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

and some personal thinking…

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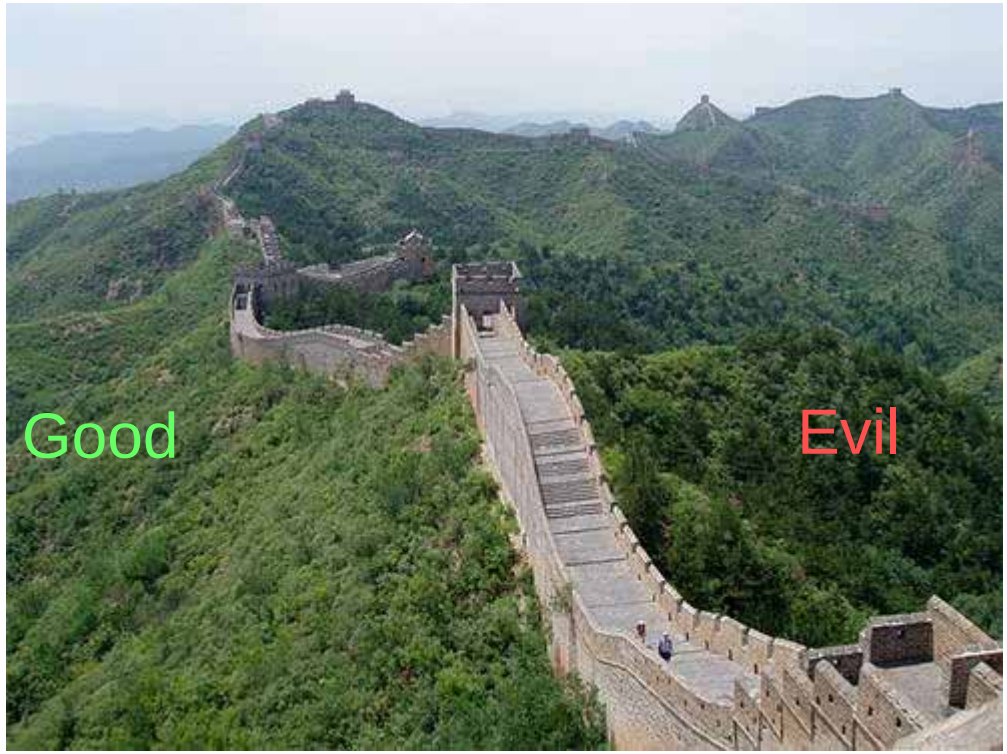
Based (largely) on presentations available from the EUCAST Web site, given to me by Gunnar Kahlmeter, or borrowed from Johan Mouton

Liège, Belgium
14 November 2006

Why do we need breakpoints ?

To be honest, I always wondered …

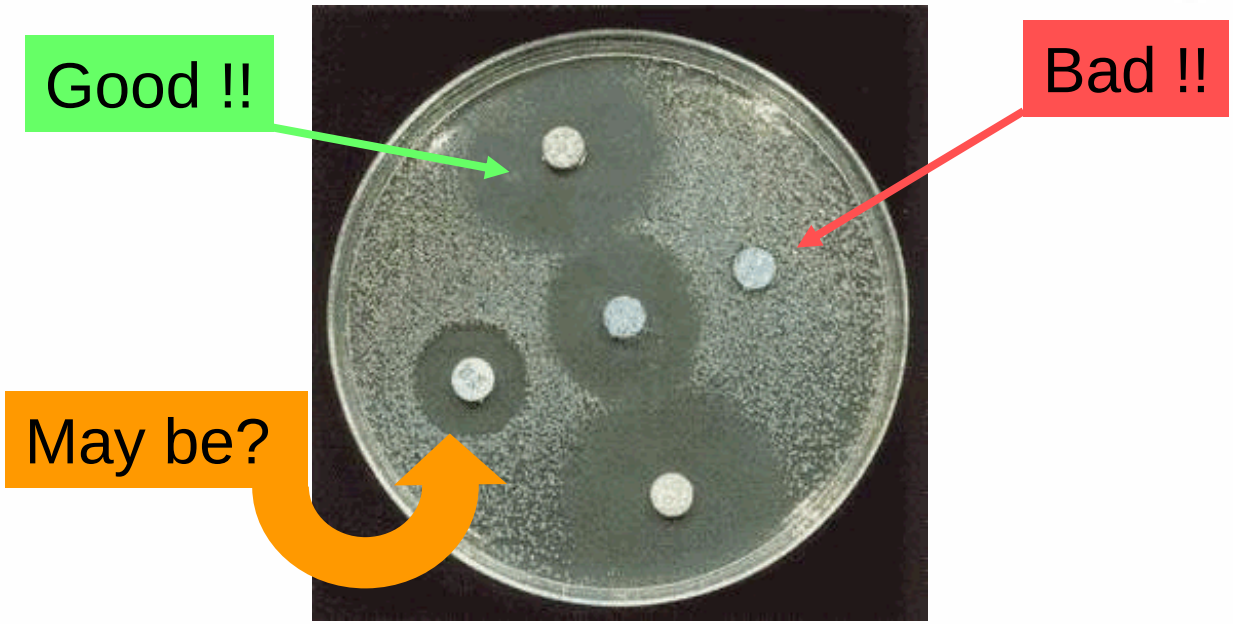


Why do we need breakpoints ?

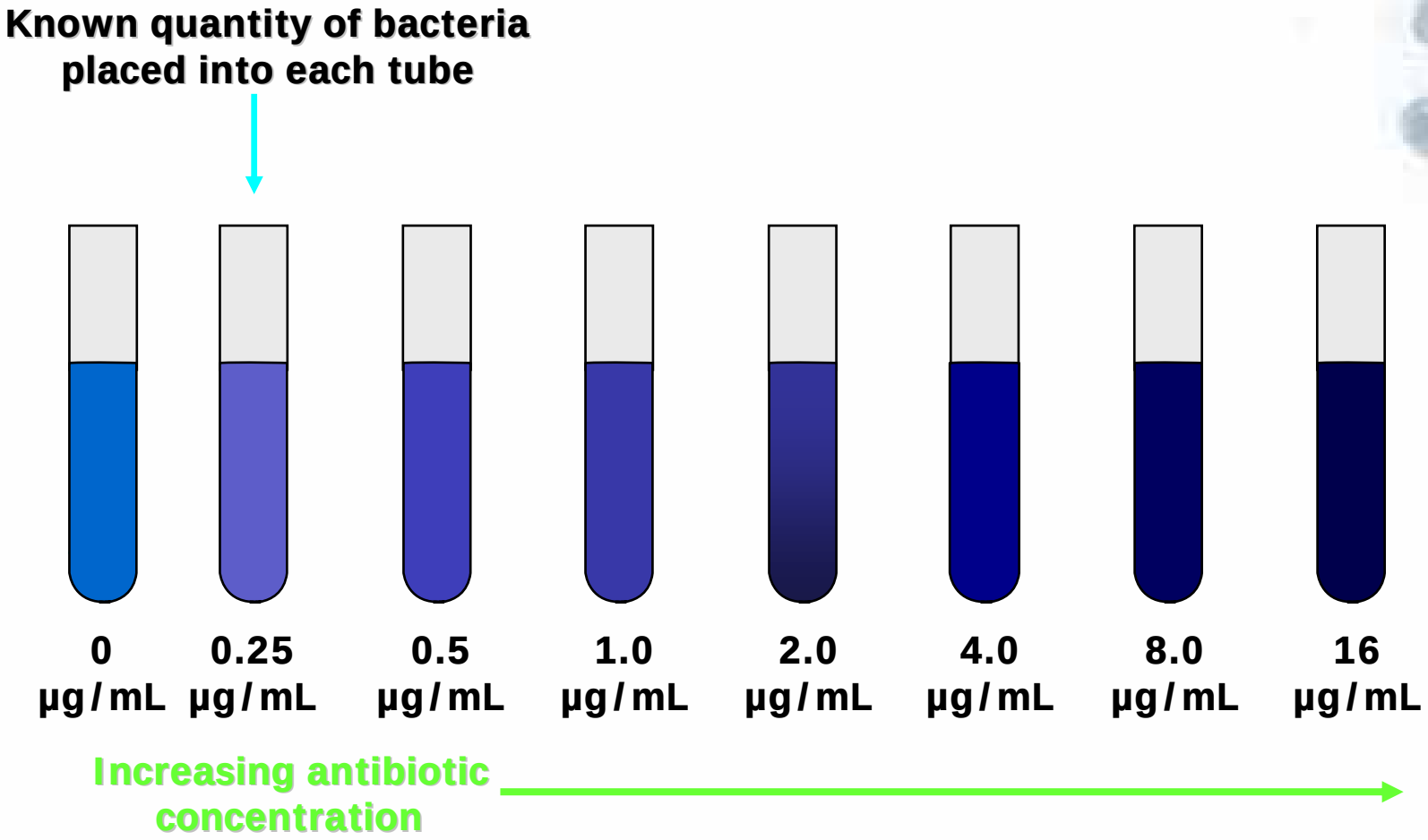
but perhaps…

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

Simple answers …



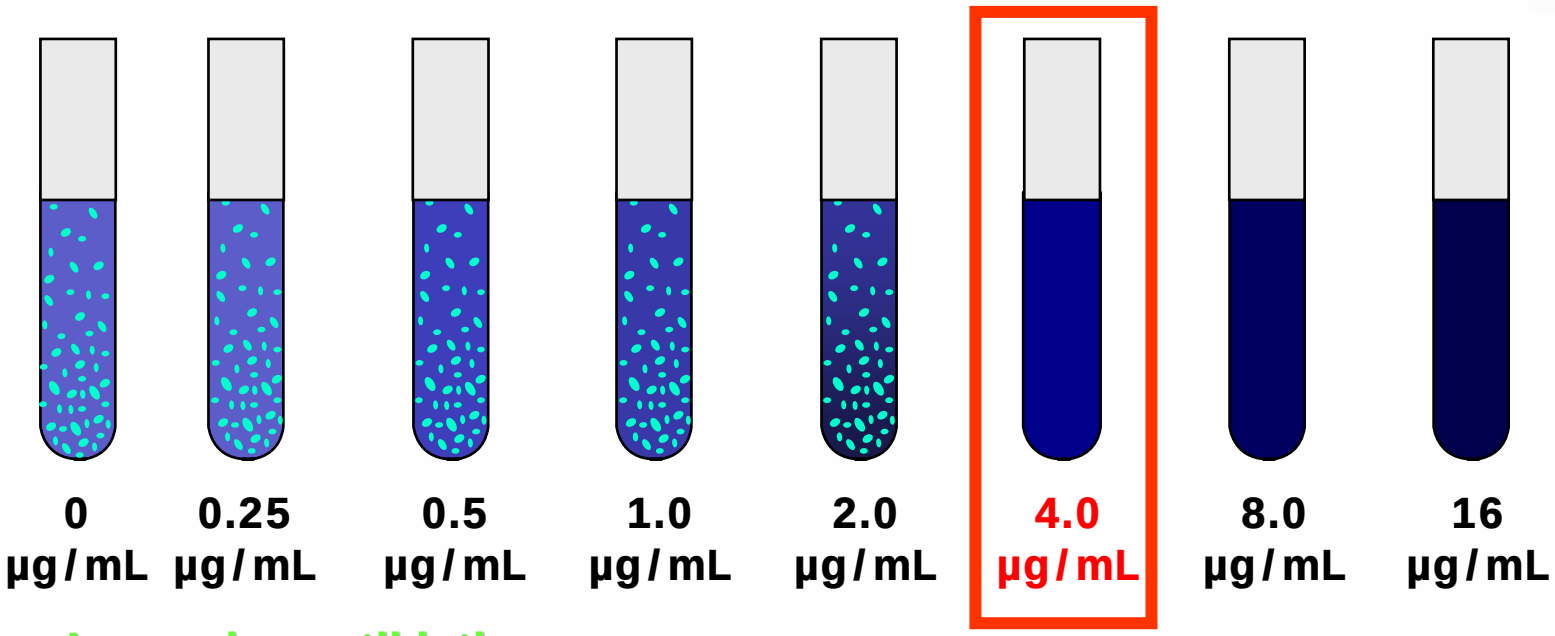
Starting from the beginning… The MIC !



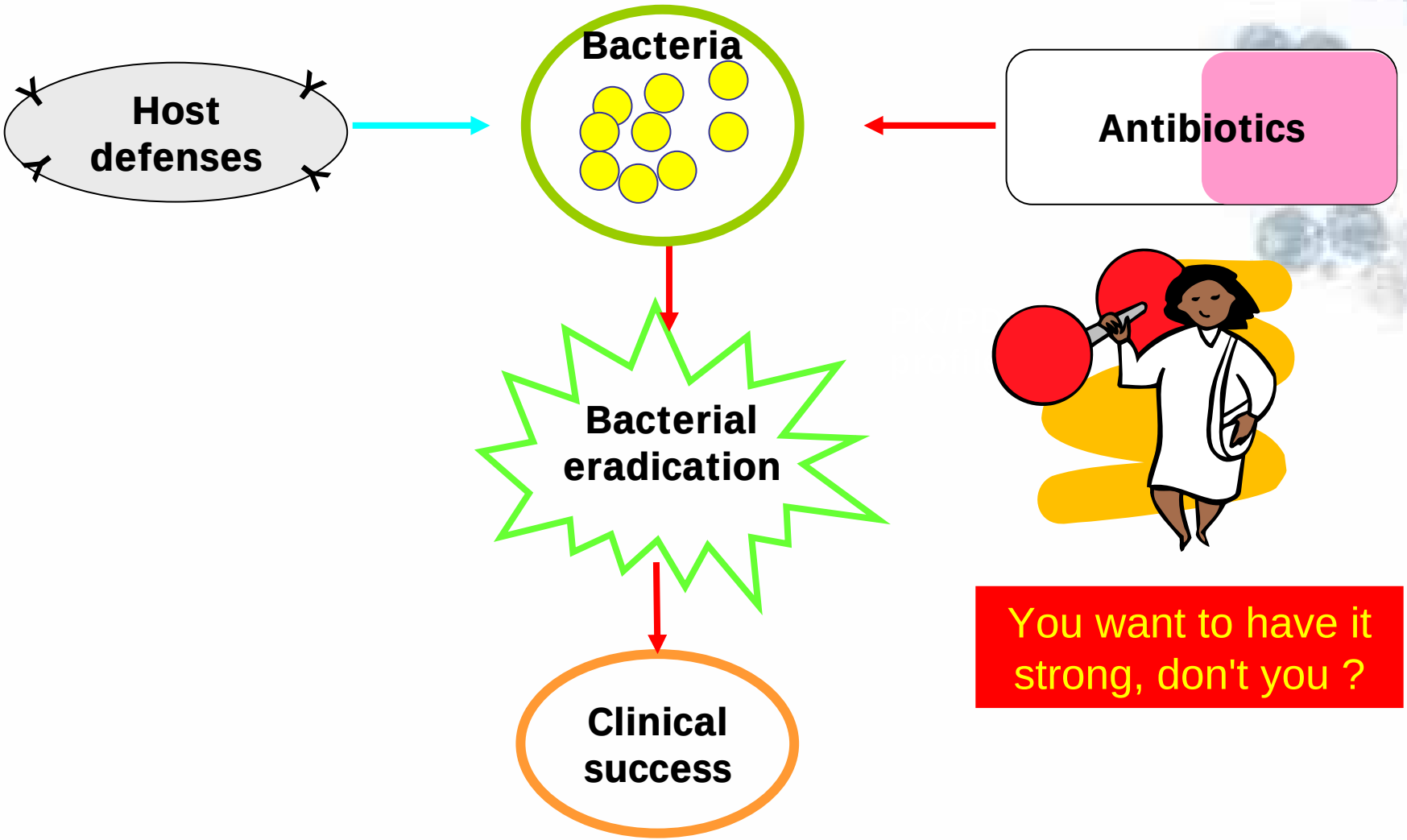
Starting from the beginning… The MIC !

24 h later ….

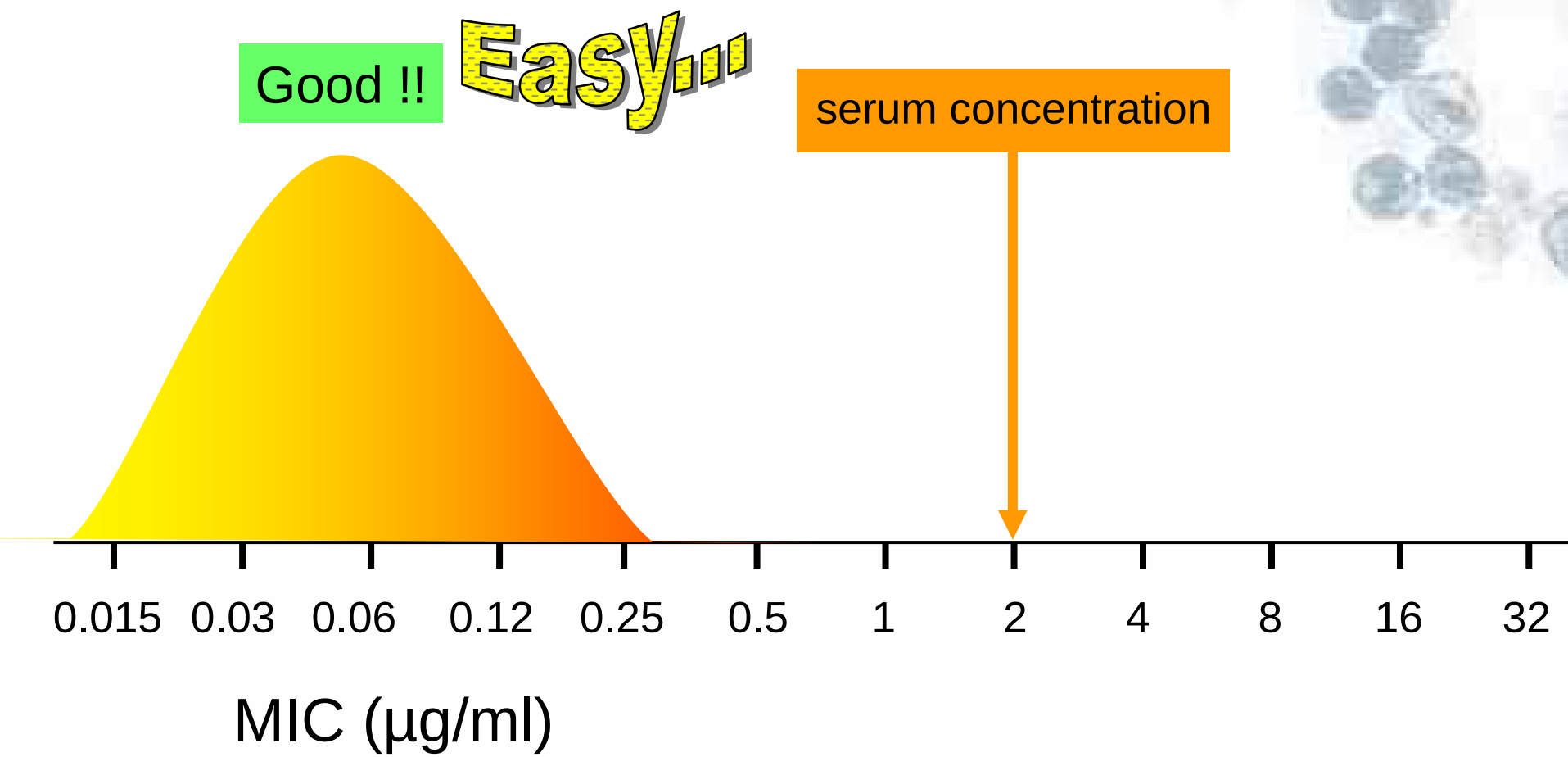
Lowest concentration of an antimicrobial that results in the inhibition of visible growth of a microorganism



What do you do with an MIC !

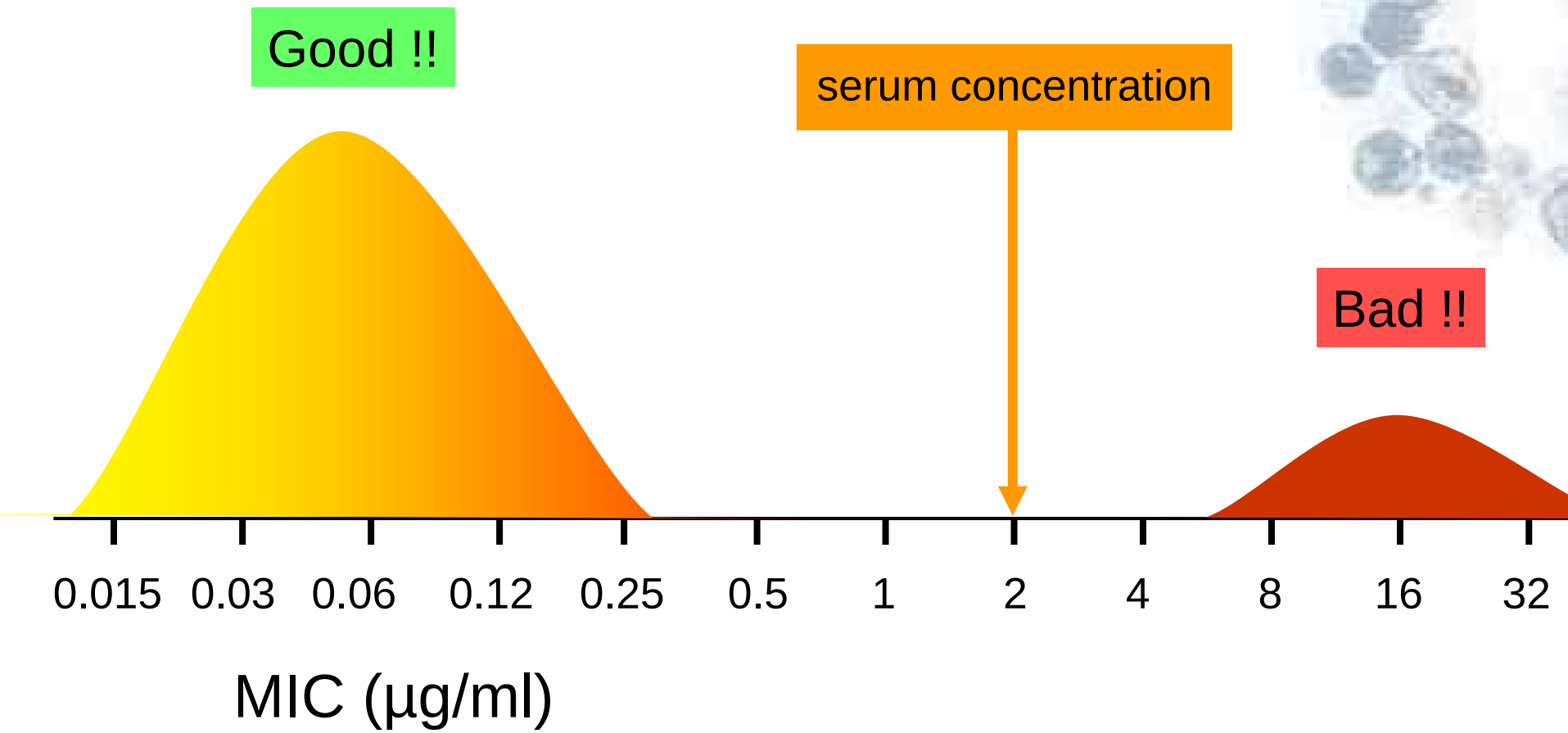


But, what is strong ?



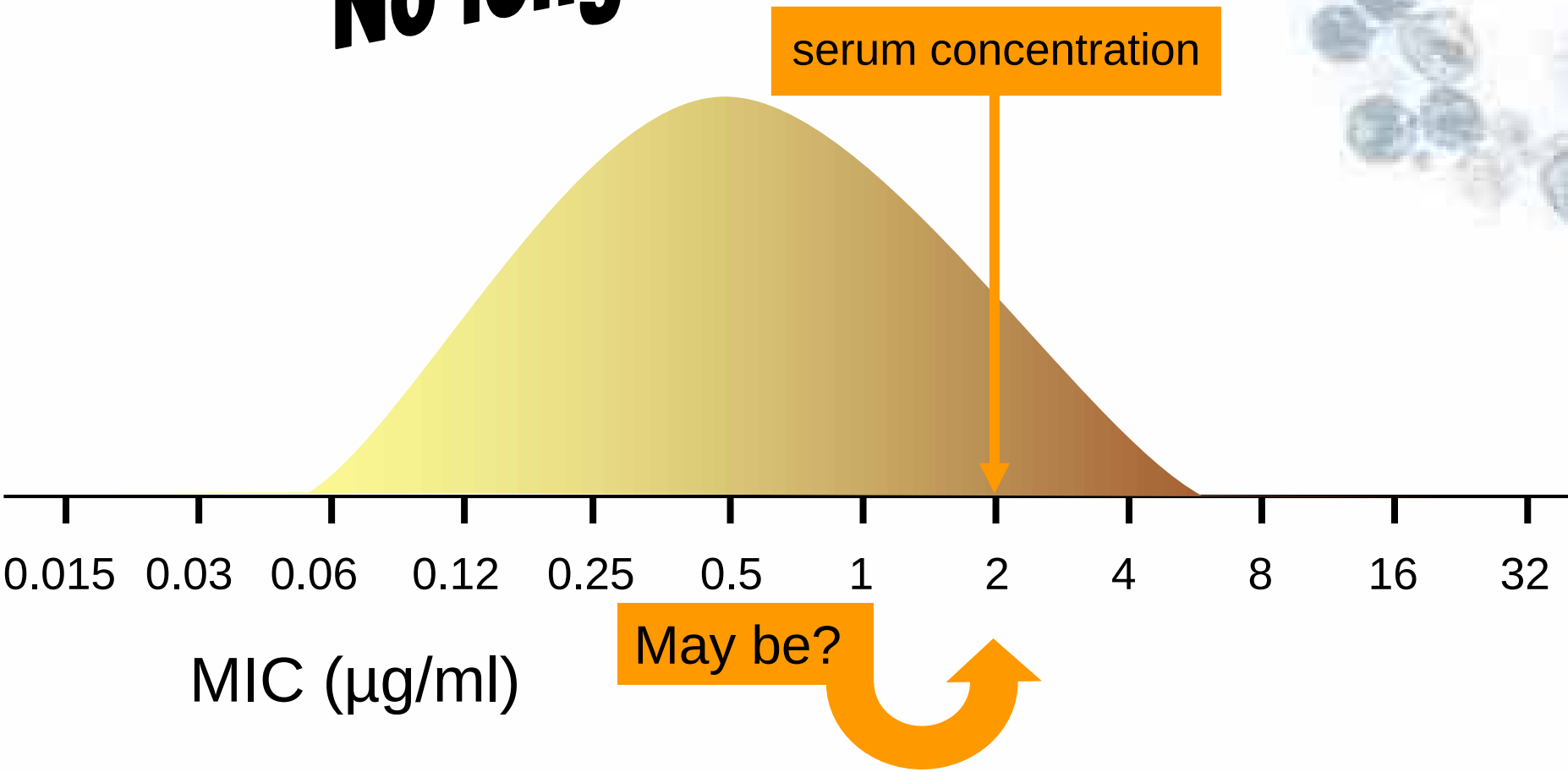
But, what is strong ?

Still Easy...

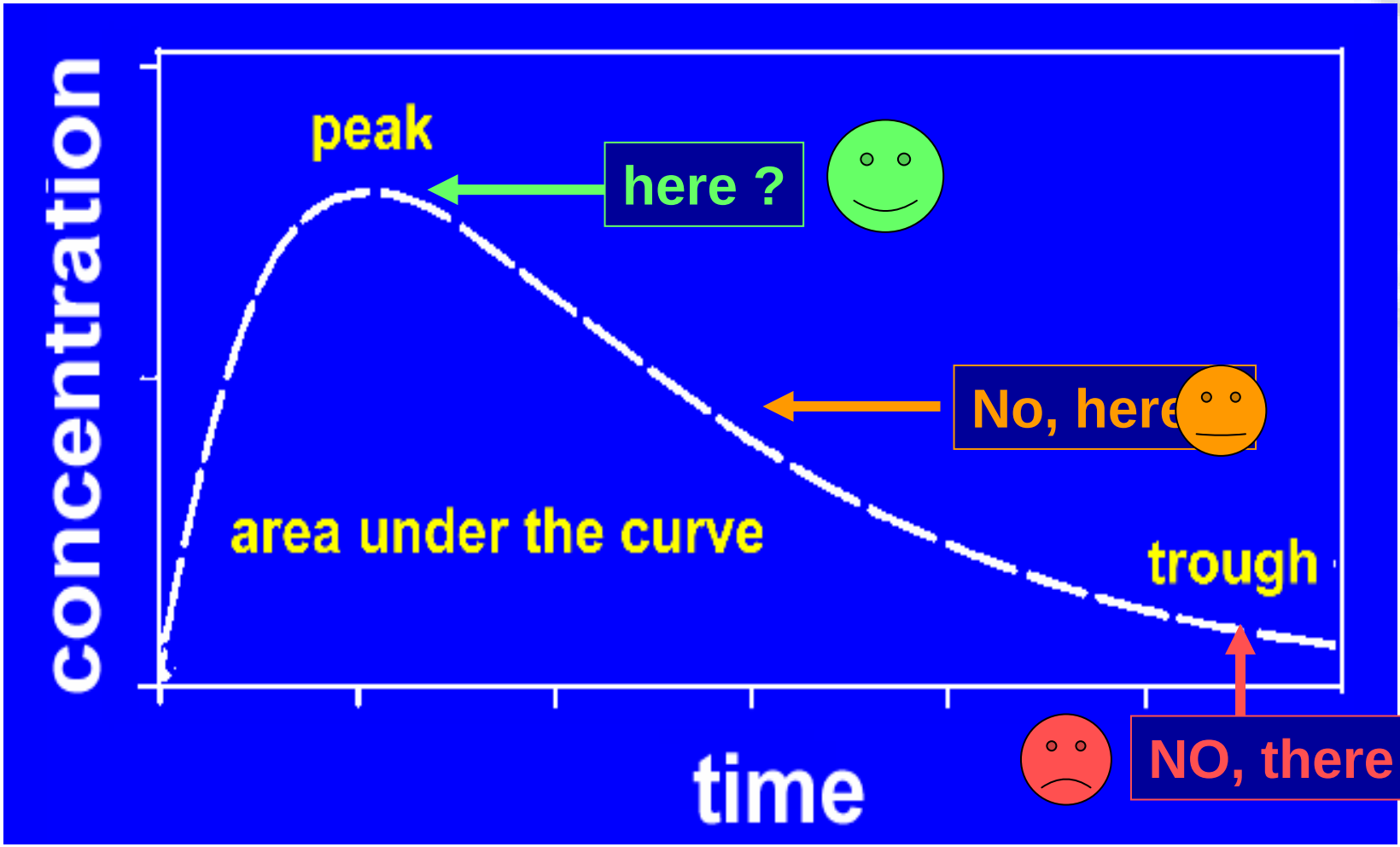


But, what is strong ?

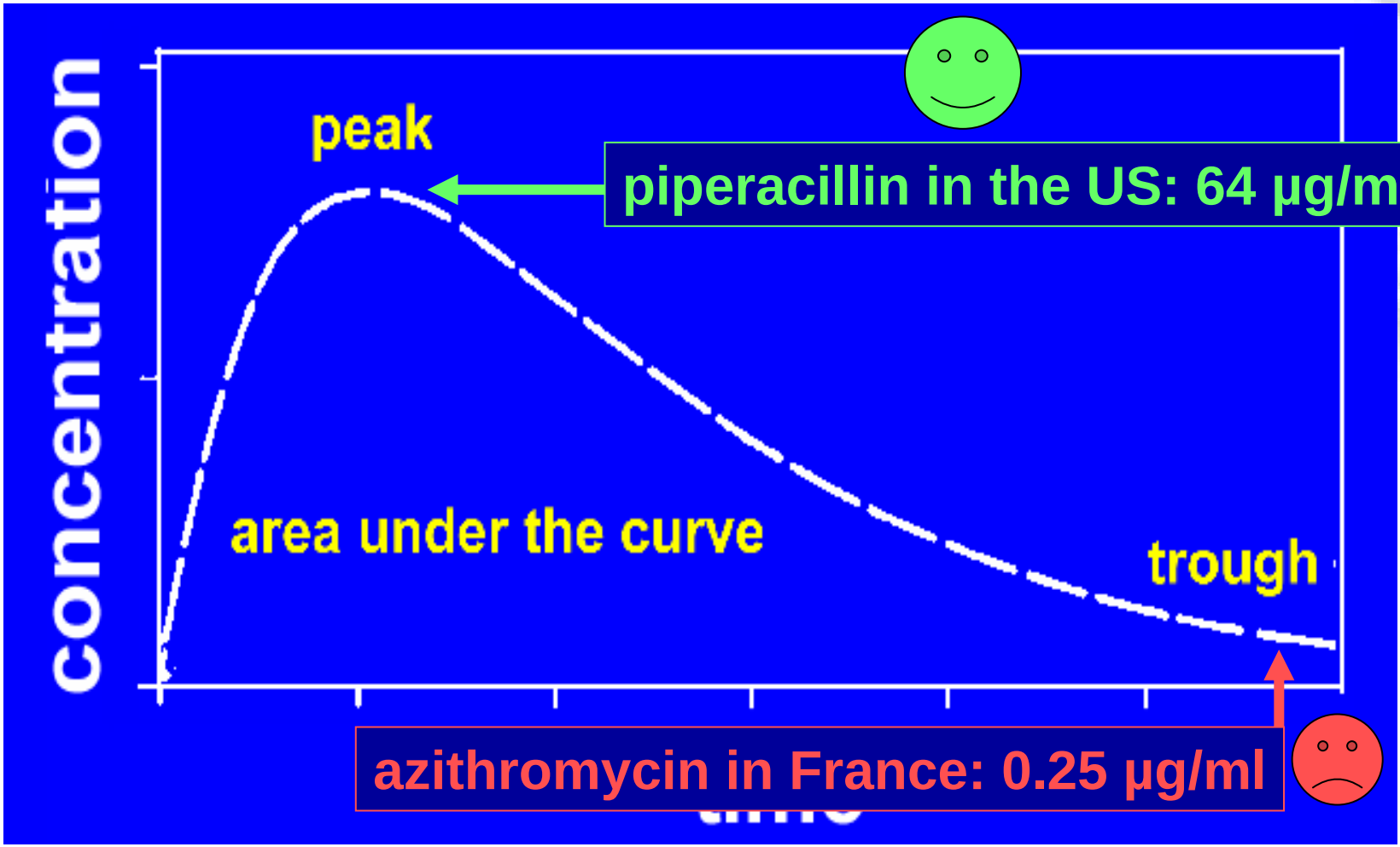
No longer so easy...



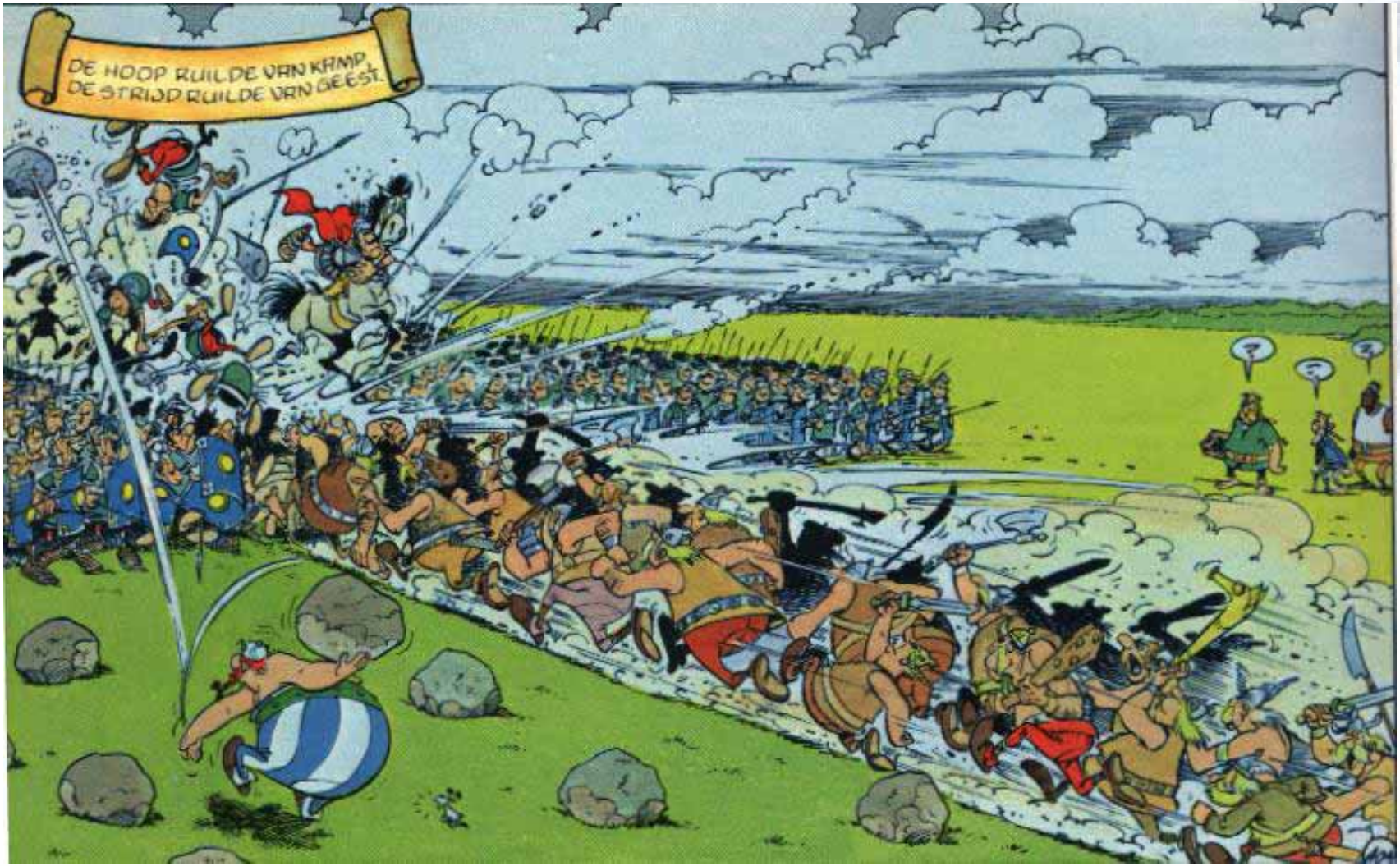
Where should the breakpoint be ?



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 <u>always</u> 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.

Menu Deconnecter

Distribution des CMI vs. Phenotypes sauvages

http://www.eucast.org

Recherche

Méthode: (•) CMI ( ) Methode de diffusion

Éléments par page: 15

Antimicrobien: Ciprofloxacin Espèce: Espèce...

Specify the drug or the bug (never both) - after a few seconds a table of MIC-distributions is shown. Click on any species in the left hand column to display the data as a bar chart, with EUCAST epidemiological cut-off values and harmonised European clinical breakpoints.

Antimicrobien:

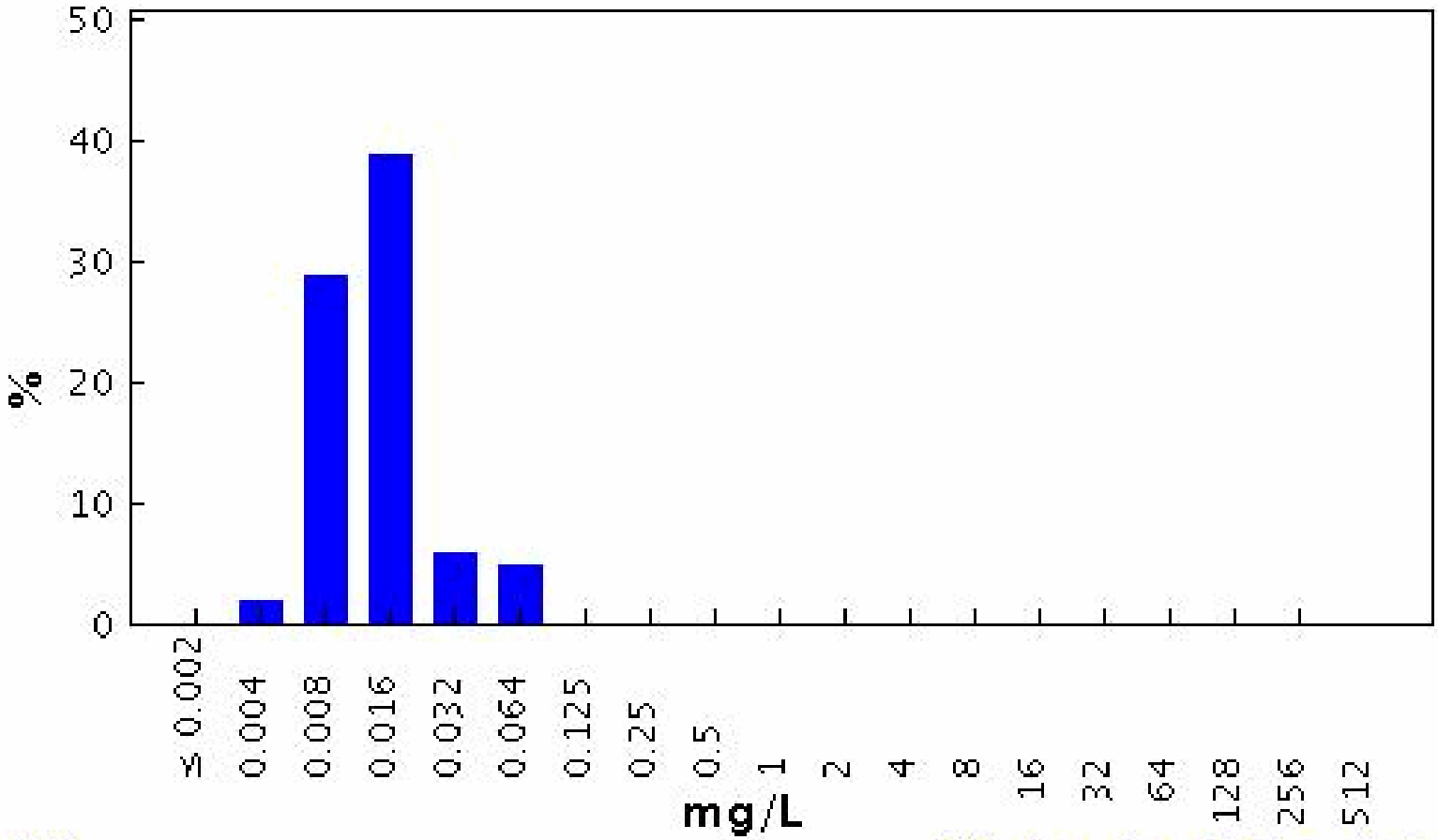
Acinetobacte																			
Bacteroides f																			
Burkholderia																			
Campylobact																			
Campylobact																			
Citrobacter s																			
Coagulase negative staphylococci	0	0	0	0	5	0	7	13	13	1	0	0	1	0	0	0	0	0	0
Enterobacter species	0	14	30	132	110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

Ac-Le Le-St St-

Retourner

Ciprofloxacin / Escherichia coli

Antimicrobial wild type distributions of microorganisms - reference database EUCAST



MIC

6423 observations (9 data sources)

Epidemiological cut-off: WT ≤ 0.064 mg/L

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

EUCAST 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.

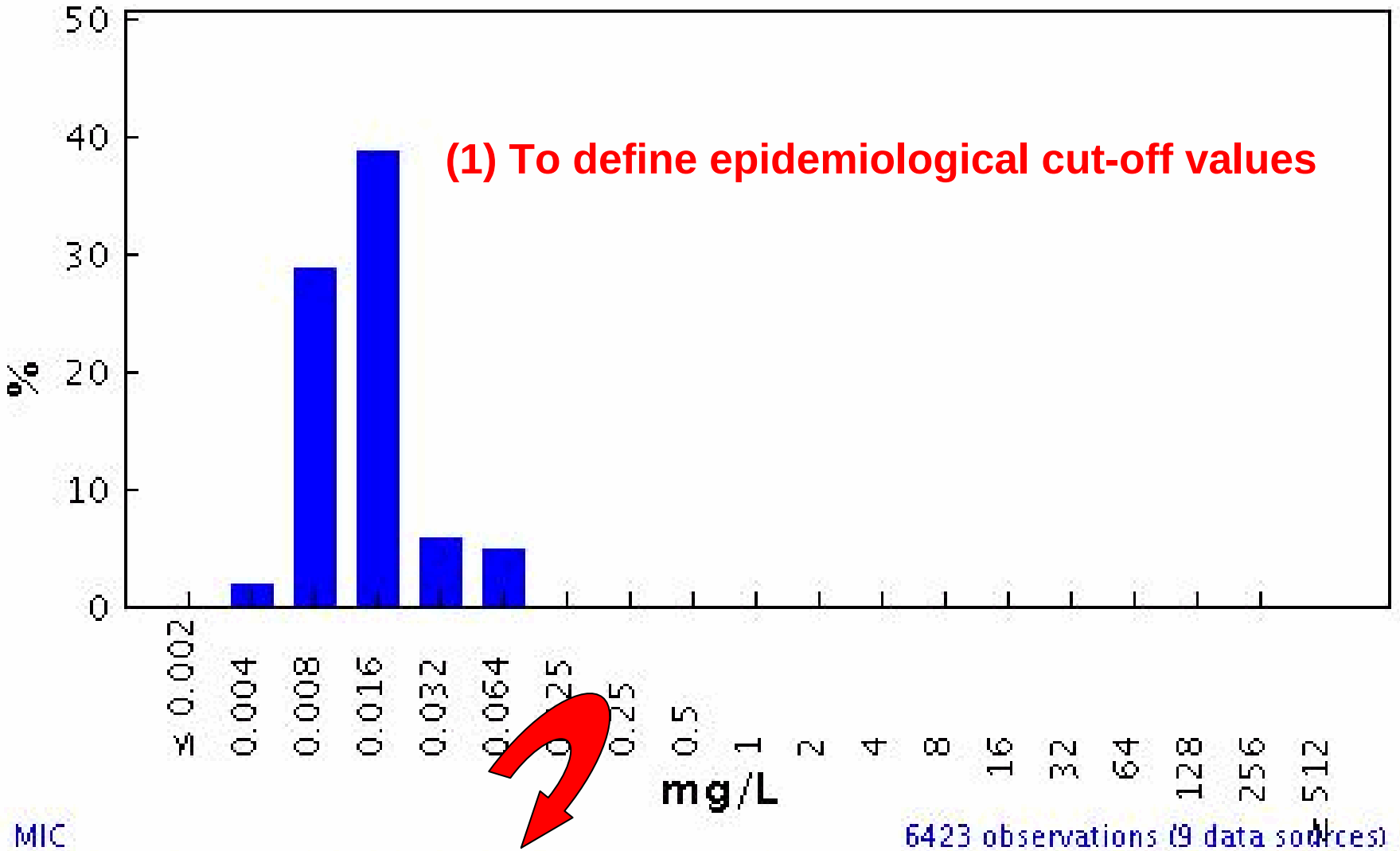
Use of EUCAST wild type MIC distributions

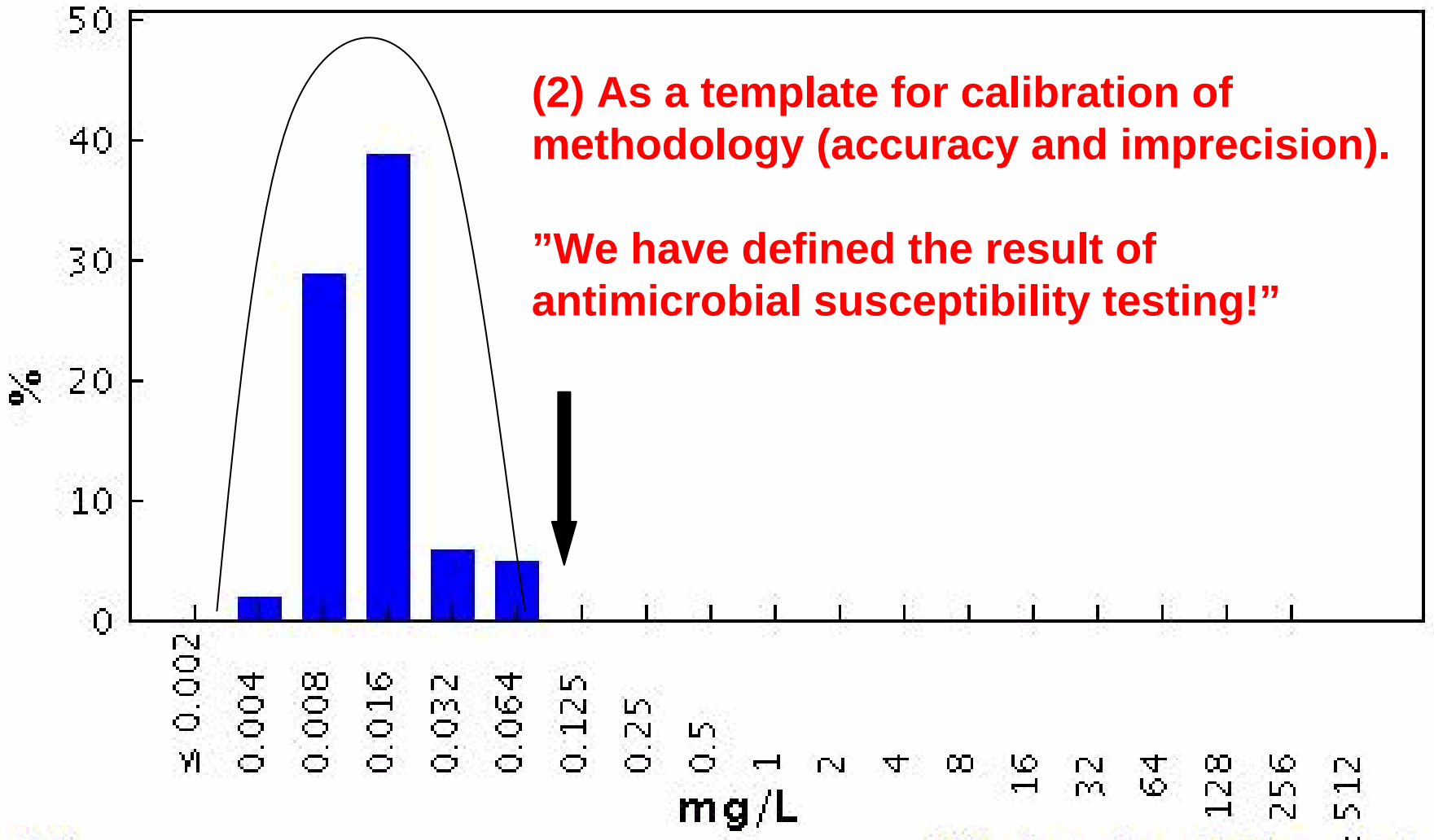
The wild type MIC distributions provide

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
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.

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”.