“Optimalisatie van antibioticum therapie: nieuwe inzichten”.

1. Rol en activiteiten van het *European Committee on Antimicrobial Susceptibility Testing* (EUCAST)
2. Klinische Farmacie en continu infuus
3. Enkele persoonlijke standpunten

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Gentse Apothekers & Artsen Biologen

Wat is een breekpunt ?

- Een ‘magisch getal’ dat ***in vitro*** bepaald wordt door de microbioloog en dat tot doel heeft te voorspellen of het antibioticum doeltreffend zal zijn ***in vivo***.
- De in vitro verkregen waarden vormen een continue functie. Het verkregen cijfer wordt echter als volgt geïnterpreteerd...
  - gevoelig … **(S)**
  - intermediair… **(I)**
  - resistent … **(R)**

en dit is wat de **clinicus** krijgt !

[1] die kan omgezet worden in een MIC (zie verder); geautomatiseerde systemen gebruiken groeisnelheid…

Waartoe dienen breekpunten?

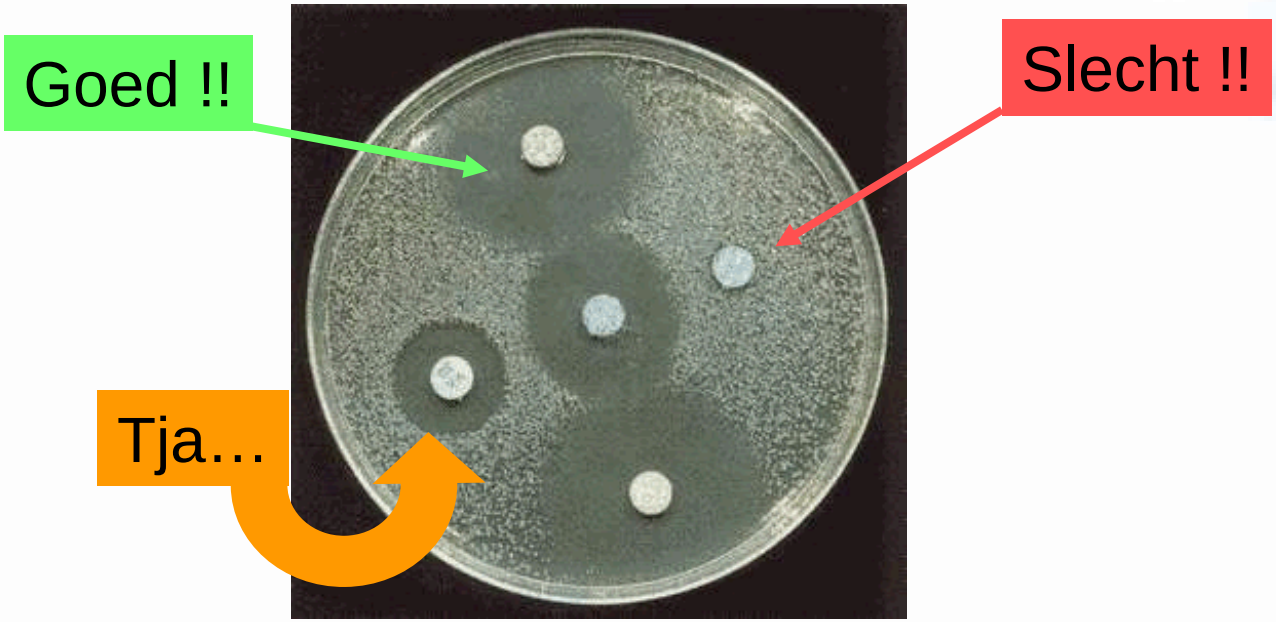
Om eerlijk te zijn, heb ik het mij al dikwijls afgevraagd…

Waartoe dienen breekpunten ?

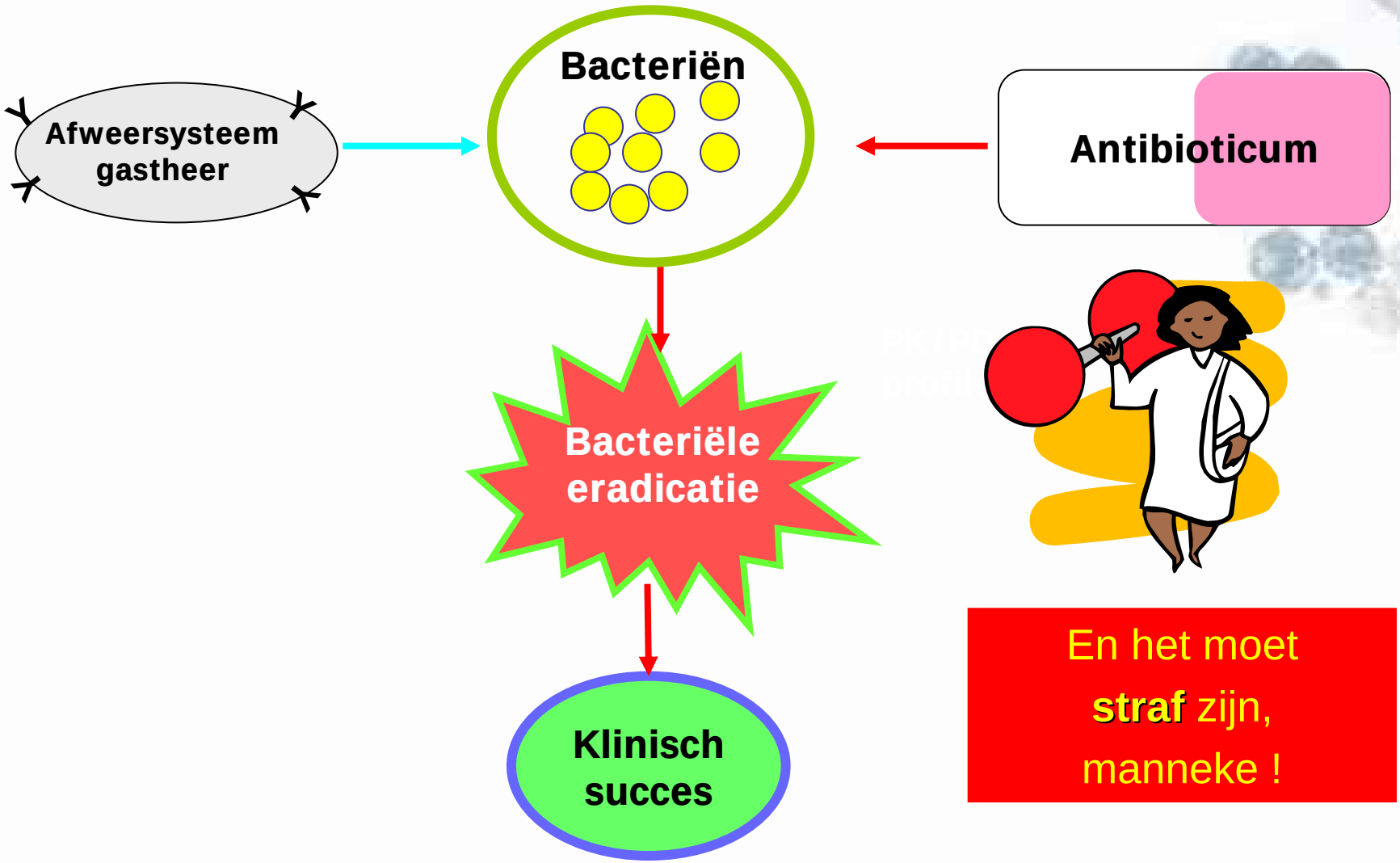
Misschien omdat…

1. Dokters willen graag weten of de bacterie **goed** of **slecht** is …
2. Overheden willen graag kunnen zeggen "**Doe dit**" en "**Doe dat niet**"...
3. De industrie wil graag weten "**Waneer kan ik**" en "**Waneer kan ik niet**"
4. Advocaten willen graag weten of U **schuldig** of **onschuldig** bent ...
5. Microbiologen willen iedereen **eenvoudige antwoorden** geven…

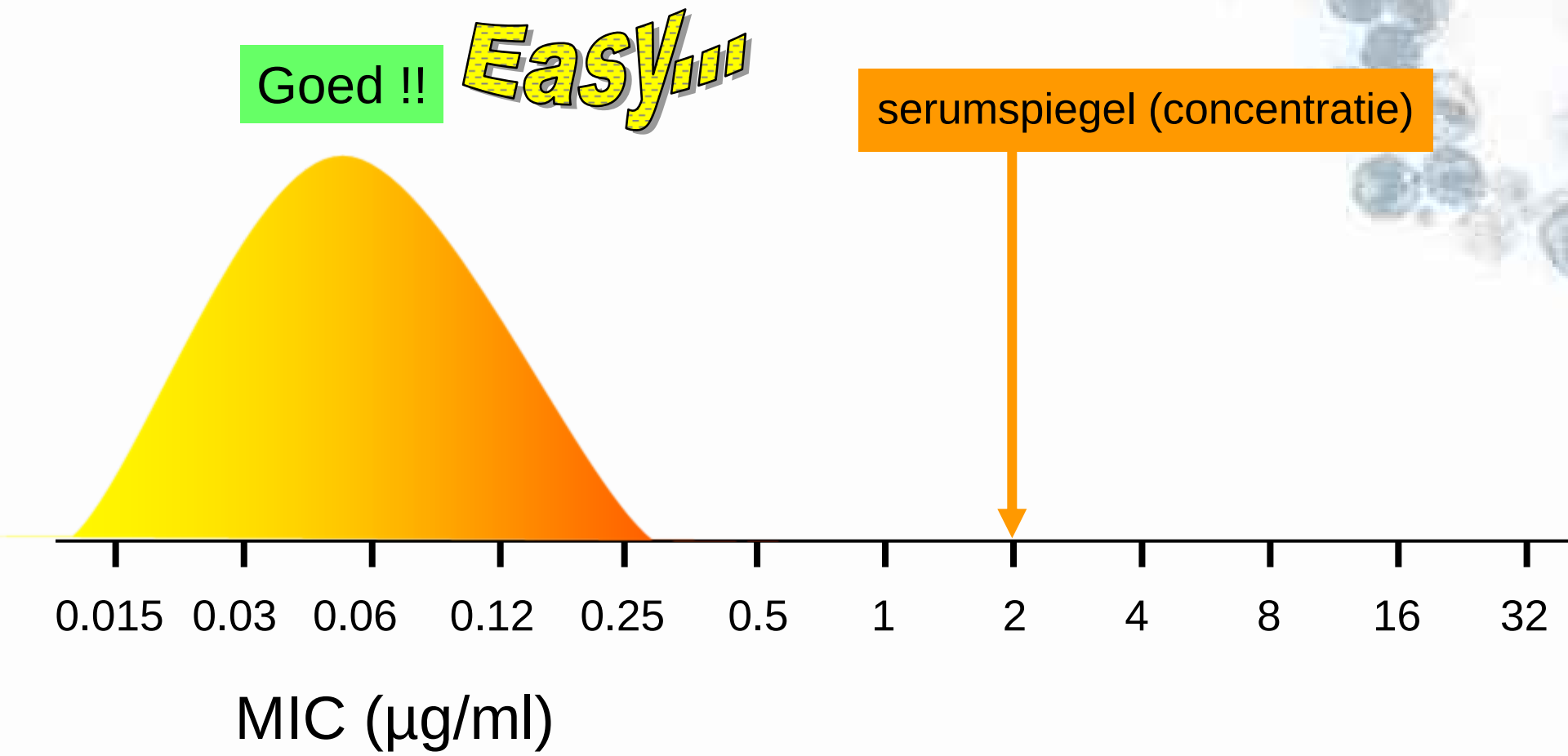
Eenvoudige antwoorden …



Maar hoe moet het nu verder ?

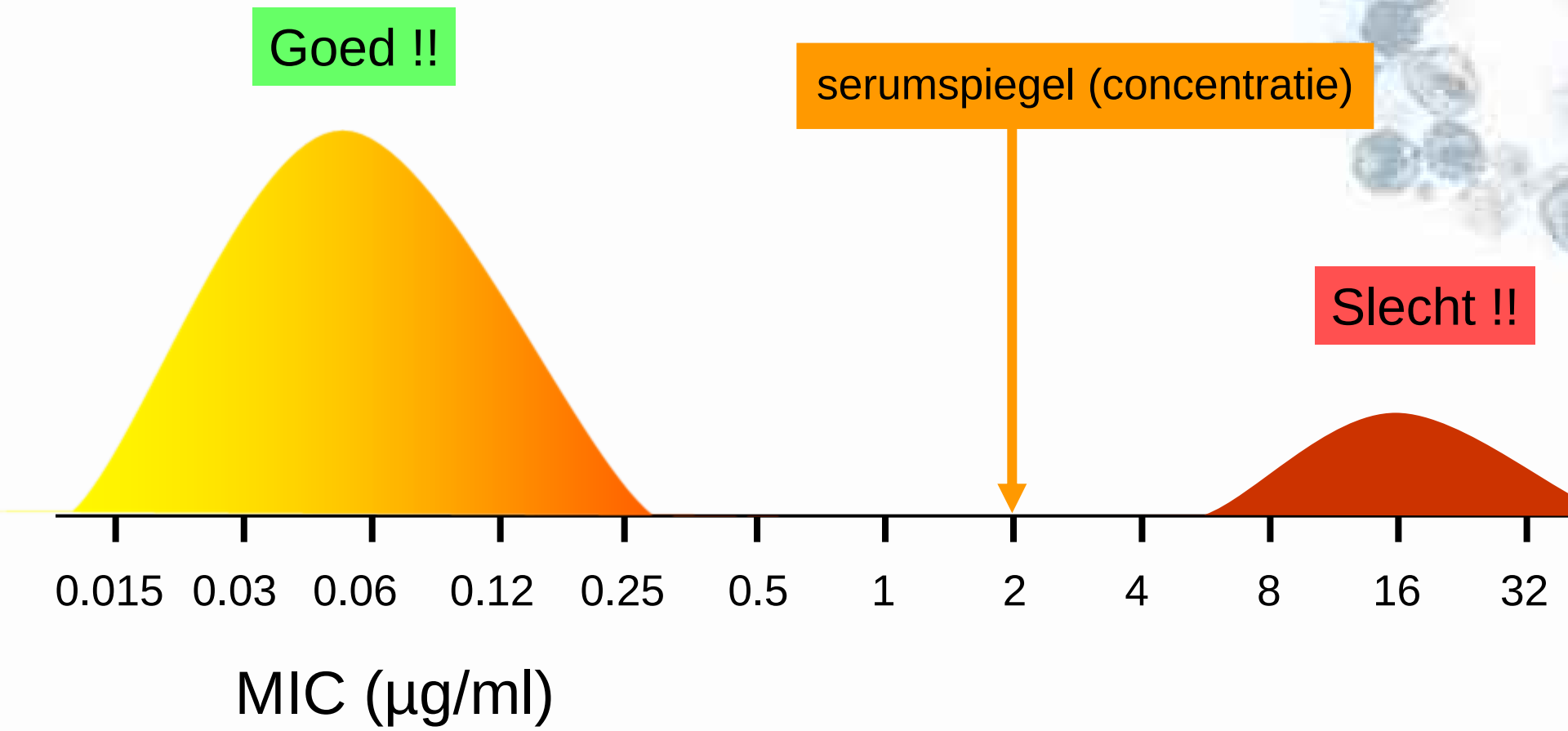


Maar, wat is straf ?



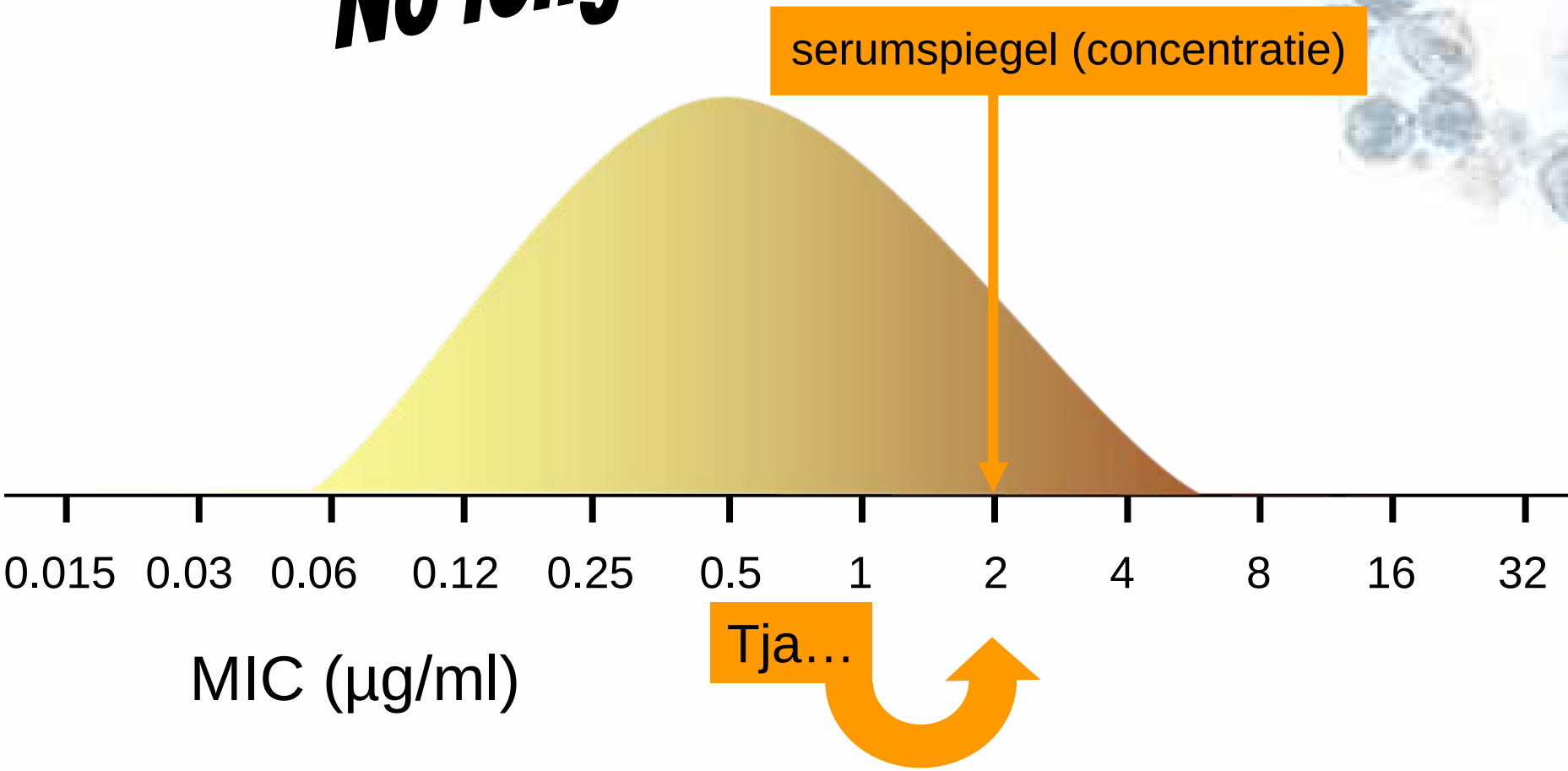
Is dit nog straf ?

Still Easy...

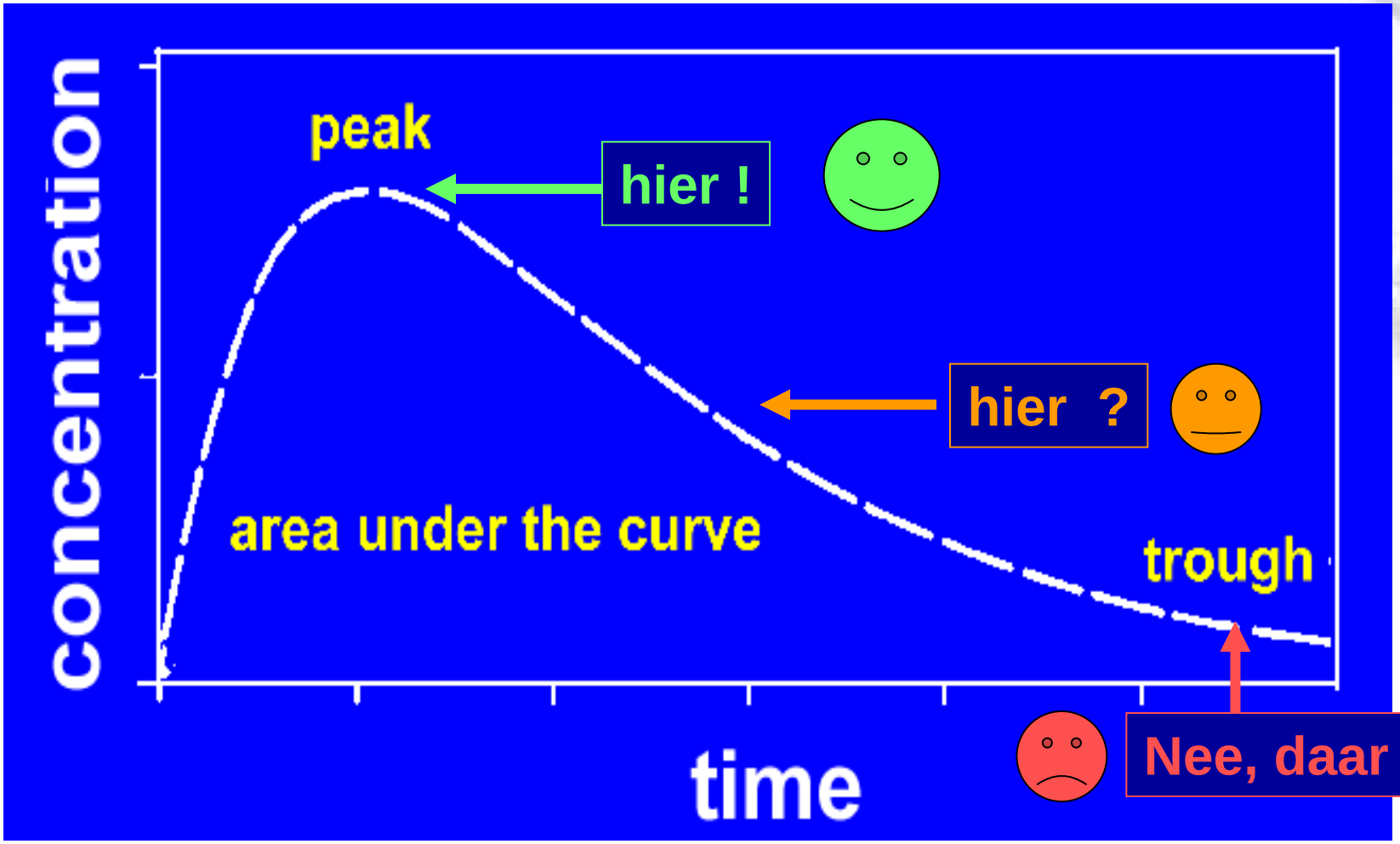


En is dit ook nog straf ?

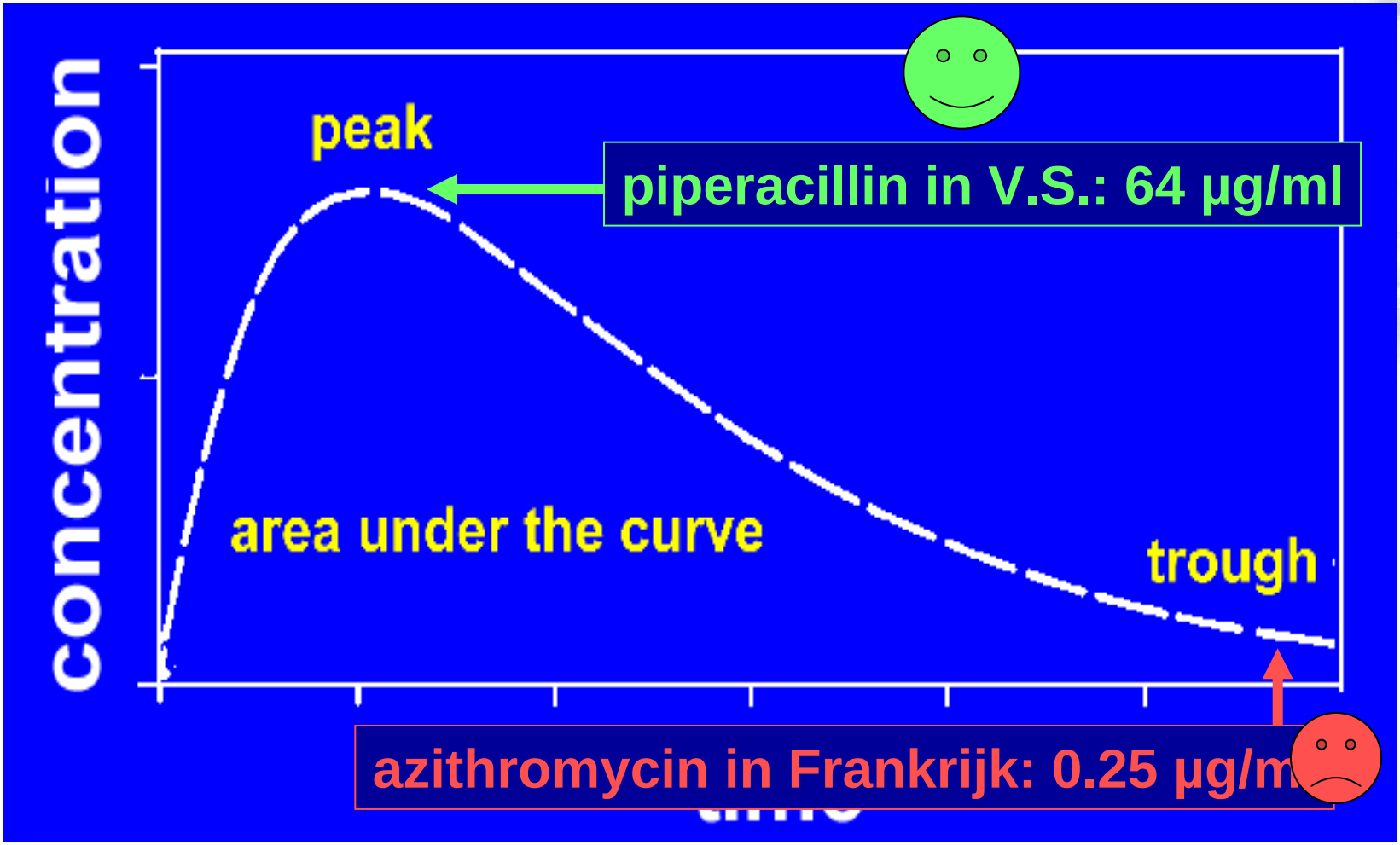
No longer so easy...



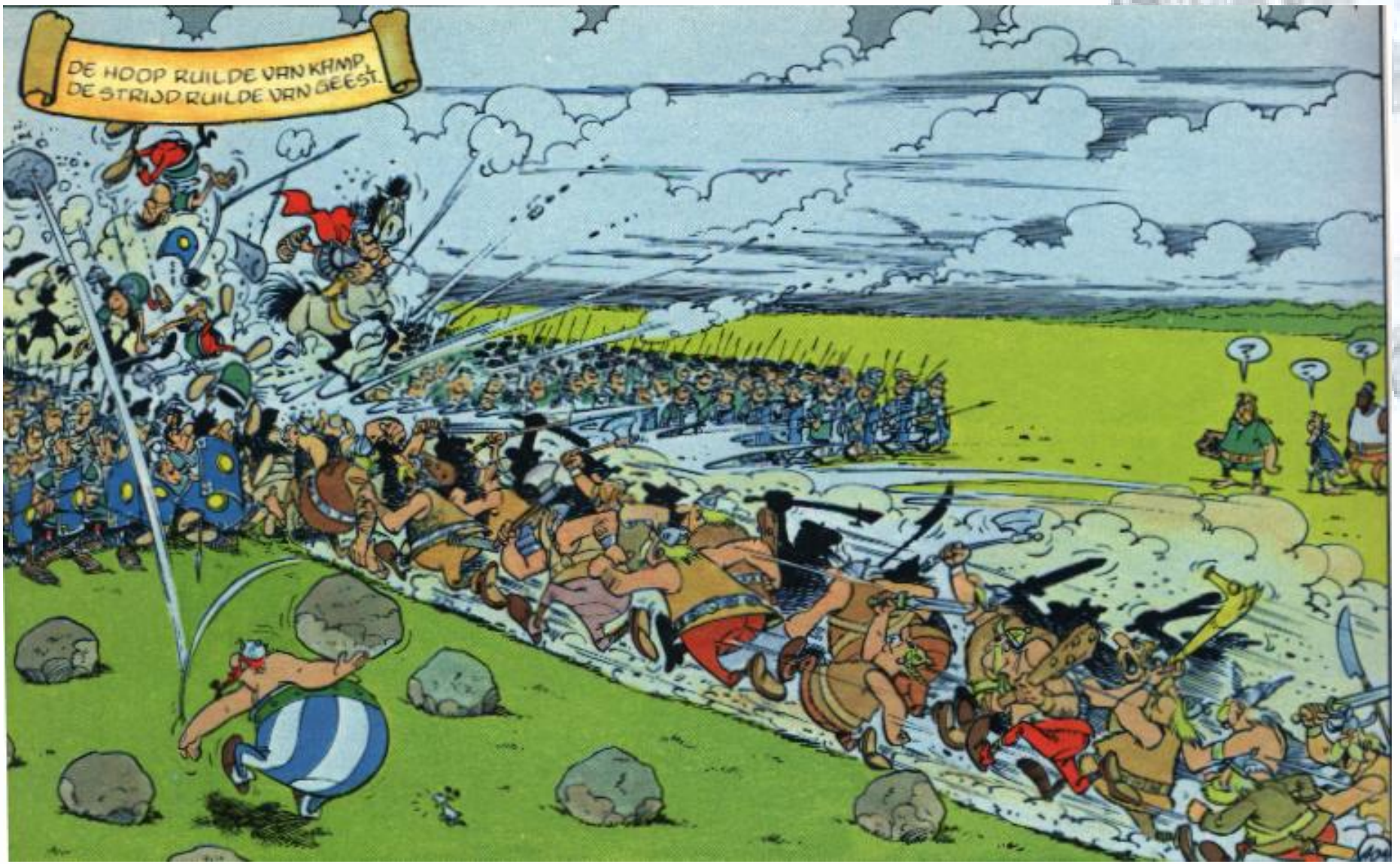
Waar moet het breekpunt liggen ?



Piek of Dal ?
Nog een voorbeeld van de verschillen tussen Amerikanen en Fransen !



Maar ook tussen de Europeanen onderling …



Naar Mouton, 8th ISAP symposium, Nijmegen, 2001

Wat was HET probleem ?

- Europa had verschillende nationale breekpuntcommissies … en daardoor verschillende breekpunten voor eenzelfde antibioticum…

- De Amerikaanse breekpunten werden door het NCCLS** vastgesteld. Maar deze waren
  - niet (altijd) rationeel en realistisch.
  - door de specifieke Amerikaanse situatie (dosering, resistentiepatronen, Industriedruk, enz…) beïnvloed
  - en … verschillend van de nationale breekpunten in Europa

Een eenvoudig voorbeeld

cefotaxime vs. *E.coli*		**S≤ / R**
BSAC	*Verenigd Koningrijk*	*2 / ≥4*
CA-SFM	*Frankrijk*	*4 / >32*
CRG	*Nederland*	*4 / >16*
DIN	*Duitsland*	*2 / ≥16*
NWGA	*Noorwegen*	*1 / ≥32*
SRGA	*Zweden*	*0.5 / ≥2*
NCCLS	*V.S.*	*8 / ≥64*

Niettemin werden deze breekpunten dagelijks gebruikt door de microbiologen om clinici in te lichten over de gevoeligheid van de bacteriën die zij moesten bestrijden

Dus, wat moet een kleine land doen ?

Een kleine land met verschillende buren…

Heeft U dit antibioticum echt nodig ?

2 / >4

2 / >16

4 / >32

Dus, U bent misschien klein … maar flink

The
"filet américain"
attitude *

* Broodjes filet américain 100% rundsvlees

Een eenvoudige oplossing…

Nu kan de clinicus **alle** patiënten behandelen

NCCLS	*U.S.A.*	*8 / ≥64*

Was dit geen goede beslissing ?

"pros" and "cons" van CLSI breekpunten

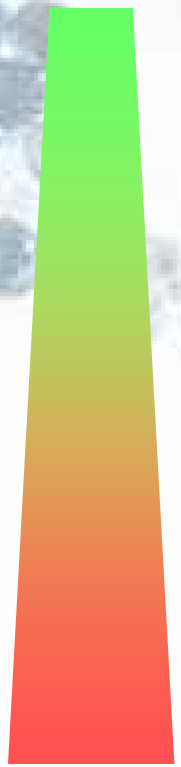
"pros"

- Dadelijk beschikbaar voor de meeste antibiotica…
- met een uitgebreide reeks richtlijnen en aanbevelingen voor het testen…
- Vaak gebruikt en beschouwd als „gouden standaard“ in meeste publicaties en de toezichtnetwerken…
- Gebaseerd op de evaluatie van molecules door een (te ?) grote commissie die wetenschappelijk en klinisch bewijsmateriaal evalueert…
- Met periodieke revisies om bij te blijven met de wetenschappelijke evolutie, met inbegrip van PK/PD en de toename van resistentie.

"pros" and "cons" van CLSI breekpunten

"Cons"

- U moet er voor betalen…
- Beslissingsproces slechts gedeeltelijk toegankelijk voor personen buiten de V.S. …
- Belangrijke invloed door de industrie (stemmende leden)
- Richtlijnen en aanbevelingen voor testen niet altijd aangepast aan de Belgische situatie…
- Revisie proces niet altijd in de goede richting (zie penicilline …)
- Voor bepaalde antibiotica, waren de CLSI breekpunten echt te hoog …en ze zijn het nog...



"pros" and "cons" van CLSI breekpunten

te Hoog ?

TABLE. Comparison of former and new penicillin breakpoints (minimum inhibitory concentrations [MIC]) for *Streptococcus pneumoniae*, by susceptibility category — Clinical and Laboratory Standards Institute, 2008

Standard	Susceptibility category MIC (µg/mL)		
	Susceptible	Intermediate	Resistant
Former (all clinical syndromes and penicillin routes)	≤0.06	0.12–1	≥2
New (by clinical syndrome and penicillin route)			
Meningitis, intravenous penicillin	≤0.06	—*	≥0.12
Nonmeningitis, intravenous penicillin	≤2	4	≥8
Nonmeningitis, oral penicillin	≤0.06	0.12–1	≥2

* No intermediate category for meningitis under new penicillin breakpoints.

Wat is EUCAST ?

European Committee on Antimicrobial Susceptibility Testing

- **in 1997 opgestart**
- **met steun van**
  - ***European Society for Clinical Microbiology and Infectious Diseases* (ESCMID)**
  - **Nationale Breekpunten Commissies in Europa (GB, F, D, NL, N, S)**
- **gefinancierd door**
  - **ESCMID**
  - **Nationale Breekpunten Commissies**
  - **DG-SANCO van de Europese Unie (E-CDC vanaf 2008)**

Doelstellingen van EUCAST

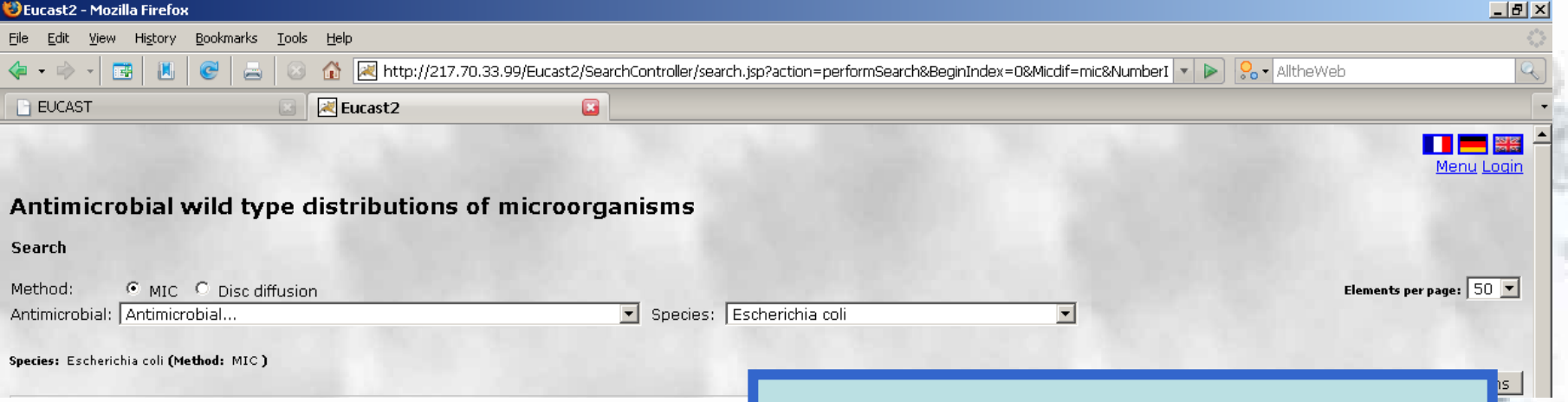
- **In Europa**
  - **gemeenschappelijke** breekpunten opstellen voor de opvolging van antibioticaresistentie
  - de **klinische breekpunten** voor bestaande antibiotica en nieuwe moleculen **harmoniseren**
  - **standaardisatie** van de gebruikte **methoden** bevorderen
  - **samenwerken** met de groepen die zich buigen over gevoeligheidsbepalingen en epidemiologie van de resistentie
  - de **Europese Unie adviseren** i.v.m. de methoden en de interpretatie van de genomen maatregelen
- **In de wereld**
  - met andere groepen (bv. CLSI [nieuwe naam van het NCCLS]) samenwerken teneinde een internationale consensus te bereiken over de methoden voor gevoeligheidsbepaling en, indien mogelijk, ook voor de breekpunten

EUCAST 1st stap: definitie van epidemiologische "cut off" waarden

(Wild type)

- **Een micro-organisme wordt als "wild-type" beschouwd bij afwezigheid van een resistentiemechanisme (mutationeel of verworven) ten aanzien van het antibioticum in kwestie**
- **De verdeling van de MIC-waarden van de "wild-type" micro-organismen is opgesteld op basis van gegevens afkomstig van laboratoria die met EUCAST samenwerken (alle laboratoria kunnen samenwerken)**
- **Dit maakt het mogelijk om een epidemiologische "cut-off" waarde te bepalen**
- **Een micro-organisme wordt als "wild-type" of "non wild-type" gecatalogeerd in functie van zijn plaats binnen of buiten de wild type distributie**

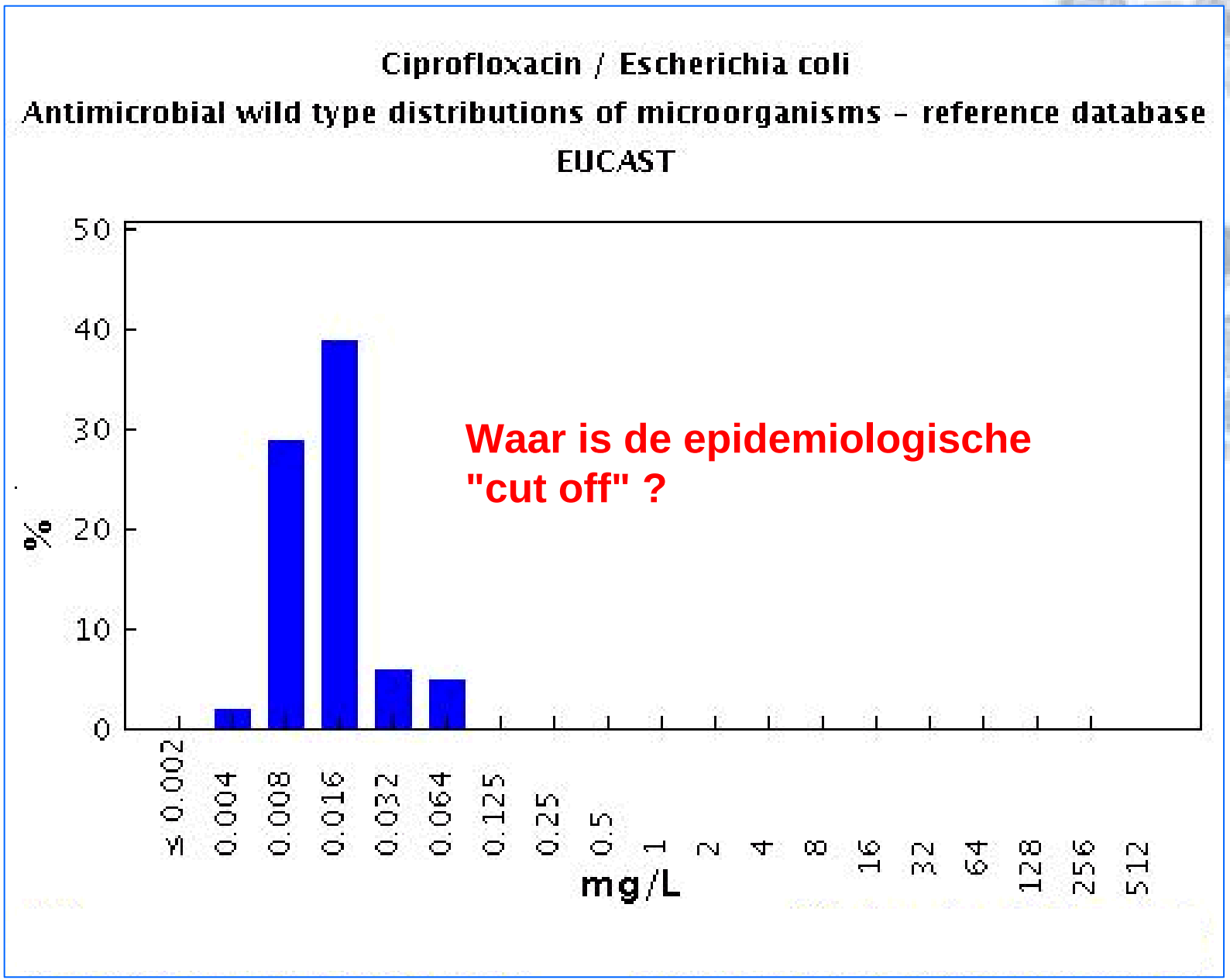
Epidemiologische "cut-off" waarden zullen niet veranderen naargelang de omstandigheden …

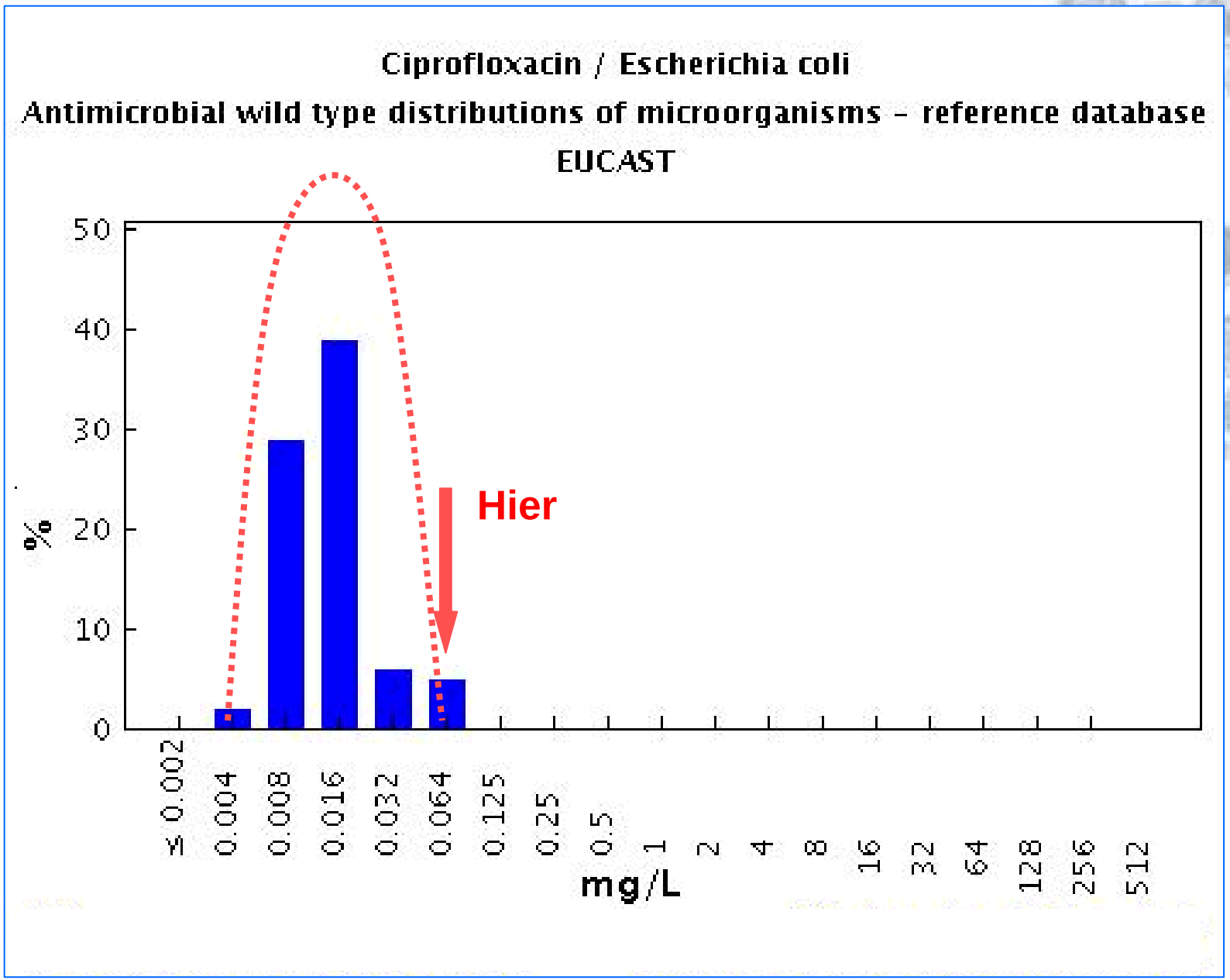


http://www.eucast.org

- **Kies een antibioticum of een micro-organisme… en na enkele seconden verschijnt een tabel met de verdeling van de MIC-waarden.**

	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				
Cefepime	0	0	10	68	282	823	129	0	0	0	0	0	0	0	0				
Cefotaxime	0	5	20	133	732	1857	1111	146	0	0	0	0	0	0	0				
Cefoxitin	0	0	0	0	0	0	2	74	1420	4546	22698	24499	8360	2488	0				
Cefpodoxime	0	0	0	0	0	0	12	28	8	0	0	0	0	0	0				
Ceftazidime	0	0	5	26	172	1051	2672	2354	475	0	0	0	0	0	0				
Ceftibuten	0	0	0	0	0	367	756	1107	225	49	0	0	0	0	0				
Ceftibuten	0	0	0	0	0	268	224	84	19	11	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				
Ciprofloxacin																			
Colistin	0	0	0	0	0	242	35	493	1794	430	82	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				
Enrofloxacin	0	0	0	0	798	1689	105	0	0	0	0	0	0	0	0				
Ertapenem	0	124	882	417	184	46	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				
Flumequine	0	0	0	0	0	0	1	37	1651	446	31	0	0	0	0				
Fosfomycin	0	0	0	0	0	0	0	0	348	611	576	346	200	0	0				
Gentamicin	0	0	4	3	18	40	386	5857	16128	9077	1774	0	0	0	0				
Imipenem	0	0	3	15	64	6202	41814	10539	12263	575	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
%
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
Waar is de epidemiologische "cut off" ?


Ciprofloxacin / Escherichia coli
Antimicrobial wild type distributions of microorganisms – reference database EUCAST
%
50
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≤ 0.002
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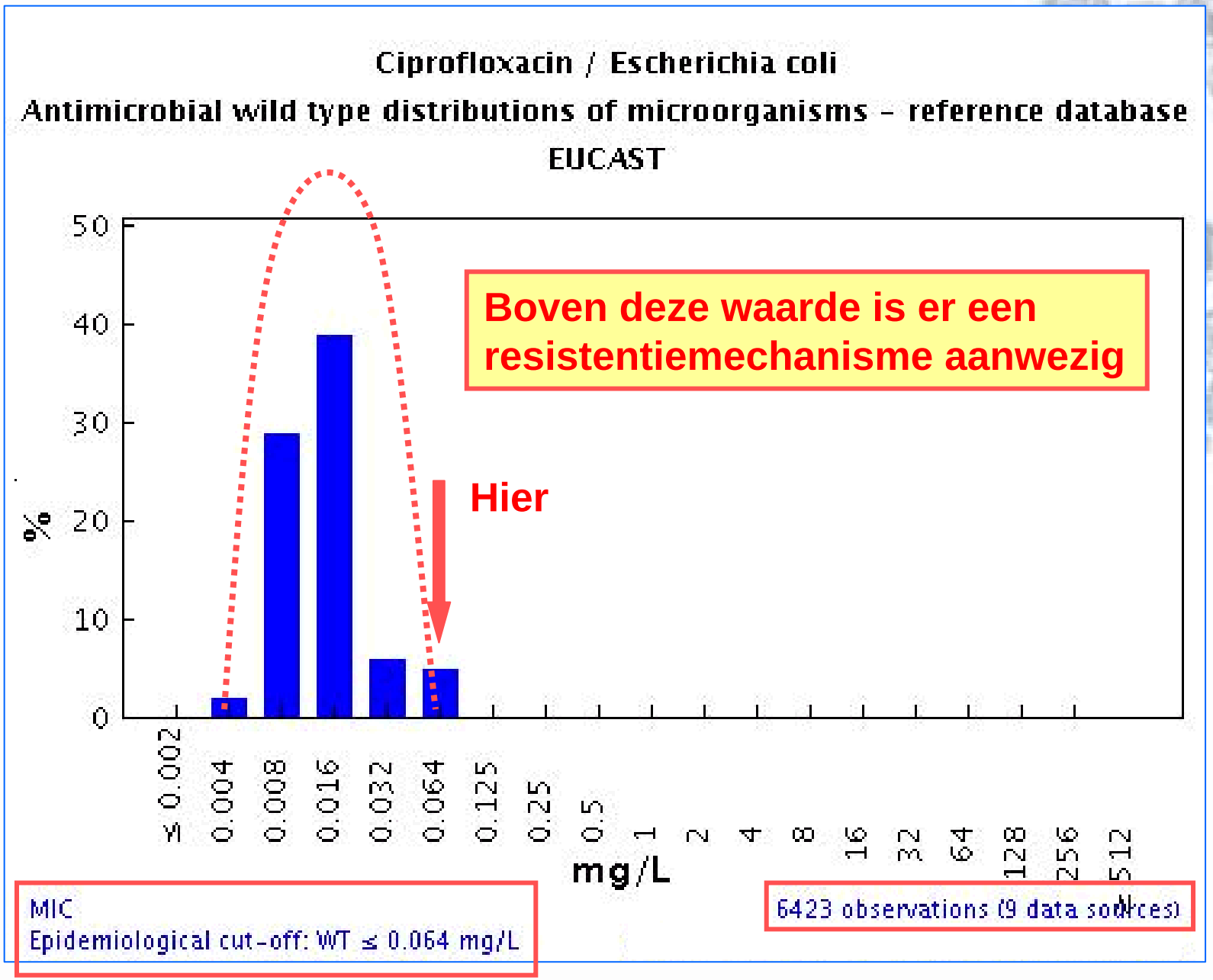
mg/L


Ciprofloxacin / Escherichia coli
Antimicrobial wild type distributions of microorganisms - reference database EUCAST
Boven deze waarde is er een resistentiemechanisme aanwezig
Hier
%
50
40
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20
10
0
≤ 0.002
0.004
0.008
0.016
0.032
0.064
0.125
0.25
0.5
1
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4
8
16
32
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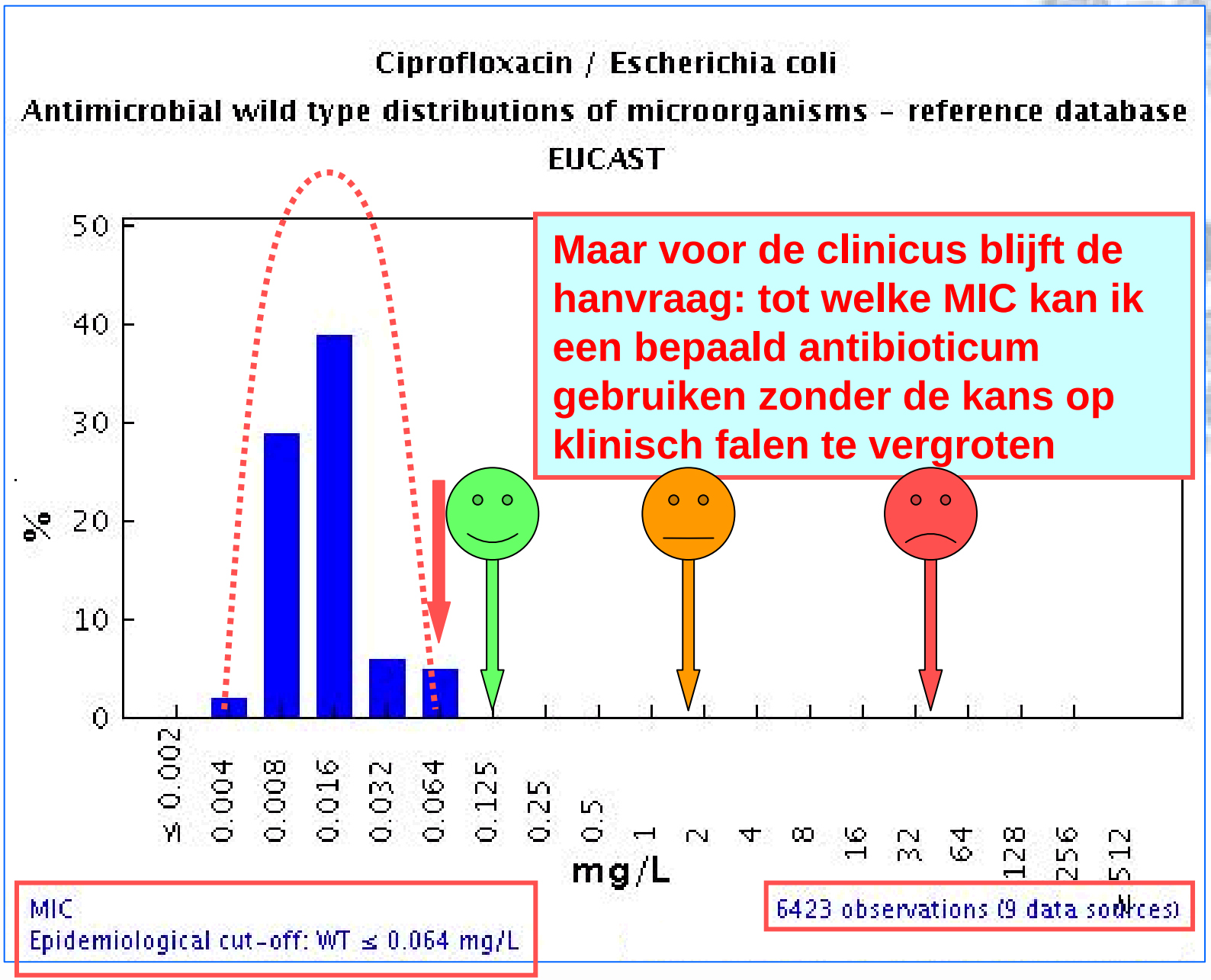
128
256
512
mg/L
MIC
Epidemiological cut-off: WT ≤ 0.064 mg/L
6423 observations (9 data sources)


Ciprofloxacin / Escherichia coli
Antimicrobial wild type distributions of microorganisms - reference database EUCAST
Maar voor de clinicus blijft de hanvraag: tot welke MIC kan ik een bepaald antibioticum gebruiken zonder de kans op klinisch falen te vergroten
%
50
40
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20
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≤ 0.002
0.004
0.008
0.016
0.032
0.064
0.125
0.25
0.5
1
2
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8
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128
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mg/L
MIC
Epidemiological cut-off: WT ≤ 0.064 mg/L
6423 observations (9 data sources)

EUCAST bepaling van klinische breekpunten

Klinisch gevoelig (S)

- Niveau van antibacteriële doeltreffendheid met hoge waarschijnlijkheid van therapeutische succes

Klinisch intermediair (I)

- Niveau van antibacteriële doeltreffendheid met onbepaalde waarschijnlijkheid van therapeutische succes

Klinich resistent (R)

- Niveau van antibacteriële doeltreffendheid met hoge waarschijnlijkheid van therapiefalen

Klinische breekpunten kunnen aangepast worden aan gewijzigende omstandigheden (verandering van dosering, b.v.)

Hoe bepaalt EUCAST de klinische breekpunten voor bestaande antibiotica ?

1. **De gegevens betreffende de dosering, de formulering, de klinische indicaties en de doelwit-organismen worden geëvalueerd, en de relevantie van de verschillende beschikbare breekpunten worden grondig geanalyseerd.**

2. **Een groot aantal MIC-verdelingen worden verzameld teneinde de epidemiologische cut-off van de "wild-type" stammen vast te leggen (WT $\leq$ X mg/L)**

3. Bestaande nationale breekpunten worden vergeleken

4. Farmacokinetische gegevens worden verzameld en geëvalueerd

- meestal vetrekkend van patiënten
- met behulp van populatiefarmacokinetische modellen indien nodig

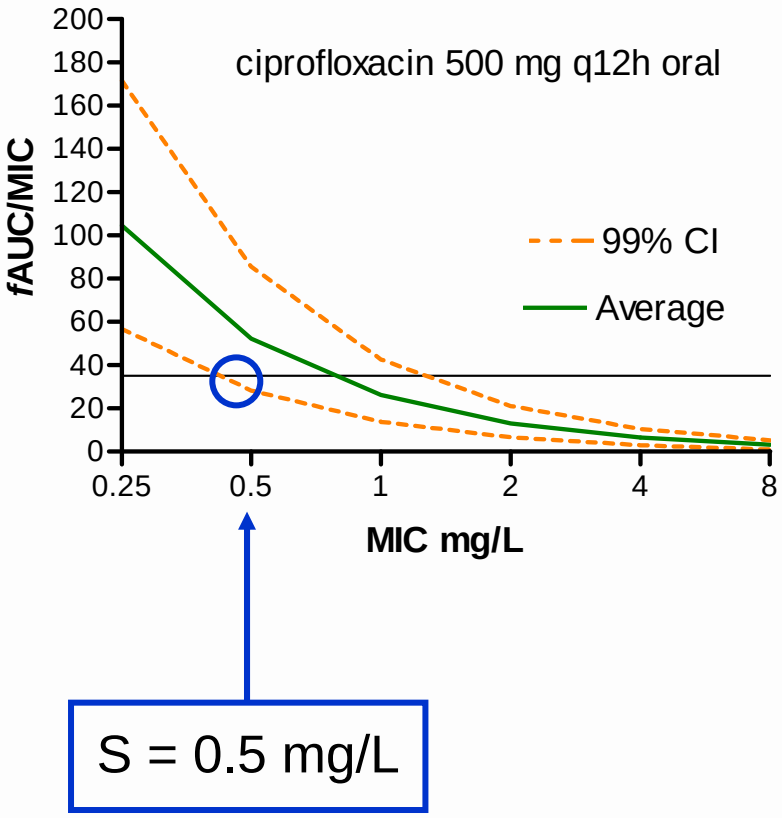
5. Pharmacodynamische data worden geëvalueerd

PK/PD-parameters (tijd boven MIC, AUC_{24u}/MIC, C_{max}/MIC…) die de doeltreffendheid bepalen op basis van:

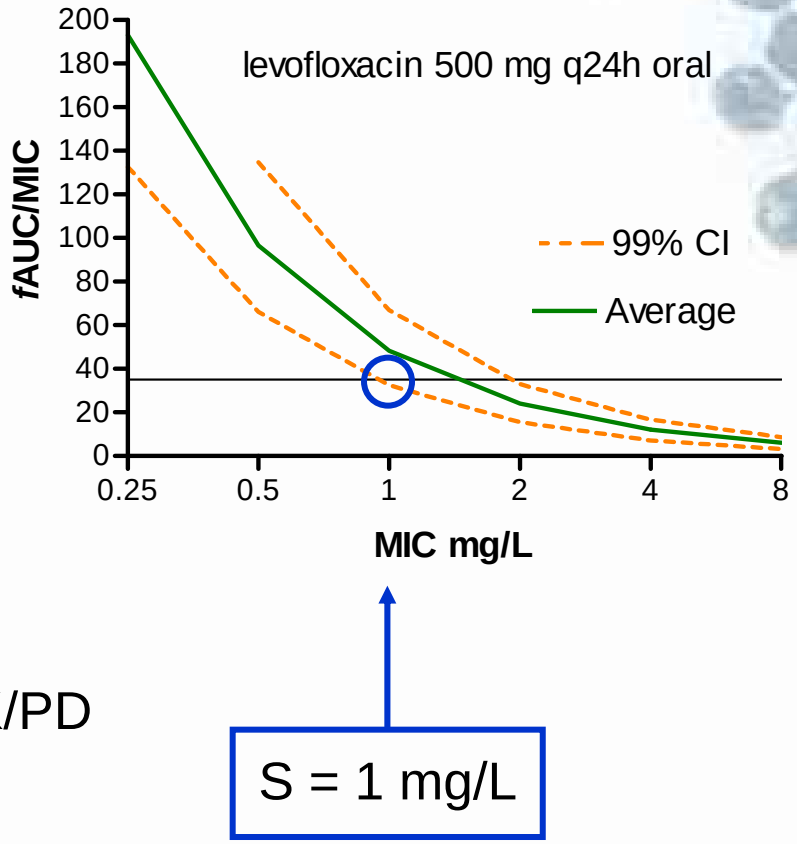
- *in vitro* studies
- *in vivo* studies
- klinische studies

- de doeltreffendheid van het antibioticum wordt op een kwantitative manier vastgesteld
- Het verband tussen de farmacokinetische profielen en het ontstaan van resistentie wordt onderzocht

Monte Carlo simulaties worden uitgevoerd om een PK/PD breekpunt te bepalen voor de meest courante doseringsschemas

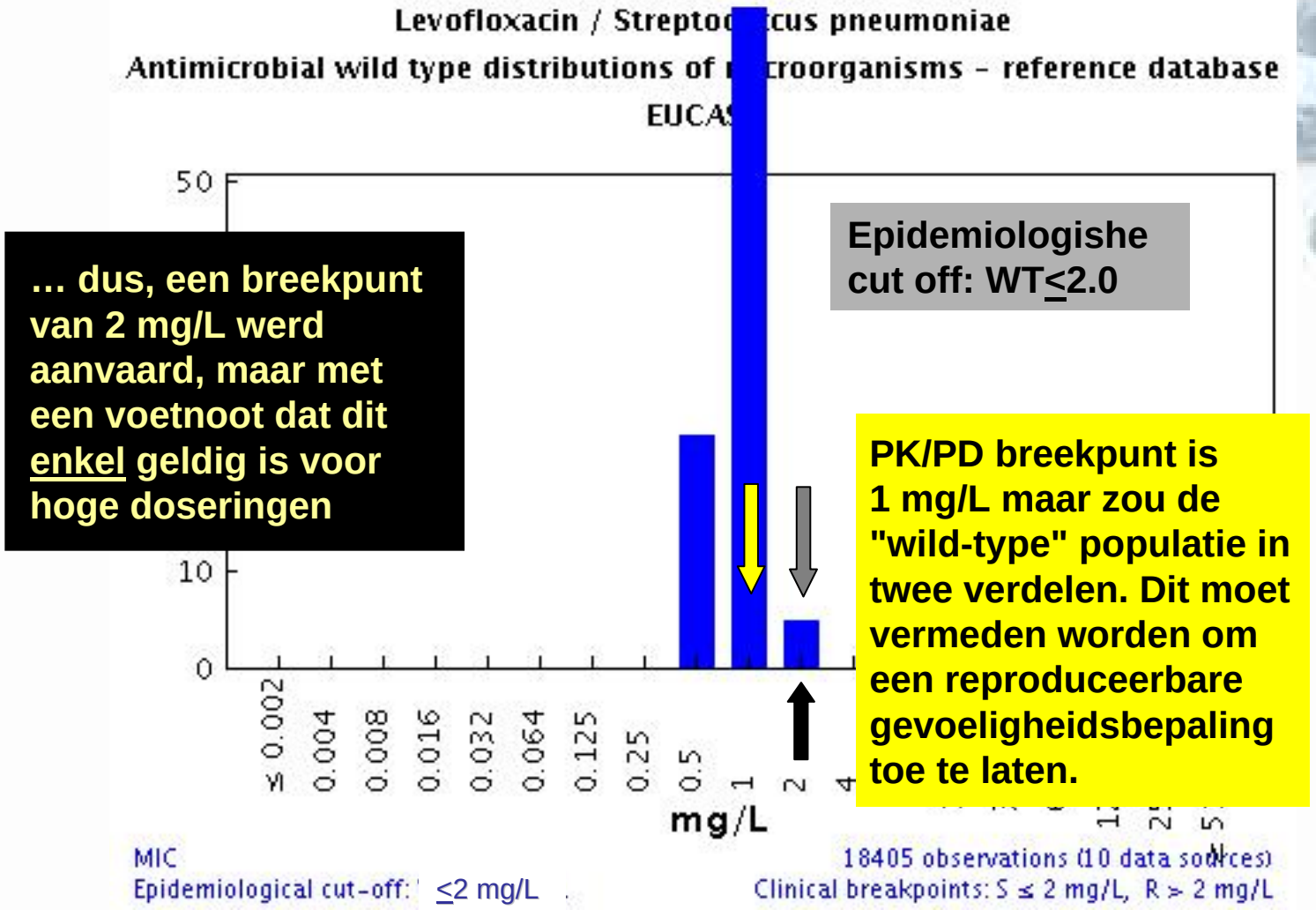


PK/PD



6. PK/PD breekpunten worden indien nodig herzien om te voorkomen dat de "wilde type" MIC verdeling erdoor in twee zou verdeeld worden

Typische voorbeeld: levofloxacin



… dus, een breekpunt van 2 mg/L werd aanvaard, maar met een voetnoot dat dit enkel geldig is voor hoge doseringen

Epidemiologishe cut off: WT≤2.0

PK/PD breekpunt is 1 mg/L maar zou de "wild-type" populatie in twee verdelen. Dit moet vermeden worden om een reproduceerbare gevoeligheidsbepaling toe te laten.

7. Voorlopige breekpunten werden aan de Nationale Commissies (GB, F, NL, N, N, S) voorgelegd voor commentaar

8. Raadpleging van:

- **EUCAST General Committee**
- **specifieke commissies van experten indien nodig (*Neisseria*, anaeroben, …)**
- **Farmaceutische Industrie**
- **Fabrikanten van diagnostische toestellen**
- **via EUCAST website**

9 . Publicatie van een "*Rational Document*" op de website van EUCAST

Dit zijn de resultaten…

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.

Vergelijking PK/PD (dicht bij EUCAST) en CLSI breekpunten …

Table 2. Pharmacokinetic parameters used for proposing PK/PD based limits of sensitivity and conditions favouring the prevention of emergence of resistance for most common organisms and systemic infections, together with the breakpoints set by European and American ad-hoc organisations

		Typical PK values		Proposed PK/PD upper limit		Breakpoints (mg/L)[d]	
Drug	Typical daily dosage[a]	C_{max} in mg/L total/free (dose)	$AUC_{24\ h}$ (mg × h/L) total/free	Efficacy[b]	Prevention of resistance[c]	EUCAST (S-R)	NCCLS (S/I/R)
Norfloxacin	800 mg	1.4/1.1 (400 mg PO)	14/11	0.1–0.4	0.1	≤ 0.5 to > 1[e]	≤4/8/>16[j]
Ciprofloxacin	1000 mg	2.5/1.75 (500 mg PO)	24/18	0.2–0.8	0.2	≤ 0.5 to > 1[f] (≤ 0.125 to > 2	≤1/2/>4[k]
Ofloxacin	400 mg	4/3 (400 mg PO)	40/30	0.3–0.9	0.4	≤ 0.5 to > 1[f] (≤ 0.125 to > 4	≤2/4/8[l]
Levofloxacin	500 mg	4/2.8 (500 mg PO)	40/28	0.3–0.9	0.3	≤ 1 to > 2[f] (≤ 2 to > 2)[h]	≤2/4/8[l]
Moxifloxacin	400 mg	3.1/1.8 (400 mg PO)	35/21	0.2–0.7	0.2	≤ 0.5 to > 1)[e] (≤ 5 to > 0.5)[i]	≤1/2/4[m]

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

Clinical breakpoints

- **Penicillins**
- **Cephalosporins (iv and oral)**
- **Carbapenems**
- **Monobactams**
- **Fluoroquinolones**
- **Aminoglycosides**
- **Glycopeptides** (current breakpoints)
- **Glycopeptides** revised (published 2009-05-25 for consultation until 2009-08-31).
- **Macrolides, ketolides & clindamycin, dalfopristine/-quinopristine,**
- **Tetracyclines**
- **Miscellaneous**

- **Fluconazole and voriconazole**
- **Itraconazole (pending)**
- **Caspofungin (pending)**

Voor welke antibiotica zijn breekpunten beschikbaar ?

Voor alle moleculen !

- **in blauw:** breekpunten zijn beschikbaar !
- **in zwart:** breekpunten nog niet beschikbaar maar dit is slechts voor antifungalen

EUCAST clinical MIC breakpoints - cephalosporins - Mozilla Firefox

File Edit View Go Bookmarks Tools Help

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]	*Acinetobacter*	*Staphylococcus*[4]	*Enterococcus*	*Streptococcus A,B,C,G*	*S.pneumoniae*	*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

EUCAST clinical MIC breakpoints - cephalosporins - Mozilla Firefox

File Edit View Go Bookmarks Tools Help

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]	*Acinetobacter*	*Staphylococcus*[4]	*Enterococcus*	*Streptococcus A,B,C,G*	*S.pneumoniae*	*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.

Vergeet niet dat klinische breekpunten altijd aan een bepaalde dosering verbonden zijn !

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 2009-06-05 (v 3.1)

Carbapenem Click on antibiotic name to see wild type MIC distributions		Species-related breakpoints (S≤/R>)												
		Enterobac-teriaceae	*Pseudo-monas*	*Acineto-bacter*	*Staphylo-coccus*	*Entero-coccus*	*Strepto-coccus A,B,C,G*	*S.pneu-moniae*	*Other strepto-cocci*	*H.influenzae M.catarrhalis*	*N.gonorr-hoeae*	*N.mening-itidis*	*Gram-negative anaerobes*	*Gram-pos anaerol*
Doripenem	RD	1/4	1/4	1/4	note[D]	--	1/1[E]	1/1[E,F]	1/1[E]	1/1[E,F]	IE	IE	1/1	1/1
Ertapenem	RD	0.5/1	--	--	note[D]	--	0.5/0.5[E]	0.5/0.5[E,F]	0.5/0.5[E]	0.5/0.5[E,F]	IE	--	1/1[H]	1/1[H]
Imipenem	RD	2/8[B]	4/8[C]	2/8	note[D]	4/8[C]	2/2[E]	2/2[E,F]	2/2[E]	2/2[E,F]	IE	--	2/8	2/8
Meropenem	RD	2/8	2/8	2/8	note[D]	--	2/2[E]	2/2[E]	2/2[E]	2/2[E,F]	IE	0.25/0.25[E,G]	2/8	2/8

A. 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 no table or footnotes.
B. *Proteus* and *Morganella* species are considered poor targets for imipenem.
C. 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. The breakpoints for Pseudomonas relate t therapy.
D. Susceptibility of staphylococci to carbapenems is inferred from the methicillin susceptibility.
E. 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 i 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 resis
F. Only meropenem is used for meningitis. In meningitis, meropenem breakpoints for *Streptococcus pneumoniae* and *Haemophilus influenzae* are 0.25/1 mg/L.
G. Meropenem breakpoints for *Neisseria meningititis* relate to meningitis only.
H. The ertapenem S/I breakpoint for anaerobes was moved from 0.5 to 1.0 to avoid dividing 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

Meropenem breekpunt voor
- **0.5 g 3 keer per dag (laagste dosis) is 2**
- **tot ten minste 1 g 3 keer per dag (hoge dosis) is max. 8**

Version*	Date	Action
3.1	*2009-06-05*	*Rationale documents publish*
3.0	*2009-02-18*	*"Other streptococci" breakp*
2.0	*2008-06-19*	*Doripenem added to table following EMEA positive opinion. "Other streptococci" breakpoints pending) added to table.*
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.

Zottegem in beeld | ESCMID: Clinical ... | EUCAST antimicro... | EUCAST clinic_

Penicillins - EUCAST clinical MIC breakpoints 2008-06-27 (version 1.2)

Penicillins		Species-rela						
Click on antibiotic name to see wild type MIC distributions.		*Enterobac-teriaceae*[A]	*Pseudo-monas*[B]	*Acineto-bacter*[C]	*Staphylo-coccus*[D]	*Entero-coccus*[E]	*Strepto-coccus A,B,C,G*[F]	*S.pneu-moniae*[G]
Benzylpenicillin	RD	–	–	–	0.12/0.12	Note[E]	0.25/0.25	0.06/2
Ampicillin[N]	RD	Note[A]/8	–	–	Note[D]	4/8	Note[F]	0.5/2
Ampicillin/sulbactam[O]	RD	Note[A]/8	–	IE	Note[D]	4/8	Note[F]	Note[G]
Amoxicillin	RD	Note[A]/8	–	–	Note[D]	4/8	Note[F]	Note[G]
Amoxicillin/clavulanate[O]	RD	Note[A]/8	–	–	Note[D]	4/8	Note[F]	Note[G]
Piperacillin	RD	8/16	16/16	IE	Note[D]	Note[E]	Note[F]	Note[G]
Piperacillin/tazobactam[O]	RD	8/16	16/16	IE	Note[D]	Note[E]	Note[F]	Note[G]
Ticarcillin	RD	8/16	16/16	IE	Note[D]	Note[E]	–	–
Ticarcillin/clavulanate[O]	RD	8/16	16/16	IE	Note[D]	Note[E]	–	–
Phenoxymethylpenicillin	RD	–	–	–	Note[D]	–	Note[F]	Note[G]
Mecillinam[P]								
Oxacillin								
Cloxacillin								
Dicloxacillin								
Flucloxacillin								

A. Enterobacteriaceae: and aminopenicillin breakpoints: The resistant breakpoint of R>8 mg/L ensures that all isolates with resistance mechanisms are reported resistant. The wide range of dosages and intravenous vs. oral administration significantly affect therapeutic efficacy. The unspecified S breakpoint enables the user to categorise wild type *Escherichia coli* and *Proteus mirabilis* S or I to the aminopenicillins. This will depend on dosing, route of administration and on whether the infection is systemic or affects the urinary tract only.

B. *Pseudomonas aeruginosa*: Piperacillin and ticarcillin breakpoints for *Pseudomonas* spp. are based on high dose therapy (for piperacillin with or without tazobactam 4 g x 4 and for ticarcillin with or without clavulanate 3 g x 4). The susceptible breakpoints were increased to avoid dividing wild type MIC distributions.

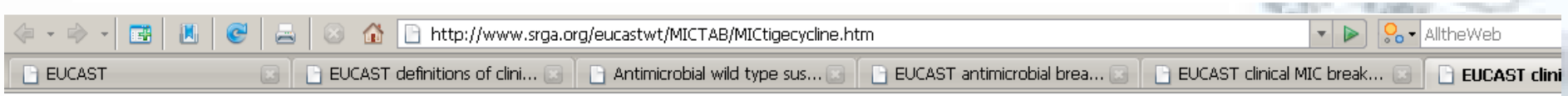
Belangrijke verschillen ?

molecule	*S. pneumoniae*	*Enterobacteriaceae*	*Pseudomonas*
penicillin (iv)	2 – 4 – 8 → 0.06 / 2		
ampicillin/amoxicilline	2 – 4 – 8 → 0.5 / 2	8 – 16 – 32 → Note / 8	
cefuroxime (oraal)	1 – 2 – 4 → 0.25 / 0.5	4 – 8,16 – 32 → 8 / 8	
cefuroxime (iv)	0.5 – 1 – 2 → 0.5 / 1	8 – 16 – 32 → 8 / 8	
clarithromycine	0.25 – 0.5 – 1 → 0.25 / 0.5		
piperacillin		16 – 32,64 – 128 → 8 / 16	64 - 128 → 16 / 16
ceftazidime		8 – 16 – 32 [b] → 1 / 8	8 - 16 - 32 → 8 / 8
cefepime		8 – 16 – 32 [b] → 1 / 8	8 - 16 - 32 → 8 / 8
meropenem		4 – 8 – 16 → 2 / 8	4 - 8 - 16 → 2 / 8
ciprofloxacin		1 - 2 - 4 → 0.5 / 1	1 - 2 - 4 → 0.5 / 1
levofloxacin	2 – 4 – 8 → 2 / 2	2 - 4 - 8 → 1 / 2	2 - 4 - 8 → 1 / 2
moxifloxacin	1 – 2 – 4 → 0.5 / 1	→ 0.5 / 1	

[a] groen = CLSI (**S≤** - **I** - **R≥**)
blauw = EUCAST (**S≤** / **R≥**) – Nota: zie dosering en plaats van infectie (urine…)

[b] met detectie van ESBL

Kunnen we het eindresultaat beoordelen ?



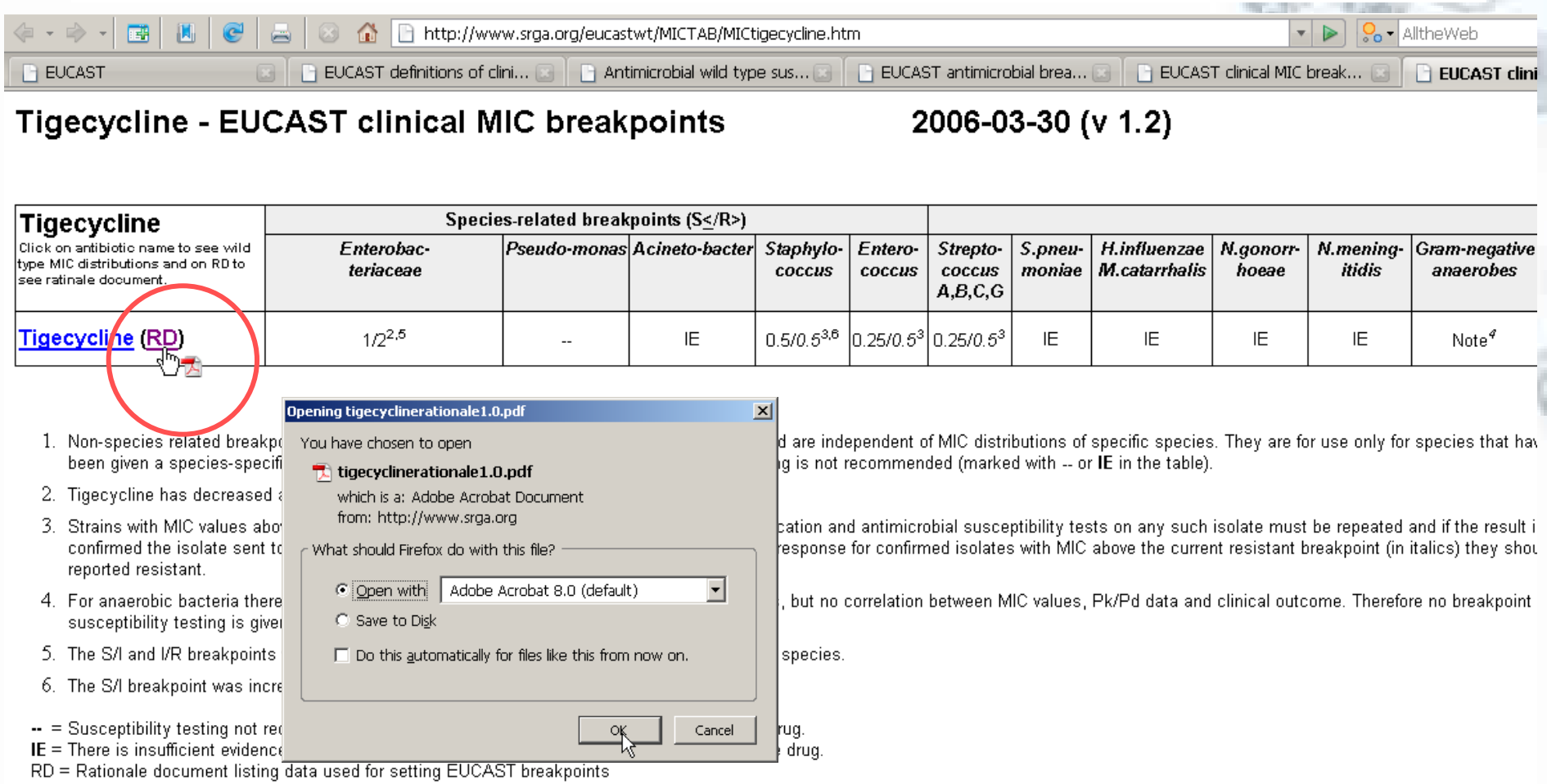
Tigecycline - EUCAST clinical MIC breakpoints 2006-03-30 (v 1.2)

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]

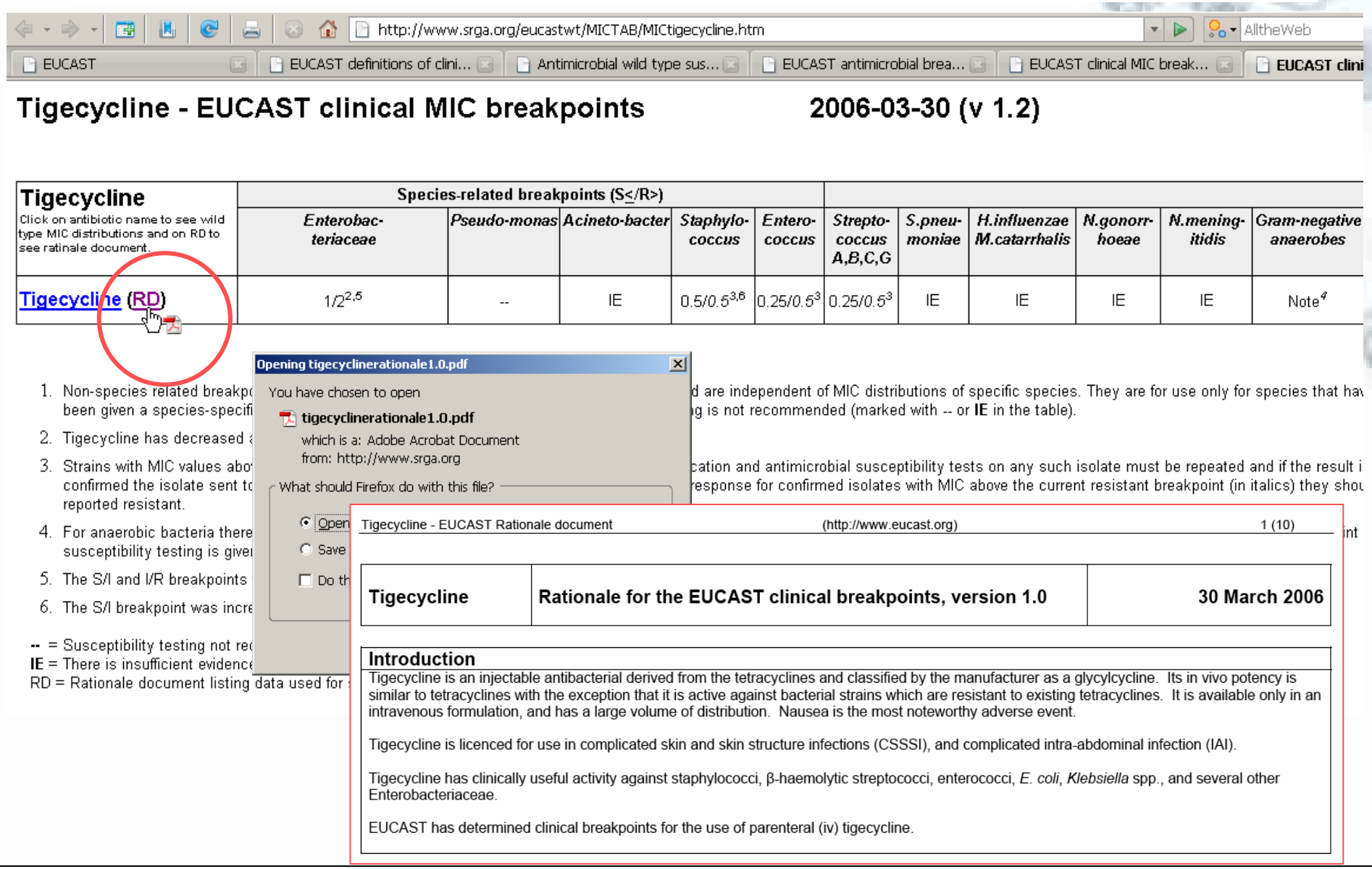
1. Non-species related breakpoints have been determined mainly on the basis of Pk/Pd data and are independent of MIC distributions of specific species. They are for use only for species that hav been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (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

Kunnen we het eindresultaat beoordelen ?



Kunnen we het eindresultaat beoordelen ?



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 rec…
IE = There is insufficient evidence…
RD = Rationale document listing data used for …

Opening tigecyclinerationale1.0.pdf

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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.

Kunnen we het eindresultaat beoordelen ?

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).

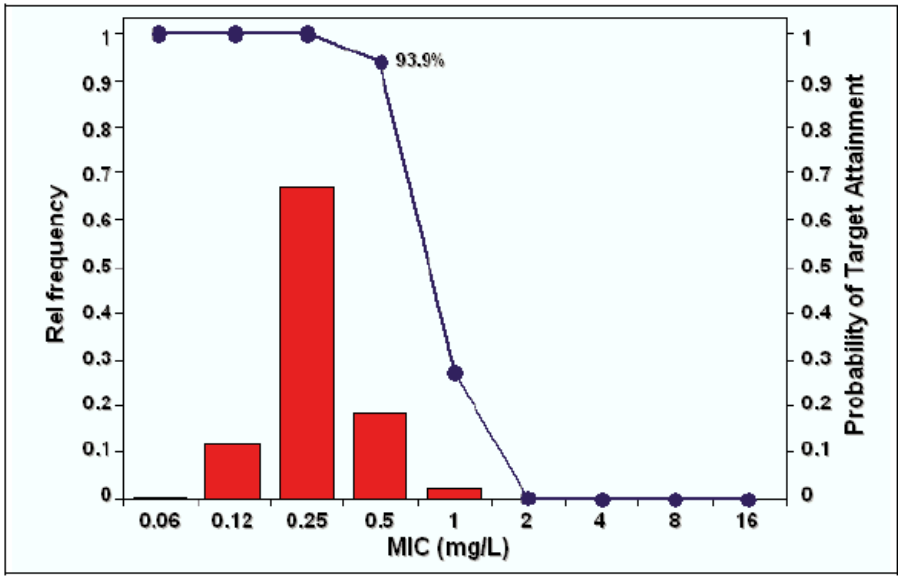


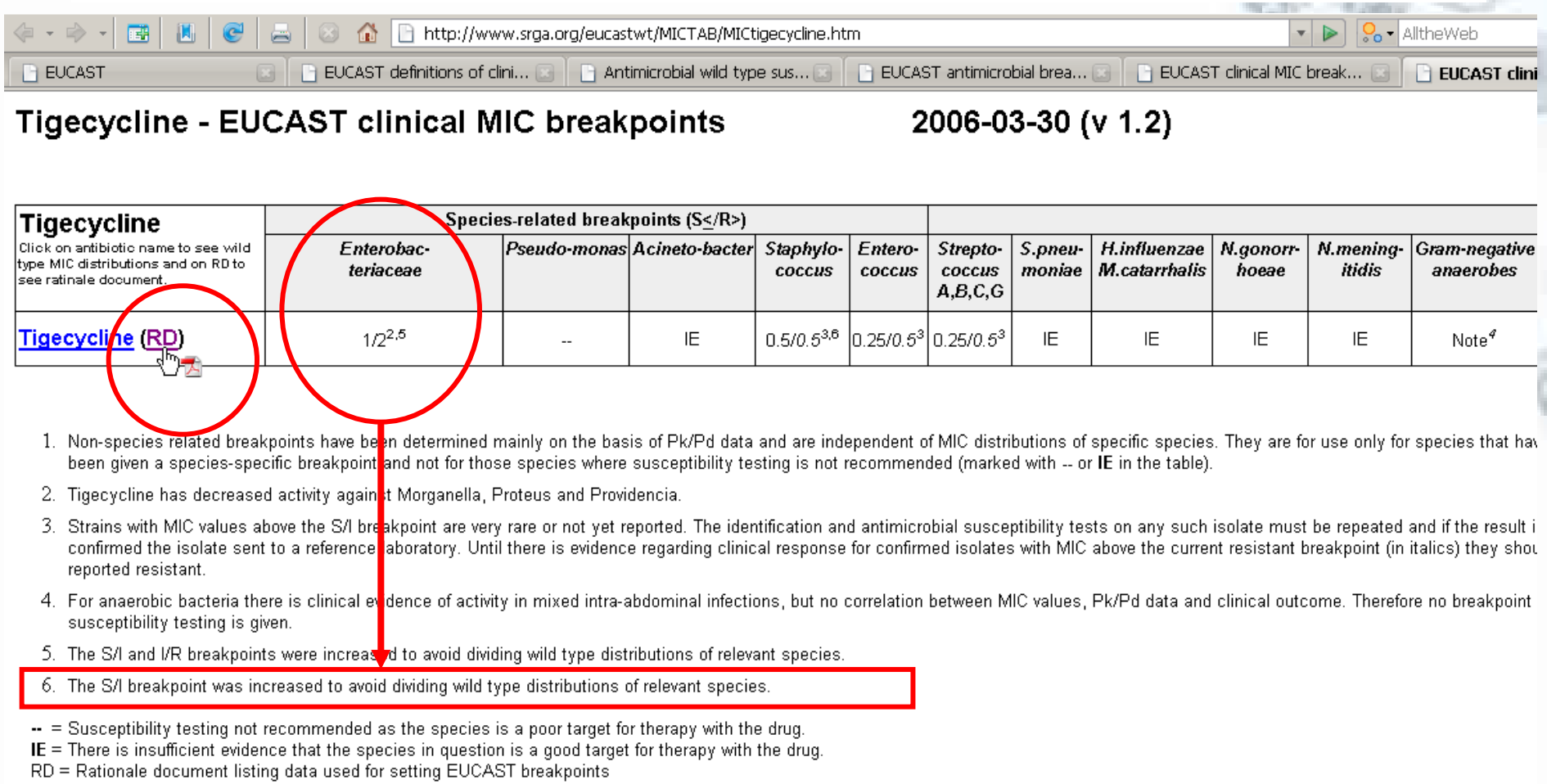
Figure 3. Probabilities of target attainment for tigecycline. Probability of Target Attainment Against *E. coli* at the CART-Identified Serum AUC/MIC Ratio of 6.96. Data on file, Wyeth Inc.

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.

Het "Rational Document" is belangrijk



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

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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

Dus, het kliniche breekpunt is 1/2 mg/L maar het PK/PD breekpunt is lager (0.25/0.5 mg/L)

Hoe zullen de EUCAST breekpunten in de praktijk gebruikt worden ?

- Breekpunten van EUCAST kunnen onmiddellijk door iedereen gebruikt worden…
- De nationale commissies hebben zich ertoe verbonden om de breekpunten van EUCAST in hun respectieve landen (GB, F, NL, D, N, S) te implementeren (geldig vanaf 2008 …)
- Het merendeel van de geautomatiseerde systemen kan vanaf nu geherprogrammeerd worden om breekpunten van EUCAST te gebruiken (vraagt aan uw leverancier)… en elk systeem kan in 2009 *up-to-date* gemaakt worden…

En wat voor België / Et en Belgique ?

Des discussions animées sont en cours …

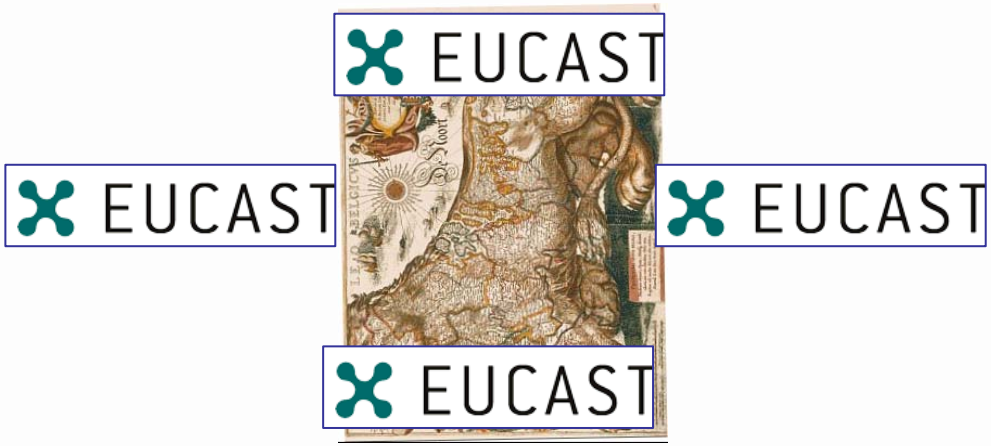
De *Belgische Vereniging voor Infectiologie en Klinische Microbiologie*
(= La Société Belge d'Infectiologie et de Microbiologie Clinique)
stuurt de operatie

Sensibiliseringscampagnes, het verzamelen van informatie en de indentificatie van problemen werden in november 2007 opgestart ... en lopen verder in 2008-2009 ...

De uiteindelijke bedoeling is de verandering in België te introduceren op 1 januari 2010

Les francophones et / en de Nederlandstaligen gaan akkoord !!

En wat voor België / Et en Belgique ?



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.

De toekomst van de EUCAST breekpunten

- Vanaf nu, zijn EUCAST breekpunten **officieel** en **verplicht** voor alle **nieuwe antibiotica** en voor **alle nieuwe indieningen** bij EMEA

EMEA registratie van doripenem

Drempelwaarden

Drempelwaarden voor de Minimum Inhiberende Concentratie (MIC), vastgesteld door het European Committee on Antimicrobial Susceptibility Testing (EUCAST) zijn als volgt:

Niet speciesgerelateerd	S ≤1 mg/l en R >4 mg/l
Stafylokokken	afgeleid uit de drempelwaarde van methicilline
Enterobacteriacea	S ≤1 mg/l en R >4 mg/l
Acinetobacter spp.	S ≤1 mg/l en R >4 mg/l
Pseudomonas spp.	S ≤1 mg/l en R >4 mg/l
Streptococcus spp. behalve *S. pneumoniae*	S ≤1 mg/l en R >1 mg/l
S. pneumoniae	S ≤1 mg/l en R >1 mg/l
Enterokokken	'ongeschikt doel'
Haemophilus spp.	S ≤1 mg/l en R >1 mg/l
N. gonorrhoeae	onvoldoende bewijs
Anaeroben	S ≤1 mg/l en R >1 mg/l

DORIBAX® SAMENVATTING VAN DE PRODUCTKENMERKEN (EMEA)

De toekomst van de EUCAST breekpunten

- Vanaf nu, zijn EUCAST breekpunten **officieel** en **verplicht** voor alle **nieuwe antibiotica** en voor **alle nieuwe indieningen** bij EMEA

- Kunnen, misschien, de nieuwe internationale standaard worden…
  (see why in a moment…)

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

Done...

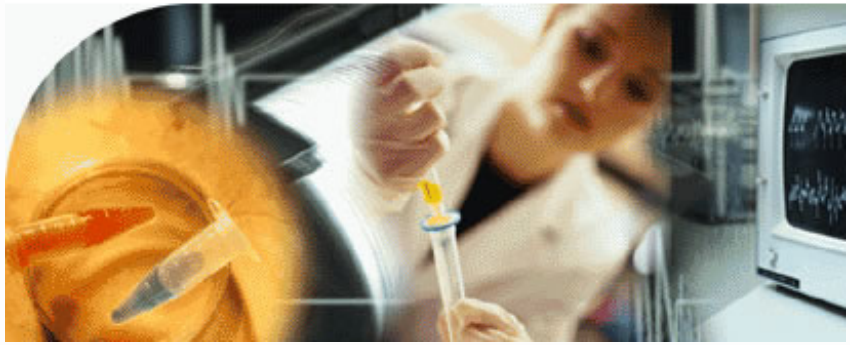
- Cephalosporin breakpoints for *Enterobacteriaceae*
- Carbapenems and Monobactams (!?)

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)

Maar zal het NCCLS (nu CLSI…) nog **officiële** breekpunten kunnen voorstellen ?

CLINICAL AND LABORATORY STANDARDS INSTITUTE®
(Formerly NCCLS)



De onzekere toekomst van CLSI breekpunten ...

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

De onzekere toekomst van CLSI breekpunten …

laatste nieuwtjes vanuit V.S.

Symposium 4.1

Updates and Controversial Issues in Susceptibility Testing from the CLSI Perspective

Mary Jane Ferraro
Massachusetts General Hospital and Harvard Medical School
Boston, MA, U.S.A.

In the course of carrying out its mission to develop new breakpoints, or to revise existing breakpoints, it is possible that different breakpoints might exist for the same microorganism/antimicrobial agent combination (e.g. a CLSI breakpoint or a EUCAST breakpoint and an U.S. Food and Drug Administration [FDA] breakpoint); or that a CLSI breakpoint might exist for which there is no breakpoint in a regulatory product label (e.g. FDA or EMEA). In recent years this has resulted in discussions in the United States among the U.S. FDA, the CLSI AST SC, and representatives for both the pharmaceutical and antimicrobial susceptibility testing devices industries. The status of these discussions among the various stakeholders to find a path forward that will allow laboratories to use the most relevant breakpoints for their clinical situation will be discussed.

Zullen goede breekpunten alles oplossen ?

- Breekpunten zijn slechts uw handleiding voor een behandeling in het algemeen
  (wat is de kans op succes voor een "gemiddelde" patiënt ?)
- MIC verdelingen (lokaal, regionaal, nationaal) blijven essentieel om gevoeligheden te beoordelen en doseringen te bevestigen of aan te passen…
- De therapie van "moelijk-te-behandelen" patiënten moet individueel beoordeeld worden in functie van de MIC-waarden …
- Het gebruik van antibiotica met twijfelachtige doeltreffendheid moet grondig onderzocht worden…

Een voorbeeld van bij ons …

Impact du traitement antibiotique sur le niveau de résistance des souches de *Pseudomonas aeruginosa* (P.a.) collectées par paires sur des patients souffrant d'une pneumonie nosocomiale dans cinq hôpitaux belges.

M. RIOU [1], Y. GLUPCZYNSKI [1], S. CARBONNELLE [1], L. AVRAIN [1,2], J. PIRNAY [3], D. DE VOS [3,4], A. SIMON [1], D. PIERARD [5], F. JACOBS [6], A. DEDISTE [7], F. VAN BAMBEKE [1], P.M. TULKENS [1]

[1]Université catholique de Louvain, Bruxelles, Belgium, [2]Coris Bioconcept s.a., Gembloux, Belgium, [3]Queen Astrid Military Hospital, Brussels, Belgium, [4]Vrije Universitair Brussel, Brussel, Belgium, [5]Universitair Ziekenhuis Brussel, Brussel, Belgium, [6]Université libre de Bruxelles, Bruxelles, Belgium, [7]Centre Hospitalier-universitaire St-Pierre, Bruxelles, Belgique

Een voorbeeld bij ons …

Tableau : Antibiotiques utilisés et sensibilité des paires collectées (n=62) selon les BP avant et durant le traitement [a]

	% d'utilisation des antibiotiques durant le traitement [a]	% S / I / R (EUCAST BP) [b]		% S / I / R (CLSI BP) [c]		Perte de sensibilité (%) durant le traitement [c]	
		Jour 0	Jour ≥ 3	Jour 0	Jour ≥ 3	EUCAST	CLSI
GEN	8,8	79,0 / 0,0 / 21,0	71,0 / 0,0 / **29,0**	79,0 / 8,1 / 12,9	71,0 / 12,9 / 16,1	8,0	8,0
AMK	21,9	87,1 / 1,6 / 11,3	72,6 / 11,3 / 16,1	88,7 / 0,0 / 11,3	83,9 / 4,8 / 11,3	14,5	4,8
MEM	18,4	64,5 / 12,9 / 22,6	50,0 / 14,5 / **35,5**	75,8 / 1,6 / 22,6	58,1 / 6,5 / **35,5**	14,5	17,7
FEP	14	59,7 / 0,0 / **40,3**	45,2 / 0,0 / **53,2**	59,7 / 12,9 / **27,4**	46,8 / 8,1 / **45,1**	12,9	12,9
PTZ	24,5	66,1 / 0,0 / **33,9**	46,6 / 0,0 / **53,2**	82,3 / 0,0 / 17,7	67,7 / 0,0 / **32,3**	19,5	14,6
CAZ	3,5	64,5 / 0,0 / **35,5**	53,2 / 0,0 / **46,8**	64,5 / 8,1 / **27,4**	53,2 / 8,1 / **38,7**	11,3	11,3
CIP	8,8	69,4 / 4,8 / **25,8**	59,7 / 4,8 / **35,5**	74,2 / 3,2 / 22,6	64,5 / 6,5 / **29,0**	9,7	9,7
						r = 0,72[d] **p = 0,02**	r = 0,27[d] p = 0,69

[a] Antibiotiques utilisés durant le traitement (%, n = 114)

[b] les chiffres en gras indique le niveau de résistance des antibiotiques excédant 25 % pour toutes les souches et selon les breackpoints correspondants :

- EUCAST ≤S / R>: gentamicine (GEN): 4 / 4; amikacine (AMK): 8 / 16; méropénème (MEM): 2 / 8; céfépime (FEP): 8 / 8 ; pipéracilline - tazobactam (PTZ): 16 / 16; ceftazidime (CAZ): 8 / 8; ciprofloxacine (CIP): 0.5 / 1.
- CLSI ≤S / R≥: gentamicine (GEN): 4 / 16; amikacine (AMK): 16 / 64; méropénème (MEM): 4 / 16; céfépime (FEP): 8 / 32; pipéracilline - tazobactam (PTZ): 64 / 128; ceftazidime (CAZ): 8 / 32; ciprofloxacine (CIP): 1 / 4.

[c] Pourcentage des souches passant de sensible à intermédiaire/résistante entre le jour J0 et le jour JX.

[d] Test non paramétrique de Spearman entre le pourcentage d'utilisation des antibiotiques et la perte de sensibilité (%).

Enkele woorden over Klinische Farmacie…

LOUVAIN MED. 122: 127-139, 2003.

LA PHARMACIE CLINIQUE, UNE NOUVELLE ORIENTATION PHARMACEUTIQUE AU SERVICE DES PATIENTS: RÉALISATIONS À L'ÉTRANGER ET POSSIBILITÉS EN BELGIQUE

A. SPINEWINE[1]

Mots clefs: évaluation; hôpital; patient; pharmacie clinique; pharmacoéconomie; pharmacothérapie

RÉSUMÉ

La pharmacie clinique est une pratique pharmaceutique centrée sur le patient. Son premier objectif est d'assurer un usage aussi efficace et aussi sûr que possible des médicaments. Un deuxième objectif, lié au premier, est d'assurer une optimisation de l'usage des médicaments susceptible d'en diminuer le coût global. Elle se pratique depuis de nombreuses années en Amérique du Nord et en Angleterre, de façon centralisée (depuis la pharmacie de l'hôpital) et décentralisée (dans les unités de soins). L'effet attendu, tant au niveau clinique qu'économique, a été démontré dans de nombreuses études. Cette discipline pourrait être développée en Belgique en raison des nombreux avantages espérés et de réelles opportunités dans le cadre de l'évolution actuelle des soins de santé dans notre pays.

Na enkele jaren…

Tijdschr. voor Geneeskunde, **62**, nr. 18, 2006

GEZONDHEIDSZORG: ACTUELE STANDPUNTEN

KLINISCHE FARMACIE: EEN POSITIEVE ONTWIKKELING OP DE WEG NAAR BETERE PATIËNTENZORG IN DE BELGISCHE ZIEKENHUIZEN

E. AMPE [1, 2], A. SPINEWINE [1], P.M. TULKEN

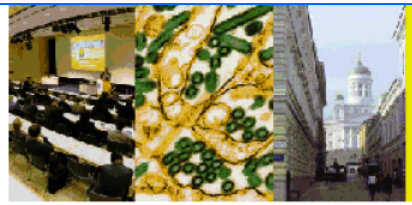
In België is klinische farmacie nu in ontwikkeling. De in 2000 gelanceerde pilootprojecten werden goed onthaald. Vanuit deze positieve ervaring werden bijkomende acties ondernomen door de universitaire ziekenhuizen en de faculteiten op het niveau van onderzoek en opleiding. De recente aanpassing van de apothekersopleiding op het niveau van de tweede cyclus sensibiliseert de jonge apothekers en bereidt hen voor op hun toekomstige beroepssituatie. Aan twee universiteiten bestaat reeds een echte derde cyclus voor specialisatie in de klinische farmacie. Apothekersverenigingen organiseren postuniversitaire vorming in farmaceutische zorg.

De erkenning van klinische farmacie op nationaal niveau is belangrijk om een correct kader te scheppen voor de klinisch apotheker. De combinatie van de beperkte ervaring bij ons en de bewezen voordelen van klinische farmacie in het buitenland maken dit project meer en meer realistisch in België.

Sedert 2008, zijn piloot projecten opgestart in 28 ziekenhuizen met een FOD budget van 500.000 euro, met geplande verlenging in 2010 …

Wat doet een klinisch apotheker met antibiotica ?

O26 - Pharmacokinetics/Pharmacodynamics: clinical relevance



19th ECCMID

Determination of pharmacokinetic/pharmacodynamic index for patients treated with high-dose vancomycin by continuous infusion

E. Ampe, P. Tulkens,
B. Delaere, J.D. Hecq, Y. Glupczynski

UCL Université catholique de Louvain

Unité de Pharmacologie cellulaire et moléculaire
Louvain Drug Research Institute
Université catholique de Louvain
<www.facm.ucl.ac.be>

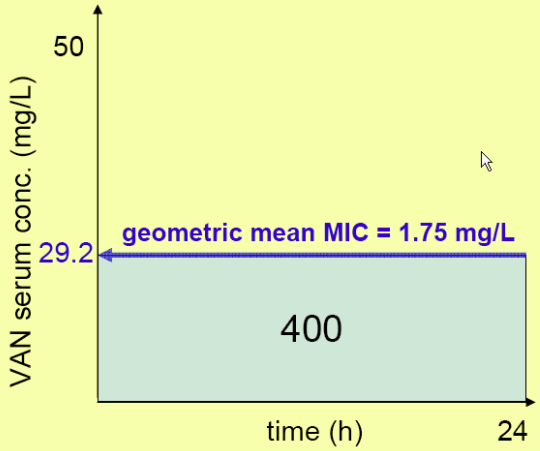
UCL MONT-GODINNE

Cliniques Universitaires de Mont-Godinne,
Yvoir,
Belgium

Wat doet een klinische apotheker met antibiotica ?

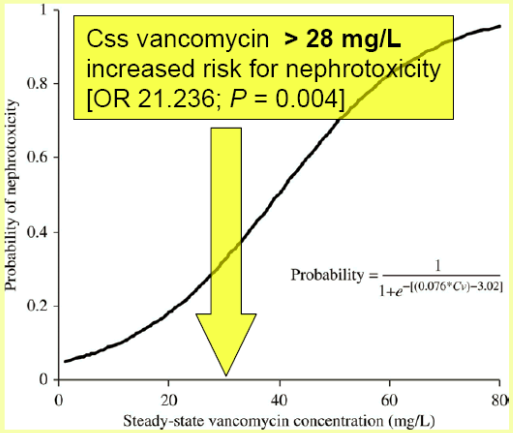
- a vancomycin AUC_{24h}/MIC ratio ≥ 400 (h^{-1}) is necessary for optimal therapy (Moise-Broder et al. Clin Pharmacokinet. 2004;43:925-42)
- we have to take into account *Staphylococci* with decreased susceptibility to vancomycin (Tenover FC et al. CID 2007; 44: 1208-1215)
  - associated with higher rates of clinical failure
  - not always detected by standard laboratory methods
- continuous infusion is easier for nursing and for therapeutic drug monitoring (TDM) than every 12h dosing (Wysocki et al AAC 2001; 45:2460-2467)

EFFICACY



Moise-Broder et al. Clin Pharmacokinet. 2004;43:925-42

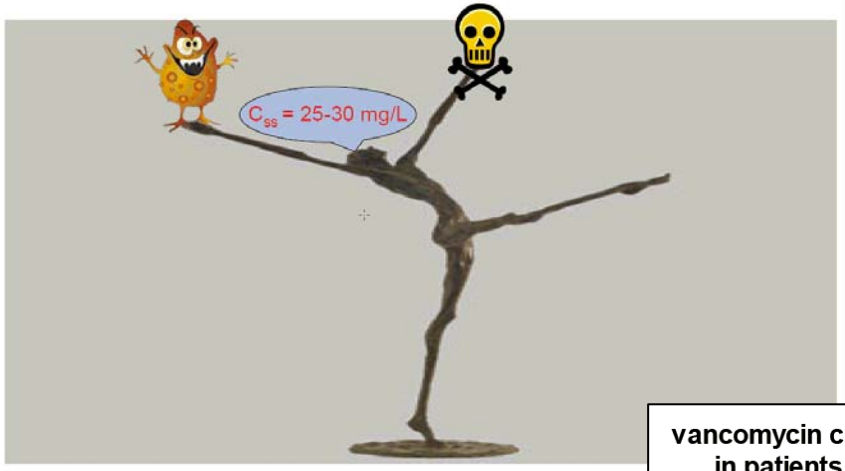
TOXICITY



Ingram, P. R. et al. J. Antimicrob. Chemother. 2008 Jul;62 (1): 168-71.

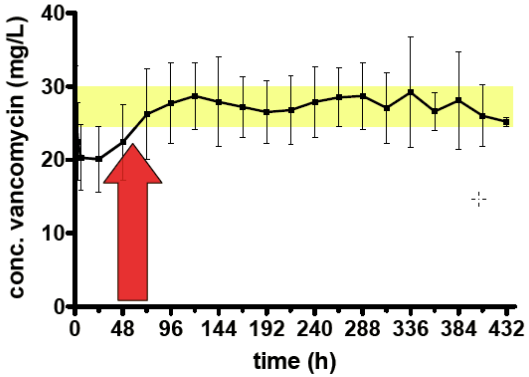
Wat doet een klinische apotheker met antibiotica ?

Which vancomycin serum concentration should we target?

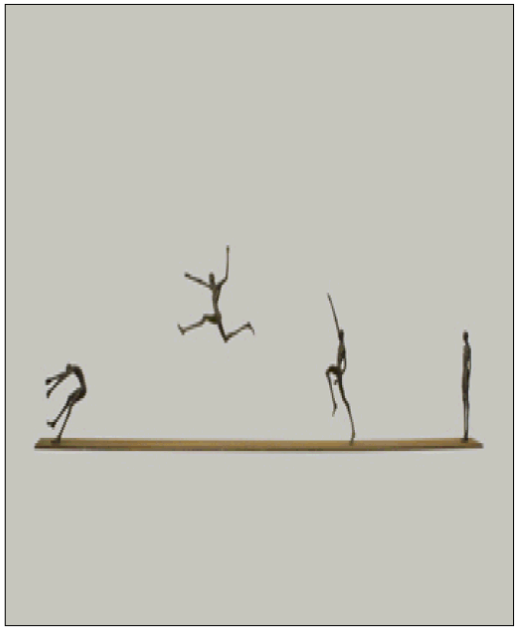


statue of Fred Bellefroid, Louvain

vancomycin concentrations measured over time in patients treated by continuous infusion

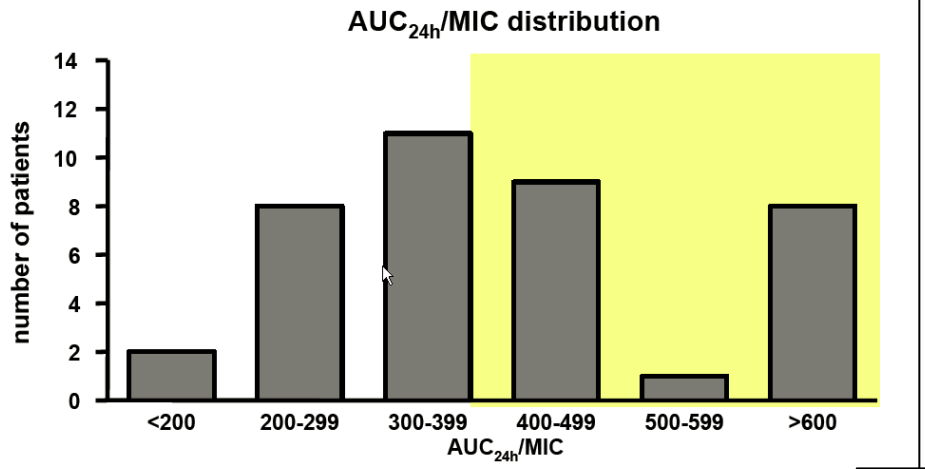


Target concentration range was reached and remained constant after 48h (infusion rate adjusted by a clinical pharmacist)

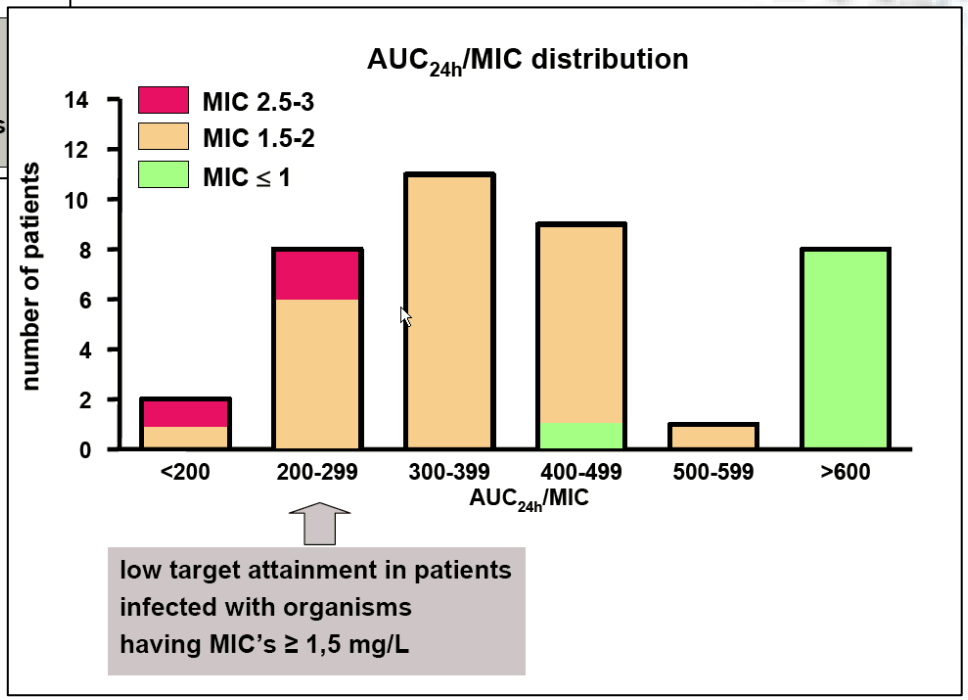


statue of Fred Bellefroid, Louvain

Wat doet een klinische apotheker met antibiotica ?



- AUC_{24h}/MIC ratio
  - mean: 525 +/- 83.4 h^{-1} [196 - 2684 h^{-1}]
  - AUC_{24h}/MIC of 400 h^{-1} was achieved in only 46% of cases



Succes...en terug naar breekpunten (of drempelwaarden…)

Conclusion

- high dose VAN by CI with dose adjustment by TDM did allow to maintain the mean VAN concentration within the target concentration range after the first 48h

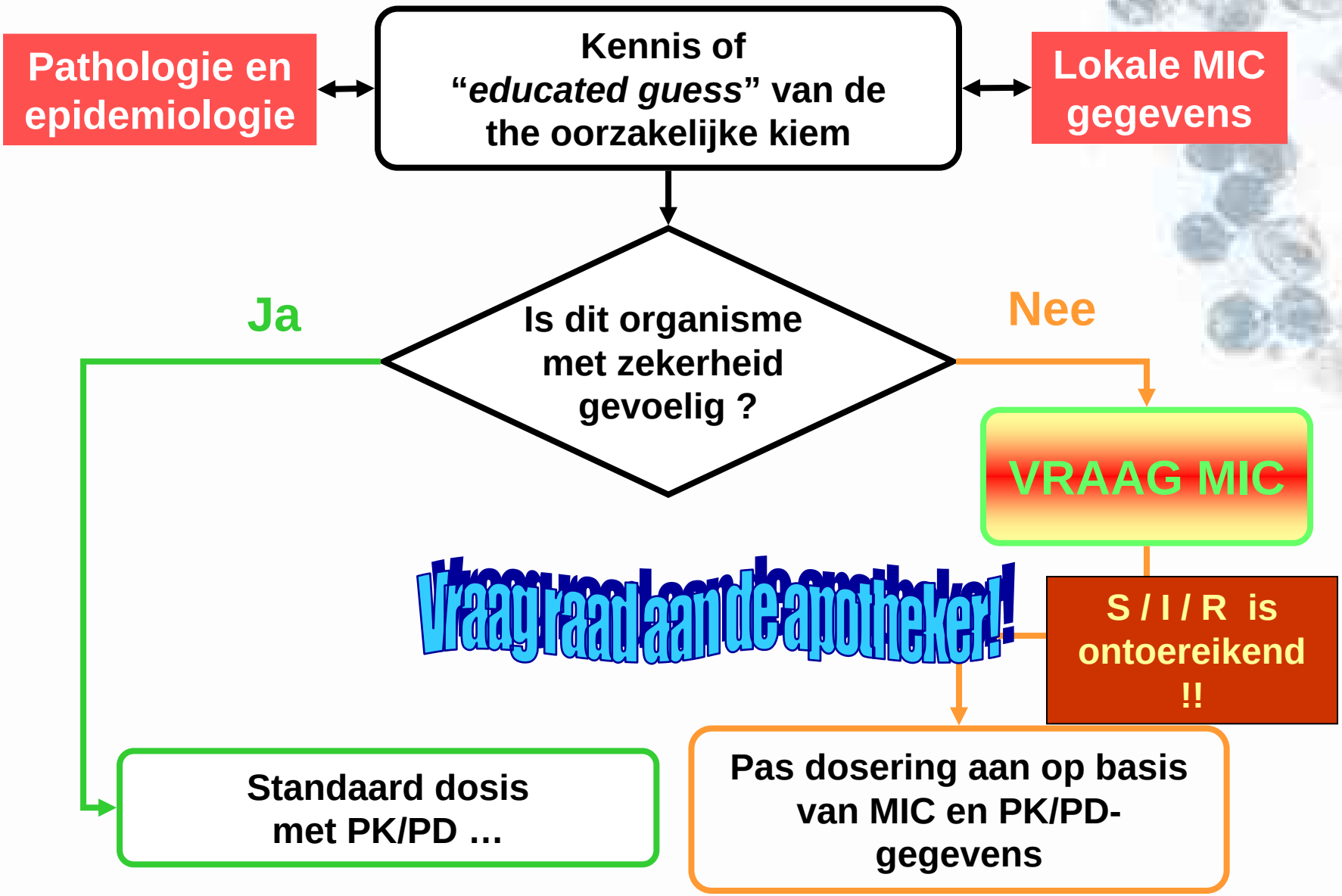
- a high variability in VAN concentrations measured was observed despite dose adjustment by a clinical pharmacist

- due to this variability and the high prevalence of organisms with reduced susceptibility to VAN, an AUC_{24h}/MIC ratio ≥ 400 (h^{-1}) was not reached in all patients

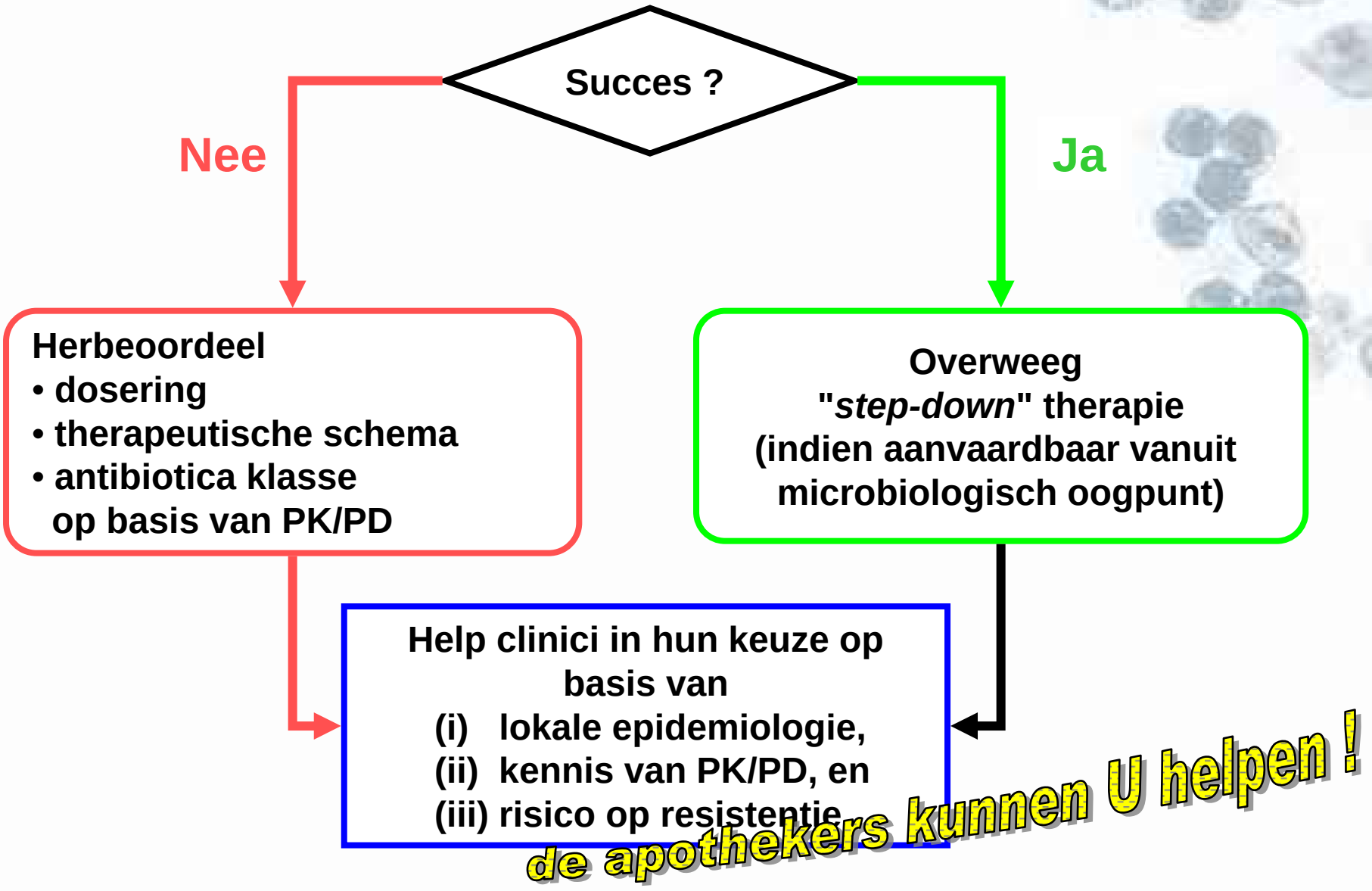
- patients infected with organisms having MIC's >1.5 mg/L should be considered at risk for treatment failure

- the PK/PD data observed in this study further suggest that lowering the current susceptibility breakpoint of VAN is justified
  - EUCAST: susceptible if MIC ≤ 4 mg/L
  - CLSI: susceptible if MIC ≤ 2 mg/L

Een sleutel tot succes …



Een sleutel to succes (vervolg…)...



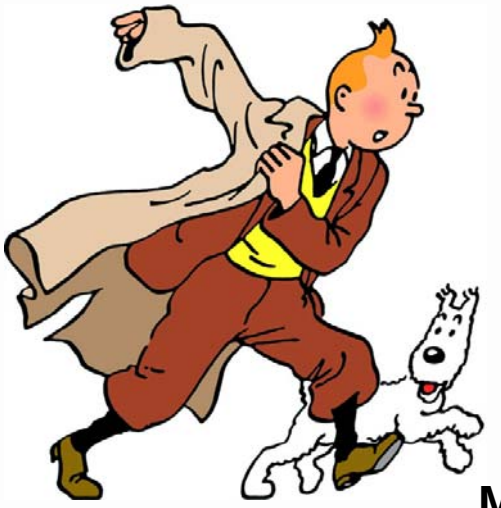
Belangenconflicten … en dankbetuigingen

- Belangenconflicten
  - onderzoekstoelagen van Bayer, Pfizer, Wyeth, GSK, …
  - Vergoedingen voor voordrachten: AstraZeneca, Aventis, Bayer, Antibioticabeleidsgroepen, ICAAC, VZA, …
  - Presentiegeld van RIZIV en FOD "Volksgezondheid"

- Dankbetuigingen
  - Gunnar Kalhlmeter (EUCAST voorzitter, voor slides en discussies)
  - ISC (en JC Pechère) voor benoeming als afgevaardigde bij EUCAST
  - Johan Mouton (voor slides over inleiding tot de populatiefarmacokinetiek, en discussies)
  - Apoth. Els Ampe (UCL) en Dr. F. Surmont (Wyeth) voor discussies, werk, … en nazicht van het Nederlands

En om te besluiten…

Laat ons de moeilijkheden niet uit de weg gaan



Maar nu is er tijd …

om samen echte successen te realiseren in Europa