

# **Towards Rational International Antibiotic Breakpoints: Actions from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) and some personal thinking...**

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

Prepared for



Destelbergen, Belgium - 15 January 2006

# Why do we need breakpoints ?

To be honest, I always wondered ...



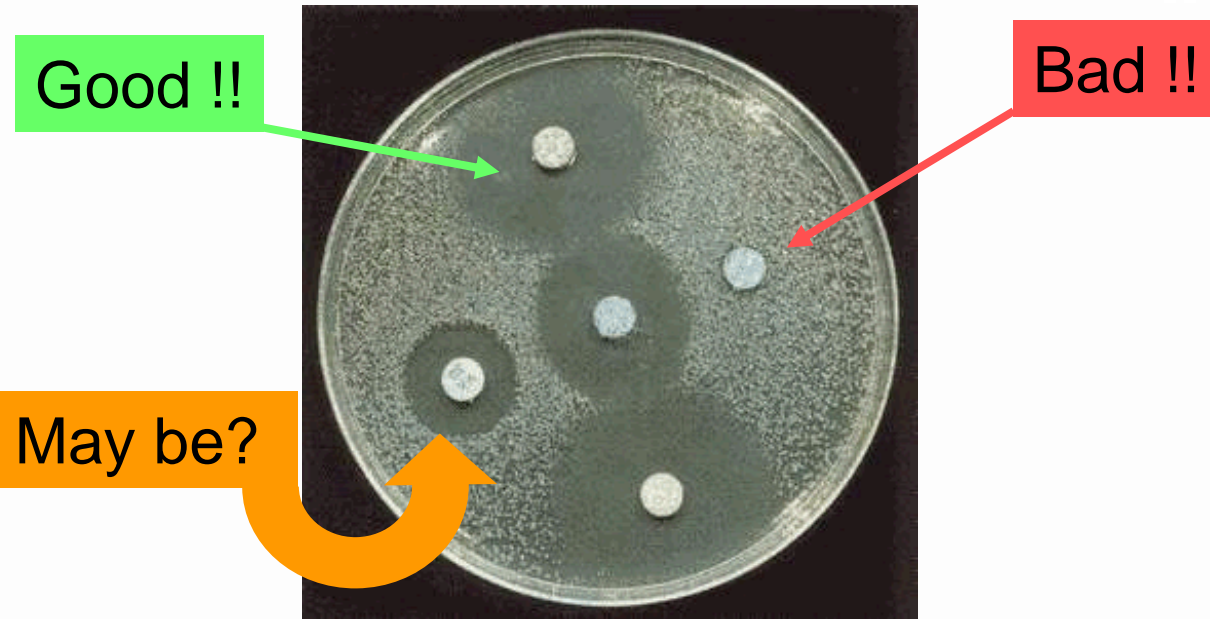
# Why do we need breakpoints ?

but perhaps...

1. Doctors like to know if the bug is "**good**" or "**bad**" ...
2. Regulators like to tell people "**DO**" or "**Don't**"
3. Industry likes to know "**When can I**" and "**When I cannot**"
4. Lawyers like you to be "**guilty**" or "**innocent**" ...
5. Microbiologists wish to give them all **simple answers...**

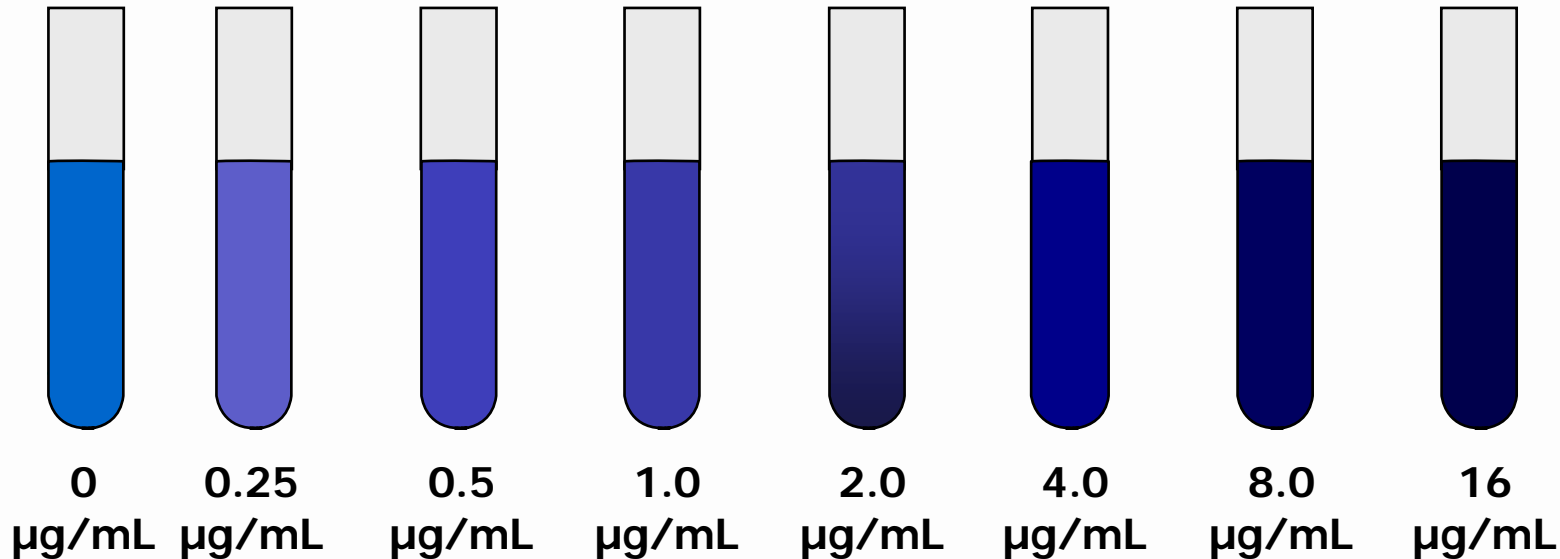


# Simple answers ...



# Starting from the beginning... The MIC !

Known quantity of bacteria  
placed into each tube



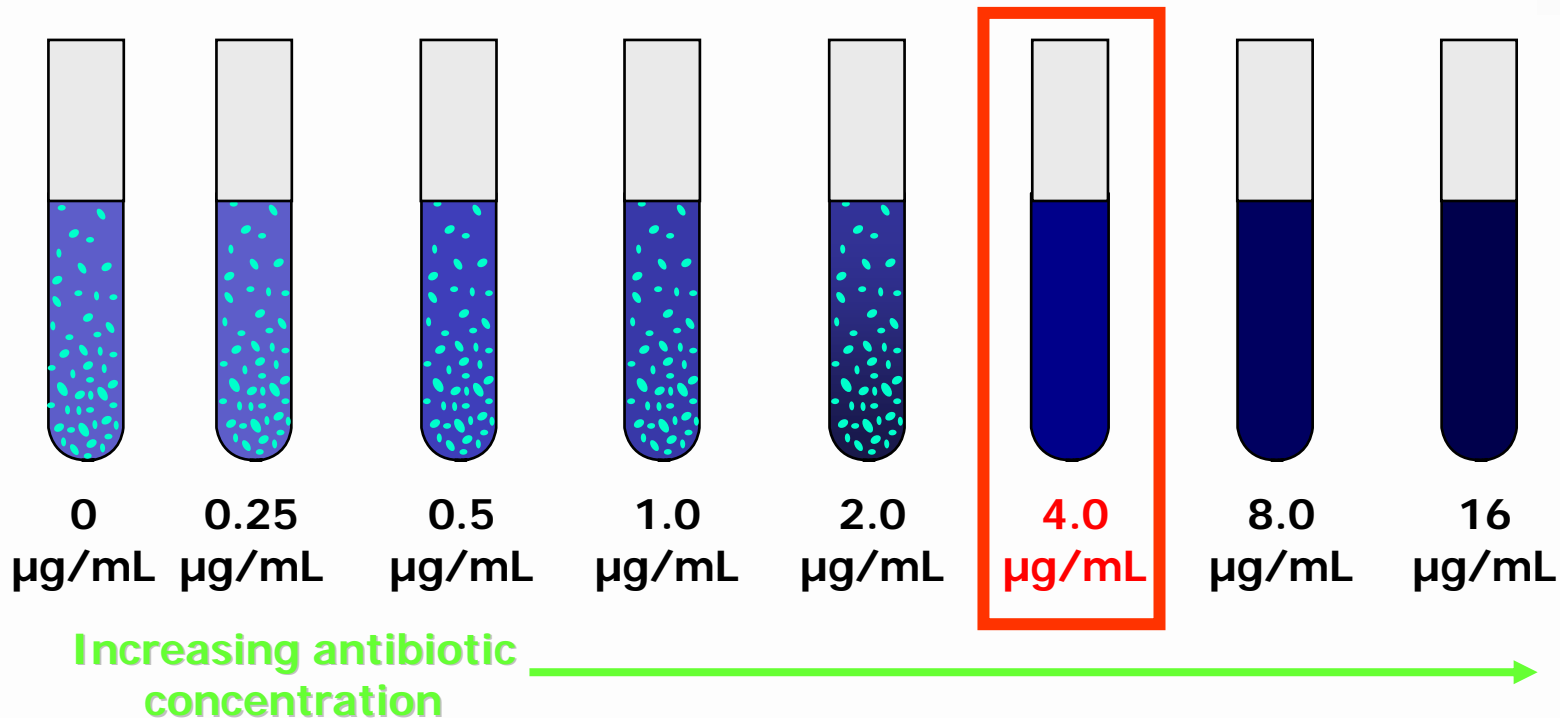
Increasing antibiotic  
concentration



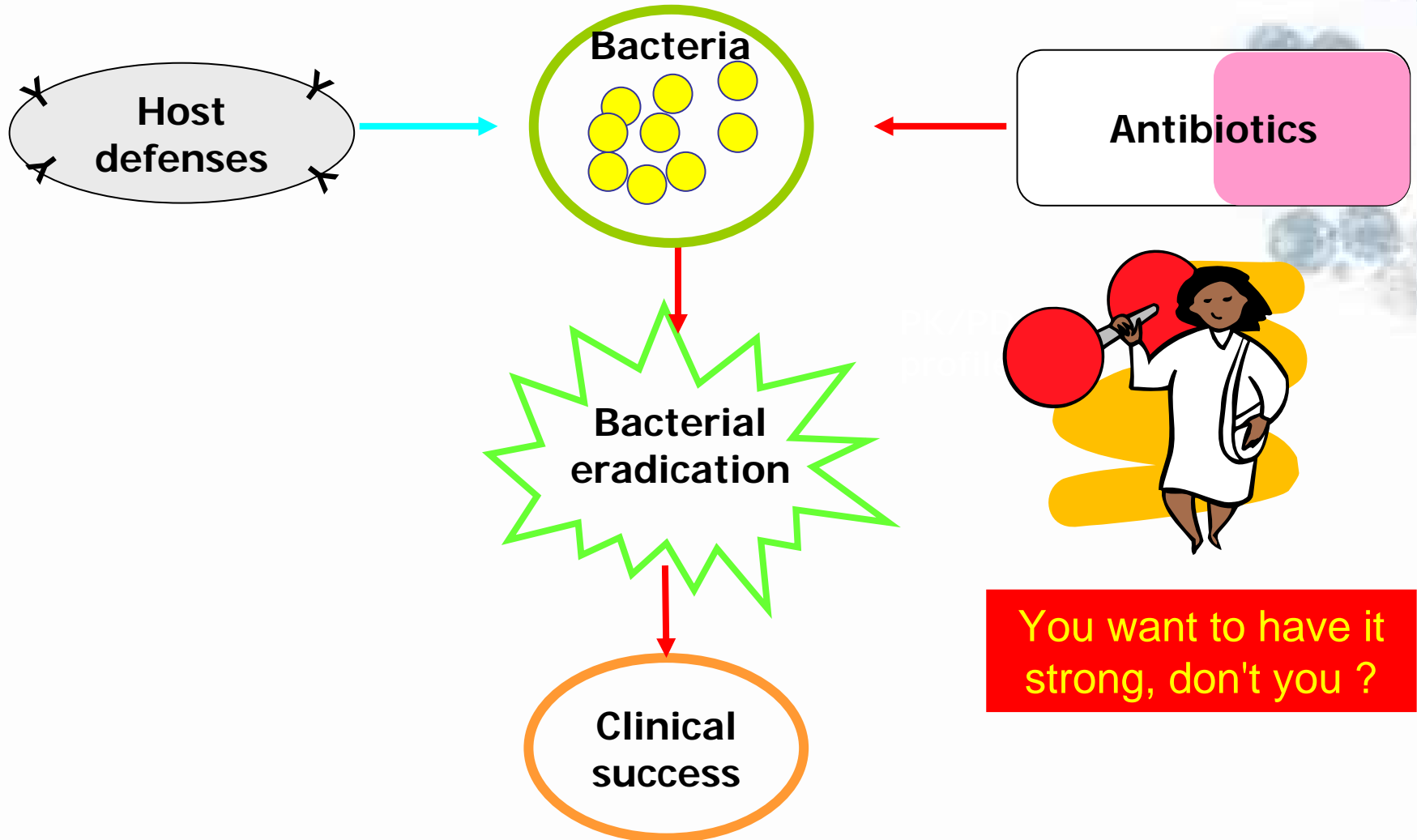
# Starting from the beginning... The MIC !

24 h later ....

Lowest concentration of an antimicrobial that results in the inhibition of visible growth of a microorganism



# What do you do with an MIC !



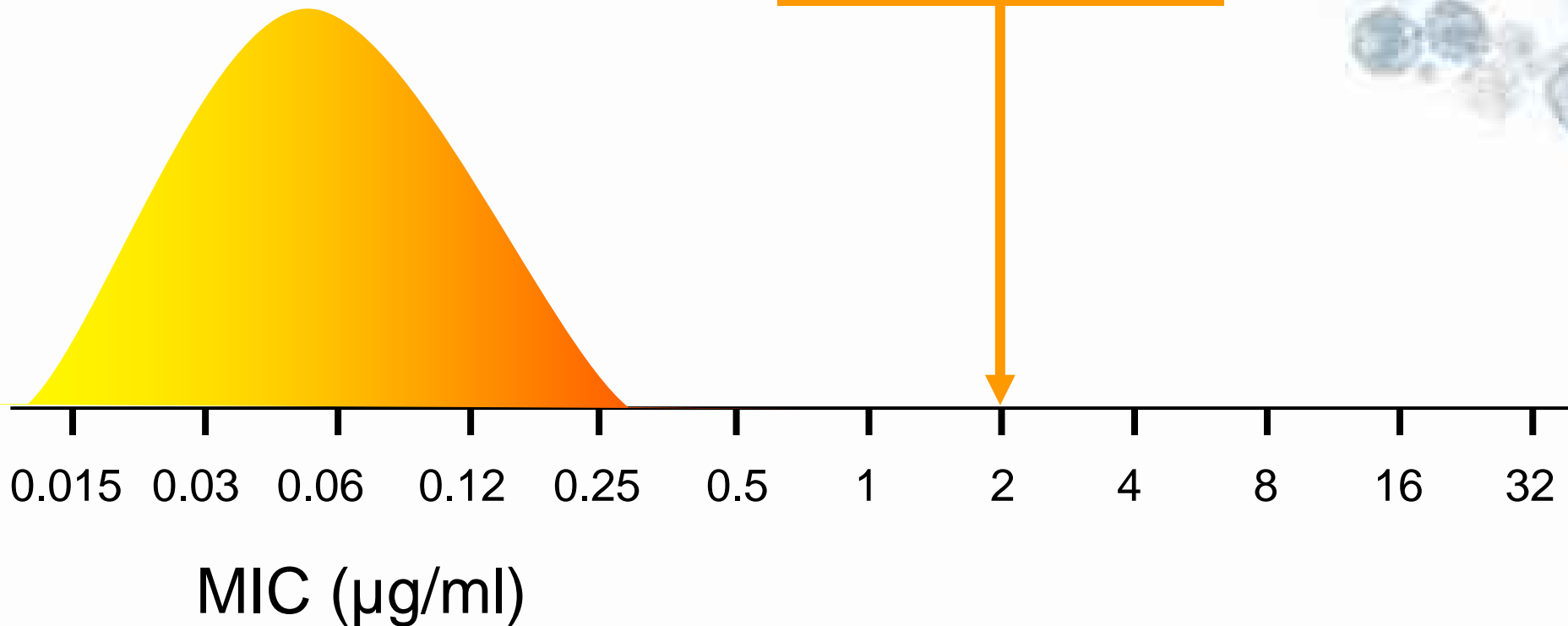
# But, what is strong ?



Good !!

*Easy!!!*

serum concentration





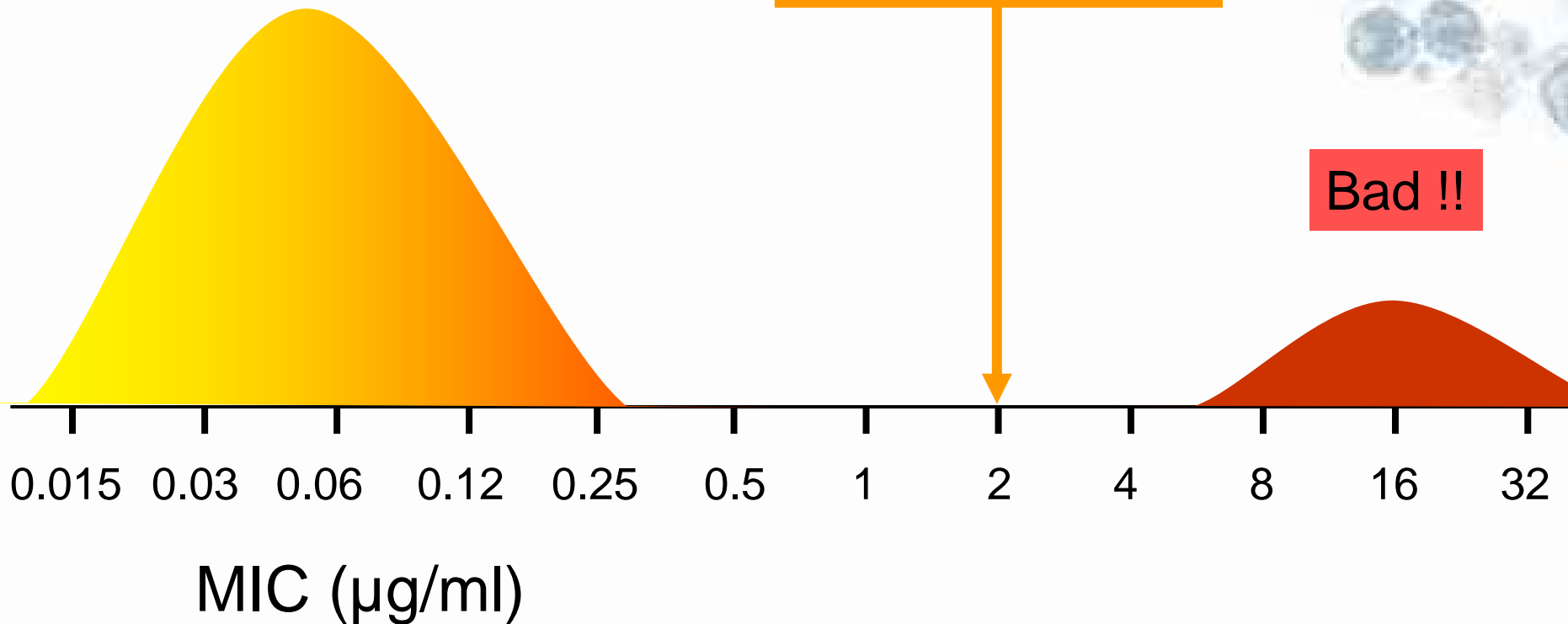
But, what is strong ?

**Still Easy!!!**

Good !!

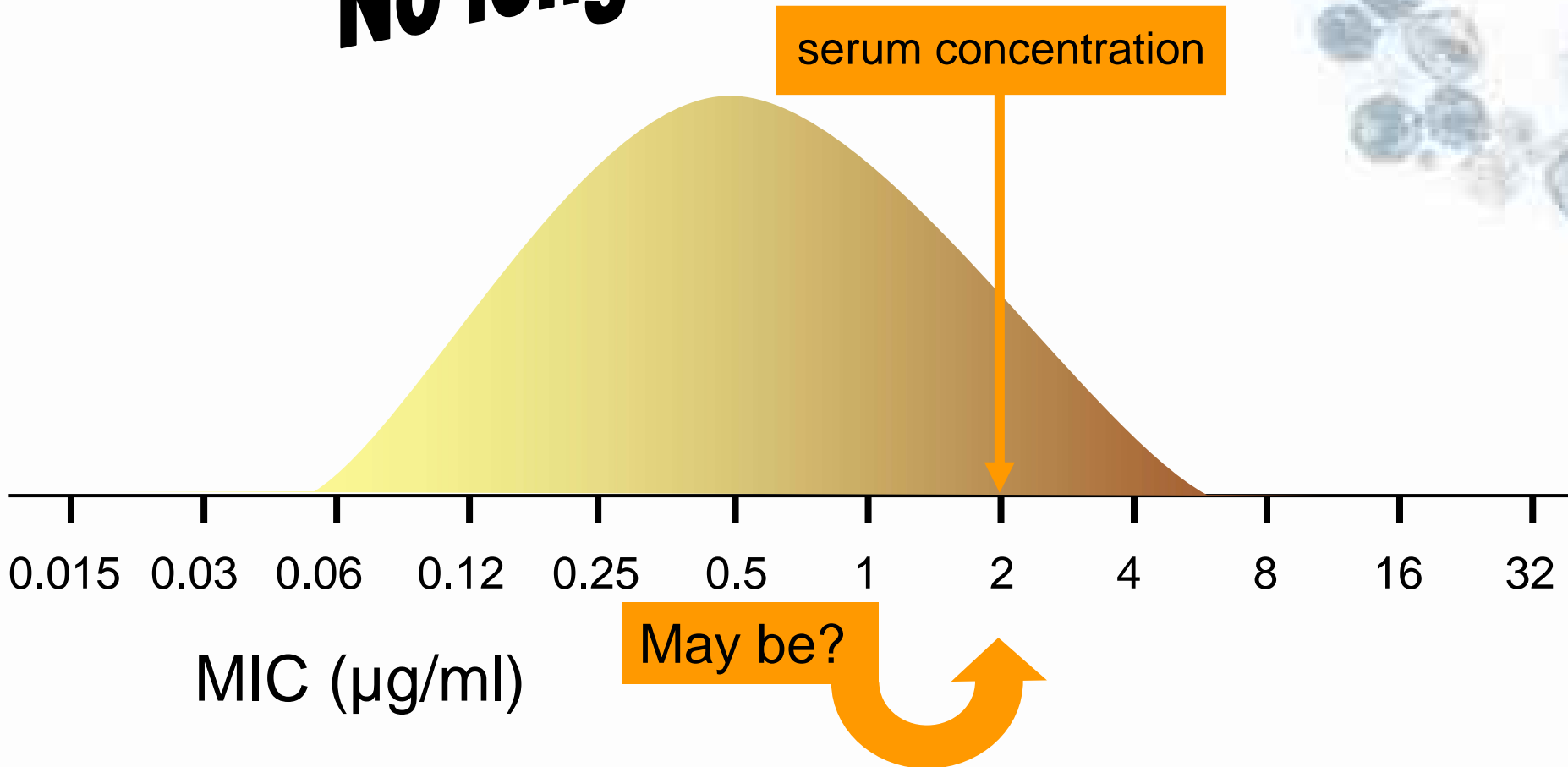
serum concentration

Bad !!

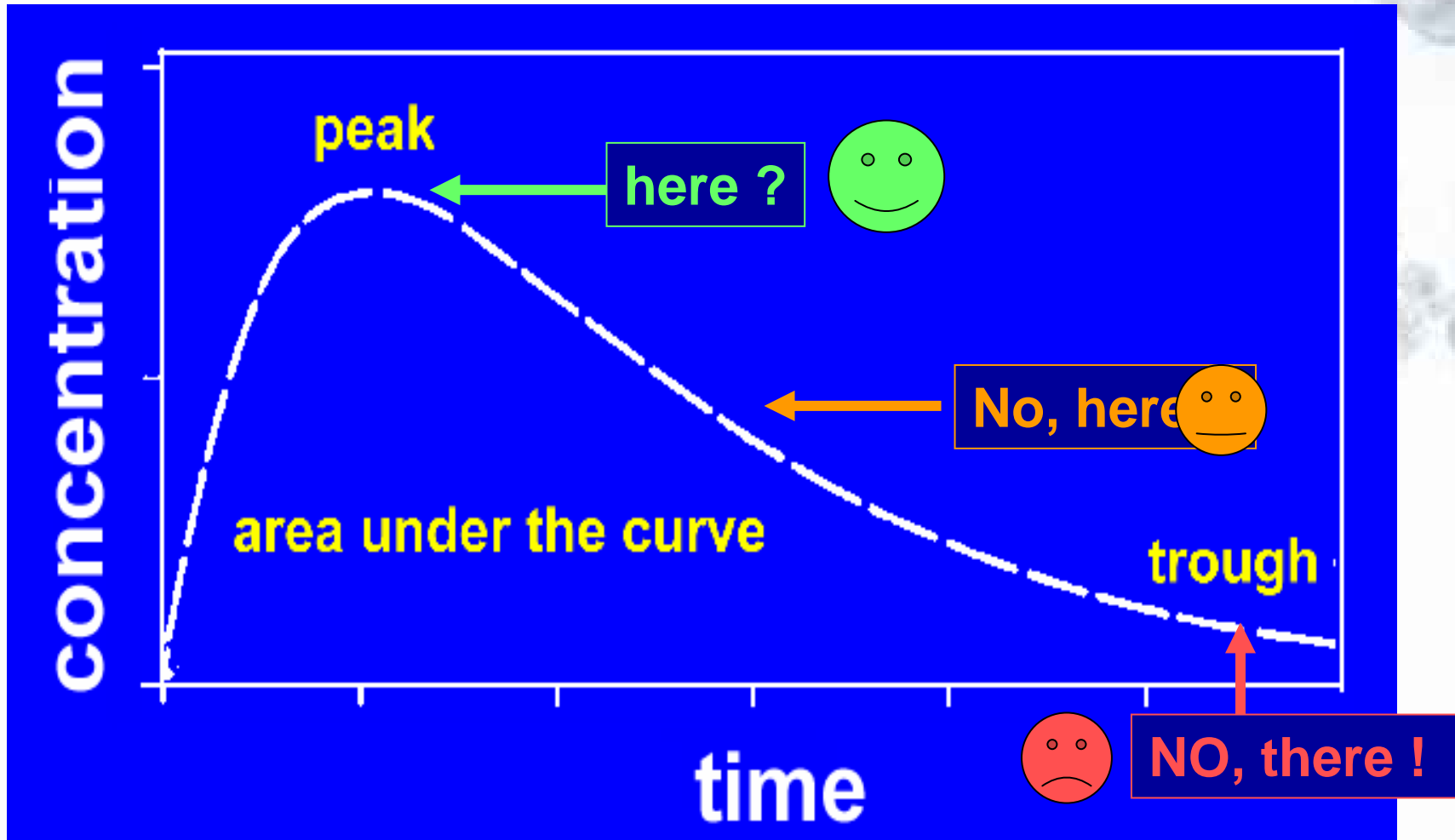


But, what is strong ?

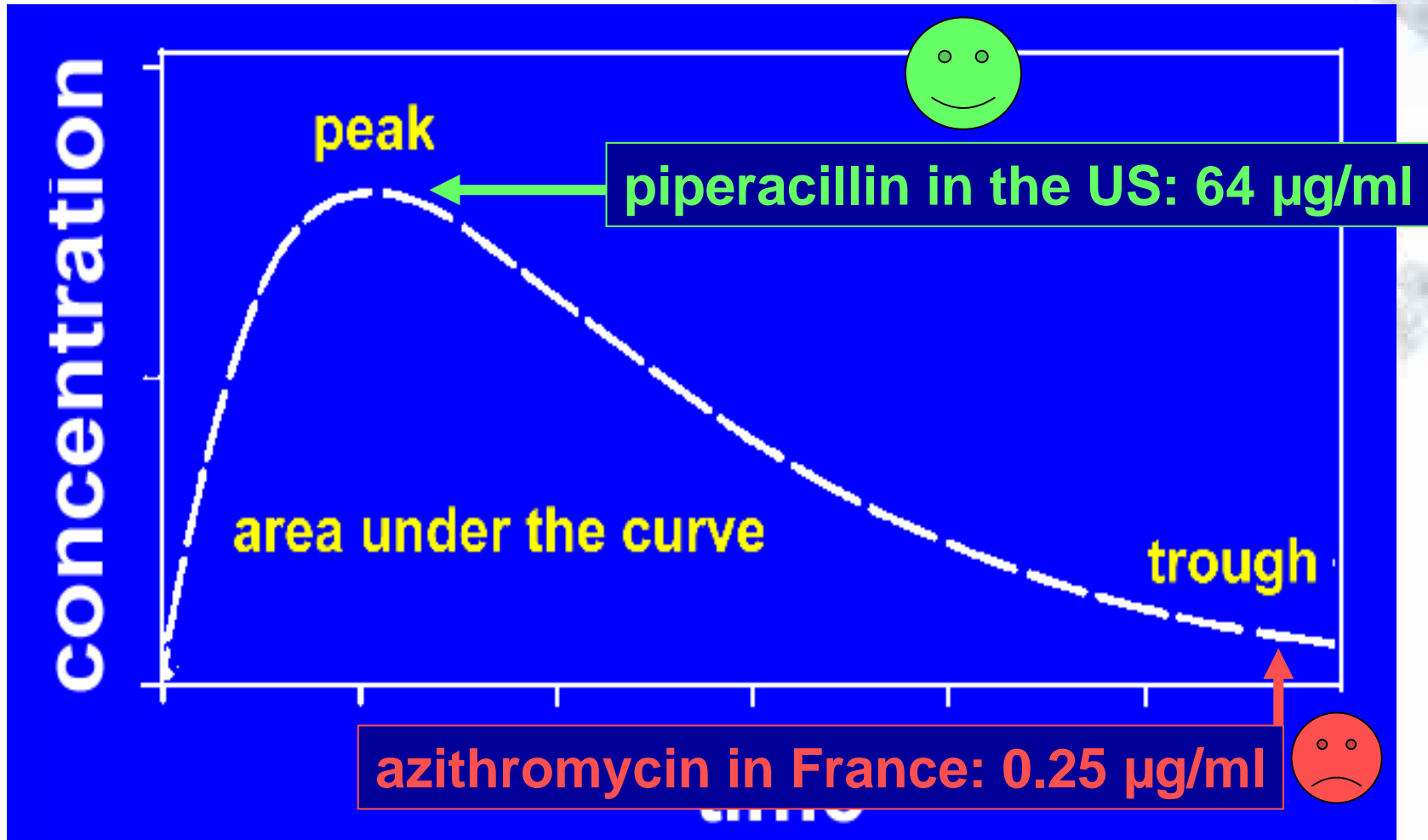
**No longer so easy...**



# Where should the breakpoint be ?



# Where should the breakpoint be ?



# And there were fierce battles ...



From Mouton, 8th ISAP symposium, Nijmegen, 2001

# What was THE problem ?

- Europe had a number of different breakpoint-setting authorities ... and, therefore (?), **MANY** different breakpoints ... \*
- In the U.S.A., the NCCLS defined the breakpoints, but those were not (always) rational and realistic, and, in any case, were always linked to the US situation (posologies, modes of administration, type of resistance, etc...)

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\* having no national breakpoint-setting authority to tell them what to do, Belgian microbiologists most often used the NCCLS breakpoints ...

# One simple example ...

cefotaxime vs. <i>E.coli</i>		$S_{\leq} / R$
BSAC	United Kingdom	2 / $\geq 4$
CA-SFM	France	4 / $> 32$
CRG	The Netherlands	4 / $> 16$
DIN	Germany	2 / $\geq 16$
NWGA	Norway	1 / $\geq 32$
SRGA	Sweden	0.5 / $\geq 2$
NCCLS	U.S.A.	8 / $\geq 64$

**Yet, breakpoints were 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.**

<http://www.eucast.org>

# Distribution des CMI vs. Phenotypes sauvages

## Recherche

Méthode: ☒ CMI ☐ Methode de diffusion

Éléments par page: 15

Antimicrobien: Ciprofloxacin Espèce: Espèce...

Antimicrobien: C

[Acinetobacter](#)

[Bacteroides](#)

[Burkholderia](#)

[Campylobacter](#)

[Campylobacter](#)

[Citrobacter](#)

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.

<a href="#">Coagulase negative staphylococci</a>	0	0	0	0	5	0	7	13	13	1	0	0	1	0	0	0	0	0
<a href="#">Enterobacter species</a>	0	14	30	132	110	27	15	9	11	5	8	4	5	6	0	8	0	0
<a href="#">Enterococcus faecalis</a>	0	0	0	0	0	0	0	0	8	9	25	0	1	0	0	0	0	0
<a href="#">Enterococcus faecium</a>	0	0	0	0	0	0	0	10	19	35	68	37	21	3	3	0	0	0
<a href="#">Escherichia coli</a>	11	158	1469	2032	147	52	116	81	31	19	8	47	85	62	60	32	5	0
<a href="#">Haemophilus influenzae</a>	6	47	258	674	367	46	3	0	0	0	0	0	0	0	0	0	0	0
<a href="#">Haemophilus parainfluenzae</a>	0	0	74	111	18	0	0	0	0	0	0	0	0	0	0	0	0	0
<a href="#">Klebsiella pneumonia</a>	0	2	38	217	295	79	30	31	17	8	1	2	0	7	7	1	2	0
<a href="#">Klebsiella spp</a>	0	12	20	86	888	126	76	39	27	29	11	18	17	0	0	0	0	0

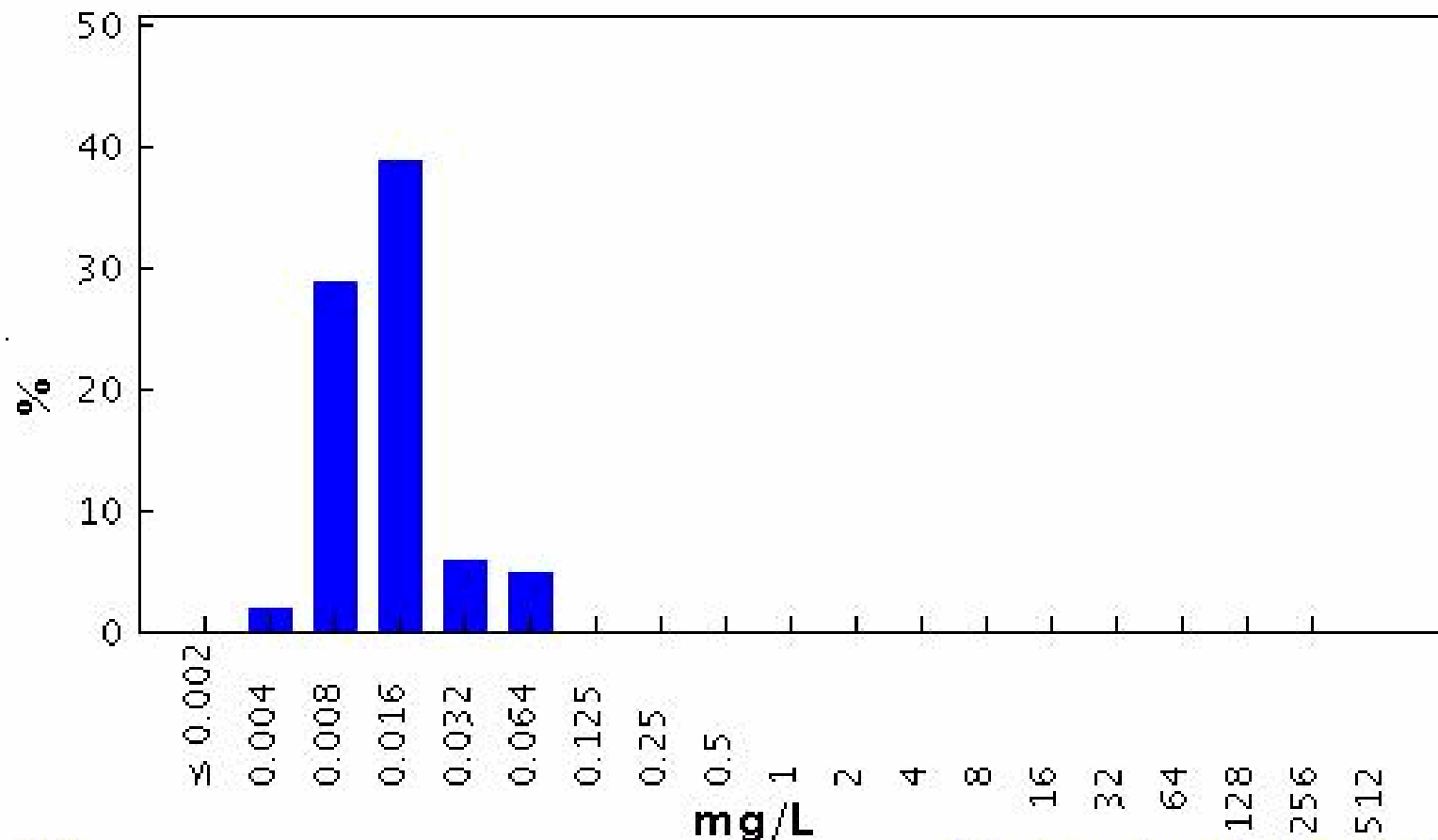
Ac-Le Le-St St-

Retourner

## Ciprofloxacin / *Escherichia coli*

Antimicrobial wild type distributions of microorganisms - reference database

EUCAST



MIC

Epidemiological cut-off: WT  $\leq 0.064$  mg/L

6423 observations (9 data sources)

Clinical breakpoints: S  $\leq 0.5$  mg/L, R  $> 1$  mg/L

Retourner

# **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

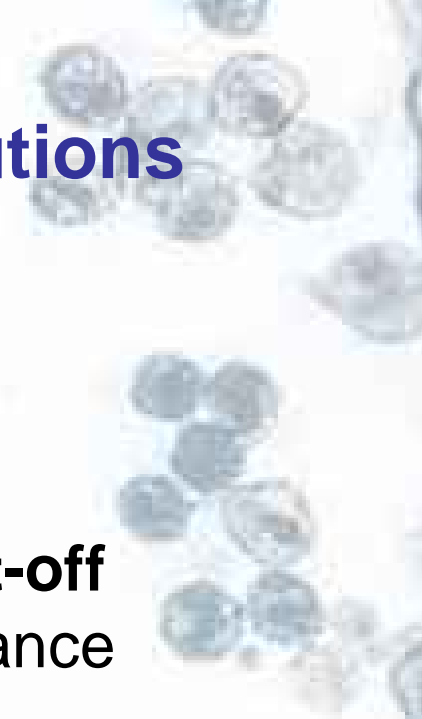
- publications in international journals
- breakpoint committees
- antimicrobial surveillance systems such as EARSS, SENTRY, the Alexander Project
- pharmaceutical companies and susceptibility testing device manufacturers.

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.

# Use of EUCAST wild type MIC distributions

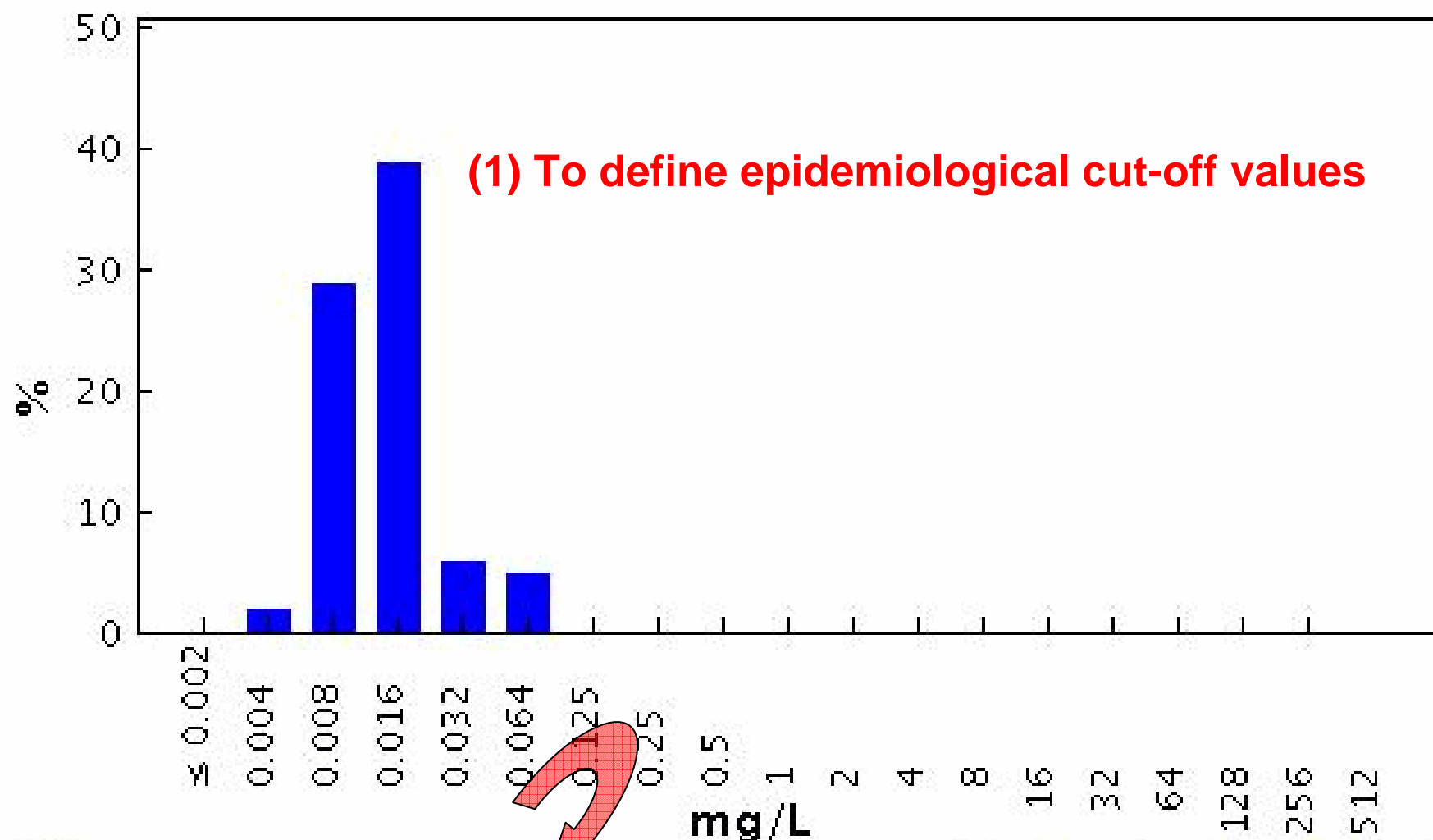
The wild type MIC distributions provide

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



MIC

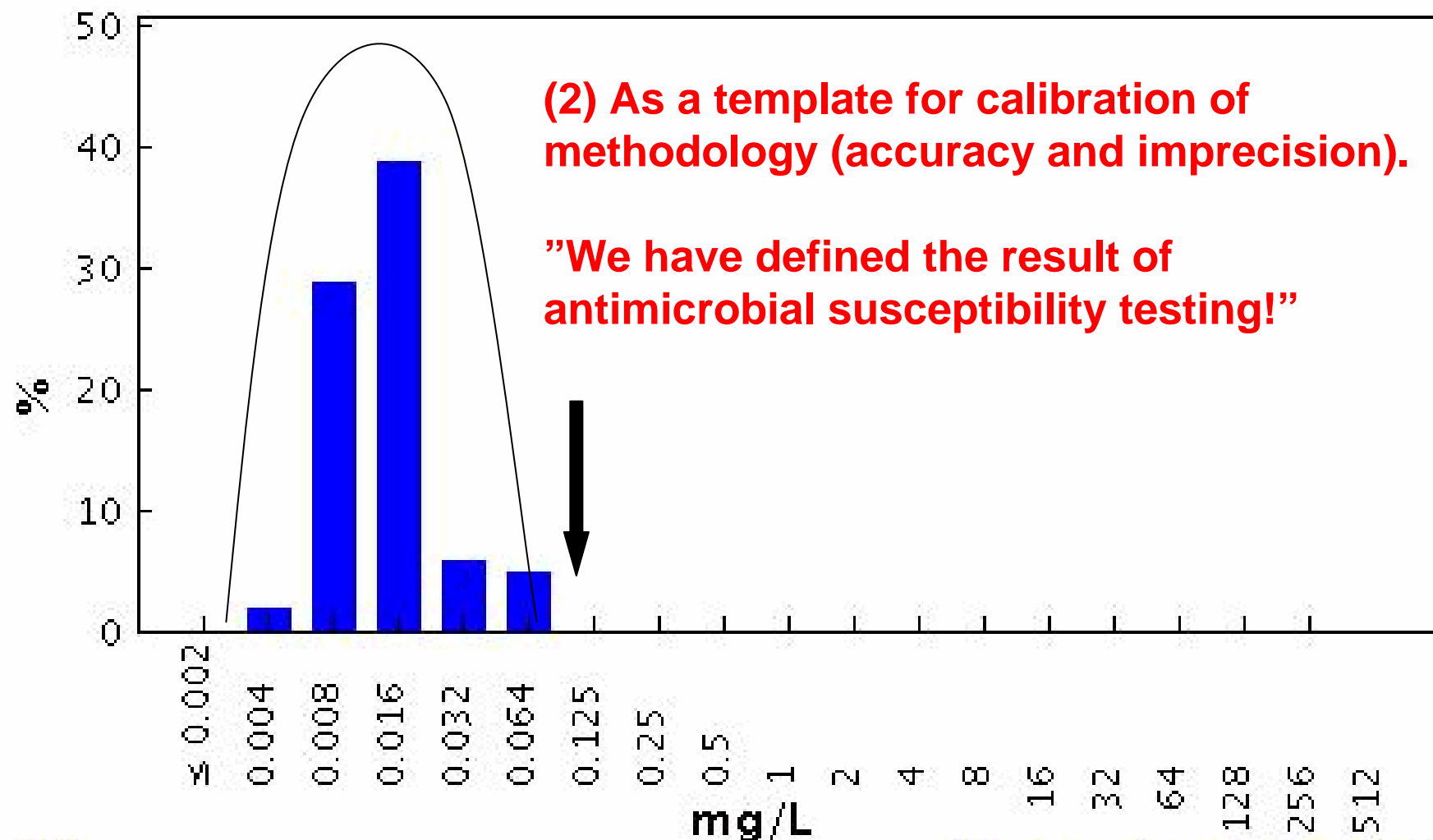
Epidemiological cut-off: WT ≤ 0.064 mg/L

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



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 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  $S \leq x \text{ mg/L}$  ;  $I > x, \leq y \text{ mg/L}$  ;  $R > y \text{ mg/L}$**



# EUCAST procedure for setting breakpoints

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

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

# 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 400 x 2 iv	500 x 2 oral 200 x 2 iv	250 x 2 oral 200 x iv	500 x 2 oral 200 x 2 iv	200-400 x 2 oral 400 x 2 iv	500 x 2 oral 400 x 2 iv	
Maximum dose schedule	750 x 2 oral 400 x 3 iv	750 x 2 oral 400 x 3 iv	750 x 2 oral 400 x 3 iv	750 x 2 oral 400 x 2 iv	data pending	750 x 2 oral 400 x 3 iv	
Available formulations	oral, iv	oral, iv	oral, iv	oral, iv	oral, iv	oral, iv	

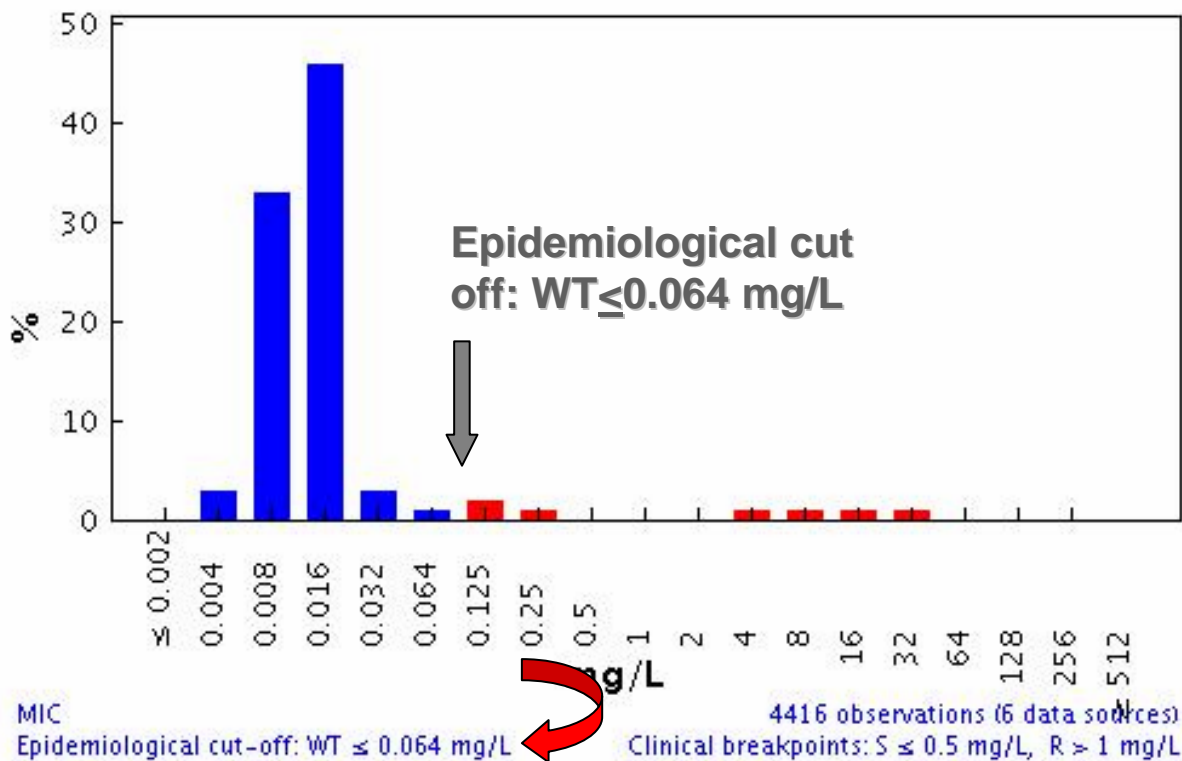
## Clinical data

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 ( $S \leq 0.064/R > 0.064$  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 ( $WT \leq X$ mg/L)

Ciprofloxacin / *Escherichia coli*  
Antimicrobial wild type distributions of microorganisms – reference database  
EUCAST



### 3. Existing national clinical breakpoints are compared

**Ciprofloxacin** was used in this example:

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

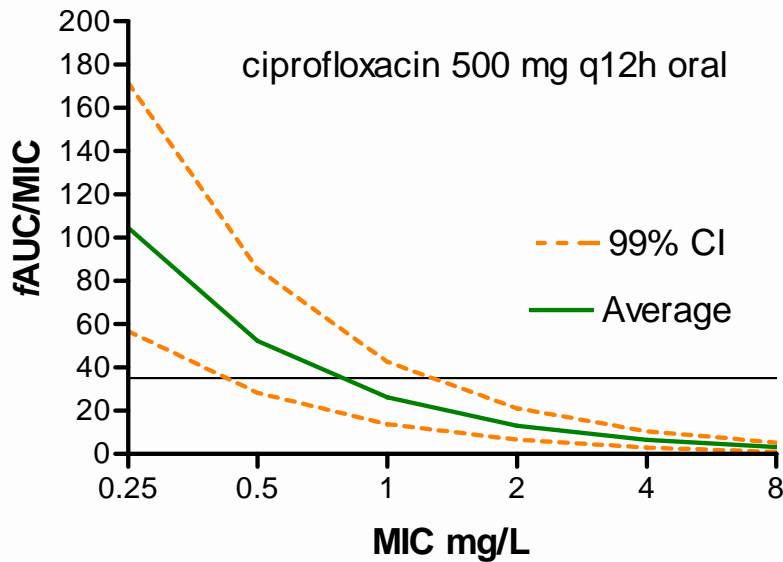
#### 5. Pharmacodynamic data are evaluated

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

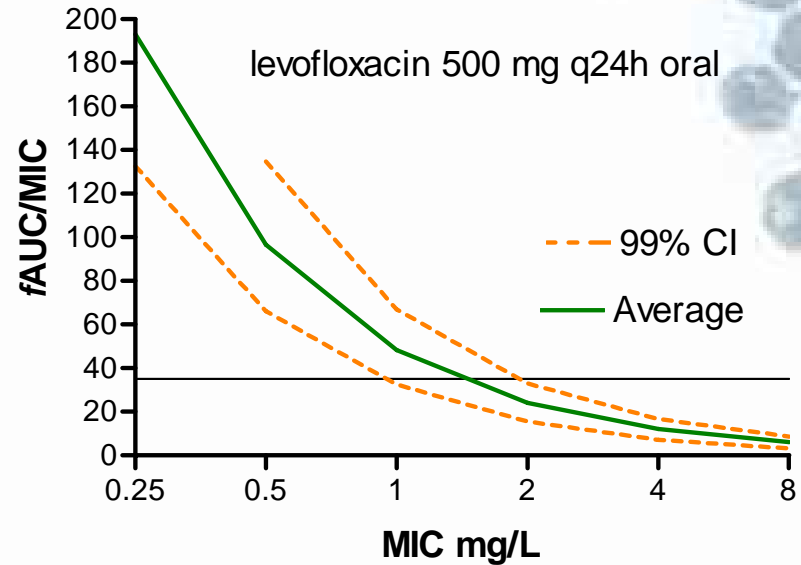
- in vitro data
- animal studies
- clinical trials
- The efficacy of the drugs is assessed quantitatively.

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

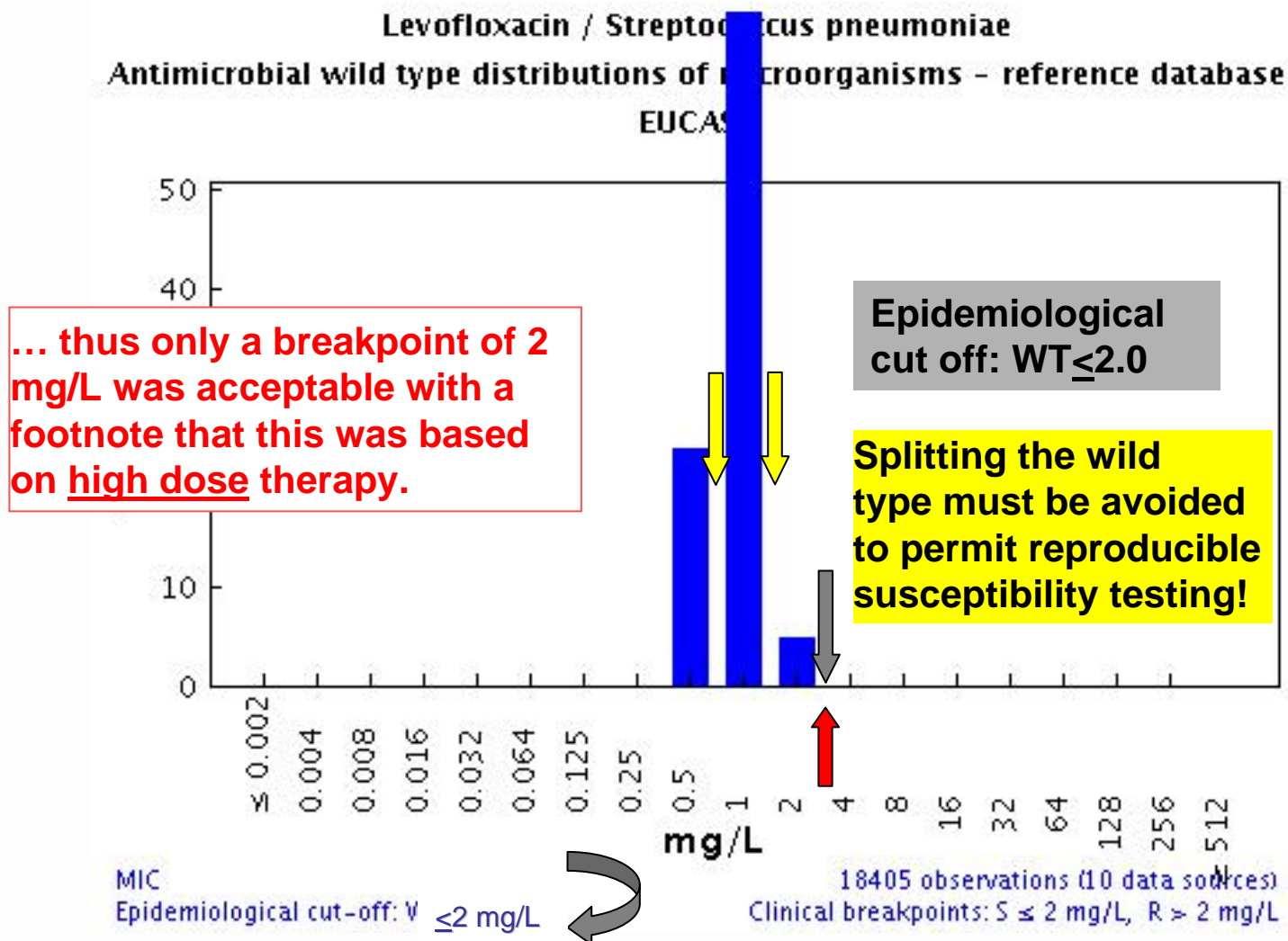
S = 1 mg/L

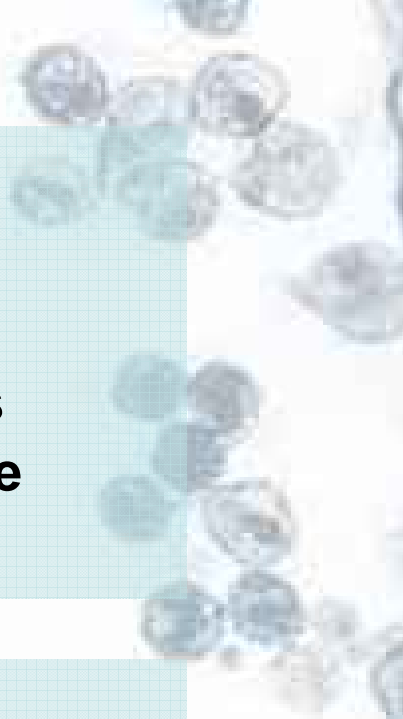
## **5. Clinical data relating outcome to MIC-values, wildtype and resistance mechanisms are assessed in relation to the tentative breakpoint**

"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".



## 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**

# And here are the results...



## Fluoroquinolones - EUCAST clinical MIC breakpoints

2006-06-20 (v 2.2)

Fluoroquinolone <sup>2</sup>		Species-related breakpoints (S</R>)											Non-species related breakpoints <sup>1</sup> S</R>
		<i>Enterobacteriaceae</i> <sup>3</sup>	<i>Pseudo-monas</i>	<i>Acineto-bacter</i>	<i>Staphylococcus</i>	<i>Enterococcus</i>	<i>Streptococcus A,B,C,G</i>	<i>S.pneumoniae</i> <sup>5</sup>	<i>H.influenzae M.catarrhalis</i>	<i>N.gonorrhoeae</i>	<i>N.meningitidis</i> <sup>8</sup>	<i>Gram-negative anaerobes</i>	
<a href="#">Ciprofloxacin</a>	RD	0.5/1	0.5/1	1/1 <sup>4</sup>	1/1 <sup>5</sup>	--	--	0.125/2	0.5/0.5 <sup>7</sup>	0.03/0.06	0.03/0.06	--	0.5/1
<a href="#">Levofloxacin</a>	RD	1/2	1/2	1/2	1/2	--	1/2	2/2	1/1 <sup>7</sup>	IE	IE	--	1/2
<a href="#">Moxifloxacin</a>	RD	0.5/1	--	--	0.5/1	--	0.5/1	0.5/0.5	0.5/0.5 <sup>7</sup>	IE	IE	IE	0.5/1
<a href="#">Norfloxacin</a>	RD	0.5/1	--	--	--	--	--	--	--	IE	--	--	0.5/1
<a href="#">Ofloxacin</a>	RD	0.5/1	--	--	1/1 <sup>3</sup>	--	--	0.125/4	0.5/0.5 <sup>7</sup>	0.12/0.25	IE	--	0.5/1

1. 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).
2. For breakpoints for other fluoroquinolones (eg. **pefloxacin** and **enoxacin**) - refer to breakpoints determined by national breakpoint committees.
3. *Salmonella* spp - there is clinical evidence for ciprofloxacin to indicate a poor response in systemic infections caused by *Salmonella* spp with low-level fluoroquinolone resistance (MIC>0.064 mg/L). The available data relate mainly to *S.typhi* but there are also case reports of poor response with other *Salmonella* species.
4. The S/I breakpoint has been increased from 0.5 to 1 mg/L to avoid dividing the wild type MIC distribution. Thus there is no intermediate category for *Acinetobacter* species
5. *Staphylococcus* spp - breakpoints for ciprofloxacin and ofloxacin relate to high dose therapy.
6. *Streptococcus pneumoniae* - wild type *S.pneumoniae* are not considered susceptible to ciprofloxacin or ofloxacin and are therefore categorized as intermediate. For ofloxacin the I/R breakpoint was increased from 1.0 to 4.0 mg/L and for levofloxacin the S/I-breakpoint from 1.0 to 2.0 to avoid dividing the wild type MIC distribution. The breakpoints for levofloxacin relate to high dose therapy.
7. Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant. *Haemophilus/Moraxella* - fluoroquinolone low-level resistance (ciprofloxacin MIC:s of 0.125 - 0.5 mg/L) may occur in *H.influenzae*. There is no evidence that low-level resistance is of clinical importance in respiratory tract infections with *H.influenzae*.
8. *Neisseria meningitidis* - breakpoints apply to the use of ciprofloxacin in the prophylaxis of meningococcal disease.

-- = 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.  
 RD = Rationale document listing data used for setting EUCAST breakpoints.

# Breakpoints available so far or with projected date...

(see next slides for examples)

## Clinical breakpoints

- Penicillins (2007)
- [Cephalosporins](#)
- [Carbapenems](#)
- [Monobactams](#)
- [Fluoroquinolones](#)
- [Aminoglycosides](#)
- [Glycopeptides](#)
- [Oxazolidones](#)
- Macrolides, ketolides & clindamycin, dalbapristine/-quinopristine (2007/08),
- Tetracyclines (2008), [Tigecycline](#)
- Chloramphenicol (2008),
- [Daptomycin](#),
- Fusidic acid (2008),
- Rifampicin (2008)
- Trimethoprim, sulfamethoxazole, co-trimoxazole (2008),
- Nitrofurantoin (2008)
- Fosfomycin (2008).

# Aminoglycosides - EUCAST clinical MIC breakpoints 23 november 2004

Aminoglycosides <sup>1</sup>	Species-related breakpoints (S≤/R>)											Non-species related breakpoints <sup>5</sup> S≤/R>
	<i>Enterobacteriaceae</i>	<i>Pseudomonas</i> <sup>2</sup>	<i>Acinetobacter</i> <sup>2</sup>	<i>Staphylococcus</i>	<i>Enterococcus</i> <sup>3</sup>	<i>Streptococcus</i> A,B,C,G	<i>S.pneumoniae</i>	<i>H.influenzae</i> <i>M.catarrhalis</i>	<i>N.gonorrhoeae</i>	<i>N.meningitidis</i>	Gram-negative anaerobes	
<a href="#">Amikacin</a>	8/16	8/16	8/16	8/16 <sup>4</sup>	--	--	--	IE	--	--	--	8/16
<a href="#">Gentamicin</a>	2/4	4/4	4/4	1/1	--	--	--	IE	--	--	--	2/4
<a href="#">Netilmicin</a>	2/4	4/4	4/4	1/1	--	--	--	IE	--	--	--	2/4
<a href="#">Tobramycin</a>	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

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 <sup>2</sup>
	<i>Enterobacteriaceae</i>	<i>Pseudomonas</i>	<i>Acinetobacter</i>	<i>Staphylococcus</i> <sup>1</sup>	<i>Enterococcus</i> <sup>1</sup>	<i>Streptococcus</i> A,B,C,G	<i>S.pneumoniae</i>	<i>H.influenzae</i> <i>M.catarrhalis</i>	<i>N.gonorrhoeae</i>	<i>N.meningitidis</i>	<i>Gram-negative anaerobes</i>	
<a href="#">Linezolid</a>	--	--	--	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.

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

Cephalosporins		Species-related breakpoints (S≤/R>)							
		<i>Enterobacteriaceae</i> <sup>2</sup>	<i>Pseudo-monas</i> <sup>3</sup>	<i>Acinetobacter</i>	<i>Staphylococcus</i> <sup>4</sup>	<i>Enterococcus</i>	<i>Streptococcus</i> A,B,C,G	<i>S.pneumoniae</i>	<i>H.influenza</i> <i>M.catarrhalis</i>
Click on antibiotic name to see wild type MIC distributions.									
<a href="#">Cefazolin</a>	RD	--	--	--	note <sup>4</sup>	--	--	--	--
<a href="#">Cefepime</a>	RD	1/8	8/8	--	note <sup>4</sup>	--	0.5/0.5 <sup>6</sup>	1/2	0.25/0.2
<a href="#">Cefotaxime</a>	RD	1/2	--	--	note <sup>4</sup>	--	0.5/0.5 <sup>6</sup>	0.5/2 <sup>6</sup>	0.12/0.1
<a href="#">Ceftazidime</a>	RD	1/8	8/8	--	--	--	--	--	--
<a href="#">Ceftriaxone</a>	RD	1/2	--	--	note <sup>4</sup>	--	0.5/0.5 <sup>6</sup>	0.5/2 <sup>6</sup>	0.12/0.1
<a href="#">Cefuroxime</a>	RD	8/8 <sup>5</sup>	--	--	note <sup>4</sup>	--	0.5/0.5 <sup>6</sup>	0.5/1	1/2

1. 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).
2. The cephalosporin breakpoints for Enterobacteriaceae will detect resistance mediated by most ESBLs and other clinically important beta-lactamases in Enterobacteriaceae. However, some ESBL-producing strains may appear susceptible or intermediate with these breakpoints. Laboratories may want to use a test which specifically screens for the presence of ESBL.
3. For cefepime and ceftazidime the susceptible breakpoint for *Pseudomonas aeruginosa* has been increased to avoid dividing the MIC wild type distribution. The breakpoint relates to high dosage of both drugs, i.e. 2 g x 3.
4. Susceptibility of staphylococci to cephalosporins is inferred from the methicillin susceptibility (except ceftazidime which should not be used for staphylococcal infections).
5. The non-species related S/I breakpoint of 4 mg/L divides the wild type MIC distributions of relevant Enterobacteriaceae. To avoid this, the S/I-breakpoint has been increased to 8 mg/L. The breakpoint pertains to a dosage of 1.5 g x 3 and to *E.coli* and *Klebsiella spp* only.
6. Strains with MIC values above the S/I breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant.

-- = 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.

RD = rationale document listing data used by EUCAST for determining breakpoints.

# Carbapenems - EUCAST clinical MIC breakpoints

2006-06-20 (v 1.1)

Carbapenem <small>Click on antibiotic name to see wild type MIC distributions</small>		Species-related breakpoints (S</R>)											Non-species related breakpoints <sup>1</sup> S</R>
		<i>Enterobacteriaceae</i>	<i>Pseudo-monas</i>	<i>Acineto-bacter</i>	<i>Staphylo-coccus</i>	<i>Entero-coccus</i>	<i>Strepto-coccus A,B,C,G</i>	<i>S.pneu-moniae</i>	<i>H.influenzae M.catarrhalis</i>	<i>N.gonorrhoeae</i>	<i>N.mening-itis</i>	<i>Gram-negative anaerobes</i>	
<a href="#">Ertapenem</a>	RD	0.5/1	--	--	<i>note</i> <sup>3</sup>	--	0.5/0.5 <sup>4,7</sup>	0.5/0.5 <sup>4,7</sup>	0.5/0.5 <sup>4,7</sup>	IE	--	1/1 <sup>8</sup>	0.5/1
<a href="#">Imipenem</a>	RD	2/8 <sup>2</sup>	4/8 <sup>6</sup>	2/8	<i>note</i> <sup>3</sup>	4/8 <sup>6</sup>	2/2 <sup>4,7</sup>	2/2 <sup>4,7</sup>	2/2 <sup>4,7</sup>	IE	--	2/8	2/8
<a href="#">Meropenem</a>	RD	2/8	2/8	2/8	<i>note</i> <sup>3</sup>	--	2/2 <sup>4,7</sup>	2/2 <sup>4,7</sup>	2/2 <sup>4,7</sup>	IE	0.25/0.25 <sup>5,7</sup>	2/8	2/8

1. 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).
2. *Proteus* and *Morganella* species are considered poor targets for imipenem.
3. Susceptibility of staphylococci to carbapenems is inferred from the methicillin susceptibility.
4. Imipenem and ertapenem are not used for meningitis. Meropenem breakpoints for *Streptococcus pneumoniae* and *Haemophilus influenzae* in meningitis are 0.25/1 mg/L.
5. Meropenem breakpoints in *Neisseria meningitis* relates to meningitis only.
6. The imipenem S/I breakpoint for *Pseudomonas* and *Enterococcus* was increased from 2 to 4 mg/L to avoid dividing the wild type MIC distribution.
7. Strains with MIC values above the S/I breakpoint are rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant.
8. The ertapenem S/I breakpoint for Gramnegative anaerobes was moved from 0.5 to 1.0 to avoid dividing the wild type MIC distributions.

-- = 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.  
 RD =Rationale document listing data used for setting EUCAST breakpoints.

Version*	Date	Action
1.1	2006-06-20	This table rearranged in reverse chronological order
1.0	2006-03-31	Released by EUCAST

\*The number before the point indicates breakpoint change. The number after the point indicates minor changes (footnotes, spelling, format, etc) without a change of breakpoints.



# 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 will soon 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.



# EMA – ISAP SOP



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

## 1. Purpose

To describe the interaction between EMEA/CHMP and EUCAST in the process of harmonisation of European 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)



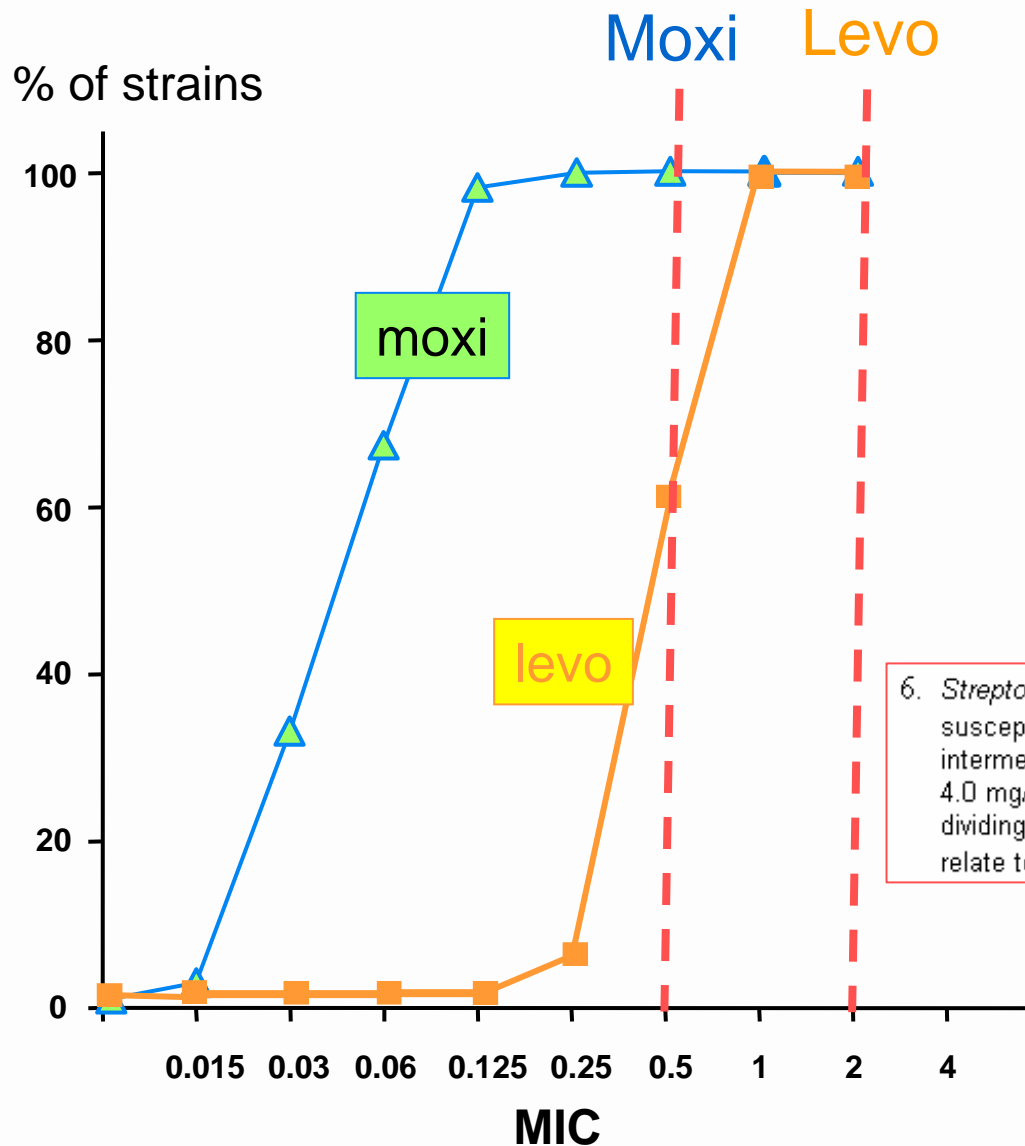
The image shows a large, well-lit conference room with a patterned carpet and chandeliers. Numerous people are seated at round tables, facing a large screen displaying a presentation slide. The slide contains text and a bar chart, likely related to the EUCAST presentation mentioned in the caption. The room is filled with people, suggesting a large-scale event or conference.



# Will good 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 posologies and/or therapeutic choices (hospital...)
- Difficult-to-treat patients must be evaluated individually (and MIC obtained ...) and questionable drugs must be scrutinized...

# Application for an existing pair of drugs in Belgium

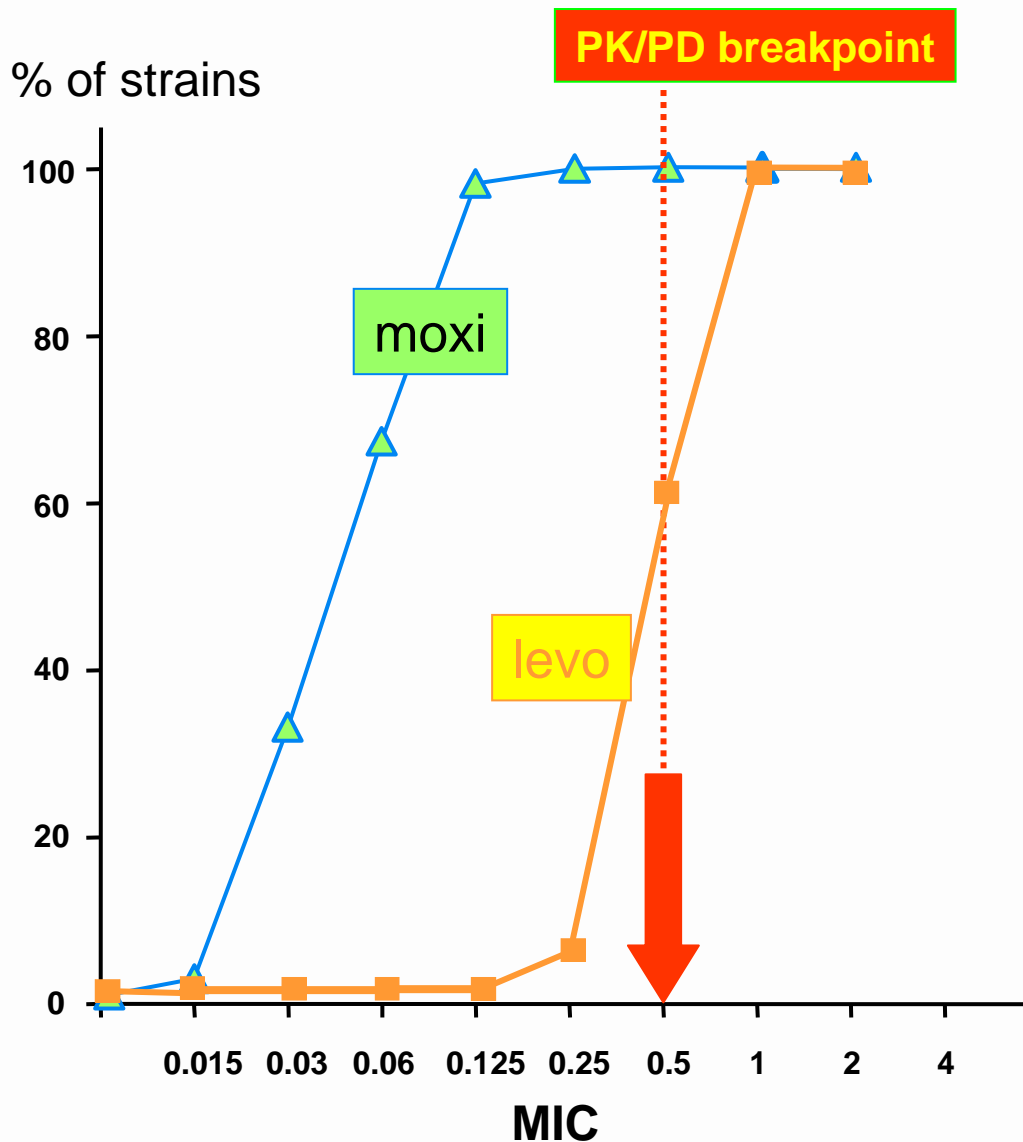


Fluoroquinolone <sup>2</sup>	
Click on antibiotic name to see wild type MIC distributions	
<a href="#">Ciprofloxacin</a>	<i>S.pneu-</i> <i>moniae</i> <sup>5</sup> 0.125/2
<a href="#">Levofloxacin</a>	2/2
<a href="#">Moxifloxacin</a>	0.5/0.5
<a href="#">Norfloxacin</a>	--
<a href="#">Ofloxacin</a>	0.125/4

6. *Streptococcus pneumoniae* - wild type *S.pneumoniae* are not considered susceptible to ciprofloxacin or ofloxacin and are therefore categorized as intermediate. For ofloxacin the I/R breakpoint was increased from 1.0 to 4.0 mg/L and for levofloxacin the S/I-breakpoint from 1.0 to 2.0 to avoid dividing the wild type MIC distribution. The breakpoints for levofloxacin relate to high dose therapy.

MIC data: J. Verhaegen et al., 2003

# My personal view...



**Levofloxacin** 500 mg  
1X / jr

- AUC [(mg/l)xh] 47
- peak [mg/l] 5

→ **MIC<sub>max</sub>** < 0.5

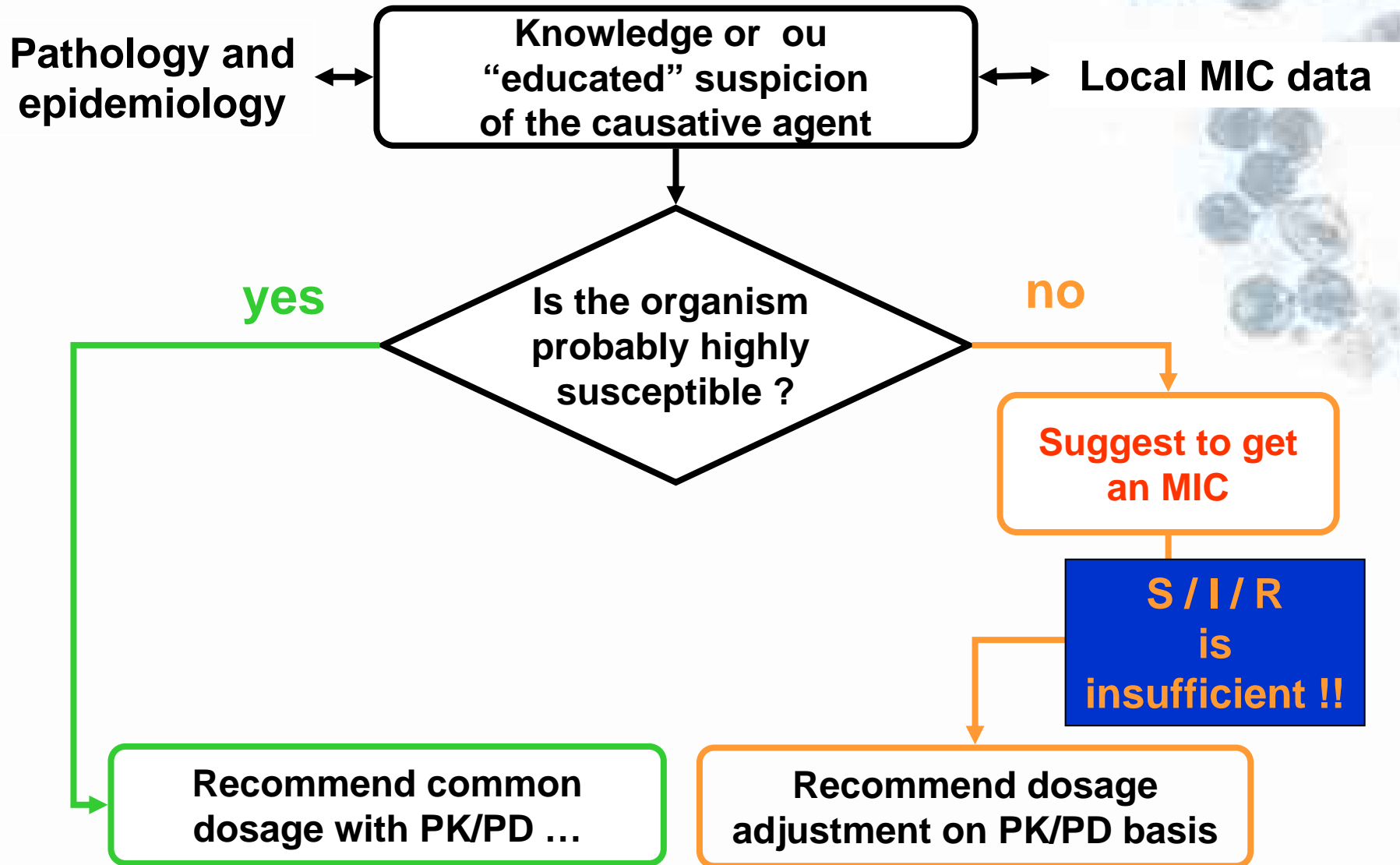
**Moxifloxacin** 400 mg  
1X /jr

- AUC [(mg/l)xh] 48
- peak [mg/l] 4.5

→ **MIC<sub>max</sub>** < 0.5

MIC data: J. Verhaegen et al., 2003

# A key to success ...





# A key to success (follow.) ...

