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

and some personal thinking…

Paul M. Tulkens

Representative of ISC to EUCAST

Unité de pharmacologie cellulaire et moléculaire

Université catholique de Louvain, Bruxelles

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

Academy of Infection, Athens, Greece – 16 November 2007

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…

Why do we need breakpoints ?

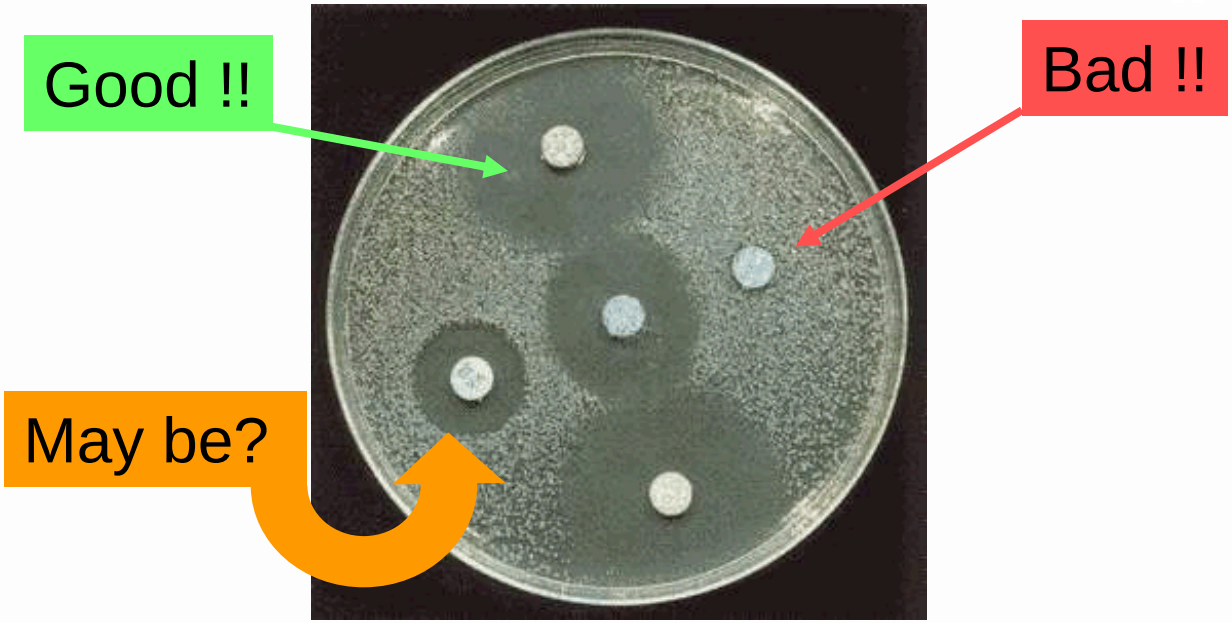
To be honest, I always wondered …

Why do we need breakpoints ?

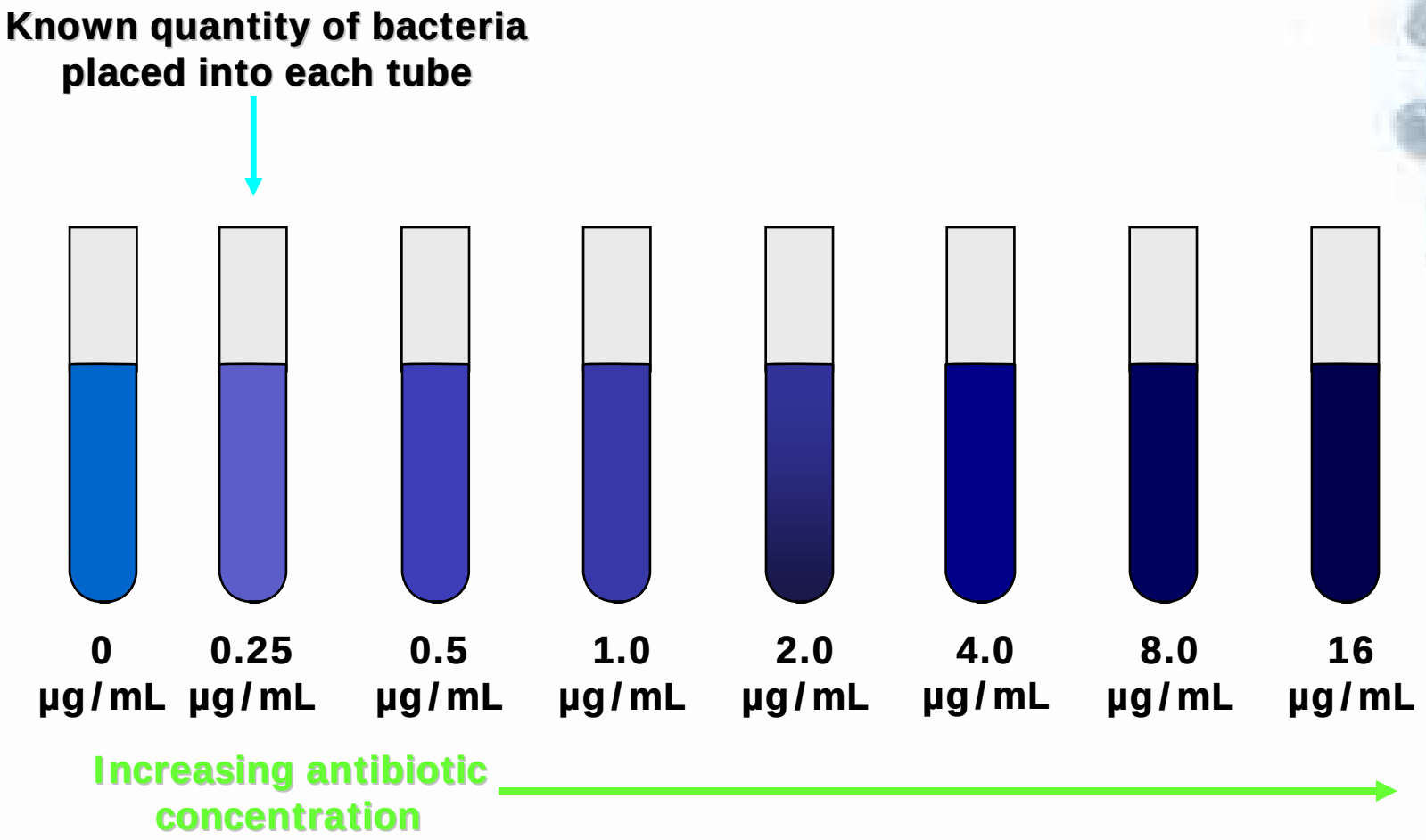
but perhaps…

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 …



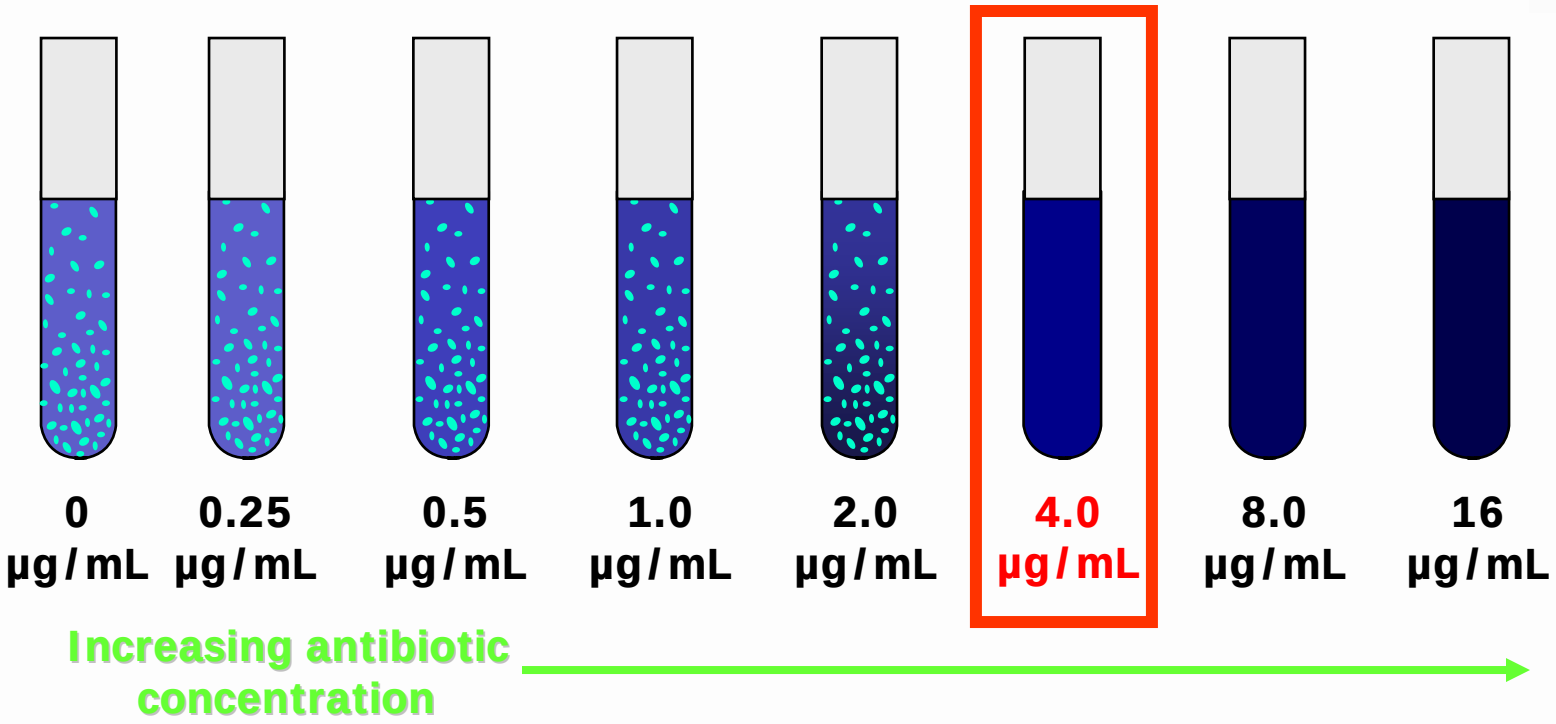
Starting from the beginning… The MIC !



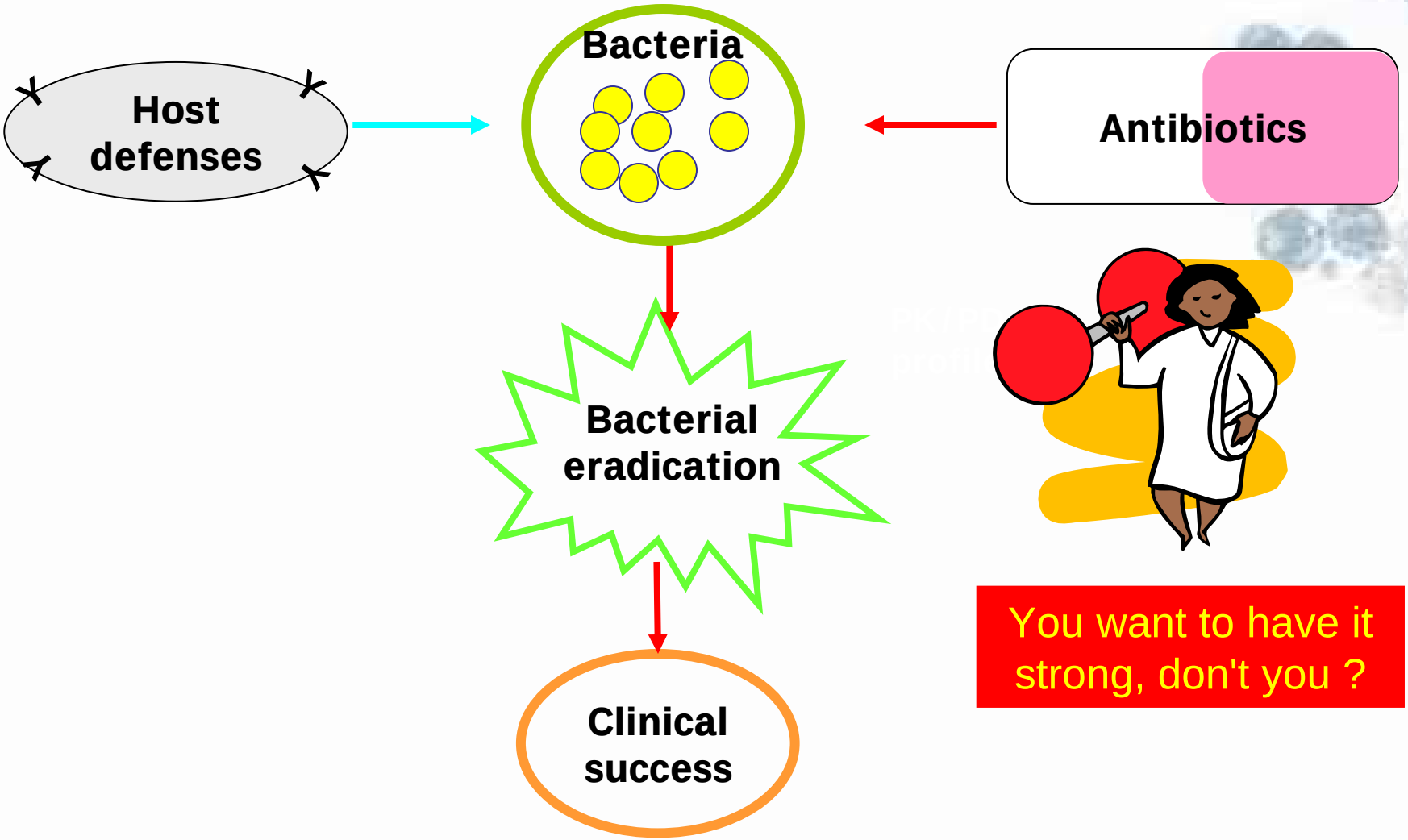
Starting from the beginning… The MIC !

24 h later ….

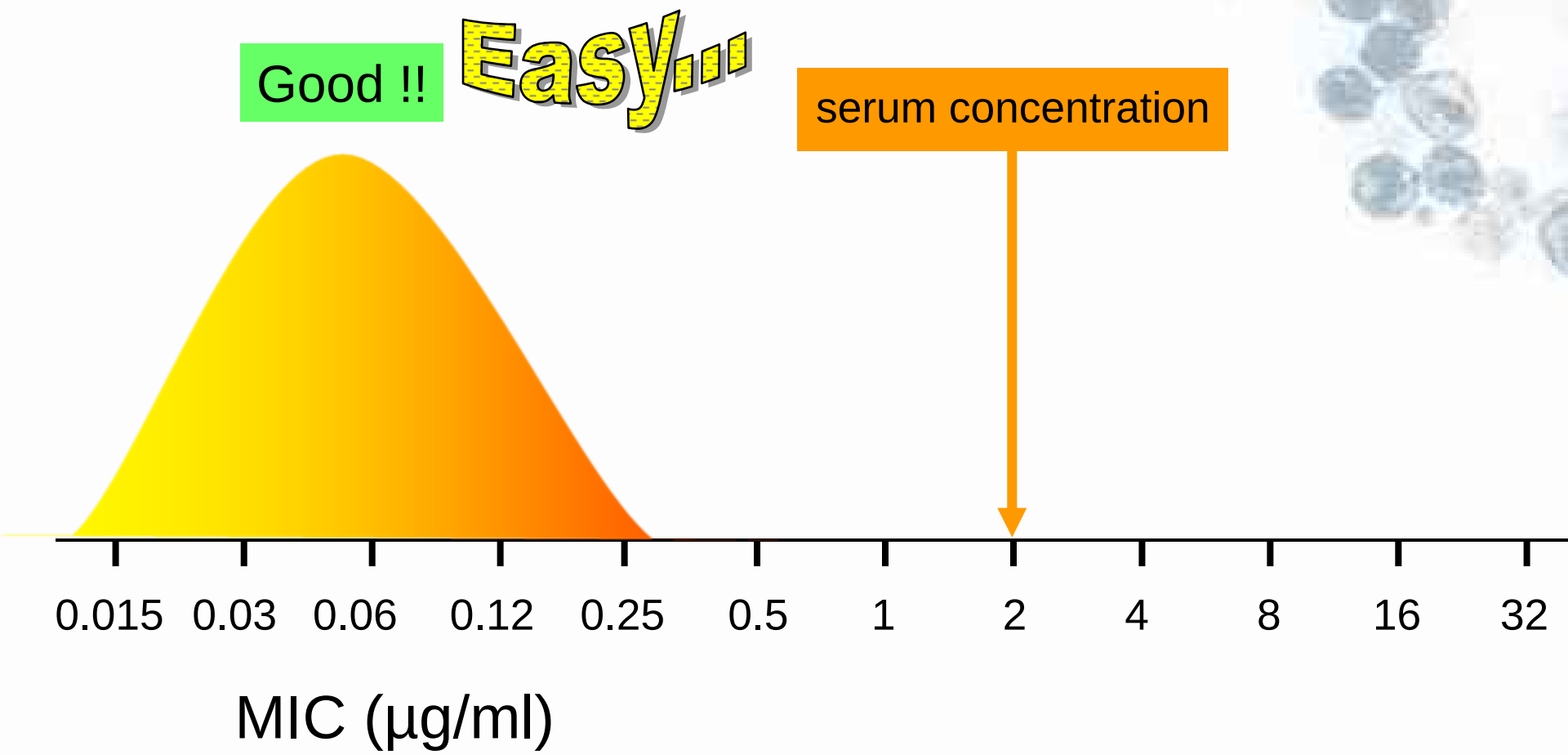
Lowest concentration of an antimicrobial that results in the inhibition of visible growth of a microorganism



What do you do with an MIC !

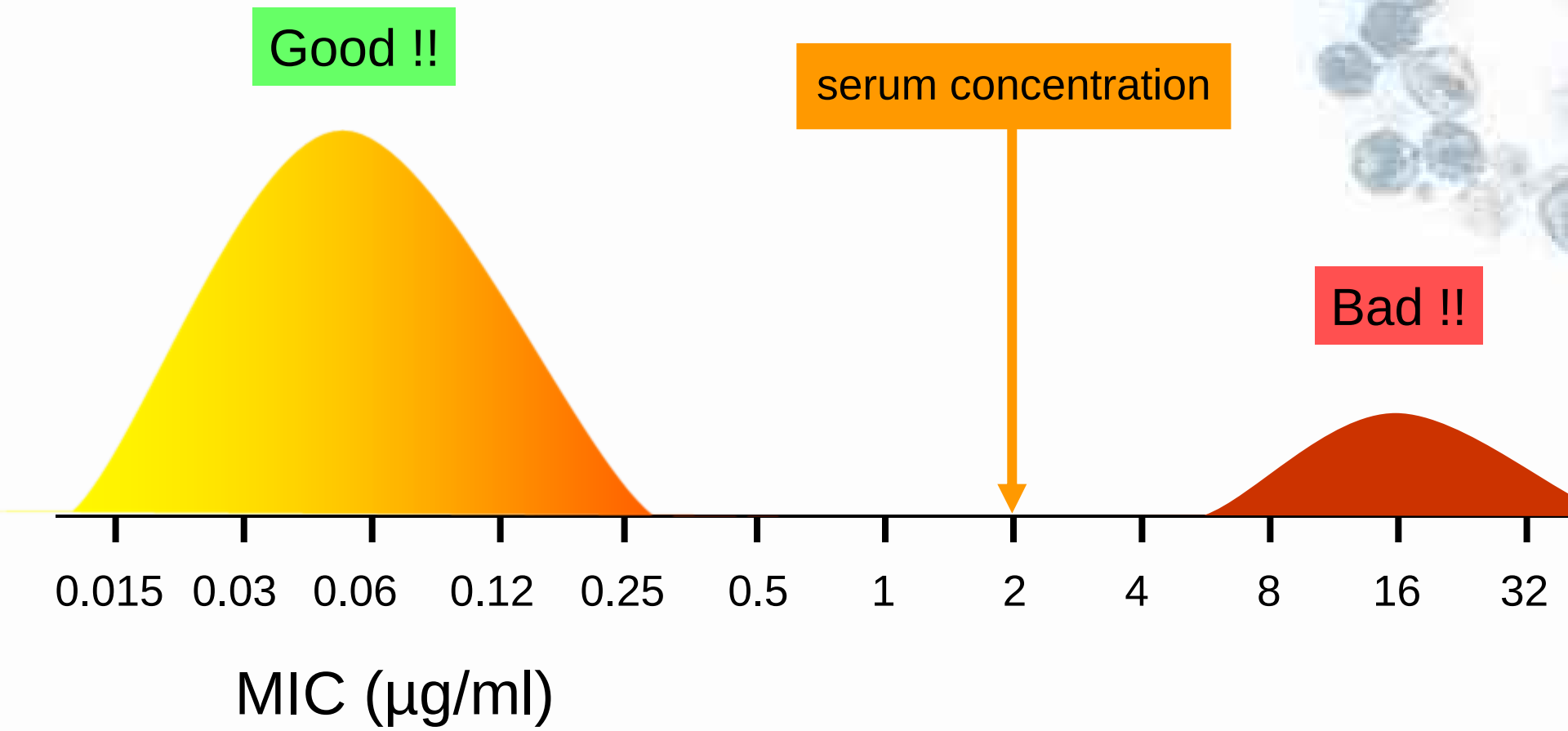


But, what is strong ?



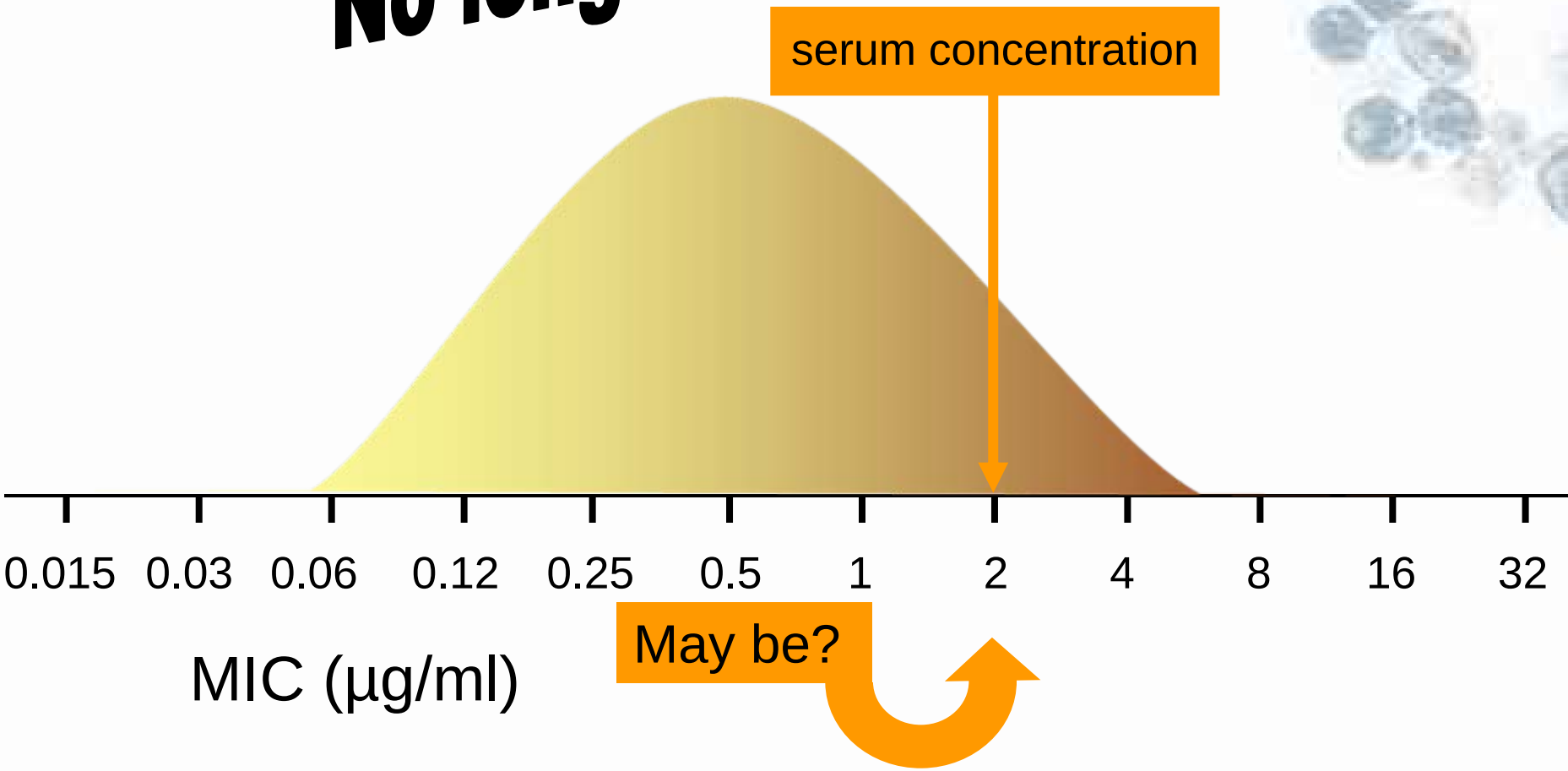
But, what is strong ?

Still Easy...

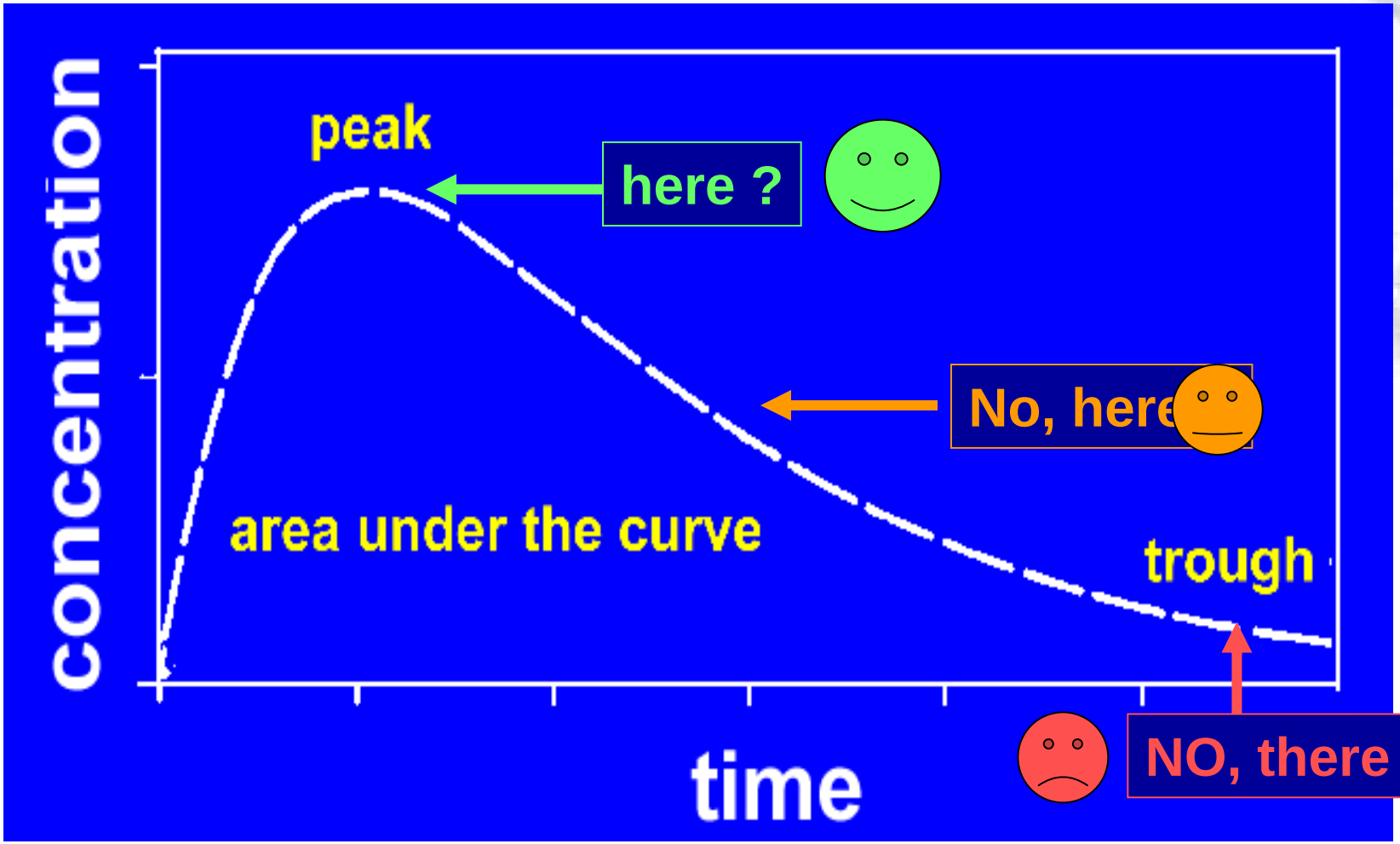


But, what is strong ?

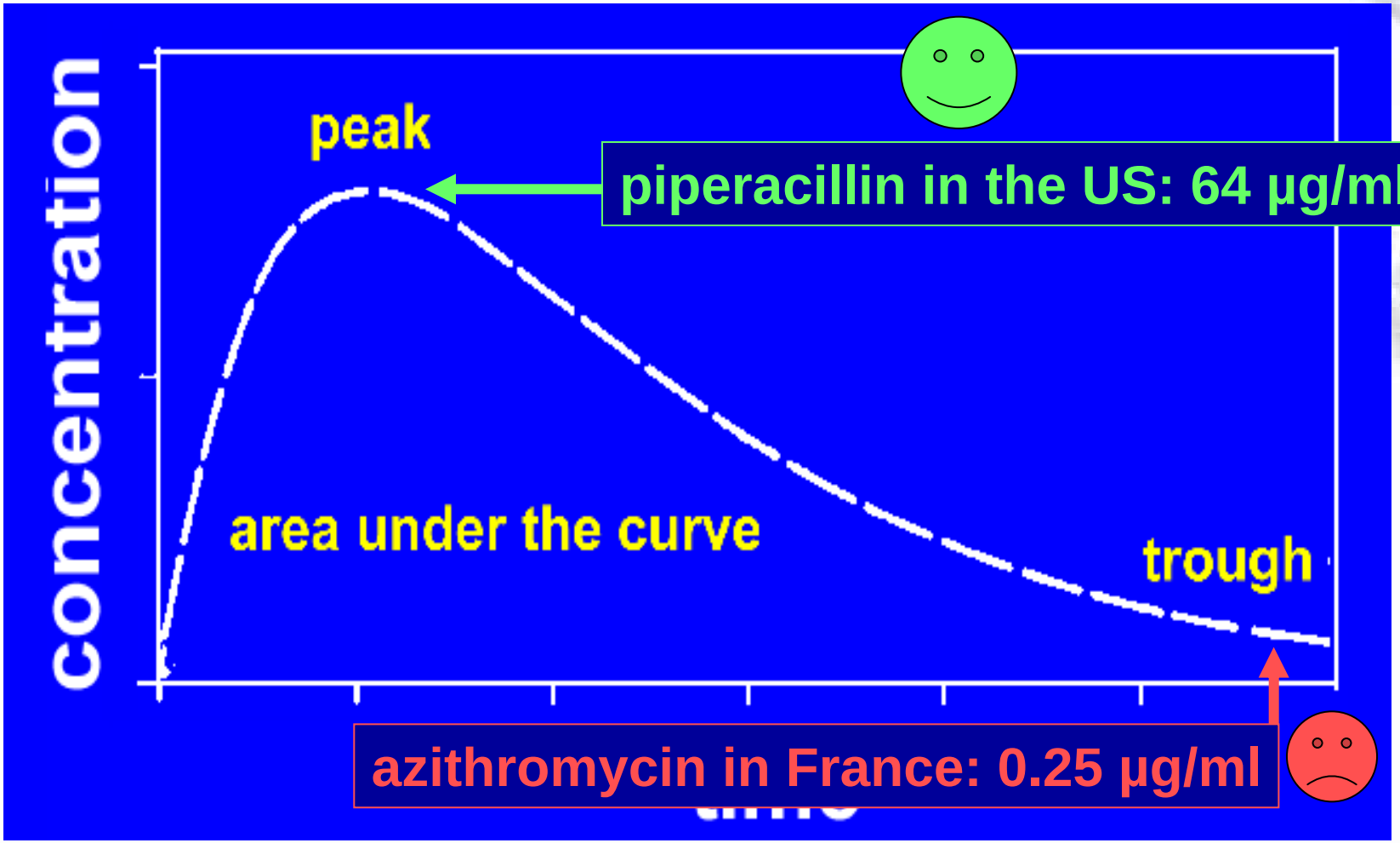
No longer so easy...



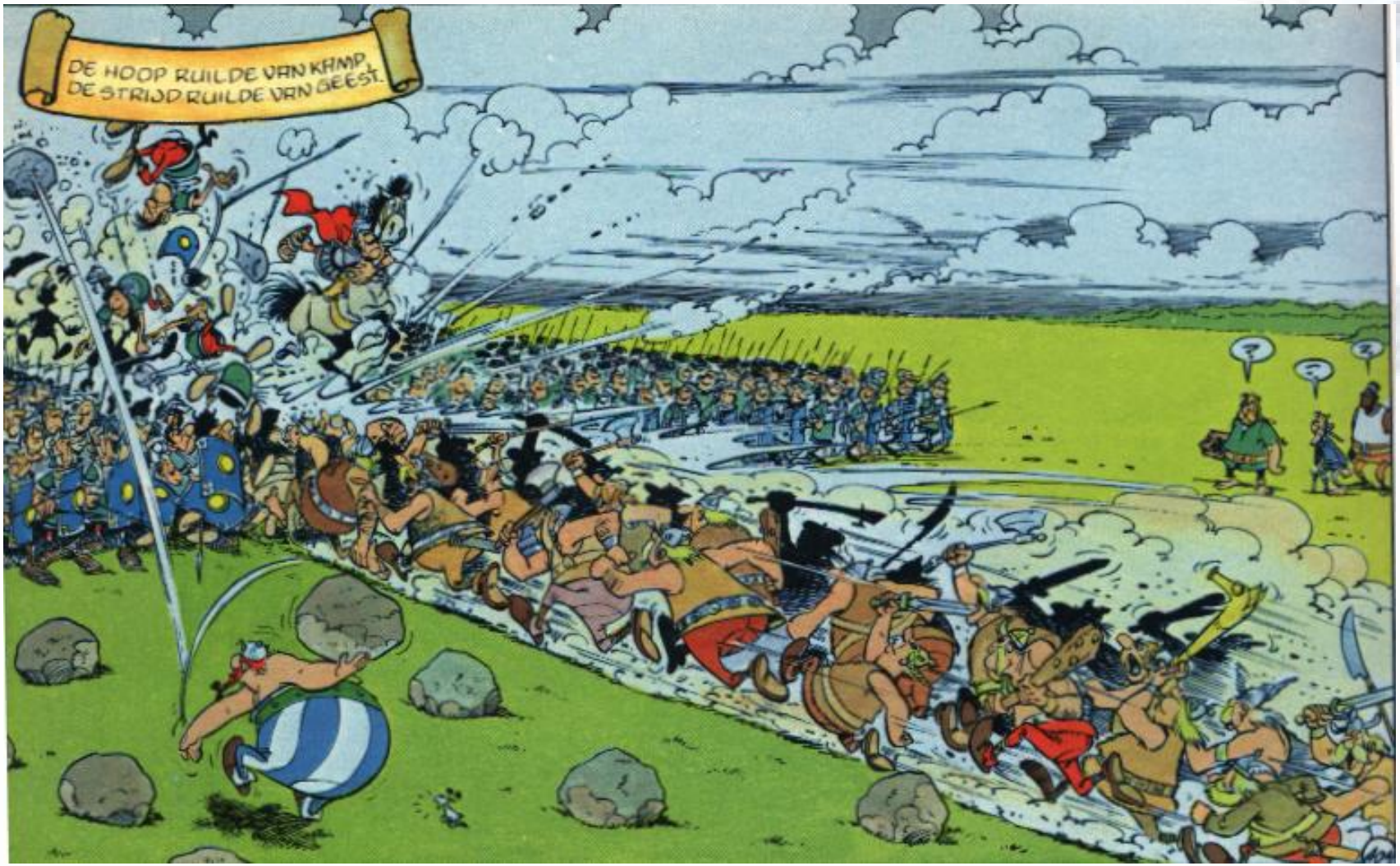
Where should the breakpoint be ?



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

Yet, breakpoints 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.

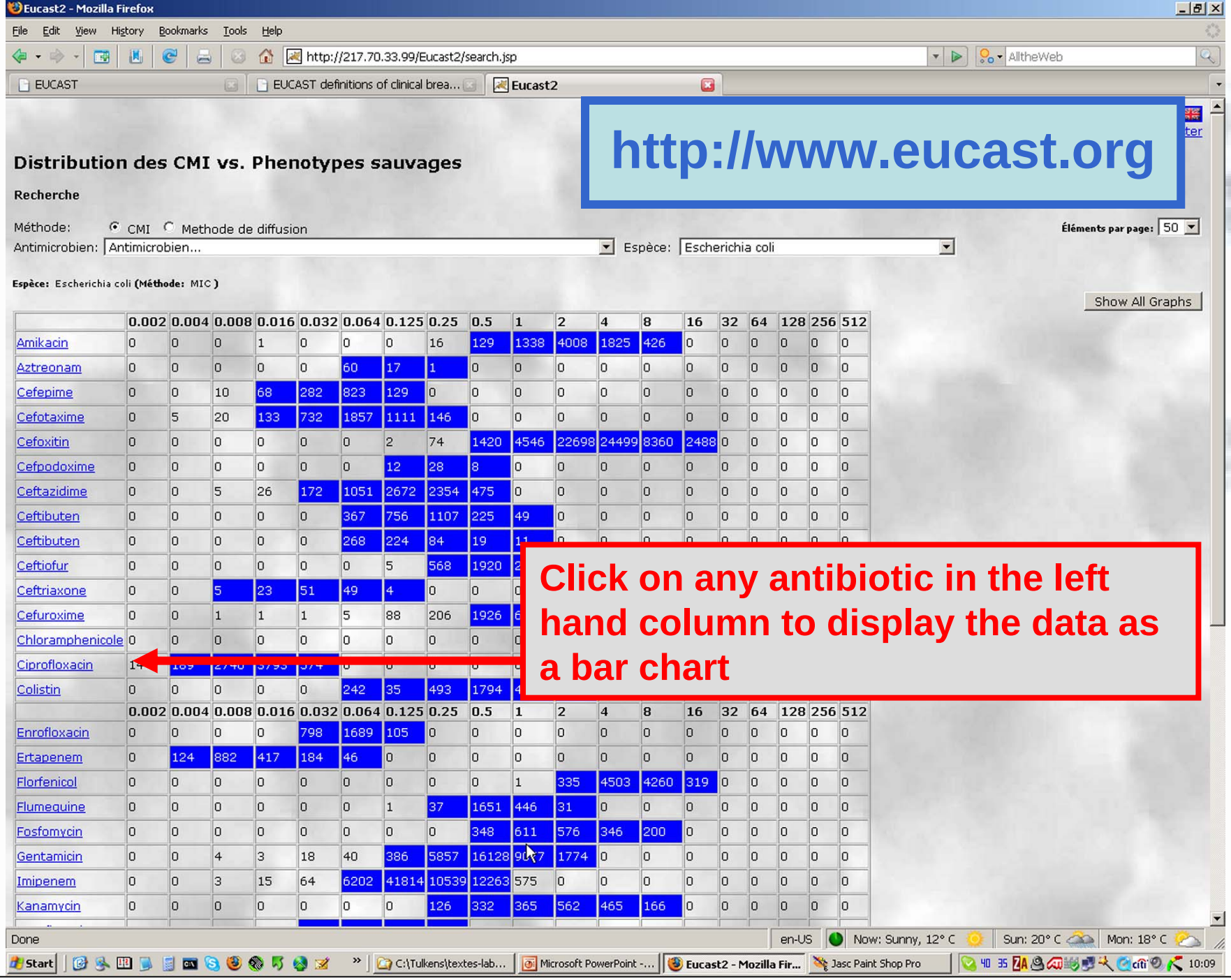
Microbiological resistance - non-wild type (NWT)

- 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

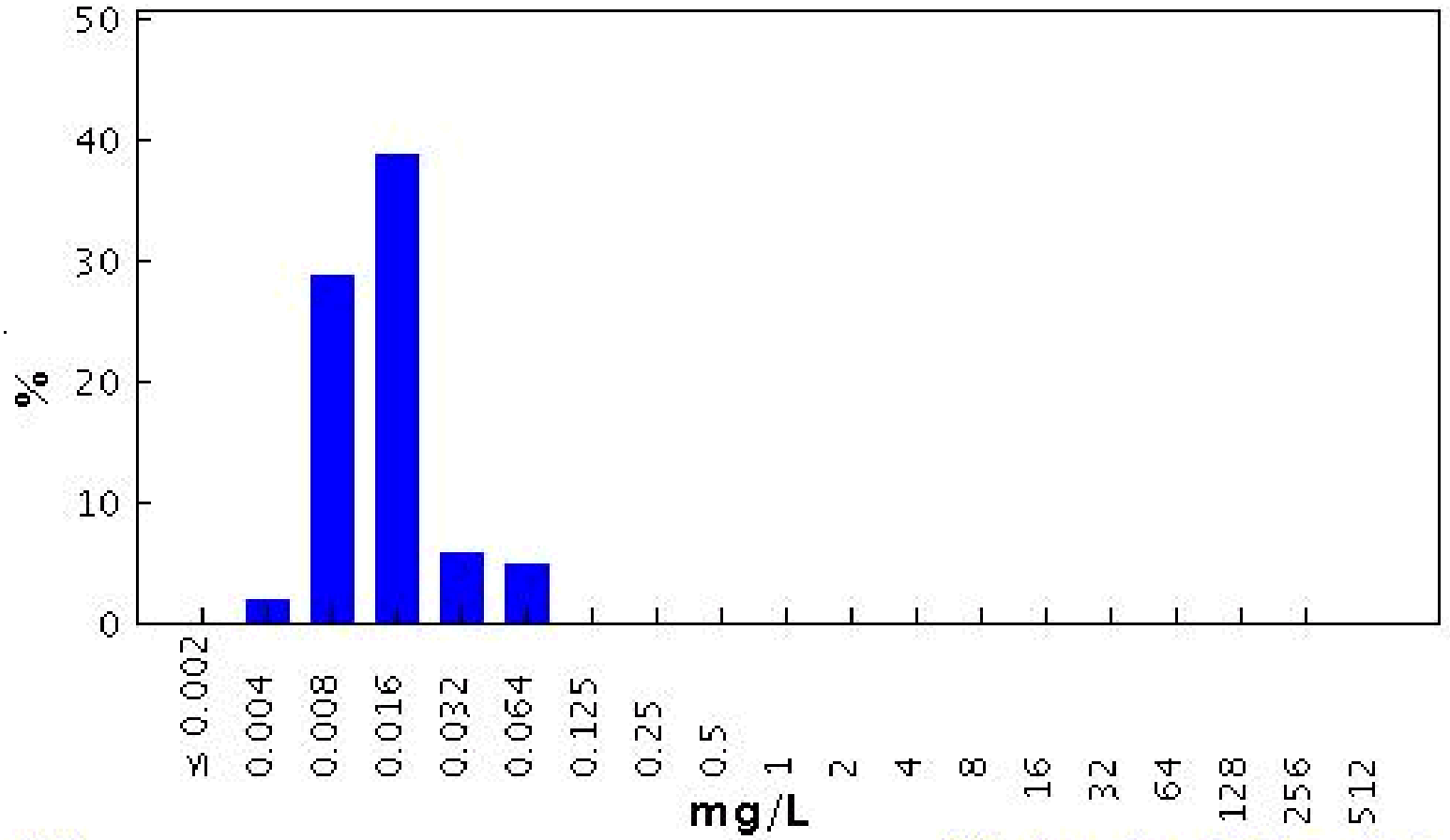
Specify the drug or the bug (never both) - after a few seconds a table of MIC-distributions is shown.



	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	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	2	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	6	0	0	0	0	0	0	0	0	0
Chloramphenicole	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ciprofloxacin	14	189	2748	3795	374	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Colistin	0	0	0	0	0	242	35	493	1794	4	0	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	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

Epidemiological cut-off: WT ≤ 0.064 mg/L

6423 observations (9 data sources)

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

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

Origin of MIC data

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

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

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

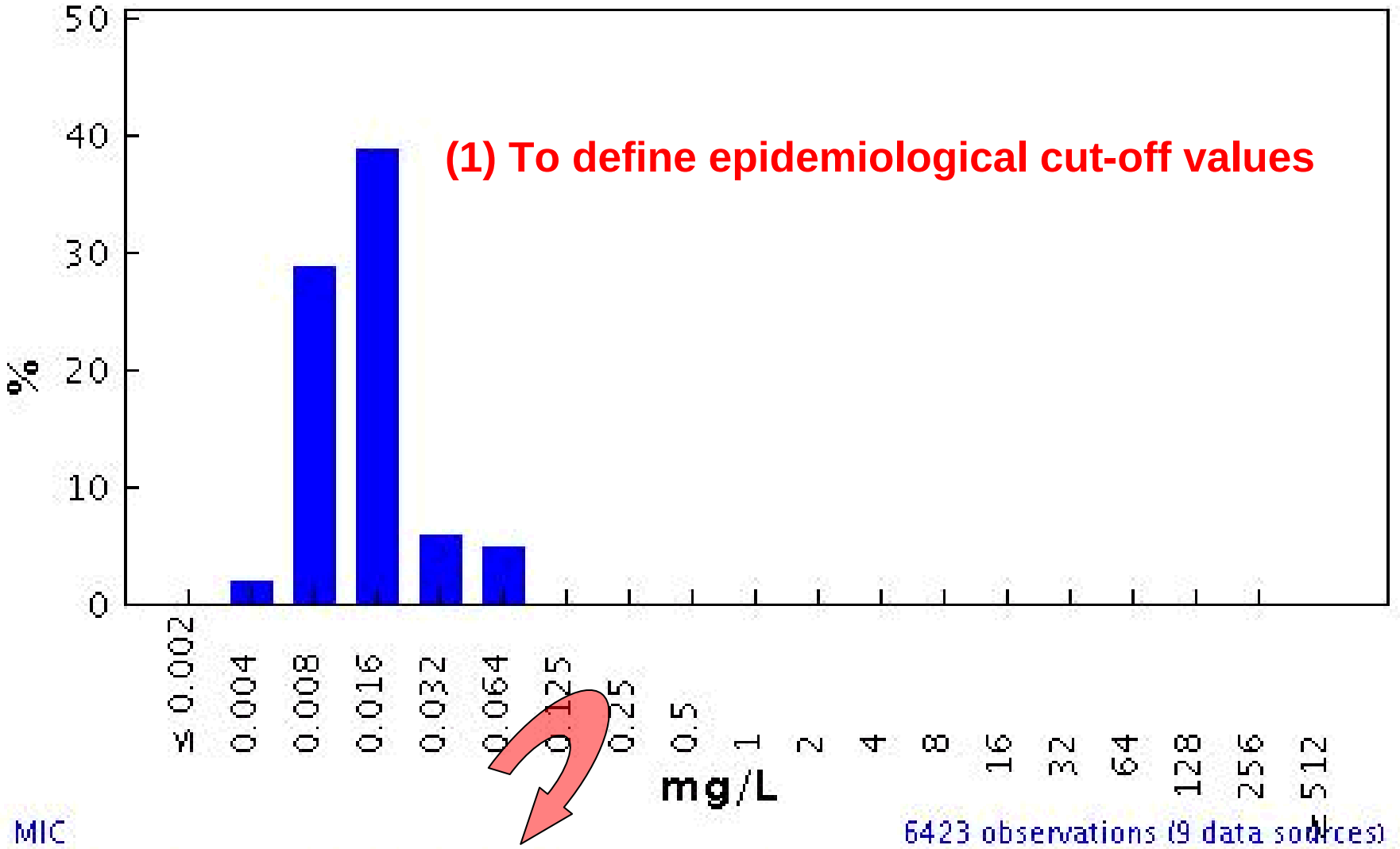
Use of EUCAST wild type MIC distributions

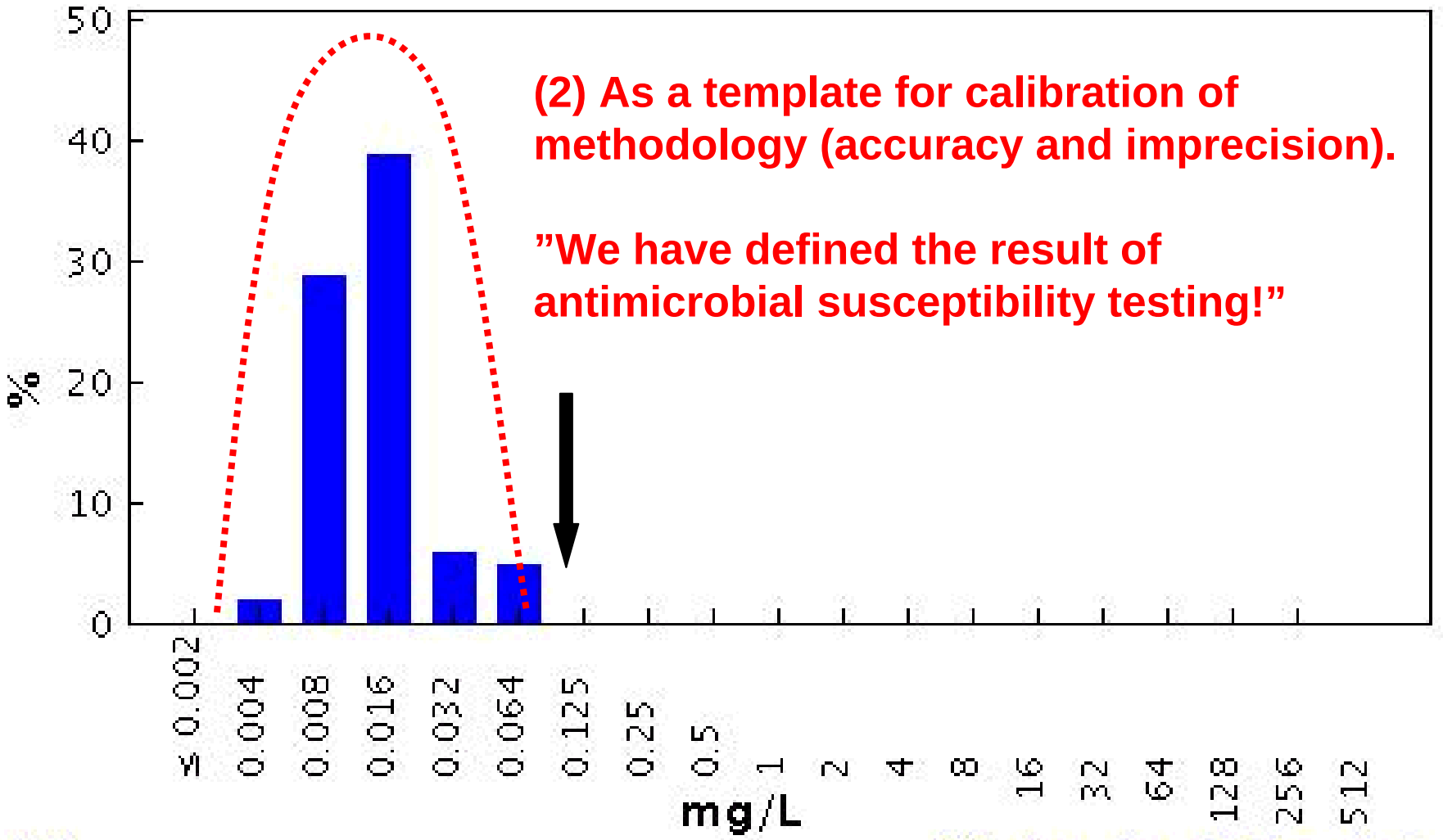
The wild type MIC distributions provide

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




Ciprofloxacin / Escherichia coli
Antimicrobial wild type distributions of microorganisms - reference database EUCAST
(2) As a template for calibration of methodology (accuracy and imprecision).
”We have defined the result of antimicrobial susceptibility testing!”
%
50
40
30
20
10
0
≤ 0.002
0.004
0.008
0.016
0.032
0.064
0.125
0.25
0.5
1
2
4
8
16
32
64
128
256
512
mg/L
N
MIC
6423 observations (9 data sources)
Epidemiological cut-off: WT ≤ 0.064 mg/L
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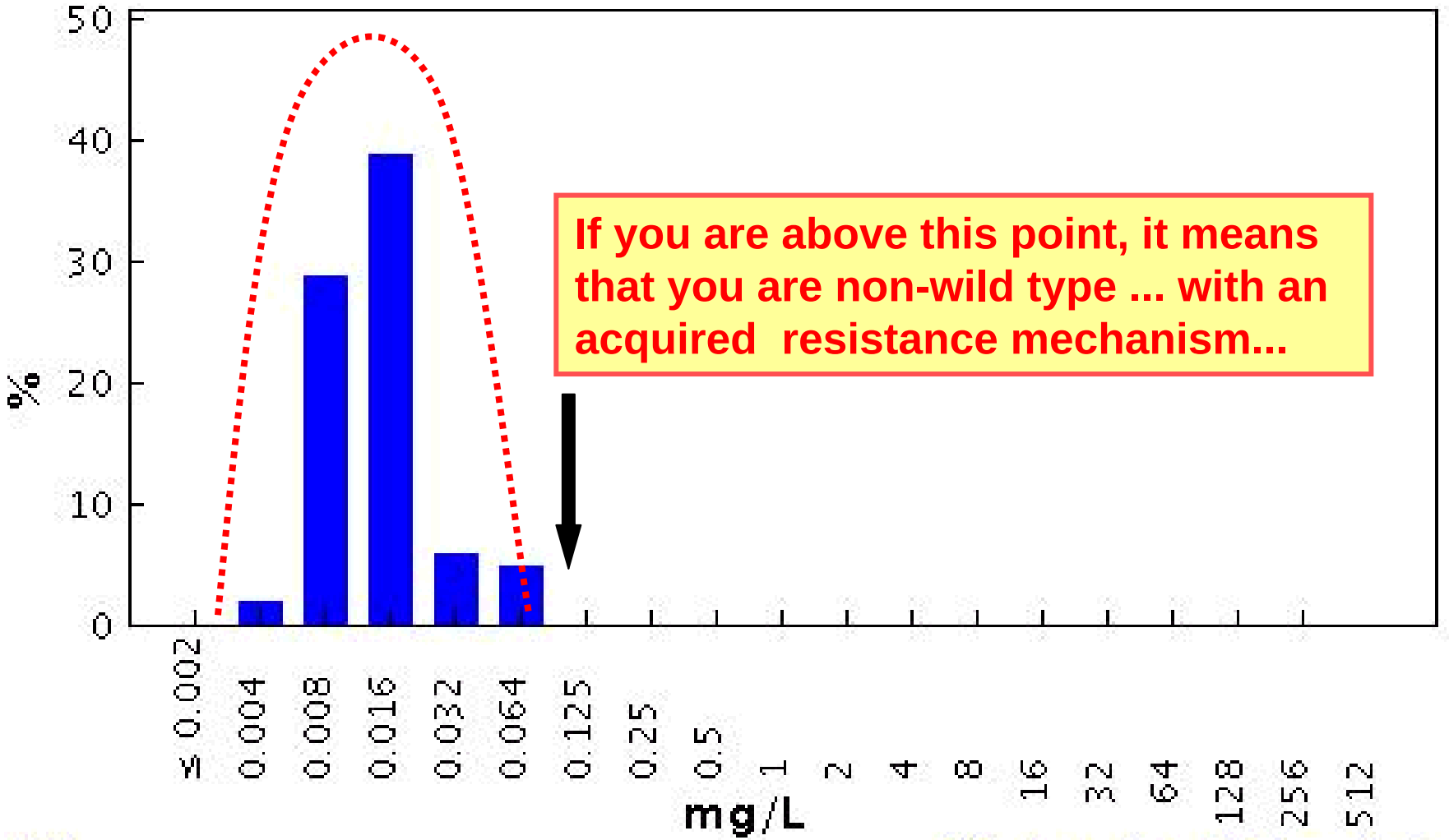
Ciprofloxacin / Escherichia coli

Antimicrobial wild type distributions of microorganisms - reference database EUCAST



MIC

Epidemiological cut-off: WT ≤ 0.064 mg/L

6423 observations (9 data sources)

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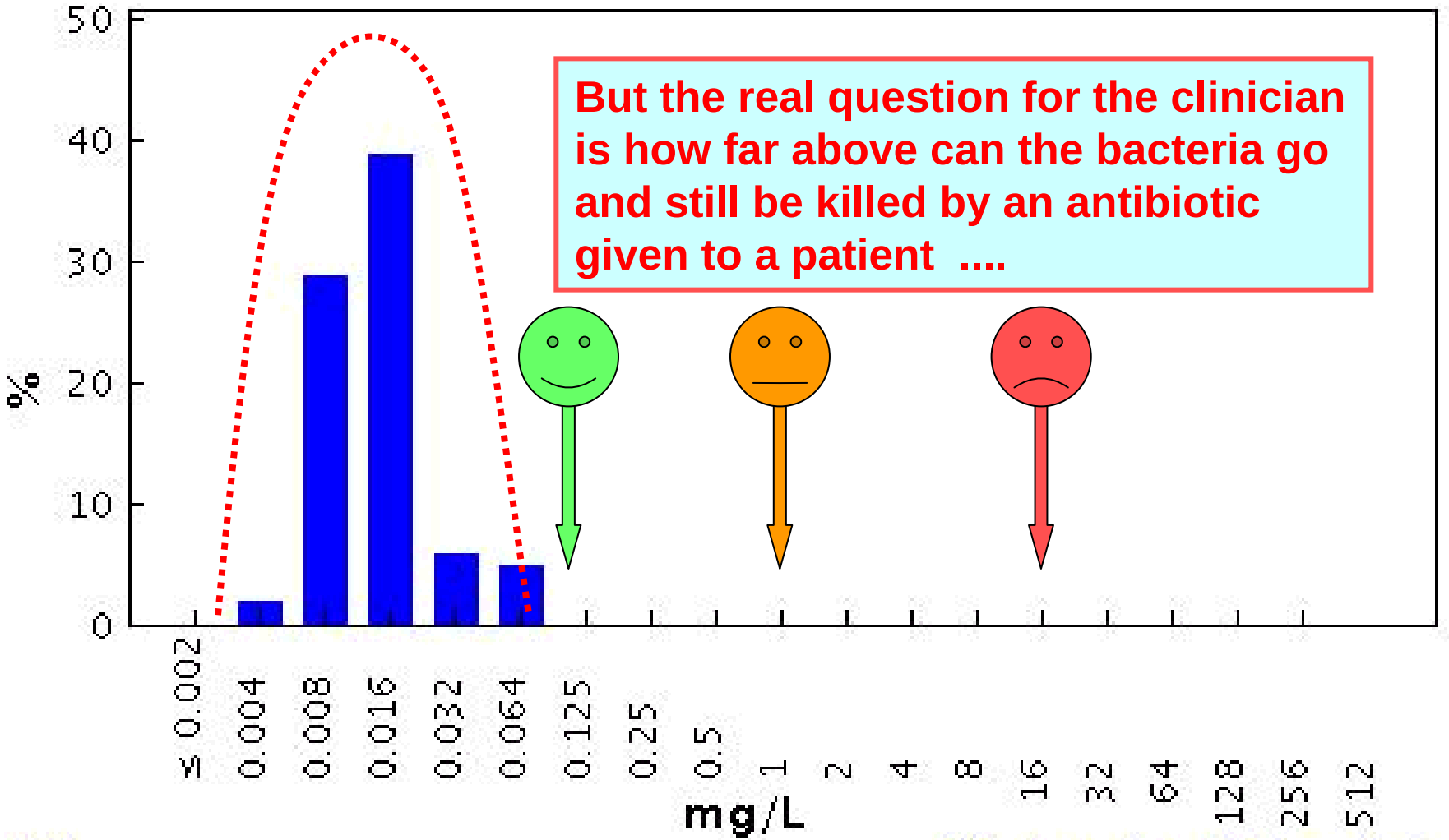
Ciprofloxacin / Escherichia coli

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

EUCAST definitions of clinical breakpoints

Clinically Susceptible (S)

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

Clinically Intermediate (I)

- level of antimicrobial activity associated with indeterminate therapeutic effect

Clinically Resistant (R)

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

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

Clinical breakpoints may be altered with legitimate changes in circumstances

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

EUCAST procedure for setting breakpoints

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

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

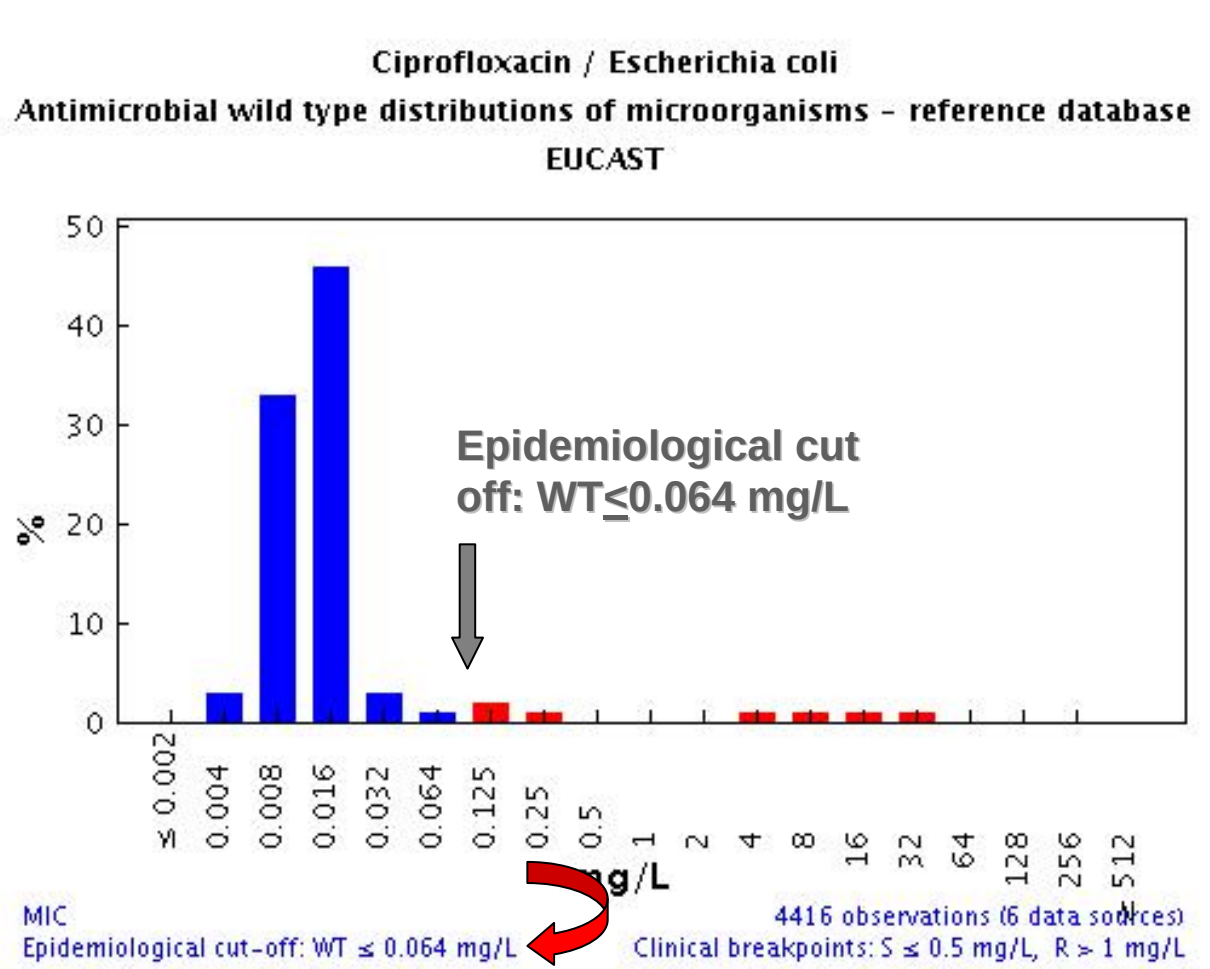
Dosage	National breakpoint committees						
Most common dose	500 x 2 oral 400 x 2 iv	500 x 2 oral 200 x 2 iv	250 x 2 oral 200 x iv	500 x 2 oral 200 x 2 iv	200-400 x 2 oral 400 x 2 iv	500 x 2 oral 400 x 2 iv	
Maximum dose schedule	750 x 2 oral 400 x 3 iv	750 x 2 oral 400 x 3 iv	750 x 2 oral 400 x 3 iv	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≤0.064/R>0.064 mg/L) be used in Salmonellae systemic infections. These strains are best found using a nalidixic acid 30 µg screen disc in routine susceptibility testing.

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

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



3. Existing national clinical breakpoints are compared

Ciprofloxacin was used in this example:

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

4. Pharmacokinetic data are collected and evaluated

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

These are necessary for PK/PD analyses, including Monte Carlo simulations

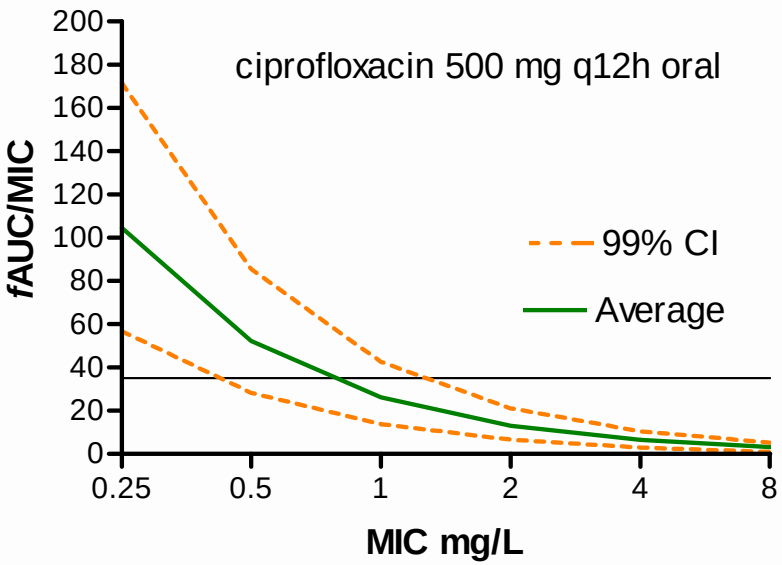
5. Pharmacodynamic data are evaluated

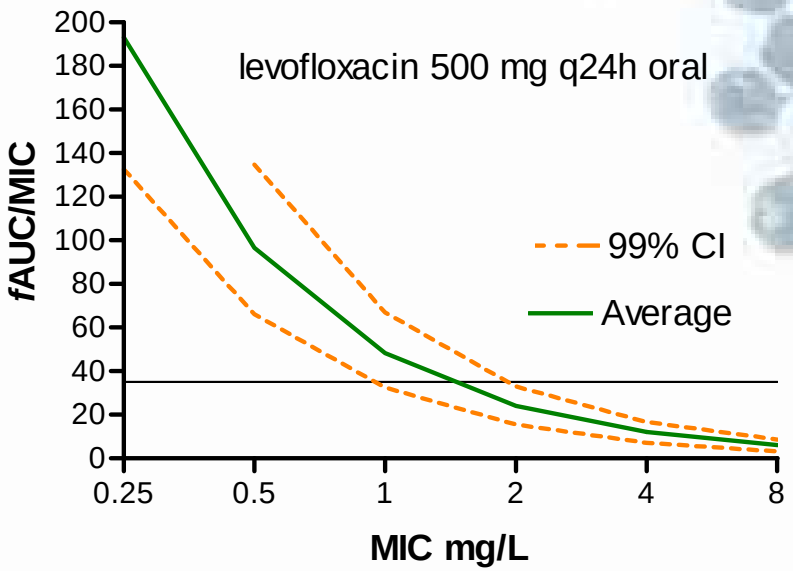
The PK/PD index value of the pertinent PK/PD parameter (time above MIC, AUC/MIC, C_{max}/MIC…) resulting in optimal outcome is determined from:

- 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

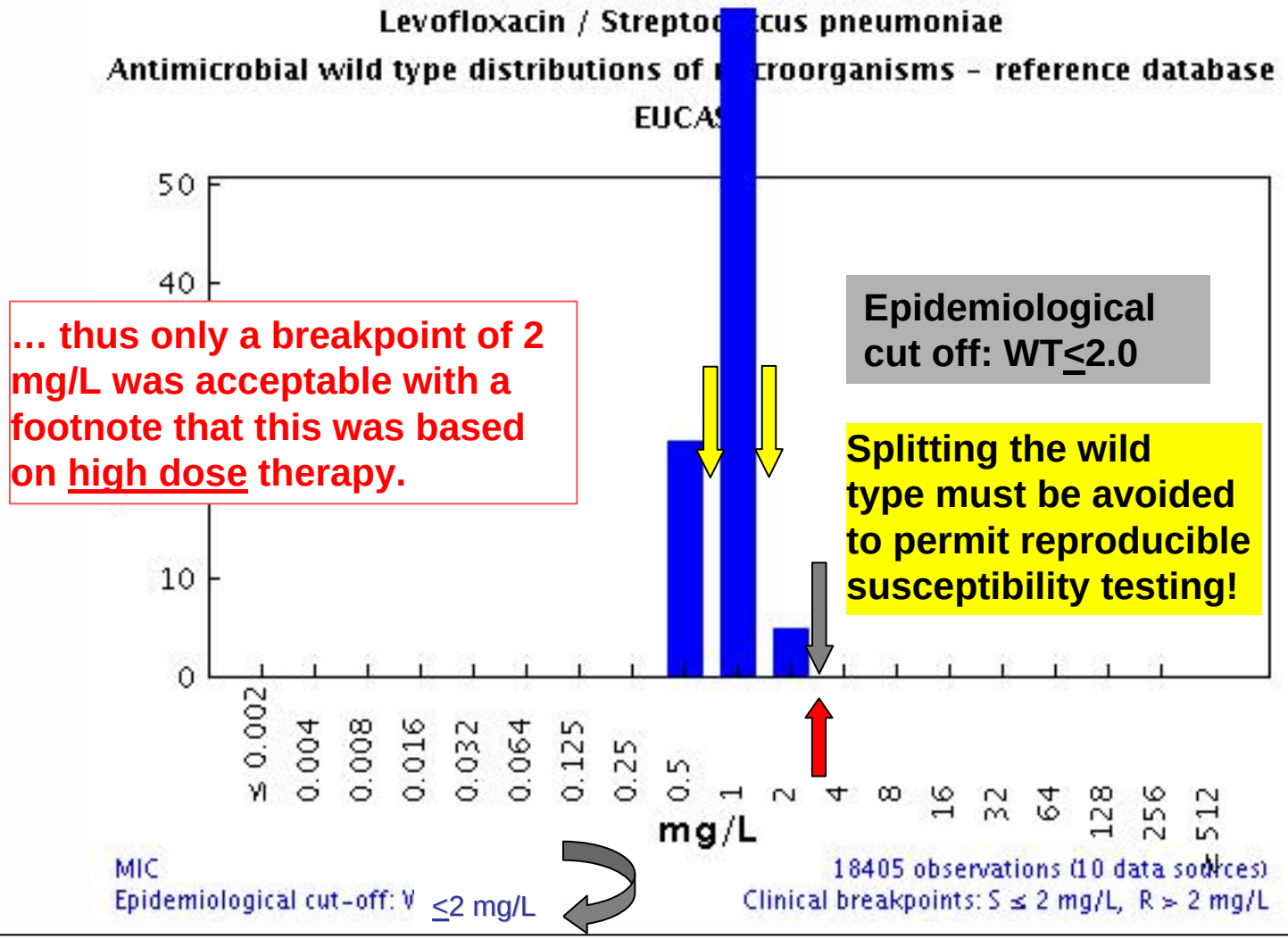
Pk/Pd

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[2] Click on antibiotic name to see wild type MIC distributions		Species-related breakpoints (S≤/R>)											Non-species related breakpoints[1] S≤/R>
		Entero-bacteriaceae[3]	*Pseudo-monas/*	*Acineto-bacter*	*Staphylo-coccus*	*Entero-coccus*	*Strepto-coccus A,B,C,G*	*S.pneu-moniae*[5]	*H.influenzae M.catarrhalis*	*N.gonorr-hoeae*	*N.menin-gitidis*[8]	*Gram-negative anaerobes*	
Ciprofloxacin	RD	0.5/1	0.5/1	1/1[4]	1/1[5]	--	--	0.125/2	0.5/0.5[7]	0.03/0.06	0.03/0.06	--	0.5/1
Levofloxacin	RD	1/2	1/2	1/2	1/2	--	1/2	2/2	1/1[7]	IE	IE	--	1/2
Moxifloxacin	RD	0.5/1	--	--	0.5/1	--	0.5/1	0.5/0.5	0.5/0.5[7]	IE	IE	IE	0.5/1
Norfloxacin	RD	0.5/1	--	--	--	--	--	--	--	IE	--	--	0.5/1
Ofloxacin	RD	0.5/1	--	--	1/1[3]	--	--	0.125/4	0.5/0.5[7]	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 to1 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)

eucast
Clinical Breakpoints

Clinical breakpoints

- Penicillins (2007)
- Cephalosporins
- Carbapenems
- Monobactams
- Fluoroquinolones
- Aminoglycosides
- Glycopeptides
- Oxazolidones
- Macrolides, ketolides & clindamycin, dalfopristine/-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[1]	Species-related breakpoints (S≤/R>)											Non-species related breakpoints[5] S≤/R>
	Enterobacteriaceae	*Pseudomonas*[2]	*Acinetobacter*[2]	*Staphylococcus*	*Enterococcus*[3]	*Streptococcus A,B,C,G*	*S.pneumoniae*	*H.influenzae M.catarrhalis*	*N.gonorrhoeae*	*N.meningitidis*	*Gram-negative anaerobes*	
Amikacin	8/16	8/16	8/16	8/16[4]	--	--	--	IE	--	--	--	8/16
Gentamicin	2/4	4/4	4/4	1/1	--	--	--	IE	--	--	--	2/4
Netilmicin	2/4	4/4	4/4	1/1	--	--	--	IE	--	--	--	2/4
Tobramycin	2/4	4/4	4/4	1/1	--	--	--	IE	--	--	--	2/4

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

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

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

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

Oxazolidinones - EUCAST clinical MIC breakpoints 30 april 2004

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

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

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

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

Breakpoints finalised at EUCAST Steering committee meeting 2004 April 30.

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

EUCAST clinical MIC breakpoints - cephalosporins - Mozilla Firefox

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http://www.srga.org/eucastwt/MICTAB/MICcephalosporins.html

Cephalosporins Click on antibiotic name to see wild type MIC distributions.		Species-related breakpoints (S≤/R>)							
		Enterobacteriaceae[2]	*Pseudomonas*[3]	*Acineto-bacter*	*Staphylo-coccus*[4]	*Entero-coccus*	*Strepto-coccus A,B,C,G*	*S.pneu-moniae*	*H.influen M.catarrh*
Cefazolin	RD	--	--	--	note[4]	--	--	--	--
Cefepime	RD	1/8	8/8	--	note[4]	--	0.5/*0.5*[6]	1/2	0.25/0.2
Cefotaxime	RD	1/2	--	--	note[4]	--	0.5/*0.5*[6]	0.5/2[6]	0.12/*0.1*
Ceftazidime	RD	1/8	8/8	--	--	--	--	--	--
Ceftriaxone	RD	1/2	--	--	note[4]	--	0.5/*0.5*[6]	0.5/2[6]	0.12/*0.1*
Cefuroxime	RD	8/8[5]	--	--	note[4]	--	0.5/*0.5*[6]	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 Enterobacteriacae. 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.

Done

Now: Partly Cloudy, 7° C Mon: 12° C Tue: 10° C

Carbapenems - EUCAST clinical MIC breakpoints 2006-06-20 (v 1.1)

Carbapenem Click on antibiotic name to see wild type MIC distributions		Species-related breakpoints (S≤/R>)											Non-species related breakpoints[1] S≤/R>
		Enterobacteriaceae	*Pseudo-monas*	*Acinetobacter*	*Staphylococcus*	*Enterococcus*	*Streptococcus A,B,C,G*	*S.pneumoniae*	*H.influenzae M.catarrhalis*	*N.gonorrhoeae*	*N.meningitidis*	*Gram-negative anaerobes*	
Ertapenem	RD	0.5/1	--	-	*note*[3]	--	0.5/0.5[4,7]	0.5/0.5[4,7]	0.5/0.5[4,7]	IE	--	1/1[8]	0.5/1
Imipenem	RD	2/8[2]	4/8[6]	1/8	*note*[3]	4/8[6]	2/2[4,7]	2/2[4,7]	2/2[4,7]	IE	--	2/8	2/8
Meropenem	RD	2/8	2/8	2/8	*note*[3]	--	2/2[4,7]	2/2[4,7]	2/2[4,7]	IE	0.25/0.25[5,7]	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 meningititis* 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.

http://www.srga.org/eucastwt/MICTAB/MICcarbapenems.html

EUCAST | EUCAST antimicrobial breakpoints | EUCAST clinical MIC breakpoin...

Carbapenems - EUCAST clinical MIC breakpoints 2006-06-20 (v 1.1)

Carbapenem Click on antibiotic name to see wild type MIC distributions		Species-related breakpoints (S≤/R>)											Non-species related breakpoints[1] S≤/R>
		Enterobac-teriaceae	*Pseudo-monas*	*Acin-to-bacter*	*Staphylo-coccus*	*Entero-coccus*	*Strepto-coccus A,B,C,G*	*S.pneu-moniae*	*H.influenzae M.catarrhalis*	*N.gonorr-hoeae*	*N.mening-itidis*	*Gram-negative anaerobes*	
Ertapenem	RD	0.5/1	--	-	*note*[3]	--	0.5/0.5[4,7]	0.5/0.5[4,7]	0.5/0.5[4,7]	IE	--	1/1[8]	0.5/1
Imipenem	RD	2/8[2]	4/8[6]	/8	*note*[3]	4/8[6]	2/2[4,7]	2/2[4,7]	2/2[4,7]	IE	--	2/8	2/8
Meropenem	RD	2/8	2/8	2/8	*note*[3]	--	2/2[4,7]	2/2[4,7]	2/2[4,7]	IE	0.25/0.25[5,7]	2/8	2/8

1. Non-species related breakpoints have been determined mainly on … given a species-specific breakpoint and not for those species where susc…
2. *Proteus* and *Morganella* species are considered poor targets for i…
3. Susceptibility of staphylococci to carbapenems is inferred from t…
4. Imipenem and ertapenem are not used for meningitis. Meropener…
5. Meropenem breakpoints in *Neisseria meningitidis* relates to meni…
6. The imipenem S/I breakpoint for *Pseudomonas* and *Enterococcu…*
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.

The breakpoints for meropenem are establisehd as minimal and maximal values

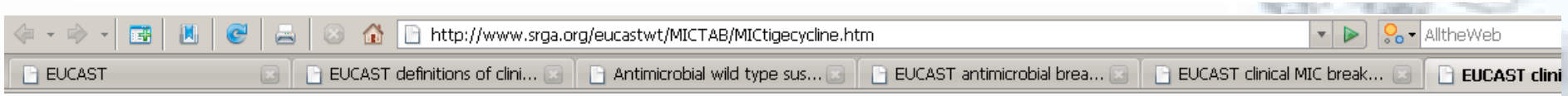
- **2 mg/L fof a low dose (0.5 g 3 X / day)**
- **max. 8 mg/L for a high dose (1 g 3 X / day).**

-- = 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.

Can we have access to the rationale ?



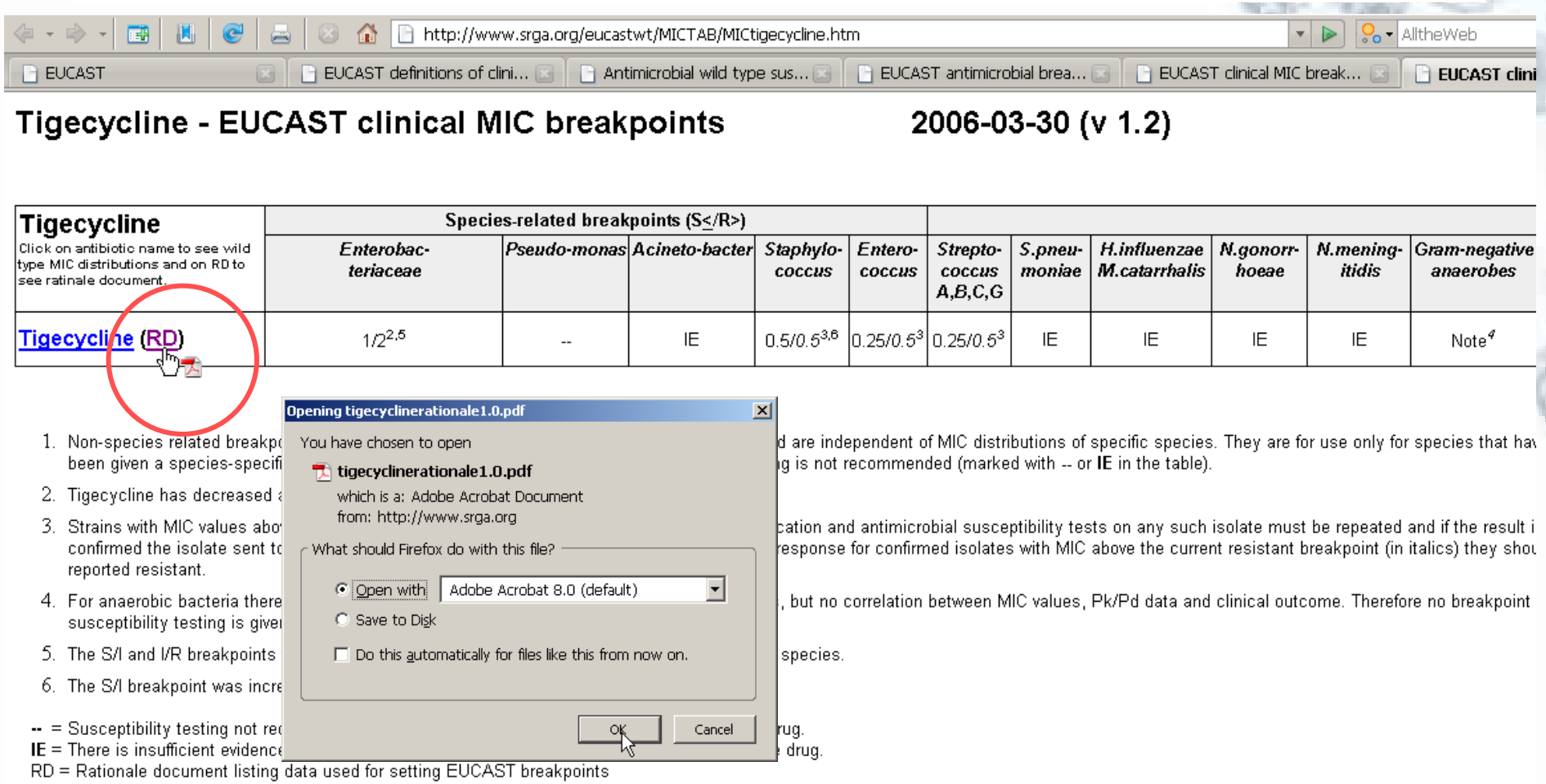
Tigecycline - EUCAST clinical MIC breakpoints 2006-03-30 (v 1.2)

Tigecycline Click on antibiotic name to see wild type MIC distributions and on RD to see ratinale document.	**Species-related breakpoints (S≤/R>)**										
	Enterobac-teriaceae	***Pseudo-monas***	***Acineto-bacter***	***Staphylo-coccus***	***Entero-coccus***	***Strepto-coccus A,B,C,G***	***S.pneu-moniae***	***H.influenzae M.catarrhalis***	***N.gonorr-hoeae***	***N.mening-itidis***	***Gram-negative anaerobes***
Tigecycline (RD)	1/2[2,5]	--	IE	0.5/0.5[3,6]	0.25/0.5[3]	0.25/0.5[3]	IE	IE	IE	IE	Note[4]

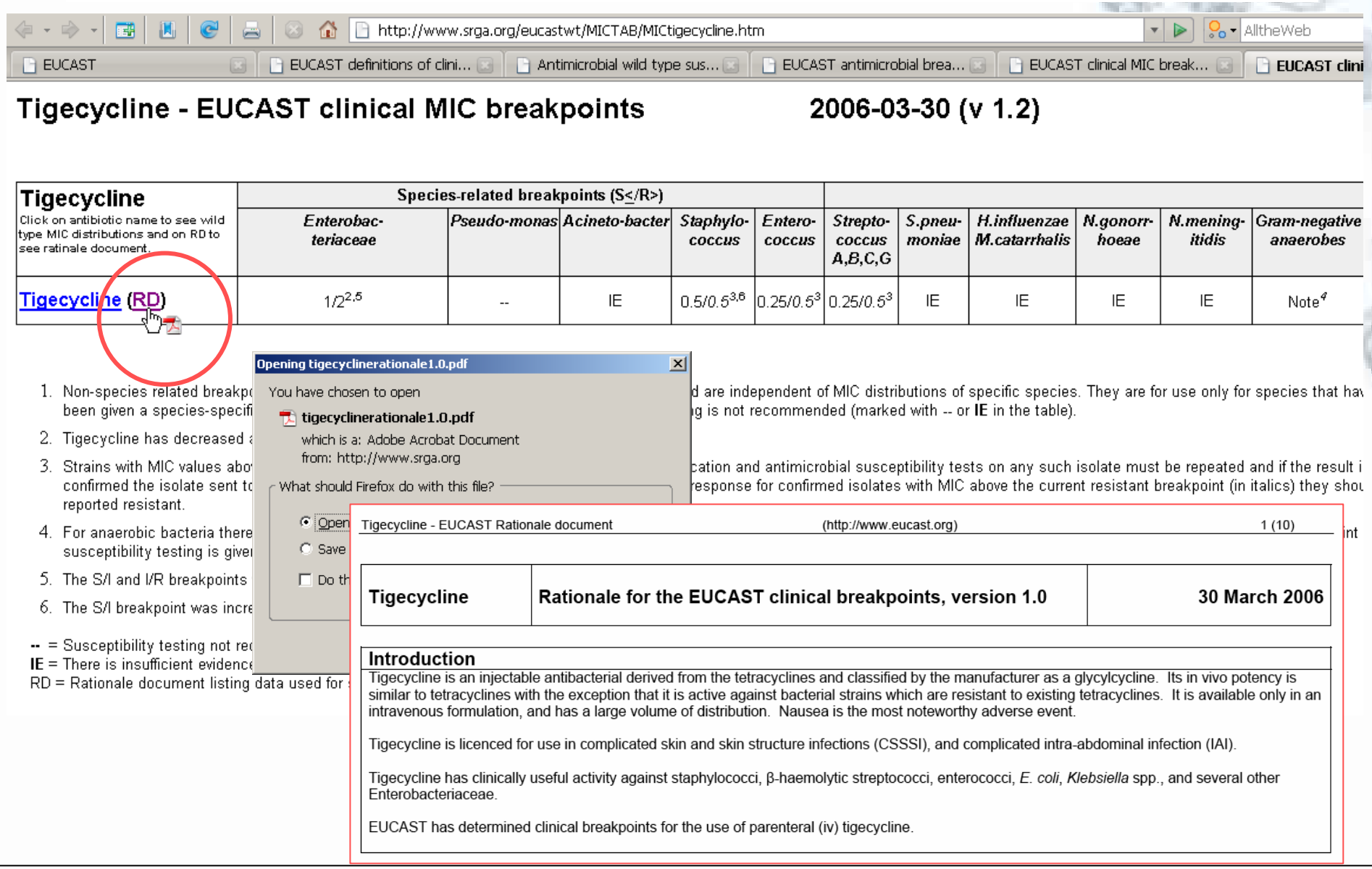
1. Non-species related breakpoints have been determined mainly on the basis of Pk/Pd data and are independent of MIC distributions of specific species. They are for use only for species that hav been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or **IE** in the table).
2. Tigecycline has decreased activity against Morganella, Proteus and Providencia.
3. 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 i 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 shou reported resistant.
4. For anaerobic bacteria there is clinical evidence of activity in mixed intra-abdominal infections, but no correlation between MIC values, Pk/Pd data and clinical outcome. Therefore no breakpoint susceptibility testing is given.
5. The S/I and I/R breakpoints were increased to avoid dividing wild type distributions of relevant species.
6. The S/I breakpoint was increased to avoid dividing wild type distributions of relevant species.

-- = 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

Can we have access to the rationale ?



Can we have access to the rationale ?



http://www.srga.org/eucastwt/MICTAB/MICtigecycline.htm

EUCAST | EUCAST definitions of clini... | Antimicrobial wild type sus... | EUCAST antimicrobial brea... | EUCAST clinical MIC break... | EUCAST clini

Tigecycline - EUCAST clinical MIC breakpoints 2006-03-30 (v 1.2)

Tigecycline Click on antibiotic name to see wild type MIC distributions and on RD to see ratinale document.	Species-related breakpoints (S≤/R>)										
	Enterobac-teriaceae	*Pseudo-monas*	*Acineto-bacter*	*Staphylo-coccus*	*Entero-coccus*	*Strepto-coccus A,B,C,G*	*S.pneu-moniae*	*H.influenzae M.catarrhalis*	*N.gonorr-hoeae*	*N.mening-itidis*	*Gram-negative anaerobes*
Tigecycline (RD)	1/2[2,5]	--	IE	0.5/0.5[3,6]	0.25/0.5[3]	0.25/0.5[3]	IE	IE	IE	IE	Note[4]

1. Non-species related breakpo... been given a species-specifi... d are independent of MIC distributions of specific species. They are for use only for species that hav... g is not recommended (marked with -- or **IE** in the table).
2. Tigecycline has decreased a...
3. Strains with MIC values abo... confirmed the isolate sent to... reported resistant. ...cation and antimicrobial susceptibility tests on any such isolate must be repeated and if the result i... response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they shou...
4. For anaerobic bacteria there... susceptibility testing is give... ...int
5. The S/I and I/R breakpoints ...
6. The S/I breakpoint was incre...

-- = Susceptibility testing not re...
IE = There is insufficient evidence...
RD = Rationale document listing data used for ...

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

Save

Do th...

Tigecycline - EUCAST Rationale document (http://www.eucast.org) 1 (10)

Tigecycline	Rationale for the EUCAST clinical breakpoints, version 1.0	30 March 2006

Introduction

Tigecycline is an injectable antibacterial derived from the tetracyclines and classified by the manufacturer as a glycylcycline. Its in vivo potency is similar to tetracyclines with the exception that it is active against bacterial strains which are resistant to existing tetracyclines. It is available only in an intravenous formulation, and has a large volume of distribution. Nausea is the most noteworthy adverse event.

Tigecycline is licenced for use in complicated skin and skin structure infections (CSSSI), and complicated intra-abdominal infection (IAI).

Tigecycline has clinically useful activity against staphylococci, β-haemolytic streptococci, enterococci, *E. coli*, *Klebsiella* spp., and several other Enterobacteriaceae.

EUCAST has determined clinical breakpoints for the use of parenteral (iv) tigecycline.

Can we have access to the rationale ?

6. Monte Carlo simulations and Pk/Pd breakpoints

Figure 3 shows the probability of target attainment for *E. coli*. The target is taken from the clinical study on and complicated intra-abdominal infection. The use of this target in the Monte Carlo simulations suggests a Pk/Pd breakpoint of ≤ 0.25-0.5mg/L. Similarly, for Gram-positives simulations suggest a Pk/Pd breakpoint of ≤ 0.25 mg/L using the target of 12.5 obtained from the clinical cSSSI study (data not shown).

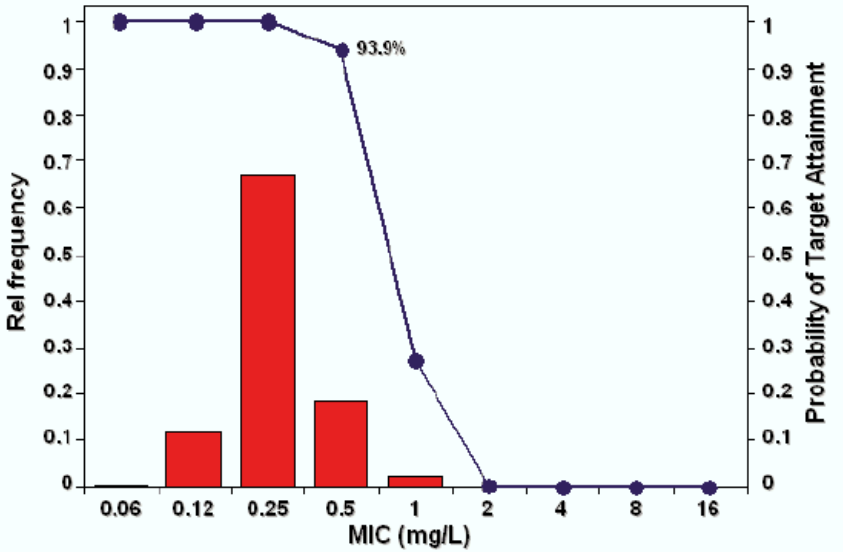


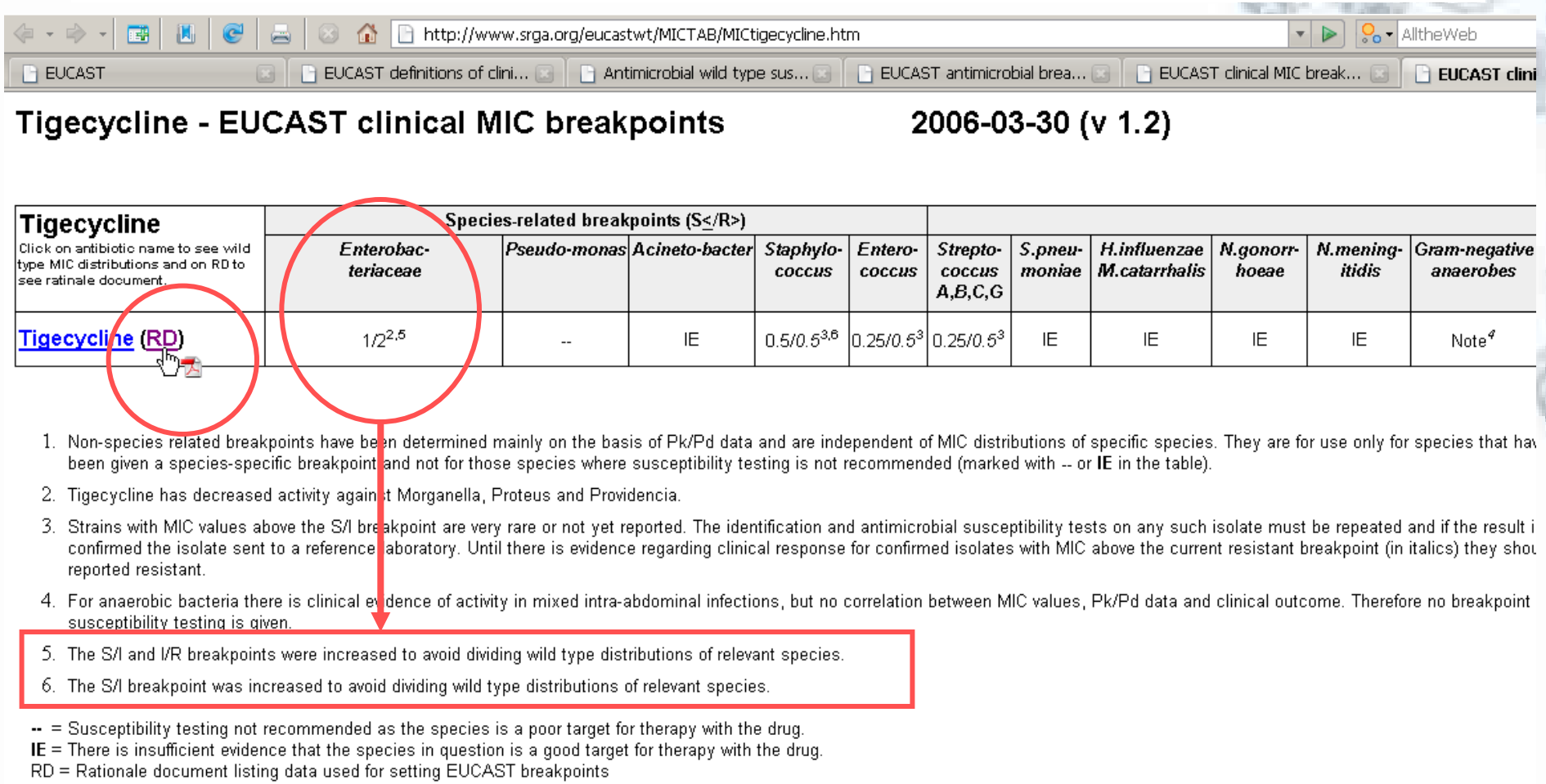
Figure 3. Probabilities of target attainment for tigecycline. Probability of Target Attainment Against *E. coli* at the CART-Identified Serum AUC/MIC Ratio of 6.96. Data on file, Wyeth Inc.

Tigecycline is licenced for use in complicated skin and skin structure infections (CSSSI), and complicated intra-abdominal infection (IAI).

Tigecycline has clinically useful activity against staphylococci, β-haemolytic streptococci, enterococci, *E. coli*, *Klebsiella* spp., and several other Enterobacteriaceae.

EUCAST has determined clinical breakpoints for the use of parenteral (iv) tigecycline.

You need to understand the rationale



http://www.srga.org/eucastwt/MICTAB/MICtigecycline.htm

EUCAST | EUCAST definitions of clini... | Antimicrobial wild type sus... | EUCAST antimicrobial brea... | EUCAST clinical MIC break... | EUCAST clini

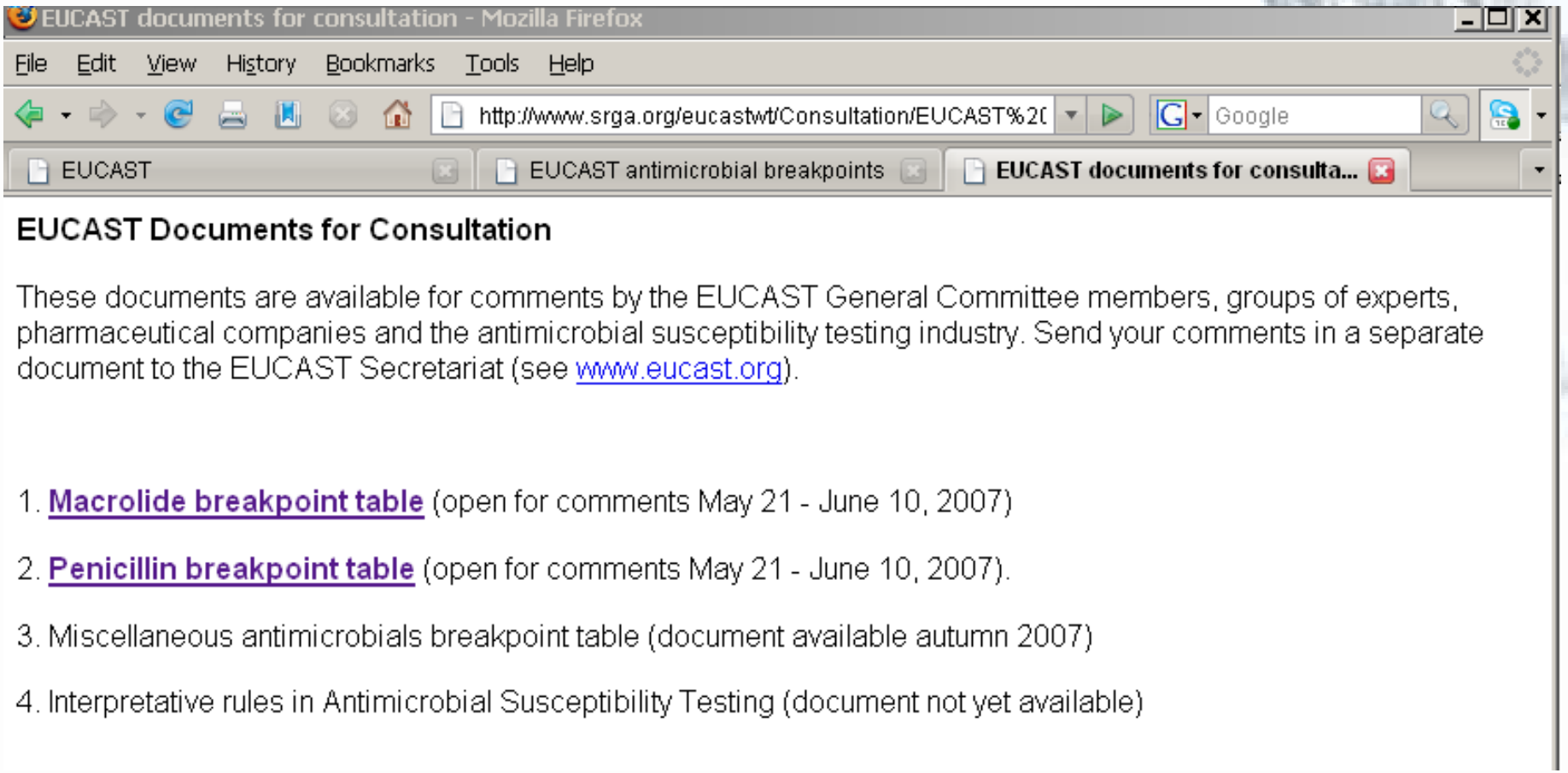
Tigecycline - EUCAST clinical MIC breakpoints 2006-03-30 (v 1.2)

Tigecycline Click on antibiotic name to see wild type MIC distributions and on RD to see ratinale document.	Species-related breakpoints (S≤/R>)										
	Enterobac-teriaceae	*Pseudo-monas*	*Acineto-bacter*	*Staphylo-coccus*	*Entero-coccus*	*Strepto-coccus A,B,C,G*	*S.pneu-moniae*	*H.influenzae M.catarrhalis*	*N.gonorr-hoeae*	*N.mening-itidis*	*Gram-negative anaerobes*
Tigecycline (RD)	1/2[2,5]	--	IE	0.5/0.5[3,6]	0.25/0.5[3]	0.25/0.5[3]	IE	IE	IE	IE	Note[4]

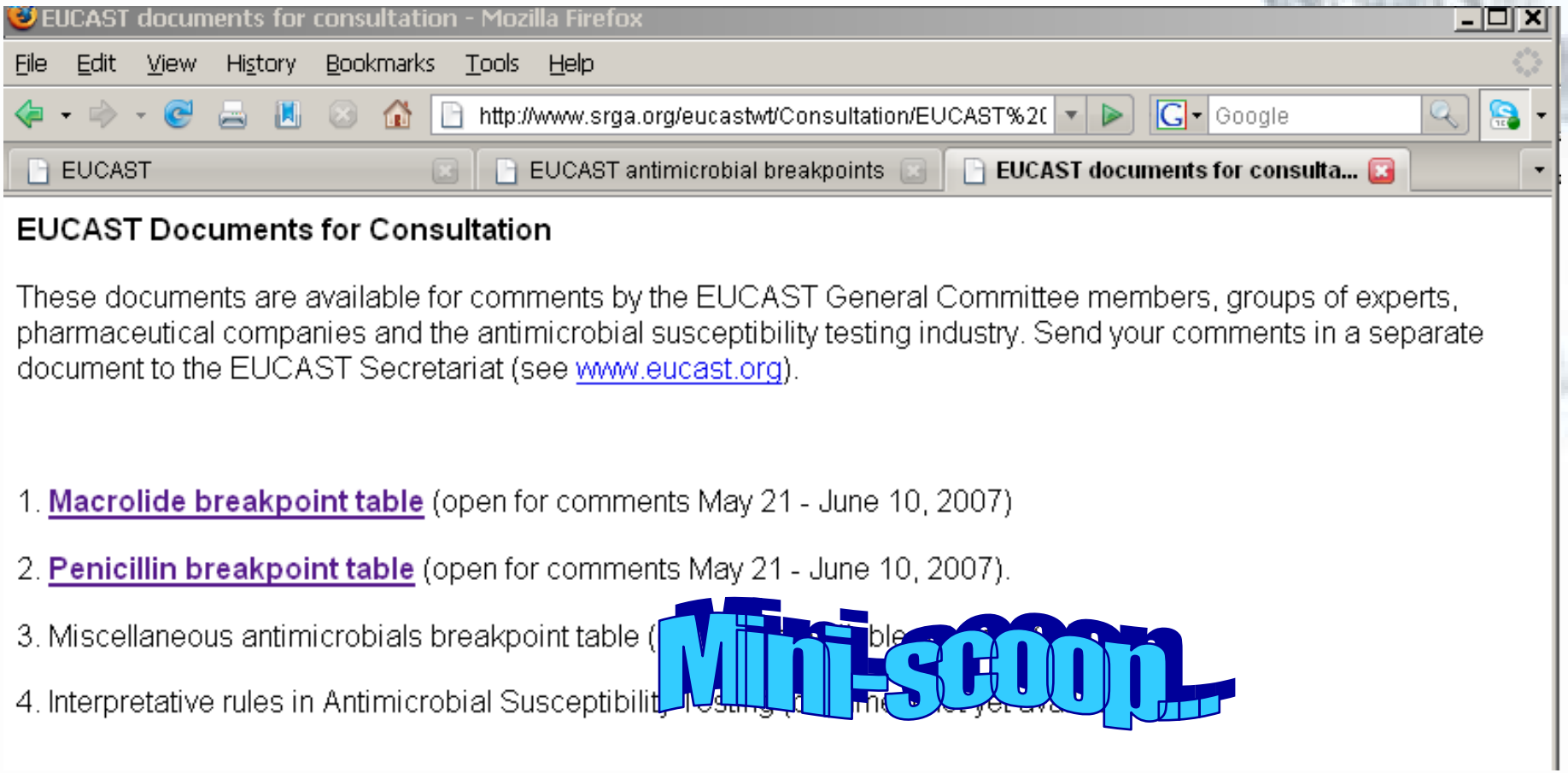
1. Non-species related breakpoints have been determined mainly on the basis of Pk/Pd data and are independent of MIC distributions of specific species. They are for use only for species that hav been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or **IE** in the table).
2. Tigecycline has decreased activity against Morganella, Proteus and Providencia.
3. 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 i 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 shou reported resistant.
4. For anaerobic bacteria there is clinical evidence of activity in mixed intra-abdominal infections, but no correlation between MIC values, Pk/Pd data and clinical outcome. Therefore no breakpoint susceptibility testing is given.
5. The S/I and I/R breakpoints were increased to avoid dividing wild type distributions of relevant species.
6. The S/I breakpoint was increased to avoid dividing wild type distributions of relevant species.

-- = 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

But about "not-yet-published" breakpoints ?



Soon ...



- **Likely breakpoint for piperacillin/tazobactam:**
  - **8/16 for *Enterobacterriaceae***
  - **16/16 for *Pseudomonas***
    (but with a high dose !!)

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.

EMEA – 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
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.

En wat voor <u>België</u> / Et en Belgique ?

Another scoop!

Des discussions animées sont en cours …

La Société belge d'infectiologie et de microbiologie clinique (= *Belgische Vereniging voor Infectiologie en Klinische Microbiologie*) pilote l'opération…

Sensibiliseringscampagnes, het verzamelen van informatie en het indentificatie van problemen starten <u>in november 2007</u>... en lopen verder in 2008 ...

De uiteindelijke bedoeling is de verandering in België te introduceren op <u>1 januari 2009</u>

Les francophones en Nederlandstaligen gaan akkoord !!

The future of EUCAST breakpoints

- Are now the official breakpoints for all new drugs and for all new resubmissions to the EMEA
- Will be implemented for diagnostic in 2007-2008 (manufacturers aleardy offer adaptations for customers requesting them)
- May become future International Standards

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

Done…

- 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)

But is NCCLS (now CLSI…) still authorized to define breakpoints ?

The (doomed) future of NCCLS (CLSI) breakpoints

- Over the last 2 years, FDA has reasserted its legal rights to define official breakpoints (and removed if from NCCLS, hence its change of name)
- CLSI may set breakpoints **after** FDA has defined them, but will NOT publish them if they are different from those of the FDA... (CLSI may petition the FDA for breakpoint revision after 2 years...)
- CLSI will try to become the specialized committee of the FDA for setting breakpoints ... But FDA may not accept this...
- In the meantime, only FDA breakpoints will be legal ... and will be essentially geared to the protection of the **American** Public
- Other countries will have no direct impact on the FDA-decision process ... and may, therefore, look for another, more "non-national" body for advice and orientation ... This may be CLSI ... or EUCAST...

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

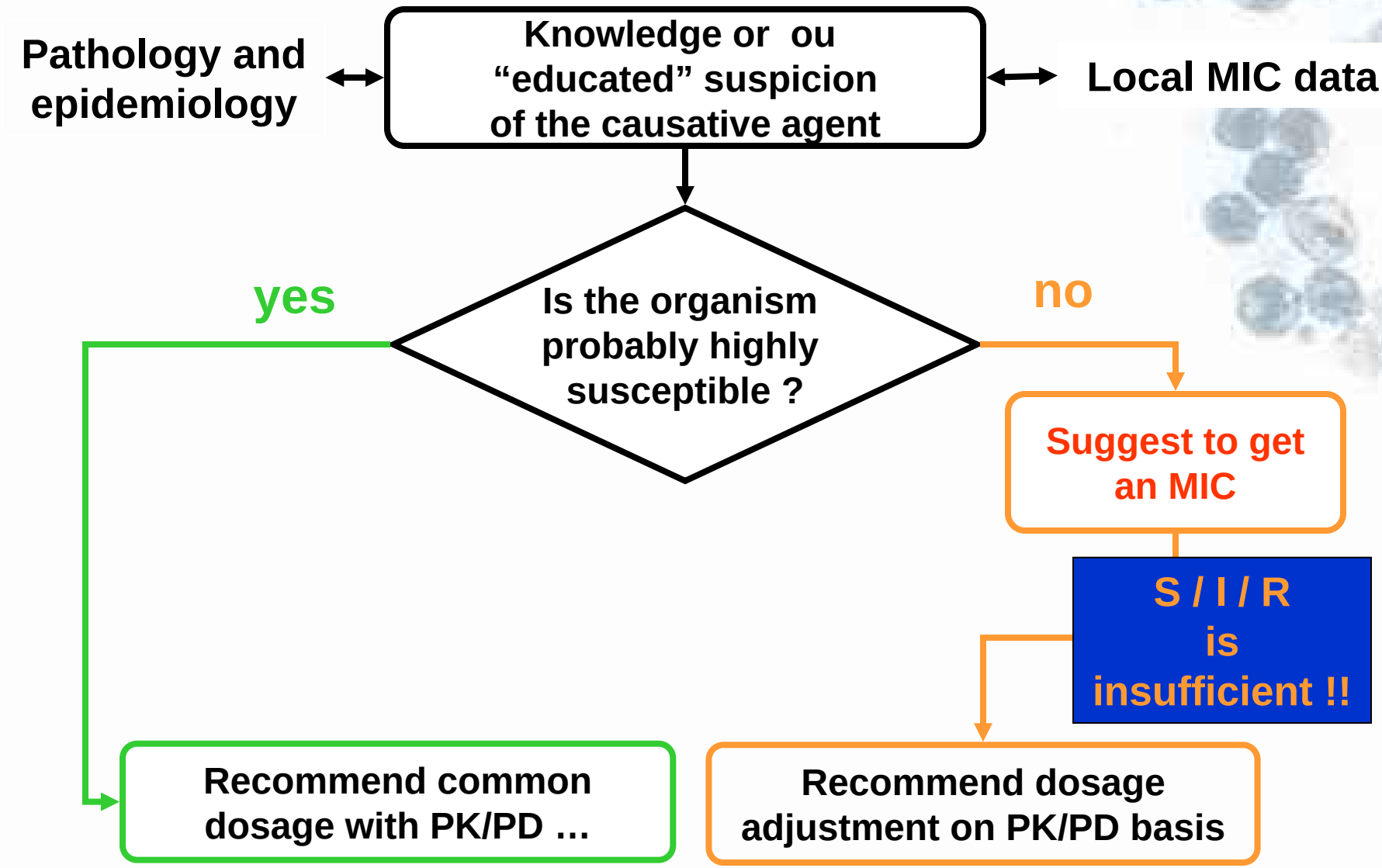
Will good breakpoints solve everything ?

- 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 ?)

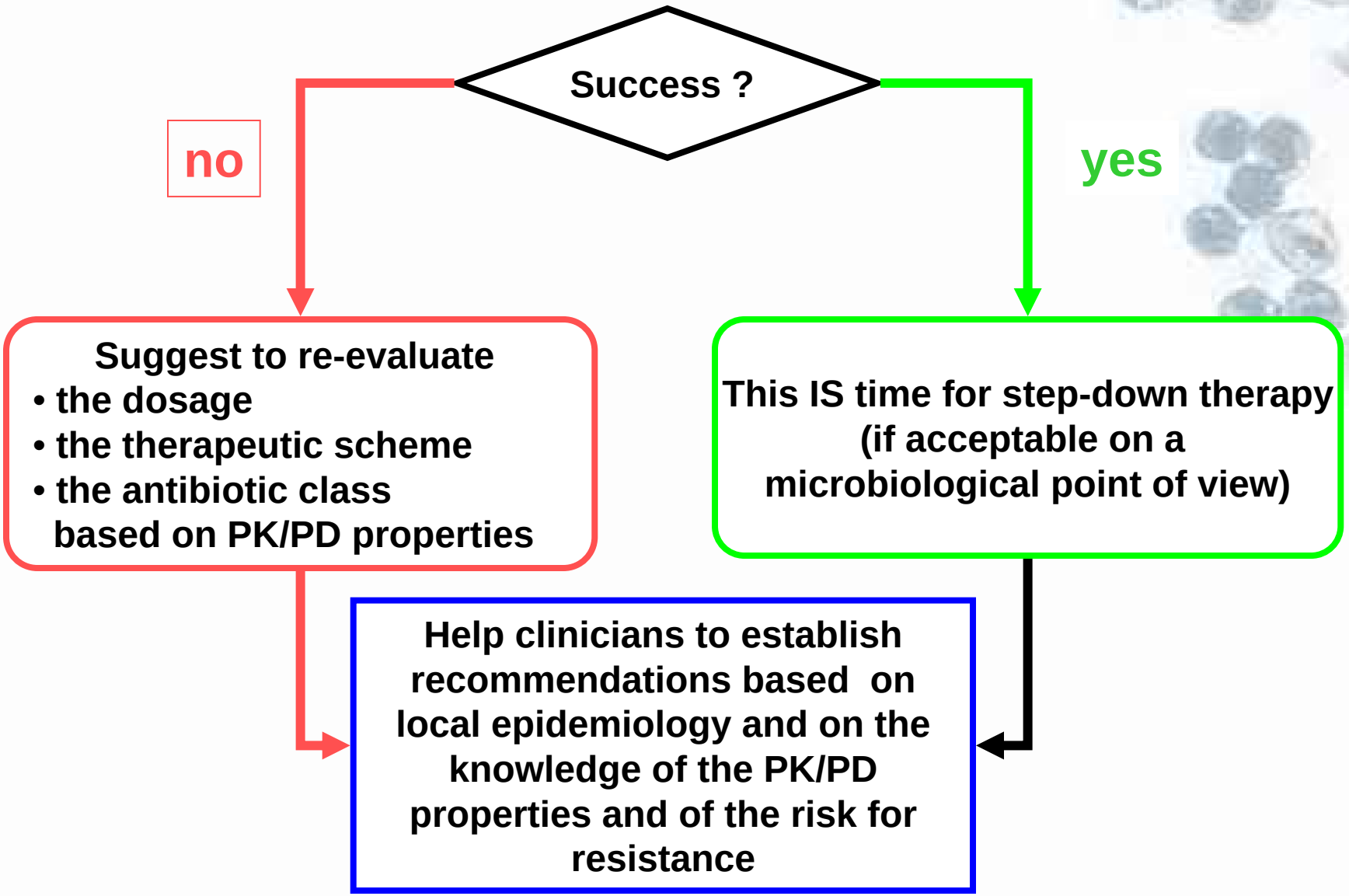
- MIC distributions (local and national) must be obtained regularly to check for decreased susceptibilities (epidemiology) and reassessment of posologies and/or therapeutic choices (hospital…)

- Difficult-to-treat patients must be evaluated individually (and MIC obtained …) and questionable drugs must be scrutinized…

A key to success ...



A key to success (follow.) ...



But do not forget to go and enjoy Athens …

All slides will be available on http://www.facm.ucl.ac.be or from AstraZeneca (upon request)