

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

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UCL



Based (largely) on presentations available from the EUCAST Web site, given to me by Gunnar Kahlmeter, or borrowed from Johan Mouton



# But before that, where are you from ?



**Belgium**

**Brussels**



**The medical campus of the  
*Université catholique de Louvain***



**The Cellular and Molecular  
Pharmacology Group**

slides are available on [www.facm.ucl.ac.be](http://www.facm.ucl.ac.be) → **Lectures**

# What are breakpoints ?

- a magic number obtained from *in vitro* susceptibility testing, which the clinical microbiologists use to determine if the antibiotic will or will not be active *in vivo* against a given pathogen;
- this number is usually a given diameter <sup>1</sup> of growth inhibition in an agar plate around a disk loaded with a standard amount of antibiotic;
- while this system give rise *per definition* to continuous variable (i.e. a diameter of any size [from 0 mm to the limit of the dish...]), microbiologists and authorities like to cut the results it in 3 discrete categories
  - less than x mm → RESISTANT
  - larger than y mm → SUSCEPTIBLE
  - between x and y → INTERMEDIATE



which is what the clinician will get...

<sup>1</sup> may be converted into an MIC (see later); automatic machines use growth rates...

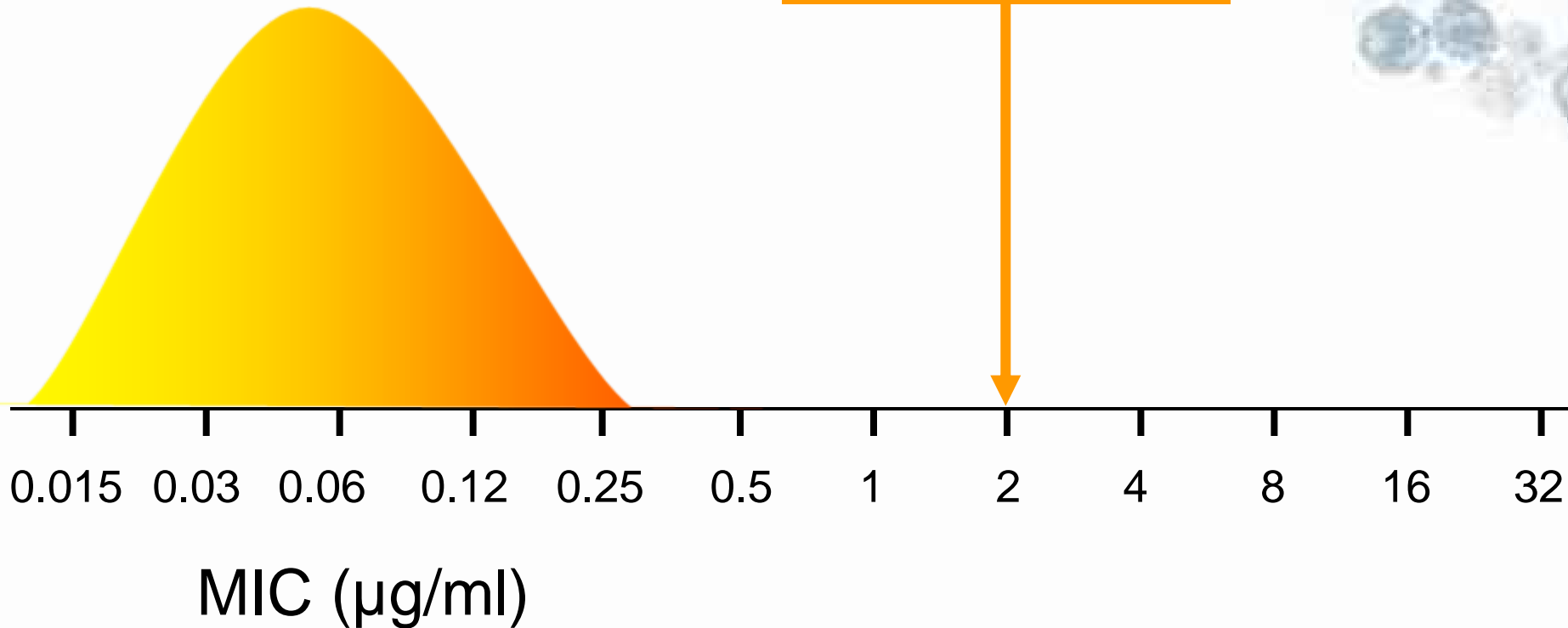
# But, what is susceptible ?



Good !!

Easy...

serum concentration



# But, what is resistant ?

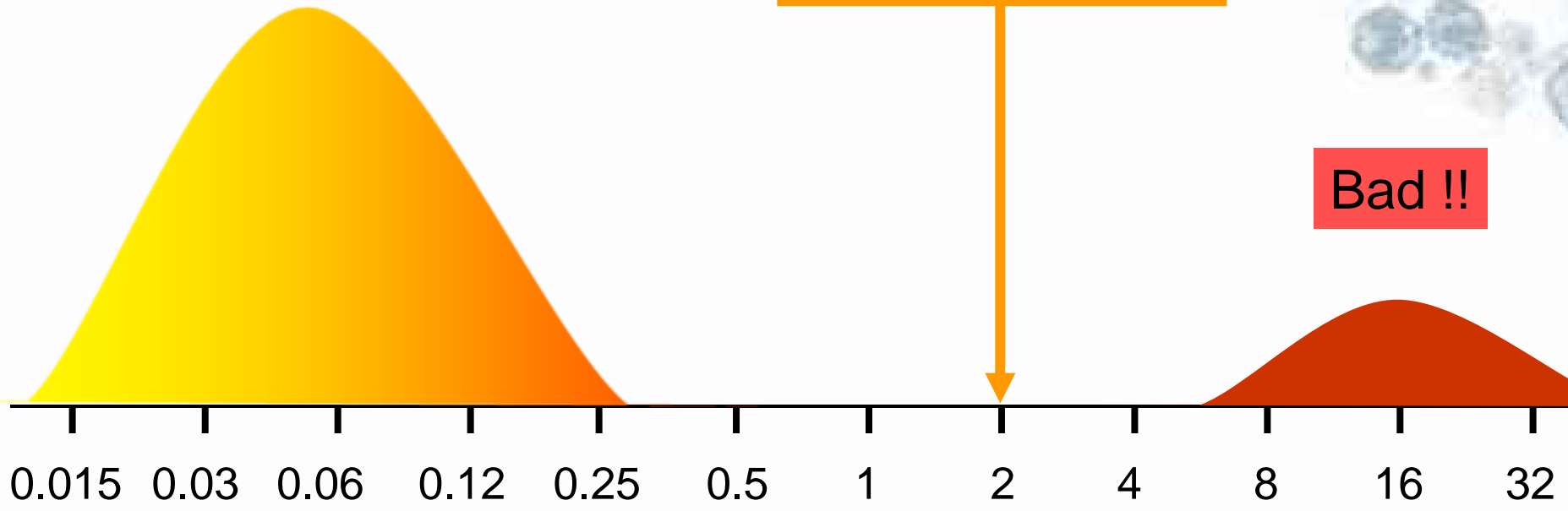
## Still Easy...



Good !!

serum concentration

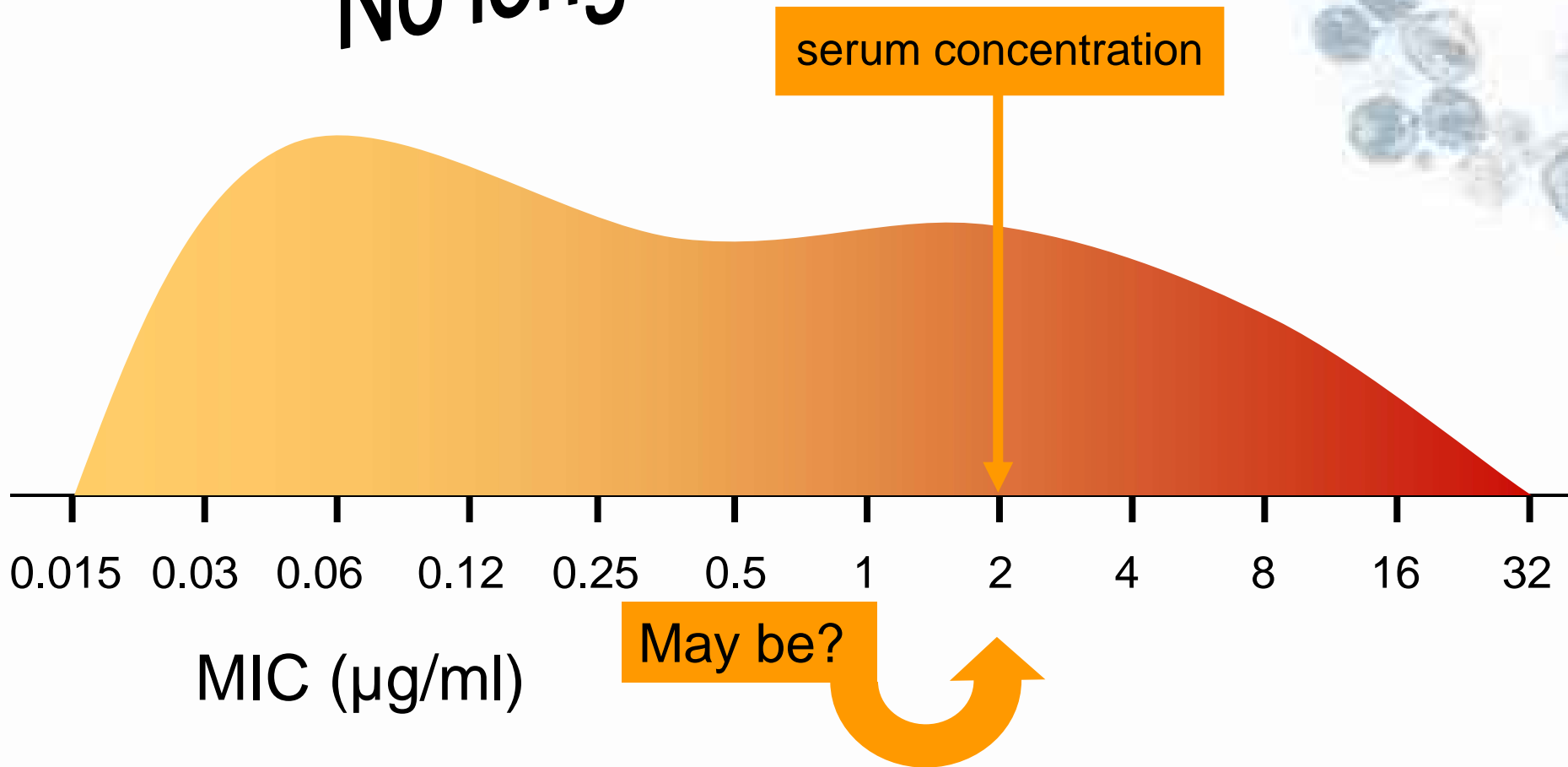
Bad !!



MIC (µg/ml)

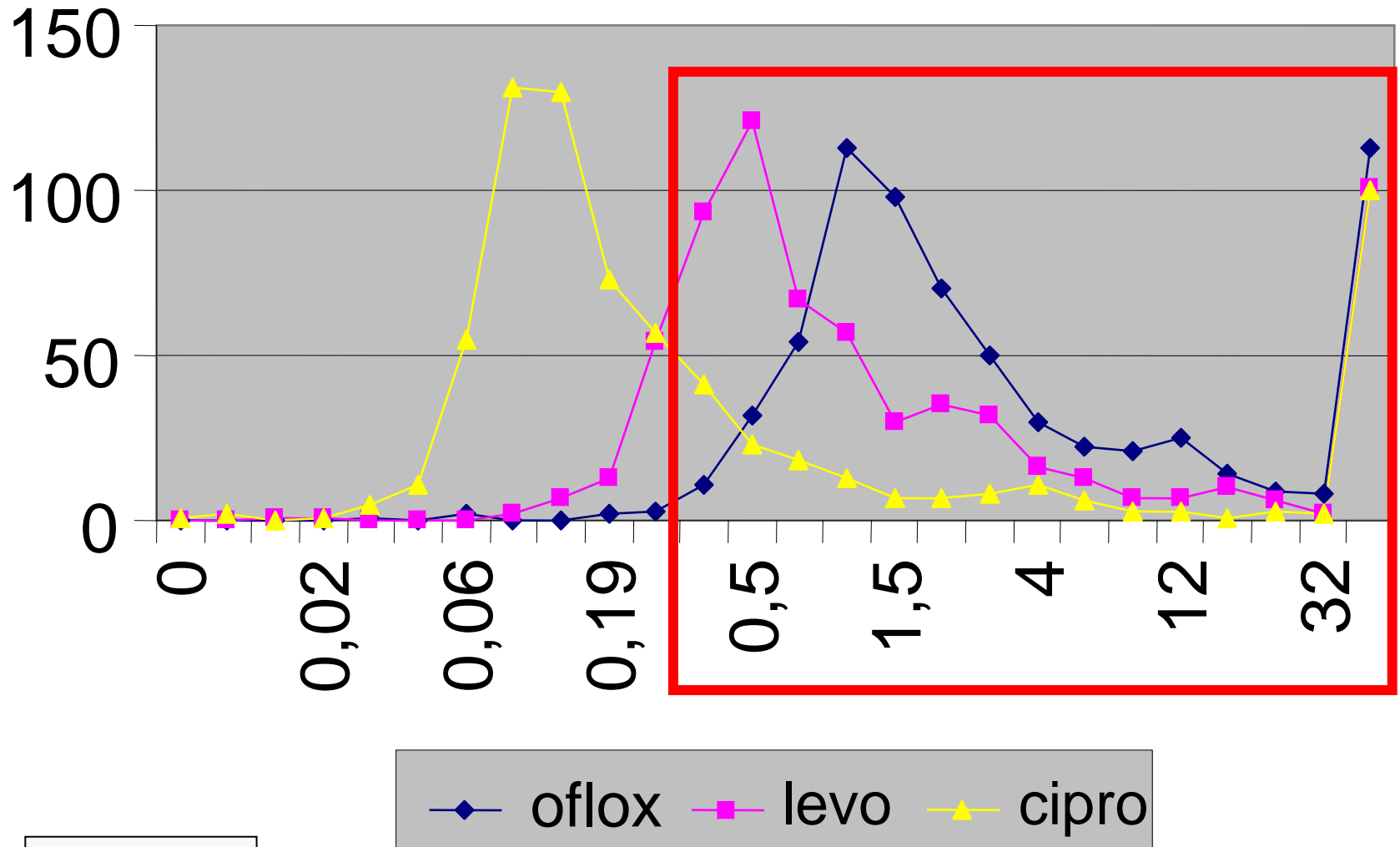
And what do you do with this ?

No longer so easy...



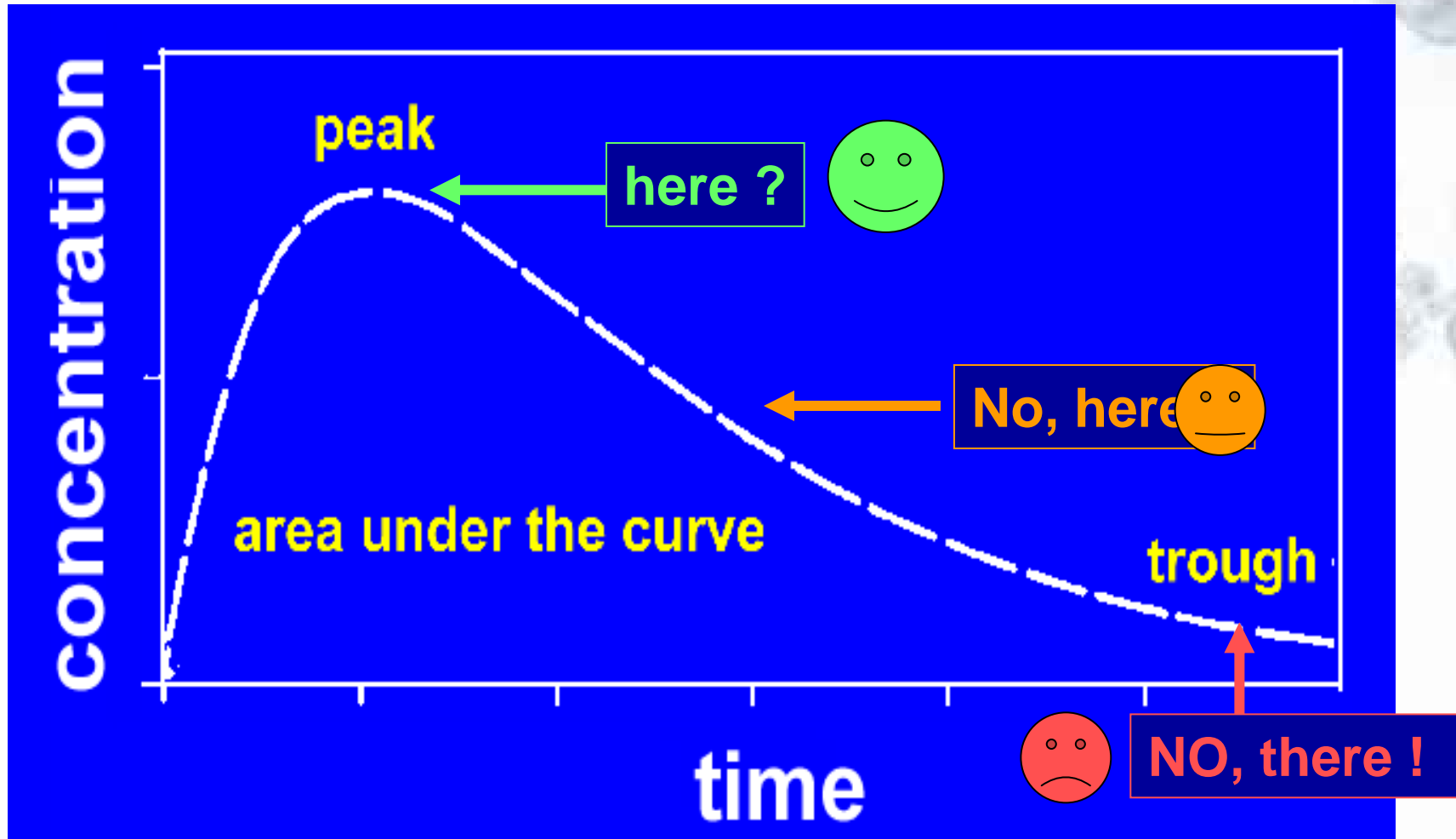
# If you do not believe me...

## MIC distribution of *P. aeruginosa* in Louvain, Belgium, for fluoroquinolones



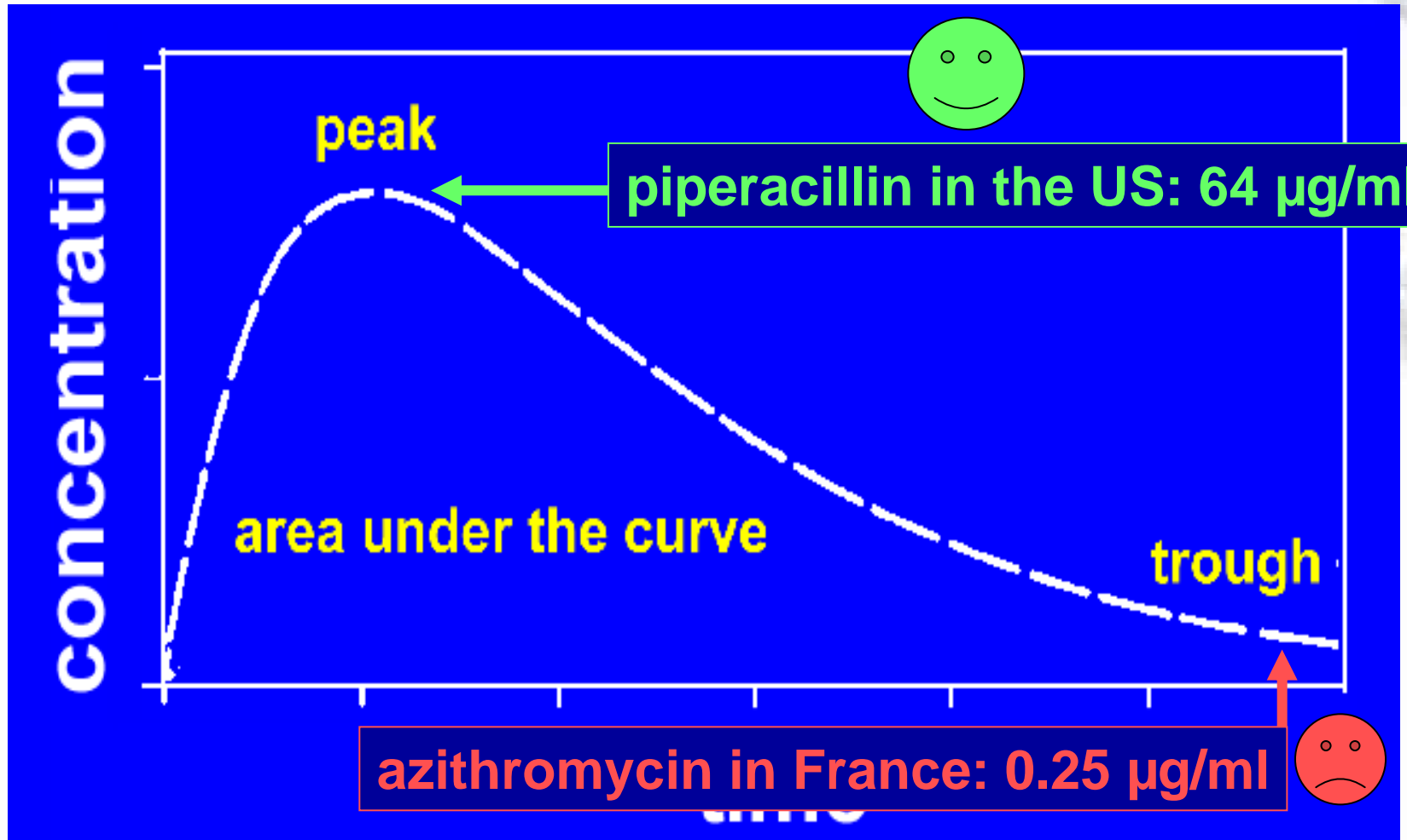
J. van Eldere, 2003

# Where should the breakpoint be ?





# Where should the breakpoint be ?



And there were fierce battles ...



From Mouton, 8th ISAP symposium, Nijmegen, 2001

# A simple example ...

<b>cefotaxime vs. <i>E. coli</i></b>		<b>S<sub>≤</sub> / R</b>
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

**Yet, these breakpoints were used everyday by clinical microbiology laboratories to advise clinicians about which antibiotic(s) they could successfully use against the bacteria they were supposed to fight ...**

# So, what if you are "another country" ? but [hopefully]) smart ...



The  
"filet américain"  
attitude \*



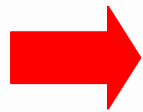
\* baguette with raw chopped 100% pure beef



# A simple decision ...



Now, the clinician can treat all patients



NCCLS / CLSI

U.S.A.

8 /  $\geq$  64

Was this not smart decision ?

# The pros and cons of using CLSI breakpoints

## Pros

- Readily available for most antibiotics
- Based on evaluation of molecules by an independent committee acting very scientifically and clinically...
- Backed by an extensive set of guidelines and recommendations for testing...
- Used widely and considered as 'gold standard' in most publications and surveillance networks...
- Subject to periodic revisions to remain in line with the evolution of science, including PK/PD and increase of resistance

# The pros and cons of using CLSI breakpoints

## Cons

- You need to pay for ...
- Limited access of non-US persons to the decision process ...
- Decisions based on proposals made by Industry...
- Guidelines and recommendations for testing not necessarily applicable specifically where you are...
- Antibiotics not registered for use in the US may not be included and/or fully studied
- Revision process not always as effective as it could be...
- **For certain antibiotics, CLSI breakpoints have been notoriously too high**

# The pros and cons of using CLSI breakpoints

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simple  
"cause to effect"  
relationship



# An example of (probably) too high CLSI breakpoints



Drug	Typical daily dosage <sup>a</sup>	Typical PK values		Proposed PK/PD upper limit		Breakpoints (mg/L) <sup>d</sup>
		C <sub>max</sub> in mg/L total/free (dose)	AUC <sub>24 h</sub> (mg × h/L) total/free	Efficacy <sup>b</sup>	Prevention of resistance <sup>c</sup>	NCCLS (S/I/R)
Norfloxacin	800 mg	1.4/1.1 (400 mg PO)	14/11	0.1–0.4	0.1	≤4/8/>16 <sup>j</sup>
Ciprofloxacin	1000 mg	2.5/1.75 (500 mg PO)	24/18	0.2–0.8	0.2	≤1/2/>4 <sup>k</sup>
Ofloxacin	400 mg	4/3 (400 mg PO)	40/30	0.3–0.9	0.4	≤2/4/8 <sup>l</sup>
Levofloxacin	500 mg	4/2.8 (500 mg PO)	40/28	0.3–0.9	0.3	≤2/4/8 <sup>l</sup>
Moxifloxacin	400 mg	3.1/1.8 (400 mg PO)	35/21	0.2–0.7	0.2	≤1/2/4 <sup>m</sup>

NCCLS, National Committee for Clinical Laboratory Standards (Clinical and Laboratory Standards Institute) (<http://www.ncc>)

Van Bambeke F, Michot JM, Van Eldere J, Tulkens PM.  
Quinolones in 2005: an update. Clin Microbiol Infect. 2005 Apr;11(4):256-80. PMID: 15760423

# An unanticipated problem since 2006 ... (if you are a non-US microbiologist)



# An unanticipated problem since 2006...

- Since 2006, FDA has reasserted its legal rights to define official breakpoints
- CLSI may determine and publish breakpoints no sooner than 24 months after FDA decision  
(and only if the company requests this [?])
- In the meantime, only FDA breakpoints will be legal in the US, and will be essentially geared to the protection of the **US** Public for drugs registered in the US.
- Non-US organizations have no direct possibility to impact on the FDA-decision process ...

communicated at the General meeting of EUCAST during the 17th ECCMID & 25th ICC (Munich, Germany) by the CLSI representative

# Two important change in Europe...


1. Each national committee in EU (UK, FR, NL, DE, SV, NO) has pledged that the EUCAST breakpoints will be part of their respective systems January the year after the decision was made. This means that any decision taken in 2008 should be into their systems in January 2009, and so on ...

In parallel, (i) the manufacturers of devices (BM and BD) have both said that it is realistic that their machines will have EUCAST breakpoints in 2010; (ii) interpretative criteria for disk-based assay have been fully released by EUCAST in 2010

# Two important change in Europe...

2. EMEA and EUCAST have set up an agreement that makes EUCAST responsible for defining breakpoints for new molecules proposed for registration in Europe.

EUCAST breakpoints will be accepted by EMEA and put into the "Summary of Product Characteristics", which is part of legal documents accompanying the marketing authorization in EU.

 European Medicines Agency Standard Operating Procedure		
Title: Harmonisation of European Breakpoints set by EMEA/CHMP and EUCAST		Document no.: SOP/H/3043
Applies to: Product Team Leaders in the Human Pre-Authorisation Unit, (Co)Rapporteurs, External Experts, EUCAST		Effective Date: 14 February 2005
<b>PUBLIC</b>		Review Date: 14 February 2007
		Supersedes: N/A
Prepared by	Approved by	Authorised for issue by
Name: Bo Aronsson	Name: Agnès Saint Raymond	Name: Patrick Le Courtois
Signature: On file	Signature: On file	Signature: On file
Date: 10 Feb 05	Date: 10 Feb 05	Date: 10 Feb 05
<b>1. Purpose</b> To describe the interaction between EMEA/CHMP and EUCAST in the process of harmonisation of European breakpoints.		

# 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.

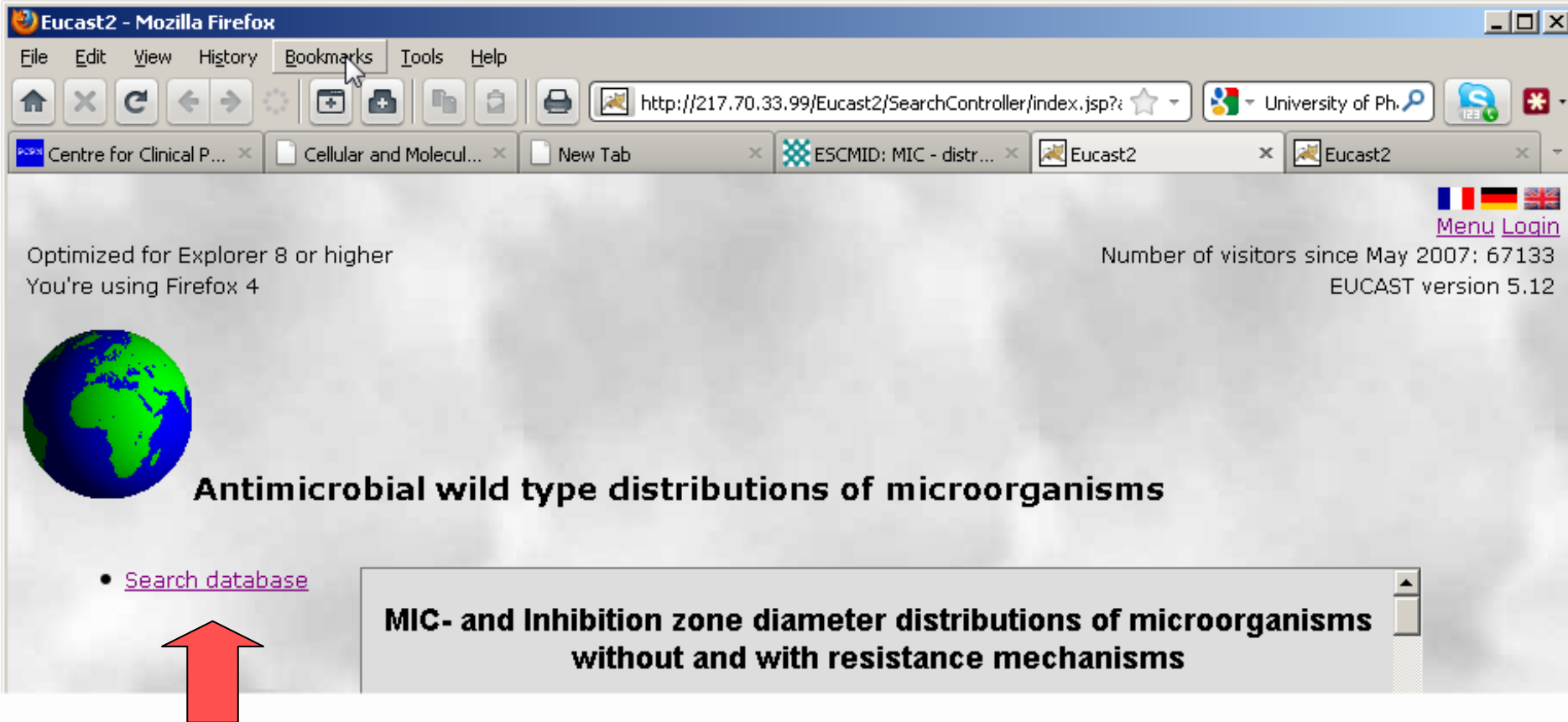
## Microbiological resistance - non-wild type (NWT)

- 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.**



[http://www.eucast.org/mic\\_distributions/](http://www.eucast.org/mic_distributions/)



Eucast2 - Mozilla Firefox

File Edit View History Bookmarks Tools Help


http://217.70.33.99/Eucast2/SearchController/index.jsp?

Centre for Clinical P... Cellular and Molecul... New Tab ESCMID: MIC - distr... Eucast2 Eucast2

Menu Login

Number of visitors since May 2007: 67133  
EUCAST version 5.12

Optimized for Explorer 8 or higher  
You're using Firefox 4



**Antimicrobial wild type distributions of microorganisms**

- [Search database](#)

**MIC- and Inhibition zone diameter distributions of microorganisms  
without and with resistance mechanisms**

# http://www.eucast.org/mic\_distributions/

Menu Connector

**Specify the drug or the bug (never both) - after a few seconds a table of MIC-distributions is shown.**

Méthode:  Antimicrob  Espèce: Esch

Amikacin	0	0	0	1	0	0	0	16	129	1338	4008	1825	426	0	0	0	0	0	0
Aztreonam	0	0	0	0	0	60	17	1	0	0	0	0	0	0	0	0	0	0	0
Cefepime	0	0	10	68	282	823	129	0	0	0	0	0	0	0	0	0	0	0	0
Cefotaxime	0	5	20	133	732	1857	1111	146	0	0	0	0	0	0	0	0	0	0	0
Cefoxitin	0	0	0	0	0	0	2	74	1420	4546	22698	24499	8360	2488	0	0	0	0	0
Cefpodoxime	0	0	0	0	0	0	12	28	8	0	0	0	0	0	0	0	0	0	0
Ceftazidime	0	0	5	26	172	1051	2672	2354	475	0	0	0	0	0	0	0	0	0	0
Ceftibuten	0	0	0	0	0	367	756	1107	225	49	0	0	0	0	0	0	0	0	0
Ceftibuten	0	0	0	0	0	268	224	84	19	11	0	0	0	0	0	0	0	0	0
Ceftiofur	0	0	0	0	0	0	5	568	1920	236	0	0	0	0	0	0	0	0	0
Ceftriaxone	0	0	5	23	51	49	4	0	0	0	0	0	0	0	0	0	0	0	0
Cefuroxime	0	0	1	1	1	5	88	206	1926	6448	26389	58851	18523	0	0	0	0	0	0
Chloramphenicol	0	0	0	0	0	0	0	0	0	0	239	3962	3857	307	0	0	0	0	0
Ciprofloxacin	14	189	2746	3793	574	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Colistin	0	0	0	0	0	242	35	493	1794	430	82	0	0	0	0	0	0	0	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
Enrofloxacin	0	0	0	0	798	1689	105	0	0	0	0	0	0	0	0	0	0	0	0
Ertapenem	0	124	882	417	184	46	0	0	0	0	0	0	0	0	0	0	0	0	0
Florfenicol	0	0	0	0	0	0	0	0	0	1	335	4503	4260	319	0	0	0	0	0
Flumequine	0	0	0	0	0	0	1	37	1651	446	31	0	0	0	0	0	0	0	0
Fosfomycin	0	0	0	0	0	0	0	0	348	611	576	346	200	0	0	0	0	0	0
Gentamicin	0	0	4	3	18	40	386	5857	16128	907	1774	0	0	0	0	0	0	0	0
Imipenem	0	0	3	15	64	6202	41814	10539	12263	575	0	0	0	0	0	0	0	0	0
Kanamycin	0	0	0	0	0	0	0	126	332	365	562	465	166	0	0	0	0	0	0

[http://www.eucast.org/mic\\_distributions/](http://www.eucast.org/mic_distributions/)

Méthode:  CMI  Methode de diffusion

Antimicrobien: Antimicrobien...

Espèce: Escherichia coli

Éléments par page: 50

Espèce: Escherichia coli (Méthode: MIC)

Show All Graphs

	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
<a href="#">Amikacin</a>	0	0	0	1	0	0	0	16	129	1338	4008	1825	426	0	0	0	0	0	0
<a href="#">Aztreonam</a>	0	0	0	0	0	60	17	1	0	0	0	0	0	0	0	0	0	0	0
<a href="#">Cefepime</a>	0	0	10	68	282	823	129	0	0	0	0	0	0	0	0	0	0	0	0
<a href="#">Cefotaxime</a>	0	5	20	133	732	1857	1111	146	0	0	0	0	0	0	0	0	0	0	0
<a href="#">Cefoxitin</a>	0	0	0	0	0	0	2	74	1420	4546	22698	24499	8360	2488	0	0	0	0	0
<a href="#">Cefpodoxime</a>	0	0	0	0	0	0	12	28	8	0	0	0	0	0	0	0	0	0	0
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<a href="#">Ceftibuten</a>	0	0	0	0	0	367	756	1107	225	49	0	0	0	0	0	0	0	0	0
<a href="#">Ceftibuten</a>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<a href="#">Ceftiofur</a>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<a href="#">Ceftriaxone</a>	0	0	5	23	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<a href="#">Cefuroxime</a>	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<a href="#">Chloramphenicole</a>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<a href="#">Ciprofloxacin</a>	14	189	2746	3793	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<a href="#">Colistin</a>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<a href="#">Enrofloxacin</a>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
<a href="#">Ertapenem</a>	0	124	882	417	184	46	0	0	0	0	0	0	0	0	0	0	0	0	0
<a href="#">Florfenicol</a>	0	0	0	0	0	0	0	0	0	1	335	4503	4260	319	0	0	0	0	0
<a href="#">Flumequine</a>	0	0	0	0	0	0	1	37	1651	446	31	0	0	0	0	0	0	0	0
<a href="#">Fosfomycin</a>	0	0	0	0	0	0	0	0	348	611	576	346	200	0	0	0	0	0	0
<a href="#">Gentamicin</a>	0	0	4	3	18	40	386	5857	16128	9017	1774	0	0	0	0	0	0	0	0
<a href="#">Imipenem</a>	0	0	3	15	64	6202	41814	10539	12263	575	0	0	0	0	0	0	0	0	0
<a href="#">Kanamycin</a>	0	0	0	0	0	0	0	126	332	365	562	465	166	0	0	0	0	0	0

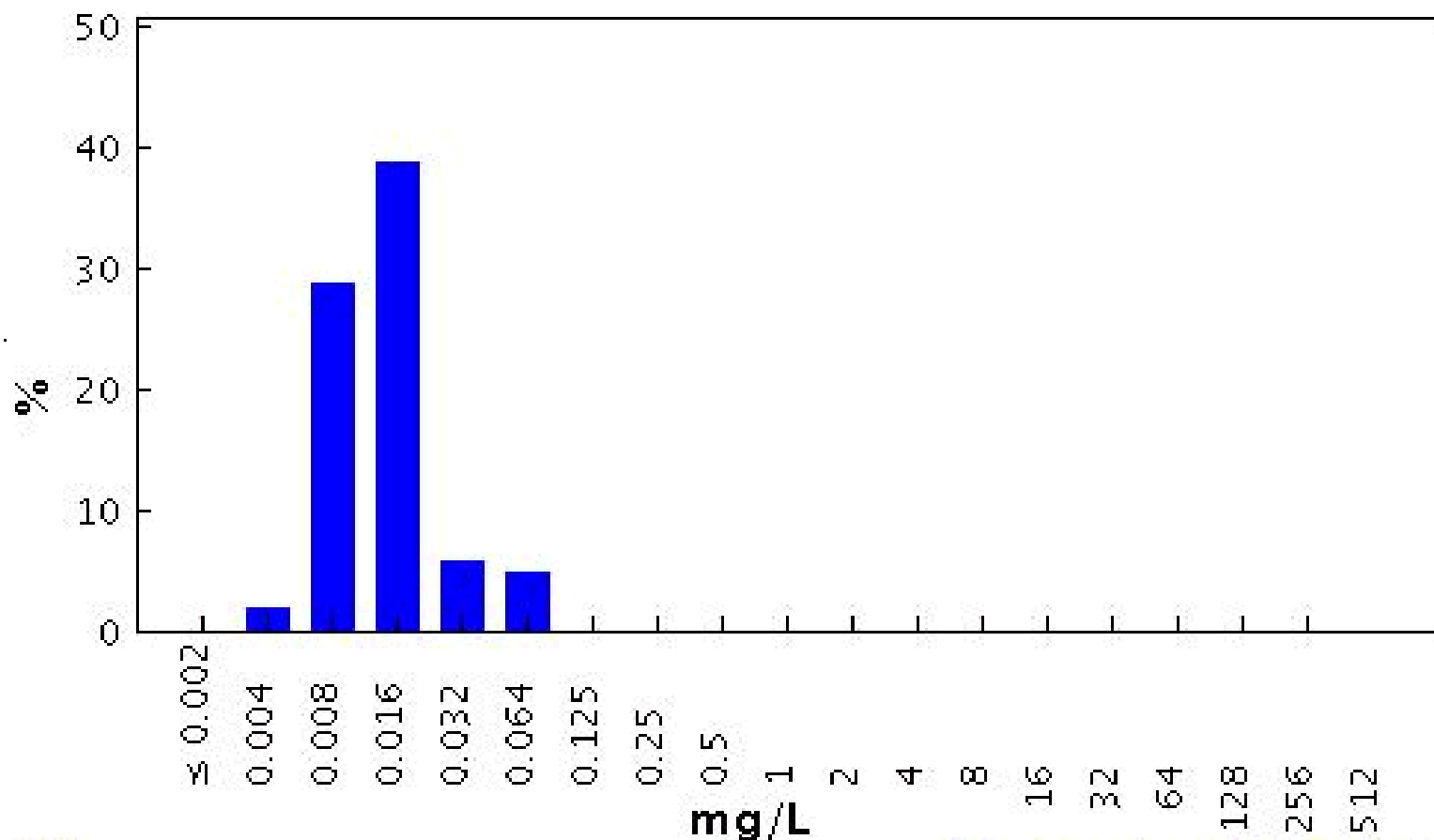
Click on any antibiotic (or species) in the left hand column to display the data as a bar chart, with EUCAST epidemiological cut-off values and harmonised European clinical breakpoints.



# Ciprofloxacin / Escherichia coli

Antimicrobial wild type distributions of microorganisms - reference database

EUCAST



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

Retourner

# 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**





# 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

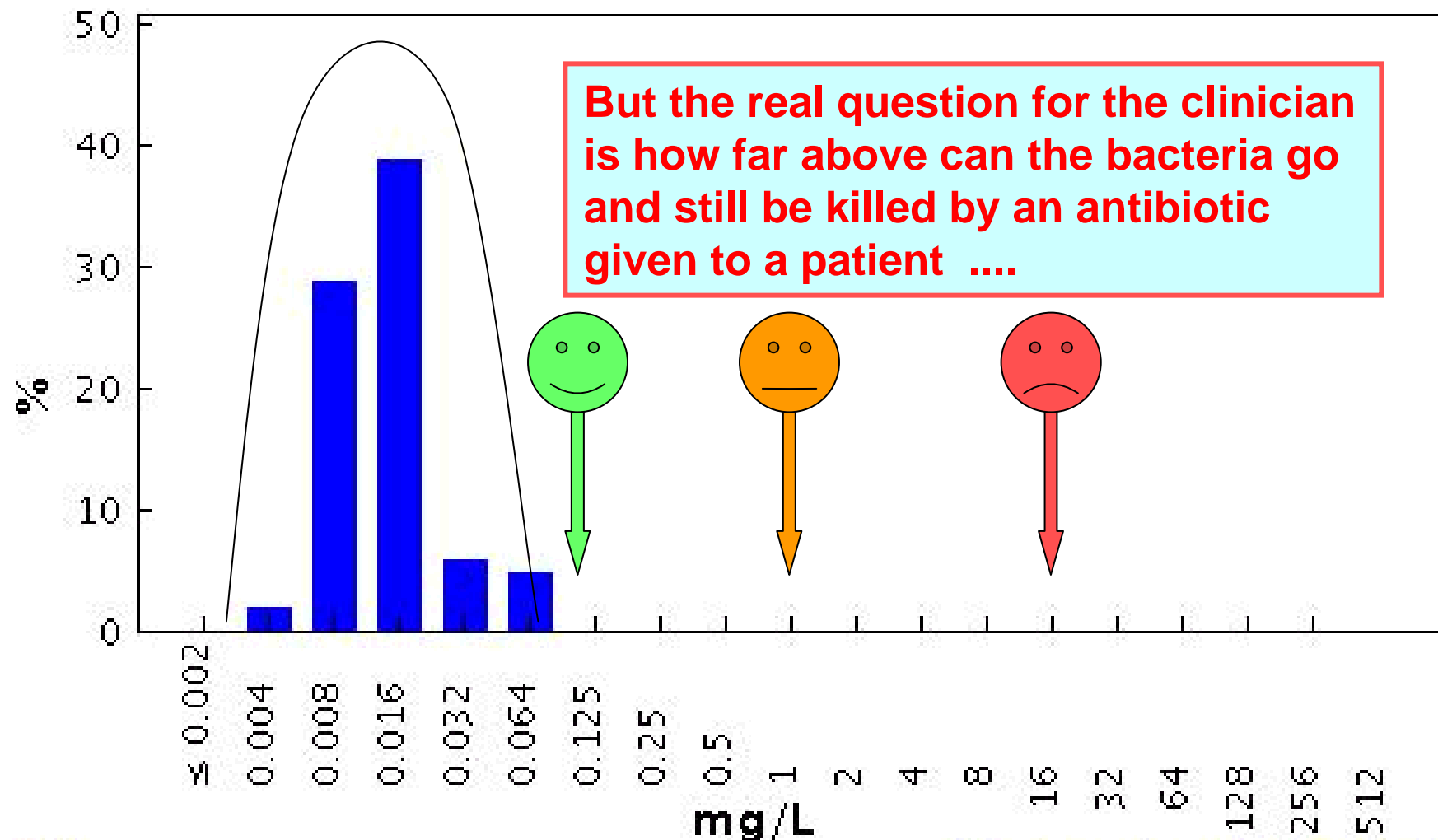
**Clinical breakpoints may be altered with legitimate changes in circumstances**

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

# Ciprofloxacin / Escherichia coli

Antimicrobial wild type distributions of microorganisms - reference database

EUCAST



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6423 observations (9 data sources)

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# EUCAST procedure for setting breakpoints

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

**All subsequent slides are an example with ciprofloxacin ...  
and, for some points, with levofloxacin...**



# EUCAST method of determining clinical breakpoints

- 1. Data on dosing, formulations, clinical indications and target organisms are reviewed and differences which might influence breakpoints are highlighted**
- 2. Multiple MIC-distributions are collected, the wild type MIC distribution is defined and tentative epidemiological cut-off values determined (WT  $\leq$ X mg/L)**
- 3. Comparison is made between available breakpoints (for already registered antibiotics)**

## 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

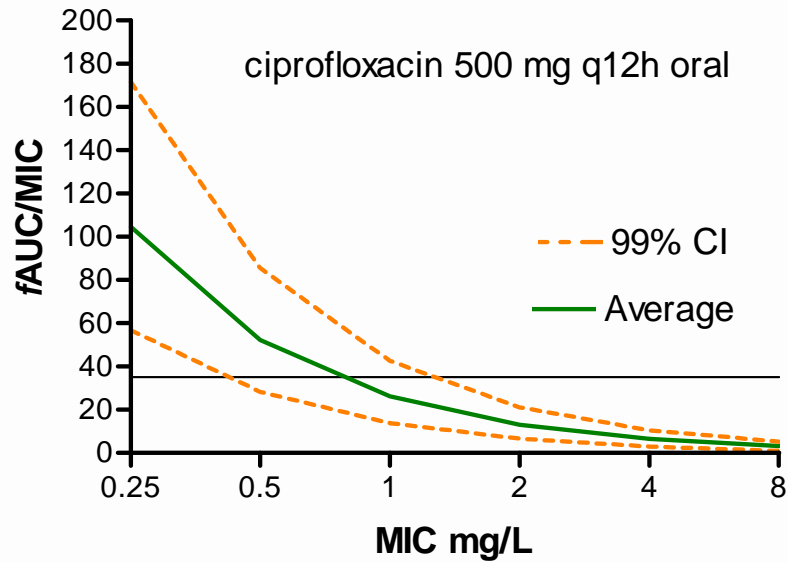
## 5. Pharmacodynamic data are evaluated

The PK/PD index value of the pertinent PK/PD parameter (time above MIC, AUC/MIC,  $C_{\max}$ /MIC...) resulting in optimal outcome is determined from:

- in vitro data
- animal studies
- clinical trials
- The efficacy of the drugs is assessed quantitatively.

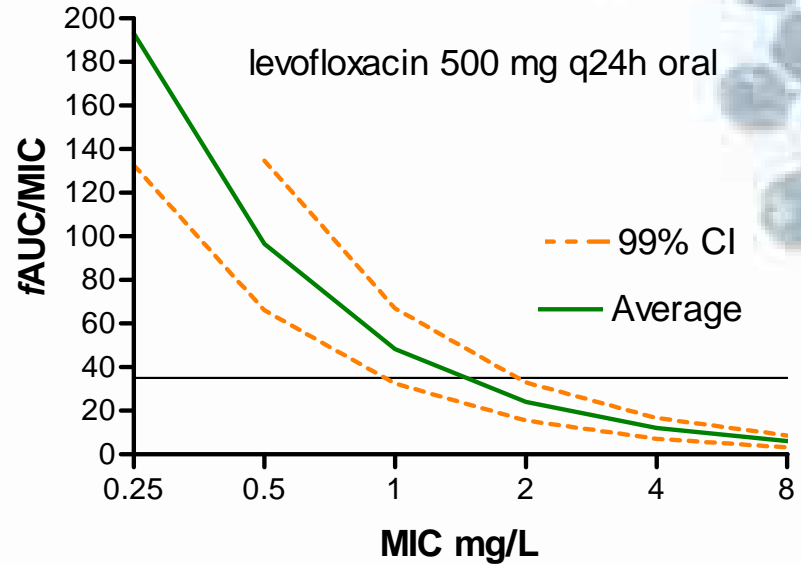
Relationships between concentration time profiles and emergence of resistance are evaluated

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



S = 0.5 mg/L

Pk/Pd

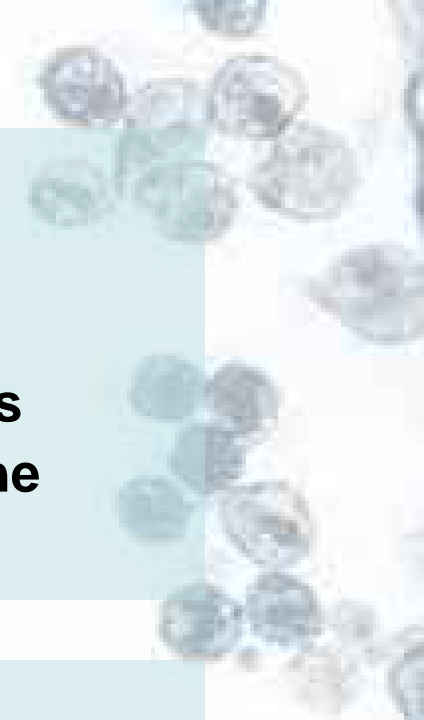


S = 1 mg/L

# EUCAST method of determining clinical breakpoints

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

6. 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**

Organization

Clinical breakpoints

Expert rules

MIC - distributions and QC

Zone diameter distributions

EUCAST disk diffusion test

Frequently Asked Questions (FAQ)

Meetings

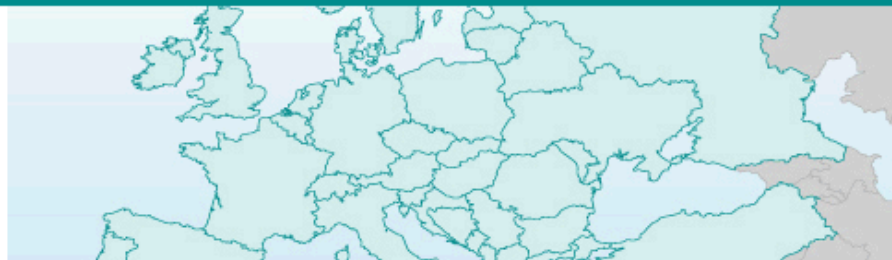
EUCAST Presentations

Documents

Information for industry

Links

Website changes



search term  Search

Clinical breakpoints

## Clinical breakpoints

Clinical breakpoints are for everyday use in the clinical laboratory to advise on patient therapy.

In EUCAST tables, the I-category is not listed. It is implied as the values between the S-breakpoint and the R-breakpoint.

For a breakpoint listed as  $S \leq 1$  mg/L and  $R > 8$  mg/L the intermediate category is 2 - 8 (technically  $> 1 - 8$ ) mg/L.

For a breakpoint listed as  $S \geq 22$  mm and  $R < 18$  mm the intermediate category is 18-21 mm.

[clinical breakpoints - bacteria \(v 1.1\)](#) - pdf-file for printing (April 27, 2010)

[clinical breakpoints - bacteria \(v 1.1\)](#) - Excelfile for screen (April 27, 2010)

[clinical breakpoints - fungi \(MIC breakpoints\)](#)

[definitions of clinical breakpoints and epidemiological cut off values](#)

[procedure for harmonizing and defining breakpoints](#)

[Recommend page](#)

**EUCAST  
breakpoints  
are freely  
available**

<http://www.eucast.org>

And here are the results... (April 2011)

## Enterobacteriaceae

Fluoroquinolones	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Ciprofloxacin <sup>1</sup>	0.5	1	5	22	19
Levofloxacin	1	2	5	22	19
Moxifloxacin	0.5	1	5	20	17
Nalidixic acid (screen)	Note <sup>2</sup>	Note <sup>2</sup>	30	16 <sup>A</sup>	16 <sup>A</sup>
Norfloxacin	0.5	1	10	22	19
Ofloxacin	0.5	1	5	22	19

These are much lower than the CLSI (current) breakpoints which are between 1 – 2 – 4 (ciprofloxacin) en 2 – 4 – 8 (ofloxacin)

but compare now with the PK/PD breakpoints ...

# PK/PD breakpoints for fluroquinolones

Drug	Typical daily dosage <sup>a</sup>	Typical PK values		Proposed PK/PD upper limit of sensitivity (μg/ml) for	
		C <sub>max</sub> in mg/L total/free (dose)	AUC <sub>24 h</sub> (mg × h/L) total/free	Efficacy <sup>1</sup>	
Norfloxacin	800 mg	1.4/1.1 (400 mg PO)	14/11	0.1–0.4	0.5-1
Ciprofloxacin	1000 mg	2.5/1.75 (500 mg PO)	24/18	0.2–0.8	0.5-1
Ofloxacin	400 mg	4/3 (400 mg PO)	40/30	0.3–0.9	0.5-1
Levofloxacin	500 mg	4/2.8 (500 mg PO)	40/28	0.3–0.9	1-2
Moxifloxacin	400 mg	3.1/1.8 (400 mg PO)	35/21	0.2–0.7	0.5-1

Van Bambeke F, Michot JM, Van Eldere J, Tulkens PM. Quinolones in 2005: an update. Clin Microbiol Infect. 2005 Apr;11(4):256-80. PMID: 15760423

**EUCAST  
breakpoints**



## Enterobacteriaceae

Carbapenems <sup>1</sup>	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Doripenem	1	4	10	24	18
Ertapenem	0.5	1	10	25	22
Imipenem <sup>2</sup>	2	8	10	21	15
Meropenem	2	8	10	22	16

- The carbapenem breakpoints for Enterobacteriaceae will detect all clinically important resistance mechanisms (including the majority of carbapenemases).
- Some strains that produce carbapenemase are categorized as susceptible with these breakpoints and should be reported as tested, i.e. the presence or absence of a carbapenemase does not in itself influence the categorization of susceptibility.
- In many areas, carbapenemase detection and characterization is recommended or mandatory for infection control purposes.

# EUCAST and cephalosporins

Cephalosporins <sup>1</sup>	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Cefepime	1	4	30	24	21
Ceftazidime	1	4	10	21	18
Ceftriaxone	1	2	30	23	20

[EUCAST\\_breakpoints\\_v1.1.pdf](#)

Why so low ?

1. The cephalosporin breakpoints for Enterobacteriaceae will detect all clinically important resistance mechanisms (including ESBL, plasmid mediated AmpC). Some strains that produce beta-lactamases are susceptible or intermediate to 3rd or 4th generation cephalosporins with these breakpoints and should be reported as found, i.e. the presence or absence of an ESBL does not in itself influence the categorization of susceptibility. In many areas, ESBL detection and characterization is recommended or mandatory for infection control purposes.

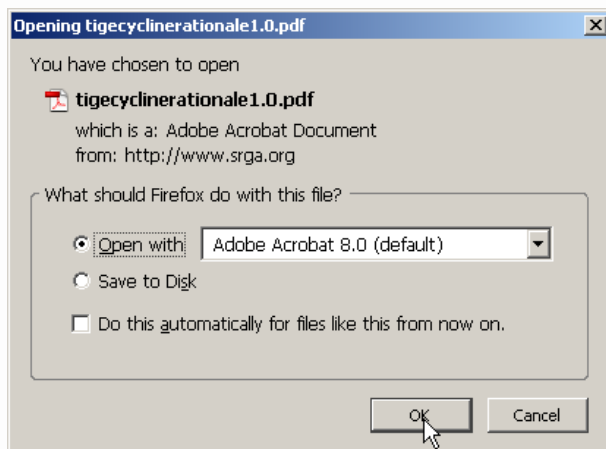
To exclude ESBL ..

# Can we have access to the rationale ?

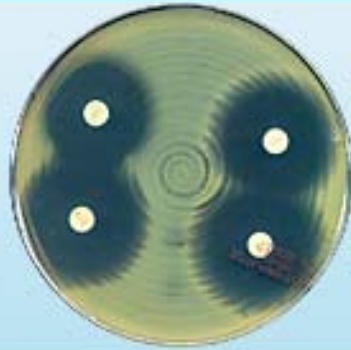
## Enterobacteriaceae

Tetracyclines	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Doxycycline	-	-		-	-
Minocycline	-	-		-	-
Tetracycline	-	-		-	-
<b>Tigecycline<sup>1</sup></b>	<b>1</b>	<b>2</b>	<b>15</b>	<b>18<sup>A</sup></b>	<b>15<sup>A</sup></b>

<http://www.srga.org/eucastwt/MICTAB/RD/tigecyclinerationale1.0.pdf>



# Can we have access to the methodology for disks ?



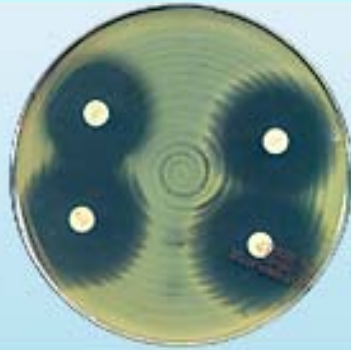
## EUCAST Disk Diffusion Test

EUCAST has developed a European disk (not tablet) diffusion test based on MH-agar and disks from several manufacturers for non-fastidious organisms and on MH-agar with 5% defibrinated horse blood and 20 mg/L beta-NAD (MH-F) for fastidious microorganisms (streptococci, H.influenzae and others). Tentative breakpoints were published on the 21 st of December, 2009.

Manufacturers of disks, tablets, media and automated AST systems are working to calibrate their products to the EUCAST standards. Some are ready while others are still facing difficulties. Users of European breakpoints are advised to consult with EUCAST before choosing AST systems alternative to:

1. MIC-determination using European breakpoints
2. European disk test method calibrated to European breakpoints
3. Automated susceptibility testing with a machine validated for use with European breakpoints.

# Can we have access to the methodology for disks ?



## EUCAST Disk Diffusion Test

EUCAST has developed a European disk (not tablet) diffusion test based on MH-agar and disks from several manufacturers for non-fastidious organisms and on MH-agar with 5% defibrinated horse blood and 20 mg/L beta-NAD (MH-F) for fastidious microorganisms (streptococci, H.influenzae and others). Tentative breakpoints were published on the 21st of December, 2009.

Manufacturers of disks, tablets, media and automated AST systems are working

to calibrate their products to the

others are still facing difficulties

consult with EUCAST before doing

1. MIC-determination using E

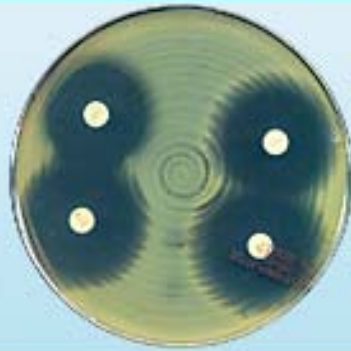
2. European disk test method

3. Automated susceptibility testing with a machine validated for use with European breakpoints.

 **Check list for implementation of EUCAST Susceptibility Testing**  
(v. 1.0 May 28, 2010)

<http://www.eucast.org>

# Can we have access to the methodology for disks ?



## EUCAST Disk Diffusion Test

EUCAST has developed a European disk (not tablet) diffusion test based on MH-agar and disks from several manufacturers for non-fastidious organisms and on MH-agar with 5% defibrinated horse blood and 20 mg/L beta-NAD (MH-F) for fastidious microorganisms (EUCAST 2009). Tentative breakpoints were published in 2009.

Manufacturers of disks, tablets, media and machines are required to calibrate their products to the EUCAST methodology. However, others are still facing difficulties. Users should consult with EUCAST before choosing a method.

1. MIC-determination using European breakpoints.
2. European disk test method calibrated to European breakpoints.
3. Automated susceptibility testing with a machine validated for use with European breakpoints.

 [Preparation of media for disk diffusion](#)

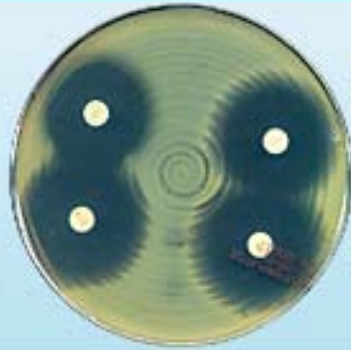
 [EUCAST Disk Diffusion - Manual](#) (v. 1.0 Dec 18, 2009)

 [EUCAST Disk Diffusion - Slide Show](#) (v. 1.1 Jun 3, 2010)

 [EUCAST Disk Diffusion - Reading Guide](#) (v. 1.0 Apr 30, 2010)

<http://www.eucast.org>

# Can we have access to the methodology for disks ?



## EUCAST Disk Diffusion

EUCAST has developed a European disk diffusion method on MH-agar and disks from several manufacturers and on MH-agar with 5% defibrinated horse blood (MH-F) for fastidious microorganisms. Tentative breakpoints were published in 2002.

Manufacturers of disks, tablets, and other products are still facing difficulties to calibrate their products to the European breakpoints. Others are still facing difficulties to consult with EUCAST before choosing a product.

1. MIC-determination using European breakpoints.
2. European disk test method calibrated to European breakpoints.
3. Automated susceptibility testing with a machine validated for use with European breakpoints.

## EUCAST MIC- and Zone diameter breakpoint tables

### EUCAST MIC and Zone diameter breakpoint tables

 [Clinical breakpoint tables v 1.3](#) (2011-01-05) - for printing

 [Clinical breakpoint tables v 1.3](#) (2011-01-05) - for screen

 [List of errata in EUCAST tables](#) (update 2011-05-05)

<http://www.eucast.org>



# Can we have access to the zone diameter values ?

ESCMID: Zone diameter distributions

ESCMID: Zone diameter distributions

Menu Login

## Antimicrobial wild type distributions of microorganisms

Search

Method:  MIC  Disk diffusion

Antimicrobial: Ciprofloxacin Species: Species... Disk content: Disk content...

Elements per page: 50

Antimicrobial: Ciprofloxacin (Method: Disk diffusion)

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

Show All Graphs

	Disk content	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	S <sub>2</sub>	R<	ECOF		
<a href="#">Acinetobacter baumannii</a>	5	16	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	1	3	2	7	6	8	6	0	2	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	21	21				
<a href="#">Acinetobacter spp</a>	5	1	0	0	0	0	0	0	0	0	1	0	0	0	0	1	2	1	1	3	9	17	18	26	9	17	6	7	4	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	21	21	
<a href="#">Aeromonas spp</a>	5	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	22	19		
<a href="#">Citrobacter freundii</a>	5	1	0	0	0	0	0	0	0	1	0	0	1	0	0	0	0	0	0	1	3	1	5	5	5	11	12	7	4	2	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	22	19	
<a href="#">Citrobacter koseri</a>	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	2	3	4	8	9	9	5	5	2	0	1	0	0	0	0	0	0	0	0	0	0	0	0	22	19		
<a href="#">Enterobacter aerogenes</a>	5	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	1	2	1	5	12	2	5	2	3	3	1	2	4	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	22	19	
<a href="#">Enterobacter cloacae</a>	5	1	0	0	0	0	0	0	1	0	0	0	0	0	0	1	2	1	1	2	5	12	19	13	16	22	21	20	10	9	11	3	1	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	22	19	
<a href="#">Escherichia coli</a>	5	222	3	4	4	1	1	9	6	7	2	2	2	1	4	6	2	15	22	17	32	35	70	131	172	347	332	332	293	248	182	127	106	72	37	26	6	6	1	2	1	0	0	0	0	0	0	0	0	22	19
<a href="#">Escherichia coli ATCC 25922</a>	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2	5	14	22	21	14	9	3	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	22	19
<a href="#">Haemophilus influenzae</a>	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	1	3	3	10	17	29	37	53	46	57	40	36	27	15	8	2	1	1	0	0	0	0	0	23	23
<a href="#">Klebsiella oxytoca</a>	5	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	2	1	3	4	6	16	23	37	39	17	19	8	7	5	3	2	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	22	19
<a href="#">Klebsiella pneumoniae</a>	5	6	2	3	5	0	1	2	5	4	0	1	1	1	2	2	4	9	9	16	25	48	65	74	62	48	30	20	9	6	5	3	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	22	19
<a href="#">Moraxella catarrhalis</a>	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	2	8	7	21	25	27	38	54	50	52	23	15	11	11	2	2	1	1	0	0	0	1	0	0	0	23	23		
<a href="#">Morqanella morqanii</a>	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	3	0	0	0	1	2	1	0	9	1	3	4	2	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	22	19	
<a href="#">Pasteurella multocida</a>	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	3	0	9	6	15	17	25	23	21	27	8	17	8	5	3	5	6	6	6	6	0	2	23	23				
	Disk content	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	S <sub>2</sub>	R<	ECOF		

you will find the disk diffusion value for all antibiotics



# Why could (should ?) non-EU countries follow EUCAST breakpoints ?

## Pros

- The procedure is rational and transparent
- All proposals are subject to open discussions through the web site and/or by direct contact
- All breakpoints and the supporting material ("rational documents") is available **free** on the web site for inspection and analysis \*
- Adaptation to local conditions can, therefore, be made seamlessly if needed (changes in dosages, PK, resistance patterns...)

## Cons

- There is no specific procedure for requesting and implementing changes based on national realities outside of EU \*
- Starting material must be submitted by the organization requesting a breakpoint.

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\* except via country representatives (see [www.eucast.org](http://www.eucast.org)), ISC (me) or FESCI (Dr D. Livermore)



Will good (EUCAST ?) breakpoints solve everything ?

- Breakpoints should only be used as a guidance for a the general usage of an existing drug (is it still worth to use it ?) or for the positioning of a new drug (has it any chance of being successful ?)
- MIC distributions (local and national) must be obtained regularly to check for decreased susceptibilities (epidemiology) and reassessment of dosing and/or therapeutic choices (hospital...)
- Difficult-to-treat patients must be evaluated individually (and MIC obtained ...)

# Useful web sites...

- <http://www.eucast.org>
  - breakpoints and rational documents
- <http://www.ema.europa.eu>
  - SPCs and European Assessment report
- <http://www.facm.ucl.ac.be>
  - This lecture and many others



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