EUCAST breakpoints

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WETENSCHAPPELIJK INSTITUUT
VOLKSGEZONDHEID
INSTITUT SCIENTIFIQUE
DE SANTÉ PUBLIQUE

UCL

Based (largely) on presentations available from the EUCAST Web site,
given to me by Gunnar Kahlmeter and other members of EUCAST steering committee

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 [1] of growth inhibition in an agar plate around a disk loaded with a standard amount of antibiotic;

- while this system yiealds *per definition* a <u>continuous</u> 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 <u>discrete categories</u>

  - less than x mm ➔ RESISTANT

  - larger than y mm ➔ SUSCEPTIBLE

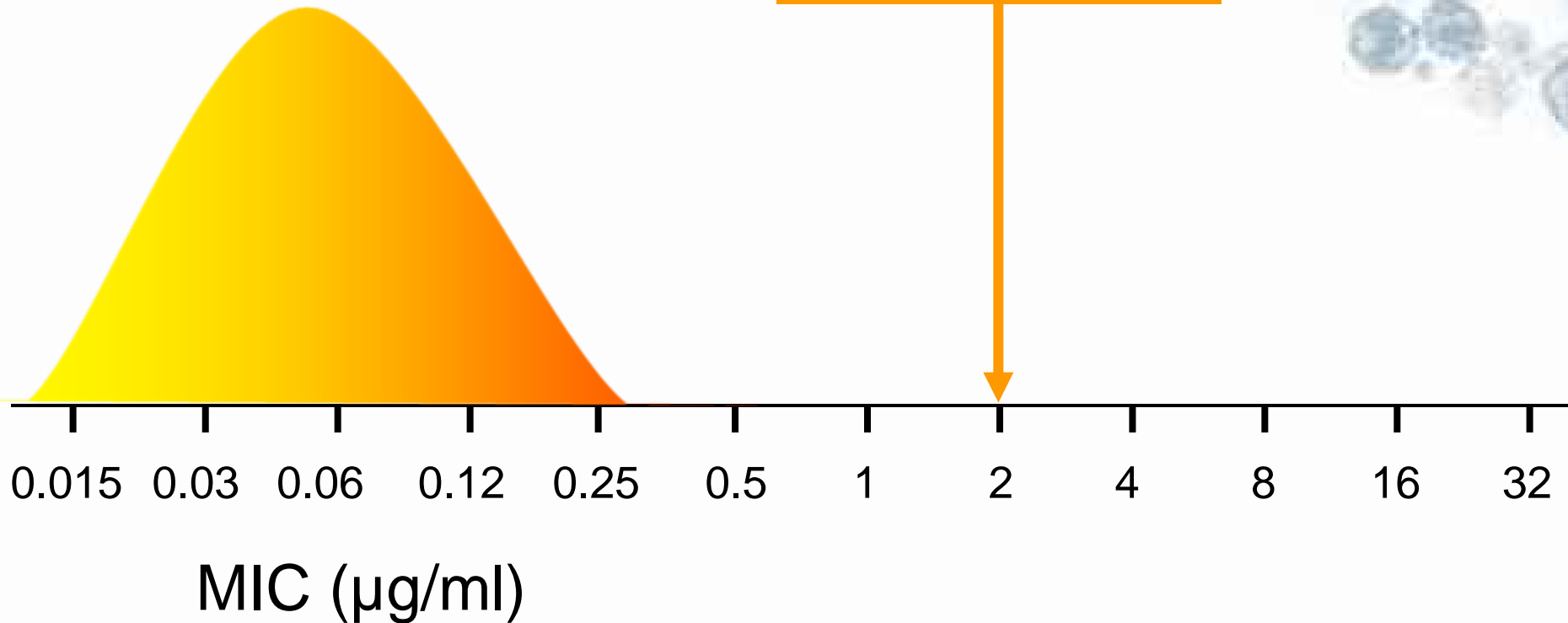 - between x and y ➔ INTERMEDIATE
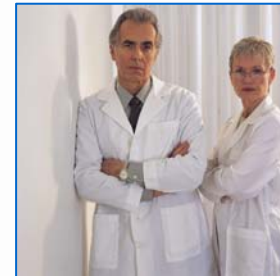
which is what the clinician will get…

_____

[1] may be converted into an MIC (see later); automatic machines use growth rates…

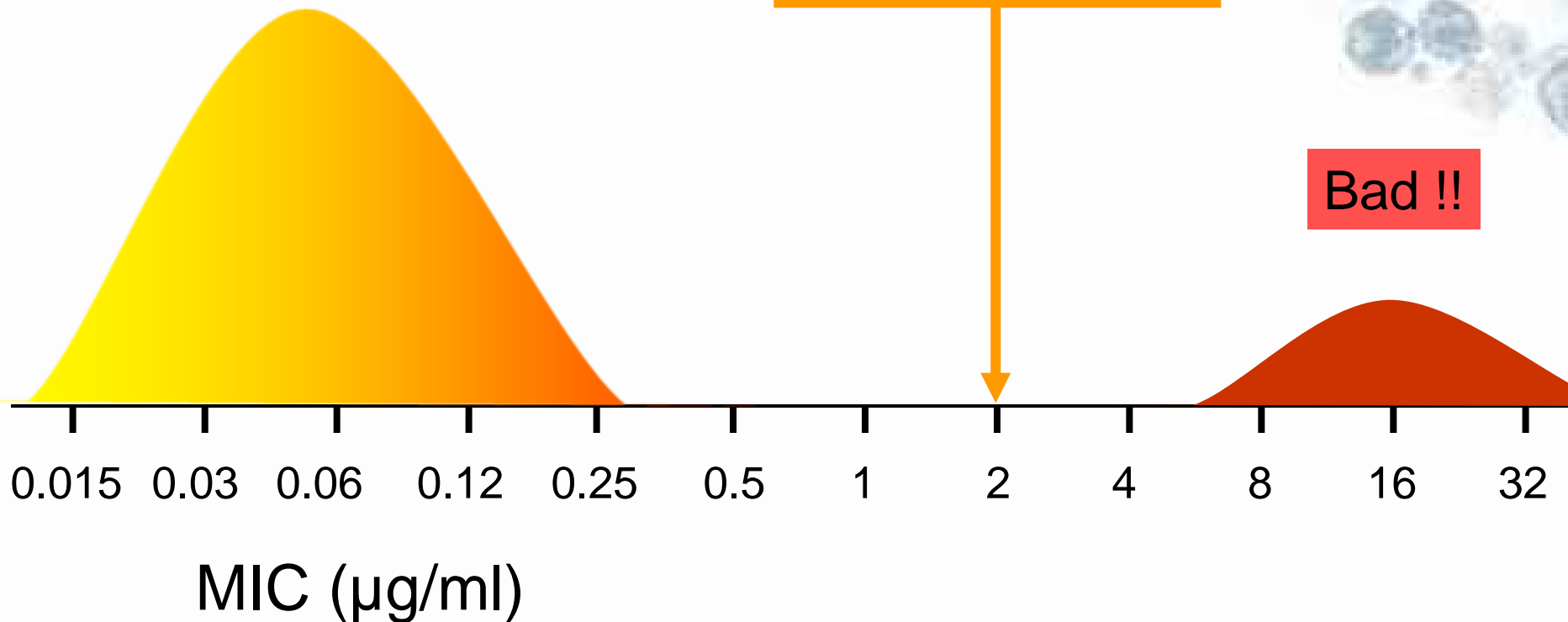# But, what is susceptible ?

Good !! Easy...

serum concentration

0.015 0.03 0.06 0.12 0.25 0.5 1 2 4 8 16 32

MIC (µg/ml)

But, what is resistant ?

Still Easy...

Good !!

serum concentration

Bad !!

MIC (µg/ml)

| 0.015 | 0.03 | 0.06 | 0.12 | 0.25 | 0.5 | 1 | 2 | 4 | 8 | 16 | 32 |

And what do you do with this ?

No longer so easy...

serum concentration

May be?

MIC (µg/ml)

0.015 0.03 0.06 0.12 0.25 0.5 1 2 4 8 16 32
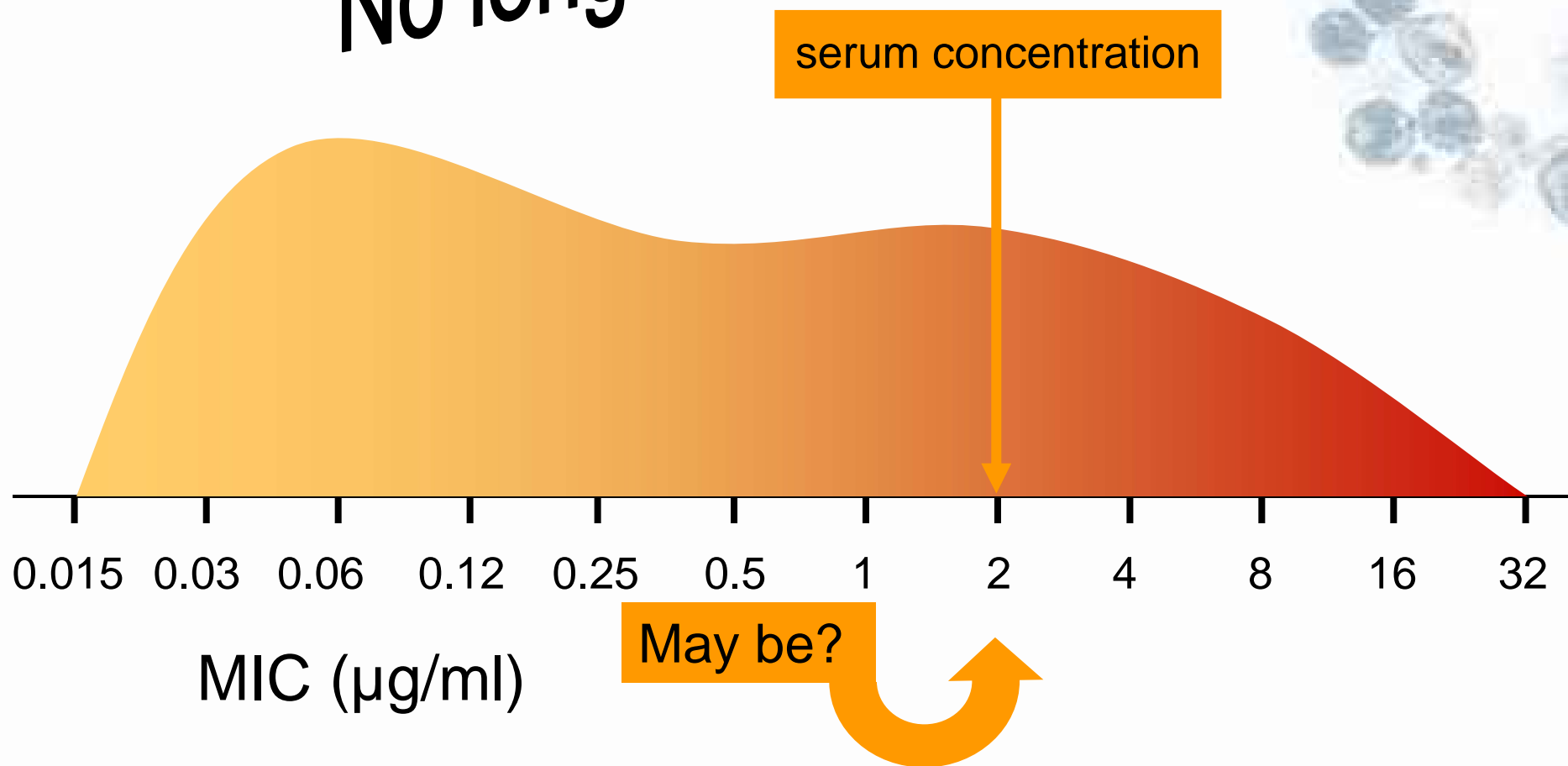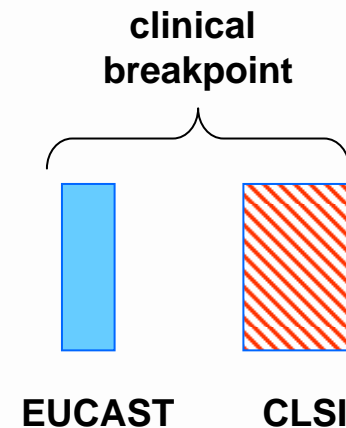
If you do not believe me…

MIC distribution of clarithromycin for *S. pneumoniae* from confirmed clinical cases of CAP in Belgium (2004-2009; n=239; 7 hospitals)
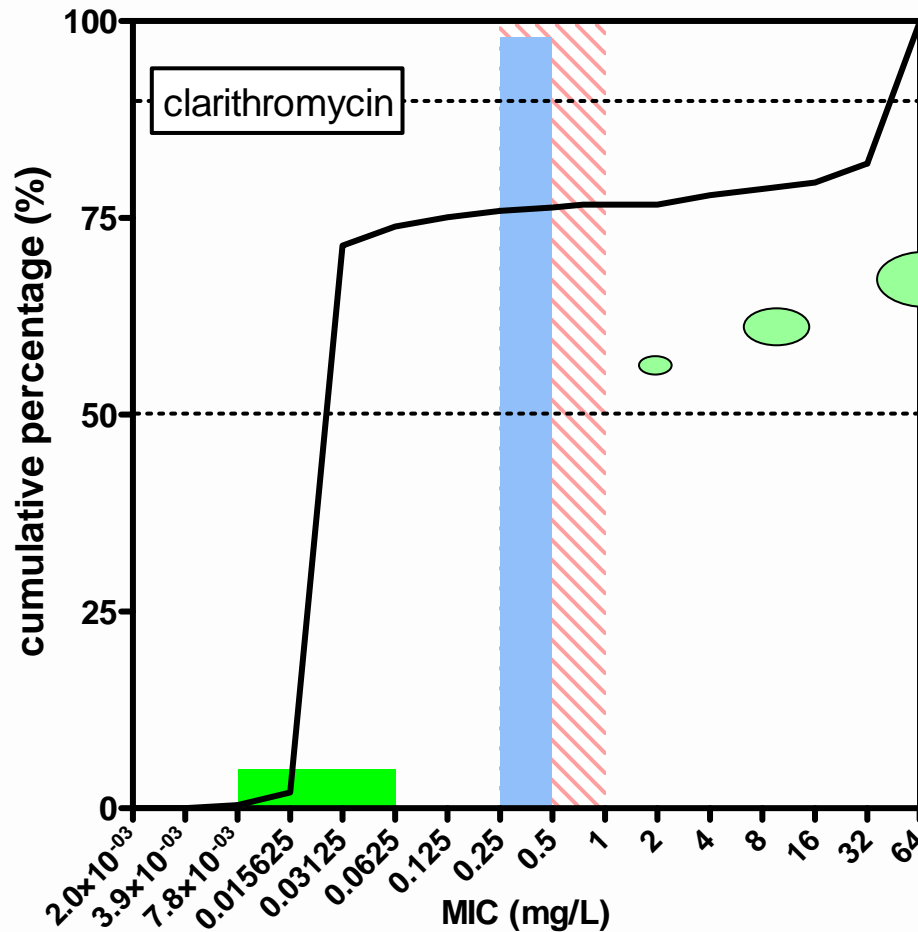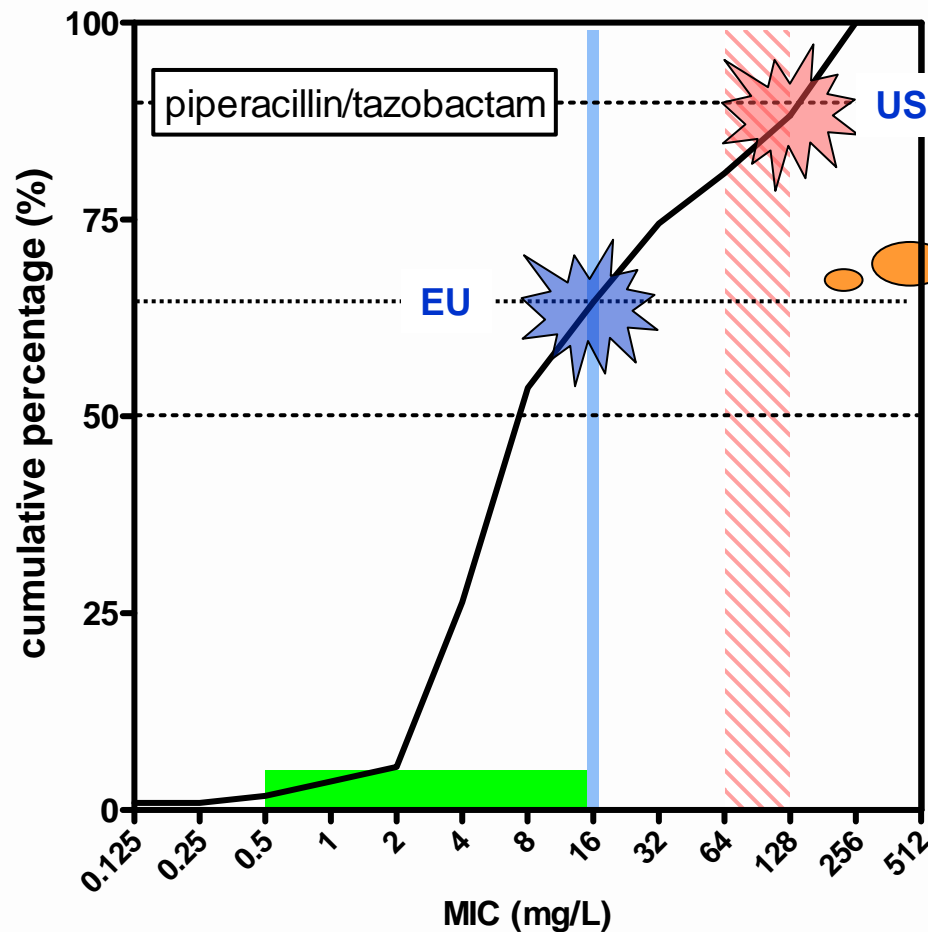

Susceptibility is largely a "yes/no" situation (an accurate breakpoint value is relatively unimportant)

clinical breakpoint

EUCAST   CLSI

"wild type" population

Lismond et al., IJAA 2012; 39:208-216

If you do not believe me…

MIC distribution of piperacillin-tazobactam for *P. aeruginosa* from confirmed clinical HAP in Belgium (2005-2009; n=90; 5 hospitals)

The population spreads over a wide range of MIC values. A correct breakpoint is critical
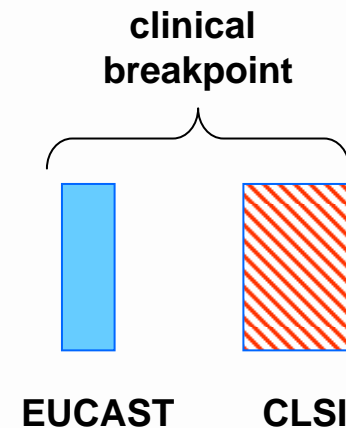
"wild type" population

Data from Riou et al. IJAA (2010) 36:513-522
Presented as by Lismond et al., IJAA 2012; 39:208-216

Another example from Belgium…

MIC distribution of *P. aeruginosa in Leuven, Belgium, for fluroquinolones*
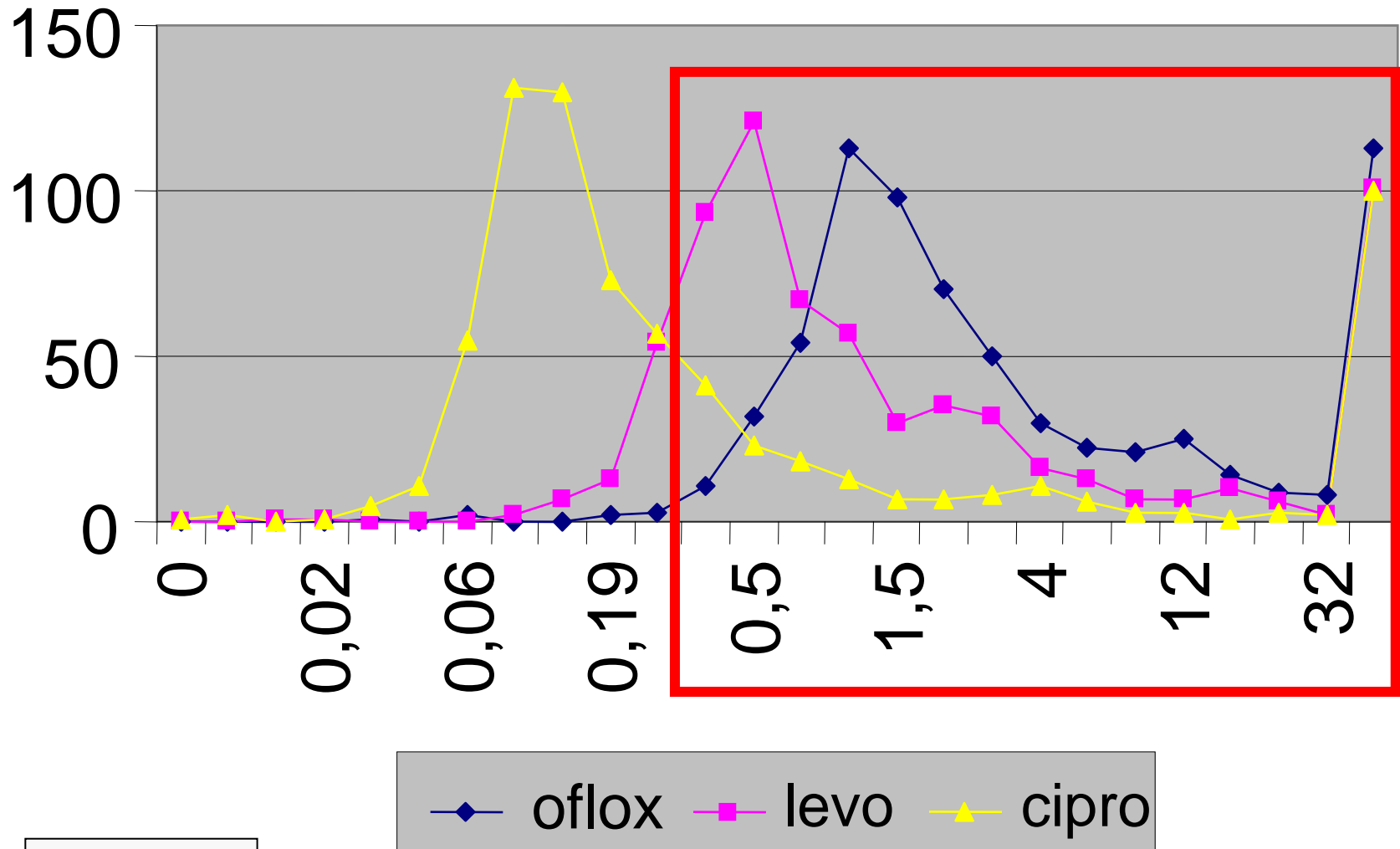
J. van Eldere, 2003

Where should the breakpoint be ?

Where should the breakpoint be ?

peak

concentration

piperacillin in the US: 64 µg/ml

area under the curve

trough

azithromycin in France: 0.25 µg/ml

time
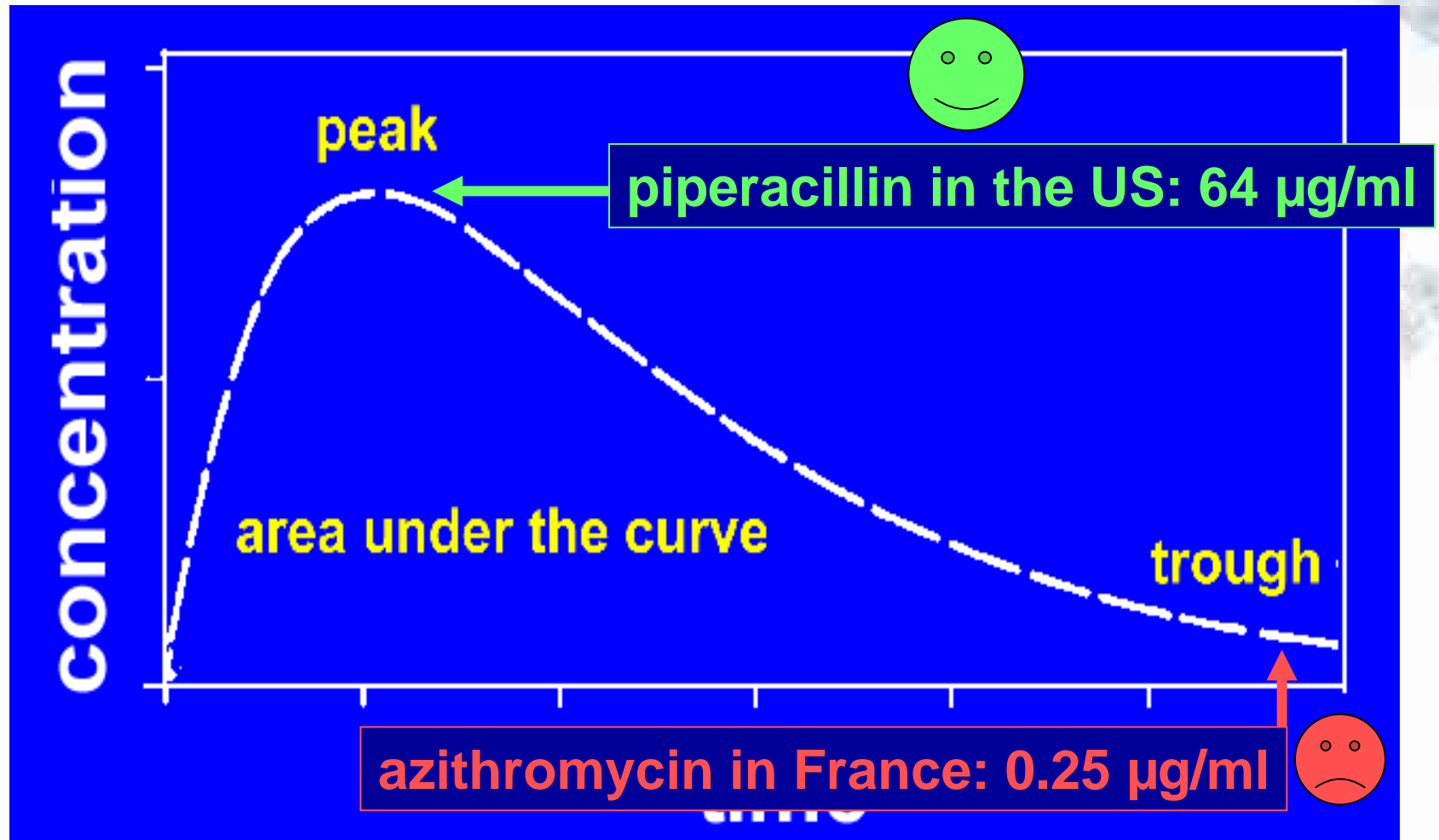
And there were fierce battles in Europe…

From Mouton, 8th ISAP symposium, Nijmegen, 2001

A simple example of European diversity…

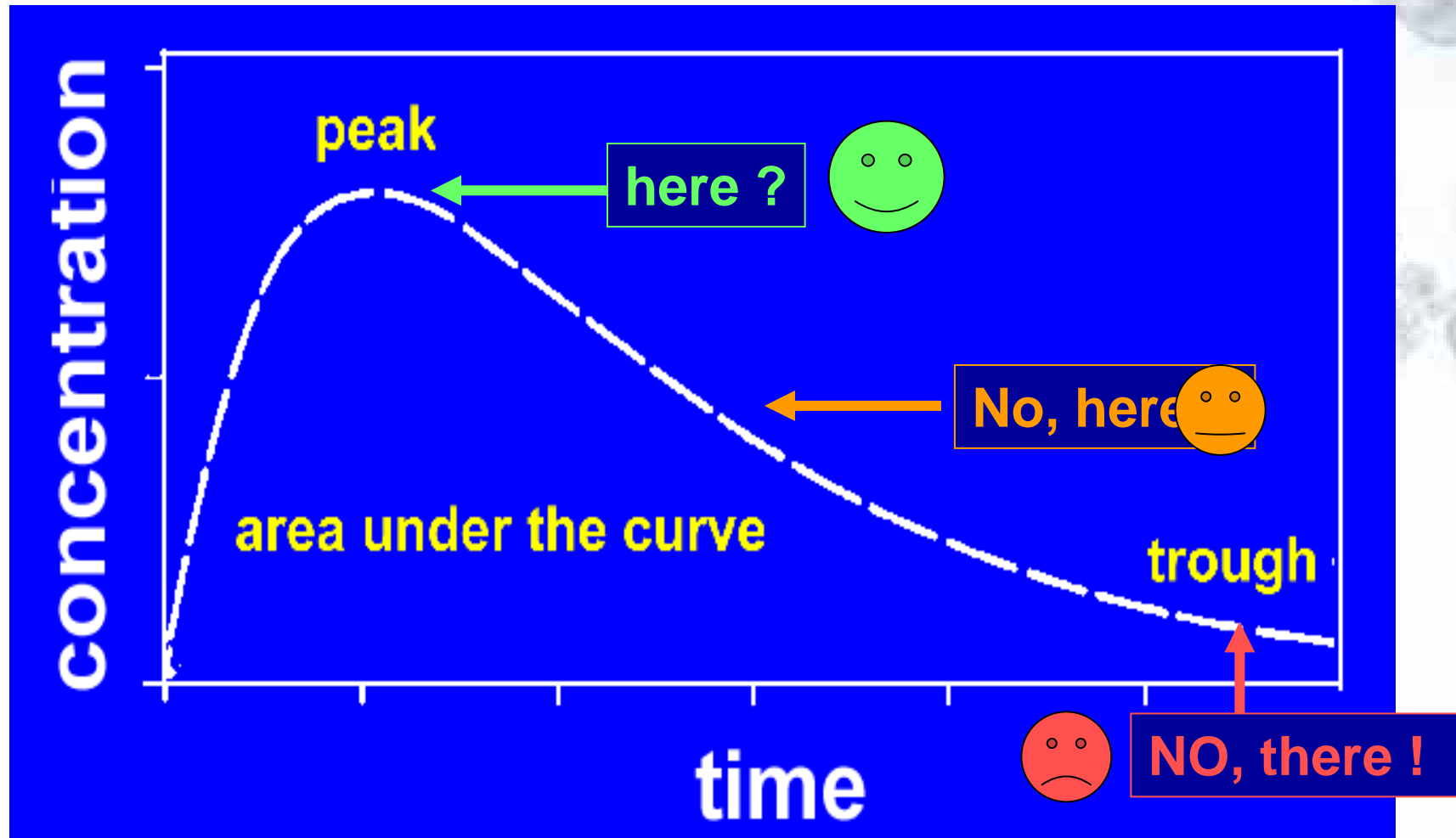| cefotaxime *vs. E. coli*		$S\leq$ / R
BSAC	United Kingdom	2 / $\geq$4
CA-SFM	France	4 / >32
CRG	The Netherlands	4 / >16
DIN	Germany	2 / $\geq$16
NWGA	Norway	1 / $\geq$32
SRGA	Sweden	0.5 / $\geq$2

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 …

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

The
"filet américain"
attitude *

_____
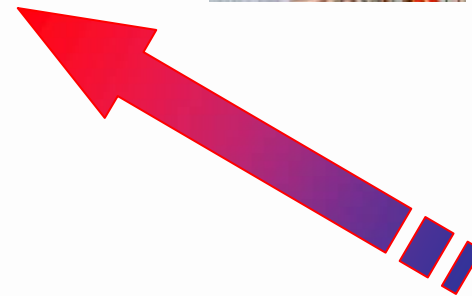
* baguette with raw chopped 100% pure beef

A simple decision …

Now, the clinician can treat all patients
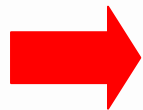
NCCLS / CLSI	U.S.A.	8 / $\geq$ 64

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 must pay for …

- Limited access to the decision process for non-US persons …

- Decisions <u>based on proposals made by Industry…</u>

- Guidelines and recommendations for testing not necessarily applicable specifically where you are…

- Antibiotics <u>not registered for use in the US may not be included and/or fully studied</u>

- Revision process not always as effective as it could be…

- **For certain antibiotics, CLSI breakpoints have been notoriously too high**

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Cons

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- **For certain antibiotics, CLSI breakpoints have been notoriously too high**

simple "cause to effect" relationship

An example of (probably) too high CLSI breakpoints

| Drug | Typical daily dosage[a] | Typical PK values | | Proposed PK/PD upper limit | | Breakpoints (mg/L)[d] |
		C_{max} in mg/L total/free (dose)	AUC_{24h} (mg × h/L) total/free	Efficacy[b]	Prevention of resistance[c]	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[j]
Ciprofloxacin	1000 mg	2.5/1.75 (500 mg PO)	24/18	0.2–0.8	0.2	≤1/2/>4[k]
Ofloxacin	400 mg	4/3 (400 mg PO)	40/30	0.3–0.9	0.4	≤2/4/8[l]
Levofloxacin	500 mg	4/2.8 (500 mg PO)	40/28	0.3–0.9	0.3	≤2/4/8[l]
Moxifloxacin	400 mg	3.1/1.8 (400 mg PO)	35/21	0.2–0.7	0.2	≤1/2/4[m]

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 <u>after</u> 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) <u>by the CLSI representative</u>

Two important changes 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 <u>disk-based assay</u> have been fully released by EUCAST in 2010

Two important changes 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
PUBLIC		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.

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; renewed an put under the umbrella of the E-CDC since 2008)**

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 (ECoff)

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

EUCAST — EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

- Organization
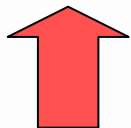- EUCAST News
- Clinical breakpoints
- Expert rules
- Setting breakpoints
- **MIC distributions**
- Zone diameter distributions

The European Committee on Antimicrobial Susceptibility Testing - EUCAST

EUCAST MIC distributions

EUCAST MIC distributions

EUCAST MIC distributions

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

Antimicrobial wild type distributions of microorganisms

Search

Method: ● MIC ○ Disk diffusion

Antimicrobial: [Antimicrobial... ▼]   Species: [Escherichia coli ▼]   Disk content: [Disk content... ▼]

Elements per page: [50 ▼]

Species: Escherichia coli (**Method:** MIC)

MIC 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]

	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	S≤	R>	ECOFF≤
Amikacin	0	0	0	2	1	1	8	46	153	1635	5440	2659	648	174	59	37	4	5	45	8.0	16.0	8.0
Amoxicillin	0	0	0	0	0	0	0	0	9	96	737	1670	669	42	11	692	600	58	693	8.0	8.0	8.0
Amoxicillin-clavulanic acid	0	0	0	0	0	0	4	4	34	1026	8970	19912	15313	7157	2931	524	330	577	65	8.0	8.0	8.0
Ampicillin	0	0	0	0	0	0	1	13	84	1845	10572	11331	2181	423	570	3796	1534	6683	187	8.0	8.0	8.0
Ampicillin-sulbactam	0	0	0	0	0	0	6	11	71	393	2935	1949	744	1998	1605	1085	0	0	0	8.0	8.0	8.0
Aztreonam	0	0	0	4	1103	1085	613	132	36	17	22	37	25	21	36	58	0	3	0	1.0	4.0	0.25
Cefaclor	0	0	0	0	0	0	0	2	31	60	25	22	3	0	4	2	0	1	0	ND	ND	4.0
Cefadroxil	0	0	0	0	0	0	0	0	0	0	0	8	27	7	2	1	3	2	0	16.0	16.0	16.0
Cefalexin	0	0	0	0	0	0	0	0	1	0	7	77	18	2	0	1	3	5	0	16.0	16.0	16.0
Cefalothin	0	0	0	0																		
Cefazolin	0	0	0	0																		
Cefepime	0	0	113	245																		
Cefixime	0	0	3	4																		
Cefoperazone	0	0	0	0																		
Cefotaxime	0	5	40	282																		

	0.002	0.004	0.008	0.016	0																	
Cefotaxime-clavulanate	0	0	15	128																		
Cefoxitin	0	0	0	0																		
Cefpirome	0	0	1	233																		
Cefpodoxime	0	0	0	0																		
Ceftazidime	0	0	21	53	243	1671	5422	5294	1229	329	201	141	137	146	141	79	25	25	5	1.0	4.0	0.5
Ceftazidime-clavulanate	0	0	60	52	193	572	909	753	178	49	56	30	41	17	9	17	2	1	0	ND	ND	0.5
Ceftibuten	0	0	2	7	23	693	1132	1412	309	76	21	13	26	66	0	0	0	1	0	1.0	1.0	1.0
Ceftiofur	0	0	0	0	0	0	5	568	1920	236	2	0	0	0	0	0	0	0	0	ND	ND	1.0
Ceftriaxone	0	0	28	144	455	186	14	5	3	2	2	2	2	0	3	0	0	0	0	1.0	2.0	0.125
Cefuroxime	0	0	1	1	1	5	93	161	1475	4624	20855	46657	14450	3200	3799	263	260	98	73	8.0	8.0	8.0
Chloramphenicol	0	0	0	0	0	0	0	0	0	2	350	4944	5102	389	210	87	387	254	0	8.0	8.0	16.0
Ciprofloxacin	14	189	3967	7300	1576	613	566	599	196	113	55	131	263	236	565	168	85	59	7	0.5	1.0	0.064
Colistin	0	0	0	0	0	243	255	2064	3074	773	143	21	13	52	7	1	30	0	0	2.0	2.0	2.0
Doripenem	0	0	6	1956	3383	213	23	12	3	3	0	3	0	0	0	0	0	0	0	1.0	4.0	0.125
Doxycycline	0	0	0	0	0	0	1	25	192	675	713	286	685	585	422	65	3	1	0	ND	ND	4.0

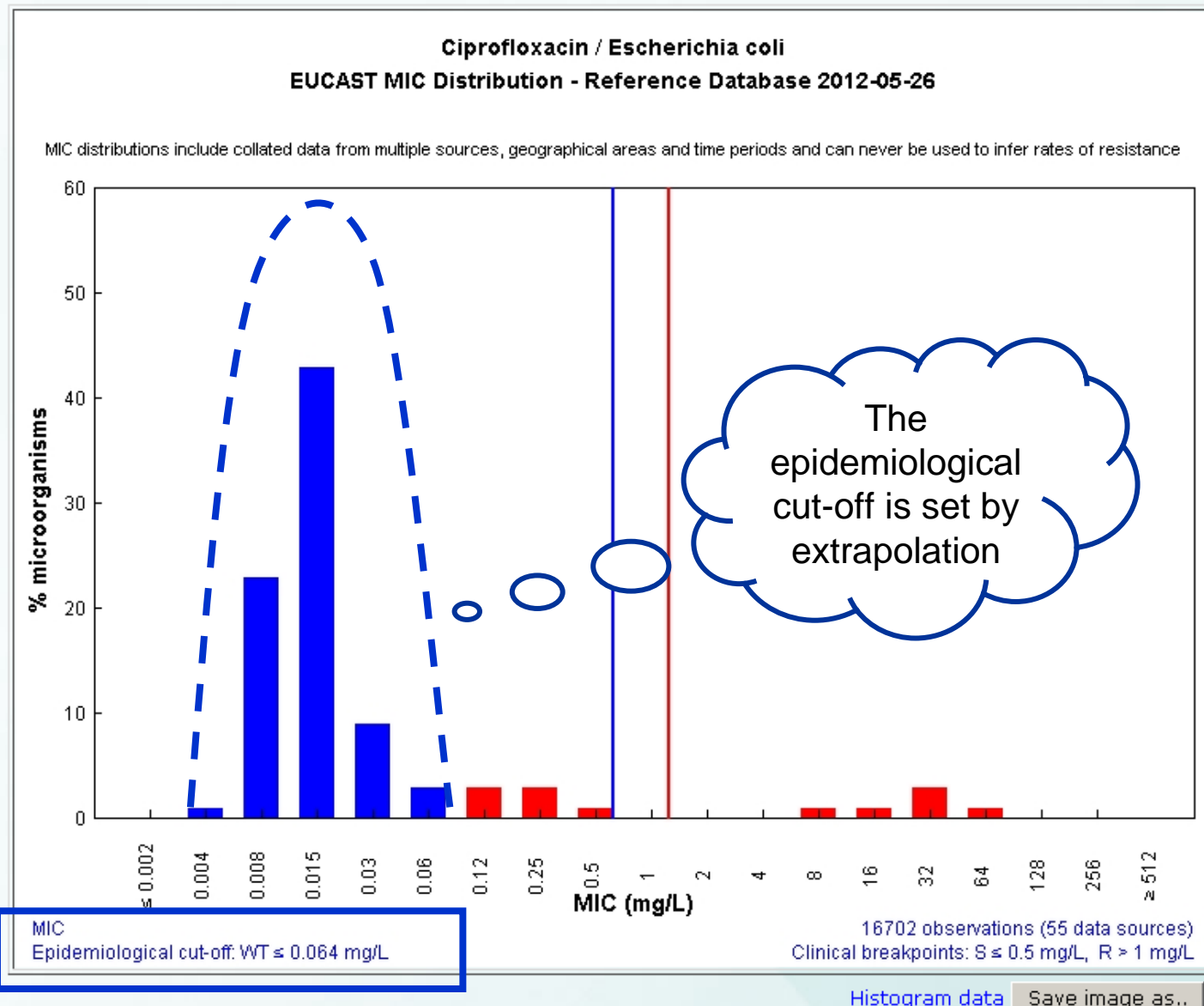**Click on any antibiotic (or species) in the left hand column to display the data as a bar chart, with EUCAST epidemiological cut-off values and harmonised European clinical breakpoints.**

Read the epidemiological cut-off

Use of EUCAST wild type MIC distributions and epidemiological cut-off

The wild type MIC distributions provide

1. reference material 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**

Moving to clinical breakpoints …

which is what the clinician will get… *

But why not giving her / him an MIC ?

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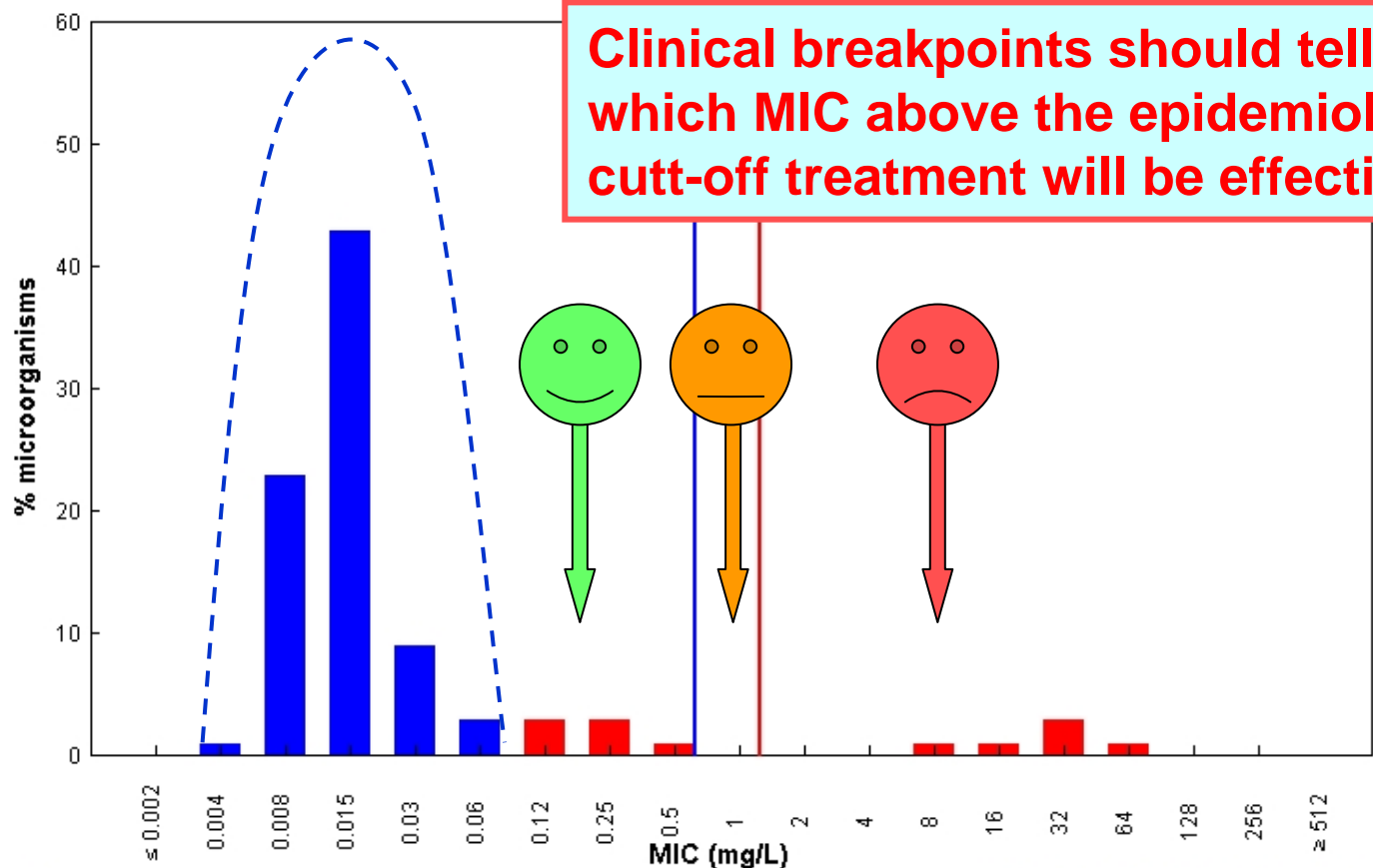
a microorganism is categorized as S, I or R by applying the appropriate breakpoint in a defined phenotypic test system

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
EUCAST MIC Distribution - Reference Database 2012-05-26

Clinical breakpoints should tell to which MIC above the epidemiological cutt-off treatment will be effective ....

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 <u>pertinent</u> 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
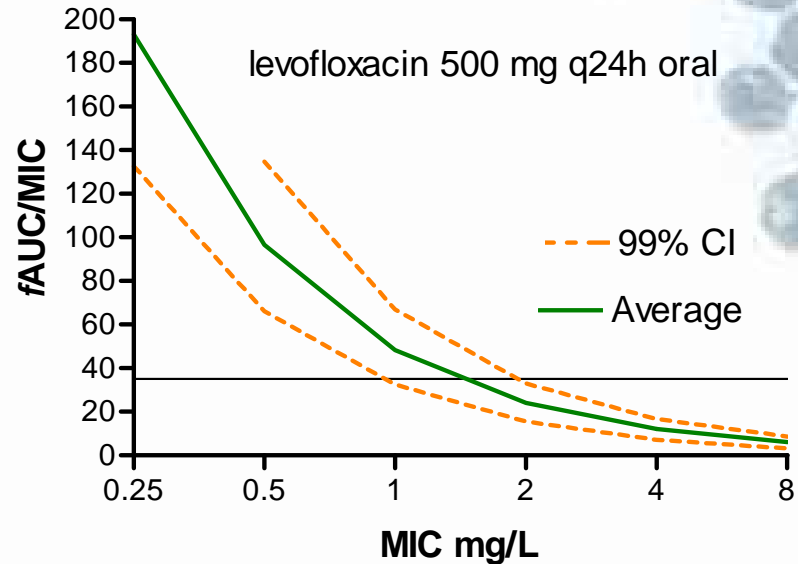- The efficacy of the drugs is assessed quantitatively.

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

ciprofloxacin 500 mg q12h oral
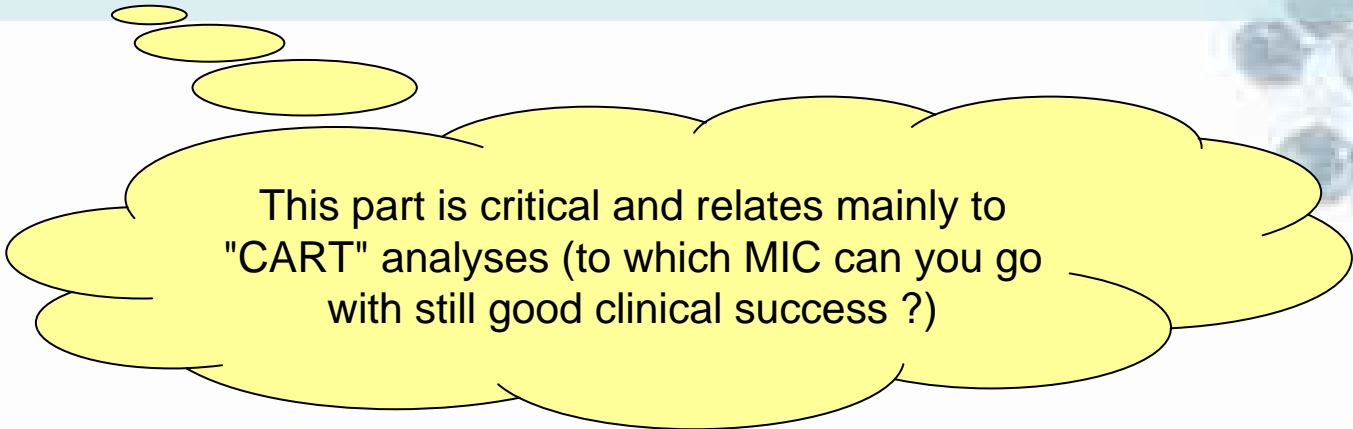
levofloxacin 500 mg q24h oral
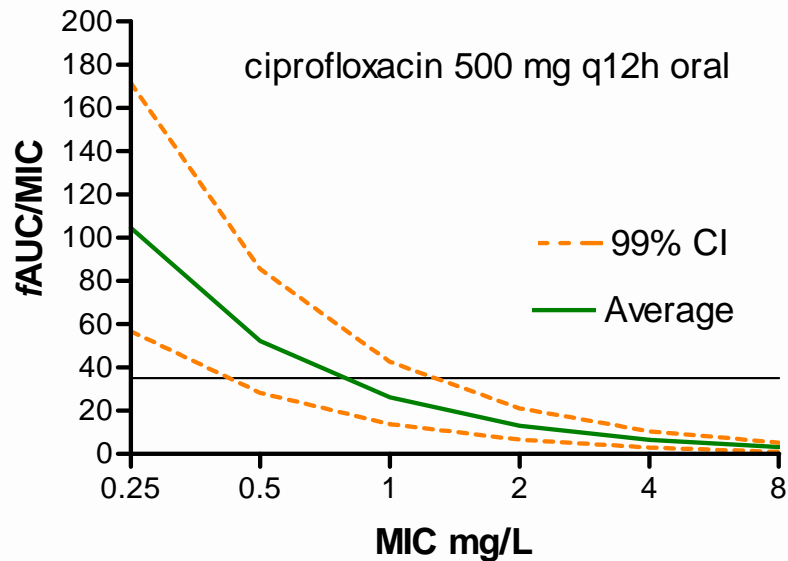
Pk/Pd

S = 0.5 mg/L

S = 1 mg/L

EUCAST method of determining clinical breakpoints

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

This part is critical and relates mainly to "CART" analyses (to which MIC can you go with still good clinical success ?)
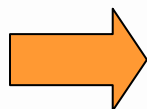
"Minimum requirement for S-category" is that the highest MIC value of the wild type MIC-distribution is consistent with the MIC derived from the PK/PD index needed for optimal efficacy based on free drug.

Important caveat for new drugs

Minium requirement and tigecycline as an example

Tigecycline / Escherichia coli
EUCAST MIC Distribution - Reference Database 2012-05-26

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

The S breakpoint is at the limit of the highest value of the wild type distribution that also corresponds to the limit of the PK/PD target attainment rate

MIC
Epidemiological cut-off: WT ≤ 1 mg/L

4238 observations (15 data sources)
Clinical breakpoints: S ≤ 1 mg/L, R > 2 mg/L

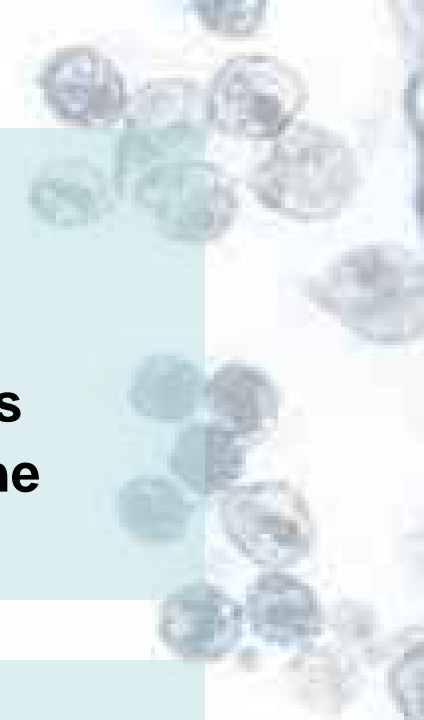# EUCAST method of determining clinical breakpoints

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

The levofloxacin dilemma …

Levofloxacin / Streptococcus pneumoniae
EUCAST MIC Distribution - Reference Database 2012-05-26

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

But the PK/PD breakpoint for 500 mg/day is 1

Epidemiological cut off is 2

Splitting the wild type must be avoided to permit reproducible susceptibility testing!

… thus the breakpoint was moved to 2 mg/L with a footnote that this was based on high dose therapy.

MIC
Epidemiological cut-off: WT ≤ 2 mg/L

85464 observations (17 data sources)
Clinical breakpoints: S ≤ 2 mg/L, R > 2 mg/L

**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

http://www.eucast.org

EUCAST breakpoints are freely available

And here are the results…

Enterobacteriaceae

Fluoroquinolones	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Ciprofloxacin[1]	0.5	1	5	22	19
Levofloxacin	1	2	5	22	19
Moxifloxacin	0.5	1	5	20	17
Nalidixic acid (screen)	Note[2]	Note[2]	30	16[A]	16[A]
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[a]	Typical PK values		Proposed PK/PD upper limit of sensitivity (µg/ml) for	
		C_{max} in mg/L total/free (dose)	AUC_{24h} (mg × h/L) total/free	Efficacy[l]	
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**

EUCAST breakpoints

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 and carbapenems

EUCAST
EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

Carbapenems[1]	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[2]	2	8	10	22	16
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_breakpoints_v2.0.pdf

EUCAST and cephalosporins

Cephalosporins[1]	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 ..

Discrepancies EUCAST – CLSI: an example…

Vancomycin breakpoints for *S. aureus*
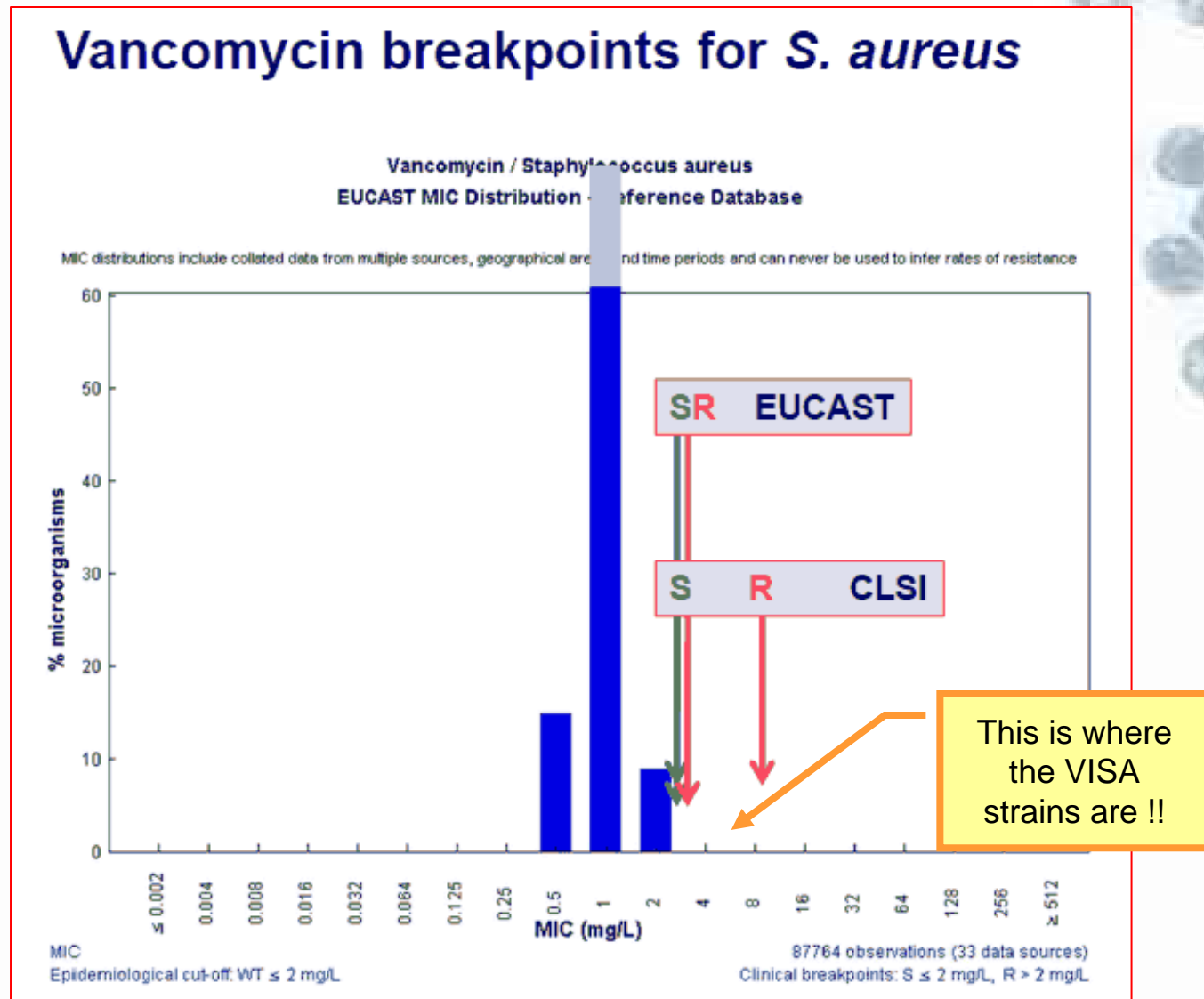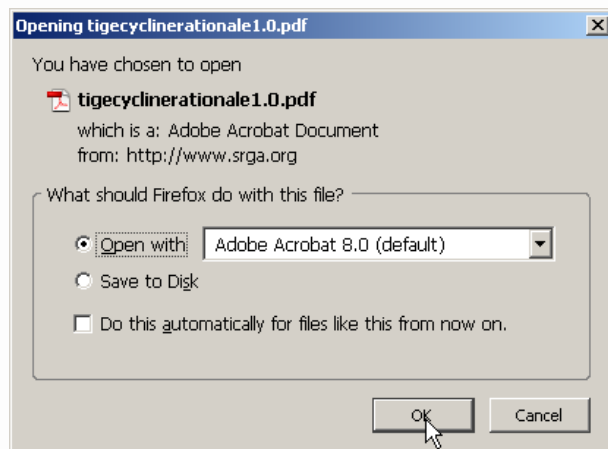
Can we have access to the rationale ?

Enterobacteriaceae

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

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

Opening tigecyclinerationale1.0.pdf

You have chosen to open

 tigecyclinerationale1.0.pdf
  which is a: Adobe Acrobat Document
  from: http://www.srga.org

What should Firefox do with this file?

⦿ Open with [Adobe Acrobat 8.0 (default) ▾]
○ Save to Disk

☐ Do this automatically for files like this from now on.

[OK] [Cancel]

What methodology do you need to use ?

- You should have an MIC…

  - Set your system to get one !

    - Microdilution (ISO method)

    - E-test (calibrate !)

    - Automatic system (not all are good…)

- But we know many labs still work with disks…

  - Any disk methodology can be used if you have the correlation table for values around S – R limits

    - BSAC, CA-SFM … or even CLSI (but …)

    - EUCAST sisk diffusion methodology

EUCAST susceptibility testing recommendations

X EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Organization

EUCAST News

Clinical breakpoints

Expert rules

Setting breakpoints

MIC distributions

Zone diameter distributions

Antimicrobial susceptibility testing

Disk diffusion methodology

Disk diffusion implementation

Compliance of manufacturers

Breakpoint tables

QC Tables

Calibration and validation

Guidance documents

Projects and data submission

Previous versions of tables

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing is performed with phenotypic or genotypic methods. The basis of phenotypic methods is the minimum inhibitory concentration (MIC). Clinical MIC breakpoints determine whether the organism is categorised as susceptible, intermediate or resistant to the agent in question. Other methods should be calibrated to reference MIC methods.

Users of EUCAST breakpoints should use the EUCAST disk diffusion method or other susceptibility testing systems calibrated to EUCAST breakpoints and terminology in accordance with EUCAST breakpoint tables.
For more information - 🖳 CLICK here.

- **Disk diffusion methodology**
  Detailed description of the EUCAST disk diffusion test
- **Disk diffusion implementation**
  Guidance documents on how to implement the disk diffusion test
- **Compliance of manufacturers**

http://www.eucast.org/eucast_disk_diffusion_test/

And what about manufacturers
(plates and/or automated systems)

Compliance of manufacturers

Compliance of manufacturers of susceptibility testing products with EUCAST recommendations

Preparedness of manufacturers of susceptibility testing devices and materials (updated 26 January, 2012)

Preparedness of Manufacturers offering materials and automated systems for EUCAST susceptibility testing

- Based on questionnaires to manufacturers of materials and systems for antimicrobial susceptibility testing.

- The tables will be updated when manufacturers report changes in their preparedness (contact erika.matuschek@ltkronoberg.se).

Last updated 2012-01-26

Disk/plates:
- most are ready

ATS
- Phoenix: OK
- Microscan : +/-
- bdMérieux: --
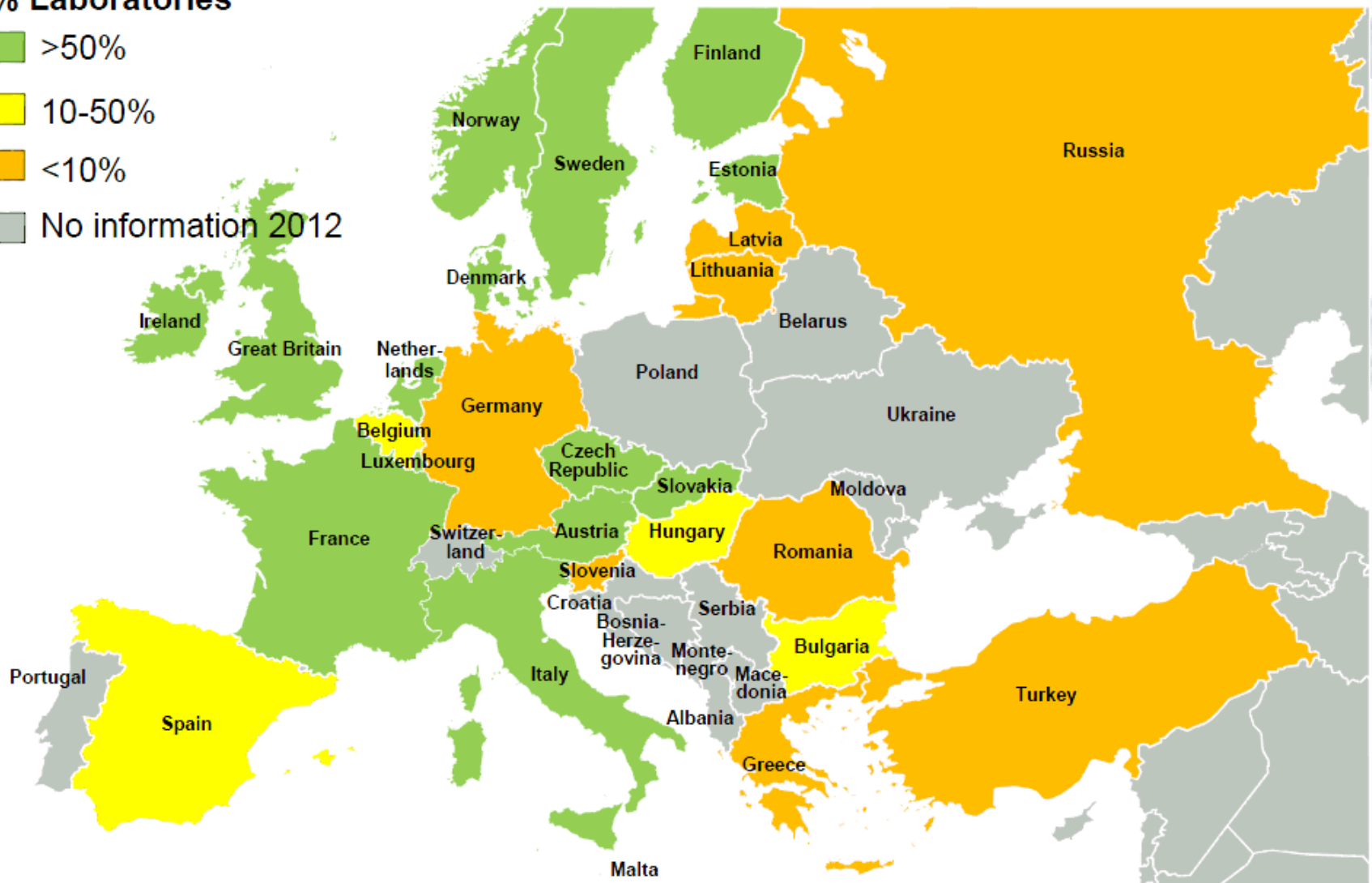
EUCAST breakpoints in Europe in 2011

% Laboratories
- 🟩 >50%
- 🟨 10-50%
- 🟧 <10%
- ⬜ No information 2012

Chairman´s presentation, General Committee meeting, 2012

EUCAST and EMA

breakpoints for new drugs with EMA

- Daptomycin   √
- Tigecycline   √
- Doripenem √
- Telavancin √
- Glycopeptides (one ongoing)
- Cephalosporins (activity against MRSA - ongoing)
- Anti-MTB (one - two agents - ongoing)

Chairman´s presentation, General Committee meeting, 2012
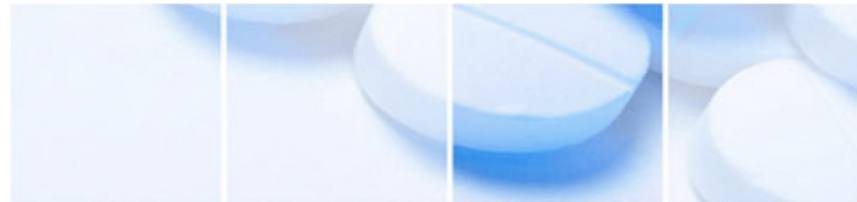
An example: doripenem (DORIBAX)

European Medicines Agency
emea
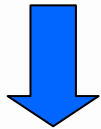
nl fr en

Andere informatie en diensten van de overheid : www.belgium.be   .be

F AFMPS G G
Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten

Uw geneesmiddelen en gezondheidsproducten, onze zorg

MENSELIJK gebruik | DIERGENEESKUNDIG gebruik

Zoeken op naam van geneesmiddel

[   ]

Zoek   Reset

Bijsluiter voor het publiek

DORIBAX 500 mg poeder voor oplossing voor infusie   FR   NL   DE

Samenvatting van de kenmerken van het product (SKP)

DORIBAX 500 mg poeder voor oplossing voor infusie   FR   NL

http://www.fagg-afmps.be/nl/

An example: doripenem (DORIBAX)

NAAM VAN HET GENEESMIDDEL

Doribax 500 mg poeder voor oplossing voor infusie

(JANSSEN-CILAG)

Drempelwaarden
Drempelwaarden voor de Minimale Inhiberende Concentratie (MIC), vastgesteld door het European Committee on Antimicrobial Susceptibility Testing (EUCAST) zijn als volgt:

Niet speciesgerelateerd	S ≤ 1 mg/l en R > 4 mg/l
Stafylokokken	afgeleid uit de drempelwaarde van methicilline
Enterobacteriacea	S ≤ 1 mg/l en R > 4 mg/l
Acinetobacter spp.	S ≤ 1 mg/l en R > 4 mg/l
Pseudomonas spp.	S ≤ 1 mg/l en R > 4 mg/l
Streptococcus spp. behalve S. pneumoniae	S ≤ 1 mg/l en R > 1 mg/l
S. pneumoniae	S ≤ 1 mg/l en R > 1 mg/l
Enterokokken	'ongeschikt doel'
Haemophilus spp.	S ≤ 1 mg/l en R > 1 mg/l
N. gonorrhoeae	onvoldoende bewijs
Anaeroben	S ≤ 1 mg/l en R > 1 mg/l

DORIBAX_500_mg_poeder_voor_oplossing_voor_infusie.pdf

EUCAST at the corner of your street

Countries are encouraged to form National AST Committees (NAC).

- **Antimicrobial susceptibility testing**
  - Strategy at national level
  - Implementation of breakpoints and methods
  - Education (national workshops, websites)
  - Liaison and consultation with EUCAST (chairman or scientific secretary GC representative)
  - Liaison with groups involved in AMR-surveillance (ECDC, EARSS, ...).
  - QA

Chairman´s presentation, General Committee meeting, 2012

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 reports
- http://www.facm.ucl.ac.be
  - This lecture and many others

ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES
PK/PD of Anti-Infectives Study Group

EUCAST

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