis. EUCAST Discussion Document E.Dis 8.1. *Clinical Microbiology and Infection* 8 (issue 10 insert),1-10.
9. Kahlmeter G, Brown DFJ, Goldstein FW et al. (2003) European harmonization of MIC breakpoints for antimicrobial susceptibility testing of bacteria. *Journal of Antimicrobial Chemotherapy* 52, 145-148.
10. Kahlmeter G & Brown D. Harmonisation of European breakpoints – can it be achieved? Clinical Microbiology Newsletter, December 15, 2005.


Discussion documents are posted on the EUCAST website for comments and after a period of consultation they are submitted for publication as Definitive Documents in CMI. Following publication they will also be available on the EUCAST website (www.eucast.org).