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 (2006 -)

Former member of the EUCAST steering committee (2008-2010)

Member of the European PK/PD of Antinfectives Study Group

Unité de pharmacologie cellulaire et moléculaire

Université catholique de Louvain (UCL), Bruxelles

UCL

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

EUCAST

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

With the support of *Wallonie-Bruxelles International*

Bach Mai Hospital, Hanoi, Vietnam – 15 April 2011

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All slides will be (soon) available on
http://www.facm.ucl.ac.be
Look for "Advanced Courses"

Bach Mai Hospital, Hanoi, Vietnam – 15 April 2011

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 ?

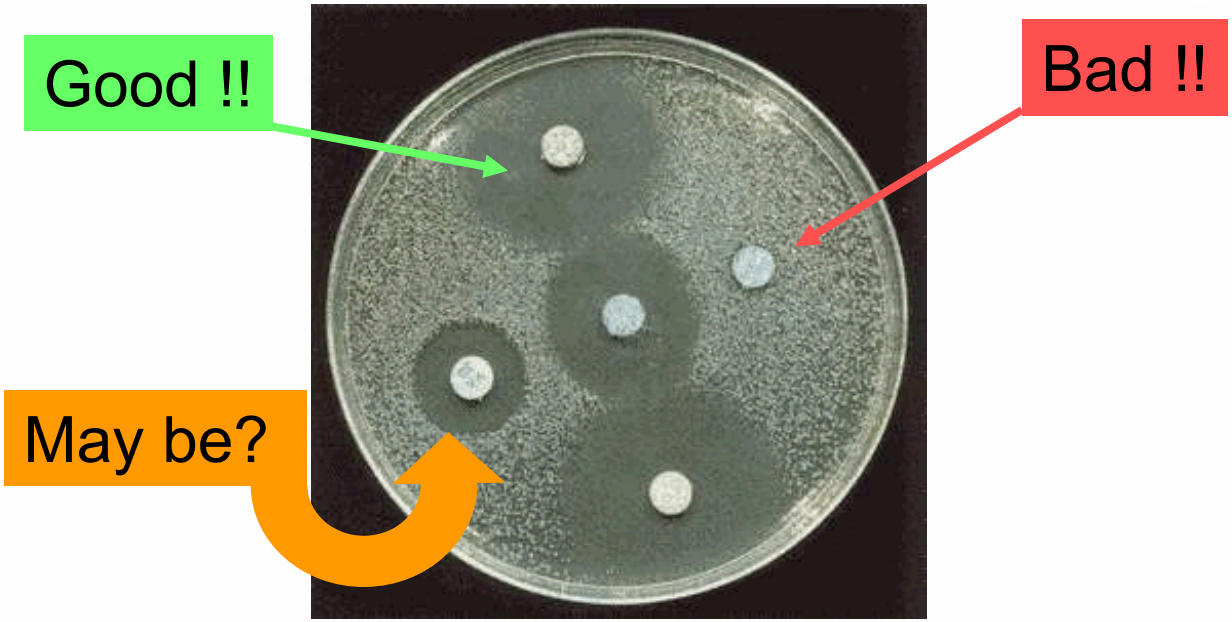
To be honest, I always wondered …

Why do we need breakpoints ?

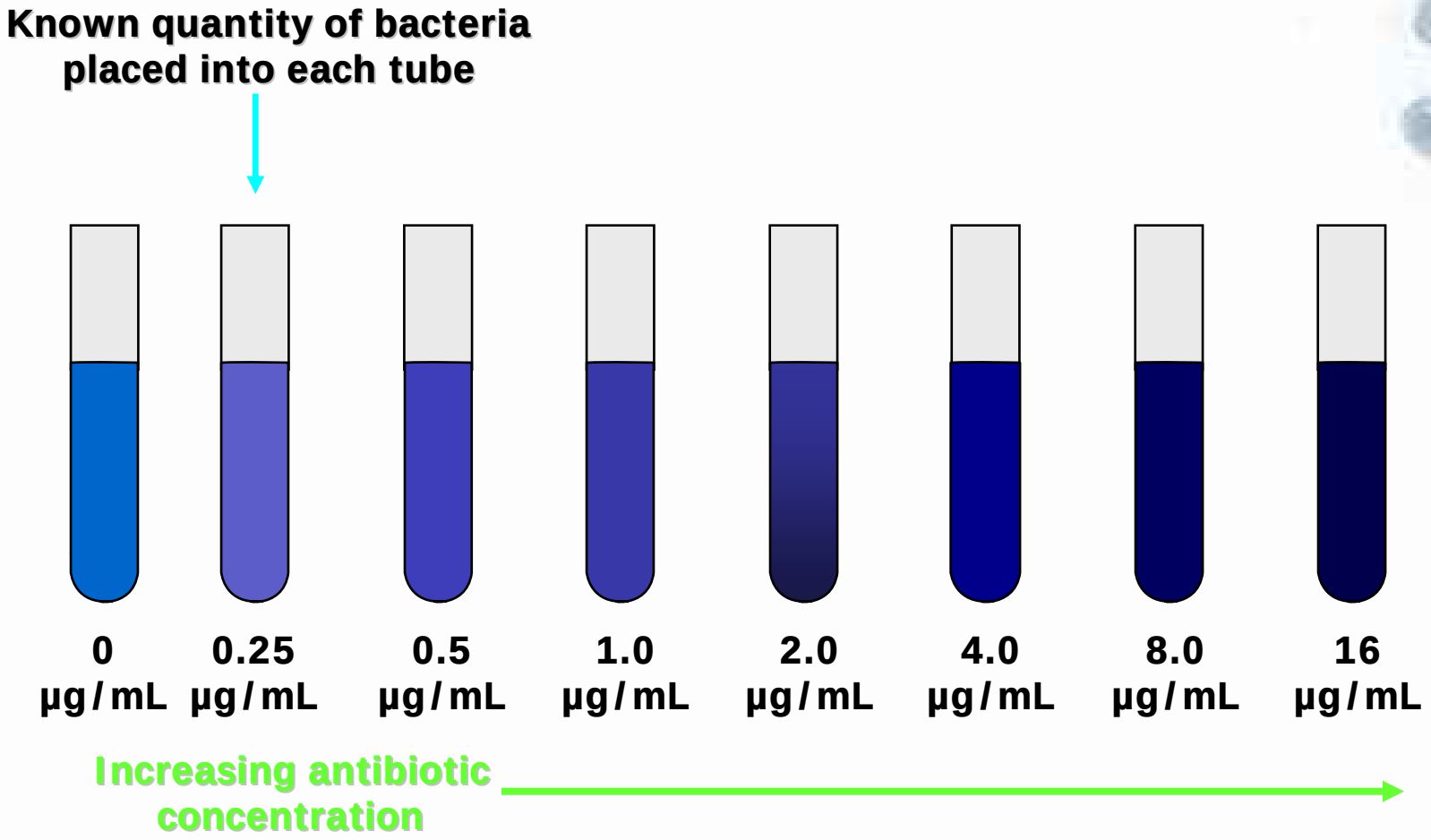
but perhaps…

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 …



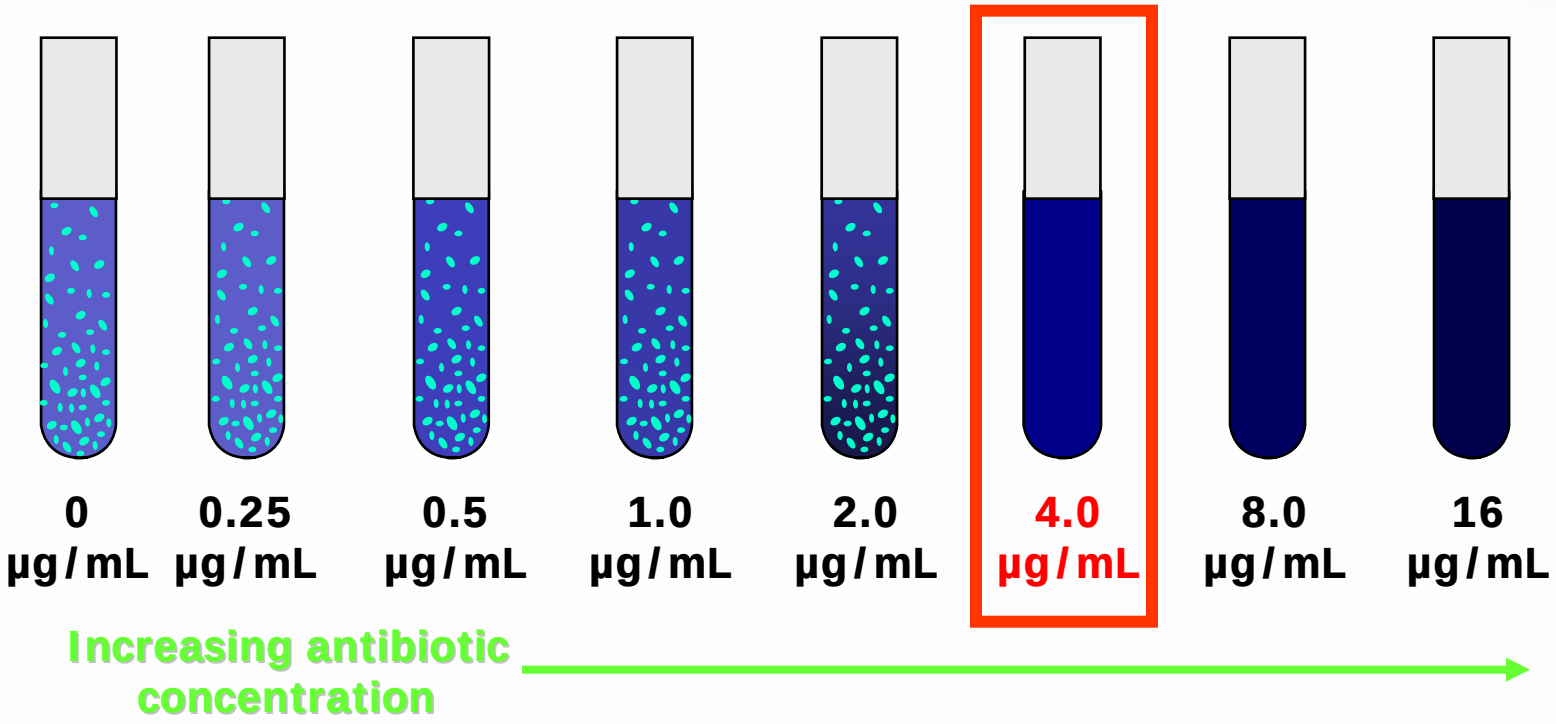
Starting from the beginning… The MIC !



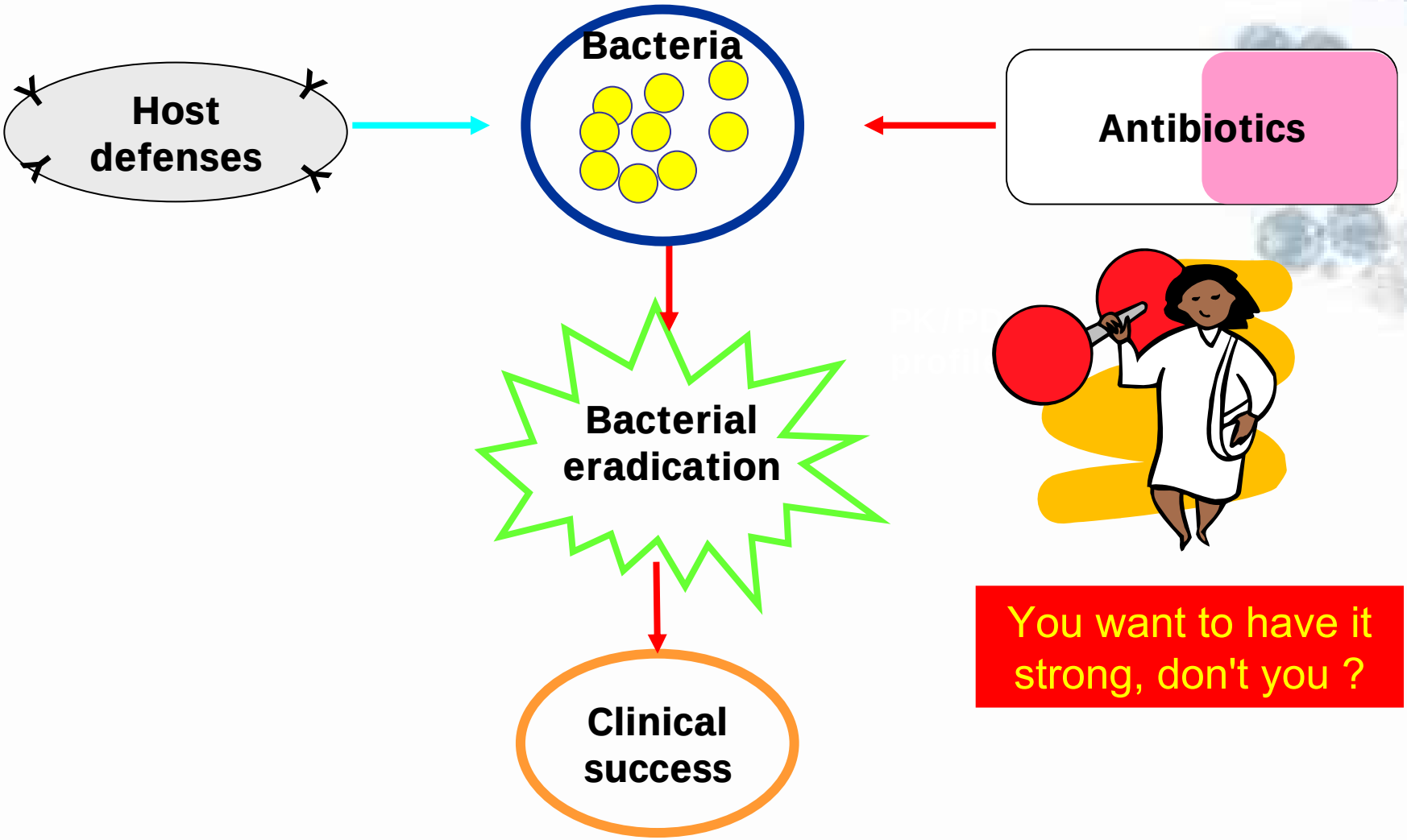
Starting from the beginning… The MIC !

24 h later ….

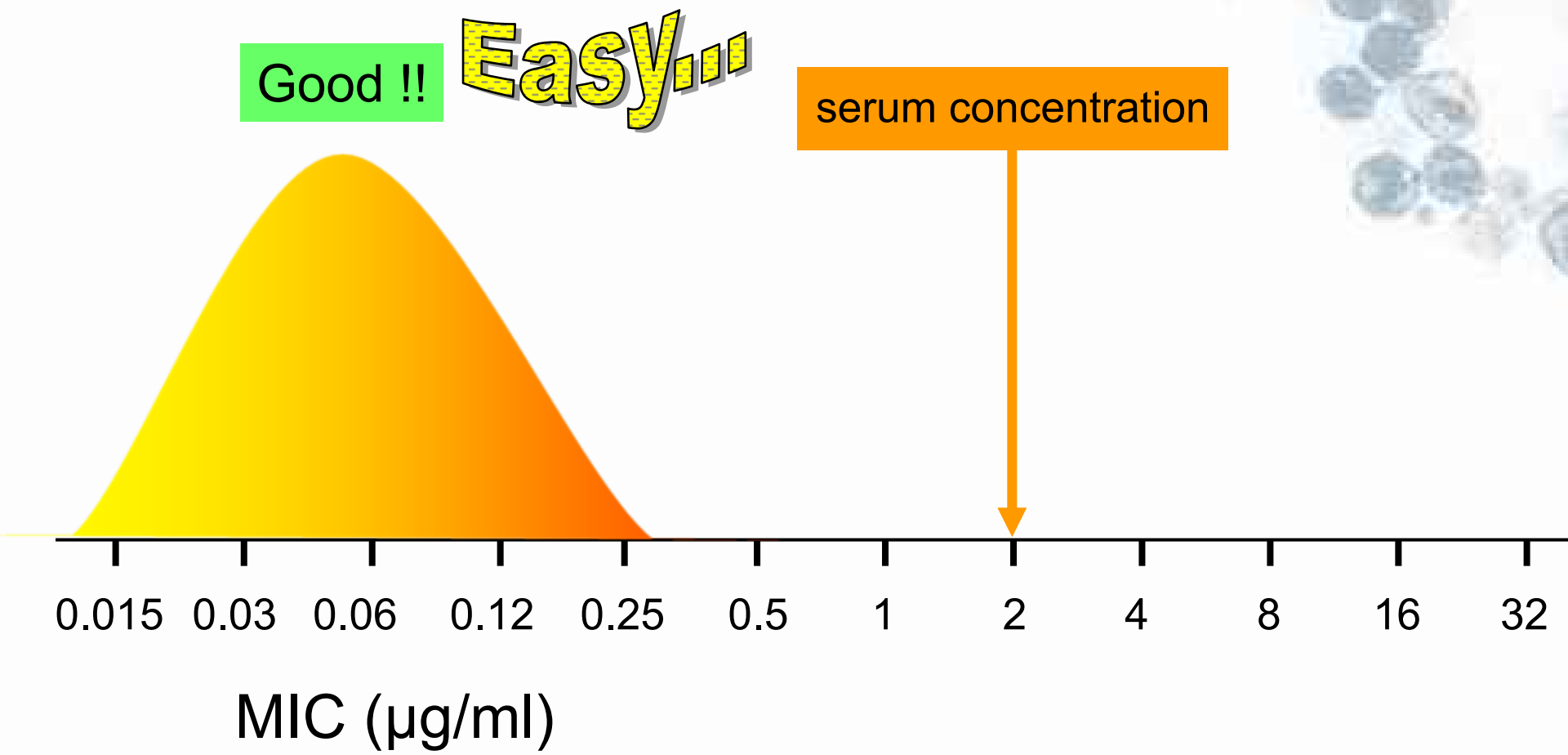
Lowest concentration of an antimicrobial that results in the inhibition of visible growth of a microorganism



What do you do with an MIC !

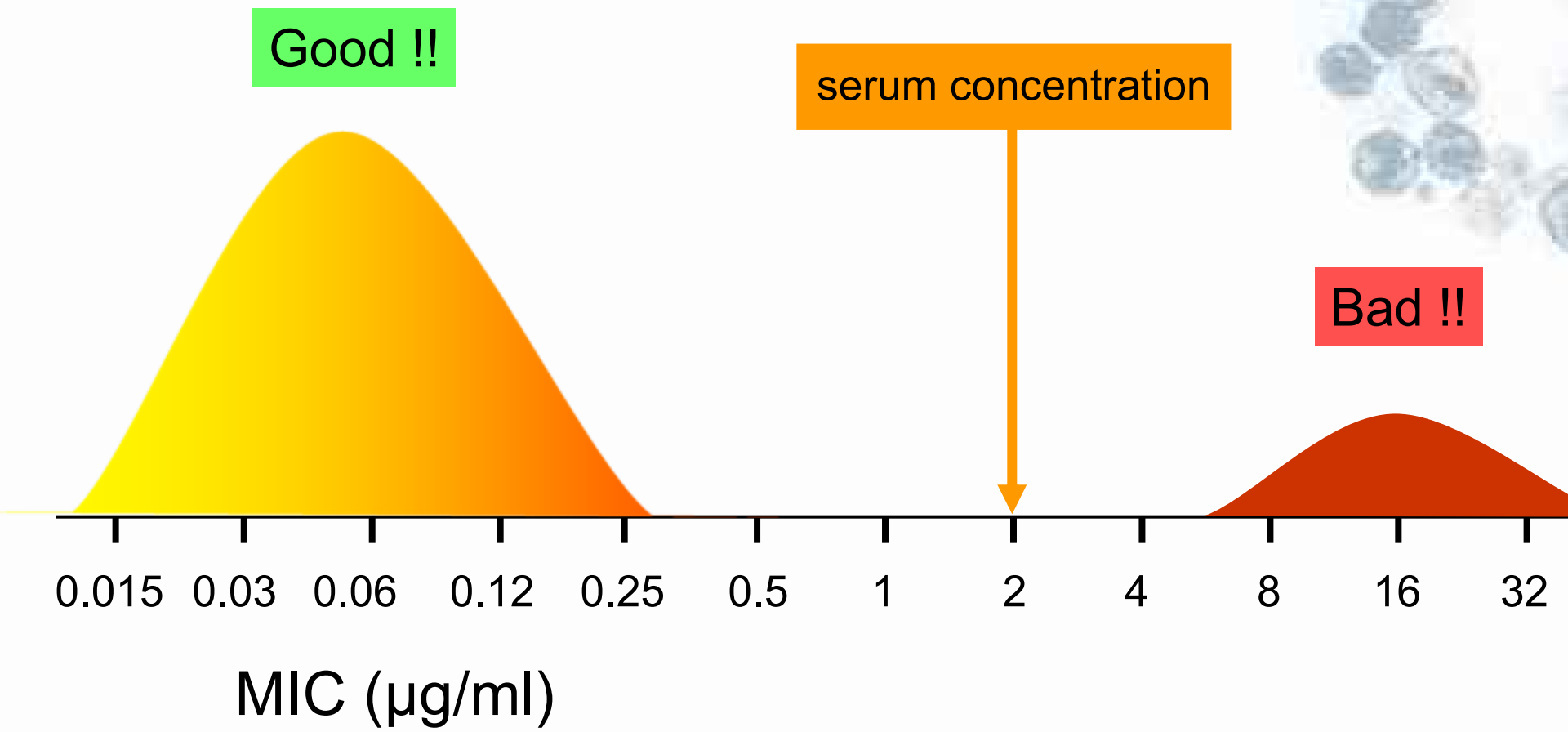


But, what is strong ?



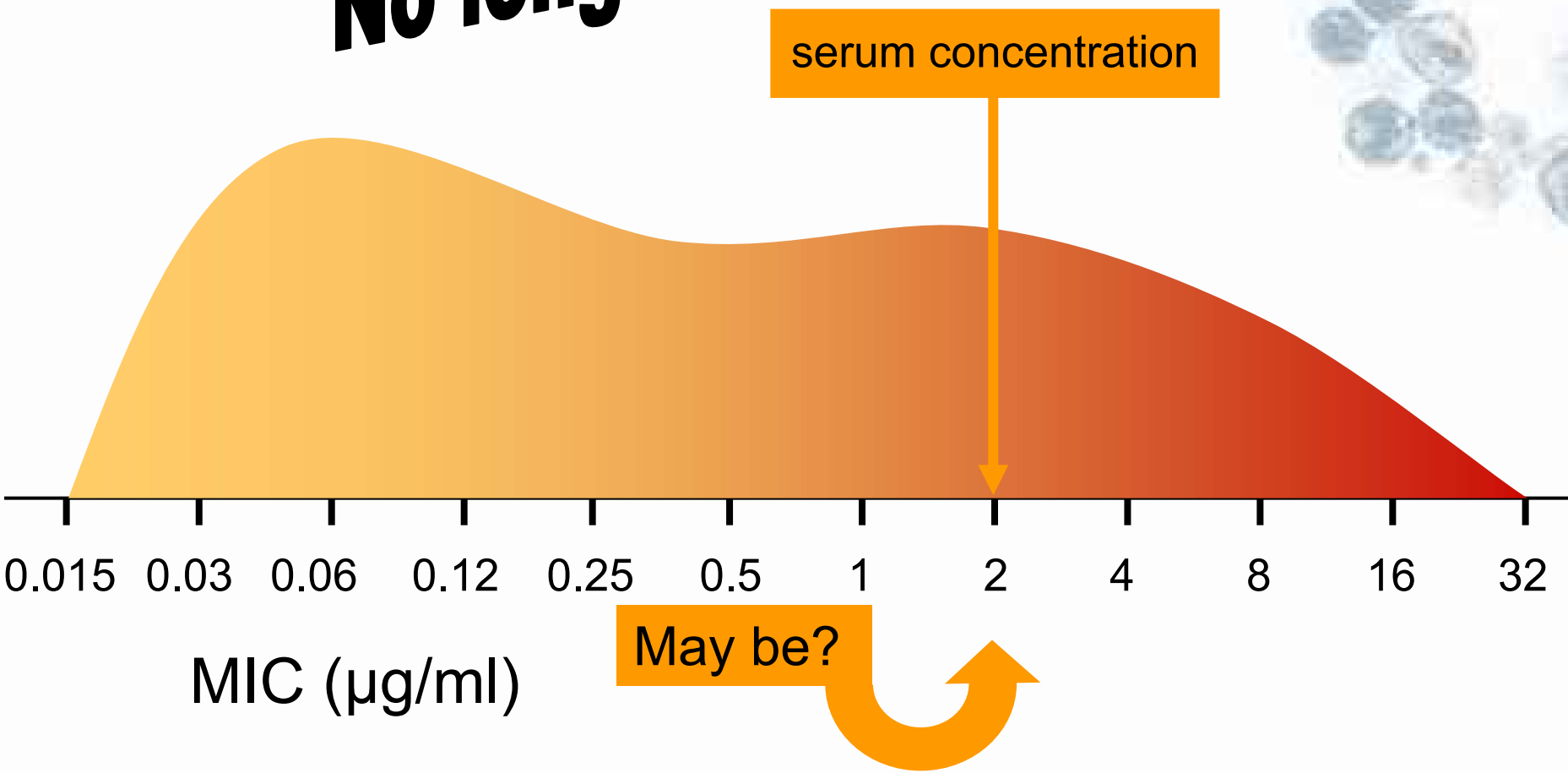
But, what is strong ?

Still Easy...



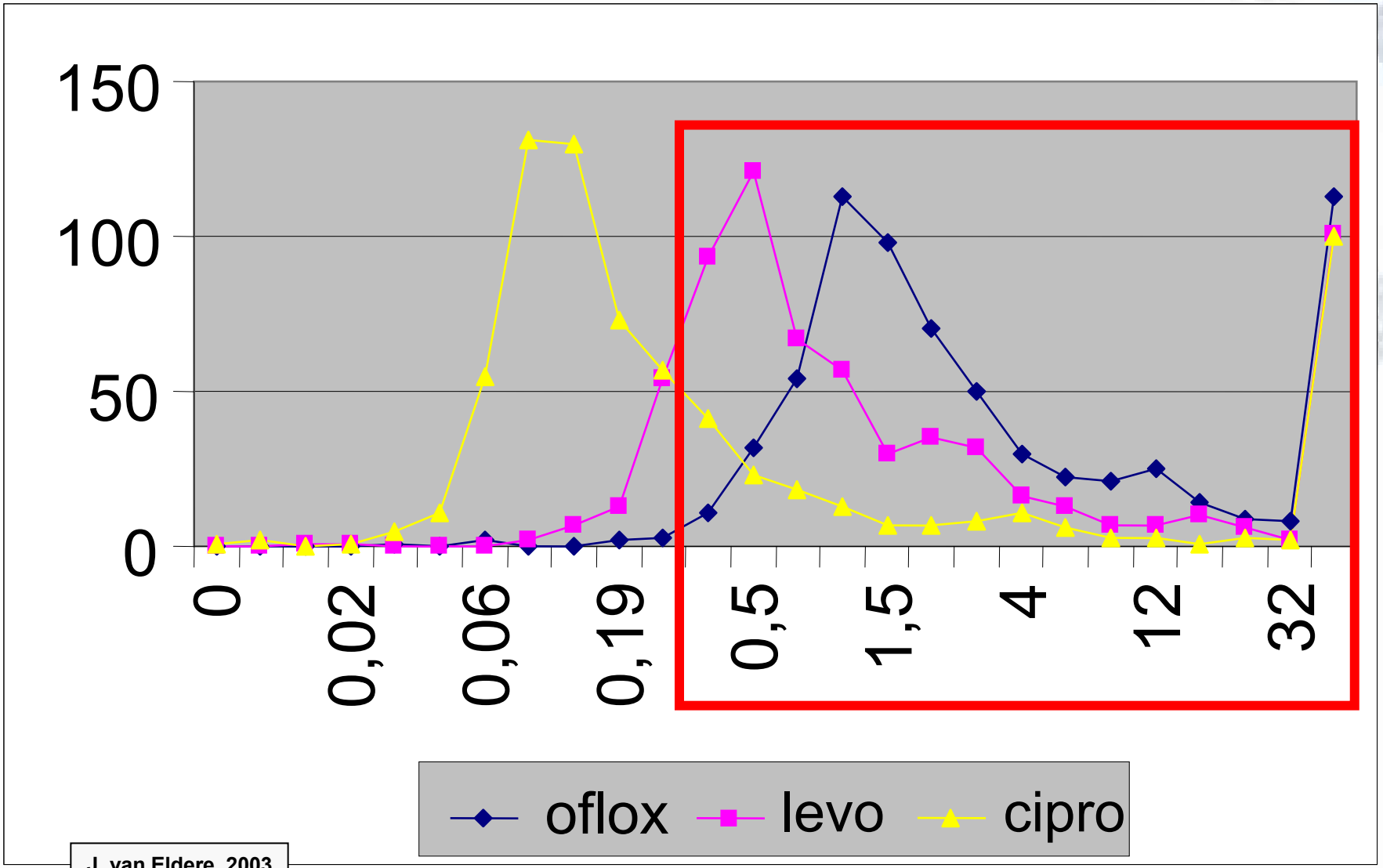
But, what is strong ?

No longer so easy...



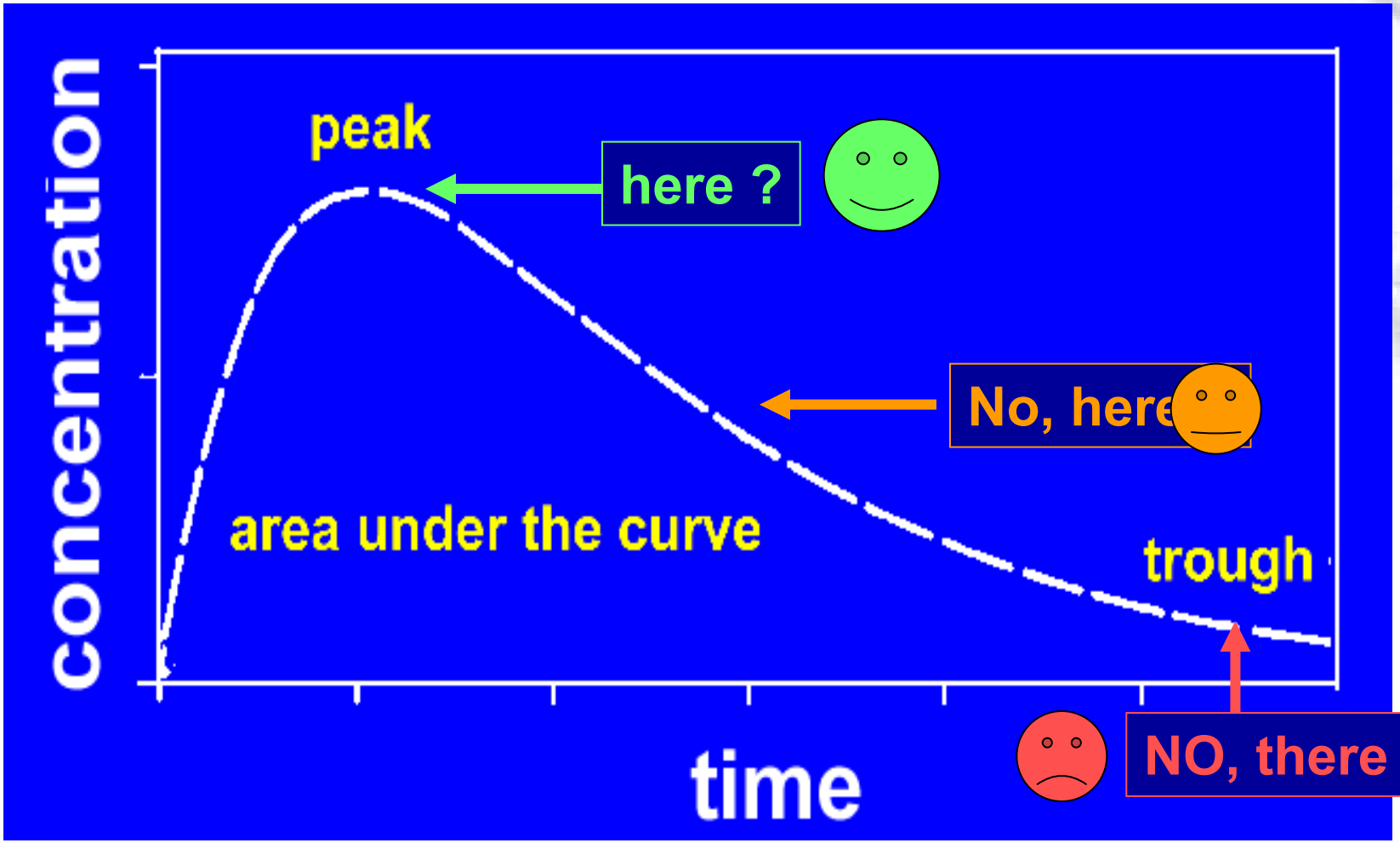
If you do not believe me…

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

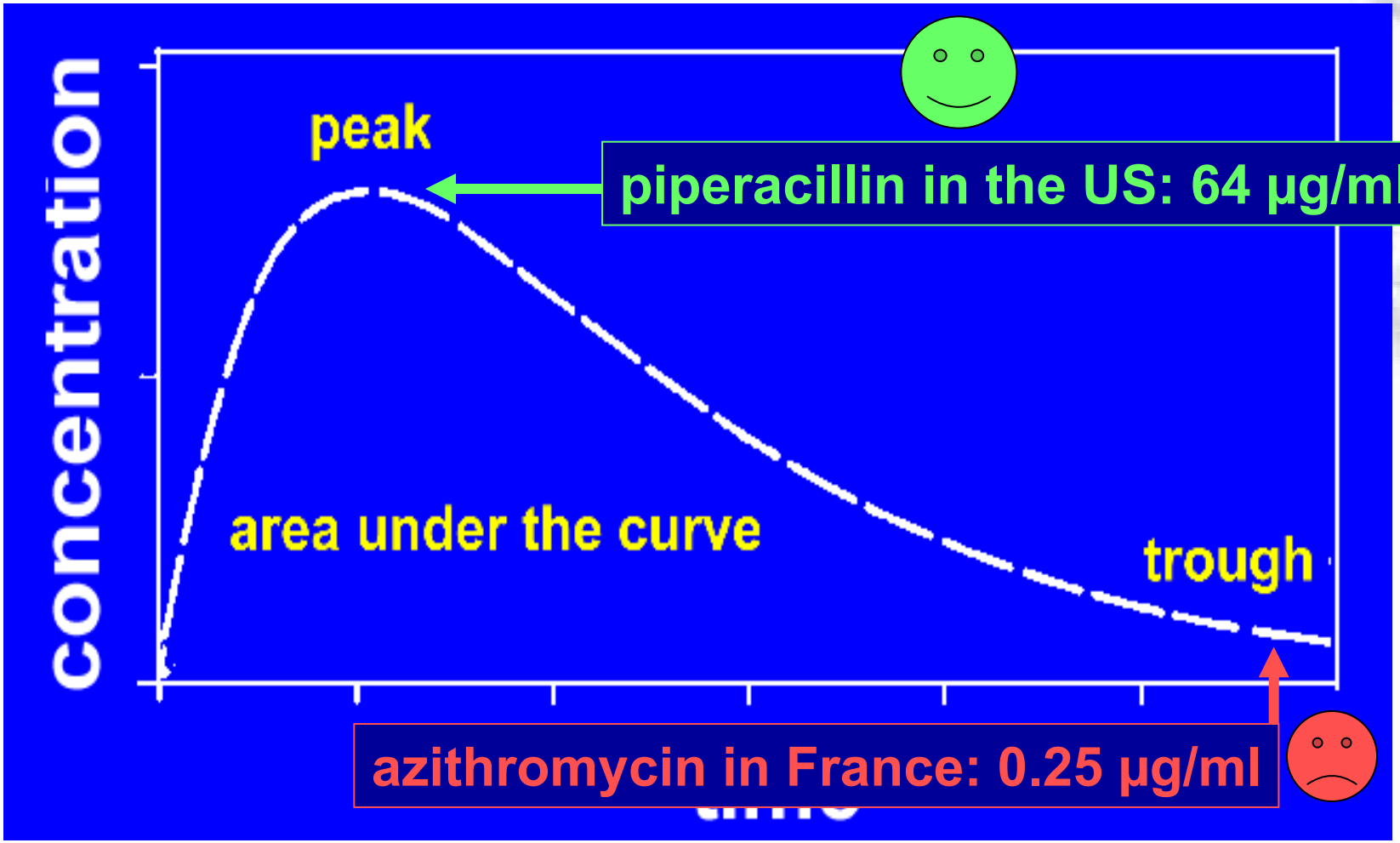


J. van Eldere, 2003

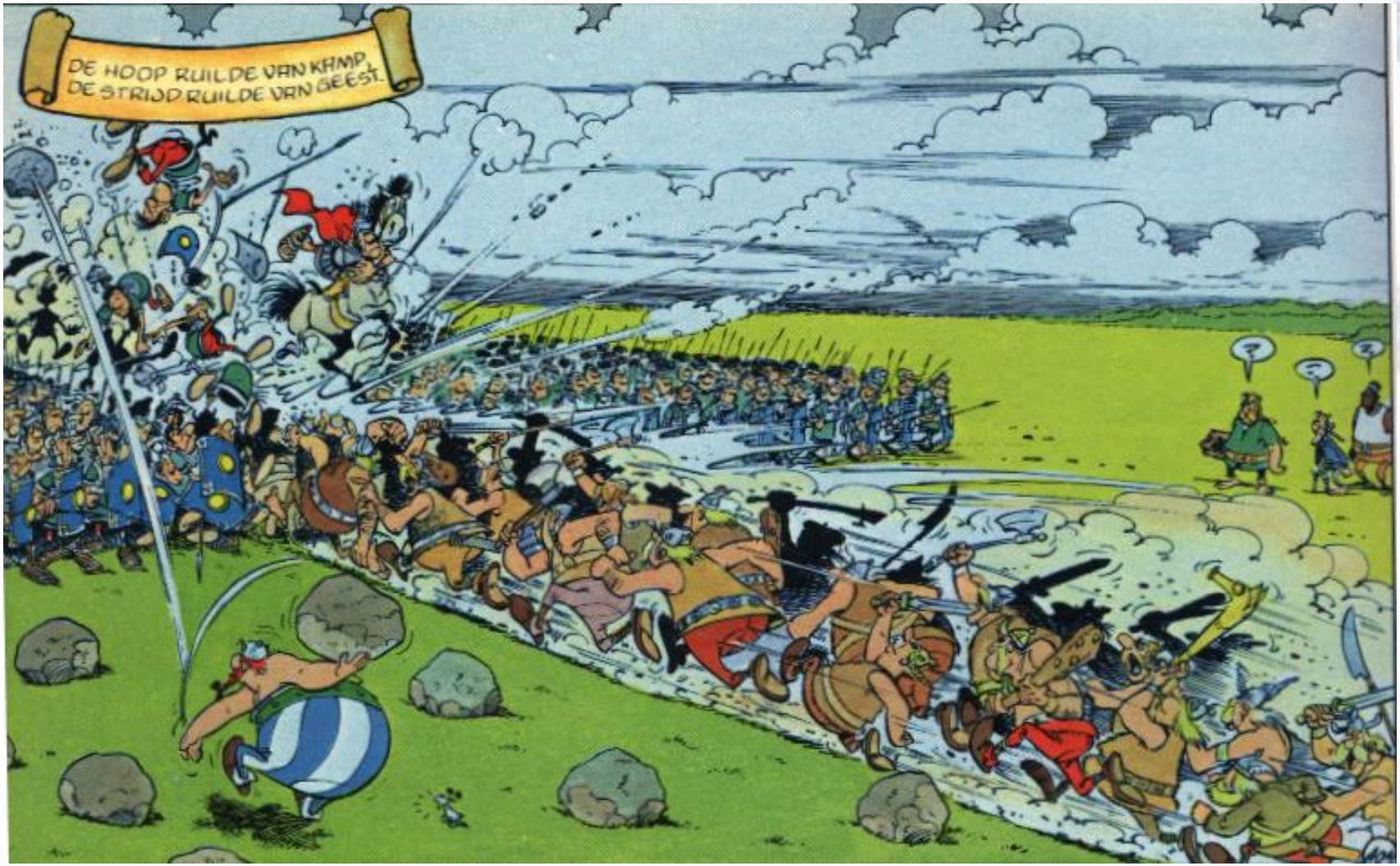
Where should the breakpoint be ?



Where should the breakpoint be ?



And there were fierce battles …



From Mouton, 8th ISAP symposium, Nijmegen, 2001

What was THE problem ?

- Europe had 6 national breakpoint- setting authorities … and, therefore (?), possibly up to 6 different breakpoints for each antibiotic – bug combination …
- The situation was not better in many other parts of the world …

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 should "Other" countries do ?

Countries without national breakpoint authorities did not really know which one to follow for guidance…

So, what should other countries do ?

Do you really need this antibiotic ?

2 / >4

2 / >16

4 / >32

So, what if you are small ?
but [hopefully]) smart …

The
"filet américain"
attitude *

* baguette filet américain 100% boeuf

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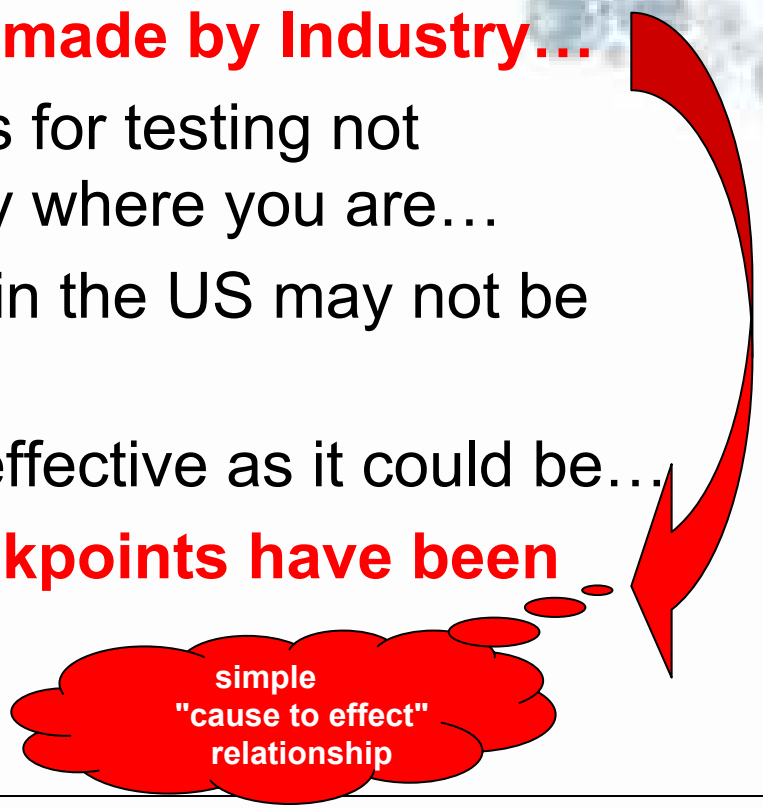
- For certain antibiotics, **CLSI breakpoints have been notoriously too high**



An example of (probably) too high CLSI breakpoints

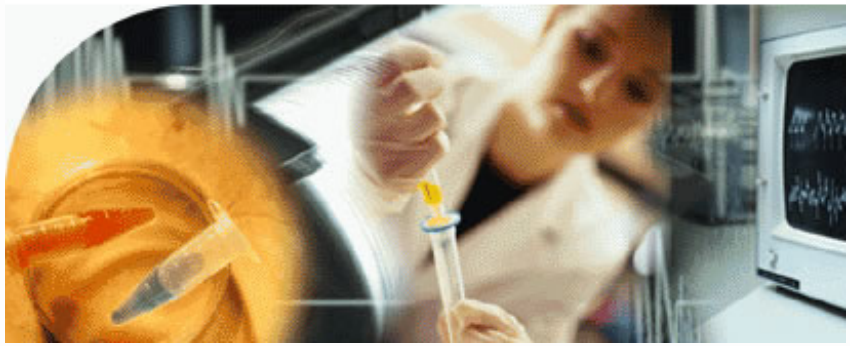
Drug	Typical daily dosage[a]	Typical PK values: C_{max} in mg/L total/free (dose)	Typical PK values: $AUC_{24\ h}$ (mg × h/L) total/free	Proposed PK/PD upper limit: Efficacy[b]	Proposed PK/PD upper limit: Prevention of resistance[c]	Breakpoints (mg/L)[d]: NCCLS (S/I/R)
Norfloxacin	800 mg	1.4/1.1 (400 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 …
(if you are a non-US microbiologist)

CLINICAL AND LABORATORY STANDARDS INSTITUTE®
(Formerly NCCLS)



An unanticipated problem …

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

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

Two important change in Europe…

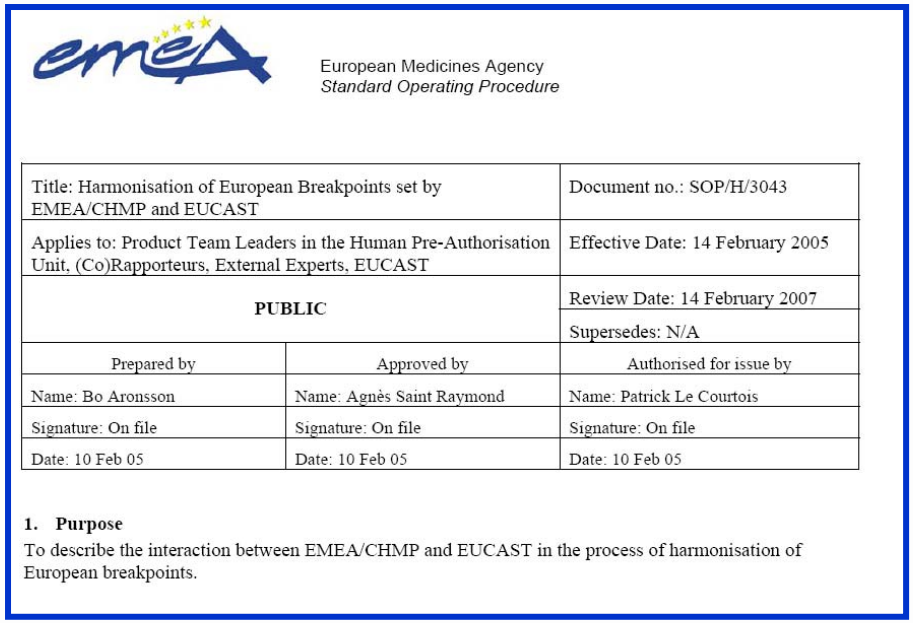
1. Each national committee in EU (UK, FR, NL, DE, SV, NO) has pledged that the EUCAST breakpoints will be part of their respective systems January the year after the decision was made. This means that any decision taken in 2008 should be into their systems in January 2009, and so on …

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

Two important change in Europe…

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

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



European Medicines Agency
Standard Operating Procedure

Title: Harmonisation of European Breakpoints set by EMEA/CHMP and EUCAST		Document no.: SOP/H/3043
Applies to: Product Team Leaders in the Human Pre-Authorisation Unit, (Co)Rapporteurs, External Experts, EUCAST		Effective Date: 14 February 2005
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.

Doripenème: concentrations critiques

Concentrations critiques

Les concentrations minimales inhibitrices (CMI) critiques établies par l'European Committee on Antimicrobial Susceptibility Testing (EUCAST) sont les suivantes :

Non liée à l'espèce	S ≤1 mg/L et R >4 mg/L
Staphylocoques	déduite de la sensibilité à la méticilline
Enterobacteriaceae	S ≤1 mg/L et R >4 mg/L
Acinetobacter spp.	S ≤1 mg/L et R >4 mg/L
Pseudomonas spp.	S ≤1 mg/L et R >4 mg/L
Streptococcus spp. autres que *S. pneumoniae*	S ≤1 mg/L et R >1 mg/L
S. pneumoniae	S ≤ 1 mg/L et R >1 mg/L
Entérocoques	« cible non appropriée »
Haemophilus spp.	S ≤ 1 mg/L et R >1 mg/L
N. gonorrhoeae	DI (données insuffisantes)
Anaérobies	S ≤ 1 mg/L et R >1mg/L

DORIBAX® Résumé des caractéristques du produit (EMEA)

What is EUCAST ?

European Committee on Antimicrobial Susceptibility Testing

- formed in 1997
- convened by
  - European Society for Clinical Microbiology and Infectious Diseases (ESCMID)
  - National Breakpoint Committees in Europe
- financed by
  - ESCMID
  - National Breakpoint Committees in Europe
  - DG-SANCO of the European Union (3 year grant from May 2004)

Main objectives of EUCAST

- **In Europe**
  - to set **common breakpoints** for **surveillance of antimicrobial resistance**;
  - to **harmonise clinical breakpoints** for existing and new antimicrobial drugs;
  - to promote **standardisation of methods**;
  - to **collaborate** with groups concerned with antimicrobial susceptibility testing and/or the epidemiology of antimicrobial resistance;
  - to **advise European Union Institutions** on the technology and interpretation of antimicrobial susceptibility testing;
- **In the world**
  - to **work with** other active groups (eg CLSI [formerly NCCLS]) to achieve international consensus on susceptibility testing;

EUCAST definitions of epidemiological cut off values

Wild type (WT)

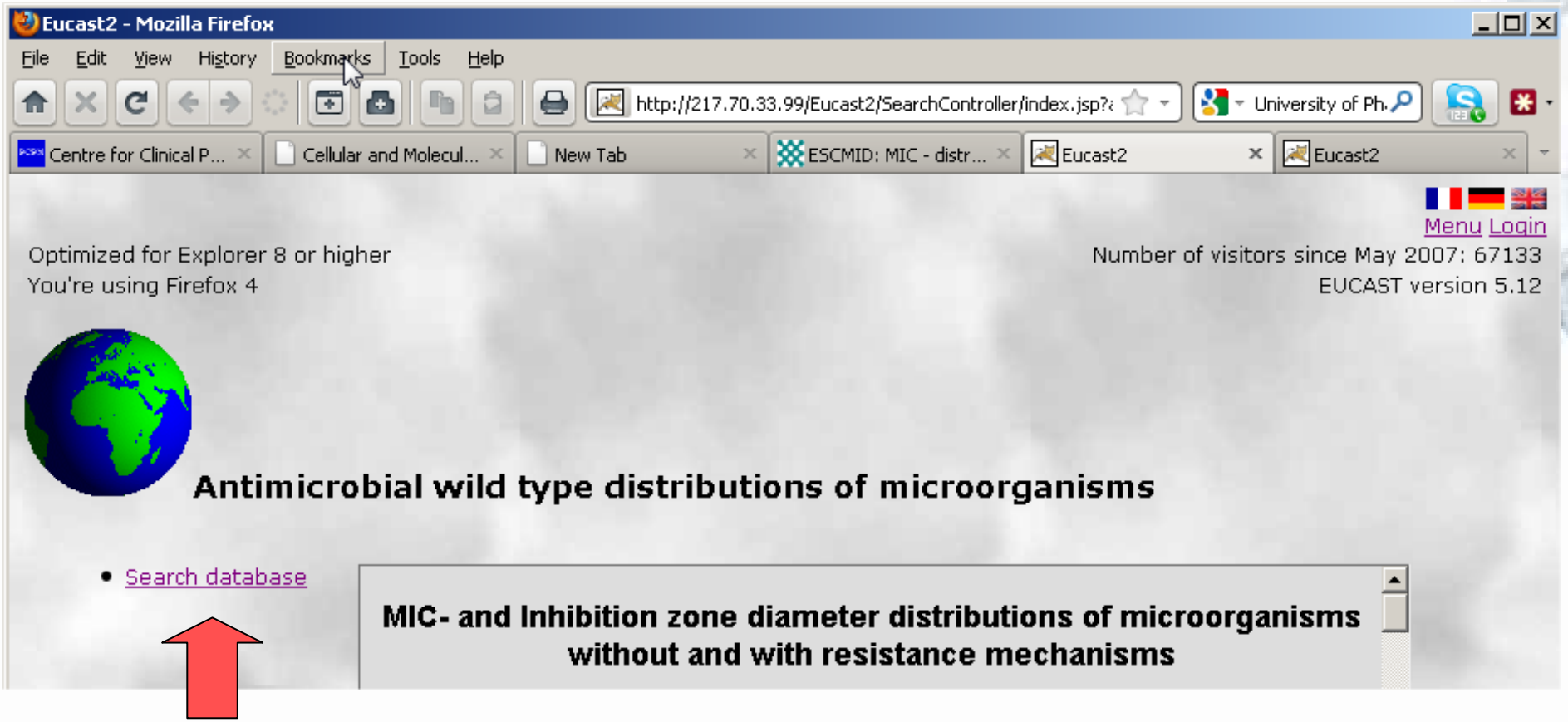
- a microorganism is defined as wild type (WT) for a species by the absence of acquired and mutational resistance mechanisms to the drug in question.
- a microorganism is categorized as wild type (WT) for a species by applying the appropriate cut-off value in a defined phenotypic test system.
- wild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

Microbiological resistance - non-wild type (NWT)

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

Epidemiological cut-off values will NOT be altered by changing circumstances.

http://www.eucast.org/mic_distributions/



http://www.eucast.org/mic_distributions/

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

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

Menu Connecter

Méthode: CMI Methode de diffusion

Antimicrobien: Antimicrobien... Espèce: Escherichia coli

Éléments par page: 50

Espèce: Escherichia coli **(Méthode:** MIC **)**

Show All Graphs

	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512
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

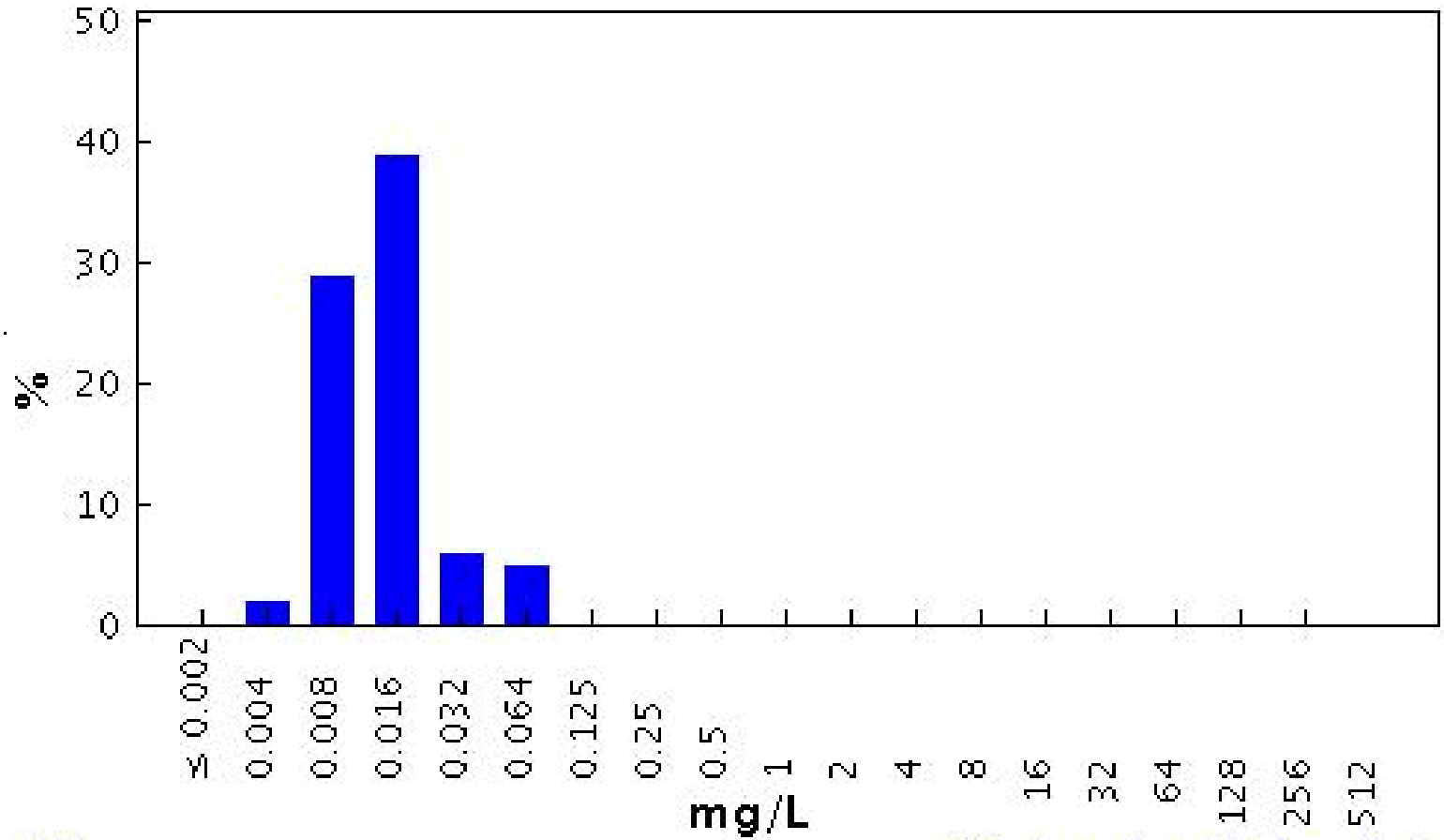
Click on any antibiotic (or species) in the left hand column to display the data as a bar chart, with EUCAST epidemiological cut-off values and harmonised European clinical breakpoints.

Done en-US Now: Sunny, 12° C Sun: 20° C Mon: 18° C

Start C:\Tulkens\textes-lab... Microsoft PowerPoint -... Eucast2 - Mozilla Fir... Jasc Paint Shop Pro 10:09

Ciprofloxacin / Escherichia coli

Antimicrobial wild type distributions of microorganisms - reference database EUCAST



MIC

6423 observations (9 data sources)

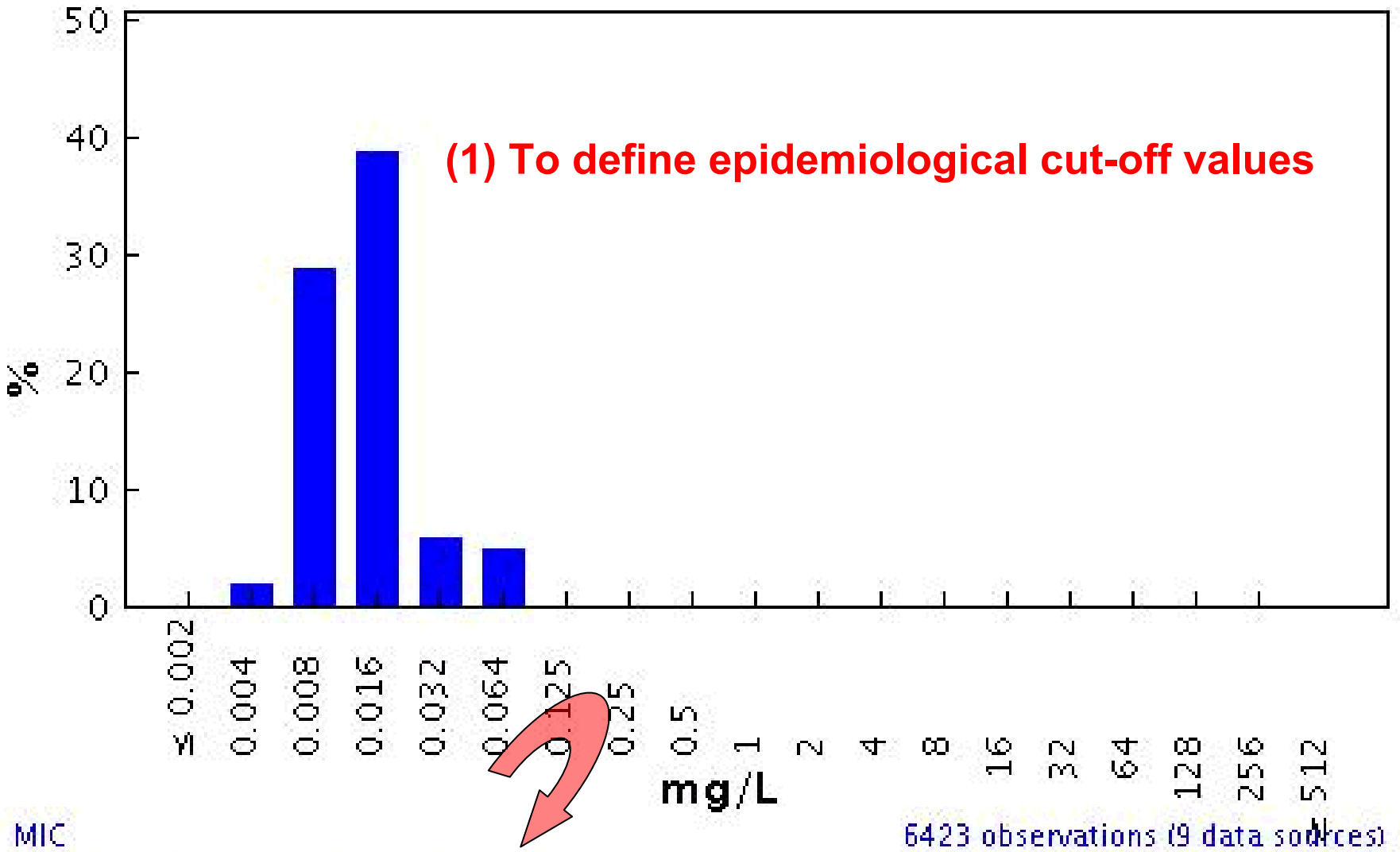
Epidemiological cut-off: WT ≤ 0.064 mg/L

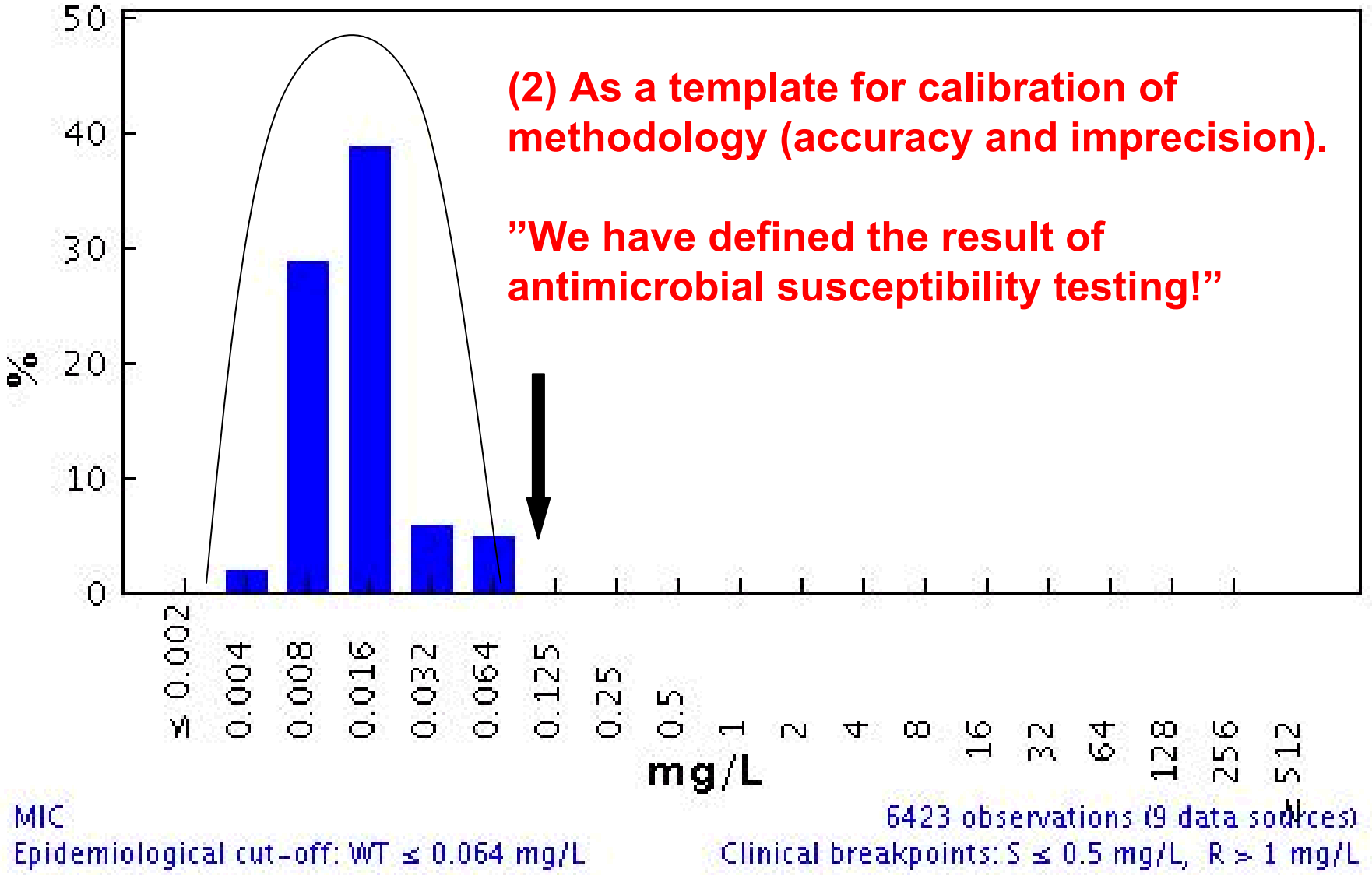
Clinical breakpoints: S ≤ 0.5 mg/L, R > 1 mg/L

Use of EUCAST wild type MIC distributions

The wild type MIC distributions provide

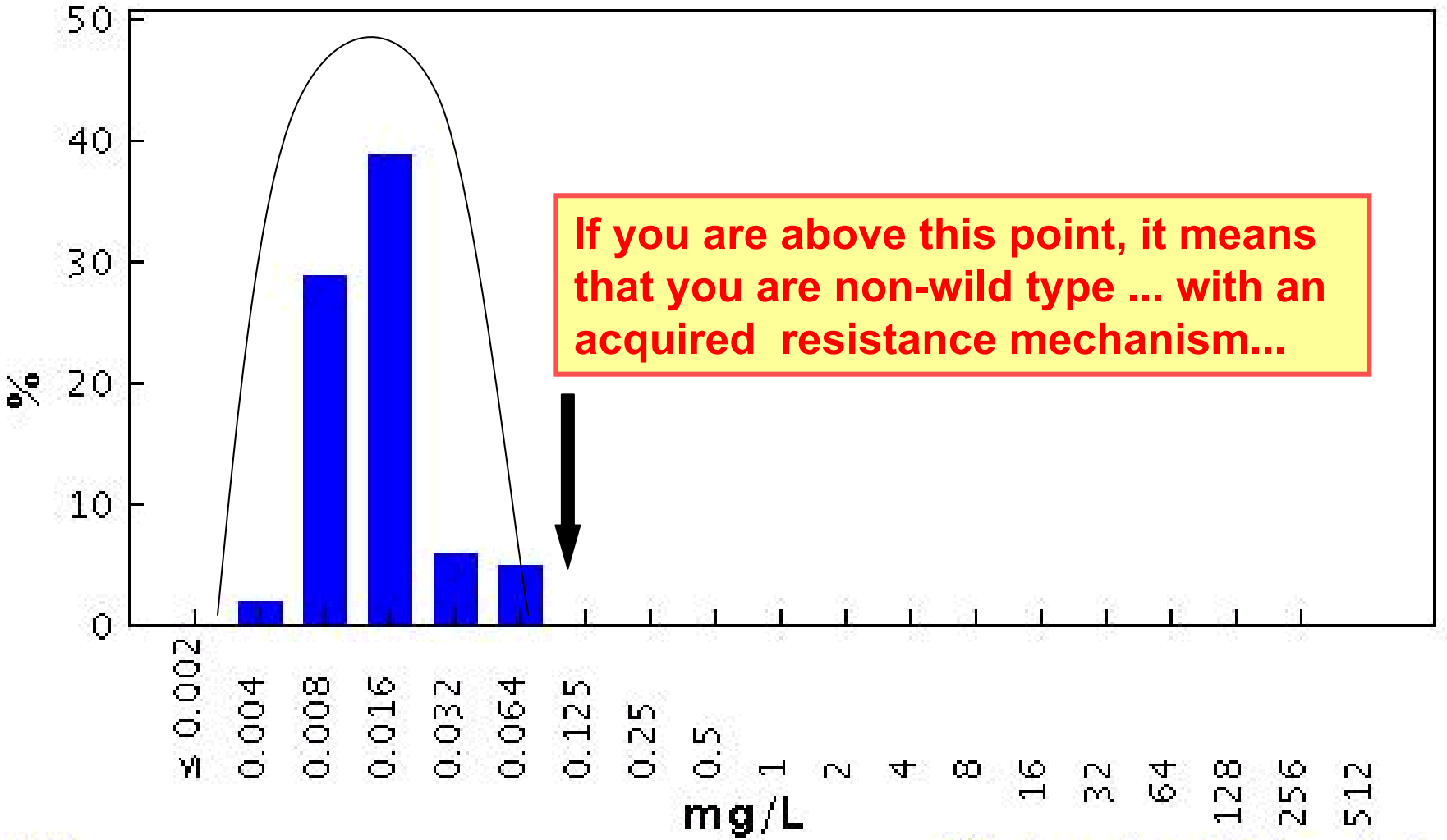
1. reference material for **epidemiological cut-off values** for antimicrobial resistance surveillance
2. an international reference for **calibration of antimicrobial susceptibility testing methods**
3. reference **MIC ranges of wild type organisms** for a wide spectrum of species and antimicrobials
4. reference material for committees involved in decisions on **clinical breakpoints**


Ciprofloxacin / Escherichia coli
Antimicrobial wild type distributions of microorganisms - reference database
EUCAST
(1) To define epidemiological cut-off values
%
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
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


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
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
N

Ciprofloxacin / Escherichia coli

Antimicrobial wild type distributions of microorganisms - reference database EUCAST



MIC

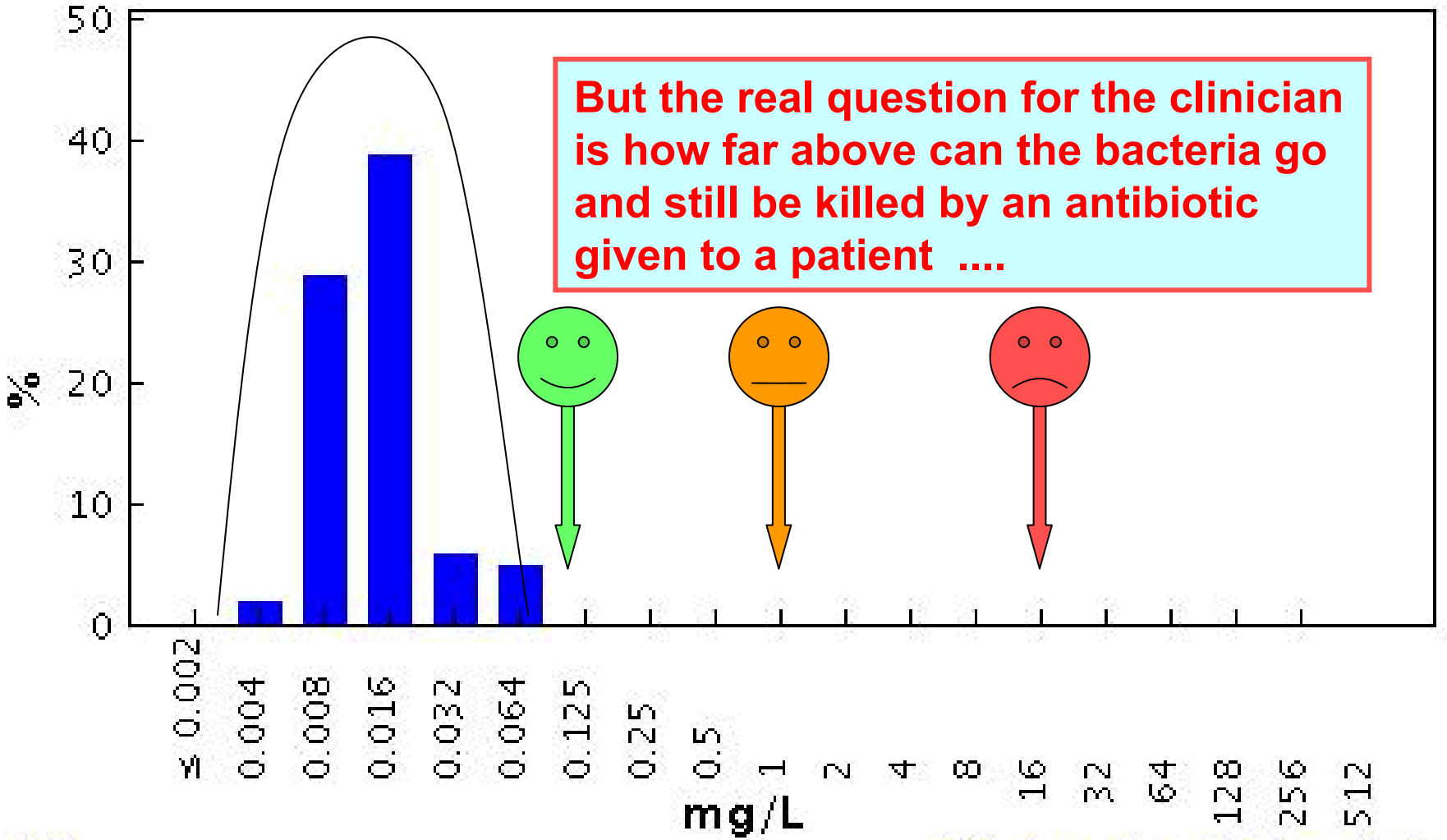
Epidemiological cut-off: WT ≤ 0.064 mg/L

6423 observations (9 data sources)

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

Ciprofloxacin / Escherichia coli

Antimicrobial wild type distributions of microorganisms - reference database EUCAST



MIC

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

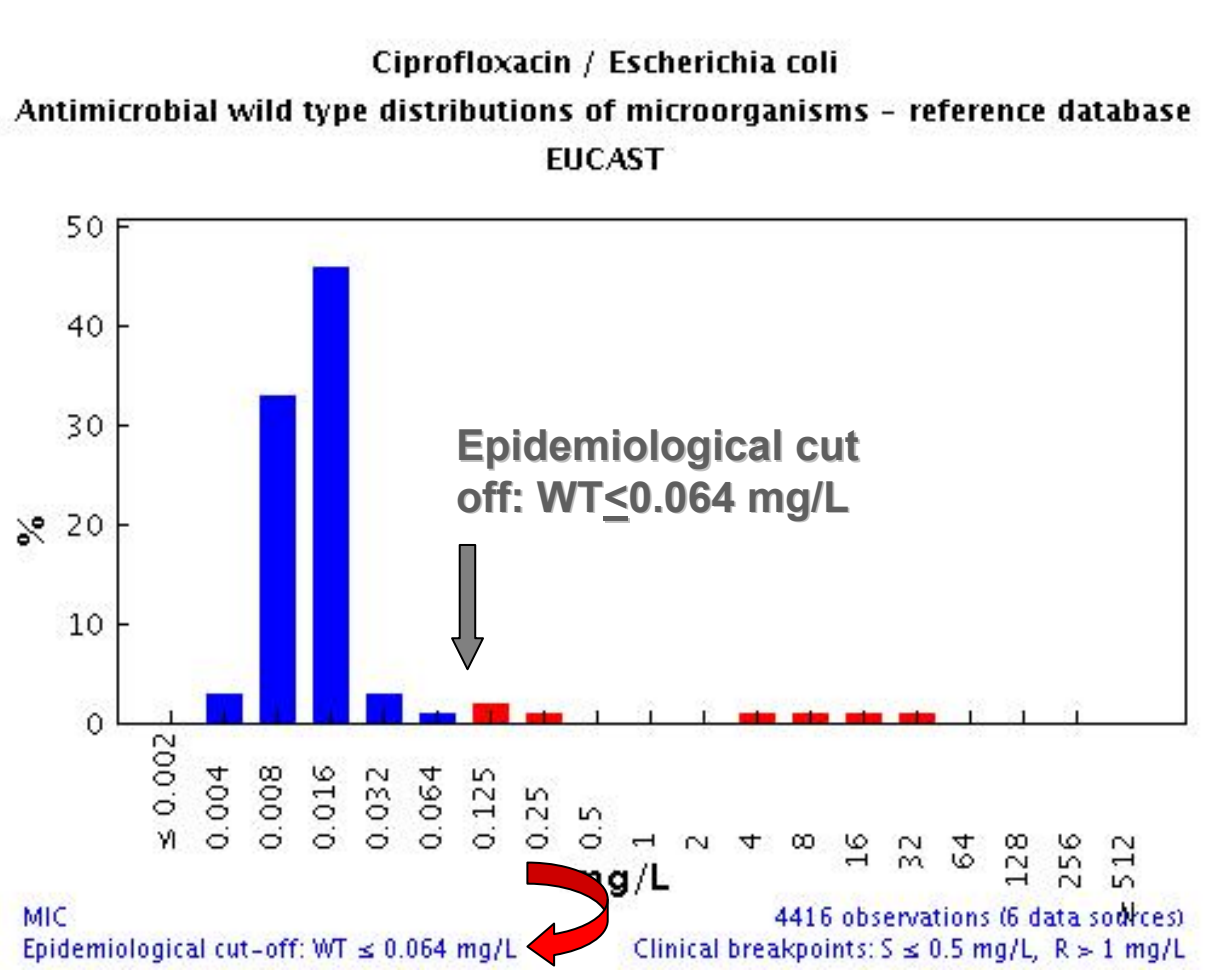
Dosage	National breakpoint committees						
Most common dose	500 x 2 oral 400 x 2 iv	500 x 2 oral 200 x 2 iv	250 x 2 oral 200 x iv	500 x 2 oral 200 x 2 iv	200-400 x 2 oral 400 x 2 iv	500 x 2 oral 400 x 2 iv	
Maximum dose schedule	750 x 2 oral 400 x 3 iv	750 x 2 oral 400 x 3 iv	750 x 2 oral 400 x 3 iv	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

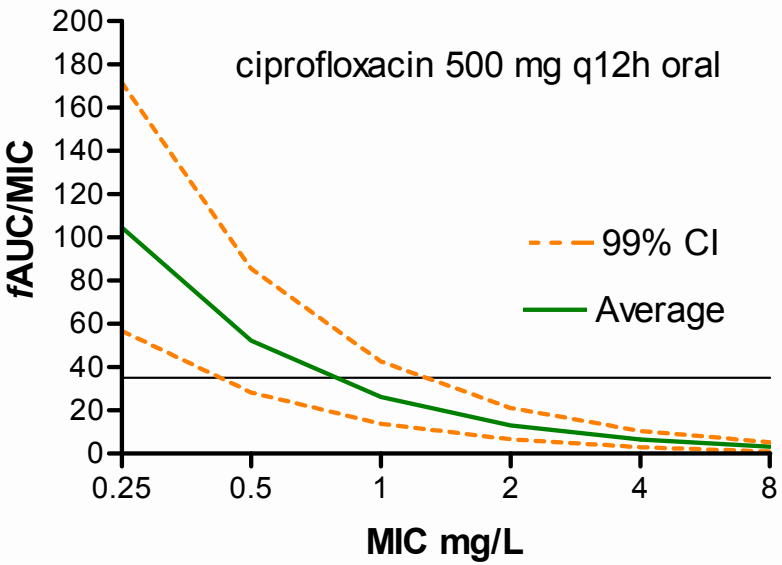
5. Pharmacodynamic data are evaluated

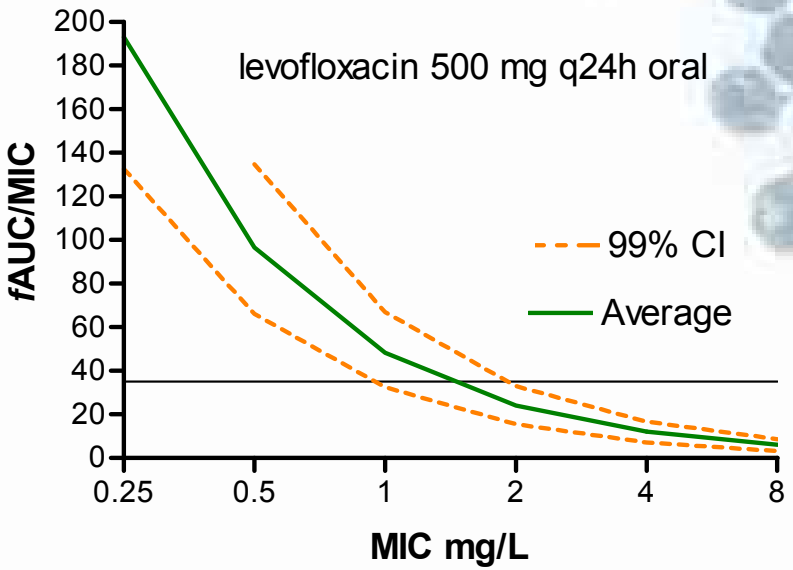
The PK/PD index value of the pertinent PK/PD parameter (time above MIC, AUC/MIC, C_{max}/MIC…) resulting in optimal outcome is determined from:

- 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

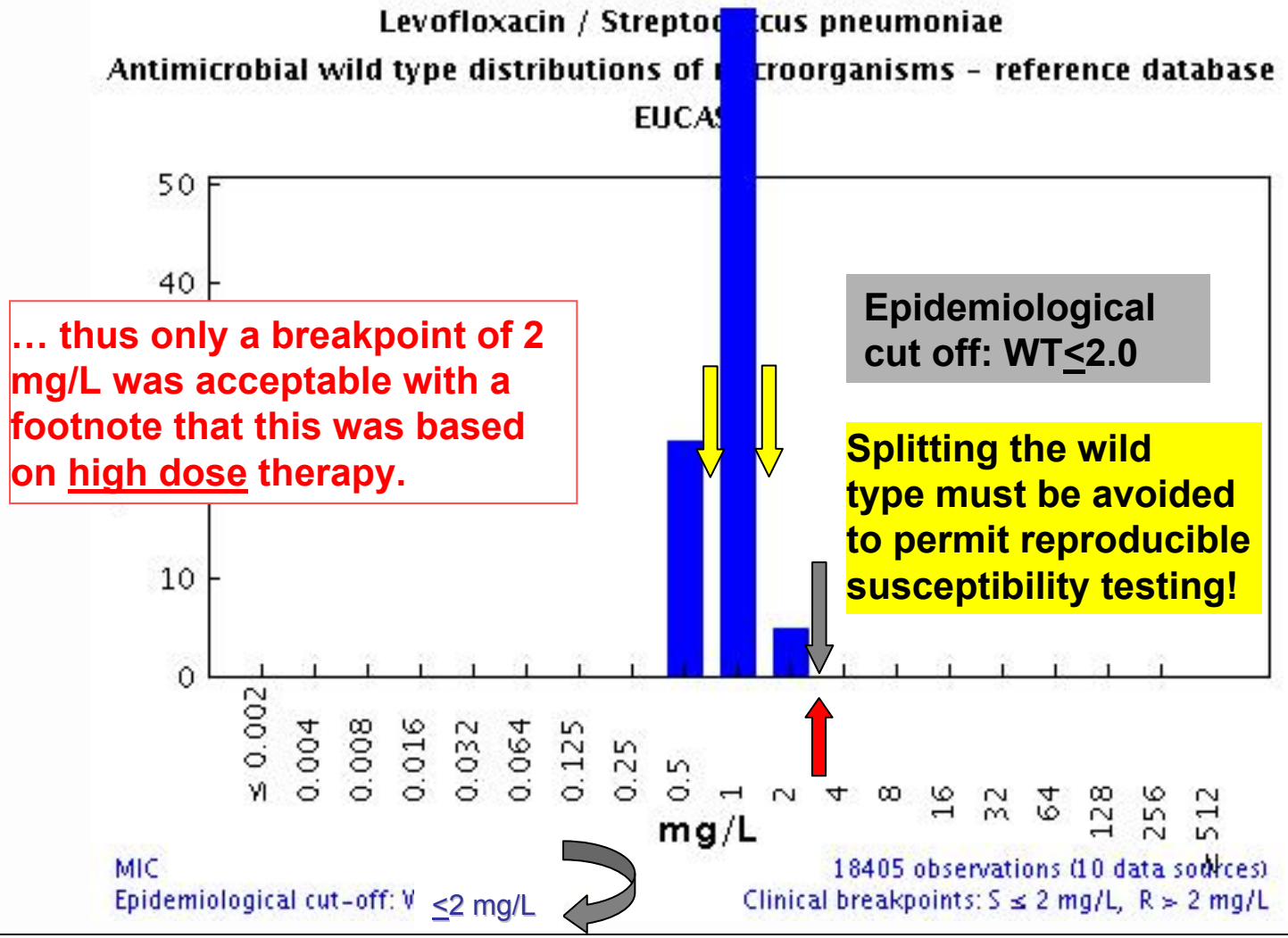
Pk/Pd

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

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

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

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- 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[1]	
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 EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

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

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

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

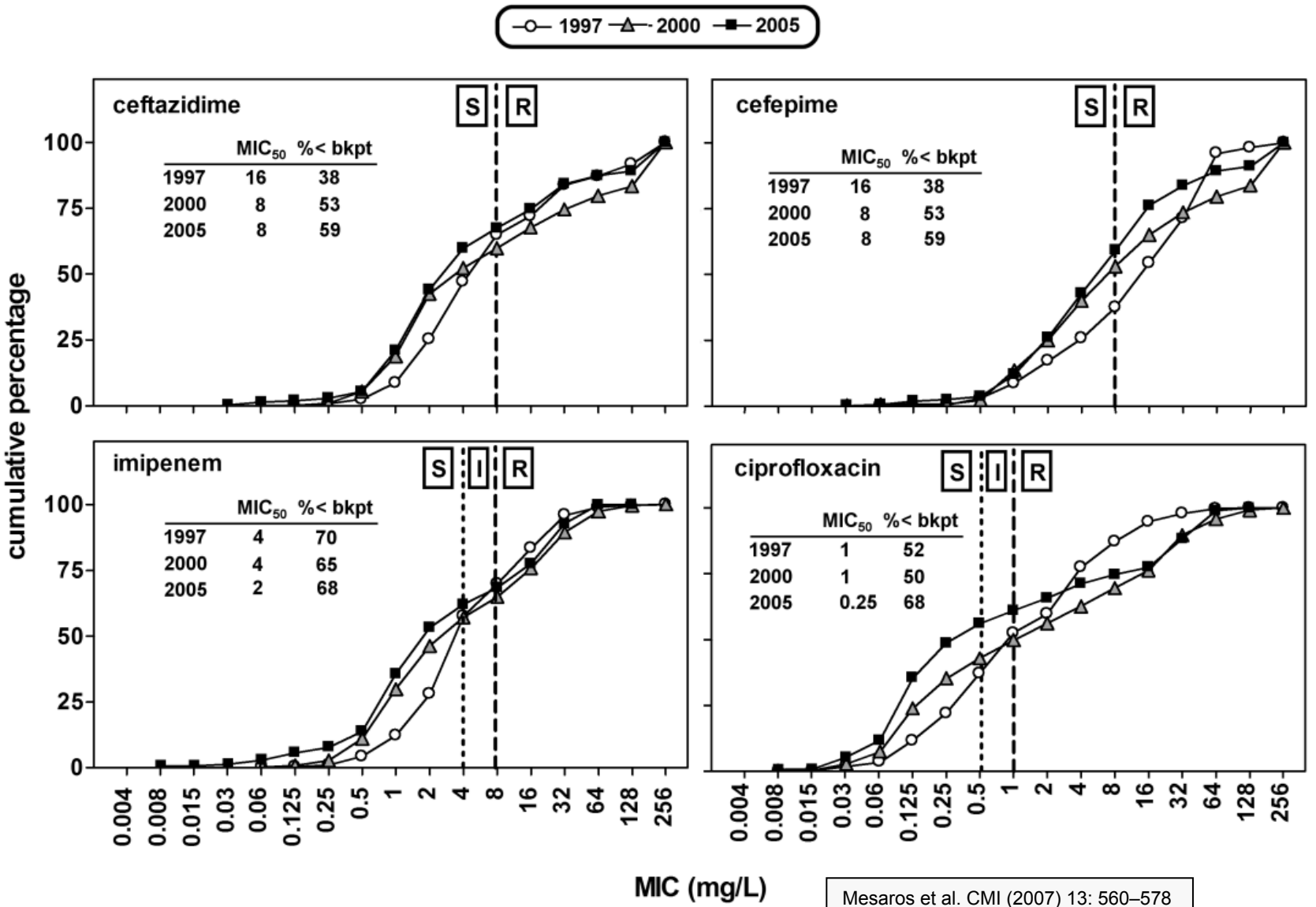
EUCAST_breakpoints_v1.1.pdf

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 ..

P. aeruginosa in Europe between 1997 and 2005



Mesaros et al. CMI (2007) 13: 560–578

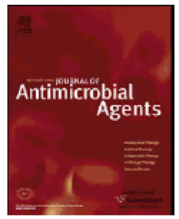
P. aeruginosa in Brussels in 2007-2009

International Journal of Antimicrobial Agents 36 (2010) 513–522

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

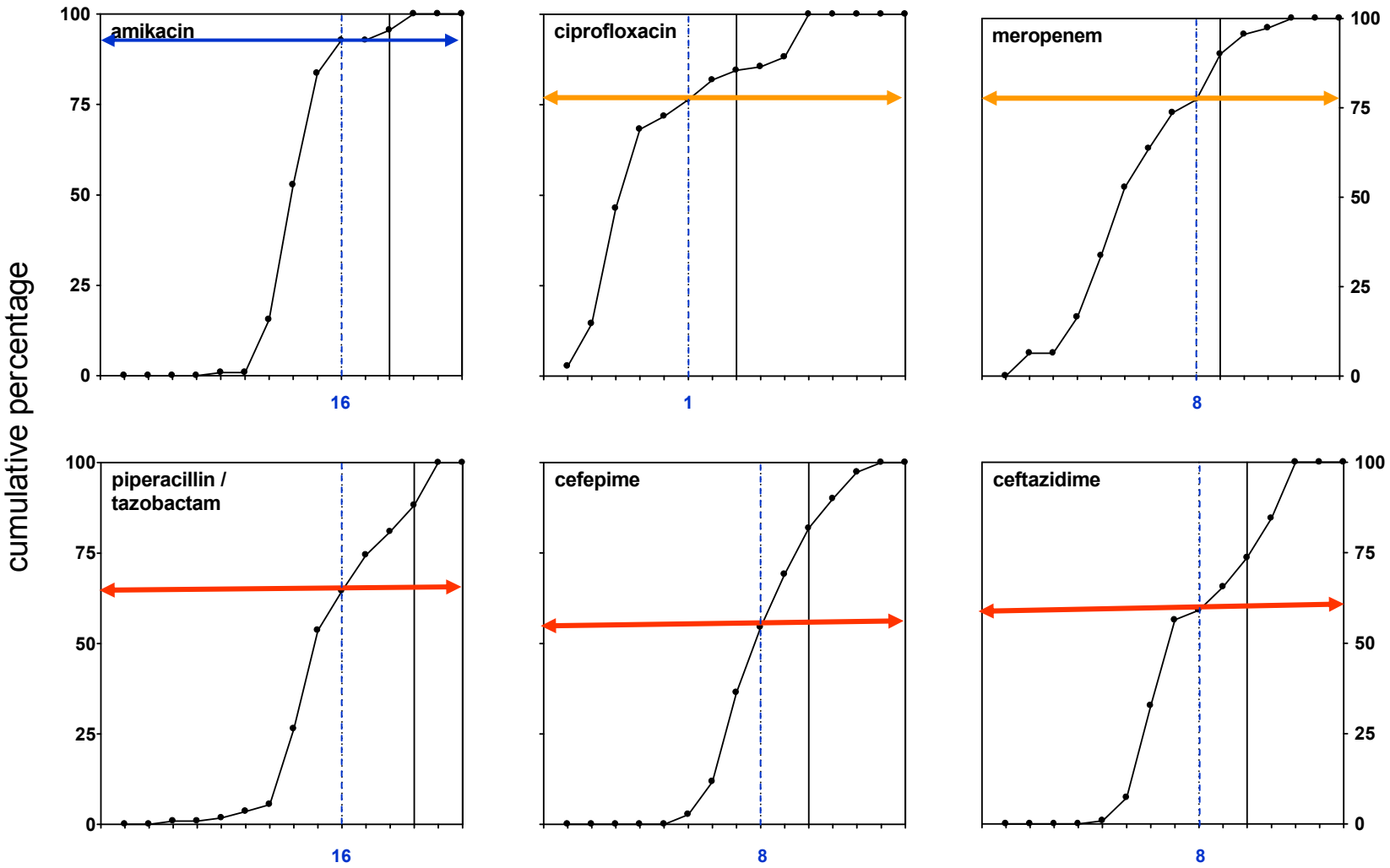


In vivo development of antimicrobial resistance in *Pseudomonas aeruginosa* strains isolated from the lower respiratory tract of Intensive Care Unit patients with nosocomial pneumonia and receiving antipseudomonal therapy

Mickaël Riou[a,1], Sylviane Carbonnelle[a,2], Laëtitia Avrain[a,b], Narcisa Mesaros[a,3], Jean-Paul Pirnay[c], Florence Bilocq[c], Daniel De Vos[c,d], Anne Simon[e], Denis Piérard[f], Frédérique Jacobs[g], Anne Dediste[h], Paul M. Tulkens[a,*], Françoise Van Bambeke[a], Youri Glupczynski[i]

Supported by the
- "Région Bruxelloise/Brusselse Gewest" (Research in Brussels)
- FNRS (post-doctoral fellowships)
- FRSM

P. aeruginosa in Brussels in 2007-2009

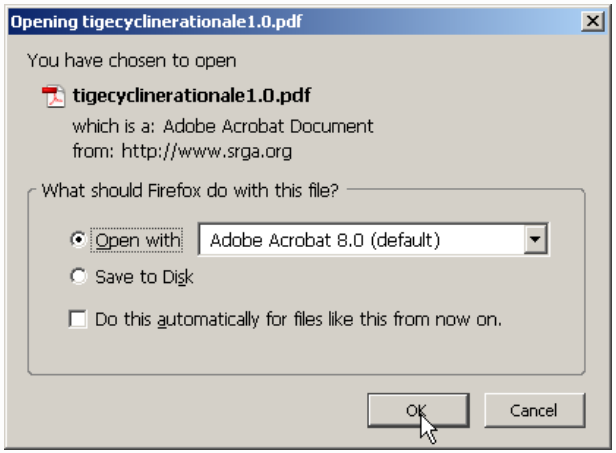


Can we have access to the rationale ?

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



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/tigecyclineration ale1.0.pdf

Opening tigecyclinerationale1.0

You have chosen to open

tigecyclinerationale1.0

which is a: Adobe Acrob

from: http://www.srga.

What should Firefox do with

Open with Adobe

Save to Disk

Do this automatically

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).

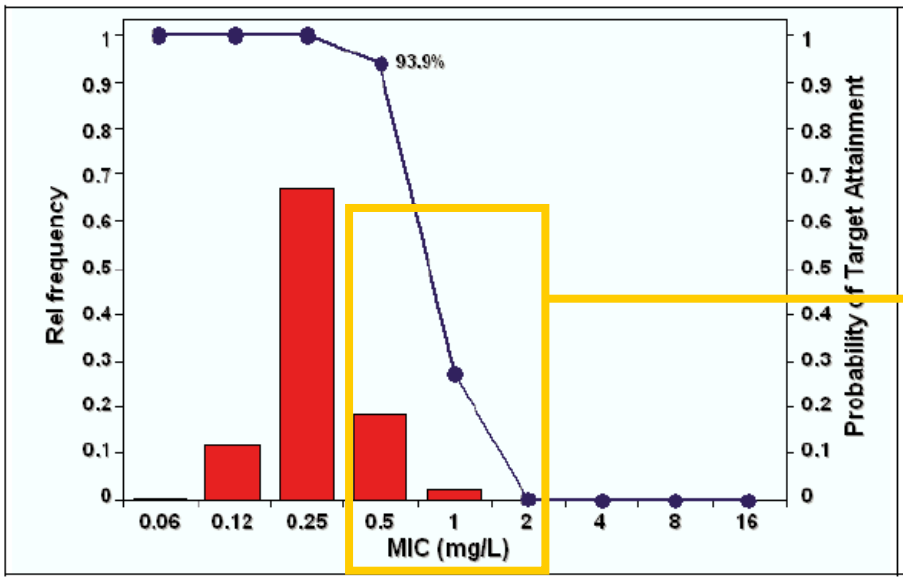


Figure 3. Probabilities of target attainment for tigecycline. Probability of Target Attainment Against *E. coli* at the CART-Identified Serum AUC/MIC Ratio of 6.96. Data on file, Wyeth Inc.

These isolates WILL create a risk of failure

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

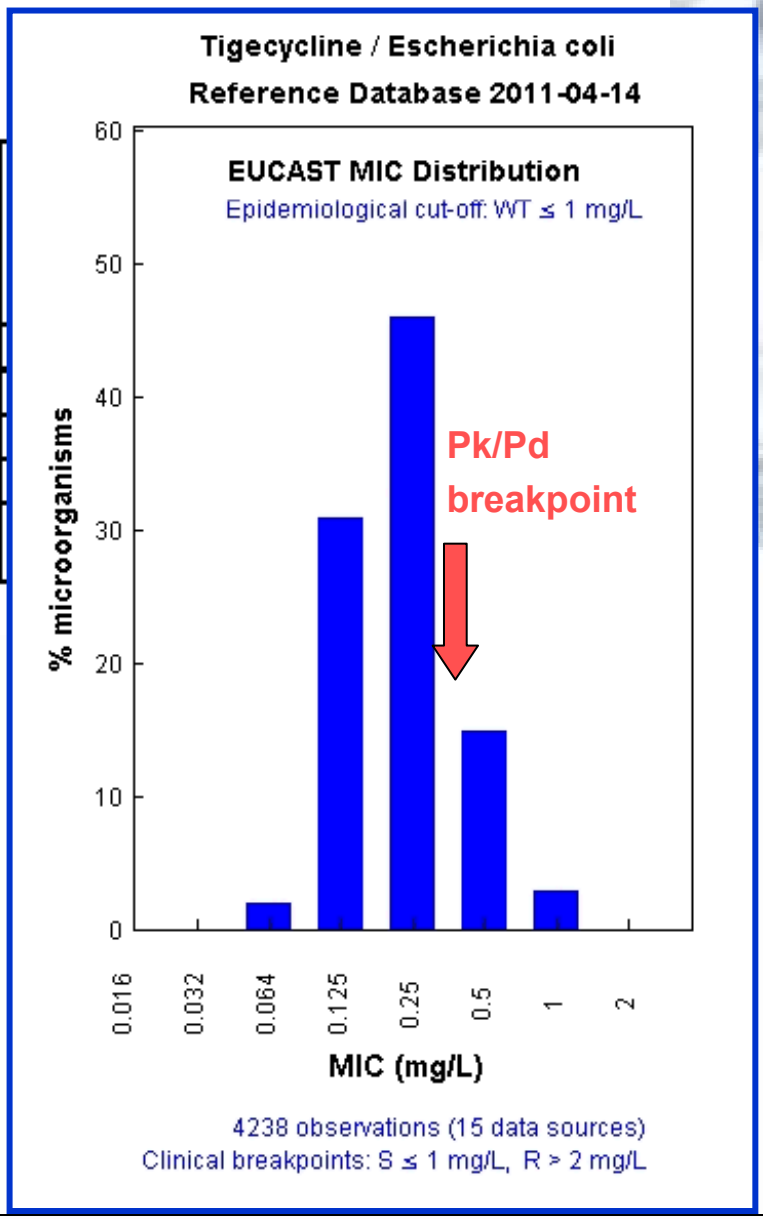
EUCAST has determined clinical breakpoints for the use of parenteral (iv) tigecycline.

But then why S ≤1 and R >2 ?

Enterobacteriaceae

Tetracyclines	MIC breakpoint (mg/L)	
	S ≤	R >
Doxycycline	-	-
Minocycline	-	-
Tetracycline	-	-
Tigecycline[1]	1	2

- The Pk/Pd breakpoint of 0.25-0.5 cuts within the wild type population
- Clinical success was obtained up to 1-2 mg/L (from clinical trials)
- BUT remember
  - the risk will increase > 0.5 mg/L
  - tigecycline is intrinsically an antibiotic with a small margin for efficacy …
  - you must monitor resistance based on MIC



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

Pros

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

Cons

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

---

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

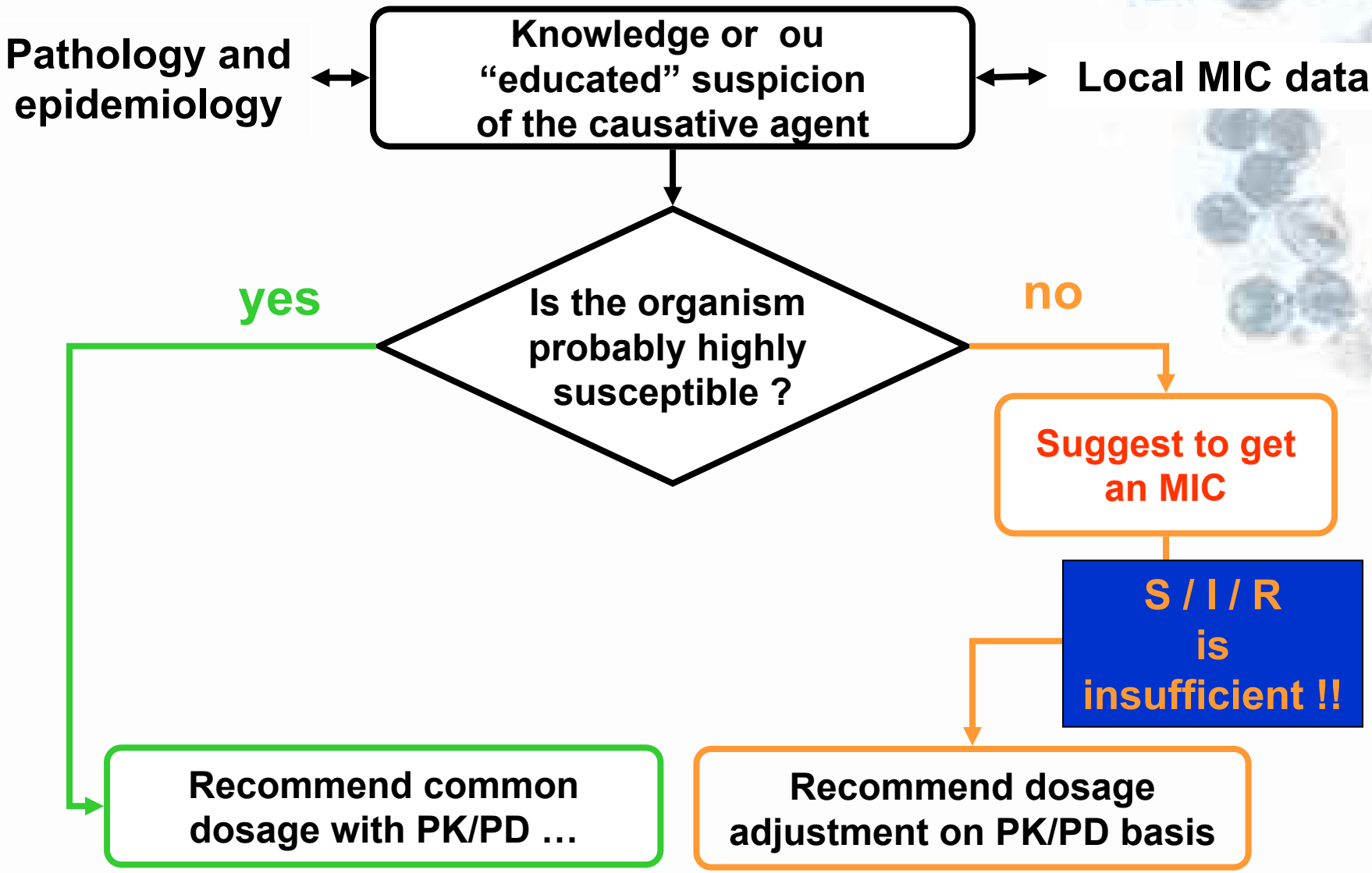
Will good (EUCAST ?) breakpoints solve everything ?

- Breakpoints should only be used as a guidance for a the general usage of an existing drug (is it still worth to use it ?) or for the positioning of a new drug (has it any chance of being successful ?)

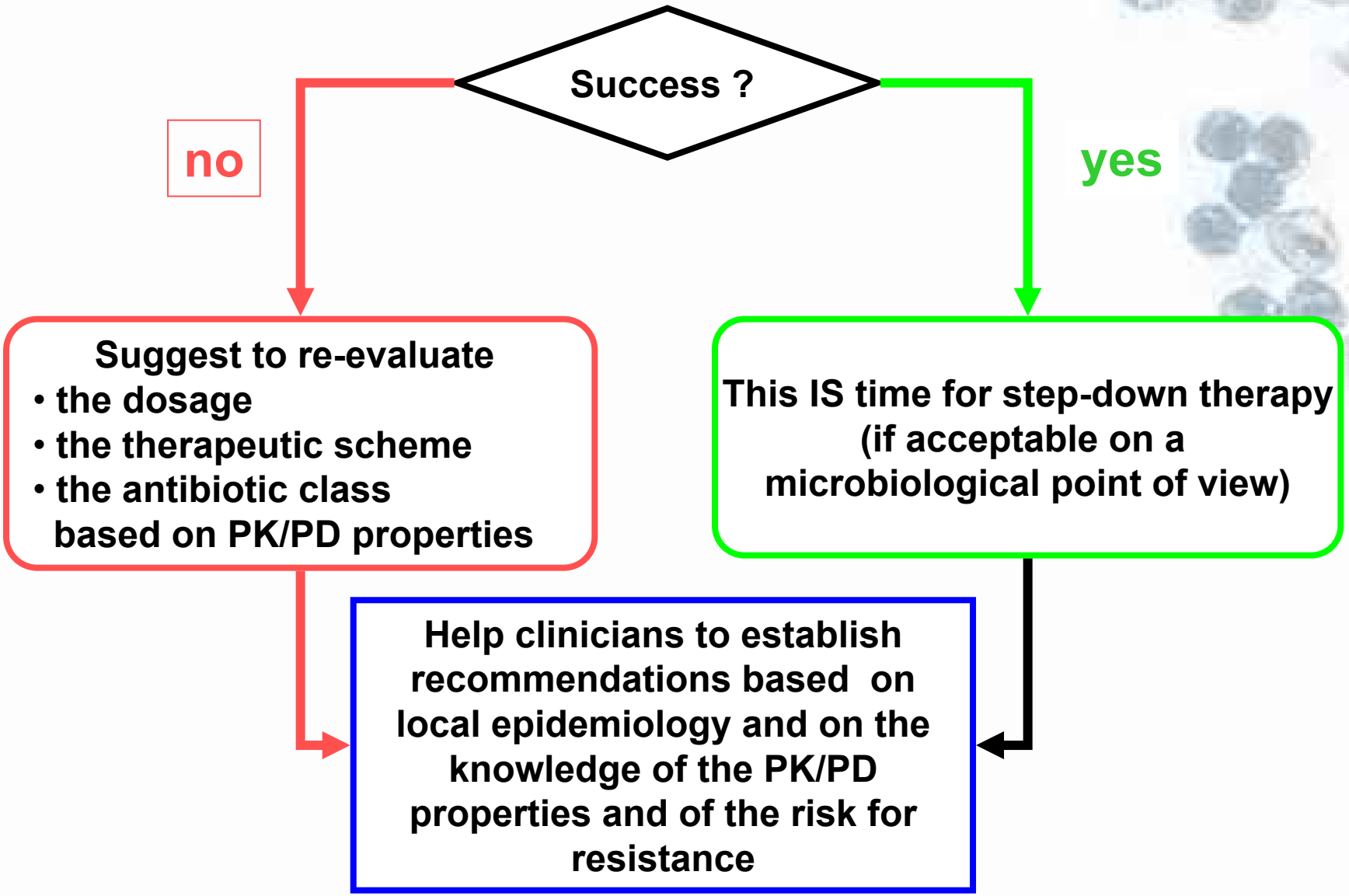
- MIC distributions (local and national) must be obtained regularly to check for decreased susceptibilities (epidemiology) and reassessment of posologies and/or therapeutic choices (hospital…)

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

A key to success ...



A key to success (follow.) ...



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

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

EUCAST

WBI Wallonie-Bruxelles International

UCL