

Adopting EUCAST breakpoints in countries currently on CLSI breakpoints ...

and some personal thinking...

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Why do we need breakpoints ?

To be honest, I always wondered ...



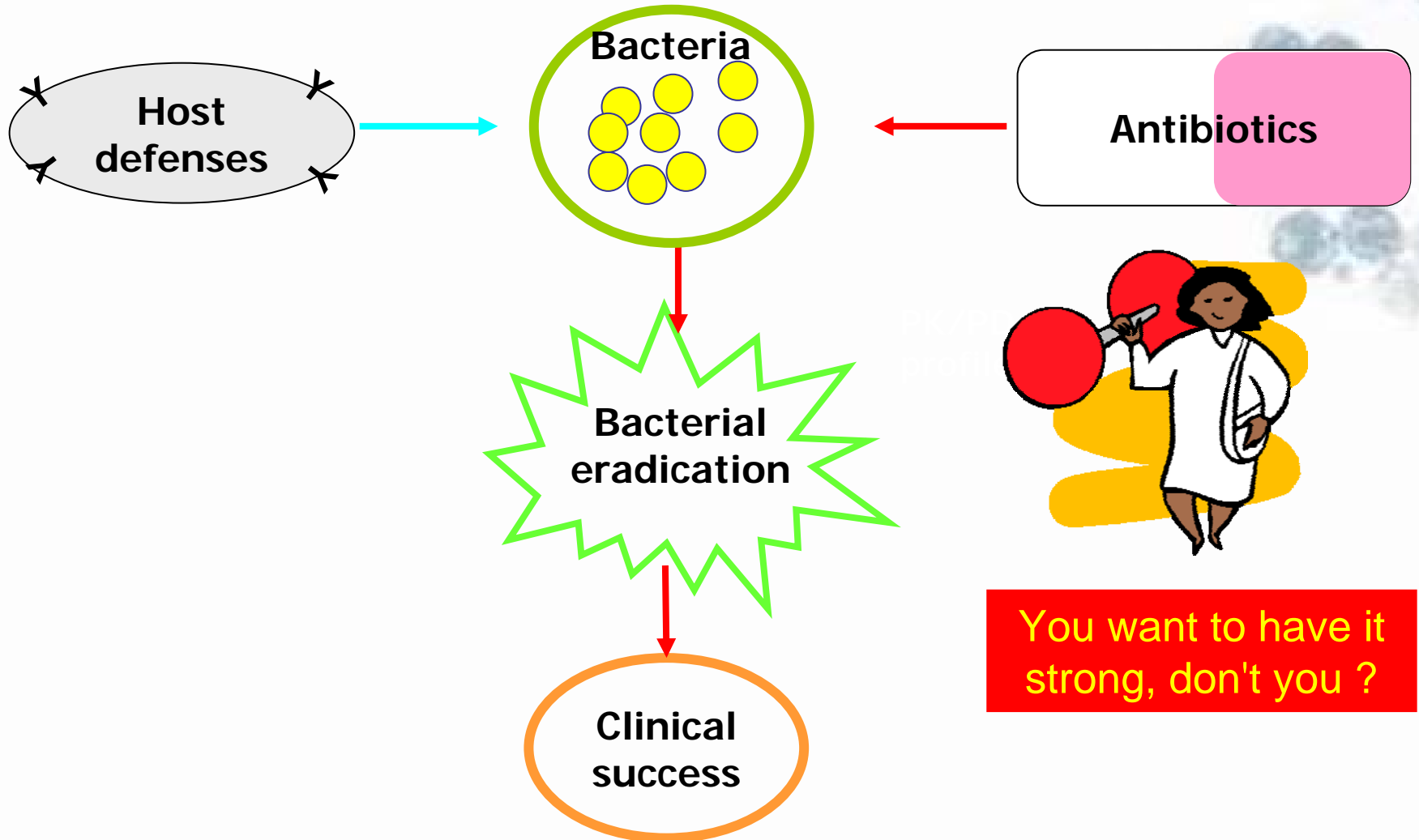
Why do we need breakpoints ?

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...**



What do clinicians want when treating an infection ?



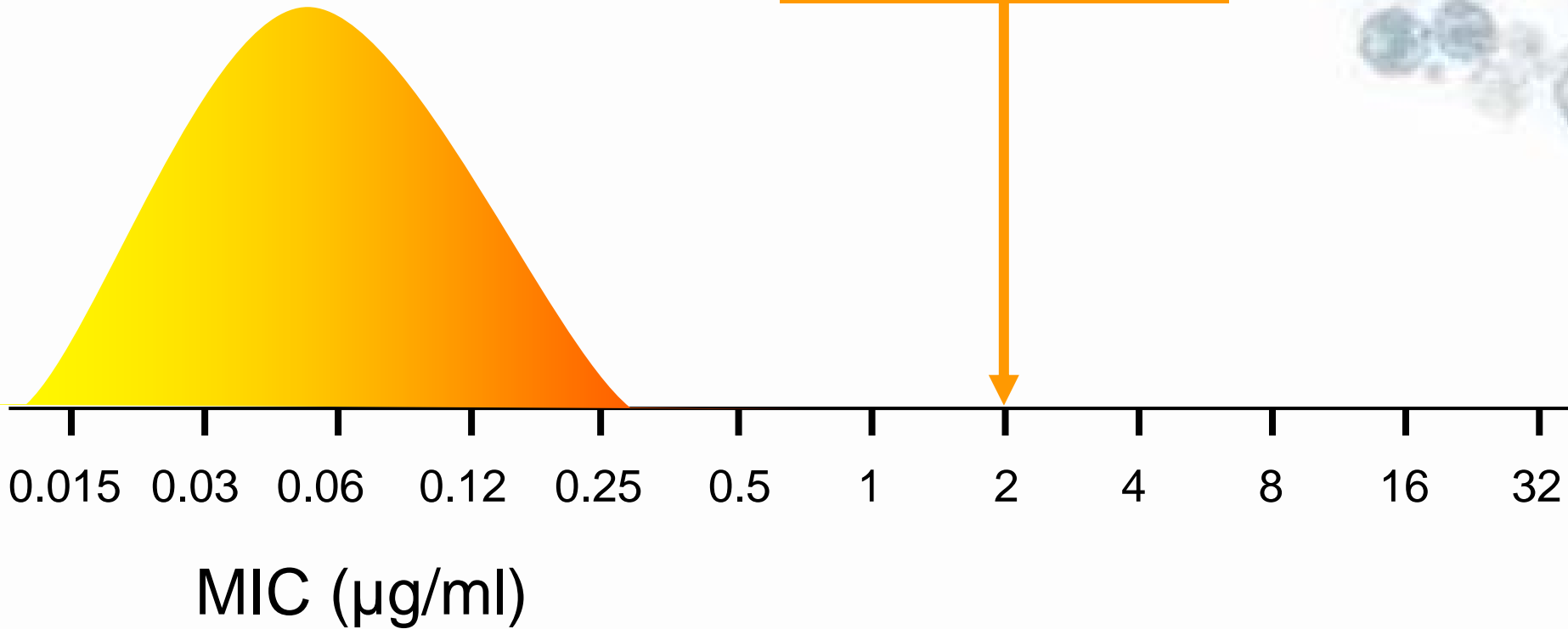
But, what is strong ?



Good !!

Easy!!!

serum concentration



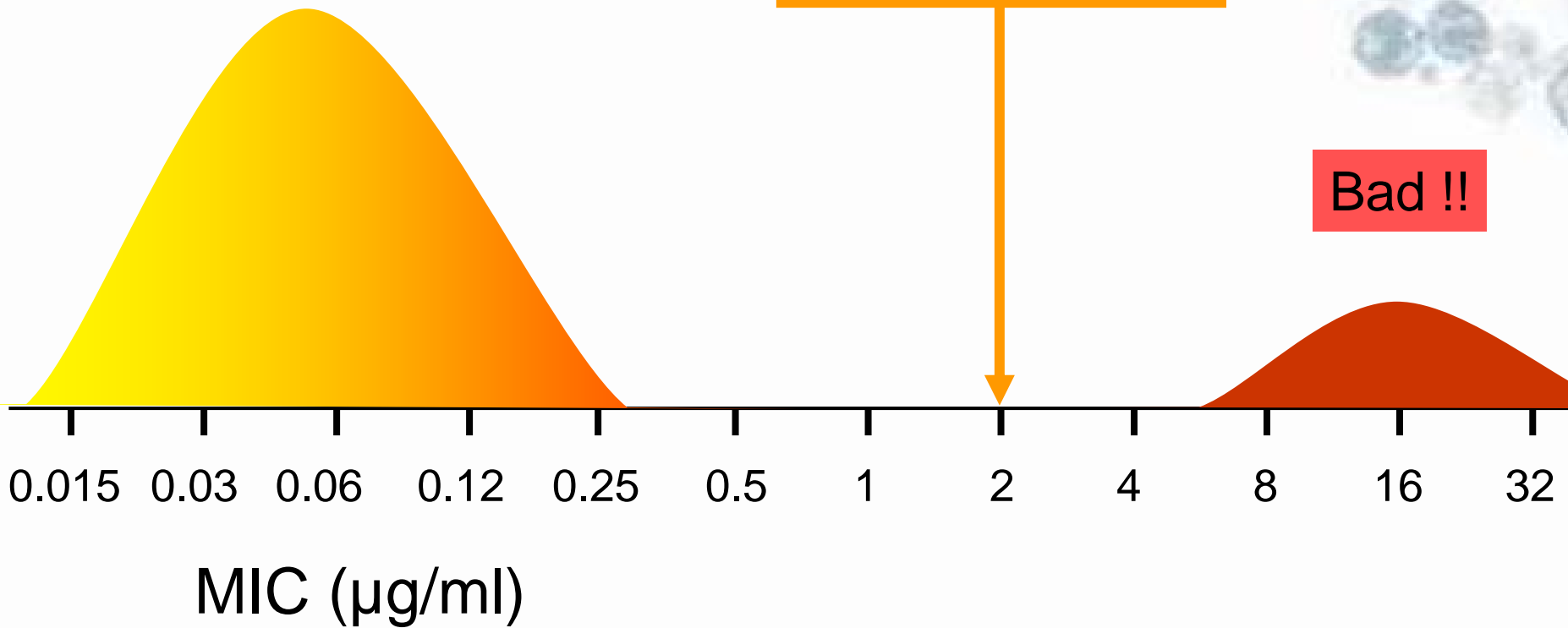
But, what is strong ?

Still Easy!!!

Good !!

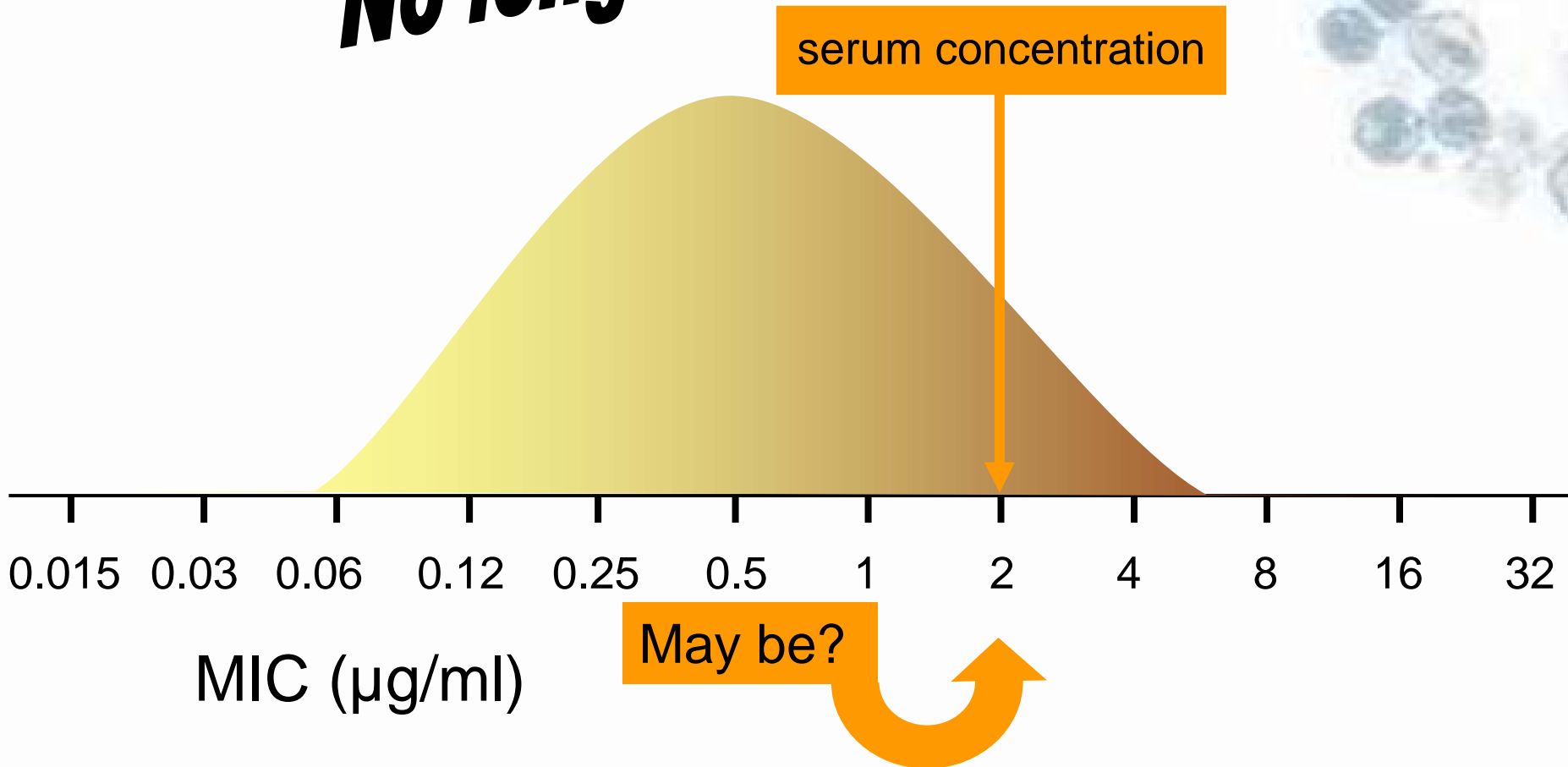
serum concentration

Bad !!

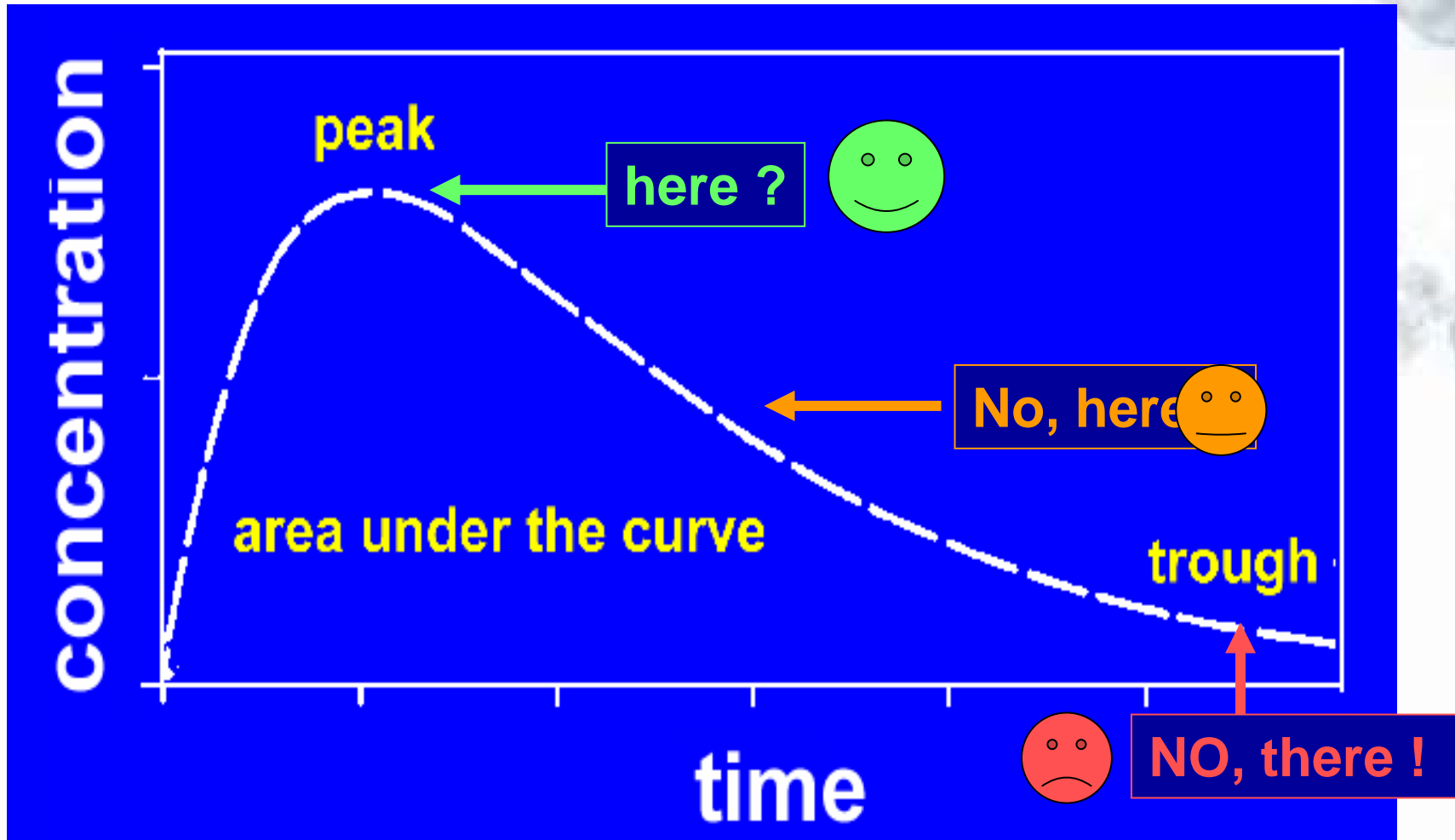


But, what is strong ?

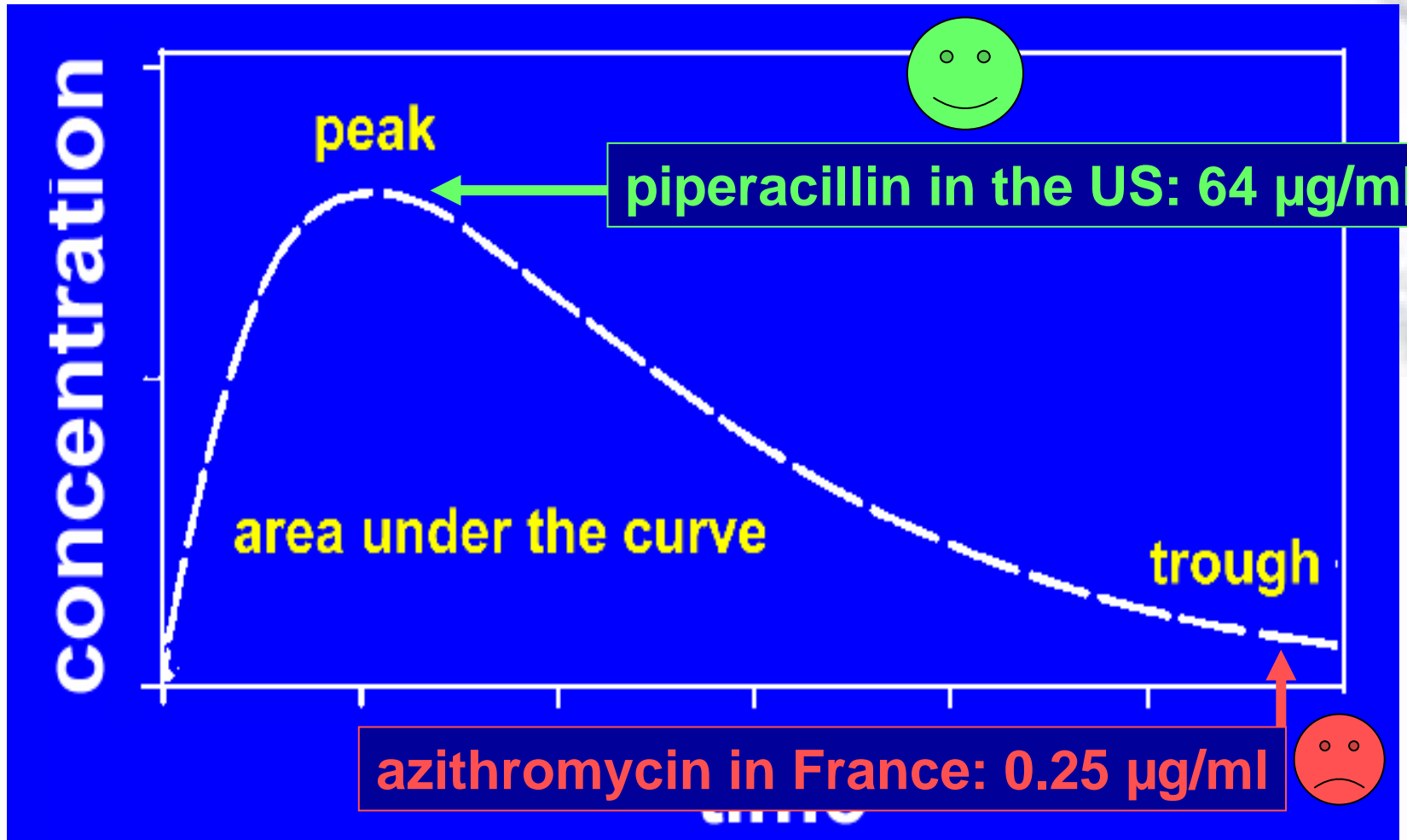
No longer so easy...



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 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. <i>E.coli</i>		S_≤ / R
<i>BSAC</i>	<i>United Kingdom</i>	2 / ≥4
<i>CA-SFM</i>	<i>France</i>	4 / >32
<i>CRG</i>	<i>The Netherlands</i>	4 / >16
<i>DIN</i>	<i>Germany</i>	2 / ≥16
<i>NWGA</i>	<i>Norway</i>	1 / ≥32
<i>SRGA</i>	<i>Sweden</i>	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



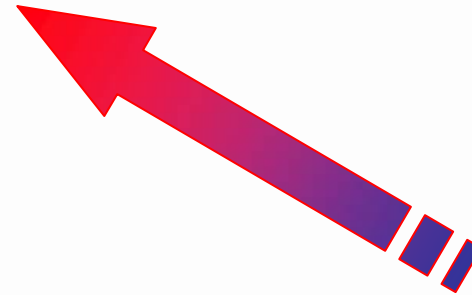
4 / >32



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



The
"filet américain"
attitude *



* Broodjes filet américain 100% rundvlees

A simple decision ...



Now, the clinician can treat all patients



NCCLS

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

An example of (probably) too high breakpoints

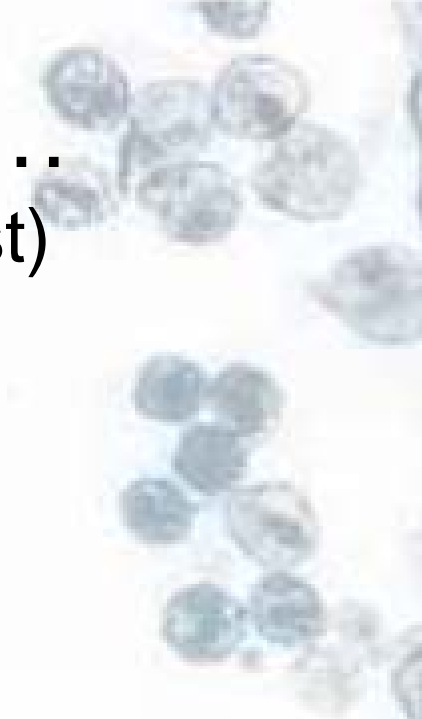


Drug	Typical daily dosage ^a	Typical PK values		Proposed PK/PD upper limit		Breakpoints (mg/L) ^d
		C _{max} in mg/L total/free (dose)	AUC _{24 h} (mg × h/L) total/free	Efficacy ^b	Prevention of resistance ^c	NCCLS (S/I/R)
Norfloxacin	800 mg	1.4/1.1 (400 mg PO)	14/11	0.1–0.4	0.1	≤4/8/>16 ^j
Ciprofloxacin	1000 mg	2.5/1.75 (500 mg PO)	24/18	0.2–0.8	0.2	≤1/2/>4 ^k
Ofloxacin	400 mg	4/3 (400 mg PO)	40/30	0.3–0.9	0.4	≤2/4/8 ^l
Levofloxacin	500 mg	4/2.8 (500 mg PO)	40/28	0.3–0.9	0.3	≤2/4/8 ^l
Moxifloxacin	400 mg	3.1/1.8 (400 mg PO)	35/21	0.2–0.7	0.2	≤1/2/4 ^m

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

Van Bambeke F, Michot JM, Van Eldere J, Tulkens PM.
Quinolones in 2005: an update. Clin Microbiol Infect. 2005 Apr;11(4):256-80. PMID: 15760423

An unanticipated problem ... (if you are a non-US microbiologist)



An unanticipated problem ...

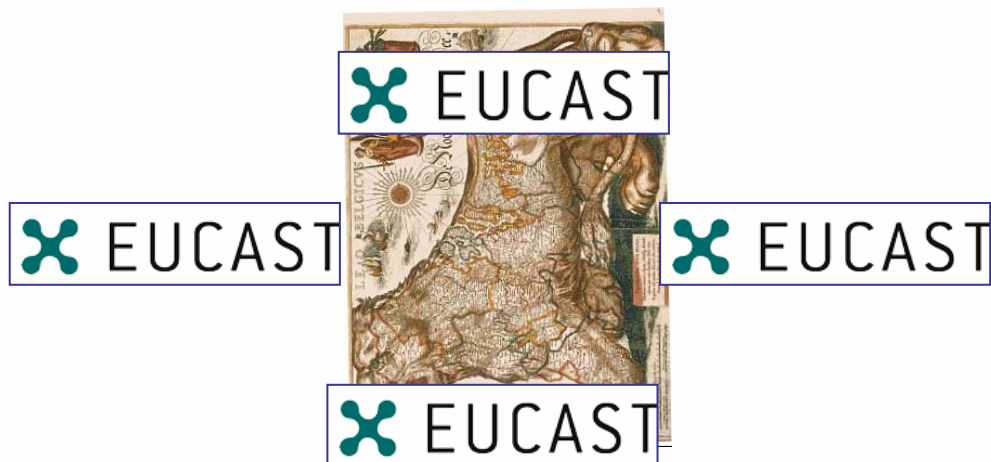
- Since 2006, FDA has reasserted its legal rights to define official breakpoints
- CLSI may determine and publish breakpoints no sooner than 24 months after FDA decision
(and only if the company requests this [?])
- In the meantime, only FDA breakpoints will be legal in the US, and will be essentially 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 2009; (ii) interpretative criteria for disk-based assay will be released by EUCAST in 2009



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.

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
<i>Enterobacteriaceae</i>	S ≤ 1 mg/L et R > 4 mg/L
<i>Acinetobacter</i> spp.	S ≤ 1 mg/L et R > 4 mg/L
<i>Pseudomonas</i> spp.	S ≤ 1 mg/L et R > 4 mg/L
<i>Streptococcus</i> spp. autres que <i>S. pneumoniae</i>	S ≤ 1 mg/L et R > 1 mg/L
<i>S. pneumoniae</i>	S ≤ 1 mg/L et R > 1 mg/L
Entérocoques	« cible non appropriée »
<i>Haemophilus</i> spp.	S ≤ 1 mg/L et R > 1 mg/L
<i>N. gonorrhoeae</i>	DI (données insuffisantes)
Anaérobies	S ≤ 1 mg/L et R > 1 mg/L

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.

* would be correct if I had made my homework as Gunnar instructed me and Derek reminded me ...

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

But, at the end, this may be better

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EUCAST, European Committee on Antimicrobial Susceptibility Testing (<http://www.eucast.org>) [241].

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

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So, if you like, you may join the club...

