EUCAST breakpoints

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

UCL

EUCAST

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

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 → Lectures**

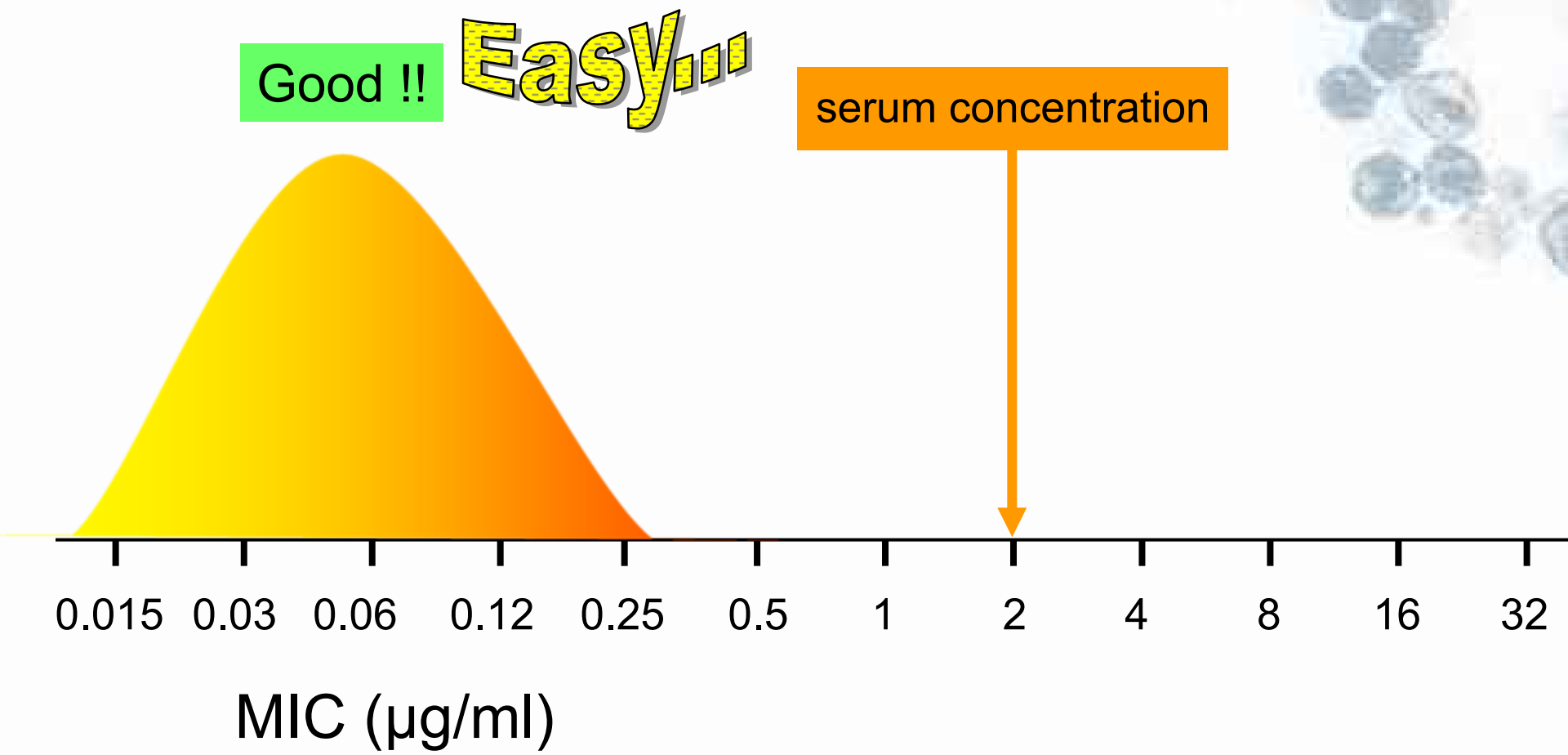
What are breakpoints ?

- 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 [1] 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…

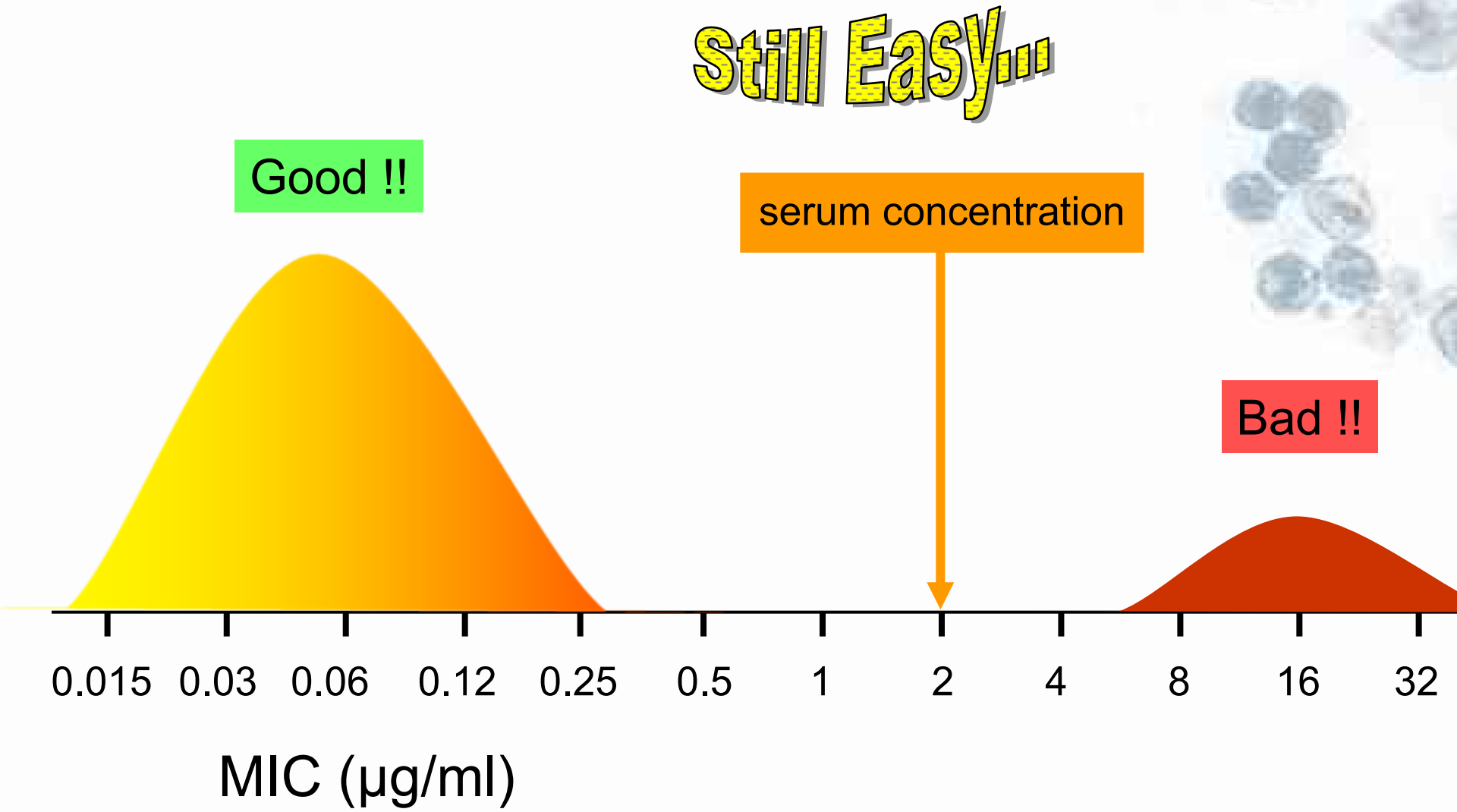
[1] may be converted into an MIC (see later); automatic machines use growth rates…

But, what is susceptible ?



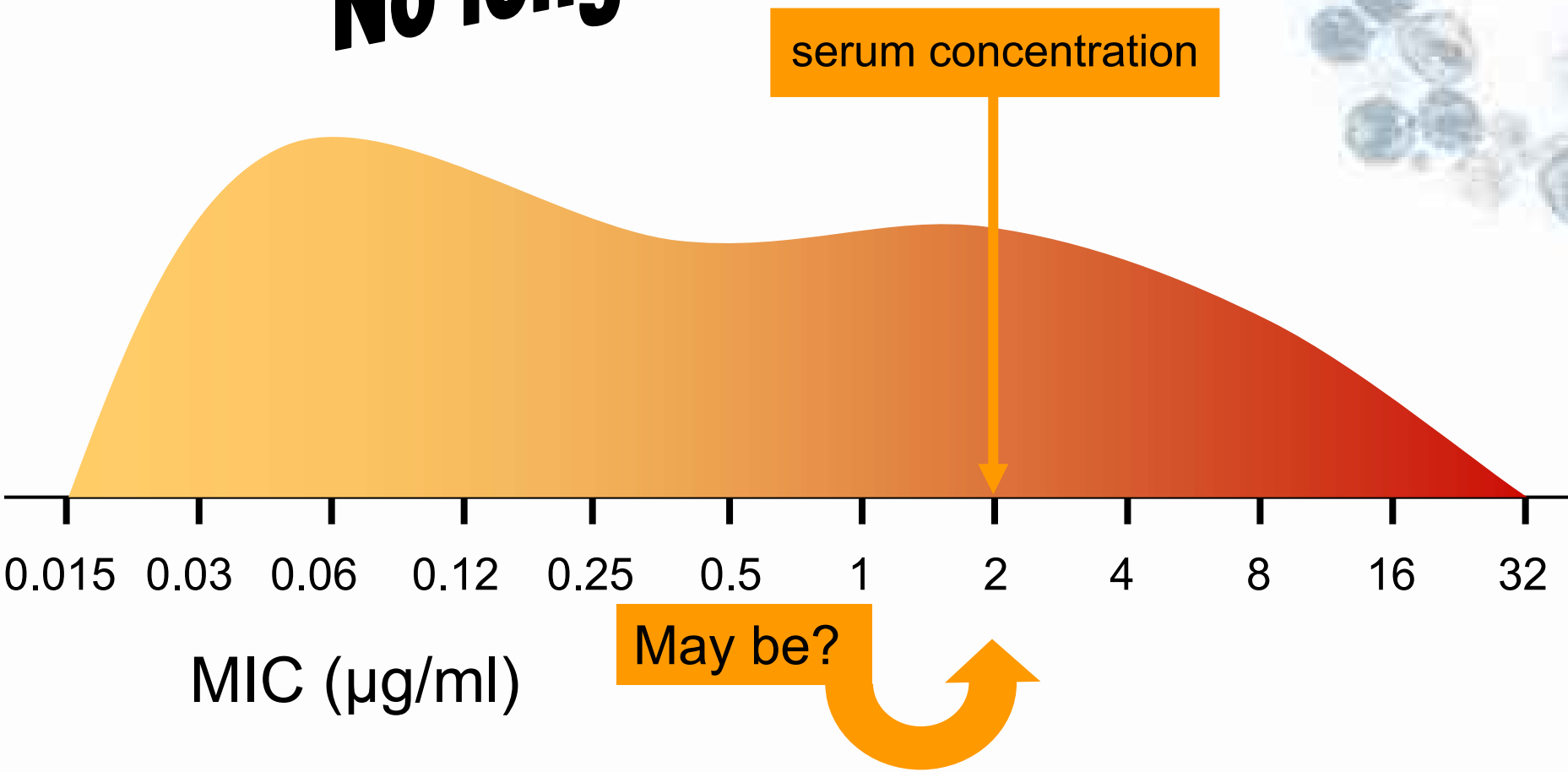
But, what is resistant ?

Still Easy...



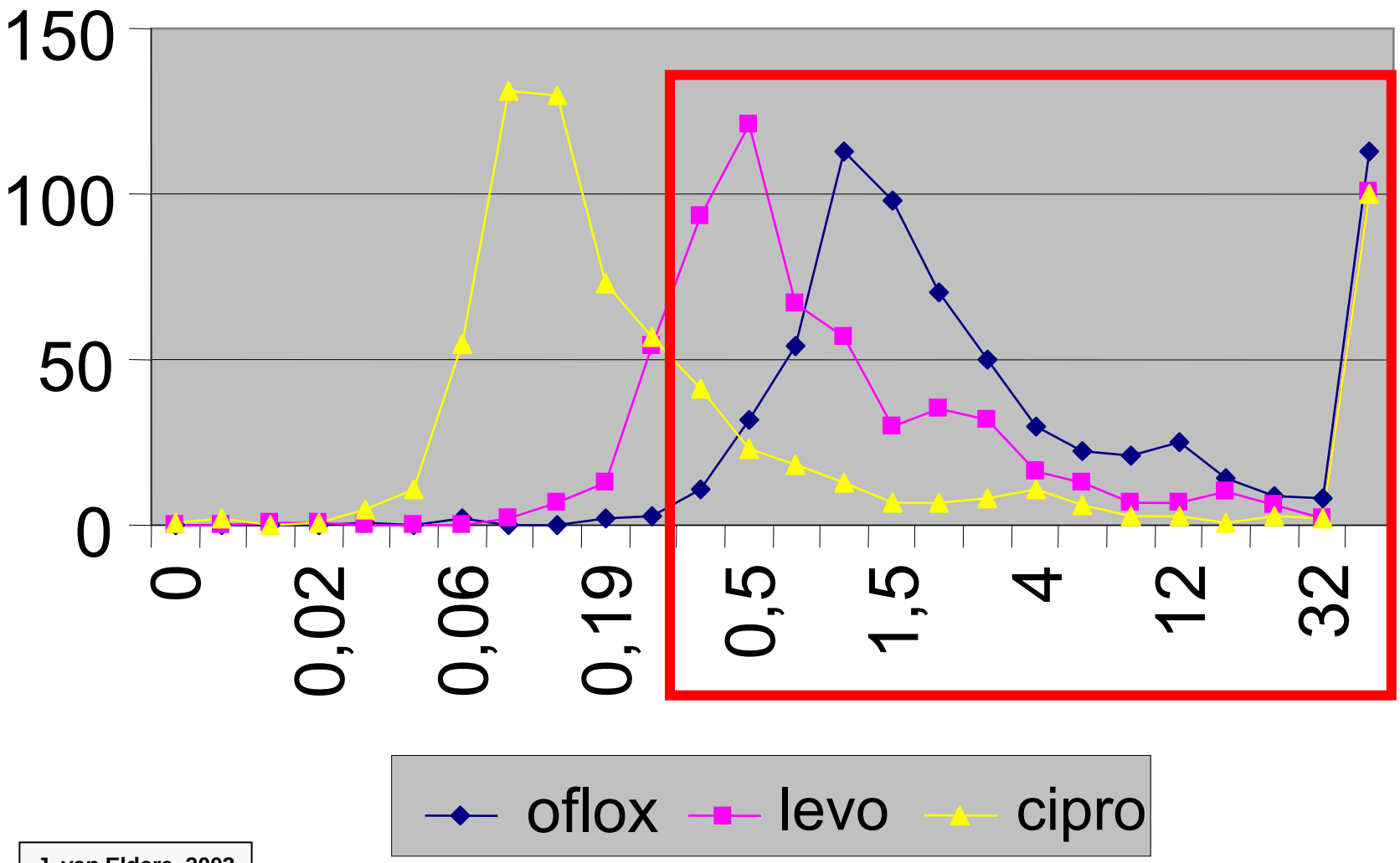
And what do you do with this ?

No longer so easy...



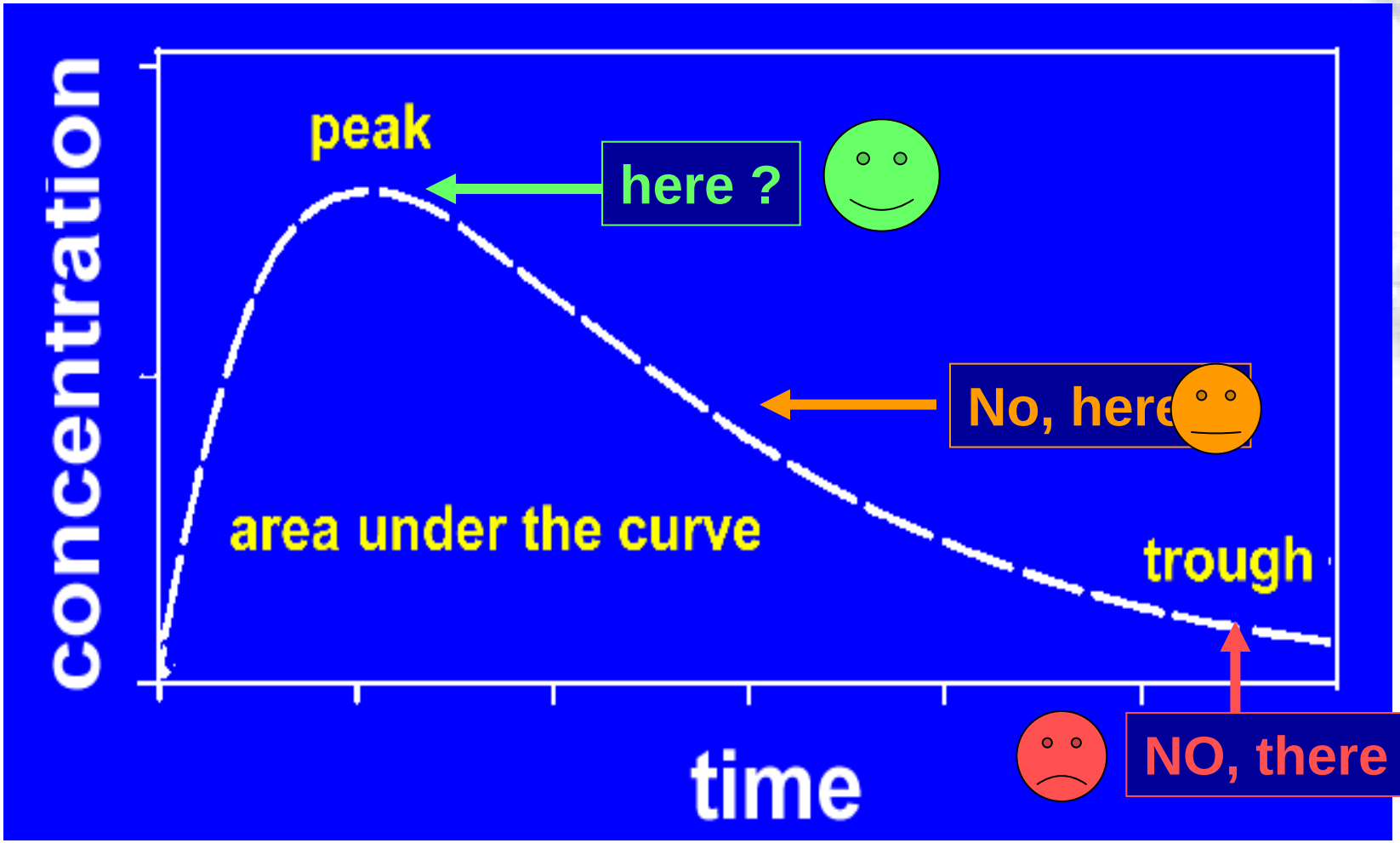
If you do not believe me…

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

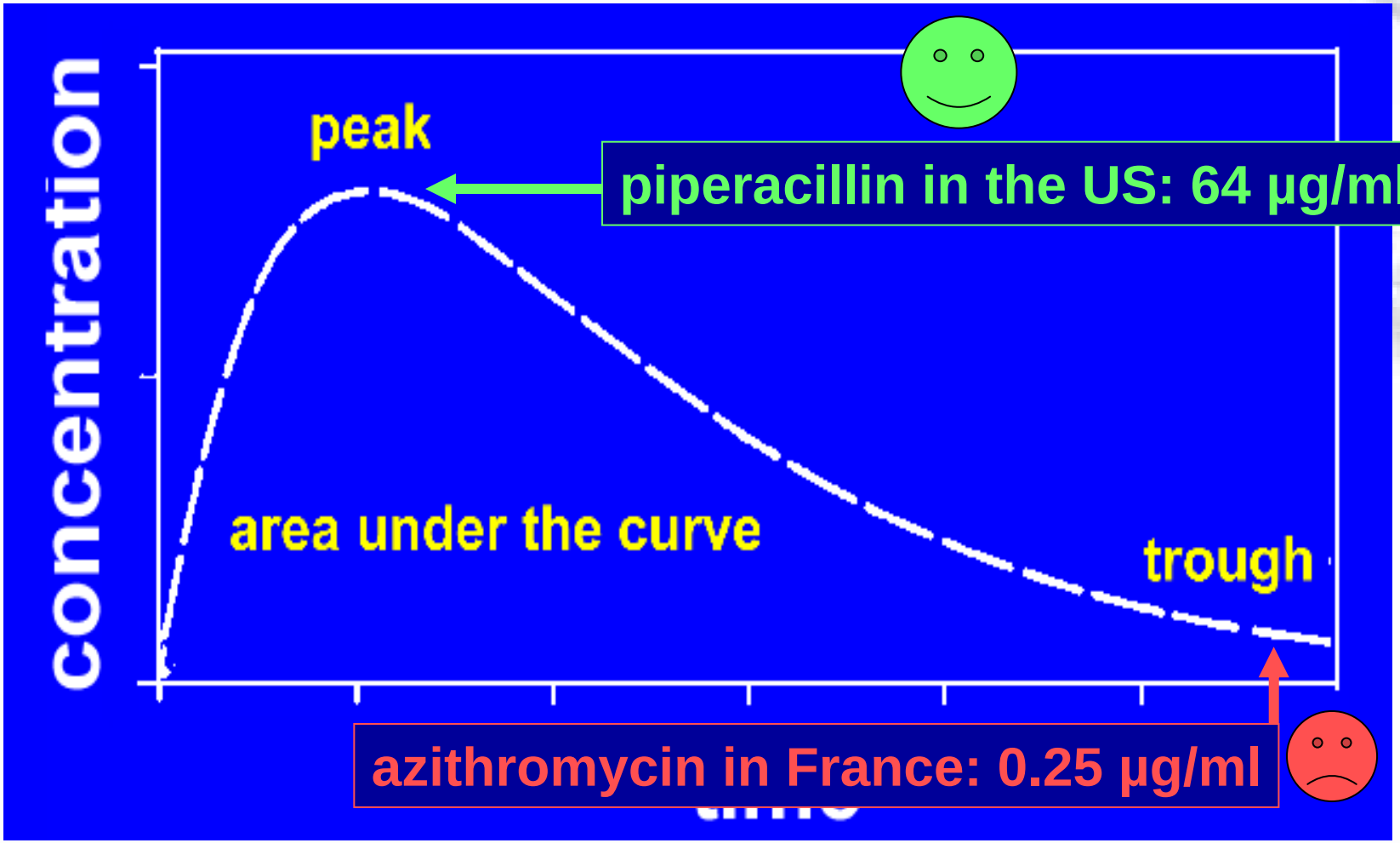


J. van Eldere, 2003

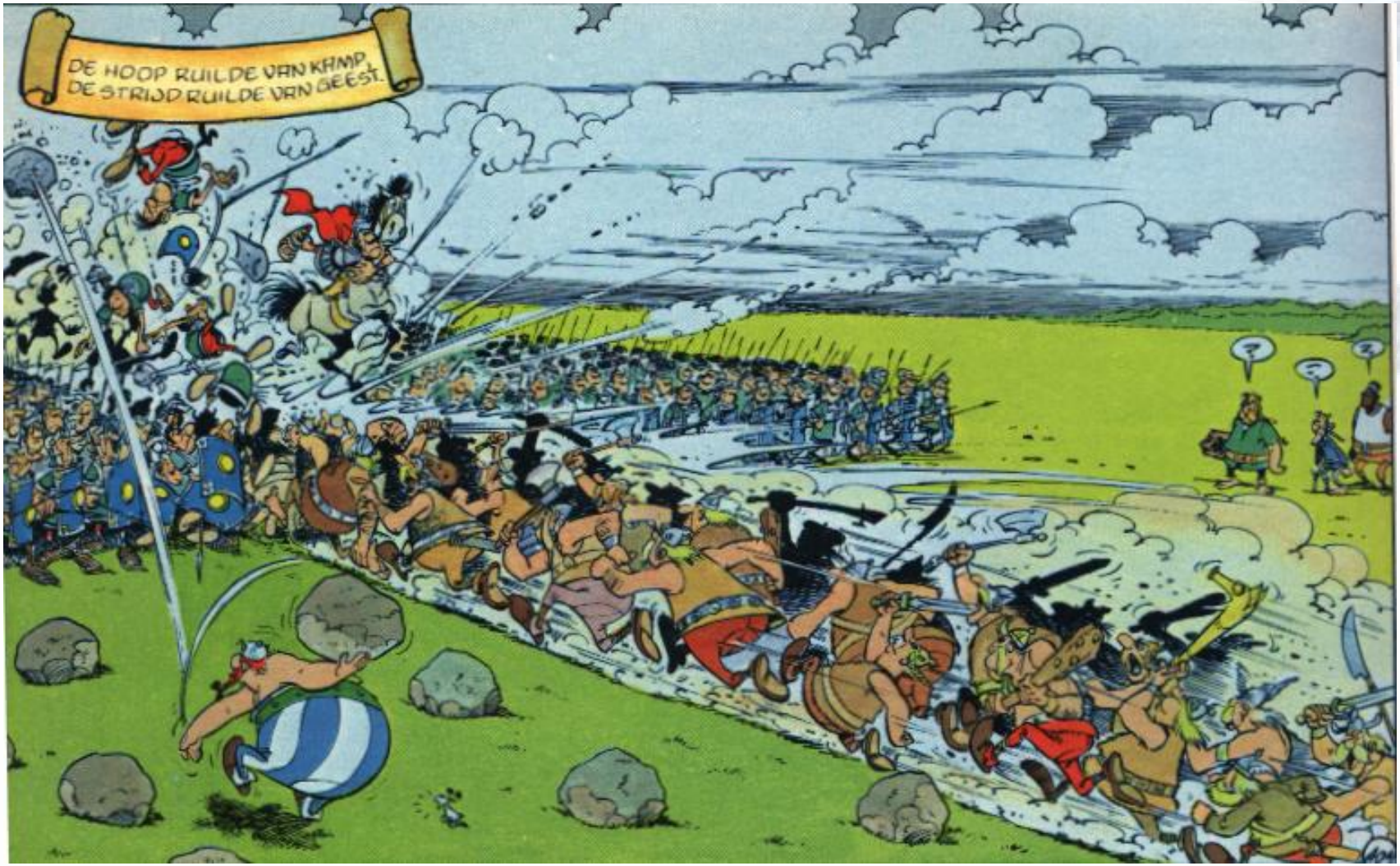
Where should the breakpoint be ?



Where should the breakpoint be ?



And there were fierce battles …



From Mouton, 8th ISAP symposium, Nijmegen, 2001

A simple example …

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

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 / ≥ 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

The pros and cons of using CLSI breakpoints

Cons

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- 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**

An example of (probably) too high CLSI breakpoints

Drug	Typical daily dosage[a]	Typical PK values: C_{max} in mg/L total/free (dose)	Typical PK values: $AUC_{24\ h}$ (mg × h/L) total/free	Proposed PK/PD upper limit: Efficacy[b]	Proposed PK/PD upper limit: Prevention of resistance[c]	Breakpoints (mg/L)[d]: 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]

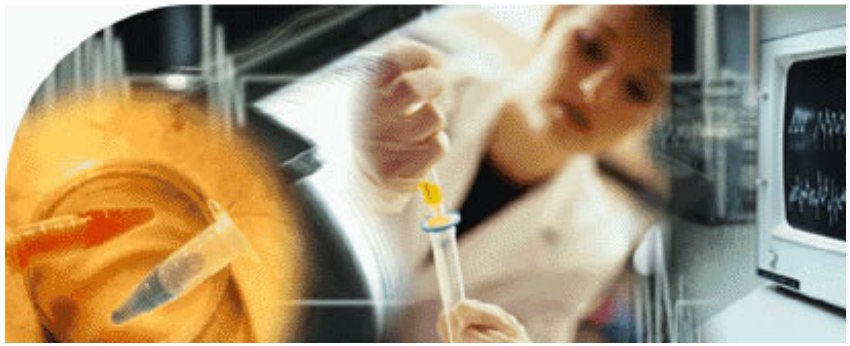
NCCLS, National Committee for Clinical Laboratory Standards (Clinical and Laboratory Standards Institute) (http://www.ncc

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)

CLINICAL AND LABORATORY STANDARDS INSTITUTE®
(Formerly NCCLS)



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 changes in Europe…

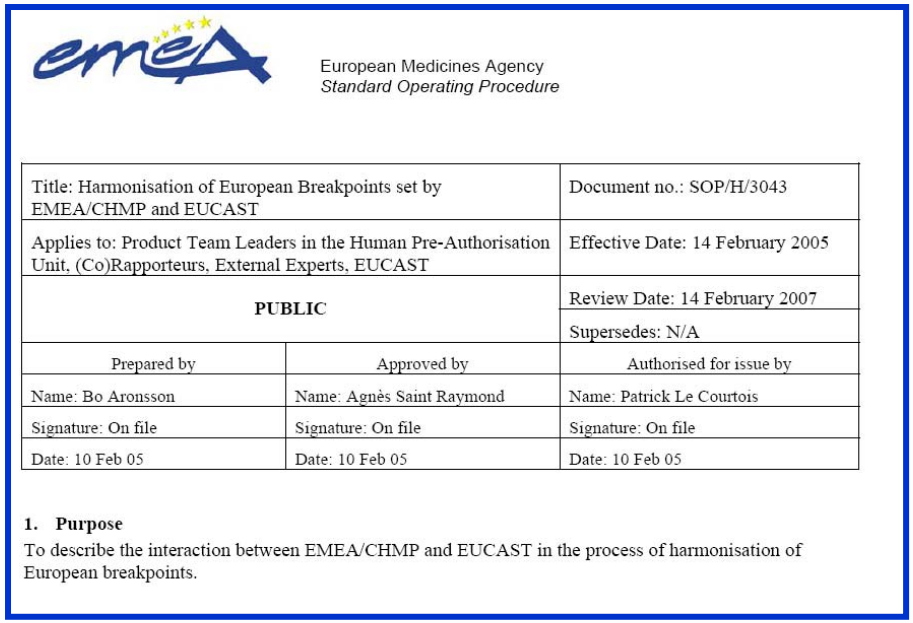
1. Each national committee in EU (UK, FR, NL, DE, SV, NO) has pledged that the EUCAST breakpoints will be part of their respective systems January the year after the decision was made. This means that any decision taken in 2008 should be into their systems in January 2009, and so on …

   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 disk-based assay 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

Wild type (WT)

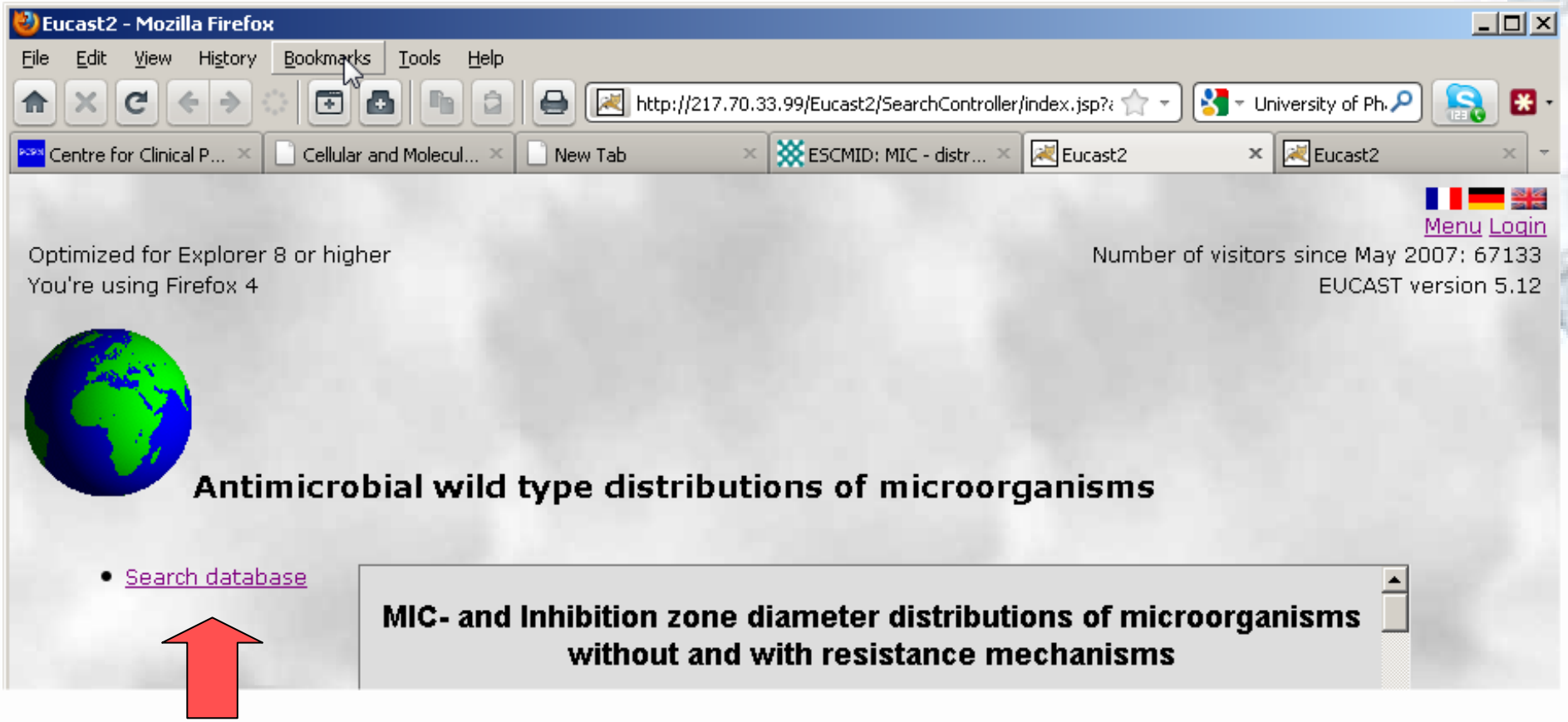
- a microorganism is defined as wild type (WT) for a species by the absence of acquired and mutational resistance mechanisms to the drug in question.
- a microorganism is categorized as wild type (WT) for a species by applying the appropriate cut-off value in a defined phenotypic test system.
- wild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

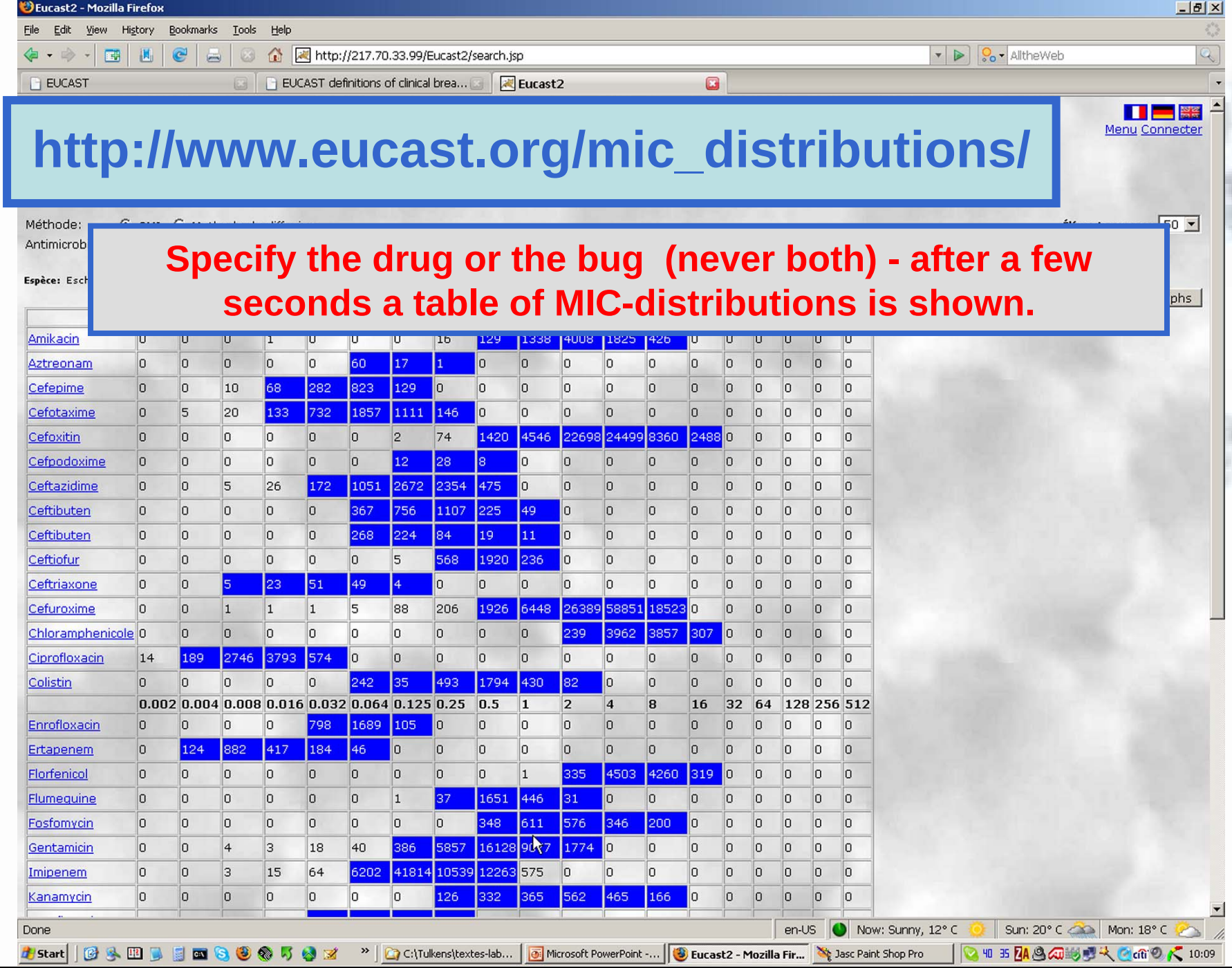
Microbiological resistance - non-wild type (NWT)

- 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/




Eucast2 - Mozilla Firefox
File Edit View History Bookmarks Tools Help
http://217.70.33.99/Eucast2/search.jsp
EUCAST
EUCAST definitions of clinical brea...
Eucast2
http://www.eucast.org/mic_distributions/
Menu Connecter
Méthode:
Antimicrob
Espèce: Esch
Specify the drug or the bug (never both) - after a few seconds a table of MIC-distributions is shown.
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
Chloramphenicole 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 9077 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
Done
en-US
Now: Sunny, 12° C
Sun: 20° C
Mon: 18° C
Start
C:\Tulkens\textes-lab...
Microsoft PowerPoint -...
Eucast2 - Mozilla Fir...
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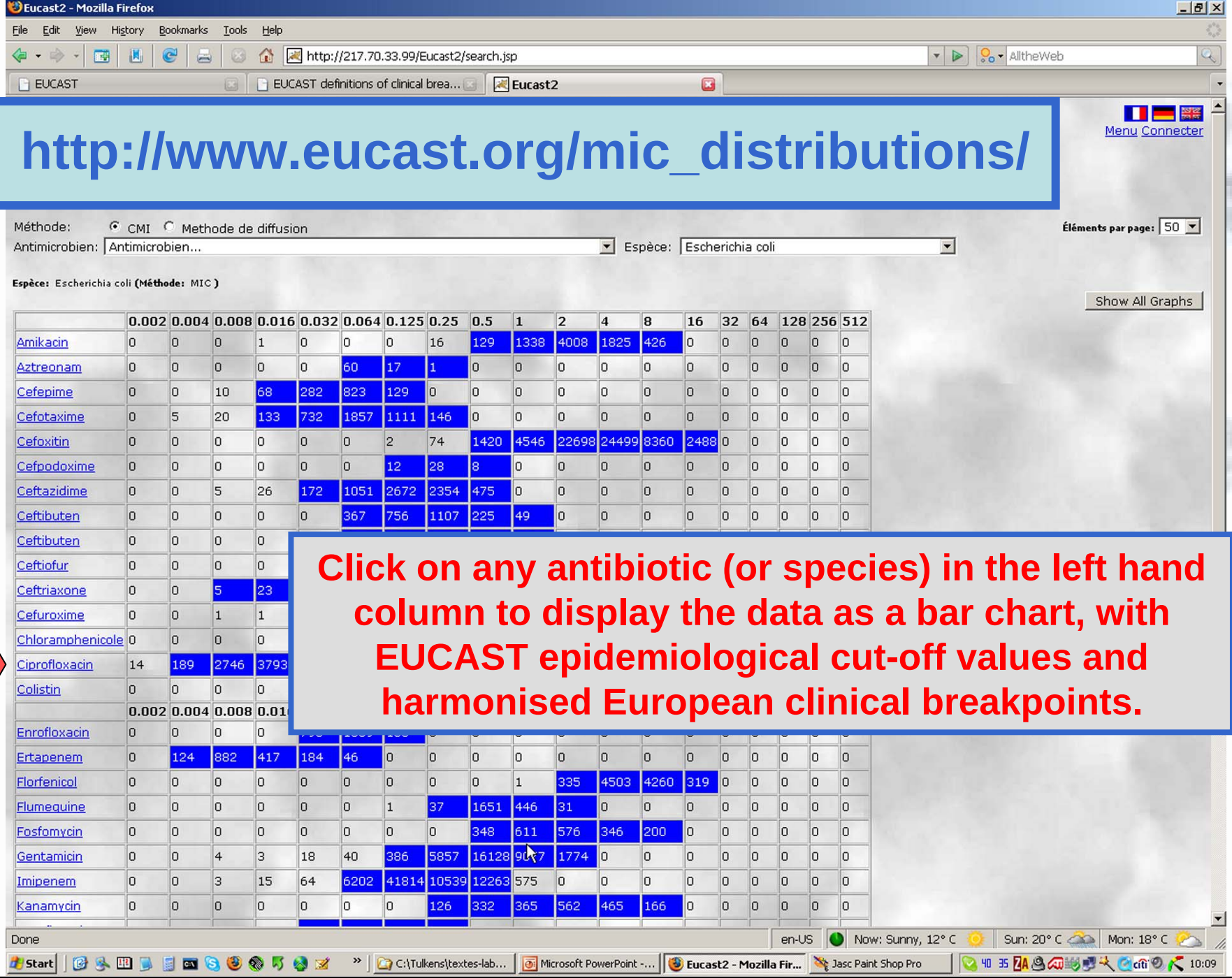
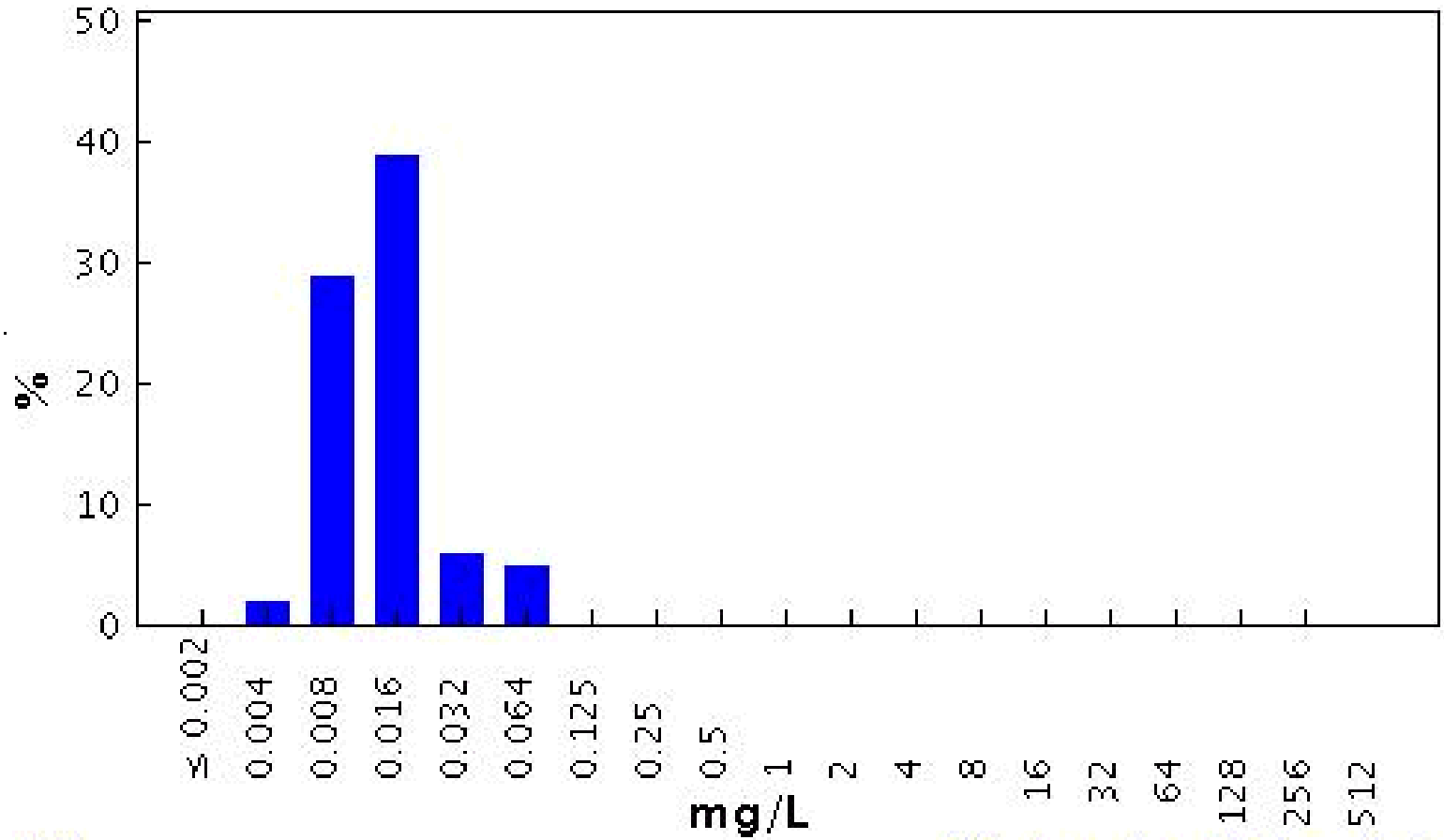


	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512
Amikacin	0	0	0	1	0	0	0	16	129	1338	4008	1825	426	0	0	0	0	0	0
Aztreonam	0	0	0	0	0	60	17	1	0	0	0	0	0	0	0	0	0	0	0
Cefepime	0	0	10	68	282	823	129	0	0	0	0	0	0	0	0	0	0	0	0
Cefotaxime	0	5	20	133	732	1857	1111	146	0	0	0	0	0	0	0	0	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															
Ceftiofur	0	0	0	0															
Ceftriaxone	0	0	5	23															
Cefuroxime	0	0	1	1															
Chloramphenicole	0	0	0	0															
Ciprofloxacin	14	189	2746	3793															
Colistin	0	0	0	0															
	0.002	0.004	0.008	0.01															
Enrofloxacin	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	9017	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

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

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.

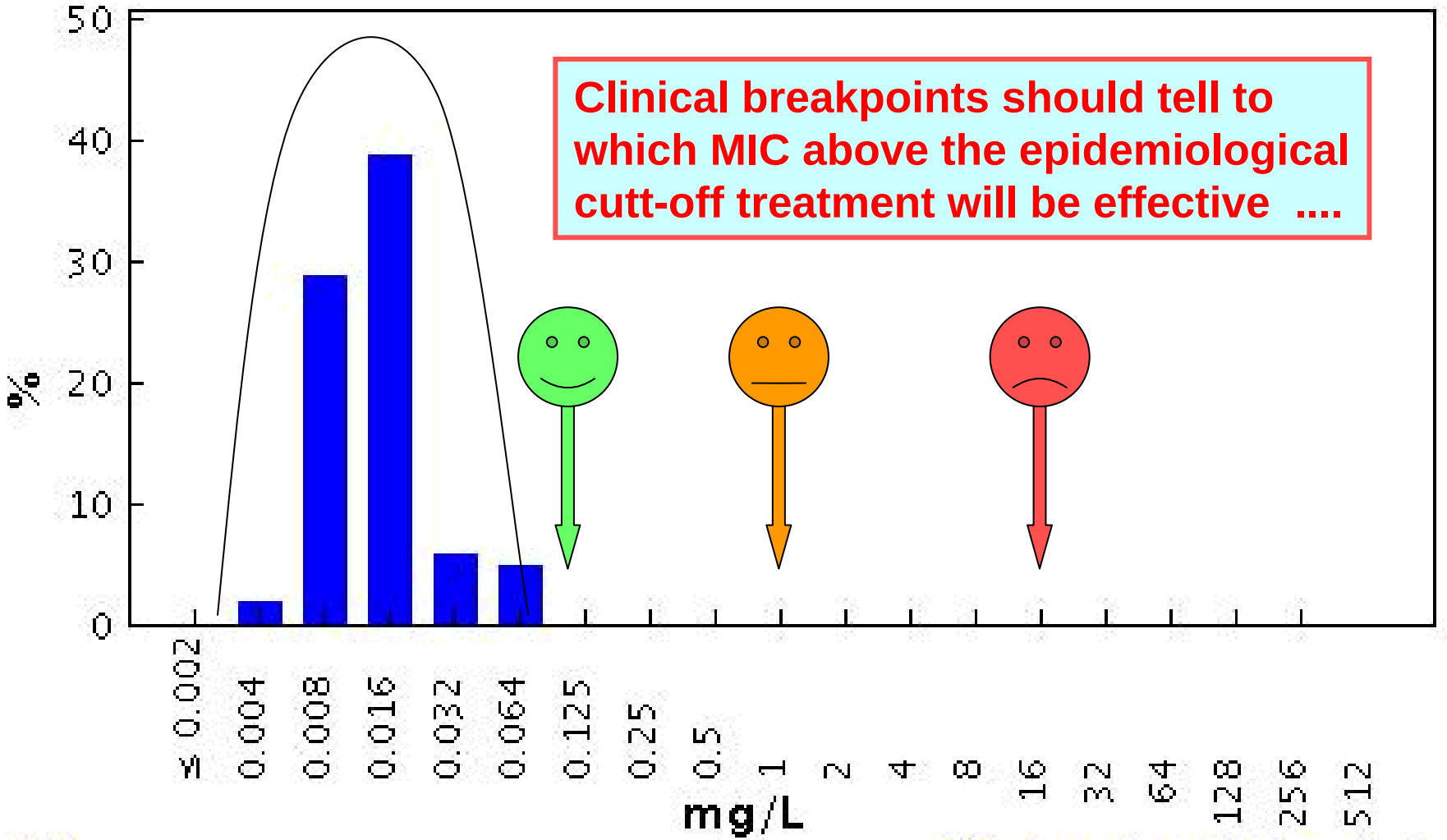
a microorganism is categorized as S, I or R by applying the appropriate breakpoint in a defined phenotypic test system

Clinical breakpoints may be altered with legitimate changes in circumstances

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

Ciprofloxacin / Escherichia coli

Antimicrobial wild type distributions of microorganisms – reference database EUCAST



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 ≤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

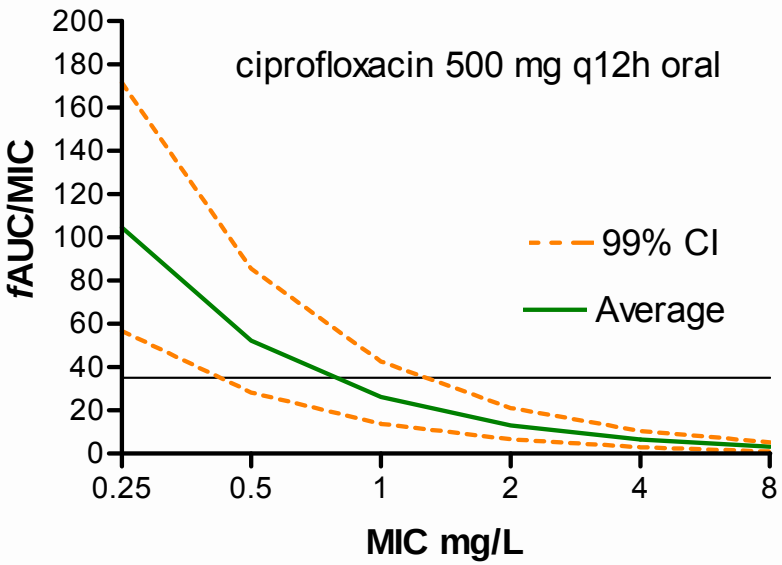
5. Pharmacodynamic data are evaluated

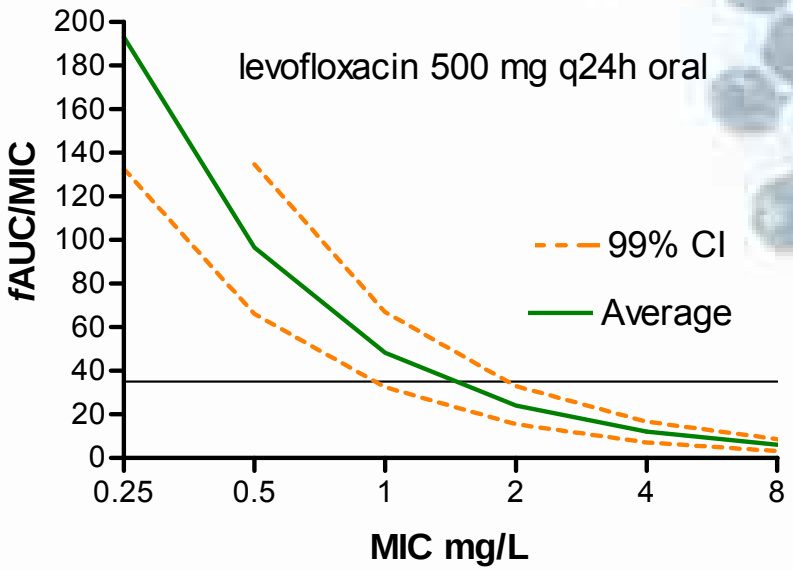
The PK/PD index value of the pertinent PK/PD parameter (time above MIC, AUC/MIC, C_{max}/MIC…) resulting in optimal outcome is determined from:

- 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

http://www.eucast.org/clinical_breakpoints/

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

Home Contact Sitemap

- 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<=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>=22 mm and R<18 mm the intermediate category is 18-21 mm.

EUCAST breakpoints are freely available

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

http://www.eucast.org

Recommend page

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[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)	$AUC_{24\ h}$ (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

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EUCAST and carbapenems

Enterobacteriaceae

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	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_breakpoints_v1.1.pdf

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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.

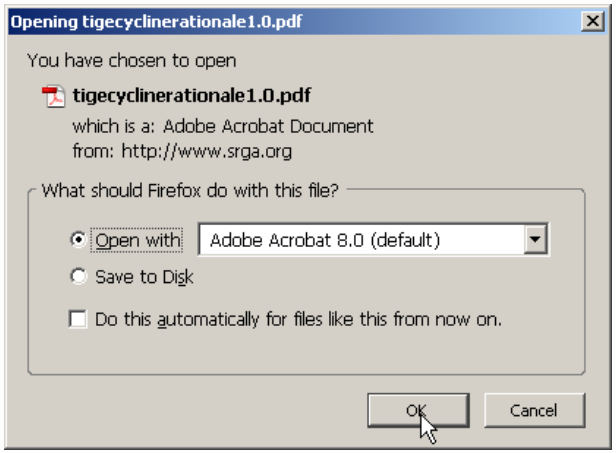
To exclude ESBL ..

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



Is the methodology available ?

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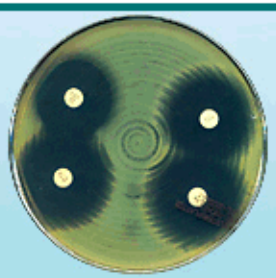
- Organization
- EUCAST News
- Clinical breakpoints
- Expert rules
- MIC - distributions and QC
- Zone diameter distributions
- **EUCAST disk diffusion test**
  - General information
  - Implementation guide
  - Guidance documents
  - Breakpoint tables
  - Disk diffusion methodology
  - QC Tables
  - Calibration and validation
  - Projects and data submission
  - Older versions of tables
- Frequently Asked Questions (FAQ)



EUCAST disk diffusion test for routine antimicrobial susceptibility testing

During 2009 - 2010 EUCAST is developing a disk diffusion test for routine antimicrobial susceptibility testing. ESCMID has decided to take responsibility for the development and upkeep of the EUCAST disk diffusion test over the next several years.

The method is derived from the Kirby-Bauer method, variants of which are currently widely used in Europe, but is calibrated to EUCAST MIC breakpoints.

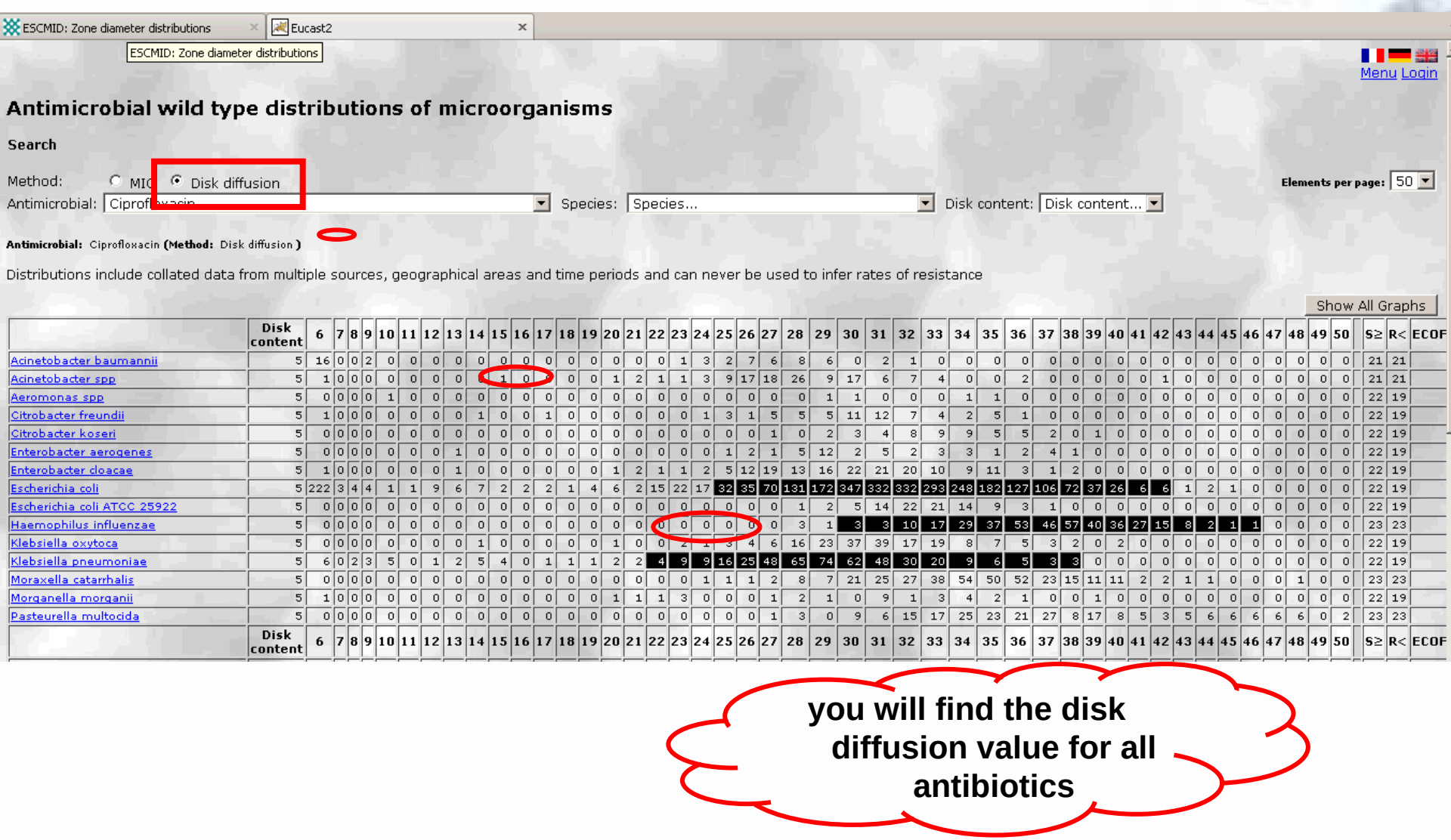
The method is based on two media, Mueller-Hinton agar without supplements (MH) for non-fastidious organisms, including enterococci, and MH with 5 % horse blood and 20 mg ß-NAD/L (MH-F) for *Streptococcus* spp. including *Streptococcus pneumoniae, Haemophilus* spp. and other fastidious organisms.

The plates are incubated at 35° ±1° C for 18 ±2 h within 15 minutes from application of the disks. MH plates are incubated in air and MH-F plates in 5% CO2.

Breakpoint tables with tentative zone diameter breakpoints were published

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

Can we have access to the zone diameter values ?



	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≥	R<	ECOF
Acinetobacter baumannii	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	0	21	21	
Acinetobacter spp	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	1	0	0	0	0	0	0	0	0	21	21	
Aeromonas spp	5	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	22	19	
Citrobacter freundii	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	22	19	
Citrobacter koseri	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	22	19	
Enterobacter aerogenes	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	22	19	
Enterobacter cloacae	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	22	19	
Escherichia coli	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	22	19	
Escherichia coli ATCC 25922	5	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	22	19	
Haemophilus influenzae	5	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	23	23	
Klebsiella oxytoca	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	22	19	
Klebsiella pneumoniae	5	6	0	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	22	19	
Moraxella catarrhalis	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	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	23	23	
Morganella morganii	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	22	19	
Pasteurella multocida	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	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≥	R<	ECOF

you will find the disk diffusion value for all antibiotics

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

EUCAST breakpoints and commercially available material and systems for AST - important information to laboratories (updated 2010-03-16).

CLICK here.

The **preparedness of manufacturers** of AST materials (media, plates, disks) and AST systems - **click here for the latest information** (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: --

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 (**http://www.eucast.org**)
- Adaptation to local conditions can, therefore, be made seamlessly if needed (changes in dosages, PK, resistance patterns…)

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

Cons

- Adopting EUCAST breakpoints will require a re-thinking about resistance levels and their significance *
- 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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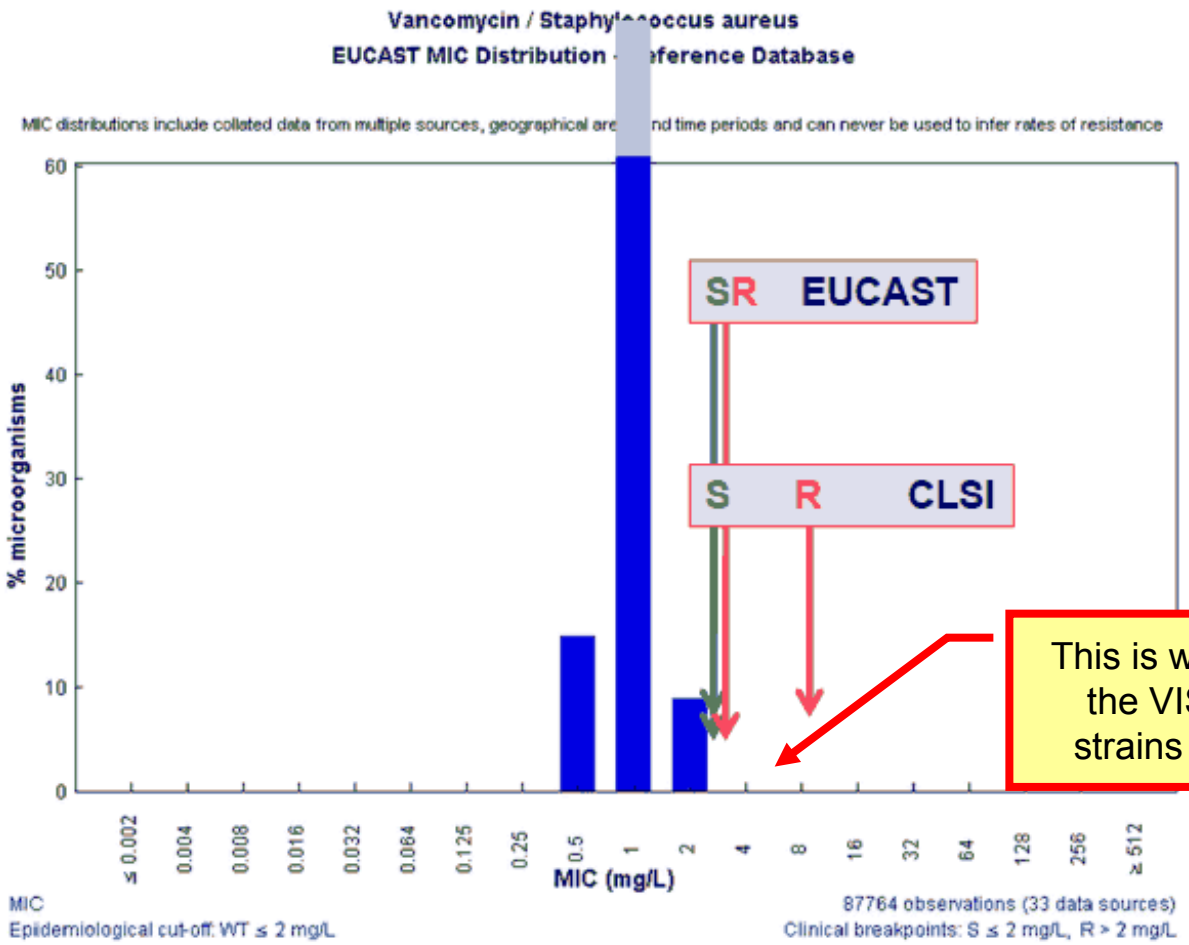
* two typical example are the R breakpoints for (i) penicillin and *S. pnenumoniae* (almost all isolates a are "S" sithe the new CLSI breakpoint….), and (ii) vancomycin and S. aureus (CLSI breakpoint of ≥ 8 m/L will classify VISA as intermediate … which they are not !; see next slide).

** except via country representatives (see www.eucast.org), ISC (me) or FESCI (Dr D. Livermore)

Discrepancies EUCAST – CLSI: an example…

Vancomycin breakpoints for *S. aureus*



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

ISC

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

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